Topological Classification of SCOPe

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Abstract

Motivation: SCOPe 2.07 is a database of 276,231 protein domains that have been partitioned into varying folds according to their shape and function. Since a protein's fold reveals valuable information about it's shape and function, it is important to find a mapping between protein's and it's fold. There are existing techniques to map a protein's sequence into a fold [2] but none to map a protein's shape into a fold. We focus on the topological features of a protein to map it into a fold. We introduce several new techniques that accomplish this.
Results: We develop a 2D-convolutional neural network to classify any protein structure into one of 1232 folds. We extract two classes of input features for each protein's carbon alpha backbone: distance matrix and the persistent homology barcodes. Due to restrictions in our computing resources, we make sample every other point in the carbon alpha chain. We find that it does not lead to significant loss in accuracy. Using the distance matrix, we achieve an accuracy of 86% on the entire dataset.

We extract significant topological simplices of the protein by using persistent homology. We format the persistent homology data into various input features: persistence images [1], simplex distance map, and simplex grouping. With persistence images of 100x100 resolution, we achieve an accuracy of 62% on SCOP 1.55. With simplex distance maps of 100x100 resolution, we achieve an accuracy of 70%. With simplex groupings, we achieve an accuracy of :TODO%.

1 Introduction

Structural Classification of Proteins (SCOP) is a database of protein structural relationships. The proteins are placed in an hierarchy in relative to their to structural and evolutionary relations [4]. SCOP was initially manually curated ordering of proteins [4]. However, as many numerous proteins continue to be discovered at a rapid pace, a need for an automatic method of classification became necessary.

Sequence based classification using deep convolutional neural networks like DeepSF

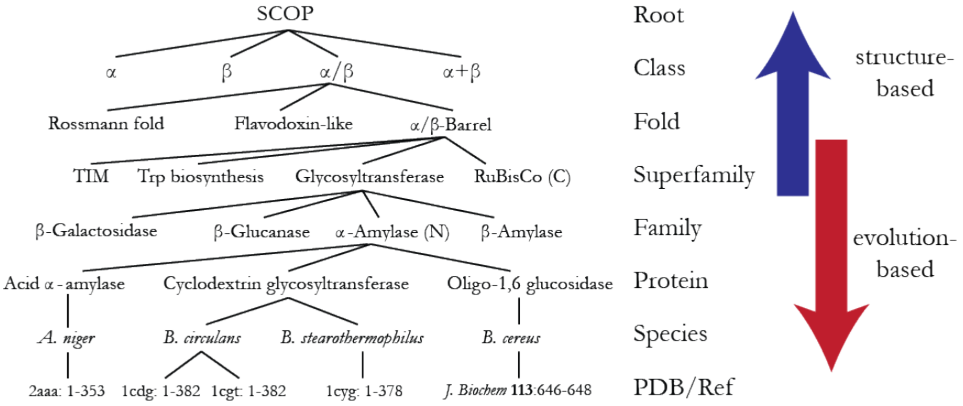


Figure 1: A partial view of the SCOP hierarchy.

show that it is possible to predict protein fold with an acurracy up to 75.3% [2]. Structural Classification of Proteins - extended (SCOPe), extends the original SCOP database by using these types of rigorously validated automated methods to classify newly discovered proteins [4].

Similar to taxonomy, SCOP was created as a hierarchy with a basis in evolutionary relationships. Species, protein, family, and superfamily, the lower levels of the SCOP hierarchy represent the evolution-based relationships between the proteins. SCOP characterizes each of these levels with the following description [4].

- **Species** representing a distinct protein sequence and its naturally occurring or artificially created variants.
- **Protein** grouping together similar sequences of essentially the same functions that either originate from different biological species or represent different isoforms within the same species
- **Family** containing proteins with similar sequences but typically distinct functions
- **Superfamily** bridging together protein families with common functional and structural features inferred to be from a common evolutionary ancestor.

Fold and class, the higher levels in our hierarchy as classified based on the similarity of structure and not necessarily evolutionary similarities [4].

- **Folds** grouping structurally similar superfamilies.
- **Classes** based mainly on secondary structure content and organization.

The highest level of the hierarchy, class, consists of 7 categories. Alpha proteins (a), beta proteins (b), alpha/beta proteins (c), alpha+beta proteins (d), multi-domain proteins (e), membrane and cell surface proteins and peptides (f), and small proteins (g). Class (f) and (g)'s name are descriptive of their members. The original SCOP publication clarifies the members of class a-e [**?**]SCOP).

- **Alpha proteins** For proteins whose structure is essentially formed by a-helices.

- **Beta proteins** For those whose structure is essentially formed by b-sheets.

- **Alpha/Beta proteins** For proteins with a-helices and b-strands that are largely interspersed.

- **Alpha+Beta proteins** For those in which a-helices and b-strands are largely segregated.

- **Multi-domain** For those with domains of different fold and for which no homologues are known at present.

Many works have been done on using the protein sequences and their evolutionary relationships with each other to predict the protein hierarchy. This is primarily due to the lack of structural information for newly discovered proteins.

In this paper, we shift the focus from a protein's sequence to the topological structure to predict the protein's fold and class. We expect the shift in focus to be quite successful in classifying the protein class and fold since these levels have been curated based on the similarity of structures between the proteins.

Since each fold belongs to only one class, predicting the protein fold also predicts the protein's class. Thus, we narrow the focus of our problem to predicting a protein's fold.

We introduce two methods for classifying protein fold. First, we use a distance matrix as an input feature to a convolutional neural network. Second, we use persistent homology to extract topological features of our data and plot these features as an input feature to a convolutional neural network.

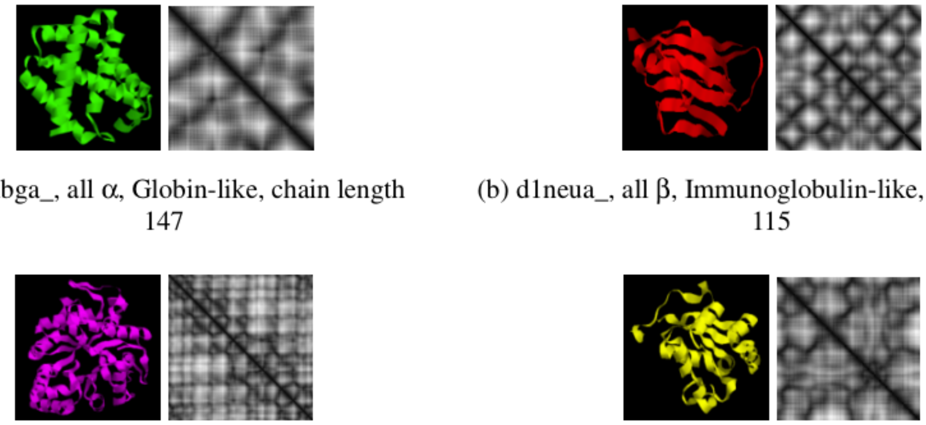
Distance Matrix

Each protein has a backbone structure that is formed by series of connecting points. The backbone structure of the protein is characteristic of the protein's general shape. A distance matrix of the protein's backbone is created, where the rth row and cth column of the matrix gives the distance between the rth point and the cth point of the protein backbone. Then this matrix is used as an input to our convolutional neural network.

There has been existing work (Fast SCOP Classification) on using the distance matrix to classify proteins from a very small subset of SCOP database [6] of 698 proteins. The distance matrix is computed for the protein and fed into a multi-class support vector machine (SVM) of the One-Versus-One (OVO) variant. This approach achieved and accuracy of 74.55% on this small subset of SCOP.

We take a look at few of the representative proteins from alpha proteins, beta proteins, alpha/beta proteins, and alpha+beta proteins. We juxtapose each protein's distance matrix to the protein's structure to see if there are significant differences between the classes. We see that the distance matrices do represent the alpha helices, the beta sheets, and also the relationship between these features.

Fast SCOP Classification extracts regions of interest (ROI) from the distance matrix by decomposing the upper triangle of the distance matrix into ROI. These regions attempt to capture the regions of the distance matrix where there are alpha helices


(a) d1hbga_, all α, Globin-like, chain length 147

(b) d1neua_, all β, Immunoglobulin-like, chain length 115

(c) d1ghra_, α/β, TIM-barrel, chain length 306

(d) d1npka_, α+β, Ferredozin-like, chain length 150

Figure 2: A comparison of the distance matrix from the proteins of different classes. We see that the distance matrix is able to pick up on characteristic alpha helix and beta sheets of each protein, making it likely that this feature will perform well.

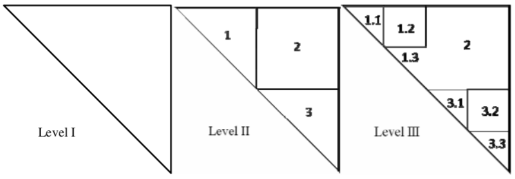


Figure 3: Fast SCOP Classification decomposing the upper triangle of a distance matrix into regions of interest (ROI) to extract important features such as alpha helices and beta sheets.

and beta sheets. The relationships between these regions of interest are abstracted into a feature set which is given to the SVM for fold classification.

In comparison, our method uses a convolutional neural network to have our model learn the ROI on it's own. The CNN has much more advantages over the decomposition method because complex relationships between regions of interest can be modeled by the hidden layer and also the regions of interests are dynamically formed as the model is trained. Furthermore, there aren't supervisions into constructing the high-level feature set of ROIs, allowing the model to learn complex behaviors that may elude or be difficult to define clearly. However, a downside to the CNN is that it is very computationally intensive, requiring a long training time and a large set of data to learn effectively.

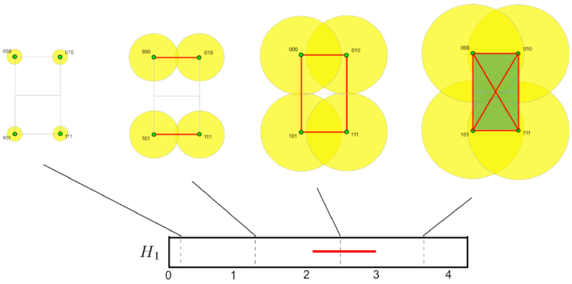


Figure 4: Here is persistent homology characterizing the point cloud of four points. We see that a rectangular cycle is formed when the 4 boundary edges of the rectangles are formed at $\epsilon = 2.6$. We see that this rectangular cycle is dies at $\epsilon = 3.4$

Persistent Homology

Persistent homology is a mathematical theory from algebraic topology that allows the characterization of a point cloud by the observing creations of cycles in the data and how long these cycles persist. We iterate over a real number variable, ϵ, and connect the edges in our point cloud whose length is smaller than ϵ.

A cycle is formed when a closed loop is formed by the path of the edges. In the example with 4 points (Fig.4), a cycle is formed when the four edges of the rectangle's boundary is formed. The ϵ value at which the cycle is formed is called the *birth* of this cycle. This cycle is destroyed when triangles a formed within our cycle to completely fill it in. The ϵ value associated with the cycle being filled in is called the *death* of the cycle. We say that the cycle persists for a duration of $birth - death$. Each cycle forms an interval, $[birth, death]$. The collection of all intervals from the cycles in the data is called a barcode.

There has been existing attempts at using Persistent Homology to classify the highest level of SCOP hierarchy [**?**]. Cang applies persistent homology on a small set of 900 proteins selected from Alpha, Beta, and Alpha/Beta classes. Each class is represented by 300 proteins and 60 proteins were selected for testing. A SVM is used to classify the classes with with an average accuracy of 85%.

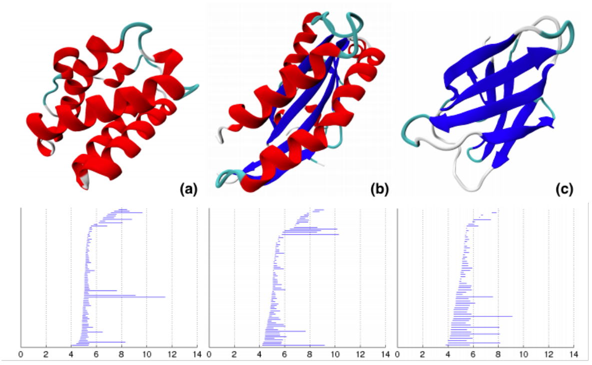


Figure 5: Here is persistent homology characterizing the point cloud of four points. We see that a rectangular cycle is formed when the 4 boundary edges of the rectangles are formed at $\epsilon = 2.6$. We see that this rectangular cycle is dies at $\epsilon = 3.4$

When we observe the barcode of the proteins from the different classes we do see some distinguishing patterns. scopHom

2 Material

2.1 Datasets

The SCOP database is a database of proteins organized into hierarchical classes based on their shape and function. There are 4 levels of the important hierarchy (top down): Class, Folds, Superfamily, Family.

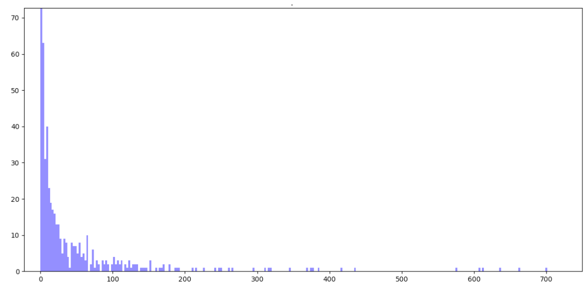


Figure 6: Here is a histogram of the number of proteins per fold for SCOP 1.55. We see that most of the folds do not have too many proteins. This could be a potential issue during learning.

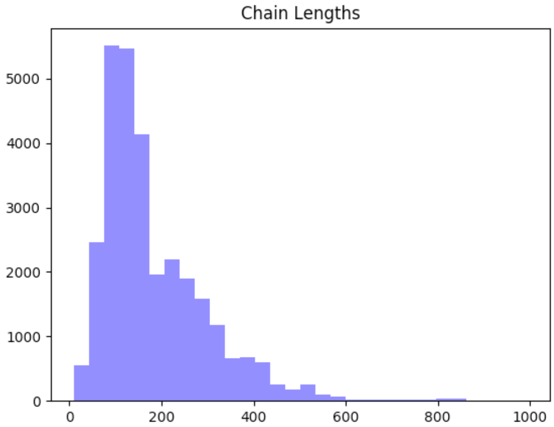


Figure 7: Here is a histogram of the protein lengths for SCOP 1.55. We see that 90% of the proteins have length less than 500

We will be primarily concerned with the Fold.

Two different versions of the dataset were used, SCOP 1.55 and SCOPe 2.07. SCOP 1.55 is a smaller dataset which is a subset of SCOPe 2.07, a larger and more recent dataset. SCOP 1.55 [Ref: Biblio] and SCOPe 2.07 [Ref: Biblio] were downloaded from the Berkeley repository as tar files and unpacked. For each of the datasets, index files [Ref:Biblo] are provided.

2.1.1 Small Dataset SCOP 1.55

SCOP 1.55 is a dataset of 31,474 proteins that have been organized into 7 Classes, 605 Folds, 947 Superfamilies, and 1557 Families. The dataset was released and updated till 2001. This dataset is a subset of the SCOPe 2.07 dataset.

We inspect the distribution of the proteins across the different folds. We see that most of the folds do not have a lot of proteins. The median number of proteins per fold was 10 and the histogram (Fig.5) show that most of our proteins have less than 50 proteins per fold. This would likely impact our learning, since there are not too many examples for the protein to learn.

We also inspect the size of the proteins in our database (Fig. 6). We define the size of the protein to be the length of the protein (Background Information: Proteins Information). We see that most of the proteins have length less than 300. We do see a small amount of our proteins having lengths between 600 to 800.

We split up 70% of the dataset for training, 15% for validation and 15% for testing. We adjust the sampling of the validation and testing so that a wide range of folds are represented.

New methods were tested on the small dataset. This allowed us to quickly prototype and optimize our methods to run on the larger dataset.

Class	Number of folds	Number of superfamilies	Number of families
a. Alpha proteins	138	224	337
b. Beta proteins	93	171	276
c. Alpha and Beta proteins (a/b)	97	167	374
d. Alpha and beta proteins (a+b)	184	263	391
e. Multi-domain proteins (alpha and beta)	28	28	35
f. Membrane and cell surface proteins and peptides	11	17	28
g: Small proteins	54	77	116
Total	**605**	**947**	**1557**

Table 1: SCOP 1.55 statistics of 13228 PDB entries

Class	Number of folds	Number of superfamilies	Number of families
a. Alpha proteins	289	516	1062
b. Beta proteins	178	370	968
c. Alpha and Beta proteins (a/b)	148	246	986
d. Alpha and beta proteins (a+b)	388	565	1338
e. Multi-domain proteins (alpha and beta)	71	71	118
f. Membrane and cell surface proteins and peptides	60	119	173
g: Small proteins	98	139	274
Total	**1232**	**2026**	**4919**

Table 2: SCOPe 2.07-stable statistics of 87224 PDB entries sorted.

2.1.2 Large Dataset SCOPe 2.07

SCOPe 2.07 is a database of 276,231 proteins that have been organized into 7 Classes, 1232 Folds, 2026 Superfamilies, and 4919 Families. The dataset was released and updated till 2017. This dataset contains and is about 9 times larger than the SCOP 1.55 dataset.

We inspect the distribution of the proteins across the different folds. We see that there are much more proteins per fold.

Once again, we inspect the size of the proteins in our dataset.

Similar to the small dataset, we split up 70% of the dataset for training, 15% for validation and 15% for testing. We adjust the sampling of the validation and testing so that a wide range of folds are represented.

2.1.3 Observation of SCOP Data

The SCOP 2.07 database consists of proteins from 7 classes and 1232 folds.

Figure 8: Here is a histogram of the number of proteins per fold for SCOP 2.07. We see that each fold has much more examples than SCOP 1.55. This may allow our model to learn better.

Figure 9: Here is a histogram of the protein lengths for SCOP 2.07. We see that 90% of the proteins have length less than 500

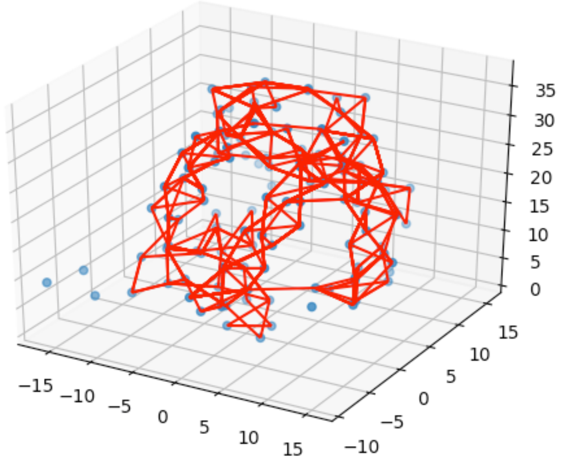


Figure 10: SCOP Viewer allows the user to view the generated persistence homology of the data at once. Here are the generated cycles of protein 1dly

2.2 SCOP Viewer

A number of tools were developed during the research to help view the data and guide the direction of the research. SCOP Viewer, a tool to visualize protein structure and the navigate through the different barcodes was developed to inspect the output of the protein backbone parse and the homology cycles generated by the persistent homology. The tool allows 3D navigation, allowing much more clarity in understanding more complex structures than a 2D image.

The tool is very flexible for general use, allowing the user to feed in a point cloud and allowing the user to view the generated persistence homology.

2.3 Third Party Tools

A number of third party tools were used as part of the research. ProDy's (Protein Dy-

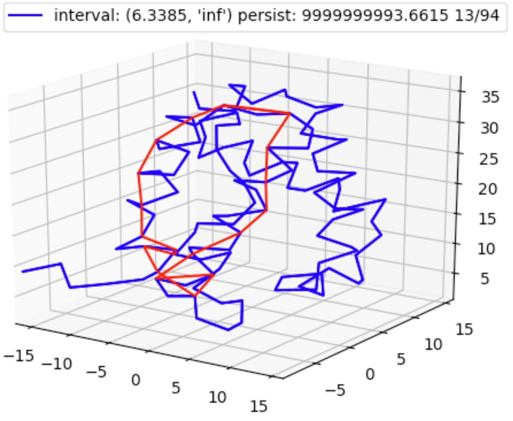


Figure 11: SCOP Viewer allows the user to cycle between the various types of persistent cycles generated for our protein. Here we have a cycle describing a beta sheet structure for protein 1dly.

namics & Sequence Analysis) python package was used to extract the backbone structure from each protein's PDB file. NumPy package was used for matrix and statistical operations. Matplotlib package was used to generate histograms and 3D plots of the proteins and the barcodes. Pillow was used to generate the 2D images of the distance matrix and the barcode images. Keras and Tensorflow were used to setup and train the convolutional neural network. CPickle package was used to serialize and deserialize processed data.

2.4 Computing Resources

Initially the research started on a personal laptop without a GPU and very limited storage space [Ref: Table]. Since the unpacked data of SCOPe 2.07 took up around 40GB and the laptop ran out of storage space, the data was stored on a flash drive.

The lack of a GPU made the training very slow. Even relatively simple methods on the smaller, SCOP 1.55, dataset took around 40 hours. Furthermore, the small storage space made it difficult to unpack and save the processed data on the larger SCOPe 2.07 dataset. These factors significantly slowed the progress of the research.

Due to the limitations of the personal laptop, a personal workstation was purchased at $500 on Winter of 2018 [Ref: Table]. Although it has modest computing power relative to industry standards, the purchased machine led to significant increases in speed and efficiency of the research. The most important changes in computer resources were the GPU, which led to increases in training speed, and the increased storage, which made it possible to work on the larger SCOPe 2.07 dataset. It is also worth nothing that Ubuntu has better support than MacOSx for running CUDA. Most of the optimized methods took around 16 hours at most to complete on the large SCOPe 2.07 database, which is 8 times larger than the smaller SCOP 1.55.

3 Methods

3.1 Background Information: Proteins

A protein is an sequence of amino acids, 2 compounds which link into a protein chain. The interaction between amino acids and the surrounding environment determine the how the protein folds into its structure.

For a protein that we are tasked to classify, we are provided with many information: Protein sequence and the sequential

	Personal Laptop	**Personal Workstation**
CPU	Intel Core i7-4650U	E5-2630 6-Core
GPU (CUDA-enabled)	None	Nvidia GTX 1060 6GB
RAM	8GB	16GB
Storage	128GB SSD	500GB SSD
OS	MacOSx	Ubuntu 16.02

Table 3: A comparison of the laptop and the workstation. Purchasing the workstation made possible significant advancements in the research by increasing the speed of computation and also allowing to work with larger datasets.

coordinates of every atom on our protein. Since we are primarily interested in the topological features of our data, we characterize the protein's shape with the protein backbone. The protein's backbone is constructed with a sequence of points, where each point represents each amino acid in a 3D space. The point representation of each amino acid is determined by the algorithm 'parsePDB' in the ProDy package.

Since we will be dealing primarily with the protein's backbone, we introduce the following notation.

Definition 3.1. A protein, P, with sequence of N amino acids will be a called a protein with length N. It's backbone will be denoted as a sequence of 3D coordinate points $\{P_i\}_{i=1}^{N}$ where $P_i \in \mathbb{R}^3$

For each coordinate point P_i, the x-coordinate is referred as $P_i(1)$, y-coordinate as $P_i(2)$, and z-coordinate as $P_i(3)$.

We extract two distinguishing types of input features from the protein's backbone chain: Distance matrix and Persistence Homology. These two features are very robust. They are both rotation and translation invariant, meaning that the features remain the same even if the protein is rotated or moved. They are also very stable: minor changes to the data does not create a significant variation in the feature.

3.2 Backbone Chain

Each the dataset of proteins are stored as PDB (Protein Data Bank) files, which describe the shape of the 3D protein. The dataset tar [Ref] files unpack into main directory, pdbstyle-1.55 and pdbstyle-2.07 for SCOP 1.55 and SCOPe 2.07 respectively. Each PDB file is stored in a subdirectory under the main directory. The name of the subdirectory is determined by the protein's name.

The index files for SCOP 1.55 and SCOPe 2.07, 'dir.cla.scop.1.55.txt' and 'dir.cla.scope.2.07-stable.txt', provide important information for each protein in our database [Ref: index example].

For each protein, protein backbone chain is parsed from the PDB file using the 'parsePDB' function in the ProDy package. The extracted coordinates of the protein backbone is saved as a list.

The class and the fold number of the protein uniquely identifies a protein's fold. We create a one to one mapping between class-fold to the integers. These integers are the

Index Entry	d1dlwa_ 1dlw A: a.1.1.1 14982 cl=46456,cf=46457 ...
Name	d1dlwa_
Class.Folds.Superfamily.Family	a.1.1.1

Table 4: Here is the relationship between the index entry of a protein and the protein in the dataset. The PDB file for this protein found under the subdirectory 'dl' as 'd1dlwa_.ent'

labels of our protein-fold classification problem.

Because all of the protein coordinates do not fit on the RAM, they are saved in batches of 10000. In each batch, the protein coordinates and the fold labels are saved into a dictionary under the keys b'x' and b'y' respectively.

3.3 Distance Matrix

With the points in the protein backbone, we construct a distance matrix of the distances between the points. The unit of the distances Ångströms, the units of provided in the protein PDB files. [Protein Data Bank]. We used the Euclidean Distance for the distances between the points.

Definition 3.2. For a protein P with length N, we denote it's distance as matrix M_P. We construct it as follows. $M_P := [M_{ij}]$ where

$$M_{ij} = EuclideanDistance(P_i, P_j) = \sqrt{P_i(1) - P_j(1))^2 + (P_i(2) - P_j(2))^2} + (P_i(3) - P_j(3))^2$$

Remark
We note the following for any distance matrix M_P.

- $M_{ii} = 0$
- $M_{ij} = M_{ji}$
- The intersection of the ith row and the jth column corresponds to M_{ij}, the distance between the ith and the jth point.

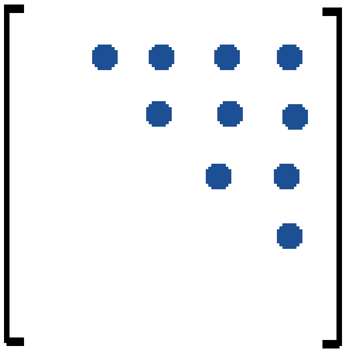


Figure 12: Here we have the entries in a matrix that correspond to the upper triangle. We note that since our distance matrix is symmetric with respect the diagonal line, we only need to calculate the distance values once for the entries in the upper triangle of our matrix.

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We see that the distance matrix is symmetric (Fig.11) since the distance between the ith and the jth point is the same as the distance between the jth point and the ith point. Because of this, we only need to compute the distance between these pairs of points once. Also, the distance between a point to itself is zero. So the pairs of ith and jth's points we need to compute the distances for lie in the upper triangular region of the distance matrix. This region is consists of $\{M_{ij} | i < j\}$ [Ref:]. Computing the distance matrix in this fashion divides the computation time by about half. Because the distance matrices of the entire dataset are larger than the size of the RAM, the data is split up into 1000 sized batches.

Algorithm 1 We fill in our distance matrix by calculating the upper triangle of a NxN matrix. Our rows and columns range from 1 to N.

```
M is distance matrix set with zeroes
Euclid(a,b) is the distance between a and b
for r ¡= N do
    for c ¡ r do
        d=Euclid(r,c)
        M(r,c)=d
        M(c,r)=d
    end for
end for
```

We inspect the topological structure of our protein '1ux8'. It is a protein of length 118. This protein has some spiral structures (alpha helix). These spiral structures sometimes lie in close promixity in parallel or anti parallel direction (beta sheet). These types of structures (secondary structures) are known in molecular biology to be important features of a protein's shape.

We analyze the distance matrix to see if important structural features are represented in the matrix. To help with visualization, the distance matrix is mapped to an image of equal size, where closest distances appear in white and furthest distances appear in black. Distances in between take a gray hue with the intensity based on its value.

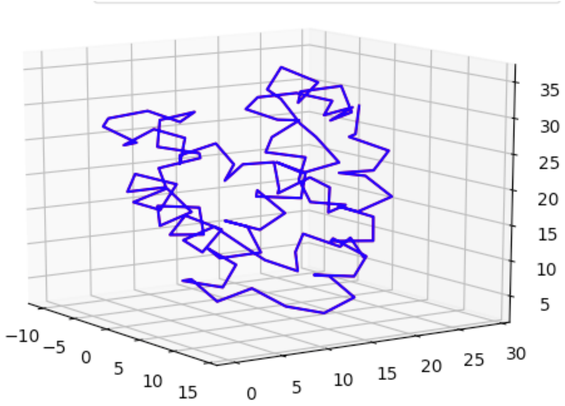

Figure 13: Here is the 3D shape of the 1ux8 protein's backbone chain. We see that there are notable features, alpha helices and beta sheets, that we would like to represent in our distance matrix.

Feature Protein Backbone: Along the diagonal line of the image, the distance matrix is completely white. This is because the distance between a point to itself is zero [Ref: Remark]. We note that this diagonal white line uniquely identifies the protein backbone chain (Since the distance between. Having a clear representation of the protein backbone is important because it is a central structure that other features can be spatially oriented around.

Feature Alpha Helix: We note thick white regions running parallel along the diagonal line of the image [Ref: Image]. These regions indicate that at a given point in the chain, it is in close proximity to the nearby neighbors [Ref Diagram]. We also note that in for a point in an Alpha Helix,

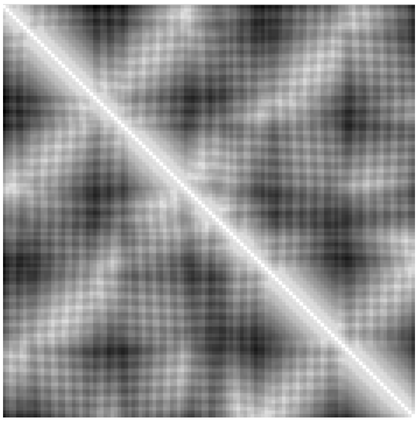

Figure 14: Here is the distance matrix of the 1ux8 protein. We see a thick diagonal line with corresponds to the protein backbone chain.

it is also in close proximity to it's nearby neighbors. In our example, these four thick white regions correspond the the four helix structures on our protein.

Definition 3.3. A helix is composed of points in the protein backbone. Suppose H is the set of indices of these points along the length of the protein. We call the row belonging to this helix as the collection of rows, R_i, of the distance matrix such that the rows contain elements of the helix. $\{R_i | i \in H\}$. Similarly we define the column belonging to the helix as $\{C_i | i \in H\}$.

Feature Beta Sheet: We note patches of thick white lines in the intersection of the rows belonging to a helix and the columns belonging to another helix [Ref Diagram]. This indicates that the points of the two helices, and hence the two helices, are in close proximity. In particular, the regions are close sequentially: the ith point in helix A is close to the jth point in helix B and the i+1 th point in helix A is close to the j-1 th point in helix B. This sequential relationship describes a Anti-parallel Beta Sheets. For Parallel Beta Sheets, the i+1 th point would be close to the j+1 th point. In our example, the 3 pairs of Beta-sheets formed the 4 helices are represented in our distance matrix.

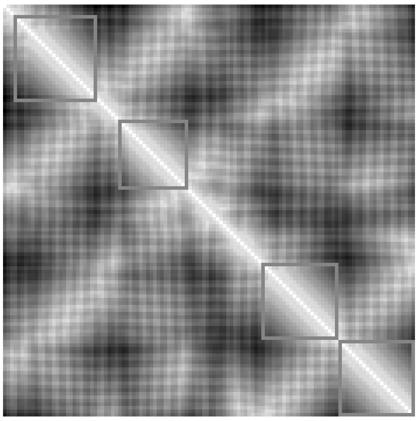

Figure 15: The red squares outline the discrete thick white regions running parrallel to the diagonal line. These regions indicate that the neighbors of points in this region are in very close proximity, indicating that there may be a helix.

3.4 Cropped Distance Matrix

Some proteins have a length of 600, making the distance matrix have a size of 600x600. However, due limitations on the GPU memory, it is not possible to construct a convolutional network with our input being 600x600. We would also like to crop the distance matrix such that the central backbone of the protein runs through the diagonal of our matrix. To crop and preserve the diagonal protein backbone, we take a 100x100 window and crop our matrix by shifting row and columns at the same time by 50 indices.

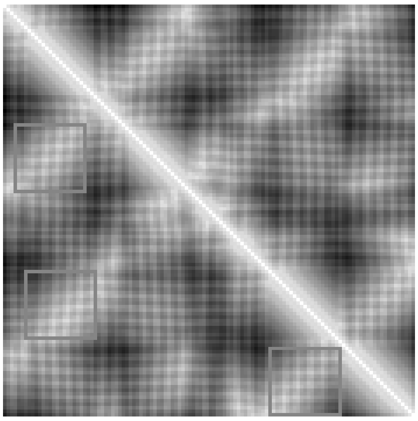

Figure 16: The green squares outline the lines of proximity between points on different helicies, suggesting that the helices are in close proximity. The direction of the lines indicate whether the two helices are parallel or anti-parallel.

Because of the limitations set by the windowed distance matrix, a point in the backbone can only see information about, on average, half of the window size forwards and backwards. This limitation affects the cropped matrix's ability to detect longer range contact information, which can be critical in determining the protein's overall shape. In our example [Ref], the cropped distance matrix would not see information about the proximity between the first alpha helix and the third alpha helix because they are too far away in the backbone index.

We note that if a distance matrix is smaller than our cropping window size, we pad the distance matrix.

Cropping the dataset increases the number of examples in the dataset. Because we don't want our training data to have similarities, we make sure that the training, validation, and testing groups do not share cropped matrices from the same protein.

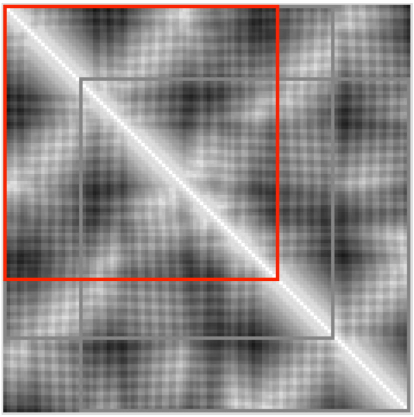

Figure 17: Due to computational restrictions, we crop our matrix by shifting the red crop window along the diagonal line of our matrix.

3.5 Sparse Distance Matrix

In our example, we see that cropping the distance matrix diminishes it's ability to represent long range contact information. We develop an alternative approach to reduce the size of the distance matrix while preserving it's ability to represent long range contact information.

Given, a protein backbone with length N, $\{P_i\}_{i=1}^{N}$, we sample every other point, $\{P_i | \text{i is odd}\}$, to create a sparse protein backbone. We graph the sparse protein backbone in 3D space [Ref] and compare it to the original protein backbone [Ref: Original Chain]. In comparison, we see that the general structure of the protein and its features are diminished but preserved.

From the sparse protein backbone, we construct a sparse distance matrix in the same fashion as a regular distance matrix. In example, we compare the sparse distance matrix [Ref:] and the unmodified distance matrix [Ref:] and see if the backbone

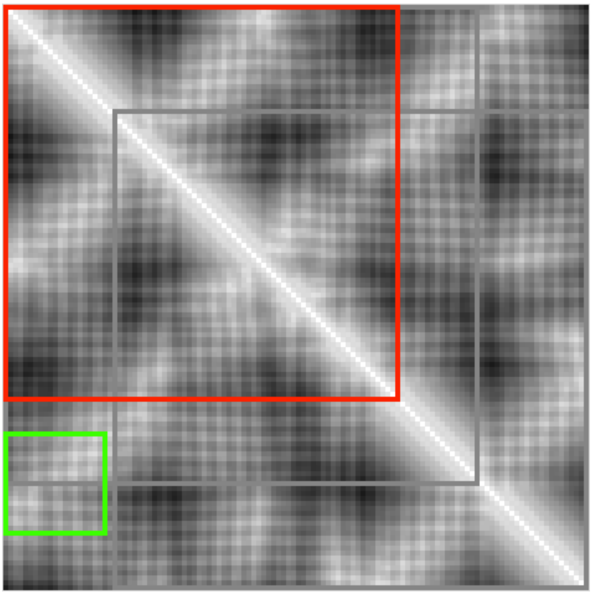

Figure 18: We note that cropping the distance matrix may cause a loss of long range contact information. In our protein 1ux8, the cropped matrices do not detect that the alpha helix 1 forms a beta sheet with alpha helix 3

chain, alpha helix and beta sheet features are preserved in the distance matrix. First, we see that the diagonal backbone is preserved in the matrix. Second, we do see that the alpha helix features are preserved, even though it is less clearly defined. Finally, we see that the beta sheet features are preserved as well.

For the protein of length 600, the sparse distance matrix would reduce the matrix's size from 600x600 to 300x300. This is still too big for due to the limitations on the GPU memory. So we crop the sparse distance matrix in the same manner as a regular distance matrix. We also take care such that the training, validation, and testing groups do not share cropped matrices from the same protein.

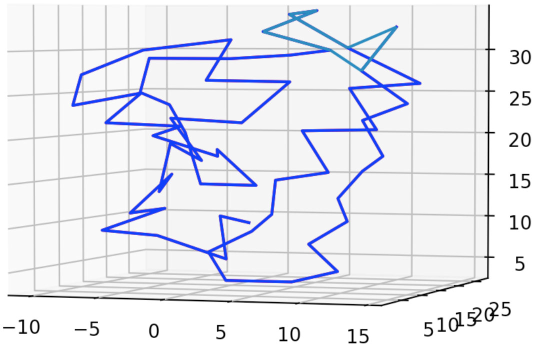

Figure 19: Due to computation restrictions, we sample every other point on our protein and compare it with the original structure. We see that, although diminished, most of the features of the protein are still distinguishable.

3.6 Convolutional Network Model

The features from each of these subsections were fed into a a 2D-convolutional network. The architecture of the 2D-convolutional network for mapping protein structure to folds contains, in order, 32 3x3 convolutional layers, 64 3x3 convolutional layers, 2x2 max pooling, 128 dense layer, and the output layer.

This is a relatively simple network. However, for our task of classifying quarter million of proteins, it performs exceptionally well.

There are a lot of benefits for a simple network performing well. First, it ensures that the model is not overfitting the data. Second, it is much more feasible to inspect the network to understand how it is learning.

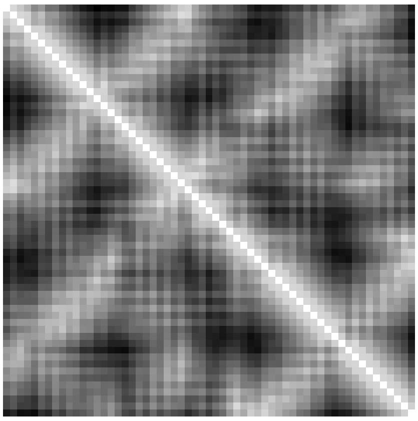

Figure 20: Here we have a distance matrix of the sampled 1ux8 protein backbone. We do see that the protein backbone, alpha helices, and beta sheets that were observed in the full distance matrix can also be observed in the sparse distance matrix.

3.7 Persistent Homology

Persistent Homology: Topological data analysis is applied to the points in the protein backbone to produce persistent barcodes. The barcodes indicate when simplexes are formed and are destroyed. Significant topological features of the data are represented by these barcodes.

3.7.1 Mathematical Background

We discuss the mathematical theory behind persistent homology prior to introducing an algorithm to compute it. First, we describe the elementary mathematical objects. Then we describe the topological features of a data that we want to extract using the structure theorem. We also discuss the stability of the topological features described by the stability theorem.

Definition 3.4. A convex set, $C \subset \mathbb{R}^n$, is a

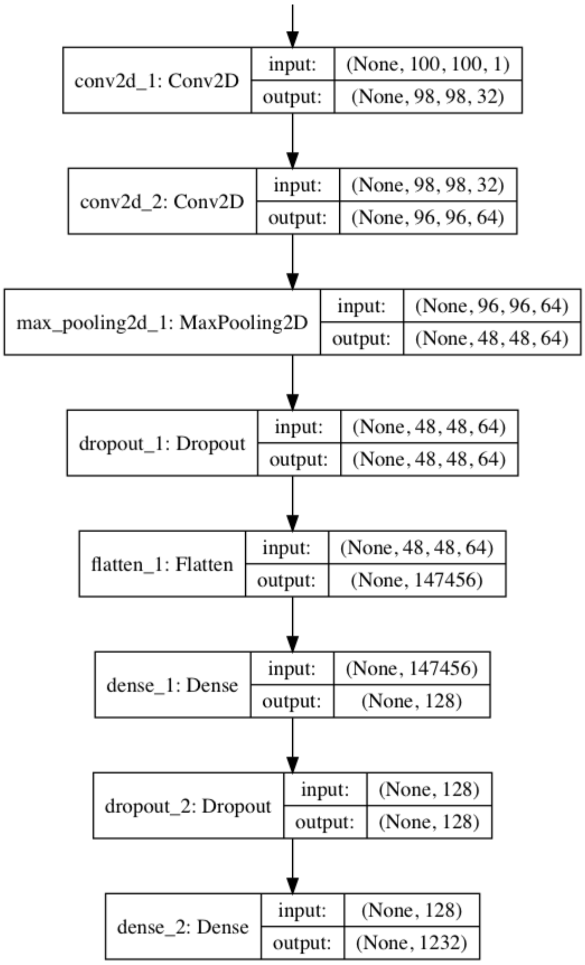
conv2d_1: Conv2D
input: (None, 100, 100, 1)
output: (None, 98, 98, 32)
conv2d_2: Conv2D
input: (None, 98, 98, 32)
output: (None, 96, 96, 64)
max_pooling2d_1: MaxPooling2D
input: (None, 96, 96, 64)
output: (None, 48, 48, 64)
dropout_1: Dropout
input: (None, 48, 48, 64)
output: (None, 48, 48, 64)
flatten_1: Flatten
input: (None, 48, 48, 64)
output: (None, 147456)
dense_1: Dense
input: (None, 147456)
output: (None, 128)
dropout_2: Dropout
input: (None, 128)
output: (None, 128)
dense_2: Dense
input: (None, 128)
output: (None, 1232)

Figure 21: The architecture of a 2D deep convolutional network for protein fold classification. Convolutional layers were added as part of a traditional image classification network. Dense layers were added to help the network use the discovered features in the images. A dropout layer was added to make our network learn an ensemble of different models

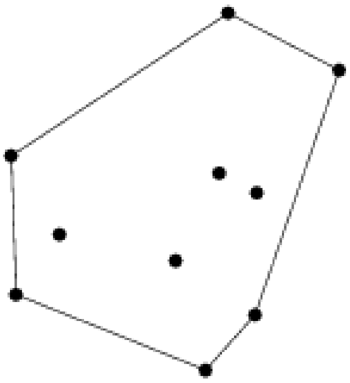

Figure 22: Illustration of a convex hull of 10 points. For a finite set of points this is just a a polygon connecting the outer most points.

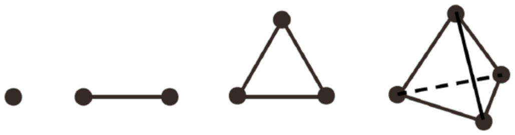

Figure 23: Here are illustrations of a 0-Simplex (a point), 1-Simplex (a line), 2-Simplex (a triangle), 3-Simplex (a tetrahedron)

set where $\forall a, b \in C, t \in [0,1] ta + (1-t)b \in C$. [Ref: Sakai]

Definition 3.5. A convex hull $< A >$ of a set of points, $A \subset \mathbb{R}^n$ is defined by

$$< A > := \bigcap \{ C \mid C \text{ convex in } \mathbb{R}^n \text{ , } A \subset C \}$$

[Ref: Sakai]

Definition 3.6. An n-simplex is a convex hull of n points. When we refer to varying sizes n-simplices or when the size is not determined, we will call them just simplices.

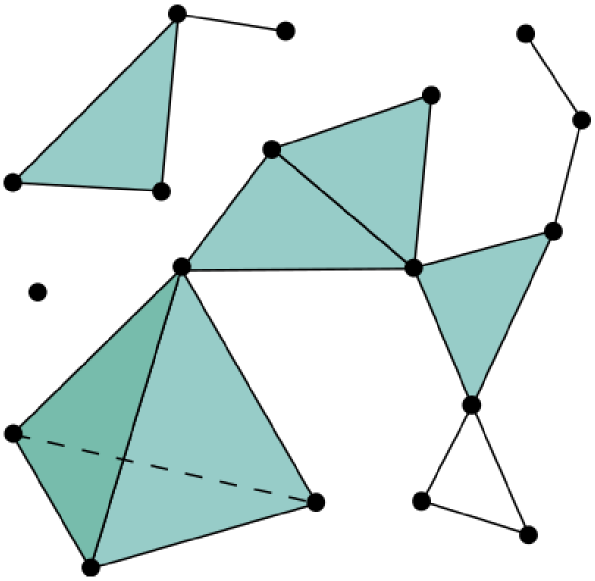

Figure 24: Here is an illustration of a simplicial complex. Notice that it is a collection of points,edges and triangles.

Definition 3.7. Let σ be a simplex. The vertices of σ are its points. The face of σ are the simplices formed by subset of the vertices of σ. A n-face is a face of σ with $n+1$ vertices.

Definition 3.8. Simplicial complex is a set of simplices, S, such that

- Any face of a simplex $\sigma \in S$ is in S.
- The intersection of any two simplices in S is in S

Now that we have defined the foundational definitions, we begin to define structures relevant to our problem of extracting topological features from our set of points in the protein backbone. First, we will observe the state of our data as we create triangular simplices from the points in our data by adding edges of increasing length. We do this by forming Vietoris-Rips complexes.

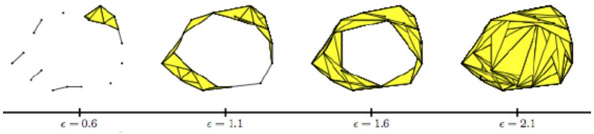

Figure 25: Here is a series of 5 Vietoris-Rips complexes. At $\epsilon = 0$ we only have a collection of points, while at $\epsilon = 1.1$ we being to see an interesting characteristic of our data beginning to form. Finally, at $\epsilon = 2.1$ we do not see much of a structure as most of the points become interconnected to each other.

Definition 3.9. Given a set of points with a metric, a ϵ-Vietoris-Rips complex is a simplicial complex which is formed on the set of points by connecting the points with distance less than or equal to ϵ

We see how the state of our data changes as we add edges between points of increasing length by ordering the ϵ-Vietoris-Rips complexes in increasing order of ϵ. This ordering is a filtration on the set of all Vietoris-Rips complexes on our data. If $\epsilon_1 \leq \epsilon_2$ then ϵ_1-Vietoris-Rips complex is contained in ϵ_2-Vietoris-Rips complex. This is because edges less than ϵ_1 are also less than ϵ_2 and thus are formed in ϵ_2-Vietoris-Rips complex.

Definition 3.10. Let $\mathbb{S}$ be a collection of sets such that $\forall A \in \mathbb{S}$, $\exists B \in \mathbb{S}$ such that $A \subseteq B$ or $B \subseteq A$. That is given an element in our collection, it is contained or contains another set in our collection. A filtration is an ordering on $S_i \in \mathbb{S}$ such that

$$S_1 \subseteq S_2 \subseteq S_3 \subseteq S_4 \subseteq ...$$

.

We transform our filtration of Vietoris-Rips complexes to persistent module, where each Vietrois-Rips complex is converted to an algebraic group, homology. This is because homology can detect holes and other topological structure in our simplicial complex. We say that we apply a 1-homology, H_1 to each simplicial complex in our filtration. We get a sequence of homologies with homomorphisms induced by the inclusion map.

$$H_1(S_1) \to H_1(S_2) \to H_1(S_3) \to H_1(S_4) \to ...$$

.

Let S be our simplicial complex. We will first construct the elements that define the homology on S.

Definition 3.11. The group of k-Chain of S is an abelian group of elements consisting of

$$\sum z_i s_i$$

where $z_i \in \mathbb{Z}$ and s_i is a k-simplex of S. We call this group C_k

Definition 3.12. The boundary operator $\partial_k : C_k \to C_{k-1}$ is a homeomorphism where

$$\partial(\sigma) :=$$

$$\partial_1(ab) := b - a$$

$$\partial_2(abc) := ab + bc - ac$$

Definition 3.13. Given a simplicial complex, S, it's j-homology is the algebraic quotient group, $\frac{Z_j}{B_j}$. We define $Z_j = Ker\partial_j$ and $B_j = Im\partial_j$. We denote the j-homology of S as $H_j(S)$ We note that the homology is a vector space over $\mathbb{Z}$

Definition 3.14. The persistent homology module is a direct sum of the

Figure 26: Here is the collection of the N points we are considering in 2D. Although our protein is in 3D, the method is concerned with the distances between points, allowing in to work in a similar fashion as this example.

Figure 27: Here is a distance matrix of our set of N points. We will only consider the edges in the upper triangular matrix, because the (i,j) edge represents the same line as the (j,i) edge

3.7.2 Computation Algorithm

We describe our implementation of the persistent homology, in addition to variations to the method to improve performance and collect more protein specific simplices. In practice, we will use the N points of a protein backbone in this algorithm but for illustrative purposes, we consider a simple collection of N points in the $\mathbb{R}^2$. (Fig.25) Because we are looking at the distances between our points, the method performs exactly the same in $\mathbb{R}^3$ or with any collection of objects with a well defined metric.

Definition 3.15. We call the (i,j) edge the edge constructed by connecting the ith and the jth point in our set of N points.

A distance matrix of the our points is calculated. We collect the upper triangular elements of the distance matrix to get the unique edges of our points (unique disregarding direction, making (i,j) edge equal to (j,i) edge). These edges are sorted by length.

Consider a protein with length 300. The total number of edges for a protein of length 300 is $\sum_{n=1}^{299} n = 44851$. The total number of triangular simplices formed by these edges $\binom{300}{3} = \dfrac{300!}{3!297!} = 4455100$. We see that the numbers of triangular simplices increase exponentially and very quickly, even for small structures. This demands a need to reduce the computation load.

A cutoff distance is determined, where we discard the edges that are larger than this value. A similar concept exists in bioinformatics, where a point of a protein are determined to be in contact with another point if their distance is within the contact distance (3 Å). The loss of information by discarding the edges larger than this value isn't an issue since because when we start considering larger edges, we start converging towards a structure where every point is connected to each other. As long as we set the cutoff distance at an appropriate value, we would still get the cycles of the protein that represent the characteristic features. Furthermore, setting of a cutoff distance has an added advantage that it filters out uninteresting cycles that are too large. We determined the cutoff distance at 6.5 Å, because we experimentally determined that 6.5 Å is an upper bound of the distances between two alpha helices. The distance between two alpha helices are less than 6.5 Å, we consider the edges that link two alpha helices together, allowing use to extract features related to the beta sheets. Furthermore, the most sequential distances between the backbone points, P_iandP_{i+1}, and the distances within the alpha helices are both less than 6.5, allowing use to extract features related to them as well. It is also know that due to tetrahedral chemical bonding at the carbon backbone atom due to the pleated appearance of beta-strand causes the distance between beta sheets to be approximately 6 Å [6].

For our set of N points, the cutoff distance is determined as $\frac{1}{6}$ of the longest length, which is ?. Below are the collection of points

Once we have the edges that we are considering, we find the triangular simplicies formed by our edges. As we loop over the edges, we index the edges from 1 to N based on the endpoints of the edge (For an edge (2,4), it is indexed as 2 and 4). Then, we check if each edge forms a triangular simplicies by looking at the indexed edges related to our edge. (For an edge (2,4), we look at the edges that have been index as 2 or 4 to see if we formed a 2-simplex). Because we are forming the triangular simplicies as we add increasing edges, triangular simplicies are ordered by when they are created.

Figure 28: Here we see the effect of the cutoff distance on the triangular simplicies we form. When a cutoff distance is not set, all the edges are considered, forming triangular simplicies where every point is connected to each other. These simplices don't convey too much about the structure of our protein. When a cutoff distance is set properly, the important distances considered, making the simplices less convoluted and increasing computation time.

Given a triangular simplex, we can compute when it was born by looking at it's edges. For example, a triangular simplex (1,2,3) has the edges (1,2), (1,3), and (3,1). Suppose the lengths of these edges were 3,5, and 7 respectively. Then the triangular simplex was formed at radius 7.

From the edges and triangular simplices, we create two matrices, D1 and D2. Let M be the number of edges we are considering and L be the number of triangular simplices we are considering.

D1 is a NxM matrix where the rows cor-

Algorithm 2 Finding triangular simplicies formed by the edges

```
for (i,j) in Edges do
    for edges indexed i and indexed j do
        See if these edges form a triangular simplicies with (i,j)
    end for
    Index (i,j) as i and j
end for
```

Figure 29: The triangular simplices are discovered as we add edges. Because we are adding the edges in increasing order, the triangular simplices are discovered in the order of their birth.

Figure 30: Here is a D2 matrix for the protein 1ux8. We notice that most of the matrix consists of zero elements.

Algorithm 3 Constructing D1

```
for hth edge (i,j) in Edges do
    $D1_{h,i} = -1$
    $D1_{h,j} = 1$
end for
```

respond to the backbone points and the columns corresponds to the edge in increasing order. We fill in D1 in the following order. For the hth edge with endpoints (i,j), we set $D1_{h,i} = -1$ and $D1_{h,j} = 1$. Suppose an edge (2,4) is the 10th smallest edge. The corresponding entries in would be $D1_{10,2} = -1$ and $D1_{10,4} = 1$.

D2 is a MxL matrix where the rows correspond the edges in increasing order and the columns correspond to the triangular simplicies in created order. We fill in D2 in the following order. For the hth triangular simplex with endpoint (i,j,k), we set $D2_{h,i} = 1$, $D2_{h,j} = 1$, and $D2_{h,k} = -1$. Suppose an edge (2,4,9) is the 10th triangular simplex. The corresponding entries in would be $D2_{10,2} = 1$, $D2_{10,4} = 1$, and $D2_{10,9} = -1$.

Algorithm 4 Constructing D2

```
for hth edge (i,j,k) in Edges do
    $D2_{h,i} = 1$
    $D2_{h,j} = 1$
    $D2_{h,k} = -1$
end for
```

Each of the matrices, D1 and D2, are reduced to echelon form with the following algorithm. A pivot at a given column is given by the last nonzero entry in the column. We try to make all the columns not share any pivots. We loop over the columns and set check if the previous columns share a pivot with the current column. If they share a pivot, a multiple of the sharing pivot is subtracted from the current pivot such that the they do not share pivots. This process is repeated until the current column does not share a pivot with any of the previous columns. Every time the matrix is modified the same operation is performed to an identity matrix, MxM identity matrix for D1 and LxL identity matrix for D2. After we finish reducing the matrix, we call the reduced matrix R1 and R2 and the corresponding modified identity matrices V1 and V2.

Algorithm 5 Reduction of a matrix

```
for column in Columns of D2 do
    for pcolumn in Columns before column do
        if column share the same pivot as pcolumn then
            k=$\frac{column[pivot]}{pcolumn[pivot]}$
            column -= k*pcolumn
        end if
    end for
end for
```

Finally, we can construct the main matrix that gives us the persistence homology of our protein. First we construct matrix B from the nonzero columns of matrix R2. Second we construct matrix Z from columns of V1 corresponding to zero columns of R1. The main matrix is then constructed by taking matrix B and appending columns from matrix Z which do not share pivots with columns of our main matrix until the total number of columns is equal to the number of columns in matrix Z.

Algorithm 6 Construction of Main Matrix

```
Main = B
for column in Columns of Z do
    if number of columns in Main equals number of columns in Z then
        Exit Loop
    end if
    if column doesn't share pivots with columns of Main then
        Append column to Main
    end if
end for
```

The columns in the main matrix which come from B correspond to the simplices which get created and filled in before our cutoff distance. The columns in the main matrix which come from Z correspond to the simplices that get created but not filled in before our cutoff distance.

From each column,we extract information about the edges that form the simplex and it's birth and death from the column in the following manner. For each column, the simplex is formed by the edges in the non-zero entries in the rows. The simplex is born when the edge corresponding to the last non-zero row is added. If our column comes from B, let d be the column of R2 that our column comes from. Then, the simplex is destroyed/filled in when the dth simplex is formed. If the column comes from Z, then the simplex is not destroyed within our cutoff distance. We notate this by denoting the death as ∞. We say that the simplex persists for $death - birth$.

We look at column ? of the main matrix for our example. Here we see that column ? forms the simplex with the edges [(),()].

Figure 31: Here we have a diagram of the matrices that we have constructed and manipulated. The final product, the main matrix, is a MxH matrix where M is the number of edges we have considered and H is the simplex with persistent homology.

We see that this simplex is born at ? and dies at ?. It doesn't persists for a long time which is indicative of it not being a significant feature of the data.

We look at column ? of the main matrix for our example. Here we see that column ? forms the simplex with the edges [(),()]. We see that this simplex is born at ? and dies at ?. It doesn't persists for a long time which is indicative of it not being a significant feature of the data.

3.7.3 Persistence Homology

We inspect the persistence homology of our protein 1ux8, a protein of length 118. At each point on the protein backbone, we search the radius around the point to find nearby points.

The red edges indicate that the two points are less than 3.5 distance away. Making them connected. As we increase the radius, we connect more and more points.

Figure 32: Here we see the main matrix of persistent homology for protein 1ux8. Each column represents a simplex that represents a significant feature of our protein.

The connections between these points form polygons (simplexes). After a certain point we want to cut off our search radius because we have extracted all the notable features from our structure. If we keep increasing the search radius then all the points will be connected to each other.

A polygon is filled in when the inner polygons of the larger polygons are filled in. We note that triangles are filled as soon as they are formed but larger structures take more time to get filled in. Persistent homology tells us when (the radius) at which these polygons are created and filled in.

Below we have two examples of the polygons.

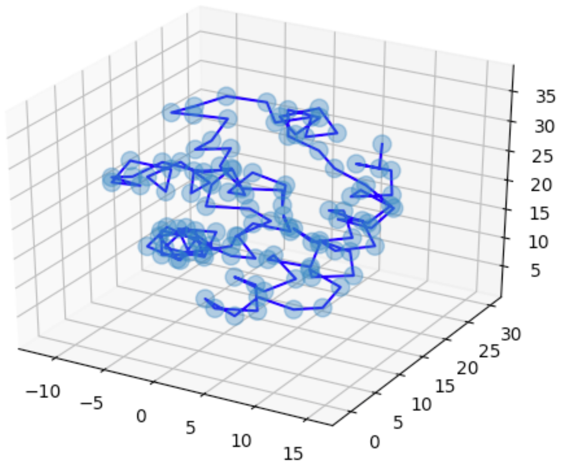

Figure 33: A search is done near each point at increasing radii to find the nearby points

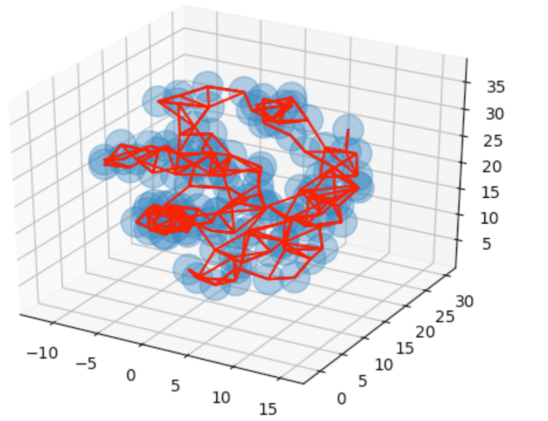

Figure 35: The structure of the protein is detected as we increase the radii at around 6 Ångströms

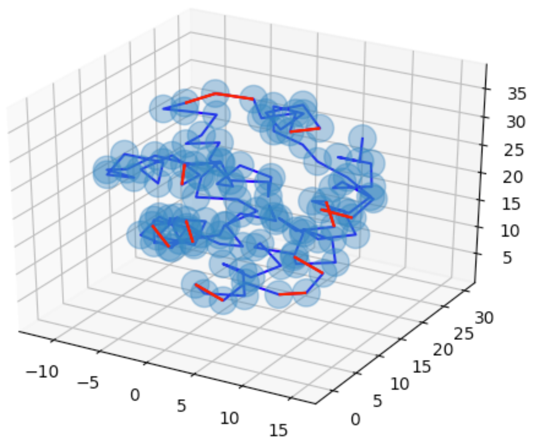

Figure 34: Edges between points are formed as the search radii become larger

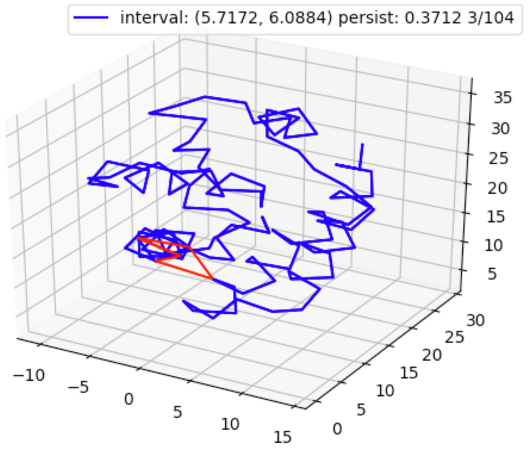

Figure 36: Persistent Homology detecting a small cycle

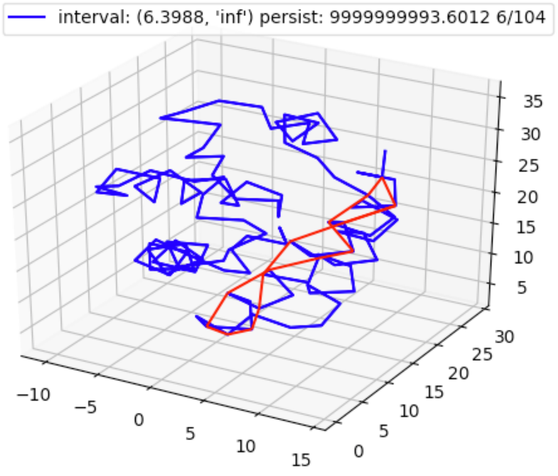

Figure 37: Persistent homology detecting an alpha helix

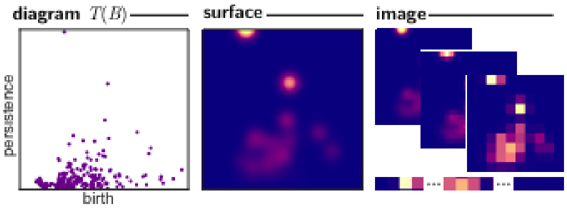

Figure 38: For a protein, a plot of the barcodes is constructed on a 2D plane where x-coordinate is the birth and the y-coordinate is the persistence. Then, a blurred resolution of the plot is taken as the persistent image.

Figure 39: Here is the plot of the simplices for the protein 1ux8. The x axis is the birth of the simplex and the y axis is the persistence of the simplex. At the very top we plot the simplices with infinite persistence.

3.7.4 Sparse Persistence Homology

3.7.5 Backbone Aware Persistence Homology

3.7.6 Persistence Images

The persistent homology of each protein is converted into an input feature called persistent images. For each simplex in the homology, we plot it on a 2-dimensional vector space with the x coordinate being the birth and the y coordinate being the persistence of the simplex. For the simplices that persist infinitely, we plot the y coordinates well above the maximum persistence.

This representation captures the essential information about each simplex as well as ordering them. The more persistent simplices are higher and the simplices that are born later appear towards the right. Fig.38 shows this plot for the protein 1ux8.

Because it is difficult to send these pairs of points to a neural network, we take a

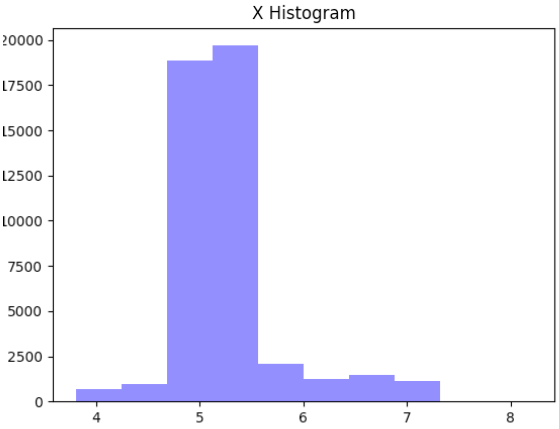

Figure 40: x range

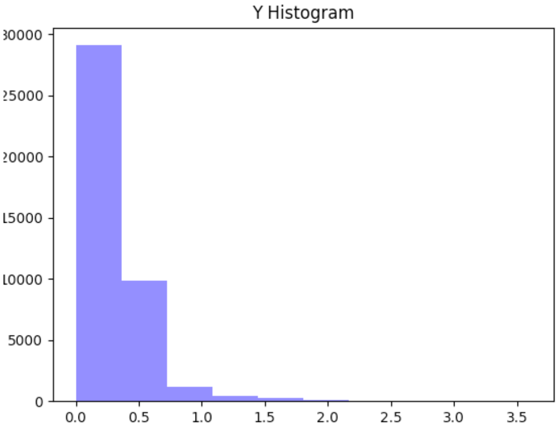

Figure 41: y range

blurred resolution of the image which is constructed as follows. First, a fixed dimensions of the blurred images is determined. Then, an interval for the x values and y values are determined experimentally by considering the intervals that contain our data.

The plot cropped and converted to a blurred image at a set resolution. The range of the first and second coordinates to crop the plot were derived from the distribution of the data.

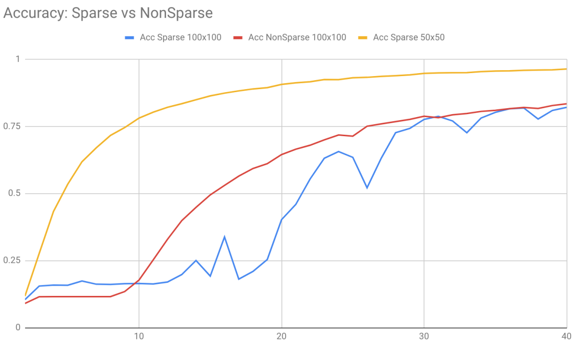

Figure 42:

4 Results

4.1 Distance Matrix

4.1.1 Cropped Distance Matrix

The distance matrix as the input feature worked pretty well for classifying the data. The best method, subsampling every other point with a window size of 50x50 gives an accuracy of 96%

The other two methods perform pretty well, at around 86%. The subsampling method probably works best because it gives the neural network model to view the long range dependencies. The smaller window size of 50x50 performs much better than the 100x100 window for the subsampling methods.

4.2 Persistent Homology

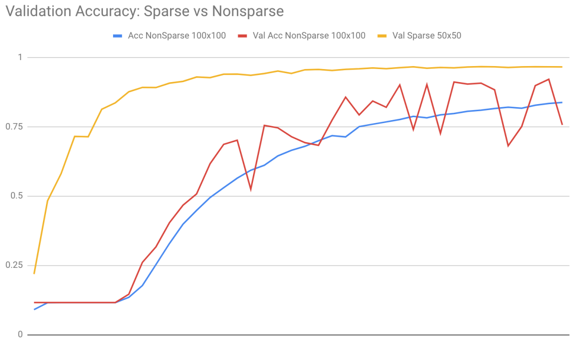

Figure 43:

Test

References

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