Compression ratios based on the Universal Similarity Metric still yield protein distances far from CATH distances

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Abstract

Motivation: Kolmogorov complexity has inspired several alignment-free distance measures, based on the comparison of lengths of compressions, which have been applied successfully in many areas. One of these measures, the so-called Universal Similarity Metric (USM), has been used by Krasnogor and Pelta to compare simple protein contact maps, showing that it yielded good clustering on four small datasets.

Results: We report an extensive test of this metric using a much larger and representative protein dataset: the domain dataset used by Sierk and Pearson to evaluate seven protein structure comparison methods and two protein sequence comparison methods.

One result is that Krasnogor-Pelta method has less domain discriminant power than any one of the methods considered by Sierk and Pearson when using these simple contact maps.

In another test, we found that the USM based distance has low agreement with the CATH tree structure for the same benchmark of Sierk and Pearson. In any case, its agreement is lower than the one of a standard sequential alignment method, SSEARCH.
Finally, we manually found lots of small subsets of the database that are better clustered using SSEARCH than USM, to confirm that Krasnogor-Pelta’s conclusions were based on datasets that were too small.

Availability: All data and programs used for the preparation of this paper are available upon request. See dmi.uib.es/people/jairo/USM/ for cluster examples.

1 Introduction

Krasnogor and Pelta (2004) represented a protein structure by means of the list of contacts (position pairs) and used a compress algorithm to approximate the Kolmogorov complexity on which the definition of the Universal Similarity Metric is based. To test the metric they applied it independently to four protein datasets comprising 122 proteins and clustered each set using an off-the-shelf hierarchical clustering software applied to the resulting inter-distance matrices. In each case they obtained an almost correct classification of the proteins. They inferred that the Universal Similarity Metric captures protein structure similarity.

Since each aminoacid has its own sequential position in a protein, and the contact pairs are pairs of these positions, we were surprised that the method could find similarities between two different proteins each with its own numbering. But the authors conclude the following in the discussion section of the above mentioned paper: “This new metric can be used as a robust measure of similarity of domains where either, there is no enough modeling information, or there is no consensus on which aspects are to be modeled. We gave mathematical and experimental evidence that USM can be used to successfully assess protein structure similarity. The USM seems to be capable of capturing protein similarities that encompasses a variety of other, more heuristic, criteria on a fully automated way. It seems that the Universal Similarity Metric is so robust that even with a rough guess of parameters it is still possible to deliver good results. One disadvantage of using USM on its own is that, although it can differentiate between protein families and sub-families and measure similarity based on a rigorous mathematical definition, it does not give indications of where these (di)similarities come from.”

Given these strong conclusions on the robustness of their method to differentiate between protein sub-families, first, we downloaded their algorithms and data-sets and confirmed exactly their results using this simple protein format. Then, we set off for verifying the results on a bigger set because if they are satisfactory we could abandon our search for sophisticated comparison methods.

We present in this paper a bigger test on almost 2800 protein domains already
used to assess the performance of the most important algorithms used nowadays for protein comparison, namely the benchmark prepared by Sierk and Pearson (2004). When we apply the same Sierk-Pearson test, a though one, that was applied to the other comparison algorithms, the method reveals to be useless for helping to decide whether two proteins are similar or not; the result is that the Universal Similarity Metric using this contact map format and compression approximation performs quite worse than any method considered by Sierk and Pearson, even the ones that only use as input the protein sequences. Therefore, the method as it stands does not encompasses other criteria for comparison as the authors claimed.

Therefore, a global analysis of the method is needed to find out under which conditions it is reliable, if any. One way to undertake this analysis is to compare the matrix generated by USM for the domains in the database used above with respect to the metrics associated to the CATH tree that represents the family relationships of the domains. We found the distance on the tree that best approximates the USM matrix. Then, we calculate the correlation between the USM matrix and the tree distance. A low correlation means that the USM matrix does not represent correctly the tree structure. As we explain in the Results Section below, we found higher correlations for the distance generated by SSEARCH (Smith and Waterman, 1981) than to for USM. In short, we have a global evidence that clusterings produced by USM are farther from the CATH tree than the ones produced by a sequential method that does not uses 3D information.

We also confirm manually this result. We found several (more than ten) easily classifiable datasets contained in the benchmark set where the proposed method does not classify correctly the domains. Since the Krasnagor-Pelta method only has three small real datasets as evidence to argue that it can be used to successfully assess protein structural similarity but we can find several easy subsets in the benchmark where it performs poorly, the robustness of the method is open to doubt. We have found subsets of proteins in very different families that the method cannot classify correctly but SSEARCH can, even though this one uses only sequence information.

In the rest of the introduction, we review the use and notation of the Kolmogorov complexity on pattern comparison.

As an alternative to general sequence and structure comparison methods based on alignments, several metrics have been proposed based on Kolmogorov complexity (Benedetto et al., 2002; Bennett et al., 1998; Keogh et al., 2004; Li et al., 2001, 2004; Varre et al., 1999). Roughly speaking, the conditional Kolmogorov complexity $K(x|y)$ of two sequences $x, y$ is the length of the shortest binary
program $P$ that computes $x$ with input $y$ (Kolmogorov, 1965). Thus, $K(x|y)$ represents the minimal amount of information required to generate $x$ by any effective computation when $y$ is furnished as an input to the computation. The Kolmogorov complexity $K(x)$ of a sequence $x$ is defined as $K(x|\lambda)$, where $\lambda$ stands for the empty sequence. Given a string $x$, let $x^*$ denote the shortest binary program that produces $x$ on an empty input; if there are more than one shortest program, we take as $x^*$ the first in alphabetic order. The Kolmogorov complexity $K(x, y)$ of a pair of objects $x, y$ is the length of the shortest binary program that produces $x$ and $y$ and a way to tell them apart. More formal definitions of all these concepts and their main properties can be found in the textbook by Li and Vitányi (2nd ed. 1997).

The most outstanding metric based on Kolmogorov complexity is the Universal Similarity Metric proposed by Li et al. (2004),

$$d_u(x, y) = \frac{\max\{K(x|y^*), K(y|x^*)\}}{\max\{K(x), K(y)\}}.$$  \hspace{1cm} (1)

These authors proved that this metric (actually, it only satisfies the axioms of metrics up to a certain additive precision) refines any other computable similarity metric, like for instance effective versions of Hamming distance, Euclidean distance, edit distances or alignment distances (Li et al., 2004, Thm. VI.2). This Universal Similarity Metric has been used successfully for instance to compute phylogenetic trees based on whole mitochondrial genomes (Li et al., 2004; Cilibrasi and Vitányi, 2005), cluster SARS virus (Cilibrasi and Vitányi, 2005), classify languages (Li et al., 2004), musical pieces (Cilibrasi et al., 2004; Cilibrasi and Vitányi, 2005; Li and Sleep, 2004), and images (Svangard and Nordin, 2004), detect plagiarism in student assignments (Chen et al., 2004), and cluster Russian literature (Cilibrasi and Vitányi, 2005). But it has failed to compare TOPS diagrams (Gilbert et al., 2006).

Actually, the Universal Similarity Metric was not used in these applications as it stands, but approximations of it. The reason is that Kolmogorov complexities are non-computable in the Turing sense, and therefore they must be heuristically approximated in practice. Since $K(x)$ is intuitively the minimal amount of information required to generate $x$, i.e., the shortest length of a compressed binary version of $x$, Kolmogorov complexities are approximated by means of lengths of compressions, and then the formula (1) given above is simplified using suitable properties of Kolmogorov complexity, so that it no longer involves conditional Kolmogorov complexities.

In this way, and once fixed a compression algorithm, the Kolmogorov complex-

4
ity $K(x)$ of an object $x$ is replaced by the length $C(x)$ of the compression of it using this algorithm. Furthermore, since according to Li et al. (2004)

$$K(x, y) = K(xy)$$

up to additive logarithmic precision, $K(x, y)$ can be replaced by the length $C(xy)$ of a compression of the concatenation of $x$ and $y$. Finally, and since

$$K(x, y) = K(x) + K(y|x^*) = K(y) + K(x|y^*)$$

up to constant additive precision (Li and Vitányi, 2nd ed. 1997), the conditional complexity $K(x|y^*)$ can be approximated by $C(xy) - C(y)$, and $K(y|x^*)$ can be approximated by $C(xy) - C(x)$ or by $C(yx) - C(x)$.

This lead Li et al. (2004) to approximate the Universal Similarity Metric by the Normalized Information Distance

$$NCD(x, y) = \frac{C(xy) - \min\{C(x), C(y)\}}{\max\{C(x), C(y)\}};$$

this distance has been thoroughly studied by Cilibrasi and Vitányi (2005). A methodological study of its application to protein sequence classification has been published recently by Kocsor et al. (2006); they show that a compression based distance combined with a BLAST score has a performance even slightly better than that of the Smith-Waterman algorithm (SSEARCH).

Krasnogor and Pelta (2004); Pelta et al. (2005) have used a slightly more general approximation of the Universal Similarity Metric to compare protein structures. The formula they use (and we use in this paper) is

$$USM(x, y) = \frac{\max\{C(xy) - C(x), C(yx) - C(y)\}}{\max\{C(x), C(y)\}}.$$

2 Methods

A subset of CATH 2.3 database (which stands for Class, Architecture, Topology, and Hierarchy (Orego et al., 1997)) was selected by Sierk and Pearson (2004) to obtain a non-redundant sample of the entire database. A 2771 subset of CATH domains and 86 prototype domains\(^1\) were selected to test the following algorithms: Dali, Structal, CE, VAST, Matras, SGM, PRIDE, SSEARCH and

\(^1\)Available at the FASTA repository ftp.virginia.edu:/pub/fasta/prot_sci_04
PS-Blast. This domain set was carefully screened in order to be considered as a valid benchmark for testing protein comparison algorithms. Of the 2771 domains, 1120 belong to the 86 families of the 86 prototypes. Therefore, when comparing each of the 2771 domains against each of the 86 prototypes, there is a maximum of 1120 correct hits. The prototypes are part of these 1120 domains.

For our experiments, the file representation is the one used by Krasnogor and Pelta: a protein is represented by a list of adjacent aminoacids, where two aminoacids are adjacent if the distance of the corresponding C\textsubscript{\(\alpha\)} atoms are below 6.5 Å, a threshold also used by them (we also tested other thresholds as we explain below). Each line in the file contains two numbers with the first one smaller than the second one. The file has a header that consists of two lines: in the first one, the number of aminoacids is followed by the comment “\# Number of Residues”; in the second one, the number of contacts is followed by the comment “\# Number of Contacts at 6.5 Angstroms”. Therefore, two concatenated files could be trivially separated from each other. The Unix compress program was used. Other representations of protein structures (binary adjacency matrix with and without end of line characters) and other compression programs were tried but are not reported because the results obtained with them were similar or even slightly worse.

We wanted to carry out two tests: The first one is to test its selectivity on the whole database. The second one is to find out why much agreement there is between the USM based distance among the domains and the tree that CATH associates to them.

With respect to the first test, the best algorithms to decide whether two proteins are similar have been tested with the 2771 domain database. Therefore, we tested if the USM based method is useful on deciding this demanding task and compare the results with the other methods. Krasnogor-Pelta’s USM approximation of the Universal Similarity Metric was applied carrying out a pairwise comparison of the 86 prototypes versus the 2771 domains. The values returned were examined from the best score to the worst. For each pair considered in this order whose domains belong to the same family, a coverage value was increased. Otherwise, an error value was increased. This is the method used by Sierk and Pearson to evaluate the other algorithms with the same database. A perfect classifier would arrive to 100% coverage before the first error arrives.

To assess the sensitivity and selectivity of the Universal Similarity Metric, we plot Errors per Query versus Coverage curves for both approximations. These curves show how much coverage is obtained at a given error level, i.e., the number of true positives detected at a given number of false positive detected.
With respect to the second test, we aim to compare the hierarchical clusterings produced by the USM based distance and the CATH clustering defined by CATH for the same domains. To do so, we find the distance on the tree that best approximates the USM distance, and calculate the linear correlation between the two distances. For each tree edge, a weight variable is introduced. Let $D$ be the domain set and $x$ be the vector of edge weight variables. We minimize the squares sum of the distances in the tree and in the known USM matrix:

$$
\min \sum_{i,j \in D} (C(x, i, j) - d_{i,j})^2,
$$

where $d_{i,j}$ is the constant USM based distance between domains $i$ and $j$ and $C(x, i, j)$ is the sum of the variables associated to the known edge path between $i$ and $j$ in the CATH tree. Under the positivity constraints for the variables, the fit is resolved using standard methods for quadratic programming. Finally, the tree distance $t_{i,j}$ between the domains $i$ and $j$ is calculated using the edge weights that produce the best fit. The cophenetic correlation between $(d_{i,j})$ and $(t_{i,j})$ is calculated, and compared to the correlation of the distance generated by SSEARCH.

3 Results

3.1 Selectivity test

According to Krasnogor and Pelta (2004), their method sometimes clusters well proteins that belong to a small number of groups. However, the most important question that needs to be answered when a new 3D structure of a protein is discovered is whether it is similar to one or more better known proteins. The problem of clustering proteins is not a crucial one, since lots of structures are not discovered at once, and clusters are already defined in public databases using lots of information sources.

The Error-Coverage curve generated with the Universal Similarity Metric approximations is quite worse than those corresponding to the methods considered by Sierk and Pearson, as seen in Figure 1 with respect to Dali. Table 1 summarizes the results.

The $Errors$ column shows the number of errors per prototype (i.e., 10 corresponds to 860 errors) and all other values are coverage percentages with respect to 1120 (i.e, 1% means 11 hits). The column USM refers to the results corresponding to the approximation explained in the introduction, the Dali column displays
Figure 1: Error-Coverage curves. Left, USM method, right, Dali.

| Errors | USM | Dali | Worst Method |
|--------|-----|------|--------------|
| 0.1    | 0.09| 19   | 10           |
| 1      | 0.4 | 43   | 17           |
| 10     | 1.7 | 71   | 28           |

Table 1: Coverage performance for a given error level for different protein distances.
the results corresponding to the structural alignment program Dali (Holm and Sander, 1996) and the Worst Method gives the worst result obtained by any method considered by Sierk and Pearson for the corresponding error rate.

So, for instance, at 0.1 errors per query on average, i.e., when 8 errors have been found, USM has only correctly covered 0.09% of the domains, i.e., 1 domain, while the Dali program at the same error rate reaches 19% of correctly covered domains (209 domains) and the worst method at this error rate (VAST) reaches a coverage of 10% (112 domains). At a rate of 1.0 errors per query (86 errors), USM covers correctly 0.4% while Dali covers 43% and the worst method in this case (SGM) covers 17%. At a rate of 10.0 errors per query (860 errors), the evaluated method covers only 1.7% while Dali covers 71% and the worst method (SGM) covers 28%. Notice that his 1.7% means 19 hits, i.e., after 860 false positives, USM has not even detected the identity of all 86 prototypes with themselves.

Other tests, where the contact map is calculated when the threshold ranges from 5 to 8 Å gave the same negative results.

3.2 Cophenetic correlation

When comparing a distance to its closest one on the CATH tree, the correlation coefficient for USM is 0.60 and for SSEARCH is 0.87. This fact confirms that USM yields weaker clusterings with respect to CATH than a method that does not uses 3D information.

We also found manually small subsubsets of domains that are wrongly clustered by USM, but that SSEARCH classifies almost perfectly, using the same clustering algorithm used in Krasnogor and Pelta (2004). Due to paper limitations, they are not shown here but in the web page dmi.uib.es/people/jairo/USM/. In the fist one in the web, for instance, there are proteins that belong to two different classes (the wider tree level) that are wrongly clustered by USM.

4 Conclusion

The USM based method under a simple contact map format clusters poorly protein groups easily discriminable and, in general, their clusters are father form CATH than the ones generated by some methods based on sequences; the three small real sets that it clusters almost correctly are by no means an evidence that the method is robust for clustering. In addition, the method is very far from becoming a reliable protein comparison method from the point of view
of deciding if two given protein structures are similar or not, one of the most
important procedures to detect protein function similarity.

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