

Normalized Compression Distance of Multisets¹ with Applications

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Abstract

Normalized compression distance (NCD) is a parameter-free, feature-free, alignment-free, similarity measure between a pair of finite objects based on compression. However, it is not sufficient for all applications. We propose an NCD of finite nonempty multisets (a.k.a. multiples) of finite objects that is also a metric. Previously, attempts to obtain such an NCD failed. We cover the entire trajectory from theoretical underpinning to feasible practice. The new NCD for multisets is applied to retinal progenitor cell classification questions and to related synthetically generated data that were earlier treated with the pairwise NCD. With the new method we achieved significantly better results. Similarly for questions about axonal organelle transport. We also applied the new NCD to handwritten digit recognition and improved classification accuracy significantly over that of pairwise NCD by incorporating both the pairwise and NCD for multisets. In the analysis we use the incomputable Kolmogorov complexity that for practical purposes is approximated from above by the length of the compressed version of the file involved, using a real-world compression program.

Index Terms— Normalized compression distance, multisets or multiples, pattern recognition, data mining, similarity, classification, Kolmogorov complexity, retinal progenitor cells, synthetic data, organelle transport, handwritten character recognition

I. INTRODUCTION

To define the information in a *single* finite object one commonly uses the Kolmogorov complexity [14] of that object (finiteness is taken as understood in the sequel). Information distance [2] is the information

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required to transform one in the other, or vice versa, among a *pair* of objects. For research in the theoretical direction see among others [23]. Here we are more concerned with normalizing it to obtain the so-called similarity metric and subsequently approximating the Kolmogorov complexity through real-world compressors [18]. This leads to the normalized compression distance (NCD) which is theoretically analyzed and applied to general hierarchical clustering in [4]. The NCD is parameter-free, feature-free, and alignment-free, and has found many applications in pattern recognition, phylogeny, clustering, and classification, for example [1], [12], [13], [24], [25], [6], [7], [31] and the many references in Google Scholar to [18], [4]. Another application is to objects that are only represented by name, or objects that are abstract like ‘red,’ ‘Einstein,’ ‘three.’ In this case the distance uses background information provided by Google or any search engine that produces aggregate page counts. It discovers the ‘meaning’ of words and phrases in the sense of producing a relative semantics [5]. The question arises of the shared information between many objects instead of just a pair of objects.

A. Related Work

In [19] the notion is introduced of the information required to go from any object in a multiset of objects to any other object in the multiset. This is applied to extracting the essence from, for example, a finite nonempty multiset of internet news items, reviews of electronic cameras, tv’s, and so on, in a way that works better than other methods. Let X denote a finite nonempty multiset of m finite binary strings defined by (abusing the set notation) $X = \{x_1, \dots, x_m\}$, the constituting elements (not necessarily all different) ordered length-increasing lexicographic. We use multisets and not sets, since if X is a set then all of its members are different while we are interested in the situation were some or all of the objects are equal. Let U be the reference universal Turing machine, for convenience the prefix one as in Section II. We define the *information distance* in X by $E_{\max}(X) = \min\{|p| : U(x_i, p, j) = x_j \text{ for all } x_i, x_j \in X\}$. It is shown in [19], Theorem 2, that

$$E_{\max}(X) = \max_{x:x \in X} K(X|x), \quad (\text{I.1})$$

up to an additive term $O(\log K(X))$. Define $E_{\min}(X) = \min_{x:x \in X} K(X|x)$. Theorem 3 in [19] states that

$$E_{\min}(X) \leq E_{\max}(X) \leq \min_{i:1 \leq i \leq m} \sum_{x_i, x_k \in X \text{ \& } k \neq i} E_{\max}(x_i, x_k), \quad (\text{I.2})$$

up to a logarithmic additive term. The information distance in [2] between strings x_1 and x_2 is denoted by $E_1(x_1, x_2) = \max\{K(x_1|x_2), K(x_2|x_1)\}$. Here we use the notation $\max_{x:x \in X} K(X|x)$. The two coincide for $|X| = 2$ since $K(x, y|x) = K(y|x)$ up to an additive constant term. In [27] this notation was introduced and the following results were obtained for finite nonempty multisets. The maximal overlap of information, concerning the remarkable property that the information needed to go from any member x_j to any other member x_k in a multiset X can be divided in two parts: a single string of length $\min_i K(X|x_i)$ and a special string of length $\max_i (K(X|x_i) - \min_i K(X|x_i))$ possibly depending on j and some logarithmic additive terms possibly depending on j, k . Furthermore, the minimal overlap property, the metricity property, the universality property, and the not-subadditivity property. With respect to normalization of the information distance of multisets only abortive attempts were given. A review of some of the above is [20].

B. Results

For many applications we require a normalized and computable version of the information distance for finite nonempty multisets of finite objects. For instance, classifying an object into one or another of disjoint classes we aim for the class of which the NCD for multisets grows the least. We give preliminaries in Section II. The normalization of the information distance for multisets which did not succeed in [27] is analyzed and performed in Section III. In particular it is proved to be a metric. We sometimes require metricity since otherwise the results may be inconsistent and absurd. Subsequently we proceed to the practically feasible compression distance for multisets and prove this to be a metric, Section IV. Next, this compression distance is normalized and proved to retain the metricity, Section V. We go into the question of how to compute this in Section VI, how to apply this to classification in Section VII, and then treat the applications Section VIII. We applied the new NCD for multisets to retinal progenitor cell classification questions, Section VIII-A, and to synthetically generated data, Section VIII-B, that were earlier treated with the pairwise NCD. Here we get significantly better results. This was also the case for questions about axonal organelle transport, Section VIII-C. We also applied the NCD for multisets to classification of handwritten digits, Section VIII-D. Although the NCD for multisets did not improve on the accuracy of the pairwise NCD for this application, classification accuracy was much improved over either method individually by combining the pairwise and multisets NCD. We treat the data, software, and machines used for the applications in Section VIII-E. We finish with conclusions in Section IX.

II. PRELIMINARIES

We write *string* to mean a finite binary string, and ϵ denotes the empty string. The *length* of a string x (the number of bits in it) is denoted by $|x|$. Thus, $|\epsilon| = 0$. We identify strings with natural numbers by associating each string with its index in the length-increasing lexicographic ordering according to the scheme $(\epsilon, 0), (0, 1), (1, 2), (00, 3), (01, 4), (10, 5), (11, 6), \dots$. In this way the Kolmogorov complexity in the next section can be about finite binary strings or natural numbers.

A. Kolmogorov Complexity

The Kolmogorov complexity is the information in a single finite object [14]. Informally, the Kolmogorov complexity of a finite binary string is the length of the shortest string from which the original can be lossless reconstructed by an effective general-purpose computer such as a particular universal Turing machine. Hence it constitutes a lower bound on how far a lossless compression program can compress. For technical reasons we choose Turing machines with a separate read-only input tape that is scanned from left to right without backing up, a separate work tape on which the computation takes place, and a separate output tape. All tapes are divided into squares and are semi-infinite. Initially, the input tape contains a semi-infinite binary string with one bit per square starting at the leftmost square, and all heads scan the leftmost square on their tapes. Upon halting, the initial segment p of the input that has been scanned is called the input “program” and the contents of the output tape is called the “output.” By construction, the set of halting programs is prefix free. An standard enumeration of such Turing machines T_1, T_2, \dots contains a universal machine U such that $U(i, p) = T_i(p)$ for all indexes i and programs p . (Such universal machines are called “optimal” in contrast with universal machines like U' with $U'(i, pp) = T_i(p)$ for all i and p , and $U'(i, q) = 1$ for $q \neq pp$ for some p .) We call U the *reference universal prefix Turing machine*. This leads to the definition of “prefix Kolmogorov complexity” which we shall designate simply as “Kolmogorov complexity.”

Formally, the *conditional Kolmogorov complexity* $K(x|y)$ is the length of the shortest input z such that the reference universal prefix Turing machine U on input z with auxiliary information y outputs x . The *unconditional Kolmogorov complexity* $K(x)$ is defined by $K(x|\epsilon)$ where ϵ is the empty string. In these definitions both x and y can consist of strings into which finite multisets of finite binary strings are encoded.

Theory and applications are given in the textbook [21]. Here we give some relations that are needed in the paper. The *information about x contained in y* is defined as $I(y : x) = K(x) - K(x|y)$. A deep,

and very useful, result holding for both plain complexity and prefix complexity, due to L.A. Levin and A.N. Kolmogorov [33] called *symmetry of information* states that

$$K(x, y) = K(x) + K(y|x) = K(y) + K(x|y), \quad (\text{II.1})$$

with the equalities holding up to a $O(\log K)$ additive term. Here, $K = \max\{K(x), K(y)\}$. Hence, up to an additive logarithmic term $I(x : y) = I(y : x)$ and we call this the *mutual (algorithmic) information* between x and y .

B. Multiset

A multiset is also known as *bag*, *list*, or *multiple*. A *multiset* is a generalization of the notion of set. The members are allowed to appear more than once. For example, if $x \neq y$ then $\{x, y\}$ is a set, but $\{x, x, y\}$ and $\{x, x, x, y, y\}$ are multisets, with abuse of the set notation. We also abuse the set-membership notation by using it for multisets by writing $x \in \{x, x, y\}$ and $z \notin \{x, x, y\}$ for $z \neq x, y$. Further, $\{x, x, y\} \setminus \{x\} = \{x, y\}$. If X, Y, Z are multisets and Z is nonempty and $X = YZ$, then we write $Y \subset X$. For us, a multiset is finite and nonempty such as $\{x_1, \dots, x_n\}$ with $0 < n < \infty$ and the members are finite binary strings in length-increasing lexicographic order. If X is a multiset, then some or all of its elements may be equal. $x_i \in X$ means that “ x_i is an element of multiset X .” With $\{x_1, \dots, x_m\} \setminus \{x\}$ we mean the multiset $\{x_1 \dots x_m\}$ with one occurrence of x removed.

The finite binary strings, finiteness, and length-increasing lexicographic order allows us to assign a unique Kolmogorov complexity to a multiset. The conditional prefix Kolmogorov complexity $K(X|x)$ of a multiset X given an element x is the length of a shortest program p for the reference universal Turing machine that with input x outputs the multiset X . The prefix Kolmogorov complexity $K(X)$ of a multiset X is defined by $K(X|\epsilon)$. One can also put multisets in the conditional such as $K(x|X)$ or $K(X|Y)$. We will use the straightforward laws $K(\cdot|X, x) = K(\cdot|X)$ and $K(X|x) = K(X'|x)$ up to an additive constant term, for $x \in X$ and X' equals the multiset X with one occurrence of the element x deleted.

C. Information Distance

The information distance in a multiset X ($|X| \geq 2$) is given by (I.1). To obtain the *pairwise information distance* in [2] we take $X = \{x_1, x_2\}$ in (I.1). The resulting formula is equivalent to $E_{\max}(x_1, x_2) = \max\{K(x_1|x_2), K(x_2|x_1)\}$ up to a logarithmic additive term.

D. Metricity

Let \mathcal{X} be the set of length-increasing lexicographic ordered nonempty finite multisets of finite binary strings. A *distance function* d on \mathcal{X} is defined by $d : \mathcal{X} \rightarrow \mathcal{R}^+$ where \mathcal{R}^+ is the set of nonnegative real numbers. Define $Z = XY$ if Z is the multiset consisting of the elements of the multisets X and Y and the elements of Z are ordered length-increasing lexicographic. A distance function d is a *metric* if

- 1) *Positive definiteness*: $d(X) = 0$ if all elements of X are equal and $d(X) > 0$ otherwise.
- 2) *Symmetry*: $d(X)$ is invariant under all permutations of X .
- 3) *Triangle inequality*: $d(XY) \leq d(XZ) + d(ZY)$.

We recall Theorem 4.1 and Claim 4.2 from [27].

Theorem II.1. *The information distance for multisets E_{\max} is a metric where the (in)equalities hold up to a $O(\log K)$ additive term. Here K is the largest quantity involved in each metric (in)equality 1) to 3), respectively.*

Claim II.2. Let X, Y, Z be three nonempty finite multisets of finite binary strings and $K = K(X) + K(Y) + K(Z)$. Then, $E_{\max}(XY) \leq E_{\max}(XZ) + E_{\max}(ZY)$ up to an $O(\log K)$ additive term.

III. NORMALIZED INFORMATION DISTANCE

The quantitative difference in a certain feature between many objects can be considered as an *admissible* distance, provided it is upper semicomputable and satisfies a density condition for every $x \in \{0, 1\}^*$ (to exclude distances like $D(X) = 1/2$ for every multiset X):

$$\sum_{X: x \in X \text{ \& } D(X) > 0} 2^{-D(X)} \leq 1. \quad (\text{III.1})$$

Thus, for the density condition on D we consider only multisets X with $|X| \geq 2$ and not all elements of X are equal. Moreover, we consider only distances that are upper semicomputable, that is, they are computable in some broad sense (they can be computably approximated from above). Theorem 5.2 in [27] shows that E_{\max} (the proof shows this actually for $\max_{x \in X} \{K(X|x)\}$) is universal in that among all admissible multiset distances it is always least up to an additive constant. That is, it accounts for the dominant feature in which the elements of the given multiset are alike.

Admissible distances as defined above are absolute, but if we want to express similarity, then we are more interested in relative ones. For example, if a multiset X of strings of each about 1,000,000 bits have

pairwise information distance 1,000 bits to each other, then we are inclined to think that those strings are relatively similar. But if a multiset Y consists of strings of each about 1,200 bits and each two strings in it have a pairwise information distance of 1,000 bits, then we think the strings in Y are very different. In the first case $E_{\max}(X) \approx 1,000|X| + O(1)$, and in the second case $E_{\max}(Y) \approx 1,000|Y| + O(1)$. Possibly $|X| \approx |Y|$. The information distances in the multisets are about the same.

To express similarity we need to normalize the universal information distance E_{\max} . It should give a similarity with distance 0 when the objects in a multiset are maximally similar (that is, they are equal) and distance 1 when they are maximally dissimilar. Naturally, we desire the normalized version of the universal multiset information distance metric to be also a metric.

For pairs of objects x, y the normalized version e of E_{\max} defined by

$$e(x, y) = \frac{\max\{K(x, y|x), K(x, y|y)\}}{\max\{K(x), K(y)\}} \quad (\text{III.2})$$

takes values in $[0, 1]$ up to an additive term of $O(1/K(x, y))$. It is a metric up to additive terms $O((\log K)/K)$ with K denotes the maximum of the Kolmogorov complexities involved in each of the metric (in)equalities, respectively. A normalization formula for multisets of more than two elements ought to reduce to that of (III.2) for the case of multisets of two elements.

Remark III.1. For example set $A = \{x\}, B = \{y, y\}, C = \{y\}, K(x) = n, K(x|y) = n, K(y) = 0.9n$ and by using (II.1) we have $K(x, y) = 1.9n, K(y|x) = 0.9n$. The most natural definition is a generalization of (III.2):

$$e_1(X) = \frac{\max_{x \in X} \{K(X|x)\}}{\max_{x \in X} \{K(X \setminus \{x\})\}}. \quad (\text{III.3})$$

But we find $e_1(AB) = K(x|y)/K(x, y) = n/1.9n \approx 1/2$, and $e_1(AC) = K(x|y)/K(x) = n/n = 1$, $e_1(CB) = K(y|y)/K(y) = 0/0.9n = 0$, and the triangle inequality is violated. But with $A = \{x\}, B' = \{y\}, C = \{y\}$, and the Kolmogorov complexities as before, the triangle inequality is not violated. In this case, $e_1(AB') = 1 > e_1(AB)$ even though $AB' \subset AB$. However it makes sense that if we add an element to a multiset of objects then a program to go from any object in the new multiset to any other object should be at least as long as a program to go from any object in the old multiset to any other object. \diamond

The reasoning in the last sentence of the remark points the way to go: the definition of $e(X)$ should be monotonic nondecreasing in $|X|$ if we want e to be a metric.

Lemma III.2. Let X, Y be multisets and d be a distance that satisfies the triangle inequality. If $Y \subseteq X$ then $d(Y) \leq d(X)$.

Proof: Let A, B, C be multisets with $A, B \subseteq C$, and d a distance that satisfies the triangle inequality. Assume that the lemma is false and $d(C) < d(AB)$. Let $D = C \setminus A$. It follows from the triangle inequality that

$$d(AB) \leq d(AD) + d(DB).$$

Since $AD = C$ this implies $d(AB) \leq d(C) + d(DB)$, and therefore $d(C) \geq d(AB)$. But this contradicts the assumption. ■

Definition III.3. Let X be a multiset. Define the *normalized information distance* (NID) for multisets by $e(X) = 0$ for $|X| = 0, 1$, and for $|X| > 1$ by

$$e(X) = \max \left\{ \frac{\max_{x \in X} \{K(X|x)\}}{\max_{x \in X} \{K(X \setminus \{x\})\}}, \max_{Y \subset X} \{e(Y)\} \right\}. \quad (\text{III.4})$$

Here the left-hand term in the outer maximalization is denoted by $e_1(X)$ as in (III.3).

For $|X| = 2$ the value of $e(X)$ is equivalently given in (III.2). In this way, (III.4) satisfies the property in Lemma III.2: If X, Z are multisets and $Z \subseteq X$ then $e(Z) \leq e(X)$. Therefore we can hope to prove the triangle property for (III.4). Instead of “distance” for multisets one can also use the term “diameter.” This does not change the acronym NID. Moreover, the diameter of a pair of objects is the familiar distance.

Theorem III.4. For every nonempty finite multiset X we have $0 \leq e(X) \leq 1$ up to an additive term of $O(1/K)$ where $K = K(X)$.

Proof: By induction on $n = |X|$.

Base case: $n = 0, 1$. The theorem is vacuously true for $n = 0, 1$.

Induction: $n > 1$. Assume that the lemma is true for the cases $0, \dots, n - 1$. Let $|X| = n$. If $e(X) = \max_{Y \subset X} \{e(Y)\}$ then the lemma holds by the inductive assumption since $|Y| < n$. Hence assume that

$$e(X) = \frac{\max_{x \in X} \{K(X|x)\}}{\max_{x \in X} \{K(X \setminus \{x\})\}}.$$

The numerator is at most the denominator up to an $O(1)$ additive term and the denominator is at most $K(X)$. The lemma is proven. ■

For $n = 2$ the definition of $e(X)$ is (III.2). The proof of the lemma for this case is also in [18].

Remark III.5. The least value of $e(X)$ is reached if all occurrences of elements of X are equal. In that case $0 \leq e(X) \leq O(1/K(X))$. The greatest value $e(X) = 1 + O(1/K(X))$ is reached if $\max_{x \in X} \{K(X|x)\} \geq \max_{x \in X} \{K(X \setminus \{x\})\} + O(1)$. For example, if the selected conditional, say y , has no consequence in the sense that $K(X|y) = K(X \setminus \{y\}|y) + O(1) = K(X \setminus \{y\}) + O(1)$. This happens if $K(z|y) = K(z)$ for all $z \in X \setminus \{y\}$.

Another matter is the consequences of (III.4). Use (II.1) in the left-hand term in both the numerator and the denominator. Then we obtain up to additive logarithmic terms in the numerator and denominator

$$\begin{aligned} \frac{\max_{x \in X} \{K(X|x)\}}{\max_{x \in X} \{K(X \setminus \{x\})\}} &= \frac{K(X) - \min_{x \in X} \{K(x)\}}{K(X) - \min_{x \in X} \{K(x|X \setminus \{x\})\}} \\ &= 1 - \frac{\min_{x \in X} \{K(x)\} - \min_{x \in X} \{K(x|X \setminus \{x\})\}}{K(X) - \min_{x \in X} \{K(x|X \setminus \{x\})\}}. \end{aligned} \quad (\text{III.5})$$

This expression goes to 1 if both

$$K(X) \rightarrow \infty, \quad \frac{\min_{x \in X} \{K(x)\}}{K(X)} \rightarrow 0.$$

This happens, for instance, if $|X| = n$, $\min_{x \in X} = 0$, $K(X) > n^2$, and $n \rightarrow \infty$. Also in the case that $X = \{x, x, \dots, x\}$ (n copies of a fixed x) and $n \rightarrow \infty$. Then $K(X) \rightarrow \infty$ and $\min_{x \in X} \{K(x)\}/K(X) \rightarrow 0$ with $|X| \rightarrow \infty$. To consider another case, we have $K(X) \rightarrow \infty$ and $\min_{x \in X} \{K(x)\}/K(X) \rightarrow 0$ if $\min_{x \in X} \{K(x)\} = o(K(X))$ and $\max_{x \in X} \{K(x)\} - \min_{x \in X} \{K(x)\} \rightarrow \infty$, that is, if X consists of at least two elements and gap between the minimum Kolmogorov complexity and the maximum Kolmogorov complexity of the elements grows to infinity when $K(X) \rightarrow \infty$. \diamond

Remark III.6. Heuristically the partitioning algorithm described in Section VIII approaches the question when to use the left-hand term of (III.4). But we can analyze directly under what conditions there is a $Y \subset X$ such that $e(Y) > e(X)$. Without loss of generality we can assume that in that case the left-hand term of (III.4) for Y is greater than the left-hand term of (III.4) for X (that is, $e_1(Y) > e_1(X)$ with e_1 according to (III.3)). This means that

$$\frac{K(Y) - \min_{x \in Y} \{K(x)\}}{\max_{x \in Y} \{K(Y \setminus \{x\})\}} > \frac{K(X) - \min_{x \in X} \{K(x)\}}{\max_{x \in X} \{K(X \setminus \{x\})\}}, \quad (\text{III.6})$$

ignoring logarithmic additive terms. Take the example of Remark III.1. Let $X = \{x, y, y\}$ and $Y = \{x, y\}$. Then $Y \subset X$. The left-hand side of (III.6) equals 1 and the right-hand side equals $\approx 1/2$. In this case $e_1(Y) > e_1(X)$ with e_1 according to (III.3) and as we have seen the triangle inequality does not hold

for e_1 . ◇

Theorem III.7. *The function e as in (III.4) is a metric up to an additive $O((\log K)/K)$ term in the respective metric (in)equalities, where K is the largest Kolmogorov complexity involved the (in)equality.*

Proof: The quantity $e(X)$ satisfies positive definiteness and symmetry up to an $O((\log K(X))/K(X))$ additive term, as follows directly from the definition of $e(X)$ in (III.4). It remains to prove the triangle inequality:

Let X, Y, Z be multisets. Then, $e(XY) \leq e(XZ) + e(ZY)$ within an additive term of $O((\log K)/K)$ where $K = \max\{K(X), K(Y), K(Z)\}$. The proof proceeds by induction on $n = |XY|$.

Base Case: $n = 0, 1$. These cases are vacuously true.

Induction $n > 1$. Assume that the lemma is true for the cases $0, \dots, n - 1$. Let $|XY| = n$. If $e(XY) = \max_{Z \subset XY} \{e(Z)\}$ then the lemma holds by the inductive assumption since $|Z| < n$. Hence assume that

$$e(XY) = e_1(XY) = \frac{K(XY|x_{XY})}{K(XY \setminus \{x_{xy}\})},$$

where we let x_u and x_v denote the elements that reach the maximum in $K(U \setminus \{x_u\}) = \max_{x \in U} \{K(U \setminus \{x\})\}$, and $K(V|x_v) = \max_{x \in V} \{K(V|x)\}$.

Claim III.8. Let X, Y, Z be multisets (finite, but possibly empty). $K(XYZ|x_{XYZ}) \leq K(XZ|x_{XZ}) + K(ZY|x_{ZY})$ up to an additive $O(\log K)$ term, where $K = K(X) + K(Y) + K(Z)$.

Proof: If one or more of X, Y, Z equal \emptyset the theorem holds trivially. Therefore, assume neither of X, Y, Z equals \emptyset . By Theorem II.1 we have that E_{\max} and hence $K(XY|x_{XY})$ is a metric up to an $O(\log K)$ additive term. In particular, the triangle inequality is satisfied by Claim II.2: $K(XY|x_{XY}) \leq K(XZ|x_{XZ}) + K(ZY|x_{ZY})$ for multisets X, Y, Z up to an additive term of $O(\log K)$. Thus with $X' = XZ$ and $Y' = ZY$ we have $K(X'Y'|x_{X'Y'}) \leq K(X'Z|x_{X'Z}) + K(ZY'|x_{ZY'})$ up to the logarithmic additive term. Writing this out $K(XZZY|x_{XZZY}) \leq K(XZZ|x_{XZZ}) + K(ZYZ|x_{ZYZ})$ or $K(XYZ|x_{XYZ}) \leq K(XZ|x_{XZ}) + K(ZY|x_{ZY})$ up to an additive term of $O(\log K)$. ■

Now consider the following inequalities (where possibly one or more of X, Y, Z equal \emptyset):

$$\begin{aligned}
e_1(XYZ) &= \frac{K(XYZ|x_{XYZ})}{K(XYZ \setminus \{x_{xyz}\})} \\
&\leq \frac{K(XZ|x_{XZ})}{K(XYZ \setminus \{x_{xyz}\})} + \frac{K(ZY|x_{ZY})}{K(XYZ \setminus \{x_{xyz}\})} \\
&\leq \frac{K(XZ|x_{XZ})}{K(XZ \setminus \{x_{xz}\})} + \frac{K(ZY|x_{ZY})}{K(ZY \setminus \{x_{zy}\})} \\
&= e_1(XZ) + e_1(ZY),
\end{aligned} \tag{III.7}$$

up to a $O((\log K)/K)$ additive term. The first inequality is Claim III.8 (by this inequality the denominator is unchanged); the second inequality follows from $K(XYZ \setminus \{x_{xyz}\}) \geq K(XZ \setminus \{x_{xz}\})$ and $K(XYZ \setminus \{x_{xyz}\}) \geq K(ZY \setminus \{x_{zy}\})$ using the principle that $K(uv) \geq K(u) + O(1)$, reducing both denominators and increasing the sum of the quotients (by this inequality the numerators are unchanged); the third inequality follows by definition (III.4).

By definition (III.4) a multiset XYZ has $e(XYZ) = e_1(XYZ)$ or it contains a proper submultiset U such that $e(U) = e_1(U) = e(XYZ)$. This $U \subset XYZ$ is the multiset (if it exists) that achieves the maximum in the right-hand term of the outer maximalization of $e(XYZ)$ in (III.4).

Assume U exists. Denote $X' = X \cap U$, $Y' = Y \cap U$, and $Z' = Z \cap U$. Then (III.7) holds with X' substituted for X , Y' substituted for Y , and Z' substituted for Z . Since $e(U) = e_1(U)$ and $e(XY) \leq e(U)$ we have $e(XY) \leq e_1(X'Z') + e_1(Z'Y')$ up to a $O((\log K)/K)$ additive term.

Assume U does not exist. Then $e(XY) \leq e(XYZ) = e_1(XYZ)$. By (III.7) we have $e(XY) \leq e_1(XZ) + e_1(ZY)$ up to a $O((\log K)/K)$ additive term.

By the monotonicity property of (III.4) and since $X'Z' \subseteq XZ$ and $Z'Y' \subseteq ZY$ we have $e(XZ) \geq e_1(X'Z')$, $e_1(XZ)$ and $e(ZY) \geq e_1(Z'Y')$, $e_1(ZY)$. Therefore, $e(XY) \leq e(XZ) + e(ZY)$ up to an $O((\log K)/K)$ additive term. ■

Remark III.9. The definition of $e(XY)$ with $|XY| = 2$ is (III.2). The proof of the lemma for this case is in [18]. The proof above is simpler and more elementary for a more general case than the one in [18].

◇

By Theorems III.4 and III.7 the distance according to (III.4) is a metric with values in $[0, 1]$ up to some ignorable additive terms..

IV. COMPRESSION DISTANCE FOR MULTISSETS

We develop the compression-based equivalence of the Kolmogorov complexity based theory in the preceding sections. This is similar to what happened in [4] for the case $|X| = 2$. We assume that the notion of the real-world compressor G used in the sequel is “normal” in the sense of [4].

Definition IV.1. By $G(x)$ we mean the length of string x when compressed by G . Consider a multiset X as a string consisting of the concatenated strings of its members ordered length-increasing lexicographic with a means to tell the constituent elements apart. Thus we can write $G(X)$.

Let $X = \{x_1, \dots, x_m\}$. The information distance $E_{\max}(X)$ can be rewritten as

$$\max\{K(X) - K(x_1), \dots, K(X) - K(x_m)\}, \quad (\text{IV.1})$$

within logarithmic additive precision, by (II.1). The term $K(X)$ represents the length of the shortest program for X . The order of the members of X makes only a small difference; block-coding based compressors are symmetric almost by definition, and experiments with various stream-based compressors (gzip, PPMZ) show only small deviations from symmetry.

Approximation of $E_{\max}(X)$ by a compressor G is straightforward: it is

$$E_{G,\max}(X) = \max\{G(X) - G(x_1), \dots, G(X) - G(x_m)\} = G(X) - \min_{x \in X}\{G(x)\}. \quad (\text{IV.2})$$

We need to show it is an admissible distance and a metric.

Lemma IV.2. *If G is a normal compressor, then $E_{G,\max}(X)$ is an admissible distance.*

Proof: For $E_{G,\max}(X)$ to be an admissible distance it must satisfy the density requirement (III.1) and be upper semicomputable. Since the length $G(x)$ is computable it is a fortiori upper semicomputable. The density requirement (III.1) is equivalent to the Kraft inequality [15] and states in fact that for every string x the set of $E_{G,\max}(X)$ is a prefix-free code for the X 's containing x . According to (IV.2) we have for every $x \in X$: $E_{G,\max}(X) \geq G(X) - G(x) \geq G(X \setminus \{x\})$. Hence, $2^{-E_{G,\max}(X)} \leq 2^{-G(X \setminus \{x\})}$ and therefore

$$\sum_{X:x \in X} 2^{-E_{G,\max}(X)} \leq \sum_{X:x \in X} 2^{-G(X \setminus \{x\})}.$$

A compressor G compresses strings into a uniquely decodable code (it must satisfy the unique decompression property) and therefore the length set of the compressed strings must satisfy the Kraft

inequality [22]. Then, for every x the compressed code for the multisets $X \setminus \{x\}$ must satisfy this inequality. Hence the right-hand side of above displayed inequality is at most 1. ■

Lemma IV.3. *If G is a normal compressor, then $E_{G,\max}(X)$ is a metric with the metric (in)equalities satisfied up to logarithmic additive precision.*

Proof: Let X, Y, Z be multisets with at most m members of length at most n . The positive definiteness and the symmetry property hold clearly up to an $O(\log G(X))$ additive term. Only the triangular inequality is nonobvious. For every compressor G we have $G(XY) \leq G(X) + G(Y)$ up to an additive $O(\log(G(X) + G(Y)))$ term, otherwise we obtain a better compression by dividing the string to be compressed. (This also follows from the distributivity property of normal compressors.) By the monotonicity property $G(X) \leq G(XZ)$ and $G(Y) \leq G(YZ)$ up to an $O(\log(G(X) + G(Y)))$ or $O(\log(G(Y) + G(Z)))$ additive term, respectively. Therefore, $G(XY) \leq G(XZ) + G(ZY)$ up to an $O(\log(G(X) + G(Y) + G(Z)))$ additive term. ■

V. NORMALIZED COMPRESSION DISTANCE FOR MULTISETS

Let X be a multiset. The normalized version of $e(X)$ using the compressor G based approximation of the normalized information distance for multisets (III.4), is called the *normalized compression distance* (NCD) for multisets: $NCD(X) = 0$ for $|X| = 0, 1$; if $|X| \geq 2$ then

$$NCD(X) = \max \left\{ \frac{G(X) - \min_{x \in X} \{G(x)\}}{\max_{x \in X} \{G(X \setminus \{x\})\}}, \max_{Y \subset X} \{NCD(Y)\} \right\}. \quad (\text{V.1})$$

This NCD is the main concept of this work. It is the real-world version of the ideal notion of normalized information distance NID for multisets in (III.4). As mentioned before, instead of “distance” for multisets it one can use also the term “diameter.” This does not change the acronym NCD.

Remark V.1. In practice, the NCD is a non-negative number $0 \leq r \leq 1 + \epsilon$ representing how different the two files are. Smaller numbers represent more similar files. The ϵ in the upper bound is due to imperfections in our compression techniques, but for most standard compression algorithms one is unlikely to see an ϵ above 0.1 (in our experiments `gzip` and `bzip2` achieved NCD’s above 1, but `PPMZ` always had NCD at most 1). ◇

Theorem V.2. *If the compressor is normal, then the NCD for multisets is a normalized admissible distance and satisfies the metric (in)equalities up to an ignorable additive term, that is, it is a similarity*

metric.

Proof: The NCD (V.1) is a normalized admissible distance by Lemma IV.2. It is normalized to $[0, 1]$ up to an additive term of $O((\log G)/G)$ with $G = G(X)$ as we can see from the formula (V.1) and Theorem III.4 with G substituted for K throughout. We next show it is a metric.

We must have that $NCD(X) = 0$ up to negligible error for a normal compressor G if X consists of equal members. The idempotency property of a normal compressor is up to an additive term of $O(\log G(X))$. Hence the positive definiteness of $NCD(X)$ is satisfied up to an additive term of $O((\log G(X))/G(X))$. The order of the members of X is assumed to be length-increasing lexicographic. Therefore it is symmetric up to an additive term of $O((\log G(X))/G(X))$. It remains to show the triangle inequality $NCD(XY) \leq NCD(XZ) + NCD(ZY)$ up to an additive term of $O((\log G)/G)$ where $G = G(X) + G(Y) + G(Z)$. We do this by induction on $n = |XY|$ where X, Y are multisets.

Base case: $n = 0, 1$. The triangle property is vacuously satisfied.

Induction: $n > 1$. Assume the triangle property is satisfied for the cases $1, \dots, n - 1$. We prove it for $|XY| = n$. If $NCD(XY) = NCD(Z)$ for some $Z \subset XY$ then the case follows from the inductive argument. Therefore, $NCD(XY)$ is the first term in the outer maximization of (V.1). Write $G(XY|x_{XY}) = G(XY) - \min_{x \in XY} \{G(x)\}$ and $G(XY \setminus \{x_{xy}\}) = \max_{x \in XY} \{G(XY) \setminus \{x\}\}$ and similar for XZ, YZ, XYZ . Following the induction case of the triangle inequality in the proof of Theorem III.7, using Lemma IV.3 for the metricity of $E_{G, \max}$ wherever Theorem II.1 is used to assert the metricity of E_{\max} , and substitute G for K in the remainder. This completes the proof. That is, for every multiset Z we have

$$NCD(XY) \leq NCD(XZ) + NCD(ZY),$$

up to an additive term of $O((\log G)/G)$. ■

For $|XY| = 2$ the triangle property is also proved in [4]. The proof above is simpler and more elementary.

VI. COMPUTING THE NORMALIZED COMPRESSION DISTANCE FOR MULTISETS

Define

$$NCD_1(X) = \frac{G(X) - \min_{x \in X} \{G(x)\}}{\max_{x \in X} \{G(X \setminus \{x\})\}}, \quad (\text{VI.1})$$

the first term of (V.1). Assume we want to compute $NCD(X)$ and $|X| = n \geq 2$. In practice it seems that one can do no better than the following (initialized with $M_i = 0$ for $i \geq 1$):

for $i = 2, \dots, n$

do $M_i := \max\{\max_Y\{NCD_1(Y) : Y \subset X, |Y| = i\}, M_{i-1}\}$ **using** (VI.1) **od**

$NCD(X) := M_n$

However, this process involves evaluating the NCD 's of the entire powerset of X requiring at least order 2^n time.

Theorem VI.1. *Let X be a multiset and $n = |X|$. There is a heuristic algorithm to approximate $NCD(X)$ from below in $O(n^2)$ computations of $G(Y)$ with $Y \subseteq X$. (Assuming every $x \in Y$ to be a binary string, $|x| \leq m$, and G compresses in linear time then $G(Y)$ is computed in $O(nm)$ time.)*

Proof: We use the analysis in Remark III.6 and in particular the inequality (III.6). We ignore logarithmic additive terms. We approximate $NCD(X)$ from below by $\max_{Y \subseteq X}\{NCD_1(Y)\}$ for a sequence of $n - 2$ properly nested Y 's of decreasing cardinality. That is, in the computation we set the value of $NCD(X)$ to $NCD_1(X)$ unless there is one of these Y 's such that $NCD_1(X) < NCD_1(Y)$ in which case we set the value of $NCD(X)$ to $NCD_1(Y)$. How do we choose this sequence of Y 's?

Claim VI.2. *Let $Y \subset X$ and $G(X) - \min_{x \in X}\{G(x)\} - \max_{x \in X}\{G(X \setminus \{x\})\} < G(Y) - \min_{x \in Y}\{G(x)\} - \max_{x \in Y}\{G(Y \setminus \{x\})\}$. Then, $NCD_1(X) < NCD_1(Y)$.*

Proof: We first show that $\max_{x \in Y}\{G(Y \setminus \{x\})\} \leq \max_{x \in X}\{G(X \setminus \{x\})\}$. Let $G(Y \setminus \{y\}) = \max_{x \in Y}\{G(Y \setminus \{x\})\}$. Since $Y \subset X$ we have $G(Y \setminus \{y\}) \leq G(X \setminus \{y\}) \leq \max_{x \in X}\{G(X \setminus \{x\})\}$.

We next show that if $a - b < c - d$ and $d \leq b$ then $a/b < c/d$. Namely, dividing the first inequality by b we obtain $a/b - b/b < (c - d)/b \leq (c - d)/d$. Hence, $a/b < c/d$.

Setting $a = G(X) - \min_{x \in X}\{G(x)\}$, $b = \max_{x \in X}\{G(X \setminus \{x\})\}$, $c = G(Y) - \min_{x \in Y}\{G(x)\}$, and $d = \max_{x \in Y}\{G(Y \setminus \{x\})\}$, the above shows that the claim holds. ■

Claim VI.2 states that the only candidates Y ($Y \subset X$) for $NCD_1(Y) > NCD_1(X)$ are the Y such that $G(X) - \min_{x \in X}\{G(x)\} - \max_{x \in X}\{G(X \setminus \{x\})\} < G(Y) - \min_{x \in Y}\{G(x)\} - \max_{x \in Y}\{G(Y \setminus \{x\})\}$.

For example, let $X = \{x_1, x_2, \dots, x_n\}$, $|Y| = 2$, $G(X) = \max_{x \in X}\{G(X \setminus \{x\})\}$ (for instance $x_1 = x_2$), and $\min_{x \in X}\{G(x)\} > 0$. Clearly, $G(Y) - \max_{x \in Y}\{G(Y \setminus \{x\})\} = G(Y) - \max_{x \in Y}\{G(x)\} = \min_{x \in Y}\{G(x)\}$. Then, $0 = G(X) - \max_{x \in X}\{G(X \setminus \{x\})\} < G(Y) - \max_{x \in Y}\{G(Y \setminus \{x\})\} + \min_{x \in X}\{G(x)\} - \min_{x \in Y}\{G(x)\} = \min_{x \in Y}\{G(x)\} + \min_{x \in X}\{G(x)\} - \min_{x \in Y}\{G(x)\} = \min_{x \in X}\{G(x)\}$.

Hence for $Y \subset X$, if $G(X) - \max_{x \in X}\{G(X \setminus \{x\})\}$ is smaller than $G(Y) - \max_{x \in Y}\{G(Y \setminus \{x\})\}$

$\{x\})\} + \min_{x \in X} \{G(x)\} - \min_{x \in Y} \{G(x)\}$ then $NCD_1(Y) > NCD_1(X)$. Note that if the x that maximizes $\max_{x \in X} \{G(X \setminus \{x\})\}$ is not the x that minimizes $\min_{x \in X} \{G(x)\}$ then $\min_{x \in X} \{G(x)\} - \min_{x \in Y} \{G(x)\} = 0$, otherwise $\min_{x \in X} \{G(x)\} - \min_{x \in Y} \{G(x)\} < 0$.

Removing the element that minimizes $G(X) - \max_{x \in X} \{G(X \setminus \{x\})\}$ may make the elements of Y more dissimilar and therefore increase $G(Y) - G(\max_{x \in Y} \{G(Y \setminus \{x\})\})$. Iterating this process may make the elements of the resulting sets ever more dissimilar, until the associated NCD_1 declines due to decreasing cardinality.

Therefore, we come to the following heuristic. Let $X = \{x_1, \dots, x_n\}$. Compute

$$G(X) - \max_{x \in X} \{G(X \setminus \{x\})\}.$$

Let I be the index i for which the maximum in the second term is reached. Set $Y_1 = X \setminus \{x_I\}$. Repeat this process with Y_1 instead of X to obtain Y_2 , and so on. The result is $Y_{n-2} \subset \dots \subset Y_1 \subset Y_0$ with $Y_0 = X$ and $|Y_{n-2}| = 2$. Set $NCD(X) = \max_{0 \leq i \leq n-2} \{NCD_1(Y_i)\}$. The whole process to compute this heuristic to approximate $NCD(X)$ from below takes $O(n^2)$ steps where a step involves compressing a subset of X in $O(nm)$ time. ■

The inequality $NCD_1(Y) > NCD_1(X)$ for $Y \subset X$ in the form of $e_1(Y) > e_1(X)$ with $|Y| = 2$ occurs in the example of Remark III.6. Here e_1 is according to (III.3), that is, the left term in (III.4) defining $e(X)$.

VII. HOW TO APPLY THE NCD

The applications in Section VIII concern classifications. For these purposes, it makes no sense to compute the NCD , but instead we consider the change in NCD_1 for each multiset that we are classifying against with and without the element that is being classified. To compare these changes we require as much discriminatory power as possible.

A. Theory

Remark III.5 shows that $NCD_1(X) \rightarrow 1$ for $G(X) \rightarrow \infty$ and $\min_{x \in X} \{G(x)\}/G(X) \rightarrow 0$ (in the form of $e_1(X)$). While possibly $NCD_1(X) < NCD(X)$, for some $X' \supset X$ we have $NCD_1(X') = NCD(X')$. In general we believe that the nondecreasing of $NCD(X)$ with larger X according to Lemma III.2 is just required to make the NCD metric. This smoothes the NCD_1 function according to (VI.1) to a nondecreasing function for increasing cardinality arguments. However, in the smoothing one obliterates differences that obviously enhance discriminatory power.

B. Practice

Suppose we want to classify x as belonging to one of the classes represented by multisets A, B, \dots, Z . Our method is to consider $NCD(A \cup \{x\}) - NCD(A)$, and similar for classes represented by B, \dots, Z , and then to select the least difference. However, this difference is always greater or equal to 0 by Lemma III.2. If we look at $NCD_1(A \cup \{x\}) - NCD_1(A)$ then the difference may be negative, zero, or positive and possibly greater in absolute value. This gives larger discriminatory power in the classes selection.

Another reason is as follows. Let Y_0 be as in the proof of Theorem VI.1. For the handwritten digit recognition application in Section VIII-D we computed Y_0 for digits 1, 2, ..., 9, 0. The values were 0.9845, 0.9681, 0.9911, 0.9863, 0.9814, 0.9939, 0.9942, 0.9951, 0.992, 0.9796. But $\max_{0 \leq i \leq n-2} \{NCD_1(Y_i)\} = 0.9953$ for the class of digit 1 where the maximum is reached for index $i = 21$. Thus $NCD(A \cup \{x\}) - NCD_1(A \cup \{x\}) = 0.0108$ for this class with the NCD computed according to Theorem VI.1. We know that $NCD(A) \leq NCD(A \cup \{x\})$ because $A \subset A \cup \{x\}$. Computing $NCD(A)$ similarly as $NCD(A \cup \{x\}) - NCD_1(A \cup \{x\})$ may yield $NCD(A) = NCD(A \cup \{x\})$ because Y_j for $A \cup \{x\}$ may be the same multiset as Y_{j-1} for A for some $1 \leq j \leq 21$. This has nothing to do with the element x we try to classify. The same may happen to $NCD(B \cup \{x\}) - NCD(B)$, and so on.

C. Kolmogorov Complexity of Natural Data

The Kolmogorov complexity of a file is a lower bound on the length of the ultimate compressed version of that file. Above we approximate the Kolmogorov complexities involved by a real-world compressor G . Since the Kolmogorov complexity is incomputable, in the approximation we never know how close we are to it. However, we assume that the natural data we are dealing with contain no complicated mathematical constructs like $\pi = 3.1415\dots$ or Universal Turing machines. In fact, we assume that the natural data we are dealing with contains only effective regularities that a good compressor like G finds. Under those assumptions the Kolmogorov complexity $K(x)$ of object x is not much smaller than the length of the compressed version $G(x)$ of the object.

D. Partition Algorithm

Section VIII-D describes an algorithm that we developed to partition data for classification in cases where the classes are not well separated so that there are no subsets of a class with separation larger than that of the smallest inter-class separation, a heuristic that we have found to work well in practice.

VIII. APPLICATIONS

We detail preliminary results using the new NCD for multisets. The NCD for pairs as originally defined [4] has been applied in a wide range of application domains. In [11] a close relative was compared to every time series distance measure published in the decade preceding 2004 from all of the major data analysis conferences and found to outperform all other distances aside from the Euclidean distance with which it was competitive. The NCD for pairs has also been applied in biological applications to analyze the results of segmentation and tracking of proliferating cells and organelles [6], [7], [29]. The NCD is unique in allowing multidimensional time sequence data to be compared directly, with no need for alignment or averaging.

Here, we compare the performance of the proposed NCD for multisets to that of a previous application of the NCD for pairs for predicting retinal progenitor cell (RPC) fate outcomes from the segmentation and tracking results from live cell imaging [7]. We also apply the proposed NCD to a synthetic data set previously analyzed with the pairwise NCD [6]. Finally, we apply the proposed NCD for multisets to the classification of handwritten digits, an application that was previously evaluated using the pairwise NCD in [4].

A. Retinal Progenitor Cell Fate Prediction

In [7], long-term time-lapse image sequences showing rat RPCs were analyzed using automated segmentation and tracking algorithms. Images were captured every five minutes of the RPCs for a period of 9–13 days. Up to 100 image sequences may be captured simultaneously in this manner using a microscope with a mechanized stage. For an example see Figure 1. At the conclusion of the experiment, the “fate” of

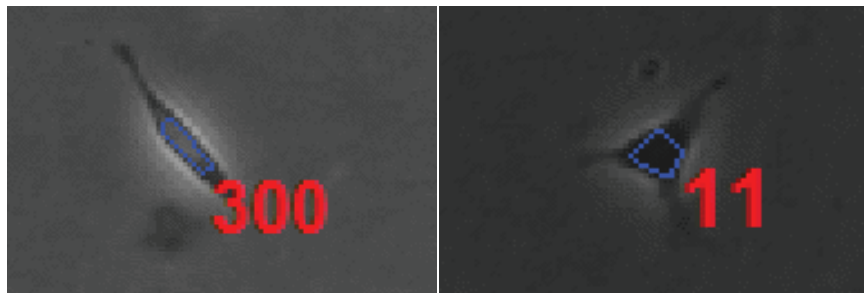


Fig. 1. Example frames from two retinal progenitor cell (RPC) image sequences showing segmentation (blue lines) and tracking (red lines) results. The type of cells the RPCs will eventually produce can be predicted by analyzing the multidimensional time sequence data obtained from the segmentation and tracking results. The NCD for multisets significantly improves the accuracy of the predictions.

the offspring produced by each RPC was determined using a combination of cell morphology and specific cell-type fluorescent markers for the four different retinal cell types produced from embryonic day 20 rat RPCs [3]. At the conclusion of the imaging, automated segmentation and tracking algorithms [28] were applied to extract the time course of features for each cell. These automated segmentation and tracking algorithms extract a time course of feature data for each stem cell at a five-minute temporal resolution, showing the patterns of cellular motion and morphology over the lifetime of the cell. Specifically, the segmentation and tracking results consisted of a 6-dimensional time sequence feature vector incorporating two-dimensional motion $(\Delta x, \Delta y)$, as well as the direction of motion, total distance travelled, cellular size or area (in pixels) and a measure of eccentricity on $[0, 1]$ (0 being linear, 1 being circular shape). The time sequence feature vectors for each of the cells are of different length and are not aligned. The results from the segmentation and tracking algorithms were then analyzed as follows.

The original analysis of the RPC segmentation and tracking results used a multiresolution semi-supervised spectral analysis based on the originally formulated pairwise NCD. An ensemble of distance matrices consisting of pairwise NCDs between quantized time sequence feature vectors of individual cells is generated for different feature subsets f and different numbers of quantization symbols n for the numerical time sequence data. The fully automatic quantization of the numeric time sequence data is described in [6]. All subsets of the 6-dimensional feature vector were included, although it is possible to use non-exhaustive feature subset selection methods such as forward floating search, as described in [6]. Each distance matrix is then normalized as described in [7], and the eigenvectors and eigenvalues of the normalized matrix are computed. These eigenvectors are stacked and ordered by the magnitude of the corresponding eigenvalues to form the columns of a new “spectral” matrix. The spectral matrix is a square matrix, of the same dimension N as the number of stem cells being analyzed. The spectral matrix has the important property that the i th row of the matrix is a point in \mathbb{R}^N (\mathbb{R} is the set of real numbers) that corresponds to the quantized feature vectors for the i th stem cell. If we consider only the first k columns, giving a spectral matrix of dimension $N \times k$, and run a K-Means clustering algorithm, this yields the well-known spectral K-Means algorithm [10]. If we have known outcomes for any of the objects that were compared using the pairwise NCD, then we can formulate a semi-supervised spectral learning algorithm by running for example nearest neighbors or decision tree classifiers on the rows of the spectral matrix. This was the approach adopted in [7].

In the original analysis, three different sets of known outcomes were considered. First, a group of 72 cells were analyzed to identify cells that would self-renew (19 cells), producing additional progenitors

and cells that would terminally differentiate (53 cells), producing two retinal neurons. Next, a group of 86 cells were considered on the question of whether they would produce two photoreceptor neurons after division (52 cells), or whether they would produce some other combination of retinal neurons (34 cells). Finally, 78 cells were analyzed to determine the specific combination of retinal neurons they would produce, including 52 cells that produce two photoreceptor neurons, 10 cells that produce a photoreceptor and bipolar neuron, and 16 cells that produced a photoreceptor neuron and an amacrine cell. Confidence intervals are computed for the classification results by treating the classification accuracy as a normally distributed random variable, and using the sample size of the classifier together with the normal cumulative distribution function (CDF) to estimate the region corresponding to a fixed percentage of the distribution [30, pp. 147-149]. For the terminal versus self-renewing question, 99% accuracy was achieved in prediction using a spectral nearest neighbor classifier, with a 95% confidence interval of [0.93, 1.0]. In the sequel, we will list the 95% confidence interval in square brackets following each reported classification accuracy. For the two photoreceptor versus other combination question, 87% accuracy [0.78, 0.93] was achieved using a spectral decision tree classifier. Finally, for the specific combination of retinal neurons 83% accuracy [0.73, 0.9] was achieved also using a spectral decision tree classifier.

Classification using the newly proposed NCD (III.4) is much more straightforward and leads to significantly better results. Given multisets A and B , each consisting of cells having a given fate, and a cell x with unknown fate, we proceed as follows. We assign x to whichever multiset has its distance (more picturesque “diameter”) increased the least with the addition of x . In other words, if

$$NCD_1(Ax) - NCD_1(A) < NCD_1(Bx) - NCD_1(B), \quad (\text{VIII.1})$$

we assign x to multiset A , else we assign x to multiset B . (The notation Xx is shorthand for the multiset X with one occurrence of x added.) Note that for classification purposes we consider the impact of element x on the NCD_1 (VI.1) only and do not evaluate the full NCD for classification. We use the NCD_1 in (VIII.1) rather than the NCD because the NCD_1 has the ability to decrease when element x contains redundant information with respect to multiset A . See also the reasons in Section VII.

The classification accuracy improved considerably using the newly proposed NCD for multisets. For the terminal versus self-renewing question, we achieved 100% accuracy in prediction [0.95,1.0] compared to 99% accuracy [0.93,1.0] for the multiresolution spectral pairwise NCD. For the two photoreceptor versus other combination question, we also achieved 100% accuracy [0.95,1.0] compared to 87% [0.78,0.93]. Finally, for the specific combination of retinal neurons we achieved 92% accuracy [0.84,0.96] compared

to 83% [0.73,0.9] with the previous method.

B. Synthetic Data

In [6], an approach was developed that used the pairwise NCD to compute a concise and meaningful summarization of the results of automated segmentation and tracking algorithms applied to biological image sequence data obtained from live cell and tissue microscopy. A synthetic or simulated data set was analyzed using a method that incorporated the pairwise NCD, allowing precise control over differences between objects within and across image sequences. The features for the synthetic data set consisted of a 23-dimensional feature vector. The seven features relating to 3-D cell motion and growth were modeled as described below, the remaining 16 features were set to random values. Cell motility was based on a run-and-tumble model similar to the motion of bacteria. This consists of periods of rapid directed movement followed by a period of random undirected motion. Cell lifespan was modeled as a gamma distributed random variable with shape parameter 50 and scale parameter 10. Once a cell reaches its lifespan it undergoes cell division, producing two new cells, or, if a predetermined population limit has been reached, the cell undergoes apoptosis, or dies. The final aspect of the model was cell size. The initial cell radius, denoted r_0 , is a gamma-distributed random variable with shape parameter 200 and scale parameter 0.05. The cells growth rate is labeled v . At the end of its lifespan, the cell doubles its radius. The radius at time t is given by

$$r(t) = r_0 + r_0 \cdot \left(\frac{t - t_0}{lifespan} \right)^v$$

In the original analysis, two different populations were simulated, one population having an v value of 3, the second having an v value of 0.9.

The data was originally analyzed using a multiresolution representation of the time sequence data along with feature subset selection. Here we repeat the analysis for a population of 656 simulated cells, with between 228 and 280 time values for each 23 dimensional feature vector. This data was analyzed using a minimum distance supervised classifier with both the original pairwise and the proposed NCD for multisets. Omitting the feature subset selection step and incorporating the entire 23 dimensional feature vector, the pairwise NCD was 57% correct [0.53,0.61] the classifying the data, measured by leave-one-out cross validation. Using NCD for multisets, we achieved 91% correct [0.89,.93] classification, a significant improvement. When a feature subset selection step was included, both approaches achieved 100% correct classification.

C. Axonal Organelle Transport

Deficiencies in the transport of organelles along the neuronal axon have been shown to play an early and possibly causative role in neurodegenerative diseases including Huntington’s disease [8]. In [29], we analyzed time lapse image sequences showing the transport of fluorescently labeled Brain Derived Neurotrophic Factor (BDNF) organelles in a wild-type (healthy) population of mice as well as in a mutant huntingtin protein population. The goal of this study was to examine the relationship between BDNF transport and Huntington’s disease. The transport of the fluorescently labeled BDNF organelles was analyzed using a newly developed multi-target tracking approach we termed ”Multitemporal Association Tracking” (MAT). In each image sequence, organelles were segmented and then tracked using MAT and instantaneous velocities were calculated for all tracks.

Image data was collected over eight time-lapse experiments, with each experiment containing two sets of simultaneously captured image sequences, one for the diseased population and one for the wild type population. There were a total of 88 movies from eight data sets. Although the pairwise NCD was not able to accurately differentiate these populations for individual image sequences, by aggregating the image sequences so that all velocity data from a single experiment and population were considered together, we were able to correctly classify six of the eight experiments as wild type versus diseased for 75% correct classification accuracy. Analyzing the velocity data from the individual image sequences using pairwise NCD with a minimum distance classifier, we were able to classify 57% [0.47,0.67] of the image sequences correctly into wild type versus diseased populations. Using the NCD for multisets formulation described in (VIII.1) with the same minimum distance approach, as described in the previous sections, we achieved a classification accuracy of 97% [0.91,0.99].

D. NIST handwritten digits

In addition to the previous applications, we applied the new NCD for multisets to analyzing handwritten digits from the MNIST handwritten digits database [16], a free and publicly available version of the NIST handwritten digits database 19 that was analyzed in [4]. The NIST data consists of 128x128 binary images while the MNIST data has been normalized to a 28x28 grayscale (0,...,255) images. The MNIST database contains a total of 70,000 handwritten digits. Here, we consider only the first 1000 digits. The images are first scaled by a factor of four and then adaptive thresholded using an Otsu transform to form a binary image. The images are next converted to one-dimensional streams of binary digits and used to form a pairwise distance matrix between each of the 1000 digits. Originally the input looks as Figure 2.

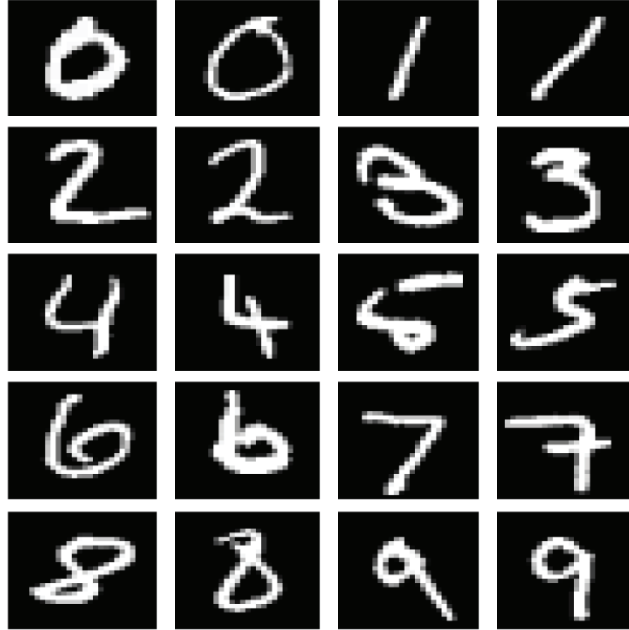


Fig. 2. Example MNIST digits. Classification accuracy for this application was improved by combining the proposed NCD for multisets with the pairwise NCD.

Following the same approach as described for the retinal progenitor cells above, we form a spectral matrix from this pairwise distance matrix. In [4], a novel approach was developed for using the distances as input to a support vector machine. Random data examples along with unlabelled images of the same size were selected and used as training data, achieving a classification accuracy of 87% on the unscaled NIST database 19 digits. We follow the same approach of incorporating the distances into a supervised learning framework, using our spectral matrix as input to an ensemble of discriminant (Gaussian mixture model) classifiers [9]. Using leave-one-out cross validation, this approach using the pairwise NCD achieved 82% correct classification [0.79,0.84] for the 1000 scaled and resized MNIST digits.

In applying the multisets NCD to this data, we measured the separation between classes or the *margin*. Given multisets A and B , each corresponding to a class in the testing data, we measure the separation between the two classes as

$$NCD_1(AB) - NCD_1(A) - NCD_1(B). \quad (\text{VIII.2})$$

This follows directly from the relevant Venn diagram. Our goal is to partition the input classes such that

the separation between classes is larger than any separation between subsets of the same class, subject to a minimum class size. We have found that this approach works well in practice. We have developed an expectation maximization algorithm to partition the classes such that there exist no subsets of a class separated by a margin larger than the minimum separation between classes.

Our expectation maximization algorithm attempts to partition the classes into maximally separated subsets as measured by (VIII.2). This algorithm, that we have termed *K-Lists*, is modeled after the K-means algorithm. Although it is suitable for general clustering, here we use it to partition the data into two maximally separated subsets. The algorithm is detailed in Figure 3. There is one important difference between proposed K-Lists algorithm and the K-Means algorithm. Because we are not using the centroid of a cluster as a representative value as in K-Means, but rather the subset itself via the NCD for multisets, we only allow a single element to change subsets at every iteration. This prevents thrashing where groups of elements chase each other back and forth between the two subsets. the algorithm is run until it either can not find any partitions in the data that are separated by more than the maximal inter-class separation, or until it encounters a specified minimum cluster size. This step is computationally demanding, but it is an inherently parallel computation.

For the retinal progenitor cell data and synthetic data sets described in the previous sections, the K-Lists partitioning algorithm was not able to find any subsets that had a larger separation as measured by (VIII.2) compared to the separation between the classes. For the NIST handwritten digits data, the partitioning algorithm was consistently able to find subsets with separation larger than the between class separation. The partitioning was run for a range of different minimum cluster sizes (10%, 20% and 30% of the original class size). This results in multiple distances to each original digit class. Here we included the two minimum distances to each class as input to the ensemble of discriminant classifiers. This resulted in a classification accuracy of for the 30% partition size of 85% [0.83,0.87]. The other two partition sizes had marginally lower classification accuracy. Finally, we combined the two minimal class distances from the partitioned multisets data along with the pairwise spectral distances described above as input to the classification algorithm, resulting in a combined leave-one-out cross validation accuracy of 99.6% correct [0.990,0.998], a significant improvement over the accuracy achieved using either the pairwise or multisets NCD alone. The current state of the art classifier for the MNIST data achieves an accuracy of 99.77% correct [26].

- 1) (Initialize) Pick two elements (seeds) of X at random, assigning one element to each A and B . For each remaining element x , assign x to the closer one of A or B using pairwise NCD to the random seeds
- 2) For each element x , compute the distance from x to class A and B using (VIII.1) and assign to whichever class achieves the smaller distance.
- 3) Choose the single element that wants to change subsets, e.g. from A to B or vice versa and whose change maximizes $NCD_1(AB) - NCD_1(A) - NCD_1(B)$ and swap that element from A to B or vice versa.
- 4) Repeat steps 2 and 3 until no more elements want to change subsets or until we exceed e.g. 100 iterations.

Repeat the whole process some fixed number of times (here we use 5) for each X and choose the subsets that achieve the maximum of $NCD_1(AB) - NCD_1(A) - NCD_1(B)$. If that value exceeds the minimum inter-class separation and the subsets are not smaller than the specified minimum size then divide X into A and B and repeat the process for A and B . If the value does not exceed the minimum inter-class separation of our training data or the subsets exceed the specified minimum size, then accept X as approximately monotonic and go on to the next class.

Fig. 3. Partitioning algorithm for identifying maximally separated subsets For each class (multiset) X , partition X into two subsets A and B such that $NCD_1(AB) - NCD_1(A) - NCD_1(B)$ is a maximum

E. Data, Software, Machines

All of the software and the time sequence data for the RPC fate outcome problem can be downloaded from <http://bioimage.coe.drexel.edu/NCDM>. The software is implemented in C and uses MPI for parallelization. All data compression was done with `bzip2` using the default settings. Data import is handled by a MATLAB script that is also provided. The software has been run on a small cluster, consisting of 100 (hyperthreaded) Xeon and i7 cores running at 2.9 Ghz. The RPC and synthetic classification runs in approximately 20 minutes for each question, while the partitioning and classification of the NIST digit data takes multiple hours for each step.

IX. CONCLUSIONS AND DISCUSSION

Information distance [2] uses the notion of Kolmogorov complexity to identify the metric where the pairwise distance is a quantification of the dominant of all differences between the digital objects. A *normalized* form of information distance, the similarity metric, was developed in [18] allowing the differences to be relative rather than absolute. With a leap of faith the Kolmogorov complexities involved were approximated with real-world compressors. In [4] this led to the NCD, with the real compressors involved required to satisfy certain properties and under this requirement the NCD is shown to be a metric as well. Moreover the evolutionary trees were liberated to hierarchical clustering of general objects. The

NCD uses standard file compression algorithms (*e.g.* `gzip`, `bzip2` or `ppmz`). In [19], it was proposed to extend the idea of information distance to multiple objects, or multisets. The idea of information distance for multisets was studied in [27], where certain properties were shown, including the positive definiteness, symmetry and triangle inequality properties required of a metric. In order to compare the relative rather than absolute differences among objects, a normalized form of this information distance is required. Previous efforts to find such a normalized form that obey the triangle inequality were not successful [27].

Here we present a normalized form of the information distance for multisets and show it to be a metric. This normalized form of information distance is based on the observation that in order to obey the triangle inequality, the distance can never decrease as elements are added to the multiset. The proposed normalized information distance for multisets reduces to the original (pairwise) formulation of normalized information distance as in [18] when applied to multisets of cardinality two. Similar to the original pairwise NCD developed as an approximation to the normalized information distance [4], we developed a practically effective approximation to the normalized information distance for multisets based on file compression algorithms. This NCD for multisets is more computationally demanding than the pairwise NCD but it is straightforward to implement the computations in parallel.

The NCD for multisets is applied to previous applications where the pairwise NCD was used so that comparison is possible. In all these applications it improved the results either alone or in combination with the pairwise version. In some applications, including retinal progenitor cell fate prediction and the analysis of simulated populations of proliferating cells, the new NCD for multisets obtain significant improvement over the pairwise NCD. In other applications such as the NIST handwritten digits, the NCD for multisets alone did not significantly improve upon the result from the pairwise NCD, but a significant overall improvement in accuracy resulted by combining both distance measures. In all cases, we applied the same parameter-free implementation of both the multiple version and the pairwise version of the NCD. That is, no features of the problems were used at all.

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