COMMUNITY DETECTION WITH APPLICATIONS TO MULTIREFERENCE ALIGNMENT

Project Number: 20.1.1.2135

Final report

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Project was done from home

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ABSTRACT

Single-particle reconstruction in Cryogenic Electron Microscopy (cryo-EM)[1] is a tool for constructing a 3D model of a biological macromolecule using 2D projections of the macromolecules taken by an electron microscope. An unsupervised classification of the 2D images is required in order to separate macromolecular projections of different conformations. Due to high noise levels and data heterogeneity, sophisticated clustering methods are needed.

In our project we employ Community Detection (CD) algorithms to cluster data generated from the Multireference Alignment (MRA) statistical model, **Fig. 1** shows a diagram of the process. The model abstracts away much of the intricacy of cryo-EM while retaining some of its essential features.

Conclusions should be added

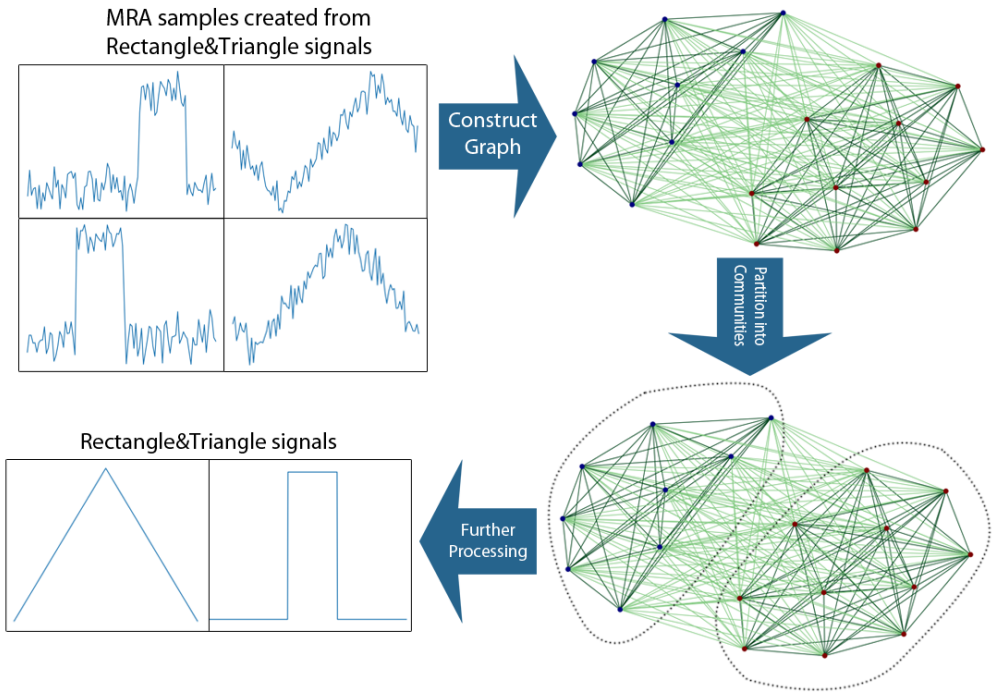

Figure 1: Project process. Further processing stage presents the idea behind clustering the data and is outside of the scope of the project.

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List of Abbreviations

C

CD Community Detection. 3, 4, 7, 9

cryo-EM Cryogenic Electron Microscopy. 3, 7, 8

F

FFT Fast Fourier Transform. 8

M

MRA Multireference Alignment. 1, 3, 4, 7–9

S

SNR Signal To Noise Ratio. 4, 7, 8

1 Introduction

Single-particle reconstruction in cryo-EM is a powerful image-processing tool used to determine the 3D structure of biological macromolecular complexes. 2D images (micrographs) of a macromolecule are taken by an electron microscope. Essentially, the set of all micrographs for a given macromolecule spans a 3D model of the macromolecule. Thus, single-particle reconstruction is using the micrographs to build a 3D model of the macromolecule.
Due to high sensitivity of the biological macromolecules to radiation damage, electron microscope provides limited electron doses when producing micrographs. This and other factors like low contrast of micrographs and digitalization of the images result in cryo-EM data having very low Signal To Noise Ratio (SNR)[1].
The cryo-EM technology has the potential to offer the ability to analyze different functional and conformational states of macromolecules, an important ability for the field of molecular biology. Practically, it entails the classification of heterogeneous cryo-EM data.
Many different approaches for cryo-EM data classification have been developed. Typically, likelihood optimization algorithms and Bayesian inference frameworks are used to deal with data heterogeneity[16, 15, 14, 17, 4].
In our project we propose a different approach for cryo-EM data classification using Community Detection (CD) algorithms that are common in the field of complex networks. According to our approach, data will be classified following the steps:

- Converting data into a weighted graph, where each node corresponds to a sample and the edges between nodes represent the degree of similarity between samples.
- Applying Community Detection algorithms to partition the graph into distinct communities
- Each community represent a single conformation of a sampled macromolecule.

For the sake of an abstraction of the cryo-EM data we will use the Heterogeneous Multireference Alignment (MRA) statistical model. Throughout our project we use the simplified 1D version of the model.

2 Background

2.1 Heterogeneous 1D Multireference Alignment model

In our project we will use the Heterogeneous 1D Multireference Alignment statistical model[3] (MRA shortly) for the sake of cryo-EM data abstraction. Bellow is the definition of the model.
Let $x_1, ..., x_K \in \mathbb{R}^L$ be K unknown normalized signals (distinct even up to shift) and let R_s be the cyclic shift operator: $(R_s x)[n] = x[\langle n - s \rangle_L]$. We are given N observations:

$$y_j = R_{s_j} x_{k_j} + \varepsilon_j, \quad j = 1, ..., N \tag{1}$$

where $s_j \sim U[0, L-1], k_j \sim U[0, K-1]$ and $\varepsilon_j \sim \mathcal{N}(0, \sigma^2 I)$ is i.i.d white Gaussian noise. Our goal is to estimate the signals $x_1, ..., x_K$ from the observations.
Simply speaking, MRA observation is a randomly chosen signal x_{k_j}, shifted randomly by s_j and distorted using white noise. **Fig. 2** shows an example of two MRA observations at different noise levels.

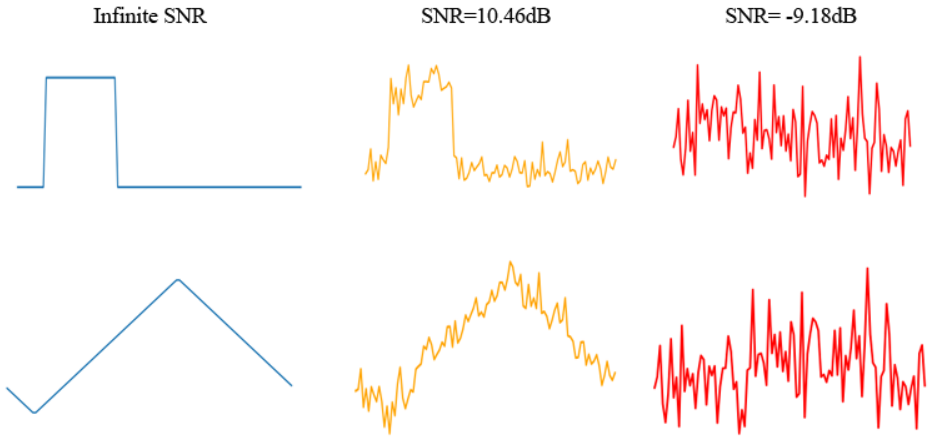

Figure 2: Example of MRA observations at different SNR levels. Each column shows a shifted distinct signal at different noise levels. We can see that for low SNR the task of signal estimation is quite challenging.

In order to build a weighted graph from MRA observations, a similarity measure between observations must be defined. We use the cross-correlation, as its invariance to shift holds great value:

$$(x \star y)_n \triangleq \sum_{l=\infty}^{\infty} x_l^*(y)_{n+l} \tag{2}$$

The convolution theorem states that the convolution of two signals equals to the inverse Fourier transform of the product of the Fourier transforms of each signal. Thus we can write the equation above in terms of Fourier transforms and later exploit FFT in our simulations.

$$(x \star y)_n = \mathcal{F}^{-1}\{X^* \cdot Y\}_n \tag{3}$$

It should be noted that in order to obtain normalized cross-correlation, MRA samples must first be normalized.

2.2 Community detection

As part of our suggested solution to the heterogeneity problem, we convert the MRA data into a weighted graph. Each node in the graph represents a different MRA observation, as was defined in **Eq.1**. Each edge connecting a pair of nodes has a weight that represents a similarity measure between the nodes, as was defined in **Eq. 3**.
Our objective is the partition of all MRA observations into K non overlapping classes, where each class represents a distinct signal before it was distorted by **Eq. 1**. Our classification process is carried out using Community Detection (CD) algorithms applied on the produced weighted graph.
Community, in a broad sense, is a set of nodes, which are similar to each other and dissimilar from the rest of the network. Community Detection (CD) algorithms aim to find these communities in a graph. **Fig. 3** shows the result of a CD algorithm.

Finding communities in a graph carries a great value to revealing hidden patterns in data and has many use-cases, such as social behaviour prediction [20] or medical diagnosis[6]. Evidently, Community Detection algorithms are well studied and widely used. In our project we study a group of state-of-the-art CD algorithms and apply them on MRA data.

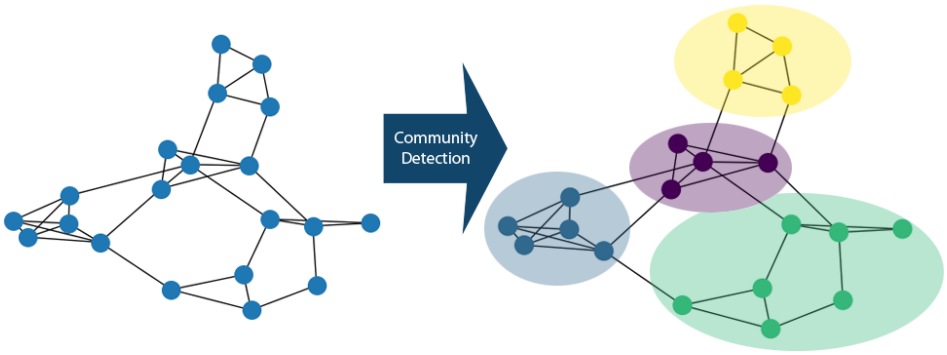

Figure 3: Graph partition by Community Detection. In this example for the sake of simplicity an unweighed graph is used. Note that in our project we used weighted graphs.

Below is a summary of the algorithms we studied.

- *Edge Betweenness*[5] uses the "edge betweenness" as its optimization parameter, which is defined as the number of shortest paths that go through an edge in a graph. Following this definition, edges with higher "betweenness" can be interpreted as connections between different communities. The algorithm computes the "edge betweenness" score for each edge in the graph and iteratively removes the edges with the highest score, while computing the score for each iteration. The end product is a disconnected graph separated into separate communities.

- *Fast Greedy*[8] is based on the idea of *modularity*. Let e_{ij} be the fraction of edges in a graph that connect nodes in group i to those in group j, and let $a_i = \sum_j e_{ij}$. Then modularity is defined as:

$$Q = \sum_i (e_{ii} - a_i^2) \tag{4}$$

  Simply speaking, modularity is the fraction of edges that fall within communities minus the expected value of the same quantity if edges fall at random. Thus, low modularity values indicate a random structure of the graph, while higher values point to deviation from randomness and more defined communities within a graph. The algorithm operates by initializing a community for each node in a graph. Then it repeatedly joins nodes in pairs such that the modularity of the graph is maximized.

- *Label Propagation*[11] exploits the basic notion of a community as a set of similar neighbouring nodes. Each node starts with a unique label, and after each iteration, a node updates its label to the most common label of its neighbours. The algorithm stops when each node has a label that the maximum number of its neighbours have.

- *Leading Eigenvector*[9] is based on the *spectral clustering*. The basic idea behind spectral clustering is to convert the graph into a *similarity matrix* and find the eigenvectors that correspond to the (second) smallest

eigenvalue of the matrix. These eigenvectors define the *minimum cut size* of the graph (cut size is defined as the number of edges running between two groups of nodes). The second smallest eigenvalue is chosen because the smallest correspond to minimum cut size of 0, where the whole graph is a single community.
Let $\mathbf{A}$ be the *adjacency matrix*:

$$A_{ij} = \begin{cases} 1 & \text{if nodes } (i,j) \text{ are connected} \\ 0 & otherwise \end{cases} \tag{5}$$

and $\mathbf{P}$, such that P_{ij} is the expected number of edges between nodes i, j given a random graph under the constraint that the expected *degree* (number of edges connected to a node) of each node equal to the degree of each corresponding node in the input graph. *Modularity matrix* is then defined as:

$$\mathbf{B} = \mathbf{A} - \mathbf{P} \tag{6}$$

Leading eigenvector algorithm uses the modularity matrix as the similarity matrix and proceeds to perform a spectral clustering of the input graph.

- *Walktrap*[10] is based on the idea that short random walks on a graph tend to stay in the same densely connected area. Each node starts in its own community and a random walk process is run on each node. Based on the random walk, distances between nodes are calculated, and nodes with the smallest distances are lumped together. The process then repeats until all nodes are in the same community. At each step modularity (**Eq.** (4)) of the partition is computed, and in the end the partition with the maximum modularity is chosen.

- *Infomap*[13] uses *Huffman code* as a way to compress the information about a path of a random walk in a graph. Each node in a graph is given a unique Id. A random walk that explores the entire graph is initialized, note that random walk tends to stay longer in a densely connected areas. This allows to combine nodes Ids into Huffman codes, that will ultimately label the communities in a graph. The algorithm then optimizes the number of Huffman codes such that the encoded information about the path of the random walk in a graph is maximally compressed.

- *Louvain*[2] maximizes modularity (**Eq.** (4)) in a hierarchical fashion. In the first phase of the algorithm, each node starts in its own community. Each node is then placed in a community with its neighbour such that a maximum modularity score is obtained for the graph. In the second phase a new graph is created, whose nodes are now the communities found during the first phase, such that the weight of the edges between these nodes equal to the edge density between the communities from the first phase. After the second phase is complete, the new graph is passed through the first phase again. The process is repeated until no modularity gain is obtained.

- *Leiden*[18] is an improvement of the Louvain algorithm. Louvain algorithm, in some cases, has proven to produce bad partitions in the form of disconnected communities (a community that contains disconnected nodes). Leiden algorithm introduces a refinement stage in the first phase (see Louvain algorithm). At the second phase, the refined partition is aggregated and initially partitioned based on the unrefined partition. By creating the aggregated graph based on the refined partition, Leiden algorithm has more room for identifying high-quality partitions.
  Simply speaking, when a community is aggregated to a node at the second phase in Louvain algorithm, no further changes inside the community are possible. Leiden, on the other hand, gives more flexibility by refining the graph in the first phase.
  Leiden also uses a faster method for implementing the nodes transitions between communities in the first phase.

- *SpinGlass*[12] adopts ideas from the field of statistical mechanics for the clustering of the graph, and is based on the Potts model [19]. The algorithm regards to the graph as a system with at most of k *spin states* (which are equivalent to the number of communities we wish to find), and tries to minimize the collective *energy* of the system by arranging its *particles* (which are equivalent to the nodes of the graph) into said spin states. The energy of the system is quantified by the *Hamiltonian* function, which is defined for a group of spin states σ_i as:

$$-\sum_{i\neq j} a_{ij} \cdot \underbrace{A_{ij}\delta\sigma_i,\sigma_j)}_{InternalEdges} + \sum_{i\neq j} b_{ij} \cdot \underbrace{(1-A_{ij})\delta\sigma_i,\sigma_j}_{Non-existingInternalEdges}$$
$$+\sum_{i\neq j} c_{ij} \cdot \underbrace{A_{ij}(1-\delta\sigma_i,\sigma_j)}_{ExternalEdges} \sum i \neq j d_{ij} \cdot \underbrace{(1-A_{ij})(1-\delta\sigma_i,\sigma_j)}_{Non-existingExternalEdges}$$

where **A** is the adjacency matrix of the graph, a_{ij},b_{ij},c_{ij} and d_{ij} are hyper parameters which affect the contribution of each factor to the hamiltonian and can be changed and $\delta(a,b)$ symbolizes Kronecker delta. In order to minimize the hamiltonian, the algorithm also uses simulated annealing[7]

3 Aim 1 Title

3.1 Introduction to Aim 1

An introduction to Aim 1.

3.2 Background to Aim 1

This section will include the most relevant literature addressing this aim.

3.3 Methods

Maybe you'll discuss some methods.

3.3.1 Some crucial details about the method

It'll probably have a sub(sub)heading.

3.3.2 Conceptual model, research questions and hypotheses

Blah blah blah.

3.4 Results of Aim 1

Blah blah blah.

3.5 Discussion of Aim 1

Blah blah blah.

3.6 Conclusion of Aim 1

Blah blah blah.

4 Aim 2 Title

4.1 Introduction to Aim 2

An introduction to Aim 2.

4.2 Background to Aim 2

This section will include the most relevant literature addressing this aim.

4.3 Methods

Maybe you'll discuss some methods.

4.3.1 Some crucial details about the method

It'll probably have a sub(sub)heading.

4.3.2 Conceptual model, research questions and hypotheses

Blah blah blah.

4.4 Results of Aim 2

Blah blah blah.

4.5 Discussion of Aim 2

Blah blah blah.

4.6 Conclusion of Aim 2

Blah blah blah.

5 Aim 3 Title

5.1 Introduction to Aim 3

An introduction to Aim 3.

5.2 Background to Aim 3

This section will include the most relevant literature addressing this aim.

5.3 Methods

Maybe you'll discuss some methods.

5.3.1 Some crucial details about the method

It'll probably have a sub(sub)heading.

5.3.2 Conceptual model, research questions and hypotheses

Blah blah blah.

5.4 Results of Aim 3

Blah blah blah.

5.5 Discussion of Aim 3

Blah blah blah.

5.6 Conclusion of Aim 3

Blah blah blah.

6 Discussion

Some detailed discussion.

6.1 A subheading

Blah blah blah

7 Conclusion

This section would contain the conclusions drawn from the entire body of work.

7.1 A subheading

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9 Appendix

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