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A Distributed Computing Platform for Large-Scale Computational Protein Design

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ABSTRACT

Motivation:

Results:

Availability:

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1 INTRODUCTION

In the past few years, Computational Protein Design (CPD) has become an important tool for protein engineering (Alvizo et al., 2007), such as peptide synthesis (Ottl et al., 1996), protein-protein interactions (Roberts et al., 2012), artificial gene synthesis (Villalobos et al., 2006), etc. In the structure-based computational protein design problem, the goal is to predict amino acid sequences that will fold to a specific protein structure. More precisely, the aim for CPD is to find the global minimum energy conformation (GMEC) based on the desired energy function.

The protein design problem has been proven NP-hard (Pierce and Winfree, 2002). This problem is modeled as a MAP-MRF inference problem (Yanover et al., 2006), which can be approximated by a Linear Programming Relaxation (LPR) problem (Wainwright et al., 2005). On the other hand, there exists several methods which can solve the GMEC problem exactly, such as DEE/A* (OSPREY, Donald Lab at DUKE University), Branch-and-Bound Search (Hong and Lozano-Pérez, 2006), tree decomposition (Xu and Berger, 2006), AND/OR Branch-and-Bound (Marinescu and Dechter, 2009), Integer Linear Programming (Kingsford et al., 2005), Cost Network Function (Traoré et al., 2013).

Our work is the first attempt to apply the branch-and-bound (BnB) search algorithm on distributed platform (such as MapReduce) to solve the Computational Protein Design problem. In our method, the DEE criteria is applied to prune the infeasible rotamers not only as a pre-filtering algorithm but also in the branch step. Since the efficiency of the branch-and-bound searching algorithm heavily depends on the tightness of the bound, we use MPLP (Globerson and Jaakkola, 2008) and mini-bucket (Rollon and Dechter, 2010) to compute the lower bound, and use Monte Carlo and simulated annealing to find a good solution as our upper bound.

2 METHODS

2.1 Definition

Consider the Pairwise Markov Networks, we have an undirected graph $G = (V, E)$. For each vertex $v \in V$, there is an available states set X_v and an energy function $\theta_v : X_v \to \mathbb{R}$. And for each edge $(u, v) \in E_G$, there is also an energy function $\theta_{u,v} : X_u \times X_v \to \mathbb{R}$, which defines interaction between vertices. The problem is to find the optimal assignment $\mathbf{x}^*$ that minimizes the total energy, namely

$$\mathbf{x}^* = \arg\min_{\mathbf{x}} \left(\sum_{v \in V} \theta_v(x_v) + \sum_{(u,v) \in E} \theta_{u,v}(x_u, x_v) \right)$$

2.2 Branch-and-Bound

Branch and Bound is a widely used search algorithm, which requires strong skills for solving different problems with it. The basic idea is to do a search on the solution space of an optimization problem with constraints. The algorithm constantly divides the solution space into smaller subsets (this procedure is called Branch) and calculate a lower bound and an upper bound for each solution in a subset(this procedure is called Bound). After each Branch procedure, the subsets whose bound is beyond known solutions will not be considered further. As a result, many subsets(i.e. nodes on search tree) can be excluded, which reduces the solution space to be searched.

To be more specific, assume that we have an optimization problem which wants to minimize the energy function. The algorithm is divided into two parts:

1. Branch: The solution space S, is divided into two (or more, we use two for example) subsets S_1 and S_2, which satisfy $S_1 \cap S_2 = \emptyset$ and $S_1 \cup S_2 = S$.
2. Bound: We evaluate S_1 and S_2 and get the lower bound of minimum solution(get the minimum lower bounds) $LB(S_1)$ and $LB(S_2)$ correspondingly, and the upper bounds $UB(S_1)$ and $UB(S_2)$. If we have $LB(S_2) \geq UB(S_1)$, we can safely throw S_2 away without losing the optimal solution.

Branch and Bound usually search the solution tree with BFS or optimum-cost-first method. Each live node has only one chance to be an expansion node, which produces all child nodes in one visit. The nodes which lead to infeasible or non-optimal solutions in the child nodes will be thrown away. The nodes left will be added to the list of live nodes.

2.3 MapReduce

MapReduce is a programming model proposed by Google which is used for massive parallel computing.

MapReduce is composed of the following two main steps:

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1. Map procedure: The input data is divided into N parts. The code for processing each part and the data will be copied to a compute node. The compute nodes run parallel and return the result.
2. Reduce procedure: The result of step 1 is distributed to M compute nodes. The nodes run parallel and return the result.

What users need to do is just implement map and reduce functions. Map tells the platform how to process the data, and reduce tells how to combine the results.

2.4 Branch-and-Bound Algorithm

Assume we have n vertices which are numbered from 1 to n, and let the states set of vertex i be X_i.

Algorithm 1 Branch and Bound Algorithm

```
1: function BranchAndBound(G = (V, E, X, θ))
2:     X_V ← X_1 × X_2 × ··· × X_n
3:     best ← UpperBound(X_V)
4:     Add(Q, X_V)
5:     while Q is not empty do
6:         X ← NextElement(Q)
7:         if LowerBound(X) ≥ best then
8:             continue
9:         end if
10:        (X^1, X^2, ..., X^m) ← Branch(X)
11:        for i ← 1 to m do
12:            best ← min(best, UpperBound(X^i))
13:        end for
14:        for i ← 1 to m do
15:            if LowerBound(X^i) < best then
16:                Add(Q, X^i)
17:            end if
18:        end for
19:    end while
20:    return best
21: end function
```

2.5 Branch-and-Bound on MapReduce

If we take a look at the search tree of the algorithm, we can observe that the expansions of nodes on the same level are independent. Therefore, the branch procedure can be done parallel for a level of nodes. After that the bound procedure is done on all nodes expanded.

This can be fit into the MapReduce model. In a MapReduce model, input data is a list of `(key, value)` pairs, which is first processed by `map` function. The `map` function takes each `(key, value)` pair as input, do some calculation on it and emits a list of `(key', value')` pairs. The outputs are then grouped by keys, and sent to the `reduce` function. The `reduce` function takes a key and a list of values as input, and outputs a list of `(key'', value'')` pairs.

In our design, we process each level of the search tree with one MapReduce job, where we call it one iteration. In the ith iteration, we expand the ith level of nodes. Therefore the whole search needs n iterations. For each iteration, the `map` function is designed as follows

Algorithm 2 Map

```
1: function Map(Key, Value, Context)
2:     X ← Value
3:     (X^1, X^2, ..., X^m) ← Branch(X)
4:     for i ← 1 to m do
5:         best ← min(best, UpperBound(X^i))
6:     end for
7:     for i ← 1 to m do
8:         if LowerBound(X^i) < best then
9:             Context.write(X)
10:        end if
11:    end for
12:    return best
13: end function
```

When we come to the `reduce` function, we should iterate over all nodes expanded to get the minimum upper bound. This results in only one reduce in each job, which significantly reduces parallelism. We use what we call *random grouping* to solve this.

Let a piece of input of map be $(key, value)$. We set key to be empty and let $value$ represent a node on the search tree, which includes $n+3$ fields. The first 3 states are minimum upper bound, lower bound and upper bound. The following n fields corresponds to the states of each vertex with -1 representing the vertex has not been searched yet.

In the map function we expand a node $k = \{globalBest, LB, UB, state_1, \ldots, state_n\}$ to a list of nodes $L = \{k_1, \ldots, k_m\}$, calculate lower bound and upper bound for each k_i and finally update the minimum upper bound for each k_i. Thus the output nodes of each map function see a 'local' view of the minimum upper bound. We assign each output node's key field with a random integer which lies in $[0, r)$. The nodes with same key will be sent to the same reduce.

In the reduce function, nodes will share their local minimum upper bound. ????

Let t be the number of nodes expanded. Since we have r random integers, the nodes will be divided into r groups where each group has approximately $t_1 = \lceil t/r \rceil$ nodes. Assume there are q maps, normally the t nodes are equally produced by the maps. Therefore, at least $t_2 = \lceil t/q \rceil$ will see the actual global upper bound after map. The probability that none of the these nodes is in some particular group is

$$\left(\frac{r-1}{r}\right)^{t_2}$$

Let p be the probability that each node sees the actual global minimum upper bound after reduce. We have

$$p \geq 1 - r\left(1 - \frac{1}{r}\right)^{t_2}$$

For instance, select r be 3-5 times the number of machines, probably 200. If we make t_2 be 10000, then we have

$$p \geq 1 - 200(1 - 1/200)^{10000} = 1$$

3 OPTIMIZATION

3.1 Local Dead-End Elimination Algorithm

The dead-end elimination (DEE) algorithm is an efficient method to eliminate infeasible variable states. For a variable x_v, and two variable states x_v^i and x_v^j in X_v, if the following condition is satisfied, then state x_v^i can be eliminated, which reduces the search space.

$$\begin{aligned}\theta_v(x_v^i) + \sum_{(u,v)\in E} \min_{x_u \in X_u} \theta_{uv}(x_u, x_v^i) \\ > \theta_v(x_v^j) + \sum_{(u,v)\in E} \max_{x_u \in X_u} \theta_{uv}(x_u, x_v^j)\end{aligned} \tag{1}$$

The more powerful criterion that improved by Goldstein (1994) is

$$\theta_v(x_v^i) - \theta_v(x_v^j) + \sum_{(u,v)\in E} \min_{x_u \in X_u} [\theta_{uv}(x_u, x_v^i) - \theta_{uv}(x_u, x_v^j)] > 0 \tag{2}$$

We apply the Goldstein DEE criterion in (2) in the function BRANCH. Let $D(X)$ be the set of variables that have been searched, and $U(X) = V \setminus D(X)$ be the set of variables which has not been determined yet. Consider two variable states x_v^i and x_v^j in an undetermined variable x_v, the Goldstein DEE criterion we use in the BRANCH functions is

$$\begin{aligned}\theta_v(x_v^i) - \theta_v(x_v^j) + \sum_{(u,v)\in E \wedge u \in D(X)} [\theta_{uv}(x_u, x_v^i) - \theta_{uv}(x_u, x_v^j)] \\ + \sum_{(u,v)\in E \wedge u \in U(X)} \min_{x_u \in X_u} [\theta_{uv}(x_u, x_v^i) - \theta_{uv}(x_u, x_v^j)] > 0\end{aligned} \tag{3}$$

So that we can eliminate a large number of infeasible variable states, and thus significantly reduces the branch space.

Here, ...

3.2 Lower Bound

Naive Lower Bound. Firstly we have a naive lower bound, the heuristic function is

$$\sum_{v\in V} \min_{x_v \in X_v} \left(\theta_v(x_v) + \sum_{(u,v)\in E \wedge u < v} \min_{x_u \in X_u} \theta_{vu}(x_v, x_u)\right) \tag{4}$$

and the form of the current state space X is

$$\begin{aligned}LB_1(X) = g(X) + \sum_{v\in U(x)} \min_{x_v \in X_v} \left(\theta_v(x_v) + \sum_{u\in D(X)} \theta_{uv}(x_u, x_v)\right. \\ \left. + \sum_{u<v \wedge u \in U(X)} \min_{x_u \in X_u} \theta_{uv}(x_u, x_v)\right)\end{aligned} \tag{5}$$

there we leave $(u, v) \in E$ out from the summation notation for convenience, and $g(X)$ is the energy that has determined, that is

$$g(X) = \sum_{v\in D(X)} \theta_v(x_v) + \sum_{u\in D(X) \wedge v \in D(X)} \theta_{uv}(x_u, x_v)$$

Efficient Lower Bound. By observing the formula of the naive lower bound, we see that every edge-energy function is only used

for the vertex that has the greater index. If we split θ_{uv} into two functions β_{uv} and β_{vu} where $\beta_{uv}(x_u, x_v) + \beta_{vu}(x_v, x_u) = \theta_{uv}(x_u, x_v)$ for all x_u, x_v, then the formula of (4) becomes

$$\max \sum_{v\in V} \min_{x_v \in X_v} \left(\theta_v(x_v) + \sum_{(u,v)\in E} \min_{x_u \in X_u} \beta_{uv}(x_u, x_v) \right) \quad (6)$$
$$s.t.\ \beta_{uv}(x_u, x_v) + \beta_{vu}(x_v, x_u) = \theta_{vu}(x_u, x_v)$$
$$\forall (u, v) \in E, x_u \in X_u, x_v \in X_v$$

The above optimization problem is a convex dual of MAPLPR, which can be solved by Convergent Message Passing Algorithms (Globerson and Jaakkola, 2008).

If we compute the best functions β^*, then the lower bound of state space X becomes

$$LB_2(X) = g(X) + \sum_{v\in U(X)} \min_{x_v \in X_v} \left(\theta_v(x_v) + \sum_{u\in D(X)} \theta_{uv}(x_u, x_v) + \sum_{u\in U(X)} \min_{x_u \in X_u} \beta^*_{uv}(x_u, x_v) \right) \quad (7)$$

Since β^* may not be the best functions for any state space, it is necessary because we can not compute it for all the searched state space.

If we compute LB_2 directly, then the time complexity is $O(n^2m^2)$. If we firstly compute a table p that $p_{uv}(x_v) = \min_{x_u \in X_u} \beta^*_{uv}(x_u, x_v)$ with time $O(n^2m^2)$ and space $O(n^2m)$, then the time of computing LB_2 decrease to $O(n^2m)$.

Mini-Bucket. The mini-bucket elimination (MBE) is a well-known approximation algorithm for graphical models, and it gives a bound when the induced width of the graph is too large. The idea of bucket elimination (BE) is to eliminate variables, and the pseudo-code is as follows.

Algorithm 3 Bucket Elimination

function BUCKETELIMINATION($\mathcal{F}, v$)
  $\mathcal{B} \leftarrow \{f \in \mathcal{F} | v \in var(f)\}$
  $g \leftarrow \mathcal{B} \Downarrow v$
  $\mathcal{F} \leftarrow (\mathcal{F} \setminus \mathcal{B}) \cup \{g\}$
  return $\mathcal{F}$
end function

There the operation $\mathcal{B} \Downarrow v$ means combine the functions in $\mathcal{B}$ with eliminating the variable v. The time and space complexity of the algorithm is exponential in the largest scope of all the functions that computed.

Mini-bucket elimination has a parameter z which restrict the size of the scopes of each functions, and also restrict the time and space complexity.

PARTITION($\mathcal{B}, z$) means that divide $\mathcal{B}$ into parts $Q_1, Q_2, ..., Q_m$ and $var(Q_i) \leq z + 1$ for $1 \leq i \leq m$.

For the current state space X, we eliminate all the variables in $U(X)$, and then summarize all the functions on $D(X)$, then we get another lower bound of state space X.

Algorithm 4 Mini-Bucket Elimination

function BUCKETELIMINATION($\mathcal{F}, v$)
  $\mathcal{B} \leftarrow \{f \in \mathcal{F} | v \in var(f)\}$
  $(Q_1, Q_2, ..., Q_m) \leftarrow$ PARTITION($\mathcal{B}, z$)
  for $i \leftarrow 1$ **to** m **do**
    $g_i \leftarrow Q_i \Downarrow v$
  end for
  $\mathcal{F} \leftarrow (\mathcal{F} \setminus \mathcal{B}) \cup \{g_1, g_2, ..., g_m\}$
  return $\mathcal{F}$
end function

3.3 Upper Bound

Different with lower bound, we make the upper bound of state space X be a better solution in X. There are many algorithm for finding a better solution of a problem, such as Simulated Annealing (SA), Genetic Algorithm.

We use Simulated Annealing as our upper bound algorithm. The initial state of SA is according to LB_2, which means

$$x^0_v = \arg\min_{x_v \in X_v} \left(\theta_v(x_v) + \sum_{u\in D(X)} \theta_{uv}(x_u, x_v) + \sum_{u\in U(X)} p_{uv}(x_v) \right)$$

Let $\mathbf{x}^S$ be the best solution that find by Simulated Annealing Algorithm, then

$$UB(X) = g(\mathbf{x}^S)$$

3.4 Refinement on MapReduce

With some experiments we notice that each iteration can be done with a map-only job, in which we omit the reduce part. This significantly reduces running time since the shuffle between map and reduce will sort the data, which we do not need. However, this will cause many nodes not seeing the global minimum upper bound, which leads to fewer nodes discarded than in random grouping. To solve this, we use a *parameter server*.

We set up a web server which stores the global minimum upper bound and supports query and modify to the bound. In each map, we start another thread, which constantly check if the local minimum upper bound is updated, and if so, this thread will interact with the web server. This thread is independent from the map function and thus will bring very little overhead. But with the server, the output nodes of each iteration reduces abount $1/3$ to $1/2$.

4 RESULTS

5 CONCLUSION

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