

# Visualizing the Protein Sequence Universe

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## ABSTRACT

Modern biology is experiencing a rapid increase in data volumes that challenges our analytical skills and existing cyberinfrastructure. Exponential expansion of the Protein Sequence Universe (PSU), the protein sequence space, together with the costs and complexities of manual curation creates a major bottleneck in life sciences research. Existing resources lack scalable visualization tools that are instrumental for functional annotation. Here, we describe a multi-dimensional scaling (MDS) implementation to create a 3D embedding of the PSU that allows visualizing the relationships between large numbers of proteins. To demonstrate the method, we use sequence similarity scores as a measure of proximity. An example of the prokaryotic PSU shows that the low-dimensional representation preserves important grouping features such as relative proximity of functionally similar clusters and clear structural separation between clusters with specific and general functions. The advantages of the method and its implementation include the ability to scale to large numbers of sequences, integrate different similarity measures with other functional and experimental data, and facilitate protein annotation. Transdisciplinary approaches akin to the one described in this paper are urgently needed to quickly and efficiently translate the influx of new data into tangible innovations and groundbreaking discoveries.

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MapReduce, data-enabled life sciences, sequence similarity, computational bioinformatics, protein annotation, protein sequence universe, PSU, COG, UniProt, UniRef, DELSA, multidimensional scaling, data visualization, BLAST, Azure, Sammon, Twister, Hadoop, Needleman-Wunsch, Hive, MPI, EM.

## 1. INTRODUCTION

Functional annotation of newly sequenced genomes and meta-genomes is one of the principal challenges of modern biology. Rapidly advancing sequencing technologies generate peta- and even exabyte scale data, exponentially expanding the PSU (see Table 1) [57, 60, 14]. Assigning functions to this glut of newly sequenced proteins is an immense computational challenge that requires advanced analytical tools and scaling capabilities [64, 67, 56, 52, 51, 44, 41, 59, 39, 29, 43].

Protein functional annotation relies on expert knowledge along with sophisticated statistical and machine-learning methods including pairwise and multiple sequence alignment algorithms [1, 2, 18, 72], structure prediction models [61, 16], motif and domain finding algorithms [65, 4, 19, 53], and clustering methods [70, 31, 34, 73, 46]. Existing information on proteins and their functions is scattered across numerous databases including general resources [5, 7], pathways [32, 71, 11, 54], protein structure [8], protein domains [19, 53], protein families [35, 31, 47, 73, 46, 70] and protein expressions [38].

In life sciences, efficient data exploration and analysis depends upon interactive visualization tools. However, modern resources lack adequate tools to coherently display the

**Table 1: Definitions of keywords and abbreviations used in this paper.**

Abbreviation/Keyword	Definition
ActiveMQ	Apache publish-subscribe environment; <a href="http://activemq.apache.org/">http://activemq.apache.org/</a> .
Apache Hadoop	A software framework that supports data-intensive distributed applications and provides a distributed file system that stores data on the compute nodes, allowing for high aggregate bandwidth across the cluster; <a href="http://hadoop.apache.org/">http://hadoop.apache.org/</a> .
Apache Hive	An open source software designed to run data warehouse-styled operations against large datasets stored in Hadoop Distributed File System. Hive allows projecting an RDBMS-like structure onto the stored data and run queries against those structures using HiveQL language; <a href="http://hive.apache.org/">http://hive.apache.org/</a> .
Azure, Microsoft Windows	Provides on-demand compute and storage to host, scale, and manage applications on the internet through Microsoft datacenters. The NCBI BLAST on Windows Azure is a cloud-based implementation of the NCBI BLAST tool; <a href="http://research.microsoft.com/en-us/projects/azure/azureblast.aspx">http://research.microsoft.com/en-us/projects/azure/azureblast.aspx</a> .
BLAST	A heuristic algorithm which is optimized to identify local alignments with high sequence similarity. After optimal alignments are determined, BLAST calculates a bit score and an e-value for each alignment where the latter considers both the bit score and additional information about search database size and the scoring system <a href="http://blast.ncbi.nlm.nih.gov/Blast.cgi">http://blast.ncbi.nlm.nih.gov/Blast.cgi</a> [1, 2].
COG	Clusters of Orthologous Groups of proteins database developed by NCBI. The database is separated into COGs for prokaryotic genomes and KOGs for eukaryotic genomes; <a href="http://www.ncbi.nlm.nih.gov/COG/">http://www.ncbi.nlm.nih.gov/COG/</a> [69, 70].
DELSA Global	Data-Enabled Life Sciences Alliance International whose mission is to accelerate the impact of data-enabled life sciences research on solutions to the pressing needs of our global society; <a href="http://delsaglobal.org/">http://delsaglobal.org/</a> .
EM	Expectation Maximization is an iterative algorithm used to find maximum likelihood estimators of the underlying distribution for incomplete data or data with missing values.
KOG	Clusters of orthologous groups for eukaryotic genomes; <a href="http://www.ncbi.nlm.nih.gov/COG/">http://www.ncbi.nlm.nih.gov/COG/</a> [70].
MapReduce	A computational paradigm, where the application is divided into many small fragments of work, each of which may be executed on any node in the compute cluster.
MDS	Multidimensional scaling finds a low-dimensional Euclidean representation of data given the matrix of pairwise similarities. The classical MDS estimates the projections so that the relation between the resulting interpoint distances and the original similarities is linear.
MPI	The Message Passing Interface designed for high performance on massively parallel machines and on workstation clusters; <a href="http://www.mcs.anl.gov/research/projects/mpi/">http://www.mcs.anl.gov/research/projects/mpi/</a> .
NW	Needleman-Wunsh dynamic programming algorithm is used to find the highest-scoring global alignment of two sequences.
PlotViz	A visualization software developed by SALSA group at Indiana University; <a href="http://salsahpc.indiana.edu/plotviz/">http://salsahpc.indiana.edu/plotviz/</a> [62].
PSU	Protein Sequence Universe is the totality, or the aggregate, of all the protein sequences that exists in nature. PSU is also an interactive visualization framework with scalable software architecture. When developed the framework will allow users to explore, browse, analyze, and visualize protein data; <a href="http://manxcatcogblog.blogspot.com/">http://manxcatcogblog.blogspot.com/</a> .
Sammon's loss	A cost function for nonlinear MDS with an emphasis on preserving small distances [63].
Sequence similarity	A score that gives the degree of matching between the two compared sequences. The examples include BLAST, NW and Smith-Waterman scores.
Twister	An open source implementation of Iterative MapReduce that supports more efficient and broader range of communication collectives (including reduce, gather, and broadcast in an MPI language) in the Reduce phase of MapReduce; <a href="http://www.iterativemapreduce.org/">http://www.iterativemapreduce.org/</a> .
UniProt	The Universal Protein Resource for protein sequence and annotation data; <a href="http://www.uniprot.org/">http://www.uniprot.org/</a> .
UniRef	The UniProt Reference Clusters database that groups members based on sequence similarity. UniRef is composed of the distinct databases UniRef100, UniRef90, and UniRef50, that have 100%, 90%, and 50% sequence similarity, respectively, within protein clusters and reduce the UniProt database size by approximately 10%, 40%, and 70%, respectively. Each cluster contains one reference sequence and all proteins within the similarity threshold to the reference. UniRef retains annotation from all members of the protein cluster to prevent information loss; <a href="http://www.ebi.ac.uk/uniref/">http://www.ebi.ac.uk/uniref/</a> .

vast amount of information across large sets of proteins. The data are typically analyzed on the experiment level and in the context of known relationships, e.g. pathways, complexes. Tools for pathway and network visualization (e.g. Ingenuity or Biobase) consider neither sequence information nor extend to the entire PSU.

Functional annotation and analysis is typically done on a gene-by-gene (protein-by-protein) basis. While the ‘manual’ approach is feasible for a small group of proteins, it quickly becomes unsustainable as the volume of sequences expands [22, 6]. Furthermore, in functional and comparative genomics approximately 30% of proteins in any newly sequenced genome have unknown function [10, 41, 39, 40, 23, 44]. This barrier remains relatively constant as more new organisms are sequenced. Combining this problem with the influx of data from novel sequencing technologies creates an ever expanding backlog of un-annotated proteins, or so called “hypothetical” proteins [10, 45, 41, 39, 23]. In addition, there is a growing number of databases that are no longer supported or updated including some of the most popular protein family resources like the Clusters of Orthologous Groups database (COG; see Table 1, [70]), SYSTERS [46], and CluStr[47].

The size and complexity of data from high-throughput technologies requires the methods to cohesively integrate information on protein expression, pathways, structure and functional annotation across different experiments, organisms and conditions, and to put these data into context with sequence information [38]. Comprehensive functional annotation of large scale data and the ability to generate new research directions fully depend on the wide range of skills and tools including expert knowledge, manual curation, compute power, analytic methods with scaling capabilities, and new transdisciplinary collaboration models between computer- and life scientists.

To demonstrate the complexities of protein annotation, we completed the first of a kind all-versus-all sequence alignment for 9.9 million proteins in the UniRef100 database (Table 1, [68]) [44]. The alignment was done on the Microsoft Windows Azure cloud system (Table 1, [17]) with 475 eight-core virtual machines that produced over 3 billion filtered records in six days. Using the normalized alignment score, we have assigned 68% of 5.1 million bacterial proteins into clusters from the COG database [44]. The remaining proteins were classified into functional groups using an innovative implementation of a single-linkage algorithm on a Hadoop compute cluster using Hive and the MapReduce paradigm (Table 1). This implementation significantly reduced the run time for non-indexed queries and optimized clustering performance [44]. Consequently, nearly 2 million proteins were agglomerated into half a million functional groups. Similarly, the eukaryotic database was expanded by over 1 million proteins with unclustered proteins classified into 100,000 new functional groups [44].

The UniRef100 clustering project showcased both the promise and the challenges of protein annotation. In particular, it has demonstrated that, in view of the exponential growth of data, a clustering approach is computationally advantageous because it can facilitate the annotation of large numbers of proteins [70, 31, 34, 73, 46, 44]. However, the project took the considerable efforts of a diverse group of researchers along with multiple cloud systems to successfully complete the task. Publicly available cluster resources are struggling

to cope with the influx of data and, as a result, are either no longer supported [70, 47, 46] or provide limited interactive and analytic capabilities [31, 35]. These problems highlight the pressing need in the biological community for a scalable and efficient computational approach to visualize, explore and assign functional annotations to new proteins.

Functional annotation of protein sequences, especially on the scale of the entire PSU, is one of the unsurmounted hurdles toward comprehensive understanding of life and medical cure. An accurate, sustainable, large-scale method for functional annotation demands focused and concentrated efforts of experts from multiple scientific fields. Given the scale of data and the range of skills required to translate it to knowledge to action, scientists forge alliances to leverage resources and expertise across different disciplines [55]. This drive for collective innovation in data-enabled sciences translates into community efforts such as DELSA Global, the Data-Enabled Life Sciences Alliance International (see Table 1) [55, 37, 44, 43, 42]. The goal of the newly founded transdisciplinary alliance is to create a synergy between the computer science and life-sciences to tackle modern biological challenges through best computational practices and advanced cyber-infrastructure.

In this paper, we propose a visualization tool to explore the structure of the protein space and relationships between the proteins. The visualization is based on the MDS approach (Table 1) that uses a parallel implementation on a multigrid platform with Iterative MapReduce, the standard Message Passing Interface (MPI; see Table 1), and threading. The MDS approach is a form of low-dimensional embedding, similar to principal component analysis, independent component analysis, principal coordinate analysis, spring embedding, feature selection and others [24, 30, 27]. While low-dimensional representation of data has been widely used by scientists, existing methods neither address large-scale biological problems nor do they offer sustainable, affordable means to cope with the influx of new information. The proposed PSU tool provides interactive, exploratory means to examine complex biological data both independently and in the context of the existing information. The low-dimensional representation allows visualizing the vastness of the PSU, its structure and complexity on a variety of scales and in different domains.

To demonstrate the performance of the method, we apply it to the COG data creating a 3D projection of the prokaryotic PSU. Prokaryotes are one of the four major biological kingdoms. Despite lack of support, the COG database remains one of the most popular scientific resources (over 6K citations according to Google Scholar). The resulting PSU can be further integrated with functional, experimental, structural, environmental and other data. Most importantly, the implementation allows for new experimental data to be mapped into the existing universe using interpolation. Interpolation allows for efficient expansion of the PSU, a feature that is essential for large-scale data. For example, the prokaryotic PSU can be efficiently updated and expanded as the new data come in. The exa-scale of data in the PSU requires cutting-edge technologies, advanced cyber-infrastructure, transdisciplinary collaboration and a wide range of skills and expertise. This work represents an example of the potential impact DELSA Global could have to solve large-scale biological problems.

In what follows, we describe the MDS method and use

100,000 sequences to create the 3D rendering of the prokaryotic PSU. We briefly describe the data, outline the implementation and discuss the results. We then elaborate on the application and merits of the proposed approach to the functional annotation of new protein data.

## 2. MATERIALS AND METHODS

### 2.1 COG Database

A major principle of molecular evolution is that functionally important proteins tend to be conserved across species. The COG database was developed by the National Center for Biotechnology Information (NCBI) [70]. The project constructed clusters of proteins from 66 prokaryotic and seven eukaryotic genomes. For each protein, the best aligned protein in every other genome was determined using a sequence similarity search [1]. If three proteins from three organisms were mutual best hits, they created a triple. COGs are the result of exhaustive, successive merging of triples with two common members. Manual curation of the clusters was done by experts to ensure correct grouping and functional annotations. The COG database is separated into COGs for prokaryotic genomes and KOGs for eukaryotic genomes (see Table 1) [69, 70]. According to Google scholar, COG project is one of the most popular protein resources with approximately 4.5K citations. However, the database was last updated in 2008 and is not currently maintained.

In this paper, we are using the COG database of prokaryotic genomes that we will refer to as COGs. We have selected a sample of 100,000 proteins from well-characterized COG clusters.

### 2.2 UniRef Databases

UniRef is composed of three databases UniRef100, UniRef90, and UniRef50, which have 100%, 90%, and 50% sequence similarity (see Table 1), respectively, within protein clusters and reduce the UniProt database size by approximately 10%, 40%, and 70%, respectively. Each cluster contains one reference sequence and all proteins within the similarity threshold to the reference. UniRef retains annotation from all members of the protein cluster to prevent information loss [5, 68].

### 2.3 Multi-Dimensional Scaling

The MDS algorithm was used to project the protein sequence similarity data into a low-dimensional space [13, 48]. The method has an  $\mathcal{O}(n^2)$  computational complexity to map  $n$  sequences into 3D. It can be heuristically solved in several ways including the expectation maximization (EM) [9, 49, 12] and Newton’s method (see Table 1) [33]. Here, we used Sammon’s loss function [63] (see Table 1) given by

$$H = \sum_{\substack{i,j=1 \\ i < j}}^n \frac{(f(\delta_{ij}) - d(x_i, x_j))^2}{f(\delta_{ij})}, \quad (1)$$

where  $\delta_{ij}$  is the dissimilarity measure between sequences  $i$  and  $j$  and  $d$  is the Euclidean distance between the corresponding 3D projections  $x_i$  and  $x_j$ . Function  $f$  in equation (1) is a monotone transformation of dissimilarity measure. The denominator term in (1) ensures a larger contribution from smaller dissimilarities thus making the clustering structure of the data more apparent. We used a highly robust

implementation of the nonlinear minimization with Levenberg - Marquardt algorithm to regularize Newton’s equations [50].

The transformation  $f$  is chosen heuristically to increase the ratio of standard deviation to mean for  $f(\delta_{ij})$  and to increase the range of dissimilarity measures. For example, if  $f$  is an identity, the high dimensional data will essentially be projected onto the surface of a 3D structure, which lowers the utility of the mapping.

### 2.4 Implementation

We used a scaling, parallel traditional MPI with threading intranode for MDS implementation [20]. In the Reduce phase of MapReduce, we used Twister (see Table 1) [72, 74, 15]. In Twister, all communication avoids using intermediate disk and is built around ActiveMQ (see Table 1) in Java Twister and around Azure primitives in the Microsoft cloud.

The method was applied to obtain a 3D projection of 100,000 sequences from well-characterized COGs in prokaryotic PSU. Here, we chose sequence alignment scores as a proximity measure. Pairwise distances were calculated using an MPI implementation of the Needleman-Wunsch (NW, see Table 1) alignment algorithm. The NW algorithm was realized by a parallel computation on the 24-core node system. The efficiency of the parallel distance computation was less than that of MDS due to saturation of memory bandwidth.

Further, we applied a monotone square-root transformation to the pairwise NW distances. To map the data into a 3D Euclidean space, we fed the transformed distances into an MPI implementation of the nonlinear MDS [36]. The resulting 3D projections were visualized in PlotViz (see Table 1) [62]. The calculations were performed on a 768 core Microsoft HPC cluster.

The NW distance calculation required one day to complete and the MDS job ran for three days. The parallel efficiency of the code was approximately 70% based on earlier studies that discuss both the inter-node and intra-node cases and find that it is essential to adopt a hybrid model with intra-node threading and MPI between nodes [20, 58, 21]. The transformation was chosen heuristically to reduce the formal dimension of distance data (in this case, from 244 with original  $\delta_{ij}$  to 14 for  $f(\delta_{ij})$  after mapping), which allows for a more uniform coverage of the target Euclidean space by the MDS projections.

The COG data was downloaded from the NCBI site. All software used to analyze and visualize the data is an open source. The results of the MDS analysis including estimated coordinates, parameters and captures are available at <http://manxcatcogblog.blogspot.com/>.

## 3. RESULTS

Figure 1 shows the 3D rendering of the prokaryotic PSU. Each point represents a particular sequence. The axis orientation is shown in the left bottom corner. The figure shows the complexity of the PSU and the presence of distinct grouping structure. We color-coded eleven COG clusters in Figure 1 so one could appreciate the diversity of the underlying protein groups with respect to their location, shape, dispersion and size. While some clusters are rather tight, others are scattered throughout a sizeable domain. For example, compare the tight COG0333 cluster of ribosomal protein L32 with the diffuse COG0454 (HPA2) and COG0477 (Permeases of the major facilitator superfamily); see also

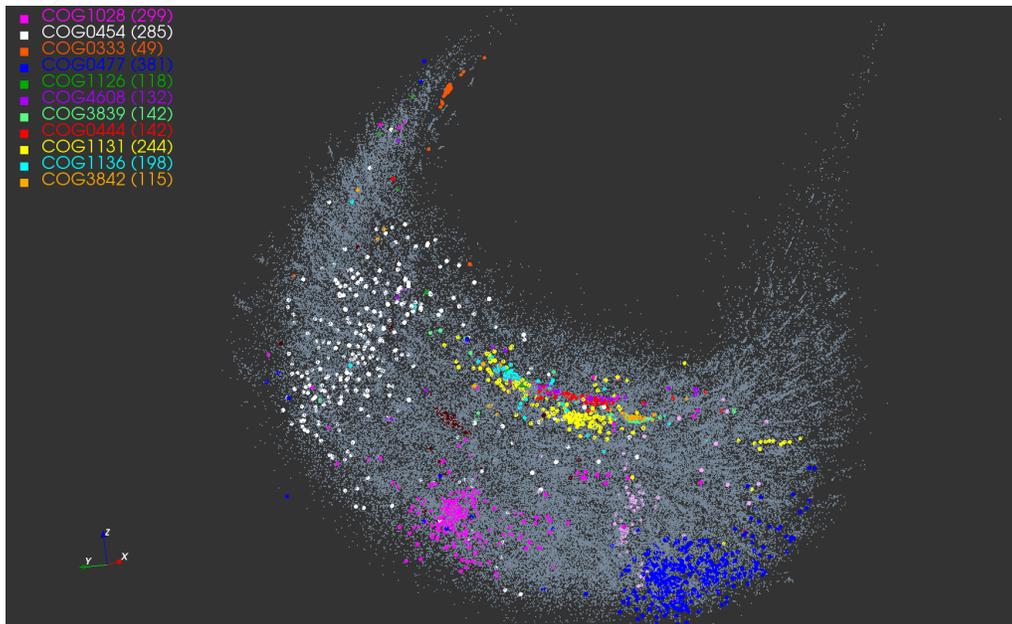


Figure 1: MDS representation of the 100,000 sequences from well-characterized COGs in prokaryotic PSU. Each point represents a protein sequence. Eleven COG clusters were color-coded as marked in the legend. The number of proteins in each cluster is given in parentheses.

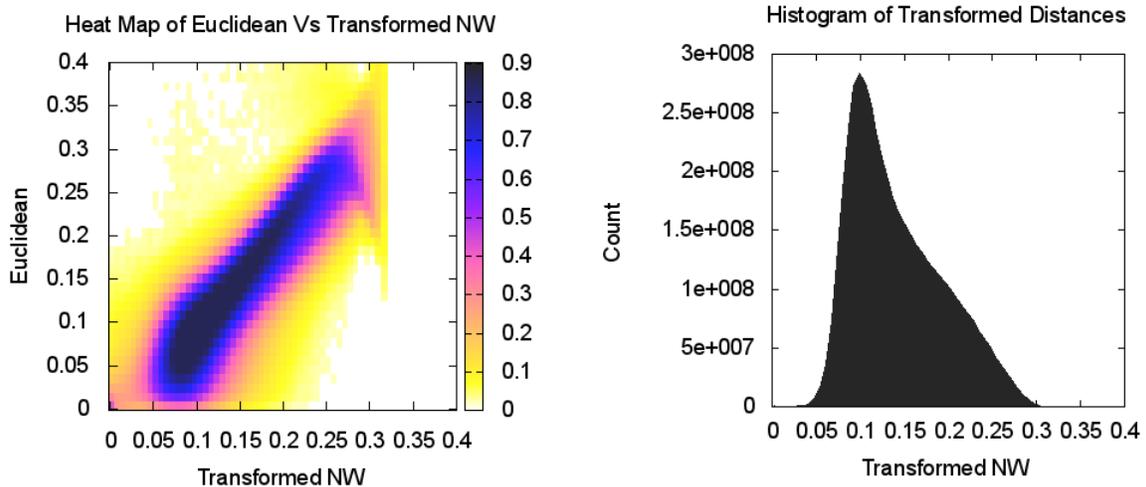
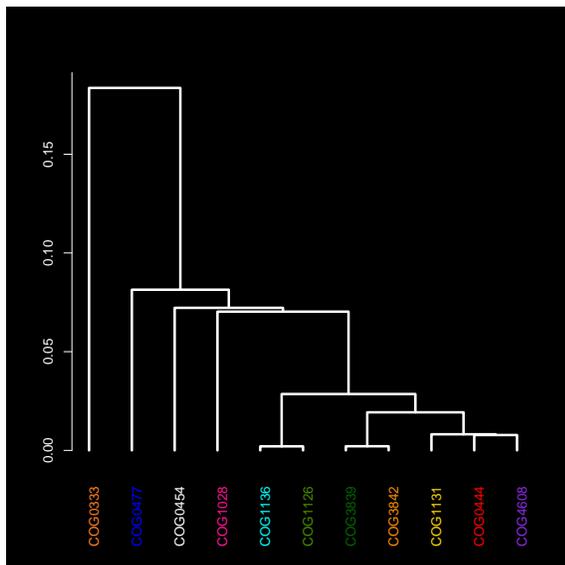


Figure 2: (left) The heatmap of the transformed NW distances versus the Euclidean distances between the MDS projections and (right) the histogram of transformed NW distances for all 100,000 COG proteins.

**Table 2: Annotations for COG clusters shown in Figures 1 and 4.**

COG	Annotation	Size	UniRef
COG1131	ABC-type multidrug TS, ATPase comp.	244	14,406
COG1136	ABC-type antimicrobial peptide TS, ATPase comp.	198	7,306
COG1126	ABC-type polar amino acid TS, ATPase comp.	118	4,061
COG3839	ABC-type sugar TSs, ATPase comp.	142	4,121
COG0444	ABC-type di-/oligopeptide/nickel TS, ATPase comp.	142	3,520
COG4608	ABC-type oligopeptide TS, ATPase comp.	132	3,074
COG3842	ABC-type spermidine/putrescine TSs, ATPase comp.	115	3,665
COG0333	Ribosomal protein L32	49	1,148
COG0454	Histone acetyltransferase HPA2 & related acetyltransf.	285	14,085
COG0477	Permeases of the major facilitator superfamily	381	48,590
COG1028	Dehydrogenases with different specificities	299	37,461



**Figure 3: The dendrogram tree of the cluster centroids. The cluster labels are color-coded as in Figure 1.**

**Table 2.**

Recall that in MDS, the goal is to create a low-dimensional representation of a high-dimensional space while preserving the similarity measures. Hence, given the choice of the similarity measure, the proximity of two points in the 3D representation in Figures 1 and 4 implies the similarity of the corresponding protein sequences as measured by the NW scores. High intensity values along the diagonal in Figure 2 (left) show a strong correlation between the NW distances and the distances based on MDS projections. The excess of points with mapped distances less than original values can be traced to equation (1) where the denominator depends on the original rather than mapped distances. Consequently, clusters that appear tight in 3D can be thought of as consisting of similar sequences, in NW sense. Similarly, scattered clusters imply greater variability of NW alignments between the proteins in the same cluster. Spatial proximity of clusters indicates the similarity of the sequences across these clusters. Note that the histogram of NW distances in Figure 2 also shows a lack of spatial separation between the clusters.

For the eleven color-coded COG clusters in Figure 1, we computed the centroids of their respective MDS projections. The dendrogram tree in Figure 3 shows the relative proximity of the cluster centroids to each other. Out of the eleven selected clusters, COG1131 (yellow) and COG1136 (cyan) are the tightest with respect to the mean intra-cluster distance. These two clusters are a part of a group that includes seven COGs in all; see right branch of the dendrogram. The other four COGs 1028, 0333, 0477, 0454 appear to be less similar to this group of seven or to each other.

The magnified view in Figure 4 details the neighborhood structure of the COG1131 and COG1136 showing five more COGs lying in close proximity. Remarkably, all seven clusters are functionally similar and correspond to the ABC-type transport system, ATPase component (see Table 2). The heatmap shows a good agreement between the NW distances and MDS projections for the seven selected clusters; see Figure 5.

From the biological standpoint, the spatial features of the MDS projection of sequence alignment scores conform well to the clusters' functions. For example, a tight COG3839 cluster contains 142 protein sequences of the sugar transport systems that are similar both in function and composition. Similarly, COG1126 of the polar amino acid transport system proteins with very specific functions appears as a very tight cluster. In turn, the apparent diffusivity of COG1131 can be explained by the fact that 244 multidrug transport system proteins that compose the cluster differ in amino acid composition and functional mechanisms. The inter-cluster distance of the 3D projections reflects the similarity between protein sequences in the corresponding clusters. For example, the two oligopeptide transport systems, COG4608 and COG0444, have similar shape and are located in close proximity to one another. The example of the COG data clearly demonstrates that MDS can effectively create a 3D projection of the PSU while preserving the fundamental grouping structure.

As mentioned, in our previous work we used all-versus-all alignment of 10 million UniRef100 proteins to populate the existing COG clusters [44]. The last column in Table 2 shows the number of UniRef100 proteins added to each of the eleven clusters from Figure 1. Notably the most diffuse clusters show the greatest expansion.

## 4. DISCUSSION

Functional protein annotation is one of the most impor-

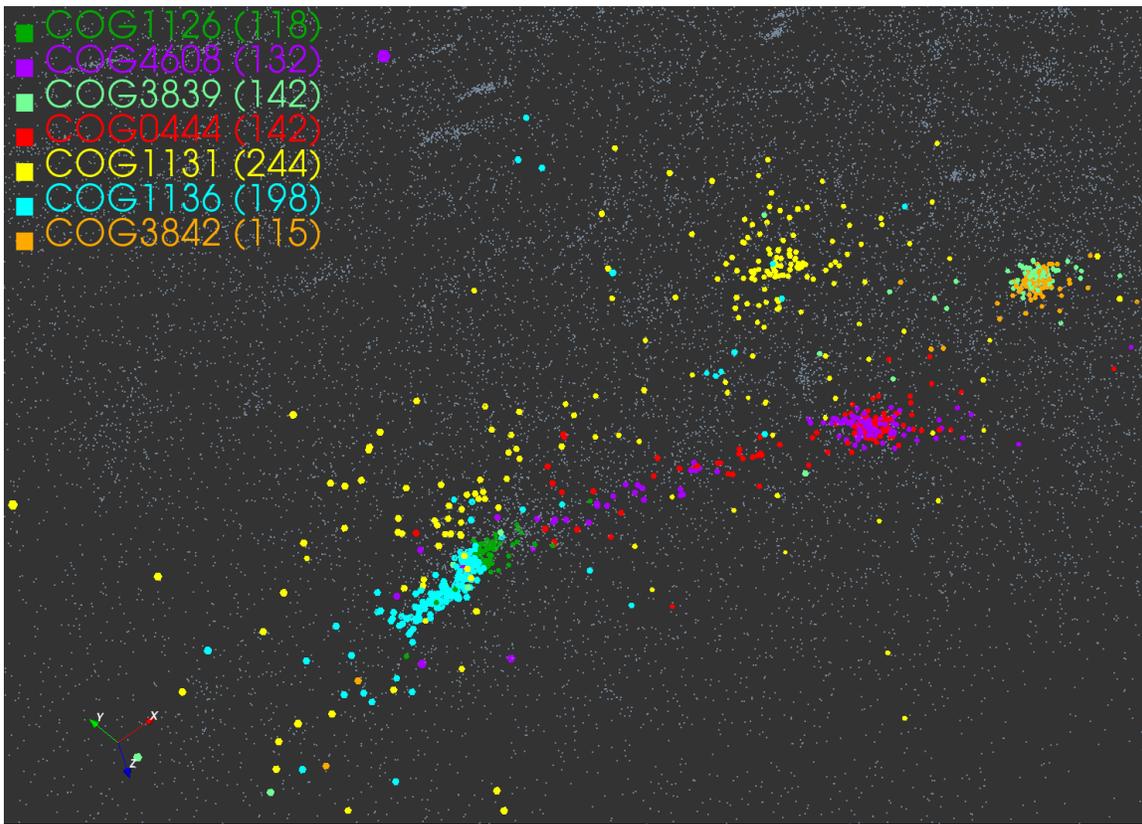


Figure 4: Magnified version of the prokaryotic PSU showing the seven functionally similar COG clusters from Figure 1.

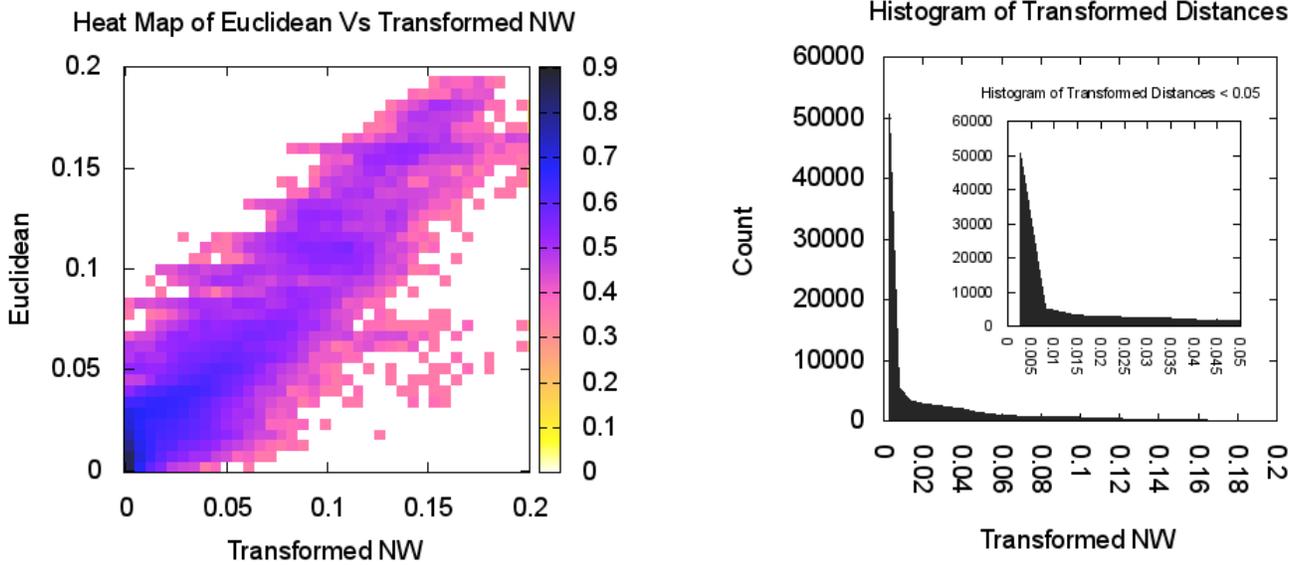


Figure 5: (left) The heatmap of the transformed NW distances versus the Euclidean distances between the MDS projections and (right) the histogram of transformed NW distances for the seven COG clusters shown in Figure 4. The inset in the top right corner shows the distribution for the distances below 0.05

tant and resource-intensive challenges in biology [6]. The rapid influx of data from newly sequenced genomes together with the limited number of annotation experts creates a major bottleneck, stalling scientific advances. The number of sequenced genomes is poised to increase in the next five years. The Earth Microbiome Project alone is expected to sequence 500,000 microbial genomes, which will contain on the order of 1.5 billion protein sequences and half a trillion amino acids [14]. This is well over a 100-fold increase in the number of sequenced microbial genomes and proteins currently contained in GenBank. The i5K Insect and other Arthropod Genome Sequencing Initiative plans to sequence the genomes of 5,000 insects and related species over the next five years, yielding nearly 100 million new protein sequences [60]. Assigning functions to this glut of newly sequenced proteins is an immense scientific challenge.

Large-scale annotation projects require expert knowledge, manual curation, significant compute power, a wide spectrum of analytic tools with scaling capabilities, and new collaboration models between computer scientists and biologists. Low-dimensional representation of data and interactive visualization tools would substantially aid functional annotation efforts, allow generating new hypotheses and provide new research directions.

The exploratory MDS tool allows interactive visualization of dependencies between a large number of proteins. Currently existing methods address large-scale biological problems or offer sustainable, affordable means to cope with the influx of new information. A low-dimensional MDS projection of biological data allows dynamic, interactive exploration that is a mandatory precursor to statistical modeling. The projection provides a unique perspective on the structure of data and can be integrated with information on function, pathways, structure, and environment, enabling analysis across domains of interest. The MDS approach can be readily adapted to incorporate a composite similarity measure based on different types of proximities and biological information [1, 66, 25]. The parallel MDS implementation used here was developed to handle large-scale data. Furthermore, the newly developed MDS interpolation methods allow for quick mapping of sequences into the existing projection space. The interpolation runs in  $\mathcal{O}(n)$  time after an initial MDS embedding with the  $\mathcal{O}(n^2)$  approach [3]. Given the ever increasing volumes of data from new sequencing technologies, this feature is essential as it facilitates prompt integration of large scale data while avoiding significant computational costs. In the future, we intend to explore the merits of our new MDS implementation that incorporates deterministic annealing into the EM approach. The deterministic annealing helps achieve significantly better results with little increase in execution time [36].

The challenges associated with the functional annotation of newly sequenced genomes cannot be solved by the life sciences community alone. A successful and sustainable solution requires a new, trans-disciplinary approach that would leverage and adopt the most prominent advances of modern sciences. This turn to collective innovation in data-enabled sciences is essential for truly ground-breaking medical discoveries and advances in public health. Scientific alliances like DELSA Global stand to harness the essential diversity of skills and expertise, thus quickly and efficiently translating the influx of new data into tangible innovations and groundbreaking discoveries [55, 37, 43, 42].

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