Multi-objective Classification and Feature Selection of Covid-19 Proteins Sequences using NSGA-II and MAP-Elites

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Abstract: The advent of the Covid-19 pandemic has resulted in a global crisis making the health systems vulnerable, challenging the research community to find novel approaches to facilitate early detection of infections. This open-up a window of opportunity to exploit machine learning and artificial intelligence techniques to address some of the issues related to this disease. In this work, we address the classification of ten SARS-CoV-2 protein sequences related to Covid-19 using k-mer frequency as features and considering two objectives; classification performance and feature selection. The first set of experiments considered the objectives one at the time, four techniques were used for the feature selection and twelve well known machine learning methods, where three are neural network based for the classification. The second set of experiments considered a multi-objective approach where we tested a well known multi-objective approach Non-dominated Sorting Genetic Algorithm II (NSGA-II), and the Multi-dimensional Archive of Phenotypic Elites (MAP-Elites), which considers quality+diversity containers to guide the search through elite solutions. The experimental results shows that ResNet and PCA is the best combination using single objectives. Whereas, for the mulit-classification, NSGA-II outperforms ME with two out of three classifiers, while ME gets competitive results bringing more diverse set of solutions.

1 INTRODUCTION

Covid-19 has become a major concern for the whole world. Currently, there is a heavy workload on pathological laboratories and many cases tested there have been instances of false-negative test results (Wetsman, 2020; Abc7news, 2020). On the other hand, even with false-positive test results, a patient can face the wrong medication.

In the current pandemic situation of Covid-19, health care systems are experiencing extremely high demand for testing of Corona infections. At the same time, health care systems struggle not to ignore the testing of other traditional infections.

The biotechnology field can benefit immensely from computer science methods such as machine learning, deep neural networks, evolutionary computing, and data mining. In a very recent development, a team at MIT (Massachusetts Institute of Technology) Artificial Intelligence agency took a novel approach to predicting peptides to provide a high population of coverage for a Covid-19 spike protein-based vaccine which is in multiple clinical trials (Rachel, 2020; Hamley, 2020).

Artificial intelligence techniques can aid in diagnostics to treatments offering support to healthcare (Bohr and Memarzadeh, 2020). One method of infection detection is offered through the pattern recognition of genetic sequences of the viral and bacterial infectious organisms.

In this research work, we address the problem of feature reduction and multi-classification of protein sequences of "Severe acute respiratory syndrome-related coronavirus", commonly named as SARS-CoV-2 (Gorbalenya et al., 2020). We conducted primarily two sets of experiments: single and multi-objective optimization approaches. In the single-objective approach, we used four techniques for the feature selection, and from their results, we per-

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formed the classification using 12 methods, where 9 are well-known traditional machine learning methods and the last three are neural network-based methods.

In the multi-objective optimization, we addressed both the feature selection and the classification problem at the same time, using Non-dominated Sorting Genetic Algorithm II (NSGA-II) (Deb et al., 2002), and Map-Elites (ME) (Mouret and Clune, 2015) applying just three of the best classifiers found in the previous process. On one hand, NSGA-II is a well known multi-objective evolutionary algorithm, where the standard implementation rewards solutions closer to the target. On the other hand, ME is a state-of-the-art method that guides the search by considering both quality and diversity.

In the literature, we can find several works using conventional methods to address deoxyribonucleic acid (DNA) sequences, to our best of our knowledge, this is the first work to apply ME on this problem domain.

The experimental results show that the protein sequences classification can be addressed using a multi-objective approach obtaining a set of solutions considering both objectives; classification performance and feature selection in the Pareto front. On the other hand, ME reaches similar classification performance and bringing more diverse solutions, and deserves a deeper study to apply this approach to solve similar problem domains.

In this paper, Section 2 describes the related work, Information on SARS-CoV-2 sequences, NSGA-II, and Map-Elites Algorithm. Section 3 is dedicated to the experimental setup, then Section 4 presents and discusses the experimental results. Finally, Section 5 gives the conclusions and future work.

2 BACKGROUND

The Coronavirus disease (Covid-19) is mainly transmitted to human beings through droplets, coughs, sneezes, or exhales from infected persons. The SARS-CoV-2 is composed of various proteins and the tissue samples collected from a person infected with the Covid-19 virus contain the samples of these same proteins.

In its replicating mechanism in a human host cell, these various structural and non-structural proteins are produced again and composed together to form a whole new viral entity. The study of virology of the Covid-19 virus gives a better understanding of the structure of the virus and the proteins it contains.

In biological terms, DNA computing is a complicated task that relies heavily on biochemical reactions of DNA molecules leading it many times to imperfect computations. To make this molecular computation reliable, more efforts are focused on designing a better DNA sequencing methods. Authors in (Kim et al., 2002) formulated the DNA sequence design by using a multi-objective evolutionary algorithm (EA) constrained in nature into the DNA sequence design system.

In another study, (Randhawa et al., 2020) used a supervised machine learning-based approach for a real-time prediction of Covid19 virus for its taxonomy predictions providing the hypothesis of the bat origin theory. They used several traditional machine learning techniques to tackle that task; Linear Discriminant, Linear SVM, Quadratic SVM, Fine KNN, Subspace Discriminant, Subspace KNN, and Accuracy.

More recently in (Alkady et al., 2020), used human protein sequences of COVID-19 to predict the country origin of the sample and considered three stages including data preprocessing, data labeling, and classification. In the classification stage, the authors applied several machine learning methods, such as Linear Regression (LR), K-Nearest Neighbor (KNN), and Support Vector Machine (SVM) classifiers.

The Covid-19 disease virus has structural and non-structural components made up of proteins. It is already well known that coronavirus disease-2019 (COVID-19) is caused by the SARS-CoV-2 virus (Romano et al., 2020).

The SARS-CoV-2 virus has one of the largest known ribonucleic acid (RNA) genomes. A common measurement used to describe the length of a DNA or RNA molecule is *kb*, which stands for 'kilobase pairs', where a base pair corresponds to approximately 3.4 Å (340 pm) of length along the strand, and to roughly 618 or 643 daltons for DNA and RNA respectively(Alberts et al., 2018). This virus is approximately 30 kb in length and is a positive sense single-stranded genomic RNA (Khailany et al., 2020; Malik, 2020).

Some viruses encode RNA genome to store their genetic information (Cm.jefferson.edu,). As the SARS-CoV-2 virus infects humans, the replicating mechanism of the virus involves the replication of the same proteins and later forming of the whole viral entity. Our aim is that the correct classification of the viral protein sequences could help towards the diagnostic assessment and detection of vaccination approaches.

A genome sequence is described in terms of four basic nucleotides; A, T, G, and C, which denote chemical bases adenine, thymine, guanine, and cytosine

respectively. An amino acid is specified by a triplet of these bases and a protein is composed of one or more chains of amino acids (Cm.jefferson.edu, ; Genome.gov,). Furthermore, the protein sequences encode regions in terms of the bases, in this work we use this specific information to address the classification of SARS-CoV-2 virus samples.

The term of k-mer is primarily used within the context of computational genomics and sequence analysis, in which k-mers are composed of nucleotides (i.e. A, T, G, and C), and they are subsequences of length k contained within a biological sequence (Compeau et al., 2011).

Given a sequence of length k, the term k-mer refers to all possible combinations of the subsequences in that sequence. More generally, a sequence of length m will have $m-k+1$ k-mers and n^k total possible k-mers, where n is the number of possible monomers, four in the case of DNA corresponding to the base nucleotides.

The use of k-mer is widely used in many of the applications related to DNA sequences; for instance, a study from (Solis-Reyes et al., 2018) used k-mer based and deep neural networks for sub-typing of HIV-1 genome having higher accuracy against a complex dataset.

In a research paper by (Kaehler, 2017), the authors used a metagenomic data with DNA sequences from bacterial communities. The raw sequence data was transformed using k-mers and a numeric summarization vector. To address the high dimensionality, some feature selection methods were used to reduce the number of dimensions.

On the other hand, there is some evidence of using evolutionary algorithms to address DNA sequences. For instance, in (Chen et al., 1999) authors used genetic algorithms to manipulate bit strings using pointwise mutation and crossover.

Furthermore, a study by (Quinonez et al., 2019) addressed the problem of feature selection using the Map-Elites algorithm in a classification problem using Bayes Classifier becoming a good choice to use in this research work.

NSGA-II resemble the process of natural selection by selecting the fittest individuals and reproduction in order to produce offspring of the next generation (Davis, 1991). In general, we can define an individual composed by a tuple of the form $I = (P,G,S)$, where P stands for the phenotype, G for the genotype, and S for the score.

The observable properties of the individual I are known as the phenotype P, i.e. protein sequences. For a classification problem, the features selected from the protein sequences are used to make a decision to what class label they belong, then that solution is evaluated trough a function, which will we refer as to the fitness function because it assigns a quality score to P, named as fitness score S.

In the evolutionary process individuals I with higher S have more chances to recombine their G with other individuals or just to mutate some position in G, creating in this way increasingly better solutions until ideally an optimal or near-optimal one appears.

The Multi-dimensional Archive of Phenotypic Elites also known as Map-Elites (ME) (Mouret and Clune, 2015) is an algorithm that illuminates the containers of quality and diversity where the solutions are stored. ME creates a map of high-performing solutions (elites) searching the higher-dimensional feature space and mapping them in a low dimensional feature space defined by the user and keeping a diverse set of high-performing solutions.

Implementing ME requires defining the feature space of interest, for instance, by classification performance and feature selection. These dimensions can be discretized and their granularity is manually or automatically specified. ME search for the highest performing solution for each cell in the already defined search space.

The overall process of ME is similar to any population-based algorithm, starting with a random population. ME concurrently map the genotypical and phenotypical storing the information into containers of the same size, this way the mapping process is easily performed.

The general process starts choosing a cell or set of cells in the container to perform genetic operations and create new solutions that are placed in the container if there is not any other solution inside. Best solutions replace the old solutions and the cell is illuminated with the new quality score. These elite solutions are replaced iteratively by new and better solutions, maintaining the diversity of solutions which helps to avoid getting into regions of local optima.

3 EXPERIMENTAL SETUP

In this section, we give a detailed explanation of the whole process to address the multi-classification of Covid protein sequences.

The samples from SARS-CoV-2 were manually collected from the viral protein dataset was downloaded from the virus repositories from (NCBI, 2020) and the search parameters were: (i) Virus: SARS-CoV-2, (ii) Texid: 2697049, (iii) Host: Homo (humans), (iv) Taxid:9605, (v) Data type: Protein coding region, (vi) File format: FASTA.

In this research, we worked with 10 classes of proteins from a downloaded dataset with 78,555 samples and the length of the protein sequences ranged from 6 to 3,822 nucleotides. In this work, we selected 10 protein sequences from the coding region; Envelope protein, Membrane glycoprotein, Nucleocapsid phosphoprotein, orf10, orf3, orf6, orf7a, orf7b, orf8, and Spike glycoprotein.

At the time of this research, there had been minimal mutation with the SARS-CoV-2 virus in humans, hence the samples from across the globe were quite identical. The raw dataset contained 72,605 duplicated samples from a total of 78,555, and after removal, we got only 5,950 unique samples.

The next step in pre-processing the dataset was to balance the classes. Three protein classes had less than 300 samples and the other three more than 700 samples. We used a resampling method to increase the lower represented classes and a downsampling method for the over-represented classes. The threshold to balance the entire dataset was 500, where just the class envelope contains 9 more samples, resulting in a total of 5,009 samples in the pre-processed dataset.

Following the conventional approach used in bioinformatics, we used sub-sequences of length k contained within the dataset samples (Kaehler, 2017; Randhawa et al., 2020).

In this work, we empirically selected $k = 6$ to use all the sub-sequences of length 6. The number of k-mers contained in the samples is variable, and a typical sample could contain more than 12,000 k-mers. The information used from the k-mers is the frequency found in each sample.

To avoid any bias from the k-mers frequency, we used the normalization technique called Term Frequency Inverse Document Frequency (TF-IDF) applied to each k-mer. TF-IDF is a well-known technique in Natural Language Processing (NLP), useful for scoring words (Prawira, 2020). Here, TF-IDF is used to evaluate how relevant a k-mer is to a collection of protein sub-sequences in each sample. This is done by multiplying the frequency a k-mer appears in a sub-sequence and the inverse sub-sequence frequency of the k-mer across a set of sub-sequences.

The protein classification problem then is addressed using the resulting frequency vector as a feature vector with a domain in $[0,1]$ to relate each sample to one of the ten protein classes. In the following sections, we explain two different sets of experiments to address the classification and feature selection. The first set of experiments addresses each task separately as a single-objective optimization problem. On the other hand, the second set of experiments addresses both at the same time as a multi-objective optimization problem.

In this set of experiments, the classification of SARS-CoV-2 protein sequences is addressed as a single-objective optimization problem. The goal is to test twelve well known classifier methods with four feature selection strategies each and using a stratified 5-fold cross-validation. From now on we refer to the features as the vector of k-mer frequency from each sample, where in some cases they can contain more than 12,000 features.

The feature selection strategies used are: (i) PCA, (ii) $75th$-Perc, (iii) α-Best, and (iv) β-Best. The first strategy for feature selection used is the principal component analysis (PCA). We extracted 9 principal components so that it covered 95% variance of the data. The second strategy used is selecting the features according to a percentile of the highest scores, where we selected the $75th$ percentile ($75th$-Perc) using the Chi-squared distribution. For this technique, the number of features obtained was 91.

The third and fourth strategies select the best features from two measures; ANOVA and the Chi-squared distribution. Using the third one, we selected α as 1,000 highest scores (α-Best), using the analysis of variance (ANOVA) and the F-test to verify the variance between the means of α features significantly different, for this technique. Using the fourth one, we selected β as 1,000 highest scores (β-Best), using the Chi-squared distribution for this technique.

Table 1 shows the list of twelve classifier methods used in our experiments, where the first nine are well known traditional machine learning methods and the last three methods are neural network-based.

For the CNN method, we used 1D convolution layer (Conv1D), rectified linear unit (activation layer), Max Pooling 1D, and finally a fully connected layer, using 50 epochs for training with the loss function 'categorical crossentropy' and the optimizer 'adam'. To apply Conv1D, we had to transform the input data by expanding the shape of the array by inserting a new axis.

Whereas, the ResNet, the residual block consists of a stacking of convolutional (Conv1D), batch normalization, rectified linear (ReLU) activation, Conv1D, and again batch normalization layers.

For the multi-objective optimization, we used two methods: (i) NSGA-II, and (ii) MAP-Elites. From the first set of experiments, we select three of the machine learning methods as classifiers: *MNB*, *SGD*, and *RF*. The dataset for these experiments was divided into 75% for training (3,756) and 25% for testing (1,253). The features used in this set of experiments are the same used for the single-objective ex-

Table 1: List of the methods used as classifiers in the experiments. Short stands for the abbreviation for the method used.

Short	Description
MNB	Naive Bayes for multinomial models
SGD	Stochastic Gradient Descent
RF	Random Forest
KNN	*k*-nearest neighbors
GNB	Gaussian Naive Bayes
LR	Logistic Regression classifier
LSV	Linear Support Vector classifier
SVM-p	SVM with polynomial kernel function
SVM-r	SVM with Radial Basis Functions
NN	Neural Network
CNN	Convolutional Neural Network
ResNet	Residual Neural Network

periments. We design the first experiment to compare NSGA-II vs MAP-Elites using 200 features randomly chosen, then we performed a second experiment to analyse the performance of MAP-Elites considering the entire features set (>12,000).

Table 2: Parameters used to run NSGA-II and MAP-Elites.

Parameter	Value
Runs	30
Generations	100
Population	100
Selection	Tournament, (size 3)
Crossover	One point, 0.9
Mutation	0.1

Table 2 shows the main parameters used to run experiments with NSGA-II and MAP-Elites. A binary representation was used on the comparison from both algorithms to perform the feature selection. In the second ME experiment, we used a discrete representation composed of integers in the range of the total number of dimensions of the dataset. We extended this experiment further by changing two parameters with population size as 1,000 and generations as 1,000. But we used only the MNB classifier.

The function used to reward the best classifiers on all the experiments is based on the accuracy performance, given by

$$Accuracy = \frac{TP+TN}{TP+TN+FP+FN} \quad (1)$$

In all the experiments we used open-source tools, such as Python3, scikit-learn, NumPy, SciPy, and matplotlib. For the multi-objective experiments, we used mainly DEAP (Fortin et al., 2012), and QDpy (Cazenille, 2018) with modification to implement the cross over rate and mutation rate for the integration with DEAP.

4 RESULTS

This section presents the experimental results from the single and multi-objective approaches to address the classification and feature selection of protein sequences of SARS-CoV-2.

4.1 Single-objective

In this set of experiments, we addressed first the feature selection and then the classification problem. The classifier methods used are listed in Table 1 and the techniques used for feature selection are (i) PCA, (ii) 75th-Perc, (iii) α-Best, and (iv) β-Best. *ResNet* is the overall best classifier from all the single objective set of experiments, particularly using PCA as the feature selection technique. *RF* is the best classifier when using 75th−*Perc*, *CNN* is the best combined with α-Best, and *MNB* with β-Best.

Table 3 shows a summary of the experimental results for accuracy performance. The table shows an averaged performance using a stratified 5-fold cross-validation for each combination.

The experimental results show a high performance from all traditional machine learning methods tested. The first three methods shown in the first section of Table 3 are used for the multi-objective experiments. The neural network-based methods perform quite well, particularly the *CNN* and *ResNet* choices.

Table 3: Summary of the single objective classification accuracy performance for the four feature selection techniques in the columns and nine well known machine learning methods in the first section of the rows and three neural networks based at the final section, best performance are bold.

Classifier	PCA	75th-Perc	α-Best	β-Best
MNB	0.9569	0.9860	0.9928	**0.9998**
SGD	0.9792	0.9898	0.9968	0.9984
RF	0.9984	**0.9934**	0.9976	0.9988
KNN	0.9986	0.9916	0.9974	0.9986
GNB	0.9858	0.9639	0.9914	0.9914
LR	0.9940	0.9908	0.9938	0.9976
LSV	0.9620	0.9914	0.9896	0.9980
SVM-p	0.9930	0.7624	0.6412	0.8491
SVM-r	0.9936	0.9840	0.9828	0.9914
NN	0.9978	0.9926	0.9952	0.9990
CNN	0.9750	0.9926	**0.9980**	0.9990
ResNet	**0.9990**	0.9978	0.9990	0.9932

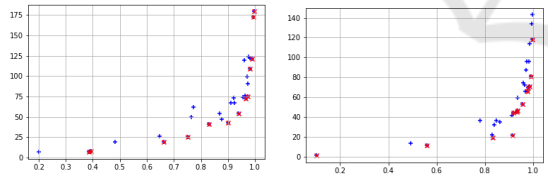
4.2 Multi-objective

In the second set of experiments, we selected just three of the best classifiers from the first set of experiments, and we addressed both feature selection and the classification problem using a multi-objective approach. As an optimizer, we used two different algorithms; (i) NSGA-II, and (ii) the quality-diversity algorithm named as MAP-Elites (ME).

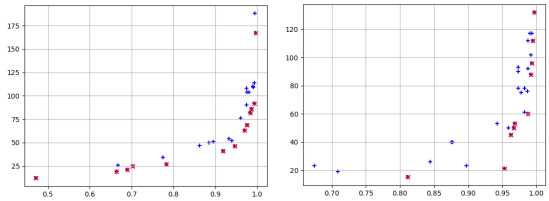
Table 4 summarizes the experimental results, and the columns show the three traditional classifiers selected from the single objective experiments. The upper section of the table shows the averaged performance results from the experiments using 200 features randomly selected for NSGA-II and ME. Whereas, in the lower section of the table, the third row shows the averaged performance results from the experiments using all the features only for ME, with 100 individuals in the population (ME2-100), and the fourth row shows the results using a similar configuration, but increasing the population size to 1,000 individuals (ME2-1000).

This comparison gives evidence that NSGA-II focuses on selecting a reduced number of features, meanwhile ME focus more on finding more diverse solutions with a higher number of features.

Furthermore, Figure 2 shows the quality and diversity containers from a typical run of ME, where each row shows both containers from each classifier used: *MNB*, *SGD*, and *RF*. The results of this experiment considers 200 randomly chosen features.



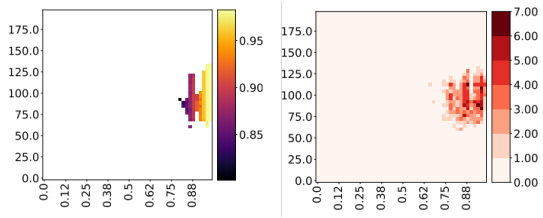
(a) ME2-MNB-100 (b) ME2-MNB-1000



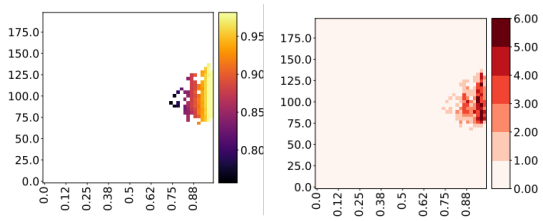
(c) ME2-SGD-100 (d) ME2-RF-100

Figure 1: Plots showing the Pareto front of a typical run from ME using all features; the postfix stands for the number of individuals used.

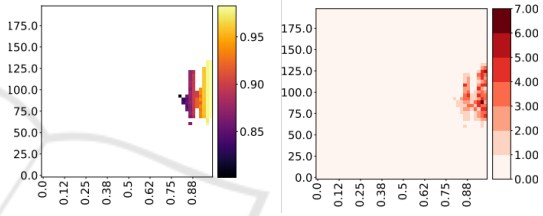
The experimental results using the multi-objective approach, using either NSGA-II or ME, showed that addressing the selection feature and the accuracy at the same time is better than the combination of the traditional machine learning methods and the feature selection techniques using a single-objective approach, but not better than the specific combination of *MNB* classifier and β-Best feature selection technique.



(a) Quality-MNB (b) Diversity-MNB



(c) Quality-SGD (d) Diversity-SGD



(e) Quality-RF (f) Diversity-RF

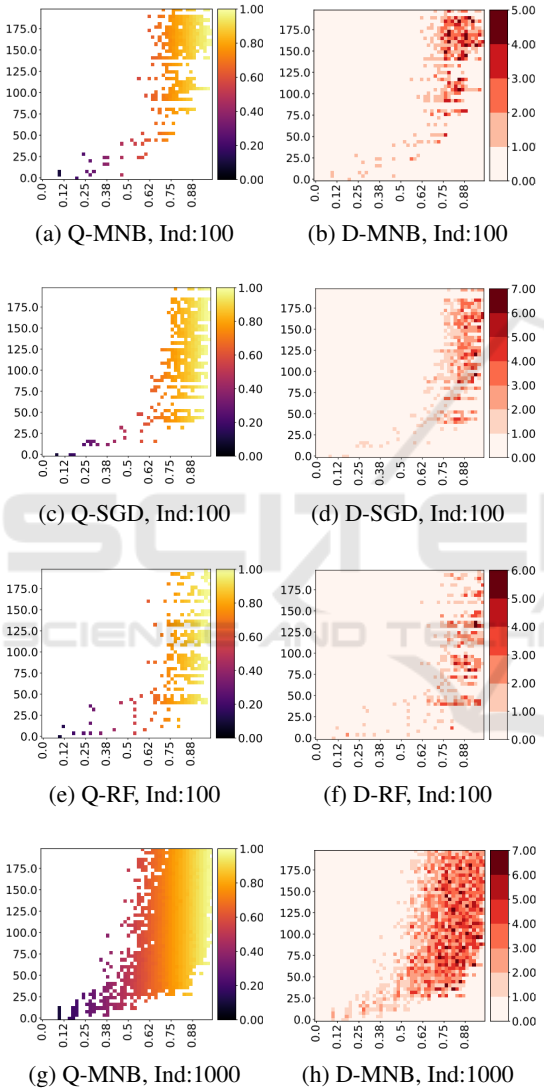
Figure 2: Illumination of the quality and diversity containers of ME from a typical run using 200 features randomly chosen.

This experiment shows that by increasing the number of individuals in the population, ME searches the space more uniformly and bring more diversity in the solutions, reaching more than 95% of accuracy, while selecting a low number of features.

In Figure 3, we can observe four sub-figures showing in the columns the quality and diversity containers for ME and in the rows the plots for the classifier used; the last row shows the plots for the choice of using 1,000 individuals. In this experiment, we used all the features available and the experimental results show that the combination of ME and *MNB* get better results as expected, and another benefit is the reduction of features selected to get this performance.

Table 4: Multi-objective averaged classification performance over 30 experimental runs for NSGA-II and MAP-Elites.

	MNB		**SGD**		**RF**	
	Accuracy	*Features*	*Accuracy*	*Features*	*Accuracy*	*Features*
NSGA-II	**0.9801** $\pm$ *0.0000*	37 $\pm$ *12*	**0.9815** $\pm$ *0.0004*	48 $\pm$ *16*	0.9815 $\pm$ *0.0004*	25 $\pm$ *3*
ME	0.9776 $\pm$ *0.0000*	78 $\pm$ *6*	0.9809 $\pm$ *0.0011*	78 $\pm$ *4*	**0.9827** $\pm$ *0.0000*	71 $\pm$ *4*
ME-2	0.8305 $\pm$ *0.2000*	70 $\pm$ *44*	0.8952 $\pm$ *0.1300*	72 $\pm$ *41*	**0.9403** $\pm$ *0.0802*	68 $\pm$ *33*



(a) Q-MNB, Ind:100 (b) D-MNB, Ind:100

(c) Q-SGD, Ind:100 (d) D-SGD, Ind:100

(e) Q-RF, Ind:100 (f) D-RF, Ind:100

(g) Q-MNB, Ind:1000 (h) D-MNB, Ind:1000

Figure 3: Illumination of the quality and diversity containers of ME from a typical run using all features. The first three rows show the classifier with 100 individuals, and the fourth row shows the containers of the *MNB* classifier using 1,000 individuals.

5 CONCLUSIONS

In this research work, we addressed the problem of multi-classification and feature selection of protein sequences of SARS-CoV-2 using single and multi-objective approaches using the protein sequences as coding regions. The pre-processing consisted of removing duplicates and balancing the dataset. The features used consisted of the normalized *k*-mer frequency. In the first set of conventional experiments, we used a single-objective approach addressing first the feature selection and then the classification problem. For the feature selection, we used four techniques for the feature selection and twelve well-known machine learning classifier methods, nine traditional ones, and three neural network-based.

In the second set of experiments, we selected just three of the best classifiers from the first set of experiments and we addressed both feature selection and the classification problem using a multi-objective approach. As an optimiser, we used two different algorithms; (i) NSGA-II, and (ii) a quality-diversity algorithm named as MAP-Elites. Furthermore, we implemented the mutation and crossover rate on the QDpy library to integrate it with DEAP.

The experimental results show that a combination of conventional methods can be used to perform separately the feature selection first and then the classification, having good results. Furthermore, the results show that this problem can be successfully addressed as a multi-classification optimization problem using a traditional evolutionary algorithm or a quality-diversity algorithm, such as MAP-Elites.

NSGA-II shows that consistently selects fewer features and getting a good classification performance. On the other hand, MAP-Elites clearly shows that explores better the search space and finds a wider Pareto front, while getting competitive results. This research shows that dimension reduction and multi-classification can be applied on long RNA-based viral genomic sequences and such a mechanism can be use for diagnostic purposes.

There are several different directions to follow from this research line, for instance, using protein se-

quences from other diseases and train models to identify correctly the samples with SARS-CoV-2. Another research line is to use genetic programming or grammatical evolution to evolve classifiers and MAP-Elites to keep a trade off between quality and diversity in the solutions and compare the evolutionary methods against state-of-the-art machine learning, such as; (i) gradient boosting, and (ii) least absolute shrinkage and selection operator (LASSO).

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