Neighborhood Selection in Constraint-Based Local Search for Protein Structure Prediction

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Abstract. Protein structure prediction (PSP) is a very challenging constraint optimization problem. Constraint-based local search approaches have obtained promising results in solving constraint models for PSP. However, the neighborhood exploration policies adopted in these approaches either remain exhaustive or are based on random decisions. In this paper, we propose heuristics to intelligently explore only the promising areas of the search neighborhood. On face centered cubic lattice using a realistic 20×20 energy model and standard benchmark proteins, we obtain structures with significantly lower energy and RMSD values than those obtained by the state-of-the-art algorithms.

1 Introduction

Ab initio methods for protein structure prediction (PSP), without using any templates or structures of known similar proteins, starts searching from the scratch for the native structure that has the minimum free energy. Due to the complexity of all-atomic detailed models and unknown factors of the energy function, the general paradigm of *ab initio* PSP has been to begin with the sampling of a large set of candidate or *decoy* structures guided by a scoring function. In the final stage, the refinements [22] are done to achieve the realistic structure. Given a primary amino acid sequence of a protein, PSP can be defined as: find a *self-avoiding* walk on a discrete lattice that minimizes a contact-based energy function. However, the conformational search space still remains huge and the problem itself remains a very challenging constraint optimization problem.

Given a current partial or complete solution, selection of the neighboring solutions for further exploration is a key factor in the performance of constraint programming (CP) and local search approaches. Neighborhood selections involves selection of variables and values. Unguided random selection [23, 28], costly exhaustive generation [5] and filtering or ordering techniques for enumeration [28, 19] are not much effective for neighborhood selection in PSP. In other domains, such as propositional satisfiability *promising* variables are selected using different variable selection strategies [20, 1].

In this paper, we propose several novel component fitness functions for neighborhood selection in PSP. These heuristics are an energy contribution function, a core-based distance function and a free lattice-neighbor count based function.

These heuristics are derived from domain knowledge and are used along with a hint based variable selection strategy. The aggregate of these heuristics are used in selecting candidate structures. To the best of our knowledge, this is the first application of intelligent variable selection strategy in PSP. We also propose a new chain growth initialization for the energy model used. Experimental results show that our method significantly improves over the state-of-the-art algorithms and produces structures with lower energy and RMSD values for standard benchmark proteins on face centered cubic lattices.

2 Related Work

Simplified models such as Hydrophobic-Polar (HP) energy model [9] and discrete lattices have been studied extensively by many researchers within various frameworks such as constraint programming [7], genetic algorithms [21], and memory-based local search approaches [24].

In contrast to HP models, elaborate energy functions derived by using statistical methods [14, 2] take into consideration all 20×20 amino-acid interactions. Using secondary information and constraint programming techniques, Dal Palu *et al.* [19] developed a method to predict tertiary structures of real proteins. They also proposed several generalized and problem specific heuristics [17]. Later, they also developed a highly optimized constraint solver named COLA [18].

A two-stage optimization method was proposed in [27] by Ullah *et al.* It uses CPSP tool by Backofen *et al.* [12] to provide initial structure for local search procedure on FCC lattice and an elaborate energy function. The two-stage optimization approach was reported to outperform simulated annealing-based local search procedure [25]. Ullah *et al.* also used large neighborhood search techniques on top of the COLA solver [28]. A fragment assembly method was proposed in [16] to produce low energy structures. Later, a filtering techniques for loop modeling [4] was proposed using CP techniques. In a recent work, several effective heuristics were used in a mixed fashion in [23] which produced state-of-the-art results on real proteins from standard benchmark set for contact-based energy models. Our work in this paper uses a hint-based variable selection strategy to generate the neighborhoods to be explored. Our work also uses a new chain growth initialization method.

Among other approaches in PSP are population based methods [8] and genetic algorithms [26] and CP techniques for side-chain models [13].

3 The Problem Model and CP Formulation

Proteins are polymers of amino-acid monomers. There are 20 different amino acids. In a simplified model, all monomers have an equal size and all bonds are of equal length. In a CP formulation, each monomer is modeled by a point in a three dimensional lattice (*lattice* constraint). The given amino acid sequence fits into the lattice: every pair of consecutive amino acids in the sequence are also neighbors in the lattice (*chain* constraint) and two monomers can not occupy the

same point in the lattice (*self avoiding* constraint). A simplified energy function is used in calculating the energy of a structure.

Two lattice points $p, q \in \mathbb{L}$ are said to be in *contact* or *neighbors* of each other, if $q = p + \mathbf{v}_i$ for some vector $\mathbf{v}_i$ in the basis of L . The Face Centered Cubic (FCC) lattice is preferred since it provides the densest packing [6] for spheres of equal size and the highest degree of freedom for placing an amino acid. The points in FCC lattice are generated by the following basis vectors: $\mathbf{v}_1 = (1, 1, 0)$, $\mathbf{v}_2 = (-1, -1, 0)$, $\mathbf{v}_3 = (-1, 1, 0)$, $\mathbf{v}_4 = (1, -1, 0)$, $\mathbf{v}_5 = (0, 1, 1)$, $\mathbf{v}_6 = (0, 1, -1)$, $\mathbf{v}_7 = (0, -1, -1)$, $\mathbf{v}_8 = (0, -1, 1)$, $\mathbf{v}_9 = (1, 0, 1)$, $\mathbf{v}_{10} = (-1, 0, 1)$, $\mathbf{v}_{11} = (-1, 0, -1)$, $\mathbf{v}_{12} = (1, 0, -1)$. In FCC lattice, each point has 12 neighbors and distance between two neighbors is $\sqrt{2}$.

In our CP model, we are given a sequence S , where each element $s_i \in S$ is an amino-acid type. Each amino acid i is associated with a point $p_i = (x_i, y_i, z_i) \in \mathbb{Z}^3$. The decision variables are the x , y and z co-ordinates of a point. For a sequence of length n , the domain of the variables is the range $[-n, n]$. Formally, $\forall_i x_i \in [-n, n]$, $\forall_i y_i \in [-n, n]$ and $\forall_i z_i \in [-n, n]$. The first point is assigned as $(0, 0, 0)$, which is a valid point in the FCC lattice. The rest of the points follows the constraint, $\forall_{i < n} (\mathbf{a}_i) \in \{\mathbf{v}_1, \dots, \mathbf{v}_{12}\}$. Here, $\mathbf{a}_i$ is the absolute vector between points $(x_{i+1}, y_{i+1}, z_{i+1})$ and (x_i, y_i, z_i) , and $\{\mathbf{v}_1, \dots, \mathbf{v}_{12}\}$ are the basis vectors for FCC lattice. Thus all points satisfy the *lattice* constraint and *chain* constraint. The *self-avoiding* constraint is defined using the *all-different* constraint $\text{all-different}(\forall_i p_i)$. We define $\text{sqrdist}(i, j)$ as the square of Euclidean distances between two points p_i and p_j . Now, $\text{contact}(i, j) = 1$, if $\text{sqrdist}(i, j) = 2$; and $\text{contact}(i, j) = 0$, if $\text{sqrdist}(i, j) \neq 2$. For any given protein sequence S , the energy of a structure c is defined as:

$$E(c) = \sum_{j \geq i+1}^n \text{contact}(i, j) \cdot \text{energy}(s_i, s_j) \quad (1)$$

where $\text{energy}(s_i, s_j)$ is the empirical energy value between two amino-acids of type s_i and s_j obtained from the energy matrix given in [2]. Given this model, PSP can be defined as follows: given a sequence S of length n , find a self-avoiding walk $p_1, \dots, p_n$ on the lattice that minimizes the energy *i.e.* $\text{obj} = E(c)$.

4 Our Approach

Our approach is based on component heuristic functions that are used with a hint based variable selection strategy and aggregate functions which are used for candidate selection. Rest of the section describes necessary details.

4.1 Search Procedure

The search starts with the greedy chain growth initialization procedure that produces a compact low energy structure. Based on a walk probability wp (initially set to 5%), a variable is selected randomly or from a hint based priority queue

with tabu on recently selected variables and the corresponding amino-acid position is determined. Neighborhood is generated only for the position selected using a set of operators. Then the generated candidate moves are simulated. Simulation of a move temporarily calculates the changes in the heuristic functions without committing the move. At each iteration, one of the heuristics are selected randomly by a uniform random distribution. After simulation, the best candidate move is selected and executed. The execution updates all cost functions, constraints and propagate hints. Ties are broken using a uniform random distribution. The search keep tracks of the global minimum found and restarts from the last found global minimum whenever it gets stuck. Stagnation is determined by a number of non-improving moves from the last found global minimum. At stagnation, the stagnation parameter sp (initially set to 500) and the walk probability wp are multiplied by a factor (set 1.2). Parameters wp and sp are set to initial values, whenever a new global minimum is found. Pseudo-code of our algorithm is given in Algorithm 1.

Algorithm 1: localSearch(conformation C)

```

1  $C \leftarrow \text{CGInitialize}()$ 
2  $nonImp \leftarrow 0$ 
3 while  $nonImp \leq stagnation$  do
4   evaluateHints()
5    $i \leftarrow \text{selectPosition}()$ 
6    $o \leftarrow \text{selectOperator}()$ 
7    $list \leftarrow \text{generateMoves}(C, i, o)$ 
8    $h \leftarrow \text{selectHeuristic}()$ 
9   simulateMoves( $list, h$ )
10   $m \leftarrow \text{selectBestMove}(list)$ 
11  executeMove( $C, m$ )
12  updateTabulist()
13  if not improving then
14     $nonImp++$ 
15  else
16     $nonImp \leftarrow 0$ 

```

For a clear outline of our contribution, it is worthwhile to note the differences of our algorithm from the algorithm in [23]. In Line 1 of Algorithm 1, we call our new initialization function while the initialization in [23] uses a structure fully contained within a sphere. In Line 4-5, we compute the hint heuristics and based on them, we select only one point, where the operators are applied. In contrast, in [23], points are selected randomly and then operators are applied in all selected points.

4.2 Heuristic Functions

The empirical energy model gives an elaborate interaction energy contribution for the amino-acid types. The points with lower contribution to the total energy functions are preferred for selection. First, we define the first component fitness function that calculates the contribution of a point to the total energy of the structure. Formally,

$$\text{contr}(i) = \sum_{0 \leq k \leq n, |i-k| > 1} \text{contact}(i, k) \times \text{energy}(s_i, s_k)$$

The intuition is to select the variables with the maximum $\text{contr}(i)$ so that the corresponding operators can lower the energy contribution. Note that, the lowest energy contributions are generally negative. However, heuristics designed from domain knowledge often provide interesting insights. One such properties of protein folding is due to the solvent type water. This property lets the hydrophobic residues buried inside the structure and helps form a compact core. Based on this fact, several methods and heuristics have been developed for HP model [12, 7]. However, interactions between two hydrophobic residues in contact in the core may result in repulsion (positive empirical energy) rather than attraction (negative empirical energy) and form a non-stable structure. For this reason, we don't use those heuristics directly into our model. We divide the 20 different amino-acids into two groups according to their similarity in interaction energy within each group. We run a simple k -means clustering algorithm on the empirical energy matrix to obtain two such groups (Group I: *Ala, Phe, Gly, Ile, Leu, Met, Pro, Val, Trp, Tyr*; Group II: *Cys, Asp, Glu, His, Lys, Asn, Gln, Arg, Ser, Thr*) such that interaction within each group minimizes the total energy contribution. We call these residues, *affine* residues and define an affine core, $a_c = (x_c, y_c, z_c)$, such that, $x_c = \frac{1}{|A|} \sum_{k \in A} x_k$, $y_c = \frac{1}{|A|} \sum_{k \in A} y_k$, $z_c = \frac{1}{|A|} \sum_{k \in A} z_k$, A is the set of affine amino acid positions and $|A|$ denotes the total number of affine positions. Now we expect to move the affine amino acids towards the core. We define, our next component fitness function:

$$\text{sqrdist-SCORE}(i) = \text{sqrdist}(i, a_c)$$

Naturally, we wish to move the distant affine positions nearer to the affine core, a_c , i.e. we wish to select the variables with maximum $\text{sqrdist-SCORE}(i)$ value. However, these component fitness functions to select the variable do not work well if there is not enough free positions in the lattice neighborhood of the point assigned to the position. Therefore, we define another component fitness function, $\text{free}(i)$. It counts the total number of free neighbors of a point i in a lattice. Formally,

$$\text{free-count}(i) = \sum_{k \in N(i)} \text{free}(k)$$

Here, $\text{free}(k) = 1$, if k is free; and $\text{free}(k) = 0$, if k is occupied and $N(i)$ is set of neighbors of i in the lattice. We wish to select the variables with the maximum

$\text{free}(i)$ so that the number of possible moves become higher. It is interesting to note that we wish to select variables that maximizes all three component functions. Now, we aggregate the component fitness functions for all amino acid position i and derive heuristic functions for the selection of candidate structures. We denote the heuristics as follows: the energy heuristic $h_E = \sum_{i \leq n} \text{contr}(i)$, the affine core heuristic $h_A = \sum_{i \leq n} \text{sqrdist-afcore}(i)$ and the compactness heuristic $h_F = \sum_{i \leq n} \text{free-count}(i)$. We wish to guide our search using these aggregate heuristic functions. The idea of component heuristics are previously used along with extremal optimization [11]. However, the heuristics used in this paper for the given energy model are novel themselves.

4.3 Hint Based Variable Selection

Now, we define two important terms: *metric* and *hint*. Each function $f(p_1, \dots, p_n)$ has the parameters p_j s that are either variables or other functions. A function f depends on a variable x , denoted by $f \rightarrow x$, if x is itself a parameter of f or f has a parameter $p \rightarrow x$. Each function f has a non-negative metric f_m denoting its evaluation. For each $x \leftarrow f$, it also has a non-negative hint $f_h(x)$ denoting the preference of changing x 's value to improve f_m . A constraint f is satisfied when $f_m = 0$ and in that case $f_h(x) = 0$ for any x , which means a constraint's metric improves when it is minimized.

In our model, all the component fitness functions are defined as constraints over the variables. For example, $\text{contact}(i, j)$ is defined as a constraint, $\text{sqrdist}(i, j) = 2$, which is satisfied only when the square of Euclidean distance between i and j is equal to 2. This function depends on the variables, x_i, y_i, z_i and x_j, y_j, z_j . The metric of the function is simply the evaluation of the constraint that tests equality with 2. If this constraint is not satisfied then the violation is added as the hint of these variables. Thus, variable violations for all the functions which are dependent on a particular variable is added as hint for that variable. Looking at these hint values, we decide which variable is to be selected in order to minimize the violation of the constraints. In our CP model, we take aggregate of all the component functions and take a summation of those aggregate functions to define another function on top as the hint provider. The variable violation for that top function is distributed as hints among the variables corresponding to amino acid positions. A simple heap or priority queue data structure with hint values is sufficient for us to decide which variable to select. We also maintain a tabu list to prevent recent variables to be selected. We use three different heuristics h_E , h_A and h_F , and sum them to form a top function that provides the hints for all the variables.

4.4 Chain Growth Initialization

The procedure is inspired from chain growth algorithms previously applied to HP models [3]. The initialization starts by assigning $(0, 0, 0)$ to the first amino acid position. The rest of the variables are assigned following a greedy strategy. One of the free neighbors of the last assigned amino acid position $i - 1$ is assigned

to position i , such that the the assignment minimizes the partial objective function, $\text{obj}_i = \sum_{k < i} \text{contact}(i, k) \times \text{energy}(s_i, s_k) + \text{free-count}(i) \times E_U[i]$. Here, k is iterated over already assigned amino acid positions and $E_U[i]$ is the per-contact expected or average energy contribution of i with possible unassigned amino acid positions in the chain. This partial objective function, obj_i is equal to the partial energy contribution, $\text{partial-E}(p_1, \dots, p_i)$. The tie-breaking is done according to a pre-defined order. Pseudo-code for variable selection for each step is given in Algorithm 3. The initialization procedure backtracks whenever, it fails to assign valid points to an amino acid position. This method guarantees to produce valid structure with low energy value. Pseudo-code of the chain growth initialization procedure is given in Algorithm 2.

Algorithm 2: CGInitialize()	Algorithm 3: selectDirection(i)
<pre> 1 $p_1 = (0, 0, 0)$ 2 for $i \leftarrow 2$ to n do 3 $\text{dir} = \text{selectDirection}(i)$ 4 if $\text{dir} = \text{null}$ then 5 backtrack() 6 else 7 $p_i = p_{i-1} + \text{dir}$ 8 return $p_1, \dots, p_n$ </pre>	<pre> 1 MinHeap $Q = \{\}$ 2 for all $\mathbf{v}_k \in \text{basis}$ do 3 $p_k = p_{i-1} + \mathbf{v}_k$ 4 if $\text{notOccupied}(p_k)$ then 5 $E_k = \text{partial-E}(p_0, \dots, p_{i-1}, p_k)$ 6 $Q.\text{add}(\mathbf{v}_k, E_k)$ 7 if $Q.\text{isEmpty}()$ then 8 return null 9 else 10 return $Q.\text{top}()$ </pre>

4.5 Operators

After a variable is selected, we can decide which amino acid position it corresponds to and apply the operators to that position. We make use of four types of operators (see Fig. 1). First two are jump move [23] and pull move [10] which are also used in the literature. We propose a single point pull move (Fig. 1(c)) similar to that of two point pull move and a single point push move which reverses the action of a single point pull move (Fig. 1(d)).

4.6 Implementation

We implemented our algorithm using C++ on top of the constraint based local search (CBLs) system, Kangaroo [15]. The functions and the constraints are defined using invariants in Kangaroo. Invariants are special constructs that are defined by using mathematical operators over the variables. Propagation of hints, simulation of moves, execution and related calculations are performed incrementally by Kangaroo.

Fig. 1. Different Operators used: (a) jump moves ($k=1,2,3$) (b) two point pull move (c) single point pull move and (d) push move

seq no	pdb id	seq len	Our Approach			Mixed [23]			Hybrid [28]		
			energy level		avg rmsd	energy level		avg rmsd	energy level		avg rmsd
			best	avg		best	avg		best	avg	
1	4rxn	54	-168.78	-164.28	5.56	-165.21	-156.32	6.29	-157.70	-140.13	9.99
2	1enh	54	-158.74	-152.43	5.33	-158.75	-146.69	6.61	-154.24	-141.99	10.04
3	4pti	58	-221.59	-205.42	5.86	-219.52	-198.42	7.07	-213.70	-196.23	11.92
4	2igd	61	-187.96	-179.36	6.34	-187.20	-174.19	9.33	-184.29	-157.20	13.30
5	1ypa	64	-257.02	-248.47	6.12	-249.90	-239.98	7.53	-221.11	-208.10	13.42
6	1r69	69	-223.12	-210.15	5.78	-213.04	-204.17	6.47	-180.62	-165.11	14.78
7	1ctf	74	-230.86	-220.04	6.14	-224.29	-213.81	7.23	-204.88	-195.23	12.65
8	3mx7	90	-332.79	-321.58	6.58	-328.12	-311.56	8.18	-	-	-
9	3nbm	108	-431.90	-415.02	6.28	-418.60	-401.99	8.58	-	-	-
10	3mqo	120	-476.06	-464.57	6.46	-465.74	-455.27	8.86	-	-	-
11	3mr0	142	-446.31	-435.69	7.32	-445.33	-430.28	10.02	-	-	-
12	3pnx	160	-603.78	-585.97	6.84	-601.23	-571.13	9.38	-	-	-

Table 1. Results obtained by different algorithms for 12 proteins

5 Experiments

We ran our experiments on a cluster of computers with nodes equipped with Intel Xeon CPU X5650 processors @2.67GHz, QDR 4 x InfiniBand Interconnect. We compare our results with the mixed heuristic approach in [23] and the hybrid approach in [28]. All the algorithms are given 1 hour to finish each run, and the best and average energy levels of 50 runs are reported in Table 1 for 12 benchmark proteins. These proteins are also used in [23]. The blank values in the table are the cases where hybrid approach failed to produce any valid structure within the time limit. PDB ids, sequence length and average RMSD values are also reported in the table. The best values are indicated in bold faced font. For all the 12 proteins, our approach achieves lower energy levels. The significance of these values are confirmed from the values reported in the *rmsd* column. For any given structure produced by an algorithm,

$$\text{RMSD} = \sqrt{\frac{\sum_{i=1}^{n-1} \sum_{j=i+1}^n (\text{dist}(i, j)^{\text{given}} - \text{dist}(i, j)^{\text{native}})^2}{n * (n - 1) / 2}}$$

Here $\text{dist}(i, j)$ is the Euclidean distance between two points p_i and p_j . In calculating the RMSD values, the distance between two neighbors in the lattice is considered to be equal to the average distance ($3.8\text{\AA}$) between two α -Carbons on the native structure. From the values reported we see, our approach also significantly improves over the other approaches in terms of the RMSD values; the lower the RMSD score, the better the performance. These values are significant since backbone reconstruction and addition of side-chain atoms can guarantee to produce real protein structures within small ($1\text{-}2\text{\AA}$) deviation [22]. However, since lattice configurations can only approximate the positions of the amino acids in the real space, lower RMSD values produced by our algorithm are satisfactory.

seq no	$\neg\text{hint}$	$+\text{hint}(h_A)$	$+\text{hint}(h_E)$	$\neg\text{hint}(h_F)$	$\neg h_{\text{select}}$	init_r	all
1	-146.61	-149.61	-151.25	-158	-156.08	-136.23	-164.28
2	-136.35	-137.62	-128.15	-147.03	-142.44	-137.08	-152.43
3	-185.52	-192.15	-189.45	-194.62	-200.6	-197.88	-205.42
4	-165.5	-158.16	-157.64	-171.24	-164.12	-149.74	-179.36
5	-235.75	-235.45	-236.88	-244.44	-244.71	-219.91	-248.47
6	-193.87	-187.64	-180.61	-183.20	-182.85	-178.25	-210.15
7	-197.83	-204.48	-198.45	-210.27	-206.84	-182.46	-220.04

Table 2. Average energy level achieved by different variants of our algorithm

In order to test the effectiveness of different components of our approach, we ran different variants of our approach on first 7 proteins and report average energy level of 20 runs for each of them in Table 2. First, we report the performance of a variant without using the hint based variable selection in column $\neg\text{hint}$. It shows how the hint based system can improve on this variant to achieve the final performance shown in ‘all’ column. The ‘all’ column, for convenience of the reader, again shows the average energy values obtained by our approach (as shown in Table 1). Then we ran two variants with hints for h_A only (column $+\text{hint}(h_A)$) and with hints for h_E only (column $+\text{hint}(h_E)$). These two variants show the effectiveness of using these two heuristics as hint provider individually. We see that these two heuristics are showing better performance than the hintless variant for most of the proteins, and $+\text{hint}(h_A)$ is performing better than $+\text{hint}(h_E)$. It reveals that the energy function itself is not enough for providing hints for the search and heuristic approximations can actually improve the performance. However, both of them shows effectiveness of hints over the no-hint variant. Then, we ran another variant with hints for both h_E and h_A , but not using hints for h_F (column $\neg\text{hint}(h_F)$). This particular variant shows the combined performance of two heuristics as hint provider and also shows the relative strength of the other hint heuristic h_F that is absent. We get a clear idea of the strength of h_F by comparing it with the final results in column ‘all’ and also strength of the combined variant by comparing the results with the individual columns of $+\text{hint}(h_A)$ and $+\text{hint}(h_E)$. We see that the combination of h_E and h_A which is $\neg\text{hint}(h_F)$ works better than the individual variants.

However, its only after adding the hints for h_F , its possible to achieve the final performance. Another variant uses the hint based system but the selection of candidate structures is guided by h_E only (column $\neg h_{select}$). This indicates the effectiveness of the heuristics to select candidate structures. The penultimate column ($init_r$) shows the results achieved by replacing our chain growth algorithm by a random initialization. From the reported values we see that chain growth initialization has a greater impact on most of the proteins with respect to the random initialization methods.

To show how the search makes progress, we plot log of average energy levels achieved, (for convenience of display in the chart) added by a threshold of 250 for the protein 4pti against iteration count in Fig. 2. We see that the variant without hint ($\neg hint$) works worst. It improves only at the beginning and then gets stagnant. Variants with hints for h_E and h_A works better than this. If we add hints for all the heuristic functions but guide the search with h_E only ($\neg h_{select}$), it can further improve. However, the best performance is only after we use all the heuristics to guide the search. In case of random initialization, we find that it can gradually improve, but most of the time is spent to achieve the initial level that is achieved by the chain growth initialization for other variants.

Fig. 2. Search progress of different variants for the protein 4pti.

6 Conclusion

In this paper, we have proposed an intelligent variable selection strategy for candidate generation in local search methods for protein structure prediction problem using 20×20 energy model on face centered cubic lattice. In addition to this, we also have proposed a new chain growth initialization procedure and heuristic functions to select variables and candidates at each iteration. Our method

significantly improves over the state-of-the-art algorithms. In future, we wish to explore the strength of our proposed scheme on other domains and on other models of protein structure prediction as well.

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