1 Introduction

Protein structure prediction is a seminal problem in computational biology. The goal of protein structure prediction is to infer the 3D structure of a protein from its amino acid sequence. Previous work in this field generally uses simulated annealing to determine protein structure, however Pacheco et. al. are currently attempting to apply the D-PMP algorithm, which had success in the sub-problem of protein side chain prediction, to full structure prediction. In order to obtain efficient inference for D-PMP it is necessary to provide a sparse graphical model. Currently, D-PMP is being provided with the true graph structure, obtained using knowledge of the correct protein structure. We propose to develop a method for estimating this sparse graphical model of a protein from its amino acid sequence (a subproblem known as protein contact prediction).

A protein can be represented with a Pairwise Markov Random Field by assigning a variable to each amino acid to keep track of its position and orientation, and adding an edge between variables if the corresponding amino acids are close enough to interact. Note that the complete graph is always a valid representation of a protein. Inter-atomic energies never vanish, but they have an inverse square relationship with distance. Therefore it is computationally beneficial to remove edges between amino acids that are beyond some specified interaction distance, and thus have inter-atomic energy near zero. On the other hand, removing edges between amino acids that are within that interaction distance can significantly impact energy evaluation and cause inference to fail. Seen in this manner, the problem of predicting a sparse graph structure is equivalent to determining the probability that two amino acids will be within the interaction distance in the final protein structure, with a goal of limiting false negatives.

2 Related Work

Predicting amino acid contacts is an active area of research in the field of protein structure prediction. An accurate set of protein contacts can be used to initialize a protein structure prediction algorithm with a restricted set of edges, reducing computational load [1]. In addition, efforts to predict a 3D protein structure *de novo* by using amino acid proximity estimates to constrain structure have proven partially successful [2]. Rather than attempt to predict amino acid contacts from solely a sequenced protein, modern contact prediction algorithms have relied on relationships between homologous protein domains, which are subdivisions of proteins that are evolutionarily related. Ekeberg et al. use sequence-aligned protein domains to fit a Potts model to protein domain families [3]. In this model, amino acid positions in a sequence are likely to be in contact if their values are correlated across many proteins domains in the sequence's family. Other approaches model protein families as Gaussian Graphical Models with some correlations existing between families [4]. Unfortunately, protein domain family models, such as the Potts model presented by Ekeberg et al., tend to produce many false negatives in their final predictions. As mentioned above, false negatives are much more detrimental to D-PMP inference than false positives. The CoinFold contact prediction system [5], combines evolutionary correlation models with sequence-level features, which may produce a model more uniquely suited to initializing a physical protein structure prediction algorithm. However, the CoinFold model still focuses on minimizing total error and obtains a large number of false negatives.

3 Model

Let $A_1, A_2, \ldots, A_N$ represent the amino acid sequence of a protein. Each variable A_i can be represented as a tuple $(i, type)$ where i denotes the position in the sequence and $type$ denotes the amino acid type. Our goal is to predict a set of binary interaction variable $y_{ij}, i \neq j$ which indicate whether the amino acids A_i, A_j are close enough to interact. Since distance is symmetric, $y_{ij} = y_{ji}$ for every i, j. Let $p(y_{ij} \mid A_i, A_j) \sim Ber(y_{ij} \mid \phi(A_i, A_j))$, where ϕ is a function on two amino acids and outputs a number in $[0, 1]$.

This is a very simple model of a protein. Note that given the observed amino acid sequence, each interaction potential is conditionally independent of every other potential. This reduces the problem to predicting estimates for a series of independent unary factors, which is both unlikely to be successful and not particularly interesting. However, it could provide a baseline against which to test other models.

Here, we suggest several possible model adjustments that could improve performance. An obvious improvement would be to place a prior on the distribution of each y_{ij}, so that

$$p(y_{ij} \mid A_i, A_j) \sim Ber(y_{ij} \mid \phi(A_i, A_j))Beta(\alpha, \beta)$$

Adjusting α and β could help encourage or discourage sparseness in final prediction. Another possible change is adding an interaction term between trios of factors y_{ij}, y_{jk}, and y_{ik} such that the presence of an edge between amino acids i and j, and of an edge between amino acids j and k, increases the probability of an edge between amino acids i and k. Including all these terms would result in the graphical model predicted in Figure 1.

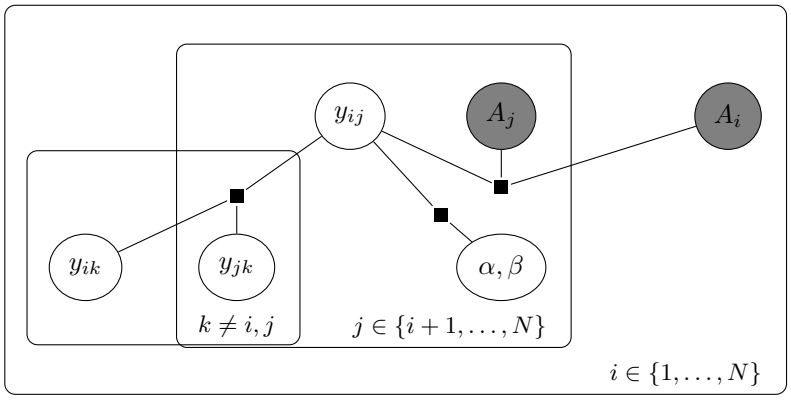

Figure 1: Potential graphical model with multiple additions. y_{ij}, y_{jk}, y_{ik} have factor increasing the probability of the third if the other two equal 1. α, β are hyperparameters on a prior on the distribution of y_{ij}.

4 Challenges

There are two challenges to overcome. First, we must learn feature functions ϕ for the probability of y_{ij} given A_i, A_j and for the joint distribution $p(y_{ij}, y_{jk}, y_{ik})$. We can obtain the true graph structures of proteins using data from the Protein Data Bank, then use these graph structures, along with the corresponding amino acid sequences, to determine these distributions. We are also looking into using evolutionary data to determine if certain types of amino acids are more or less likely to interact. Second, we must perform inference on the graphical model. This may be possible using loopy belief propagation (although with the additional factor $p(y_{ij}, y_{jk}, y_{ik})$ the graph will be very loopy).

5 Data

To train and test our model, we are using protein data from the Protein Data Bank. PDB files contain x, y, z coordinates for each atom in each amino amino acid of a protein. From these coordinates, distances between atoms can be computed and converted into a graph, where edges exist between amino acids if they lie within a threshold distance d of each other, with $d = 10$ for our initial data processing. We are using a 1000-protein set for our initial model training and testing, with 750 allocated for training and 250 for test. These graphs will serve two primary purposes: training and testing our factor potentials, as well as providing ground-truth data for our edge prediction model. Fig. 2 contains example of a graph produced from a processed PBD file:

We observe that for this protein, most edges are highly localized among adjacent amino acids. However, many edges have connections across the protein, which is in and of itself an indicator of protein fold structure. We also observe that this graph is relatively sparse (compared to the complete graph), with 882 edges connecting 108 amino acids.

6 Evaluation

As mentioned above, methods for protein contact prediction already exist, at least two of which are freely available on the internet[3] [5]. The CoinFold model described by Wang et al. uses

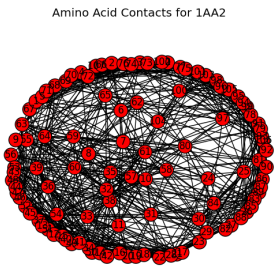

Figure 2: Amino Acid Contact graph for Protein 1AA2.

both the amino acid sequence and evolutionary data to predict contact between amino acids in a protein. It is not a direct parallel, because CoinFold attempts to minimize total error, while we seek to minimize false negatives. Despite this, CoinFold would likely provide a good baseline against which to evaluate. The Ekeberg et al. [3] Potts model could also provide a valuable baseline for our model. A key concept used in the evaluation of both systems is the difference between short, medium, and long-range contacts. Predicting contacts between amino acids that are close in the sequence is intuitively simpler than predicting long-range contacts, which may implicitly represent complex secondary and tertiary protein structure.

We also plan to evaluate different models against each other. For example, the model with joint $p(y_{ij}, y_{jk}, y_{ik})$ can be evaluated against the naive model involving only unary factors (assuming A_i, A_j are observed). To evaluate the use of our model combined with D-PMP inference, we plan to initialize D-PMP inference with different graph structures including a complete graph, a random graph, and a graph with connections only along the backbone (i.e. between amino acids A_i and A_{i+1}). This will help determine what improvements come from our model versus from D-PMP inference.

7 Timeline

Week 1: Create features based on distance in amino acid sequence and amino acid type. Implement and test simple model. Run on CoinFold and other benchmarks. **Week 2:** Experiment with different models (e.g. factors between triplets of edge indicator variables). Experiment with adding priors to the models. **Week 3:** Look into contextual feature functions (take into account surrounding amino acids). Look into evolutionary-based feature functions **Week 4:** Preliminary evaluation (750 training, 250 test proteins). Create presentation. **Week 5-6:** Experiment with iterative improvement via DPMP. Stretch goal: use secondary structure prediction to estimate contacts. Stretch goal: use CryoEM data to predict contacts. Write paper.

References

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