A Universal Non-Parametric Approach For Improved Molecular Sequence Analysis

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Abstract. In the field of biological research, it is essential to comprehend the characteristics and functions of molecular sequences. The classification of molecular sequences has seen widespread use of neural network-based techniques. Despite their astounding accuracy, these models often require a substantial number of parameters and more data collection. In this work, we present a novel approach based on the compression-based Model, motivated from [1], which combines the simplicity of basic compression algorithms like Gzip and Bz2, with Normalized Compression Distance (NCD) algorithm to achieve better performance on classification tasks without relying on handcrafted features or pre-trained models. Firstly, we compress the molecular sequence using well-known compression algorithms, such as Gzip and Bz2. By leveraging the latent structure encoded in compressed files, we compute the Normalized Compression Distance between each pair of molecular sequences, which is derived from the Kolmogorov complexity. This gives us a distance matrix, which is the input for generating a kernel matrix using a Gaussian kernel. Next, we employ kernel Principal Component Analysis (PCA) to get the vector representations for the corresponding molecular sequence, capturing important structural and functional information. The resulting vector representations provide an efficient yet effective solution for molecular sequence analysis and can be used in ML-based downstream tasks. The proposed approach eliminates the need for computationally intensive Deep Neural Networks (DNNs), with their large parameter counts and data requirements. Instead, it leverages a lightweight and universally accessible compression-based model. Also, it performs exceptionally well in low-resource scenarios, where limited labeled data hinder the effectiveness of DNNs. Using our method on the benchmark DNA dataset, we demonstrate superior predictive accuracy compared to SOTA methods.

Keywords: Classification, Sequence Analysis, Compression, Gzip

1 Introduction

Molecular sequence analysis stands as a pivotal pursuit in contemporary research, holding the key to unraveling the intricate language encoded in molecular sequences, such as DNA and proteins. The accurate comprehension and classification of these molecular sequences offer profound insights into their structural, functional, and evolutionary characteristics. As the foundation of numerous biological studies, including functional gene annotation, drug discovery, and evolutionary biology, molecular sequence analysis plays an indispensable role in advancing our understanding of the fundamental processes governing life. The pursuit of innovative methodologies in this realm is driven by the quest for more accurate, efficient, and resource-effective approaches to decipher the rich information concealed within the sequences, ultimately contributing to transformative breakthroughs in the broader landscape of molecular biology.

Several methods have been used for the classification of molecular sequences involving Neural Networks, language models, Feature Embedding, and Kernel functions. All these methods face certain challenges when it comes to achieving good accuracy in cases when the available data is less. Neural Network (NN) based methods are one of the most widely employed in molecular sequence classification and have demonstrated impressive accuracy in many cases [2]. However, these methods come with significant limitations including the requirement of a substantial number of parameters and long training times, making them computationally expensive and resource-demanding. Additionally, neural networks and NN-based language models heavily rely on large-scale training data, which may not be readily available for certain biological datasets, particularly in low-resource or rare species scenarios.

Designing low-dimensional embedding for molecular sequences is a challenging task. One of the most feasible solutions to this challenge is sequence data compression. Some of the well-known compression methods include Gzip, zlib, Bz2 [3] etc. Gzip is used on a large scale for lossless data compression [4], it became popular because of certain characteristics which include being free, open source, robust, compact, portable, has low memory overhead, and has reasonable speed [5]. Due to its inertia and its integration with so many sequence analysis tools, even today most of the sequence databases rely on Gzip [5]. The zlib and Bz2 compression algorithms efficiently detect non-randomness and low information content [6]. Their performance gets better as the string length increases. Bz2 compression is used to compress the strings and is not affected by the mass ratios, it does not include character order information due to the process of permuting characters during compression, this negatively affects the accuracy [1]. Our compression-based model offers several notable advantages over traditional neural network-based approaches. Firstly, it eliminates the computationally intensive nature of deep neural networks, reducing the parameter requirements and making them more lightweight and accessible. Secondly, by leveraging Gzip compression, our approach can efficiently handle low-resource biological datasets where labeled data is scarce or limited. This enables us to analyze molecular sequences even in resourceconstrained scenarios. Our contributions can be summarized as follows:

- We propose a novel approach for analyzing and classifying molecular sequences, using compression-based models including Gzip and Bz2.
- We develop an algorithm for Distance Matrix computation, in which we take a set of sequences as input and output a non-symmetric Distance matrix using Normalized Compression Distance (NCD) and different compressors.

A Universal Non-Parametric Approach For Improved Molecular Sequence Analysis

- We convert the distance matrix into a kernel matrix and extract the low dimensional numerical representation in the end, which can be used as input to any linear and nonlinear machine learning model for supervised and unsupervised analysis. In this way, we also addressed the limitation in [1] where they were only able to apply the k-nearest neighbor classifier for the classification purpose. Hence we show that our proposed method can generalize better for sequence classification.
- We also discuss the theoretical justifications for the proposed pipeline including the symmetry of the distance matrix and reproducing Kernel Hilbert Space for the kernel matrix along positive semi-definite, smoothness, continuity, and sensitivity.

The rest of the paper is organized as follows: In Section 2 we will give details of the literature review followed by the proposed method along with the experimental setup in Section 3. Our results and experimental evaluation are reported in Section 4. Finally, Section 5 concludes the paper, emphasizing the effectiveness and potential of our compression-based model in advancing molecular sequence analysis and classification.

2 Related Work

Molecular sequence analysis is based on two types of methods, alignment-based and alignment-free. Alignment-based is suitable for small sequences (due to higher dimensionality). The alignment-free method works well for both short and long sequences [7]. Several methods have been used for the analysis of molecular sequences, including neural networks (NN) [8], language models [9], feature embedding [10], and kernel functions [11]. In recent work, it was seen that the performance of protein prediction tasks can be improved by training language models on protein sequences [12]. Pretrained language models and word embedding methods have proved to be successful in embedding molecular sequences forming easy-to-process representations that are contextsensitive [13]. In the analysis of big data in proteomics, SeqVec provides a scalable approach for the analysis of the protein data [12], which has improved the study of the structure and composition of proteins. ProtBert is a transformer-based model, that uses a masked language model [9] it requires positional encoding and has a high memory requirement. In the case of NN, several methods have been proposed for sequence analysis [14]. Variational AutoEncoder-based methods are also used in the literature for molecular sequence analyses [8]. These NN-based methods prove to be computationally expensive, face increased risk of overfitting, and are resource-demanding. In recent works, deep learning-based feature representation methods have been proposed [15,16]. Several authors proposed feature engineering-based methods to design embeddings for the molecular sequences [17]. Although such methods are efficient in terms of predictive performance, they usually face the problem of the "curse of dimensionality" due to the higher dimensions of the generated vectors. Another method used for the sequence analysis is to project the data into high dimensional feature space using kernel matrices [18,11]. However, these methods could cause an overfitting problem along with scalability issues (memory intensive) [19]. Some prominent sequence comparison methods include Normalized Compression Distance (NCD) [20], Normalized Information Distance (NID) [21], Euclidean Distance, and Manhattan Distance. The NCD, derived from the concept of Kolmogorov complexity [22], provides a measure of similarity between sequences by considering their compressed file sizes. However, such methods are not used in the literature for representation learning, specifically for molecular sequence analysis.

3 Proposed Approach

We propose an Embedding generation method based on lossless compressors and Normalized Compression Distance (NCD) metric. We start this section by discussing the lossless compression methods below.

3.1 Compression Methods

Bz2 Compressor: Bz2 compressor is a general-purpose lossless compressor, based on the Burrows-Wheeler transform (BWT) and Huffman coding [23]. The BWT is a permutation of the letters of the text (in our case characters/nucleotides of the sequence). After applying BWT to the input, an easily compressible form is generated as it groups symbols into runs of similar units, more precisely the input is divided into blocks of at most 900 kB, which is compressed separately, keeping in regard to the local similarities in the data. The compression of the transform includes an initial move-to-front encoding with run length encoding and then Huffman encoding.

Gzip Compressor: Gzip uses very few bits to represent information, which is based on the lossless compression algorithm LZ77 (Lempel-Ziv 77 compression algorithm) [24] and dynamic Huffman algorithm [4]. LZ77-Lempel-Ziv compression algorithm encodes a string based on sequential processing. If the present substring was encountered earlier as well then it is encoded with reference to the previous one. A sliding window is used for every new sequence encountered. Huffman coding is statistical-based compression, where the symbols are encoded using statistical information such as frequency distribution. There are two types of Huffman coding, dynamic and static. As the data we use is not real-time we use the Dynamic Huffman algorithm, which is a two-pass algorithm. In the first pass, the frequency distribution of symbols is calculated and in the second pass, symbols are encoded. In this technique, depending on the occurrence of the symbols variable length codes are assigned to symbols such that symbols with less occurrence are encoded with more significant bits and symbols with high frequency are encoded with fewer bits, as a result, a good compression ratio is obtained.

Remark 1. Note that our proposed method uses both the compression methods described above separately.

3.2 Problem Formulation

Given a pair of sequences s_1 and s_2 , where $s_1, s_2 \in S$ (S is a set of all sequences), we first encode s_1 and s_2 using UTF-8 encoding [25], which will give us E_{s_1} and E_{s_2} . After encoding, the E_{s_1} and E_{s_2} are compressed using Gzip or Bz2. We will then get the compressed form, denoted by C_{s_1} and C_{s_2} . In the next step, we compute the length L_{s_1} and L_{s_2} of the compressed sequences. In a similar way, we compute $L_{s_1s_2}$, which denotes the length of compressed encoded form for the concatenated sequence s_1s_2 . We then use L_{s_1} , L_{s_2} , and $L_{s_1s_2}$ as input to Normalized Compression Distance (NCD) approach to get the final distance value, which is calculated using the following expression:

$$NCD(s_1, s_2) = \frac{Ls_1 s_2 - min\{Ls_1, Ls_2\}}{max\{Ls_1, Ls_2\}}$$
(1)

In the condition where $s_1 \neq s_2$, the bytes *B* needed to encode s_2 based on s_1 information, i.e. B_{12} can be computed using the following expression:

$$B_{12} = Ls_1 s_2 - Ls_1 \tag{2}$$

Similarly, for s_1 and s_3 sequences, we have

$$B_{13} = Ls_1 s_3 - Ls_1 \tag{3}$$

where B_{13} represents the number of bytes needed to encode s_3 based on s_1 information. Given a scenario where s_1 and s_2 belong to the same category but s_3 belongs to a different category than s_1 and s_2 , we have the following expression:

$$B_{12} < B_{13}$$
 (4)

The formulation of the concept mentioned in Equation (4) can be linked to Kolmogorov complexity Z_s (where $s \in S$) and its derived distance metric [22]. Z_s is the lower bound for measuring information as it represents the length of the shortest binary program that outputs s, but there is a limitation that it cannot be used to measure the information content shared between two objects due to the incomputable nature of Z_s [1]. To overcome this limitation, Normalized Compression Distance (NCD) is proposed [26], which is computable and uses compressed length L_s to approximate Kolmogorov complexity Z_s .

The underlying concept of using compressed length in Equation 1 is that the compressed length is close to Z_s . The general rule says, that the higher the compression ratio, the closer L_s is to Z_s . Using the NCD-based distance (from Equation 1), we compute pairwise distances for a set of sequences to generate the required distance matrix.

3.3 Our Algorithm

In our algorithmic approach (i.e. in Algorithm 1), we take in a set of sequences (S) as input and output a Distance Matrix (D). We iterate through the Set S, for every sequence referred to as s in our data S and carry out the following steps:

- 1. Encoded form is generated and stored in a variable Es_1 (line number 2 of Algorithm 1 and step c(i) of Figure 1)
- 2. Encoded Es_1 is further compressed using Gzip compressor and fed into Cs_1 (line number 3 of Algorithm 1 and step d(i) of Figure 1)
- 3. Calculate the length of the compressed Cs_1 and store in a variable referred to as Ls_1 .(line number 4 of Algorithm 1 and step e(i) of Figure 1)

To save the Normalized Compression Distance (NCD) between every s and the rest of the sequences in the Set S, we initialize an array termed as D_{-} local as shown in the line number 5 of Algorithm 1.

In another sub-iterative loop, we repeat the steps from 1 to 3 mentioned above for every other sequence in set S (line number 6 of Algorithm 1). To calculate NCD we first require concatenation of s_1 and s_2 (line number 10 of Algorithm 1 and step (b) of Figure 1), followed by encoding, compression, and calculating its length which is stored in a variable Ls_1s_2 (line numbers 11-13 of Algorithm 1 and steps (c)-(e) of Figure 1).

Now using the length of the compressed encoded sequences Ls_1 , Ls_2 and Ls_1s_2 , we calculate NCD (line number 14 of Algorithm 1 and step (f) of Figure 1) and store in the list referred to as D₋ local(line number 15 of Algorithm 1). At the end of the inner iterative loop, this list is appended in a distance matrix D which would contain the NCD values between every sequence in the set of sequences(S)(line number 17 of Algorithm 1).



Fig. 1: Overview of the proposed approach.

The Figure 1 shows the overview of the proposed approach.

Remark 2. Our method is better than Deep Neural Networks as there is no need for preprocessing or training, making it simpler. Secondly, fewer parameters with no GPU resources are needed for distance matrix computation, making it lighter, and the absence of underlying assumptions (e.g., assumptions about the data) makes it universal.

Remark 3. To further understand the idea of NCD-based pairwise distance computation between text/molecular sequences, readers are referred to [1],

3.4 Distance Matrix Symmetry

The Distance matrix (D) obtained using Normalized Compression Distance (NCD) is of size $n \times n$ where n represents the cardinality of the input set S. This Distance Matrix D is non-symmetric, so to convert it to symmetric matrix D' we take the average of upper and lower triangle values and replace the original values of the matrix with the average values. A Universal Non-Parametric Approach For Improved Molecular Sequence Analysis

Algorithm 1 Distance matrix computation with Gzip

```
Input: Set of sequences(S)
      Output: Distance Matrix(D)
1: for s_1 in S do
2: Es_1 \leftarrow encoded \ s_1
2:
3:
              Cs_1 \leftarrow Gzip \ compressed \ Es_1
4:
5:
              Ls_1 \leftarrow length \ of \ Cs_1
           D\_local \leftarrow []
for s_2 in S do
6:
7:

\begin{array}{l} Es_2 \leftarrow encoded \quad s_2 \\ Cs_2 \leftarrow Gzip \quad compressed \quad Es_2 \end{array}

8:
9:
                    Ls_2 \leftarrow length \ of \ Cs_2
10:
                      s_1s_2 \leftarrow Concatenate(s_1, s_2)
11:
                      Es_1s_2 \gets encoded \ \ s_1s_2
                  \begin{array}{l} \sum_{i=1}^{n} \sum_{j=1}^{n} C_{s_{1}s_{2}} \leftarrow Grip compressed \quad Es_{1}s_{2} \\ Ls_{1}s_{2} \leftarrow length \quad of \quad Cs_{1}s_{2} \\ \text{NCD} \leftarrow \frac{Ls_{1}s_{2} - Min(Ls_{1}, Ls_{2})}{NCD} \end{array}
12:
13:
14:
                                          Max(Ls_1, Ls_2)
15:
                      D\_local.append(NCD)
             end for
16:
17:
              D.append(D\_local)
18: end for
19: return D
```

3.5 Kernel Matrix Computation

We generate a Kernel matrix from the symmetric distance matrix (D') of size $n \times n$ using a Gaussian Kernel, where.

$$d'_{ii}, d'_{ik} \in D' \tag{5}$$

Euclidean Distance (E) between two pairs of distances d'_{ij} and d'_{ik} (i.e. distance values computed from pairs of sequences) is calculated using the following equation:

$$E_{d'_{ij},d'_{ik}} = ||d'_{ij} - d'_{ik}|| \tag{6}$$

The Gaussian Kernel (K) is defined as a measure of similarity between d'_{ij} and d'_{ik} . It is represented by the equation below:

$$K(d'_{ij}, d'_{ik}) = exp(\frac{-||d'_{ij} - d'_{ik}||^2}{\sigma^2})$$
(7)

where σ^2 represents the bandwidth of the kernel. The kernel value is computed as follows:

$$\int K = 1 \quad \text{if } d'_{ij} \text{ and } d'_{ik} \text{ are identical}$$
(8)

$$K \to 0$$
 if d'_{ij} and d'_{ik} move further apart (9)

The kernel value is computed for each pair of distances in D' to get the $n \times n$ dimensional kernel matrix. Once the kernel matrix is computed, we can leverage kernel Principal Component Analysis (PCA) to derive a lower-dimensional representation of the data. The resulting embeddings, known as kernel principal components, effectively preserve the essential information while retaining the relationships among the molecular sequences including non-linear relations. This representation proves valuable for various downstream tasks, including classification.

3.6 Experimental Setup

Here we describe dataset statistics and evaluation metrics in detail. The experiments are performed on a computer running 64-bit Windows 10 with an Intel(R) Core i5 processor running at 2.10 GHz and 32 GB of RAM. For experiments, we randomly split data into 60-10-30% for training-validation-testing purposes. The experiments are repeated 5 times, and we report average results. Our code is available online for reproducibility¹. We use real-world molecular sequence data comprised of nucleotide sequences. The summary of the dataset used for experimentation is given in Table 1.

Name	Seq. Classes		Sequence Statistics			Reference	Description				
	1~-4.11	212000	Max	Min	Mean						
Human DNA	4380	7	18921	5	1263.59	[27]	Unaligned nucleotide sequences to classify gene family to which humans belong				
Table 1: Dataset Statistics.											

We used a variety of ML models for classification, including Support Vector Machine (SVM), Naive Bayes (NB), Multi-Layer Perceptron (MLP), K-Nearest Neighbours (KNN), Random Forest (RF), Logistic Regression (LR), and Decision Tree (DT). For performance evaluation, we used average accuracy, precision, recall, F1 (weighted), F1 (macro), Receiver Operator Characteristic Curve (ROC), Area Under the Curve (AUC), and training runtime. The baseline models we used for results comparisons include PWM2Vec [10] which gives each amino acid in the k-mers a weight based on where it is located in a k-mer position weight matrix (PWM), String Kernel [11] determines the similarity between the two sequences based on the total number of k-mers that are correctly and incorrectly aligned between two sequences, WDGRL [15] a neural network based unsupervised domain adoption technique that uses Wasserstein distance (WD) for feature extraction from input data, Autoencoder [28] that uses a deep neural network to encode data as features which involves iterative optimization of the objective through non-linear mapping from data space X to a smaller-dimensional feature space Z, SeqVec [12] an ELMO (Embeddings from Language Models) based method for representing biological sequences as continuous vectors, and Protein Bert [29] which is an end-to-end model that does not design explicit embeddings but directly performs classification using a previously learned language model.

3.7 Justification of Employing the Kernel Matrix

The generation of a kernel matrix from the NCD-based distance matrix offers several technical justifications and significant benefits:

Nonlinearity: Constructing a kernel matrix based on NCD distances implicitly
maps the data into a higher-dimensional feature space, enabling the capture of intricate nonlinear relationships. This is particularly advantageous when dealing with
the complex non-linear interactions often present in molecular sequences.

8

¹ https://github.com/sarwanpasha/Non-Parametric-Approach

A Universal Non-Parametric Approach For Improved Molecular Sequence Analysis

- Capturing Complex Relationships: Utilizing the Gaussian kernel in generating the kernel matrix allows for the capture of intricate relationships between sequences. It assigns higher similarity values to similar sequences and lower values to dissimilar ones. This capability enables the representation of complex patterns and structures in the data, surpassing the limitations of linear methods.
- 3. Theoretical Properties of Gaussian Kernel: The use of the widely adopted Gaussian kernel leverages several underlying theoretical properties. These include the Reproducing Kernel Hilbert Space (RKHS) [30], enabling the application of efficient kernel methods like support vector machines. The Universal Approximation property [31] allows the kernel to approximate any continuous function arbitrarily well, making it a powerful tool for modeling complex relationships and capturing nonlinear patterns. Mercer's Theorem [32] guarantees that the kernel matrix is positive semi-definite, while the smoothness, continuity, and sensitivity to variations further enhance its ability to capture local relationships and adapt to variations in the data distribution.
- 4. Flexibility and Generalization: The kernel matrix derived from the NCD-based distance matrix can be effectively employed with various machine learning algorithms that operate on kernel matrices. This flexibility allows for the application of a wide range of techniques, including kernel PCA and kernel SVM. Leveraging these algorithms enables the exploitation of the expressive power of the kernel matrix to address diverse tasks, such as dimensionality reduction and classification.
- 5. Preserving Nonlinear Information: Applying kernel PCA to the kernel matrix captures crucial nonlinear information embedded in the data. This process facilitates the extraction of low-dimensional embeddings that preserve the underlying structure and patterns. Projecting the data onto the principal components retains discriminative information while reducing dimensionality. This proves particularly valuable for handling high-dimensional datasets.
- 6. Enhanced Performance: The utilization of the NCD-based distance matrix and kernel matrix can lead to improved performance in various tasks. The incorporation of NCD distance and the capturing of complex relationships in the data enhance the discriminative power of the embeddings. This results in a more accurate classification of the sequences.

4 Results And Discussion

The classification results that are averaged over 5 runs are reported in Table 2 for the Human DNA dataset. For the evaluation metrics including average accuracy, precision, recall, weighted and macro F1, and ROC-AUC, our proposed Gzip-based representation outperformed all baselines. For classification training runtime, WDGRL with Naive Bayes performs the best due to the minimum size of embedding compared to other embedding methods.

To test the statistical significance of results, we used the student t-test and observed the *p*-values using averages and SD results of 5 runs. We observed that the SD values for all datasets and metrics are very small i.e. mostly < 0.002, we also noted that *p*-values were < 0.05 in the majority of the cases (because SD values are very low). This confirmed the statistical significance of the results.

Embeddings	Algo.	Acc. \uparrow	Prec. \uparrow	Recall ↑	F1 (Weig.) ↑	F1 (Macro) ↑	ROC AUC ↑	Train Time (sec.) \downarrow
	SVM	0.302	0.241	0.302	0.165	0.091	0.505	10011.3
	NB	0.084	0.442	0.084	0.063	0.066	0.511	4.565
	MLP	0.310	0.350	0.310	0.175	0.107	0.510	320.555
PWM2Vec	KNN	0.121	0.337	0.121	0.093	0.077	0.509	2.193
	RF	0.309	0.332	0.309	0.181	0.110	0.510	65.250
	LR	0.304	0.257	0.304	0.167	0.094	0.506	23.651
	DT	0.306	0.284	0.306	0.181	0.111	0.509	1.861
	SVM	0.618	0.617	0.618	0.613	0.588	0.753	39.791
	NB	0.338	0.452	0.338	0.347	0.333	0.617	0.276
String	MLP	0.597	0.595	0.597	0.593	0.549	0.737	331.068
Varnal	KNN	0.645	0.657	0.645	0.646	0.612	0.774	1.274
Kerner	RF	0.731	0.776	0.731	0.729	0.723	0.808	12.673
	LR	0.571	0.570	0.571	0.558	0.532	0.716	2.995
	DT	0.630	0.631	0.630	0.630	0.598	0.767	2.682
	SVM	0.318	0.101	0.318	0.154	0.069	0.500	0.751
	NB	0.232	0.214	0.232	0.196	0.138	0.517	<u>0.004</u>
	MLP	0.326	0.286	0.326	0.263	0.186	0.535	8.613
WDGRL	KNN	0.317	0.317	0.317	0.315	0.266	0.574	0.092
	RF	0.453	0.501	0.453	0.430	0.389	0.625	1.124
	LR	0.323	0.279	0.323	0.177	0.095	0.507	0.041
	DT	0.368	0.372	0.368	0.369	0.328	0.610	0.047
	SVM	0.621	0.638	0.621	0.624	0.593	0.769	22.230
	NB	0.260	0.426	0.260	0.247	0.268	0.583	0.287
	MLP	0.621	0.624	0.621	0.620	0.578	0.756	111.809
Autoencoder	KNN	0.565	0.577	0.565	0.568	0.547	0.732	1.208
	RF	0.689	0.738	0.689	0.683	0.668	0.774	20.131
	LR	0.692	0.700	0.692	0.693	0.672	0.799	58.369
	DT	0.543	0.546	0.543	0.543	0.515	0.718	10.616
	SVM	0.656	0.661	0.656	0.652	0.611	0.791	0.891
	NB	0.324	0.445	0.312	0.295	0.282	0.624	0.036
	MLP	0.657	0.633	0.653	0.646	0.616	0.783	12.432
SeqVec	KNN	0.592	0.606	0.592	0.591	0.552	0.717	0.571
-	RF	0.713	0.724	0.701	0.702	0.693	0.752	2.164
	LR	0.725	0.715	0.726	0.725	0.685	0.784	1.209
	DT	0.586	0.553	0.585	0.577	0.557	0.736	0.24
Protein Bert	-	0.542	0.580	0.542	0.514	0.447	0.675	58681.57
	SVM	0.692	0.844	0.692	0.699	0.692	0.771	2.492
	NB	0.464	0.582	0.464	0.478	0.472	0.704	0.038
	MLP	0.831	0.833	0.831	0.830	0.813	0.890	7.546
Gzip (ours)	KNN	0.773	0.792	0.773	0.776	0.768	0.856	0.193
1 . ,	RF	0.810	0.858	0.810	0.812	0.811	0.858	6.539
	LR	0.621	0.822	0.621	0.616	0.581	0.712	0.912
	DT	0.648	0.651	0.648	0.648	0.624	0.780	2.590
	SVM	0.545	0.769	0.545	0.524	0.501	0.669	2.856
	NB	0.403	0.577	0.403	0.411	0.410	0.653	0.034
	MLP	0.696	0.702	0.696	0.698	0.670	0.809	7.601
Bz2 (ours)	KNN	0.697	0.715	0.697	0.699	0.677	0.813	0.215
- ()	RF	0.720	0.804	0.720	0.722	0.721	0.798	6.000
	LR	0.488	0.721	0.488	0.449	0.401	0.626	0.899
	DT	0.574	0.577	0.574	0.574	0 547	0.735	2.290

Sarwan Ali^{+,*}, Tamkanat E Ali⁺, Prakash Chourasia, Murray Patterson

10

Table 2: Classification results (averaged over 5 runs) on **Human DNA** dataset for different evaluation metrics. The best classifier performance for every embedding is shown with the underline. Overall best values are shown in bold.

From the overall average classification results, SD results, and statistical significance results, we can conclude that the proposed NCD compression-based method can outperform the SOTA for predictive performance on real-world molecular sequence dataset. Moreover, even after fine-tuning the Large language model (LLM) such as SeqVec, the proposed parameter-free method significantly outperforms the LLM for all evaluation metrics. With the theoretical justifications and statistical significance of the results, we can conclude that using the proposed method in a real-world scenario for molecular sequence analysis can help biologists understand different viruses and deal with future pandemics efficiently.

5 Conclusion

In conclusion, we propose lightweight and efficient compression-based models for classifying molecular sequences. By combining the simplicity of the compression methods (e.g., Gzip and Bz2) with a powerful nearest neighbor algorithm, our method achieves state-of-the-art performance without the need for extensive parameter tuning or pretrained models. The compression-based Model successfully overcomes the limitations of neural network-based methods, offering a more accessible and computationally efficient solution, especially in low-resource scenarios. In the future, we will be exploring the applications of our model in other bioinformatics domains and investigating ways to further optimize and tailor the approach for specific biological datasets.

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