Classifying Sequences by the Optimized Dissimilarity Space Embedding Approach: a Case Study on the Solubility Analysis of the E. coli Proteome

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Abstract

We evaluate a version of the recently-proposed Optimized Dissimilarity Space Embedding (ODSE) classification system that operates in the input space of sequences of generic objects. The ODSE system has been originally presented as a labeled graph classification system. However, since it is founded on the dissimilarity space representation of the input data, the classifier can be easily adapted to any input domain where it is possible to define a meaningful dissimilarity measure. We demonstrate the effectiveness of the ODSE classifier for sequences considering an application dealing with recognition of the solubility degree of the Escherichia coli proteome. Overall, the obtained results, which we stress that have been achieved with no context-dependent tuning of the ODSE system, confirm the validity and generality of the ODSE-based approach for structured data classification.

Index terms—Dissimilarity representation; Sequence matching and classification; E. coli proteome analysis; Entropy-based data characterization.

1 Introduction

A considerable number of pattern recognition applications deal with data represented as sequences of objects [4, 44]. The handwriting on-line recognition problem provides a good example: each object in the sequence is a distinct stroke written by a user through a suitable input device [40]. The objects of the sequence can originate from a finite alphabet, as in the problem of text excerpt classification [14], where the objects are usually words of the corresponding language. Another interesting example in this case pertains biochemical compounds, such as DNA and proteins [10, 39, 43]. Many applications deal with objects originating from infinite domains, such as in the case of series of real-valued data (e.g., 3D spatial positions of a moving agent, financial time-series, and sequences of measurements related to a physical plant or device) [12, 29]. Often the ordering of the objects is assumed to be over the time domain; in this case, the objects are referred to as events. When dealing with classification problems defined on an input space of sequences, modeling the abstract classification function underlying the unknown data generating process can become a very complex
task. To this end, the problem can be faced by mapping the sequences into \( \mathbb{R}^d \) vectors, using a suitable feature extraction procedure \([3, 16, 18, 33, 35]\). In this scenario, features are elaborated from the dataset at hand, and therefore can be considered as a local reference framework on which ground the new vector-based representation of the input data. This solution is supported by the fact that there are many effective and well-established data-driven inductive inference systems that deal with real-valued vectors as input patterns \([23, 25, 32, 36, 37]\).

The dissimilarity representation is a powerful framework for dealing with pattern recognition and data mining problems defined in spaces with no trivial (geo)metric structure \([4, 5, 7, 13, 21, 31, 42]\). Pairwise dissimilarity values of input data are generated according to a suitable dissimilarity measure, \( d : \mathcal{X} \times \mathcal{X} \rightarrow \mathbb{R}^+ \), which operates directly in the input domain, \( \mathcal{X} \). Such a dissimilarity measure, which can also diverge from a common metric distance (e.g., Euclidean distance), is usually defined by parameters that allow to tailor the matching method to the particular data type at hand. The dissimilarity representation is developed with respect to a local base of prototypes, \( \mathcal{R} \), called representation set. Dissimilarity-based classification systems for sequences of objects have been proposed on various data types, such as simple atomic elements \([35]\) (e.g., sequences of numbers or characters belonging to a finite alphabet) and more complex data structures, like type-2 fuzzy sets \([19, 22, 26]\) and pen strokes \([2, 40]\).

The recently proposed classification system called Optimized Dissimilarity Space Embedding (ODSE) is founded on the dissimilarity representation. It has been originally developed as a classification system for labeled graphs, denoting state-of-the-art test set performances on various well-known benchmarking datasets \([17, 21]\). The synthesis of the classification model is implemented by exploiting an information-theoretic interpretation of the dissimilarity matrix. Such an interpretation allows to conceive suitable compression and expansion operations of the representation set, implementing the optimization of the dissimilarity space. The ODSE system performs all operations (i.e., synthesis of the model, test set evaluation etc.) starting from the construction of the dissimilarity matrix, which in turn is completely elaborated through a dissimilarity measure. Therefore, by adapting the dissimilarity measure to the particular context at hand, it is possible to easily adapt the whole ODSE system accordingly.

In this paper, we present and test a version of the ODSE system tailored to work in the input space of sequences. The main aim of this study is to demonstrate the versatility and effectiveness of the ODSE classifier design, which is quickly adaptable to different input domains. Toward this end, we evaluate the ODSE classifier for sequences on an important application concerning the solubility analysis of sequences of amino acid residues, elaborated from the Escherichia coli (E. coli) proteome \([27, 28]\). Folding is a chemico-physical process of extraordinary difficulty and complexity from the viewpoint of prediction. This fact is due to (i) the large number of residues constituting protein molecules and to (ii) the multiplicity of different energetic constraints involved in the underlying physical process \([6]\). Moreover, the process of folding is in strict competition with the aggregation process (low propensity of a molecule to be soluble), that is, with the tendency of establishing inter-molecular bonds. This results in the formation of large multi-molecular “aggregates” which, analogously to what happens for artificial polymers, are insoluble and hence precipitate in solution \([6, 8, 10]\).

The herein considered data as been already processed by different groups \([1, 35]\), although in slightly different settings. Therefore, we use such results \([35]\) for comparison in the experiments.

This paper is structured as follows. Section 2 quickly introduces the ODSE system; initially we describe the system in terms of graph-based patterns. Section 2.2 discusses the straightforward adaptation of the ODSE system for processing sequences. In Section 3 we discuss the experiments performed on the E. coli dataset. Finally, Section 4 concludes the paper.

## 2 The ODSE Classification System

The ODSE graph classification system \([17, 21]\) is based on the interplay between different techniques, among which we have graph matching, dissimilarity space representation, cluster analysis, and information-theoretic data analysis methods. The classifier is founded on an explicit graph embedding mechanism that represents the input graphs \( S, n = |S| \), using a suitable representation set, \( \mathcal{R}, m = |\mathcal{R}| \), by computing the dissimilarity
matrix $D^{n \times m}$. Originally, the system has been conceived to operate on the labeled graphs domain $\mathcal{G}$ by means of a suitable inexact graph matching procedure [15]. The vector configuration representing the input data in the embedding space $\mathcal{D}$ is derived directly using the rows of $D$.

An important component of the ODSE graph classification system is the inner feature-based classifier, which operates directly on the developed dissimilarity space embedding; its own classification model is synthesized along with the ODSE synthesis. Such a classifier can be any well-known classification system, such as a neuro-fuzzy Min-Max network [9, 32].

2.1 A Quick Look Into the ODSE Design

Test patterns are classified by ODSE feeding the corresponding dissimilarity representation to the (already synthesized) feature-based classifier, which assigns proper class labels to the test patterns. Figures 1(a) and 1(b) provide, respectively, the diagrams of the ODSE embedding procedure and of the model synthesis. The ODSE classification model is defined by the representation set $R_i$, the setting of the graph parameters (denoted as $P_i$), and the feature-based classifier (denoted as $M_i$ in Figure 1(b)) on the developed dissimilarity space. During the synthesis stage, additional parameters are optimized, which are fundamental to the determination of the optimal classification model. Those parameters, which are synthetically denoted as $\Sigma_i$ in Figure 1(a), are the kernel size $\sigma$ used by the entropy estimator and the two entropy thresholds $\tau_c, \tau_e$, which play a fundamental role in the compression and expansion operations, respectively. The former is used to reduce the number of prototypes, while the latter replaces targeted prototypes that do not help discriminating the input data represented in the dissimilarity space. Both operations make use of a suitable non-parametric $\alpha$-order Rényi entropy estimator to characterize the informativeness of the prototypes. Since the dissimilarity values fall into a continuous interval, the underlying distribution is assumed to be continuous as well. So far, the ODSE system has been tested considering two well-known entropy estimators. The first estimator has been proposed by Príncipe [30], and it is referred to as the Quadratic Rényi entropy (QRE) estimator, while the second one is based on the construction of the so-called entropic Minimum Spanning Tree (MST) among the data samples [11]. While both estimators showed, as ODSE components, comparable performances, the latter is considerably faster and less sensible to the dimensionality of the data (i.e., dissimilarity vectors).

In current implementations [17, 21], the ODSE model is optimized through a genetic algorithm (GA). The GA operates by performing roulette wheel selection, two-point crossover, and random mutation on the variables representing the model parameters; it implements also an elitism strategy that includes the fittest individual into the next population. The GA, in practice, evolves a population of ODSE model instances that are evaluated by considering a suitable fitness function. Such a fitness function takes into account a combination of the recognition rate $\pi_i$ achieved on a validation set, $S_{va}$, the cardinality of the compressed-and-expanded representation set, and finally the estimated entropy related to the embedded training data. Convergence criterion is determined as a combination of a maximum number of iterations and a check that evaluates the variation of the fitness in the last five iterations.

![Figure 1: Schematic description of the ODSE embedding space and classification model synthesis. Taken from [21].](image-url)
2.2 Classifying Sequences with ODSE

It is easy to realize that ODSE can be straightforwardly adapted to operate in other input spaces (i.e., different from the labeled graphs domain). In fact, once an effective dissimilarity measure \( d(\cdot, \cdot) \) that operates in the specific input space at hand (e.g., a domain of sequence of characters) is defined, all ODSE operations are automatically valid and well-defined, since they are performed on the vectors derived from the dissimilarity matrix \( D \) (i.e., compression, expansion, and entropy estimation). Therefore, adaptation of ODSE to process sequences of generic objects is performed by implementing \( d(\cdot, \cdot) \) as a suitable sequence matching algorithm.

From the software implementation point of view, ODSE flexibility is due to the C++ template metaprogramming approach\(^1\)\(^2\)[20]. In fact, the designer is in charge to define just a class implementing a suitable dissimilarity measure, passing it as an argument to the main procedure.

3 Recognition of the E. coli Protein Solubility

Aggregation propensity of proteins is strongly related to “errors” in the folding process [6]. In fact, protein aggregation is at the basis of pathologies defined as misfolding diseases (which include Alzheimer and Parkinson) [11]. Nevertheless, protein–protein interactions are of vital importance for proteins exerting their physiological role, so that a refined balance between aggregation (inter-molecular connections) and folding (intra-molecular connections) is of utmost importance. This balance is so crucial for life that does exist a class of protein molecules called “chaperones”, whose specific role is to help other proteins in completing a correct folding process [38]. However, the nature of the code by which a linear sequence of amino acid residues is transformed into a functional 3D structure is still elusive [6]. It is well-known that some proteins are capable to easily reach the stable state, so that they can undergo different folding–unfolding cycles even when isolated from the cell micro-environment. On the other hand, there are other proteins that cannot be folded when isolated from their cellular environment, necessitating a chaperone-driven folding process.

Niwa et al. [27] studied, in a strictly controlled setting, the aggregation/solubility propensity of the E. coli proteins. Proteins having difficulty in performing the folding “autonomously” tend to aggregate and hence precipitate in the solution (water in this case). Agostini et al. [1] in a recent work clearly demonstrated that the solubility degree in the same Niwa et al. data base negatively correlates with the aggregation propensity (the aggregation is estimated from the folded state). This result implies that it is possible to consider the solubility as a measure of the relative stability of both the folded and aggregated states (i.e., the higher the solubility the higher the protein stability in its native state).

3.1 Dataset Description

The 3173 E. coli proteins elaborated by Niwa et al. [27] were transcribed and translated from the E. coli DNA extracts in strictly controlled conditions. Their solubility was assessed in terms of percentage of protein concentration at saturation point. The authors demonstrated a bi-modal distribution of solubility, with many poorly soluble proteins and a smaller class of very soluble proteins (see Figure 2(a)). For instance, when considering \([0, 0.3]\) and \([0.7, 1]\) as the two intervals of normalized solubility characterizing the insoluble and soluble proteins, the dataset would be split into 1631 insoluble and 180 soluble proteins, respectively, which makes the corresponding classification problem very unbalanced [35]. Those interval of solubility, although they generate an unbalanced classification problem, are of the same length and they are placed at the extremes of the (normalized) solubility range. This fact reassures us to perform a fair (although perhaps non-optimal) construction of the soluble and insoluble classes (see Fig. 2(b)). The input of ODSE is hence the E. coli sequences of amino acid identifiers. The classifier outputs the predicted “soluble” or “insoluble” class.

As a consequence of the aforementioned bi-modality of the solubility distribution, the experiments have been organized by considering two different splits of the original dataset. The first experiment (setting previously considered here [35]) operates over a perfectly balanced (small) dataset made of the 100 proteins

\(^1\)http://sourceforge.net/p/libspare/home/Spare/
with the highest solubility degree and the 100 with the lowest solubility degree. We refer to this dataset as DS-200. The training set $S_{tr}$ contains 140 proteins and the test set $S_{ts}$ the remaining 60. Training and test set are characterized by the same number of soluble and insoluble proteins. The second experiment, which we introduce here, takes into account instead a larger dataset of 1811 proteins (DS-1811), obtained by considering the aforementioned solubility ranges (see Fig. 2(b)). The training set, in this case, contains 180 proteins, 70 of which belong to the soluble class and the remaining 110 to the insoluble class. The test set is considerably larger, since in fact it contains 1631 proteins, 1521 of which are insoluble proteins. The training set, although it is much smaller than the test set, it is suitably conceived to “cover” the considered data instance with characterizing proteins, that is, with proteins that suitably represent the soluble or insoluble prototypical patterns – those proteins are selected as suitable prototypes of the respective classes by exploiting a clustering-based analysis.

3.2 Test Set Classification Accuracy Results

In this paper, we adopt the ODSE version described in \cite{17, Sec. 3}. For the sake of shortness, we do not report the details of this particular ODSE implementation here, referring the reader to given reference. We setup ODSE to operate in the input space of sequences by means of a dissimilarity measure implemented through the Levenshtein sequence matching algorithm \cite{19, 34}. We consider in the Levenshtein global alignment scheme suitable pre-computed substitution weights; notably, we used the weights provided by the “PAM120” matrix, which have been retrieved from: ftp://ftp.ncbi.nih.gov/blast/matrices/ We report the results obtained with two different feature-based classifiers operating on the dissimilarity space: a $k$-NN rule operating the Euclidean distance (kNN) and the C-SVM classifier (C-SVM) equipped with a Gaussian kernel. We compare ODSE with the recently-proposed sequence classification system based on another embedding technique \cite{35}, which is denoted as GRAPSEC in the following. We consider also two reference systems that operate directly in the input space. The first one is a $k$-NN rule based classifier, equipped with the same weighted Levenshtein matching scheme used in ODSE (kNN); the second one is the kernelized C-SVM classifier operating in the input space of sequences through the kernel function elaborated from the Levenshtein metric – no corrections are performed to assure positive definiteness of the resulting kernel. Setting of meta-parameters (e.g., $C$ of C-SVM) have been defined by preliminary tests. In the following, “0” indicates the insoluble class, while “1” the soluble class. For DS-1811, we considered 10 different randomized re-samplings; split percentages of the datasets are defined as described in the previous section. The following results on DS-1811 are thus intended as averages (with related standard deviations).
Table 1 shows the results on DS-200. Results achieved with the kNN classifier (for $k = 5$) are comparable with those of GRAPSEC, although for different $k$ values ODSE obtains slightly inferior results. Test set accuracy results obtained with C-SVM operating in the embedding space equate those of GRAPSEC (same per-class errors). The kNN based reference system is systematically outperformed by the others, while the C-SVM classifier achieves a good result, however inferior to those obtained by ODSE and GRAPSEC.

Table 2 shows results on DS-1811. ODSE systematically outperforms GRAPSEC and the kNN reference system, especially when using the C-SVM classifier in the dissimilarity space. We note a more balanced per-class error distribution; in particular less errors are committed for the class of very soluble proteins (1), which proved to be hard to recognize also in our previous study [35]. Results obtained with the kNN operating directly in the input space are of poor quality, except for the $k = 5$ case, where the system achieves competitive results. Finally, the results achieved with C-SVM operating in the input space are comparable (slightly better) with the best result of ODSE. Standard deviations are in general low, demonstrating the stability of the results with respect to the different splits of the data.

Table 1: Test set classification accuracy results achieved on DS-200, containing the 100 most soluble and the 100 most insoluble proteins in the original dataset.

| Class. Sys. | Core Class. | Params | # Err. 0 | # Err. 1 | TS Accuracy |
|-------------|-------------|--------|---------|---------|-------------|
| ODSE        | k-NN        | $k = 1$ | 1/30    | 7/30    | 86.7%       |
|             |             | $k = 3$ | 1/30    | 6/30    | 88.4%       |
|             |             | $k = 5$ | 1/30    | 4/30    | 91.7%       |
|             | C-SVM       | $C = 2$ | 0/30    | 4/30    | 93.3%       |
| GRAPSEC     | k-NN        | $k = 1$ | 1/30    | 6/30    | 88.4%       |
|             |             | $k = 3$ | 1/30    | 4/30    | 91.7%       |
|             |             | $k = 5$ | 0/30    | 4/30    | 93.3%       |
|             | $k = 1$     | 24/30   | 0/30    | 60.0%   |
|             | $k = 3$     | 20/30   | 0/30    | 66.6%   |
| kNN         |             | $k = 5$ | 24/30   | 0/30    | 66.0%       |
| C-SVM       |             | $C = 2$ | 2/30    | 6/30    | 88.3%       |

Table 2: Average test set classification accuracy results achieved on DS-1811. We report the average number of per-class errors and the average global test set accuracy (with related standard deviation).

| Class. Sys. | Core Class. | Params | # Err. 0 | # Err. 1 | TS Accuracy (std. dev.) |
|-------------|-------------|--------|---------|---------|------------------------|
| ODSE        | k-NN        | $k = 1$ | 343.6   | 39.6    | 76.5% (± 0.002)        |
|             |             | $k = 3$ | 306.6   | 36.0    | 78.5% (± 0.001)        |
|             |             | $k = 5$ | 306.5   | 31.4    | 75.9% (± 0.001)        |
|             | C-SVM       | $C = 2$ | 245.6   | 28.2    | 83.2% (± 0.001)        |
| GRAPSEC     | k-NN        | $k = 1$ | 382.4   | 41.0    | 74.0% (± 0.001)        |
|             |             | $k = 3$ | 375.0   | 40.6    | 74.5% (± 0.001)        |
|             |             | $k = 5$ | 368.2   | 39.8    | 74.9% (± 0.002)        |
| kNN         |             | $k = 1$ | 1228.2  | 7.4     | 24.3% (± 0.001)        |
|             |             | $k = 3$ | 1315.6  | 1.2     | 19.4% (± 0.002)        |
|             |             | $k = 5$ | 322.4   | 1.0     | 80.1% (± 0.001)        |
| C-SVM       |             | $C = 2$ | 233.0   | 34.0    | 83.6% (± 0.002)        |

4 Conclusions

In this paper, we have evaluated the effectiveness and versatility of the ODSE classification system when processing sequences. Notably, we have considered an application dealing with the E. coli proteome classification. We focused on the recognition/discrimination of soluble and insoluble proteins, on the base of sequences of identifiers describing amino acid residues. Experiments have been carried out considering different reference systems, showing competitive test set classification accuracy percentages. Overall, the results of this paper strengthen the effectiveness of the ODSE system when dealing with structured data. It is
important to underline that the tests have been performed without any need to tune any system component specifically for the considered problem (i.e., the E. coli solubility recognition), thus confirming that ODSE can be considered as a widely applicable classification system.

Future research directions involve the application of ODSE in other sequence-based pattern recognition problems. We also plan to cast the herein presented E. coli proteome analysis as a function approximation problem, i.e., by considering the continuous solubility degree as the target output signal.

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