Novel Approaches to the Protein Design Problem

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1 Introduction

The protein design problem can be described as follows. Given a set of backbone coordinates $\mathbf{c} = (\vec{c_1}, \vec{c_2}, \ldots, \vec{c_n})$ and rotamer library R of length r, identify the optimal rotamer assignment sequence $\vec{r} = (r_1, r_2, \ldots, r_n)$, $r_i \in R$, $1 \leq i \leq n$ according to an energy function $E(\vec{r})$. This assignment sequence is known as the global minimum energy conformation (GMEC). This problem has been proven to be NP-hard [1], and algorithms such as DEE [2] have been created to allow for combinatorial pruning of the residue search space and make the design problem computationally tractable. However, such algorithms cannot guarantee a time complexity less than the worst-case $O(nr^n)$.

Recent graph based algorithms such as BWM* [3] use sparse residue interaction graphs in order to more efficiently compute functions over the residue space and identify optimal assignments more rapidly. Such graph-based algorithms have been able to achieve combinatorial speedups while maintaining provable accuracy and returning ensemble of minimum energy conformations.

Probabilistic models of protein design assign a probability distribution for rotamers in each position of the protein sequence. In algorithms such as belief propagation, the beliefs or the approximate marginal probabilities of each rotamer are computed iteratively. These approximations are computationally less intense, but they are not always provably accurate [4]. Furthermore, such algorithms are only guaranteed to converge on tree graphs, which are not commonly observed in natural proteins [5].

2 Graph Cuts and the GMEC

2.1 The Graph Labeling Problem

The goal of this project was to apply graph cut-based algorithms to the protein design problem. We began by attempting to characterize the protein design problem as a graph cut problem and identifying relevant algorithms that might allow efficient approximations of the GMEC.

The protein design problem is most accurately represented not as solely a graph cut problem, but as a graph labeling problem, where each rotamer is a label. The Graph Labeling (GL) problem can be stated as follows: classify a set $\mathcal{V}$ of n objects by assigning to each object a label from a given set $\mathcal{L}$ of labels, given a weighted graph $\mathcal{G} = (\mathcal{V}, \mathcal{E}, w)$. For each $p \in \mathcal{V}$ there is a label cost $\mathbf{c}_p(a) \geq 0$ for assigning the label $a = f_p$ to p, and for every edge pq there is a pairwise cost $\mathbf{c}_{pq}(a, b) = w_{pq} d_{pq}(ab)$ where $d_{pq}(ab)$ is the distance between (or cost of) label a on vertex p and b on vertex q. Thus, the cost of a labeling f is as follows:

$$\mathrm{COST}(f) = \sum_{p \in \mathcal{V}} \mathbf{c}_p(f_p) + \sum_{(p,q) \in \mathcal{E}} w_{pq} d_{pq}(f_p, f_q) \tag{1}$$

The most promising algorithm for an efficient solution was [6], which provides an approximation algorithm based on graph cuts for the non-metric labeling problem, which requires a distance function $d(a, b)$ such that $d(a, b) = 0 \iff a = b$ and $d(a, b) \geq 0$. The algorithm provides a labeling with a cost that is an f-approximation to the minimum-cost labeling, where $f = \frac{d_{max}}{d_{min}}$, where d_{max} is the maximum distance between any two rotamers and d_{min} is the minimum distance.

2.2 Application to the Protein Design Problem

The internal energy of a protein can easily be modeled by equation 1, where the function $\mathbf{c}_p(f_p)$ is held to represent the internal energy of a rotamer f_p at position p and the function $w_{pq} d_{pq}(f_p, f_q)$ is held to represent the pairwise interaction of a rotamer f_p at position p and a rotamer f_q at position q. In addition, each residue is modeled by a single node in the vertex set $\mathcal{V}$, and interactions between residues are represented by edges between nodes in the edge set $\mathcal{E}$.

In order to maintain the distance constraint $\mathbf{c}_{pq}(a, b) = w_{pq} d_{pq}(ab)$, the label set L was set as the Cartesian product $R \times \mathcal{V}$ of the set of all rotamers with the set of all positions. Thus, a given label $l \in \mathcal{L}$ represents a specific rotamer at a particular position. The pairwise interaction between a label and itself can then be set as zero. In order to ensure that a rotamer for position 1 was not assigned to position 2, the cost of labeling a rotamer to the wrong position was set to be prohibitively high.

References

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