A Novel Feature Generation Method for Sequence Classification
Mutated Subsequence Generation

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Abstract: In this paper, we present a new feature generation algorithm for sequence data sets called Mutated Subsequence Generation (MSG). Given a data set of sequences, the MSG algorithm generates features from these sequences by incorporating mutative positions in subsequences. We compare this algorithm with other sequence-based feature generation algorithms, including position-based, k-grams, and k-gapped pairs. Our experiments show that the MSG algorithm outperforms these other algorithms in domains in which presence, not specific location, of sequential patterns discriminate among classes in a data set.

1 INTRODUCTION

Finding useful patterns in sequential data is an active research area. Within this area, supervised sequence classification deals with the problem of learning models from labelled sequences. The resulting models can be used to assign appropriate class labels to unlabelled sequences. Sequence classification methods can be used for example to predict whether a segment of DNA is the promoter region of a gene or not.

In general, sequence classification is more difficult than classification of tabular data, mainly because of two reasons: in sequence classification, it is unclear what features should be used to characterize a given data set of sequences (Figure 1 shows three different candidate features whose presence, or lack of, in a sequence can be used to characterize the sequence); and the number of such potential features is very large. For instance, given a set of sequences of maximum length l, over an alphabet B, where $|B| = d$, if subsequences that contain k symbols are considered as features, then there are d^k potential features. Furthermore, the number of potential features will grow exponentially as the length of subsequences under consideration increases, up to d^l. Thus, how to obtain features from sequences is a crucial problem in sequence classification.

A mutation is a change in an element of a sequence. Like in DNA sequences, this could result from unrepaired damage to DNA or from an error when it is replicating itself. We are interested in whether these changes affect the sequences' function. Thus, our research focuses on generating features that represent mutation patterns in the sequences; and on selecting the generated features that are most suitable for classification.

More specifically, our proposed algorithm generates features from sequence data by regarding contiguous subsequences and mutated subsequences as potential features. Briefly, it first generates all contiguous subsequences of a fixed length from the sequences in the data set. Then it checks whether or not each pair of candidate feature subsequences that differ in only one position should be joined into a mutated subsequence. The join is performed if the resulting joint mutated subsequence has a stronger association with the target class than the two subsequences in the candidate pair do. If that is the case, the algorithm keeps the joint subsequence and removes the two subsequences in the candidate pair from consideration. Otherwise, the algorithm keeps the candidate pair instead of the joint mutated subsequence. After all the generated candidate pairs of all lengths have been checked, a new data set is constructed containing the target class and the generated features.

The features in the resulting data set represent (possibly mutated) segments of the original sequences that have a strong connection with the sequences' function. We then build classification

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models over the new data set that are able to predict the function (i.e., class value) of novel sequences.

The main contributions of this paper are the introduction of a new feature generation method based on mutated subsequences for sequence classification, and a comparison of the performance of our algorithm with that of other feature generation algorithms.

The rest of this paper is organized as follows: section 2 surveys related work; section 3 provides background on the techniques used in this paper; section 4 describes the details of our algorithms; section 5 compares the performance of our algorithm with that of other sequence-based feature generation algorithms from the literature; and section 6 provides some conclusions and future work.

2 RELATED WORK

Feature-based classification algorithms transform sequences into features for use in sequence classification (Xing, Pei, & Keogh, June 2010). A number of feature-based classification algorithms have been proposed in the literature. For example, k-grams are substrings of k consecutive characters, where k is fixed beforehand, see Figure 1(a). Damashek used k-grams to calculate the similarity between text documents during text categorization (Damashek, 1995). In (Ji, Bailey, & Dong, 2005), the authors vary k-grams by adding gap constraints into the features, see Figure 1(b). Another kind of feature, k-gapped pair, is a pair of characters with constraint $l_2 - l_1 = k$, where k is a constant, and l_1 and l_2 are the locations in the sequence where the characters in the pair occur, see Figure 1(c). The k-gapped pair method is used to generate features for Support Vector Machines in (Chuzhanova, Jones, & Margetts, 1998) and (Huang, Liu, Chen, Chao, & Chen, 2005). In contrast with our method, the features generated by their approach can not represent mutations in the sequences.

Another method is mismatch string kernel (Leslie, Eskin, Cohen, Weston, & Noble, 2004). It constructs a (k, m) – mismatch tree for each pair of sequences to extract k-mer features with at most m mismatches. It then uses these features to compute the string kernel function. A similarity between this method and our method is that both generate features that are subsequences with mutations. However, there are three major differences between them.

1) In mismatch string kernel, the features are generated from pairs of sequences and used to update the kernel matrix. In contrast, our MSG method generates features from the entire set of data sequences in order to transform the sequence data set into a feature vector data set.
2) In the process of computing candidate mutated subsequences, our MSG method does not only consider mutations in the subsequences, but also takes into account correlations between these mutated subsequences and the target classes. In contrast, the mismatch string kernel method disregards the latter part.
3) The mismatch string kernel method can be used in support vector machines and other distance based classifiers for sequence data. Our MSG approach is more general as it transforms the sequences into feature vectors. In other words, the data set that results from the MSG transformation can be used with any classifier defined on feature vectors.

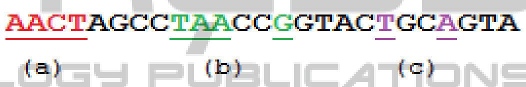


Figure 1: Example of different candidate features for a given sequence. (a) 4-grams: AACT; (b) 4-grams with gap 1: g(TAAG,1); (c) 2-gapped pair: k(TA,2).

3 BACKGROUND

3.1 Feature Selection

Feature selection methods focus on selecting the most relevant features of a data set. These methods can help prediction models in three main aspects: improving the prediction accuracy; reducing the cost of building the models; and making the models, and even the data, more understandable.

To obtain the features that maximize classification performance, every possible feature set should be considered. However, exhaustively searching all the feature sets has been known as a NP-hard problem (Amaldi & Kann, 1998). Thus, a number of feature selection algorithms has been developed, based on greedy search methods like best-first and hill climbing. See (Kohavi & Johnb, 1997). These greedy algorithms use three main search strategies: forward selection, backward deletion, and bi-directional selection.

- *Forward Selection*: it starts at a null feature set. In each step, the importance of each unselected feature is calculated according to a specified metric, and then the most important feature is added into the feature set. This will go on until there is no important feature to be added.

- *Backward Deletion*: it starts at the full feature set, and in each step, it removes an unimportant feature from the feature set, until there is no more unimportant feature in the remaining feature set.
- *Bi-directional Selection*: it also starts at a null feature set. In each step, it first applies forward selection on the unselected features, then it uses backward deletion on the selected features. This ends when a stable feature set is reached.

3.2 CFS Evaluation

The *Correlation-based Feature Selection (CFS)* algorithm introduces a heuristic function for evaluating the association between a set of features and the target classes. It selects a set of features that are highly correlated with the target classes, yet uncorrelated with each other. This method was introduced in (Hall & Smith, 1999). In this paper, we use this algorithm to select a subset of the generated features that is expected to have high classification performance.

3.3 GINI Index

In decision tree induction, the GINI Index is used to measure the degree of impurity of the target class in the instances grouped by a set of attributes (Gini, 1912). Similarly in our research, the GINI Index is used to measure the strength of the association between candidate features and the target class. Specifically, we use it during feature generation to determine whether or not to replace a pair of subsequences (candidate features) that differ just in one position with their joined mutated subsequence. Details are described in section 4.1.3. The GINI Index of a data set is defined as: $1 - \sum_{c \in C} p(c)^2$, where C is the set of all target classes, and p denotes probability (estimated as frequency in the data set). Given a discrete feature (or attribute) X, the data set can be partitioned into disjoint groups by the different values of X. The GINI Index can be used to calculate the impurity of the target class in each of these groups. Then, the association between X and the target class can be regarded as the weighted average of the impurity in each of the groups: $Gini(X) = \sum_{x \in X} p(x) * (1 - \sum_{c \in C} p(c|x)^2)$.

4 OUR MSG ALGORITHM

4.1 Feature Generation

Our *Mutated Subsequence Generation (MSG)* algorithm belongs in the category of feature-based sequence classification according to the classification methods described in (Xing, Pei, & Keogh, June 2010). The MSG algorithm transforms the original sequences into contiguous subsequences and mutated subsequences, which are used as candidate features in the construction of classification models.

The MSG algorithm generates features of different lengths according to two user-defined parameters: the *minimum length* $l_{\min}$ and the *maximum length* $l_{\max}$. The MSG algorithm first generates the candidate subsequences of length $l_{\min}$, then length $l_{\min} + 1$, and all the way to the subsequences of length $l_{\max}$. Then it takes the union of all the generated subsequences of different lengths. Finally, the MSG algorithm constructs a new data set containing a Boolean feature for each generated subsequence. Each sequence in the original data set is represented as a vector of 0's and 1's in the new data set, where a feature's entry in this vector is 1 if the feature's corresponding subsequence is present in the sequence, and 0 if not.

The feature generation process consists of five main steps described below. Figure 2 shows an example of the transformation of a sequence data set into the subsequence features, from Step a to Step d.

a) The MSG algorithm generates all the contiguous subsequences of a specific length from each original sequence (see section 4.1.1);
b) It divides the contiguous subsequences into n categories according to which class they are most frequent in. n is the number of different classes (see section 4.1.2);
c) For each category, it generates the mutated subsequences based on the GINI measure (see section 4.1.3);
d) It combines together all the features from each category (see section 4.1.4).
e) It repeats Step a to Step d with a different length, until features of all the lengths in the user defined range are generated. Then it combines these features prior to constructing the new data set (see section 4.1.5).

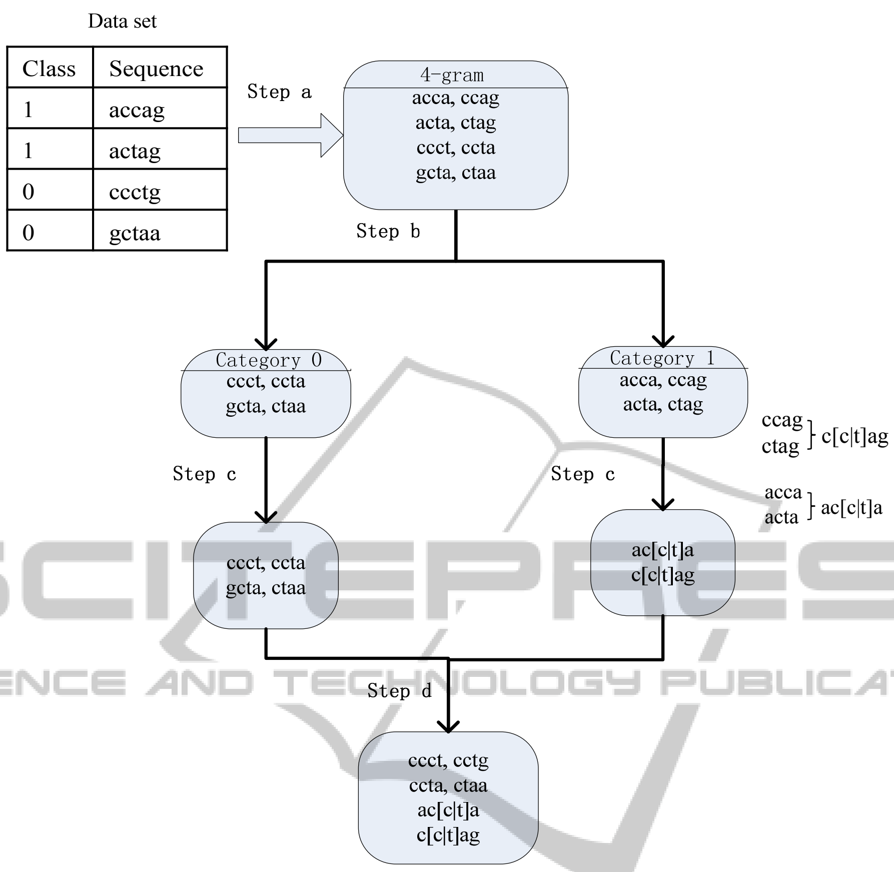


Figure 2: This figure illustrates the mutated subsequence generation process from Step a) to Step d). In this example, features of length 4, including mutated subsequences and contiguous subsequences, are obtained. Here, the GINI Index of each of the mutated subsequences (ac[c|t]a and c[c|t]ag) is better than the GINI Indexes of its forming contiguous subsequences.

4.1.1 Computation of Contiguous Subsequences

Contiguous Subsequence: given $k \geq 1$, a contiguous subsequence of length k is a subsequence formed by taking k consecutive symbols from the original sequence. For example, gc is a contiguous subsequence of length 2 in the sequence $gcta$, while gt is not.

Mutated Subsequence: a mutated subsequence is a subsequence of length k ($k \geq 1$) which contains r mutative positions, where $1 \leq r \leq k$. In each mutative position, there are two or more substitutions. In this paper, we consider mutated subsequences with only one mutative position. For example, in the subsequence $g[c|a]t$, the second position is a mutative position, with two possible substitutions c and a. Thus, a mutated subsequence has many representations, in our example gct and gat. We say that a mutated subsequence is contained in an original sequence when any of its representations is contained in the original sequence. For example, the mutated subsequence $g[c|a]t$ is contained in the sequence $gcta$, as well as in the sequence $gata$.

The MSG algorithm starts with the generation of contiguous subsequences. Suppose that the original sequences have length t, and that the contiguous subsequences to be computed have length k. First, each sequence is traversed and all of its contiguous subsequences of $k$symbols are extracted from starting locations 1 through $(t-k+1)$. Then, duplicate subsequences are removed. For example, the features in Table 1 are contiguous subsequences of length 4 for the sequences of the data set in Figure 2. The table also includes the number of occurrences of each feature in data set sequences of a given target class.

Table 1: contiguous subsequences of length 4 and their frequency in each class of the data set in Figure 2.

Feature	Class 0	Class 1
acca	0	1
ccag	0	1
acta	0	1
ctag	0	1
cact	1	0
actg	1	0
gcta	1	0
ctaa	1	0

4.1.2 Separation

In this step, the algorithm separates the contiguous subsequences into n categories. n is the number of different classes in the data set. Each subsequence is assigned to a category according to which class it is most frequent in. For example, the first four features in Table 1 are assigned to Category 1, because they are more frequent in Class 1 than in Class 0, and the other four to Category 2. If a subsequence is maximally frequent equally in more than one class, it is randomly assigned to one of those classes.

4.1.3 Generation of Mutated Subsequences

Candidate pair: a candidate pair is a pair of subsequences which are different from each other in only one position. For instance, $'acca'$ and $'acta'$ is a candidate pair. The candidate pair could also contain mutated subsequences, like for instance $'acca'$ and $ac[t|g]a$.

Joinable checking: joinable checking is used to determine whether or not to join a candidate pair of subsequences together, depending on their correlation with the target class. In this paper, we use GINI to measure this correlation. For example, suppose $sub1$ is $acca$ and $sub2$ is $acta$ in Table 1. Their joint sequence $sub3$ is $ac[c|t]a$. By matching them to the original sequences of the data set in Figure 2, the data is split into two groups by each one of these sequences: one group consists of the original sequences which contain the subsequence, marked as $group_1^{subi}$; the other group consists of the rest of sequences, marked as $group_2^{subi}$. Taking $sub1$ as an example, there is only one sequence in $group_1^{sub1}$, and it is in class 1; there are three sequences in $group_2^{sub1}$, two of which are in class 0, and the other one is in class 1. Thus, by using the formula in section 3.3, we can calculate the GINI Index for $sub1$ as followings:

$$impurity(g_1^{sub1}) = 1 - \left(\frac{0}{1}\right)^2 - \left(\frac{1}{1}\right)^2 = 0$$
$$impurity(g_2^{sub1}) = 1 - \left(\frac{1}{3}\right)^2 - \left(\frac{2}{3}\right)^2 = 0.444$$
$$\begin{aligned} GINI(sub1) &= p(g_1^{sub1}) * impurity(g_1^{sub1}) \\ &\quad + p(g_2^{sub1}) * impurity(g_2^{sub1}) \\ &= 0 * \frac{1}{4} + 0.44 * \frac{3}{4} = 0.333 \end{aligned}$$

Similarly, we get the values $GINI(sub2) = 0.333$, $GINI(sub3) = 0$. Since $sub3$ has the best measure value, implying that it has the strongest association with the target class, then the candidate pair $sub1$ and $sub2$ is joinable.

In this step, MSG performs joinable checking on every candidate pair in each category. Once a candidate pair is determined to be joinable, then the two subsequences are joined together to create a new subsequence, called $subi$, and they are also marked. Then the joinable checking is performed on $subi$ with every other subsequence in the category. If there are other subsequences that are joinable with $subi$, then they are also joined together with $subi$ and marked. Finally, $subi$ is added into the mutated subsequence set. After all candidate pairs are checked, the algorithm deletes the marked subsequences and the duplicate mutated subsequences. The pseudo code of mutated subsequences generation is shown in Figure 3.

4.1.4 Combination of Categories

In the previous step, some contiguous subsequences might remain intact. That is, they are not joined with other subsequences. Thus, in each category, there might be two types of features: mutated subsequences and unchanged contiguous subsequences. In this step, the algorithm combines the feature sets of all categories together into one feature set. In this set, all features have length t, as defined in Step 4.1.1.

Table 2: Transformed data set obtained by applying MSG to the data set in Figure 2, with subsequence length 3 and 4.

original sequence		taa	gct	ctg	cac	act	cca	acc	[t|c]ag	ctaa	gcta	actg	cact	c[t|c]ag	ac[t|c]a	Class
accag	1	0	0	0	0	0	1	1	1	0	0	0	0	1	1	1
actag	2	0	0	0	0	1	0	0	1	0	0	0	0	1	1	1
ccctg	3	0	0	1	1	1	0	0	0	0	0	1	1	0	0	0
gctaa	4	1	1	0	0	0	0	0	0	1	1	0	0	0	0	0

```
Procedure: Mutated_Gen(C): generate the mutated subsequences from subsequence set C
Initialization: S <- {}
  for each pair of subsequences, sub1 and sub2, in C do
    if sub1 and sub2 is joinable then
      sub3 <- sub1 ⊕ sub2
      mark sub1;
      mark sub2;
      for each sequence subi in C do
        if sub3 and subi is joinable then
          sub3 <- sub3 ⊕ subi
          mark subi
        end if
      end for
      S <- S U {sub3}
    end if
  end for
  for each sequence subj in C do
    if subj is marked then
      C <- C - subj
    end if
  end for
```

Figure 3: The pseudo code for mutated subsequences generation. $\oplus$ is the join operator. For example, $acca \oplus acta = ac[c|t]a$ and. $acca \oplus ac[t|g]a = ac[c|t|g]a$.

4.1.5 Combination of Features of Different Length

After all the features of the lengths in the user-defined range are generated in Step 4.1.1 through Step 4.1.4, the MSG combines these features of different lengths together and constructs a new data set with them by matching them to the original sequence data. In this new data set, each data instance corresponds to a sequence in the original data set. The instance's value for each feature is a Boolean value describing whether or not the feature is a subsequence of the instance. Table 2 shows the transformed data from the data set in FigureFigure 2 in the range of length 3-4.

4.2 Feature Selection

In this paper, we use bi-directional feature selection based on the CFS evaluation, as described in section 3, to select the best feature set from the transformed data set. This feature set is then used to build classification models.

5 EXPERIMENTAL EVALUATION

The performance of our MSG algorithm is compared with that of other feature generation algorithms which are commonly used for sequence classification. Such algorithms are:

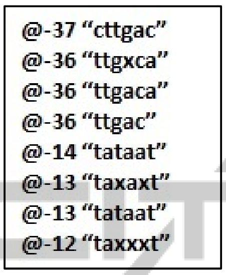
- **Position-based** (Dong & Pei, 2009): each position is regarded as a feature, the value of which is the alphabet symbol in that position.
- ***k*-grams** (Chuzhanova, Jones, & Margetts, 1998): a k-gram is a sequence of length k over the alphabet of the data set. The value of a k-gram induced feature for a sequence S is whether the k-gram occurs in S or not.
- ***k*-gapped pair** (Park & Kanehisa, 2003): in a k-gapped pair (xy, k), xy is an ordered pair of letters over the alphabet of the data set, k is a non-negative integer. The value of a k-gapped pair induced feature for a sequence S is 1 if there is a position i in S, where $s_i = x$ and $s_{i+k+1} = y$. Otherwise, the value is 0.

To compare the performance of these algorithms, a number of experiments are carried out on three data sets, the first two are collected from UCI Machine Learning Repository (Bache & Lichman, 2013), and the third one was collected in our prior work (Wan, Barrett, Ruiz, & Ryder, 2013) from WormBase (WormBase, 2012):

- ***E.coli* promoter gene sequences data set**: this data set consists of 53 DNA promoter sequences and 53 DNA non-promoter sequences. Each sequence has length 57. Its alphabet is {a, c, g, t}.
- **Primate splice-junction gene sequences data set**: this data set contains 3190 DNA sequences of length 60. Also, its alphabet is {a, c, g, t}. Each sequence is in one of three classes: exon/intron boundaries (EI), intron/exon boundaries (IE), and non-splice (N). 745 data instances are classified as EI; 751 instances as IE; and 1694 instances as N.
- ***C.elegans* gene expression data set:** this data set contains 615 gene promoter sequences of length 1000. We use here expression in EXC cells as the classification target. 311 of the genes in this data set are expressed in EXC cells, and the other 304 genes are not.

The performance comparison in the following sections focuses on the prediction level of models built on the generated features, and on differences among the models. We implemented the four feature generation methods, MSG, k-grams, position-based, and k-gapped pairs, in our own Java code. To measure the prediction level, we utilize The WEKA

System of version 3.7.7 (Hall, et al., 2009) to build three types of prediction models: J48 Decision Trees, Support Vector Machines (SVMs), and Logistic Regression (LR). We use n-fold cross validation to test the models. Then we regard the models' accuracy as their prediction level. To measure the difference between two models, we perform a paired t-test on their n-fold test results, and use p-value from the paired t-test to determine whether or not the difference in model performance is statistically significant.



@-37 "cttgac"
@-36 "ttgxca"
@-36 "ttgaca"
@-36 "ttgac"
@-14 "tataat"
@-13 "taxaxt"
@-13 "tataat"
@-12 "taxxxt"

Figure 4: Patterns taken from (Towell, Shavlik, & Noordewier, 1990). Promoter sequences share these segments at the given locations. In these segments, "x" represents the occurrence of any nucleotide. The location is specified as an offset from the Start of Transcription (SoT). For example, "-37" refers to the location 37 base pair positions upstream from SoT.

5.1 Results on the *E.coli* Promoter Gene Sequences Data Set

5.1.1 Patterns from the Literature

As found in the biological literature (Hawley & McClure, 1983) (Harley & Reynolds, 1987), and summarized in (Towell, Shavlik, & Noordewier, 1990), promoter sequences share some common DNA segments. Figure 4 presents some of these segments. As can be seen in the figure, these segments can contain mutated positions. Also the segments are annotated with specific locations where the segments occur in the original sequences. This is an important characteristic distinguishing these segments from the subsequences generated by our algorithm. The data set constructed by our MSG algorithm captures only presence of the subsequences (not their positions) in the original sequences.

However, after examining the occurrences of the aforementioned segments in the Promoter Gene Sequences data set, we found that for the most part each segment occurs at most once in each sequence. Hence computational models created over this data set that deal only with presence of these patterns are expected to achieve a prediction accuracy similar to that of computational models that take location into consideration. Therefore, since the precise location of the patterns seems to be irrelevant, we expect our MSG algorithm to perform well on this data set.

5.1.2 Experimental Results

Each of the four feature generation methods under consideration (MSG, k-grams, position-based, and k-gapped pair) was applied to the Promoter Gene Sequence data set separately, yielding four different data sets. Parameter values used for the feature generation methods were the following: for MSG, the range for the length of transformed subsequences was 1-5; for k-grams, $k \leq 5$; and for k-gapped, $k \leq 10$. Then, Correlation-based Feature Selection (CFS), described in section 3.2, was applied to each of these data sets to further reduce the number of features. The resulting number of features in each of the data sets was: 61 for the MSG transformed data set, 43 for k-grams, 7 for position-based, and 29 for k-gapped pair. 5-fold cross validation was used to train and test the models constructed on each of these data sets. Three different model construction techniques were used: J4.8 decision trees, Logistic Regression (LR), and SVMs. Figure 5 shows the prediction accuracy of the obtained models. Table 3 depicts the statistical significance of the performance difference between the models constructed over the MSG-transformed data set and the models constructed over data sets constructed by other feature generation methods.

From Figure 5, we can observe that the prediction levels of the models constructed over features generated by MSG are superior to those of models constructed on other features. The t-test results in Table 3 indicate that this superiority of MSG is statistically significant at the $p < 0.05$ level in the cases highlighted in the table. As expected, the MSG algorithm generates a highly predictive collection of features for this data set. This is in part due to the fact that for this data set, the presence alone, and not location, of certain subsequences (or segments) discriminates well between promoter and non-promoter sequences.

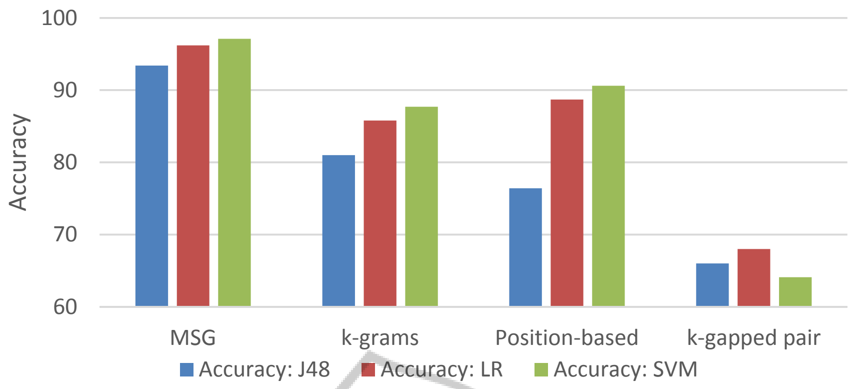


Figure 5: Accuracy of models built on the features from four different feature generation methods (MSG, k-gram, Position-based, and k-gapped pair), using three classification algorithms on the Promoter Gene Sequences data.

Table 3: p-values obtained from t-tests comparing the prediction accuracies of models constructed over MSG-generated features and models constructed over data sets generated by the other 3 feature generation methods. T-tests were performed using 5-fold cross-validation over the Promoter Gene Sequence data set. Highlighted in the table are the cases in which the superiority of MSG is statistically significant at the p < 0.05 level.

Baseline: MSG	*k*-grams	Position-based	*k*-gapped pair
p-value: J48	0.08	0.02	0.03
p-value: LR	0.01	0.06	0.01
p-value: SVM	0.08	0.08	0.01

Table 4: Sample features constructed by the MSG algorithm over the Promoter Gene Sequences data set, together with their correlation with the class feature.

MSG features	Correlation with target
at[t|a]	-0.37
ccc[a|g]	-0.41
t[t|a]ta	-0.61
[a|c]aaa	-0.58
aaa[g|a|t|c]t	-0.50
ta[a|g|c|t]aa	-0.58
ct[g|t|c|a]tt	-0.41
at[g|a|c]at	-0.51
ata[t|c|a|g]t	-0.53
tta[t|a|c]a	-0.44
aatt[c|a|t|g]	-0.51
a[a|g|c|t]aat	-0.56
aaa[t|c|a|g]c	-0.44
c[a|c|g|t]ggt	0.42
tgag[g|a]	0.43

5.2 Results on the Primate Splice-Junction Gene Sequences Data Set

5.2.1 Patterns from the Literature

Some patterns in this data set have been identified in the literature (Noordewier, Towell, & Shavlik, 1991). Briefly, these patterns state that a sequence is in EI or IE classes if the triple nucleotides, known as stop codons, are absent in certain positions of the sequence. Such triplets are "TAA", "TAG", and "TGA". Conversely, if a sequence contains any stop codons in certain specified positions, then the sequence is not an EI (or IE) sequence. To examine the effect of position in the patterns, we generated the following rules, and calculated their confidence (that is, prediction accuracy) on this data set.

- *Stop codons are present → not EI (74%)*
  Stop codons are present at specified positions → not EI (95%)
- *Stop codons are present → not IE (77%)*
  Stop codons are present at specified positions → not IE (91%)

As can be seen, the position information is very important in these patterns. Hence, we might expect that the MSG algorithm will not perform well on this data set, because its generated features do not contain information about the location where subsequences appear in the original sequences.

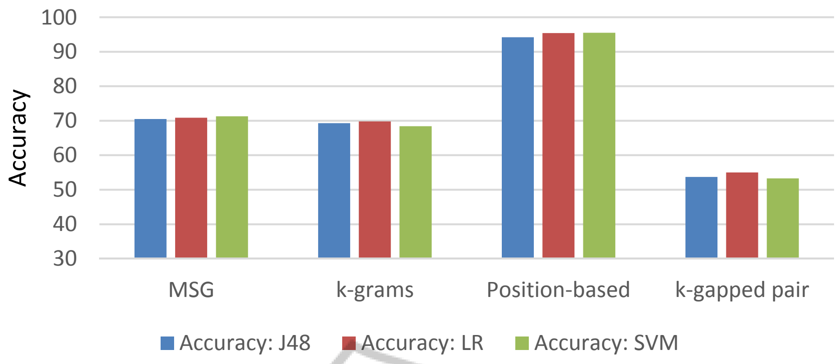


Figure 6: Accuracy of models built on the features from four different feature generation methods (MSG, k-gram, Position-based, and k-gapped pair), using three classification algorithms on the Splice-junction Gene Sequence data.

Table 5: p-Values obtained from t-tests comparing the prediction accuracies of models constructed over MSG-generated features and models constructed over data sets generated by the other 3 feature generation methods. T-tests were performed using 10-fold cross-validation over the Splice-junction Gene Sequences data set. Highlighted in the table are the cases in which the superiority of MSG is statistically significant at the $p < 0.05$ level.

Baseline: MSG	*k*-grams	Position-based	*k*-gapped pair
p-value: J48	0.23	6.5E-18	2.12E-13
p-value: LR	0.72	6.78E-16	7.3E-13
p-value: SVM	0.15	2.3E-17	3E-14

Table 6: Sample features constructed by the MSG algorithm over the Splice-junction Gene Sequences data set, together with their correlation with the class feature.

MSG features	Correlation with target
GT[A|G]A	-0.35
GGT[A|G]	-0.38
[G|T|A]GGTA	-0.32
GTA[G|A]G	-0.34
GTG[C|A]G	-0.35
GT[A|G]AG	-0.50
GGT[A|G]A	-0.44
AGGT[A|G]	-0.35
[T|C]AG	-0.02
T[C|T]TC	0.01
TC[T|C]T	-0.03

5.2.2 Experimental Results

Once again, each of the four feature generation methods under consideration (MSG, *k*-grams, position-based, and *k*-gapped pair) was applied to the Splice-junction Gene Sequences data set separately, yielding four different data sets. As in section 5.1.2, the parameters used for the feature generation algorithms were: for MSG, the range for the length of transformed subsequences was 1-5; for *k*-grams, $k \leq 5$; and for *k*-gapped, $k \leq 10$. Then, Correlation-based Feature Selection (CFS), described in section 3.2, was applied to each of these resulting data sets. The size of the feature set generated by the MSG algorithm was 28, by *k*-grams was 29, by position-based was 22, and by *k*-gapped pair was 49.

10-fold cross validation was used to construct and test models over these four data sets. Average accuracies of the resulting models are shown in Figure 6, and the t-test results in Table 5. On this data set, the position-based algorithm performed the best. This is expected given that location information is relevant for the classification of this data set's sequences, as discussed above. The MSG generated features yielded prediction performance at the same level of that of k-grams; and statistically significantly higher performance (at the $p < 0.05$ significance level) than that of k-gapped pair.

5.3 Results on the *C.elegans* Gene Expression Data Set

5.3.1 Patters from the Literature

Motifs are short subsequences in the promoter sequences that have the ability to bind transcription factors, and thus to affect gene expression. For example, a transcription factor CEH-6 is necessary for the gene aqp-8 to be expressed in the EXC cell, by binding to a specific subsequence (ATTTGCAT) in the gene promoter region (Mah, et al., 2010). The binding sites for a transcription factor are not completely identical, as some variation is allowed. These potential binding sites are represented as a position weight matrix (PWM), see Table 7. A motif is a reasonable matching subsequence according to a specific PWM.

It has been shown that motifs at different locations in the promoter have different importance in controlling transcription (Reece-Hoyes, et al., 2007), and that the order of multiple motifs and the distance between motifs can also affect gene expression (Wan, Barrett, Ruiz, & Ryder, 2013).

5.3.2 Experimental Results

Once again, each of the four feature generation methods under consideration (MSG, k-grams, position-based, and k-gapped pair) was applied to the *C.elegans* Gene Expression data set separately, yielding four different feature vector data sets. The parameters used for the feature generation algorithms were: for MSG, the range for the length of transformed subsequences was 1-6; for k-grams, $k \leq 6$; and for k-gapped, $k \leq 10$. After CFS, the size of the feature set generated by the MSG algorithm was 97, by k-grams was 63, by position-based was 122, and by k-gapped pair was 4. The average accuracies of the resulting models with 10-fold cross validation are shown in Figure 7.

On this data set, the MSG algorithm produced the best results, and the p-values in Table 6 indicate that these results are significantly better than the results of position-based and k-gapped pair (at the p < 0.05 significance level). MSG performed slightly better than k-grams, but not significantly better.

Table 7: A PWM for PHA-4, found in (Ao, Gaudet, Kent, Muttumu, & Mango, 2004). It records the likelihood of each nucleotide at each position of the PHA-4 motifs.

	A	C	G	T
1	0.097	0.144	0.52	0.238
2	0.003	0.755	0.003	0.238
3	0.003	0.097	0.003	0.896
4	0.003	0.896	0.097	0.003
5	0.003	0.99	0.003	0.003
6	0.849	0.003	0.144	0.003
7	0.99	0.003	0.003	0.003
8	0.614	0.05	0.191	0.144

Table 8: p-Values obtained from t-tests comparing the prediction accuracies of models constructed over MSG-generated features and models constructed over data sets generated by the other 3 feature generation methods. T-tests were performed using 10-fold cross-validation over the Gene Expression data set. Highlighted in the table are the cases in which the superiority of MSG is statistically significant at the p < 0.05 level.

Baseline: MSG	k-grams	Position-based	k-gapped pair
p-value: J48	0.18	0.41	0.01
p-value: LR	0.18	6.89E-6	1.45E-5
p-value: SVM	0.21	8.39E-5	4.59E-5

5.4 Discussion

Computational Complexity Comparison of the Methods. Suppose that a data set consists of n sequences of length l, over an alphabet B, where $|B| = d$ (for the three data sets considered in this paper, $d = 4$). The position-based method has the lowest computational complexity out of the four feature generation methods employed in this paper. It takes $O(l)$ time to extract each location as a

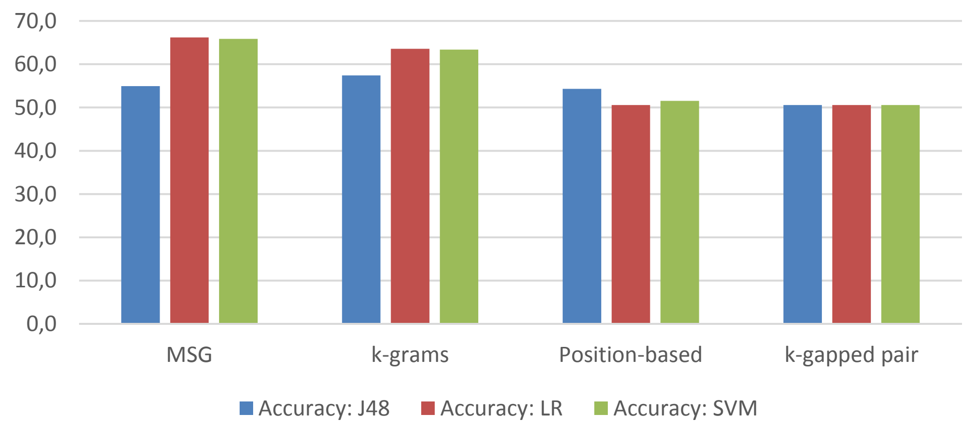


Figure 7: Accuracy of models built on the features from four different feature generation methods (MSG, k-gram, Position-based, and k-gapped pair), using three classification algorithms on the Gene Expression data.

feature for each sequence, so its total complexity is $O(nl)$. K-gapped pair method needs to compute $l-k-1$ pairs of symbols for each sequence for a given gap size k. In our experiments, we considered pairs with gap $\leq k$, and since k is much less than l, the time complexity for each sequence is $O(kl)$. Its total complexity is $O(nkl)$. Similarly, the k-gram method takes $O(nkl)$ time complexity to generate features of length $\leq k$.

The MSG method has the highest computational complexity among the four methods. Suppose that m subsequences are given as input to the mutated subsequences generation process (pseudo code in Figure 3). There are two outer loops and one inner loop in this process. The first outer loop goes over all the $\binom{m}{2}$ pairs of subsequences, and its inner loop takes at most m iterations. The second outer loop traverses m subsequences to delete the marked ones. So the time complexity of this method is $O\left(m*\binom{m}{2}+m\right)=O(m^3)$. For a given length k, we can extract at most d^k subsequences from the sequence data. Thus, its computational complexity is $O(d^{3k})$ in the worst case.

Experimental Comparison of the Methods. The experimental results on the three data sets above provide evidence of the usefulness of the proposed MSG feature generation algorithm. As we discussed above, patterns in the *E.coli* promoter gene sequences data set are position-independent, while patterns in the primate splice-junction gene sequences data set are position-dependent. Given that the MSG-generated features do not take location into consideration, MSG was expected to perform very well on the first data set but not on the second data set. Our experimental results confirm this hypothesis. In summary, MSG-generated features are most predictive in domains in which location is irrelevant or plays a minor role. Nevertheless, even in domains in which location is important, our MSG algorithm performed at the same level, or higher, than other feature generation algorithms from the literature.

In the *C.elegans* gene expression data set, patterns are much more complex than in the other two data sets considered. Due to the simplicity of the transformed data set – binary values representing the presence/absence of features occurring in sequences, the MSG algorithm does not produce high classification accuracies on this data set. However, when compared to the other algorithms under consideration, MSG generates features that yield more accurate prediction models. One aspect that contributes to MSG's comparably better performance on this data set is its ability to represent mutations in the data sequences.

6 CONCLUSIONS AND FUTURE WORK

In this work, we present a novel feature generation method, called Mutated Subsequence Generation (MSG), for feature based sequence classification. This method considers subsequences, possibly containing mutated positions, as potential features for the original sequences. It uses a metric based on the GINI Index to select the best features. We compare this method with other feature generation methods on three genetic data sets, focusing on the accuracy of the classification models built on the features generated by these methods. The experimental results show that MSG outperforms other feature generation methods in domains where presence, not specific location, of a pattern within a sequence is relevant; and can perform at the same level or higher than other non-position-based feature generation methods in domains in which specific location, as well as presence, is important. Additionally, our MSG method is capable of identifying one-position mutations in the subsequence generated features that are highly associated with the classification target.

Further experimentation on much larger data sets is needed to confirm the aforementioned findings. This will be addressed in future work. Other future work includes a refinement of our MSG algorithm to reduce its time complexity. We also plan to extend our MSG method to allow for mutations in more than one subsequence position. Additionally, we plan to investigate approaches to and the effects of incorporating location information in the MSG generated features.

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