LocalMove: Computing on-lattice fits for biopolymers

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Abstract

Given an input PDB file for a protein or RNA molecule, `LocalMove` is a web server that determines an on-lattice representation for the input biomolecule. The web server implements a Markov Chain Monte-Carlo (MCMC) algorithm with simulated annealing to compute an approximate fit for either the coarse-grain model or backbone model on either the cubic or face-centered cubic lattice. `LocalMove` returns a PDB file as output, as well as dynamic movie of 3-dimensional images of intermediate conformations during the computation. The `LocalMove` server is publicly available at

`http://bioinformatics.bc.edu/clotelab/localmove/`.

Running Title: Computing best on-lattice-fits using LocalMove.

Key words: RNA, protein, local search, lattice model, face-centered cubic lattice.

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Introduction

Predicting the structure of biopolymers is one of the most important and well-studied computational problems of the 20th century – a problem, that despite enormous advances, remains only partially solved. In an effort to minimize the number of conformations to be explored, coarse-grain lattice models (beads on a string) have been studied by many authors (1, 2, 3, 4) while coarse-grain off-lattice models have been used in discrete molecular dynamics (5). In this paper, we present the `LocalMove` web server, which implements a Markov Chain Monte-Carlo (MCMC) algorithm to compute an approximate cubic or face-centered cubic lattice fit of either the coarse-grain or backbone model for an input Protein Data Bank (PDB) (6) file for a protein or RNA molecule.

Finding a self-avoiding walk on the cubic lattice that minimizes the coordinate root mean square deviation[1] with the original PDB file, after normalization to ensure unit distance between successive monomers, is known to be NP-complete (7). Thus various heuristic approaches (8, 9, 10, 11, 12, 13) have been proposed to approximately solve this problem, including Hopfield nets, self-consistent field optimization, integer programming,[2] etc. Unfortunately, none of these methods are publicly available, so that `LocalMove` is the only publicly available tool for on-lattice fit of biopolymers, allowing users to postprocess certain threading energies (aka knowledgs-based potentials) for structure classification and prediction.

The method `LocalMove`, presented in this paper, performs a *Monte-Carlo* exploration of the on-lattice conformational landscape through a sequence of *local moves*, which generalize the single-monomer *end* and *corner moves*, and the 2-monomer *crankshaft* moves used in (14) for the cubic lattice. At each step, a measure of similarity, distance root mean square deviation (`dRMS` [3])is evaluated and the candidate move is either accepted or stochastically rejected, according to the Metropolis criterion. Different levels of representation are supported by `LocalMove`, scaling from the coarse-grain monomer model (C_α for amino acids, $C_{1'}$ for RNA nucleotides, or alternatively nucleotide centers of mass), to all backbone atoms. `LocalMove` supports the cubic and face centered cubic (FCC) lattices. Various termination conditions can be defined for the walk.

There appears to be little data on the quality, in terms of coordinate root mean square deviation, `cRMS`, of on-lattice fits, an exception being the data of Reva et al.

[1]Given sequences $p_1, \ldots, p_n$ and $q_1, \ldots, q_n$ of 3-dimensional points, the coordinate root mean square deviation, denoted **rms** or `cRMS`, is $\sqrt{\sum_{i=1}^{n}(p_i - q_i)^2/n}$.

[2]The application of integer programming (13) provides an optimal, not just approximate, solution, however with exponential run time.

[3]Distance root mean square deviation (`dRMS`) between two conformations $P = p_1, \ldots, p_n$ and $Q' = q_1, \ldots, q_n$ is defined by $\texttt{dRMS}(P, Q) = \sqrt{\frac{\sum_{1 \le i < j \le n}(d_{i,j} - e_{i,j})^2}{\binom{n}{2}}}$ where $D(P) = (d_{i,j})$ and $D(Q) = (e_{i,j})$ are the corresponding

(15) for approximate *cubic lattice* fits of C_α-atom traces of proteins from a small representative sample. See Tables 1 and 2 for a comparison of `LocalMove` with the method of Reva et al. (15, 16) on the only published data of on-lattice fits that we could find.

Materials and Methods

`LocalMove` addresses the problem of finding the best on-lattice fit for the coarse-grain model or backbone model for proteins and RNA, with a number of parameter choices for the user. Lattice type can be either the cubic or face-centered cubic (FCC) lattice, described later.

`LocalMove` applies the Monte-Carlo algorithm (17, 18) where *energy* is defined as follows. Given a conformation $P = p_1, \ldots, p_n$, where each $p_i \in \mathbf{R}^3$, define the *distance matrix* $D(P) = (d_{i,j})$, where $d_{i,j}$ is the Euclidean distance between p_i and p_j. Define the *distance root mean square deviation* (`dRMS`) between two conformations $P = p_1, \ldots, p_n$ and $Q' = q_1, \ldots, q_n$ by $\texttt{dRMS}(P,Q) = \sqrt{\frac{\sum_{1 \le i < j \le n} (d_{i,j} - e_{i,j})^2}{\binom{n}{2}}}$ where $D(P) = (d_{i,j})$ and $D(Q) = (e_{i,j})$ are the corresponding distance matrices. To determine approximate on-lattice fit, define the energy $E(C)$ of a given lattice conformation by $\texttt{dRMS}(C, P_0)$, where P_0 is the normalized conformation of monomers C_α or $C_{1'}$ in the coarse-grain model, or backbone atoms, as depicted in Figure 1 in the backbone model. The off-lattice conformation P_0 is normalized so that distance between successive atoms is 1.

In `LocalMove`, if C' denotes the temporary conformation obtained by replacing a k-monomer segment in the current conformation C, then C' becomes the next configuration, provided that C' is a self-avoiding walk and either $E(C') \le E(C)$ or a random real z is less than $e^{-(E(C')-E(C))/RT}$, i.e. the Metropolis criterion holds. Details and parameter choices for the user are suggested below. Algorithmic details, computational experiments for various parameters, and extensive benchmarking will appear in a companion methods paper in preparation.

Models

Backbone representation

For protein, on-lattice models have historically considered the coarse-grain representation where each residue is represented by a single point, yielding the C_α-trace. For proteins, this level of granularity seems reasonable, since the average distance between consecutive C_α carbons in proteins extracted from the Nucleic Acid Database (NDB) (19) yields an average of 3.8Å with a low standard deviation of 0.04Å. In the case of RNA, a coarse-grain model is less able to capture the essence of an RNA

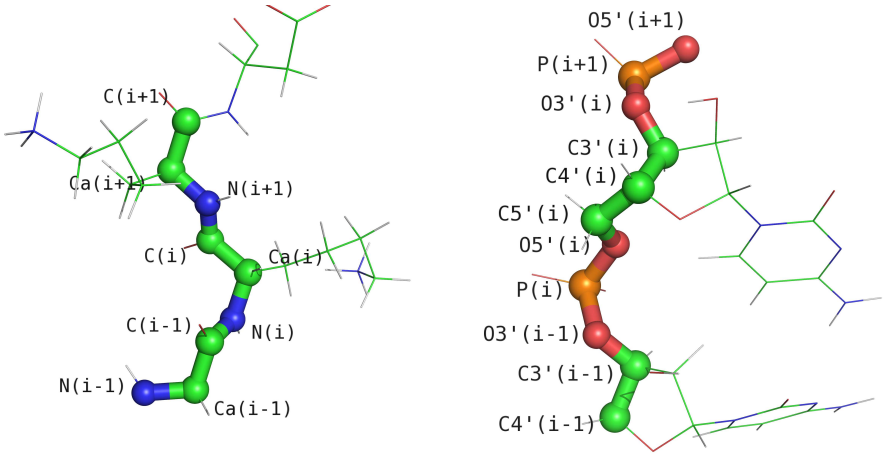


Figure 1: Backbones of protein (left) and RNA (right). Note that residue resp. nucleotide positions increase from the bottom of the figure towards the top.

conformation, since the average distance between successive $C_{4'}$ atoms is 6.1Å with a standard deviation of 0.46Å. In the case of RNA, the backbone model thus appears to be a better representative of the conformation than is the coarse-grain model.

While it is beyond the scope of the current paper to answer the question of choosing the best representation of biopolymers backbone for general on-lattice applications, we tried to offer the user the choice of a suitable representation. Namely, our algorithm extracts a subset of the atoms in the model/chain of interest, and performs its search for the best fit of this selection. The different levels of representation currently supported by `LocalMove` are:

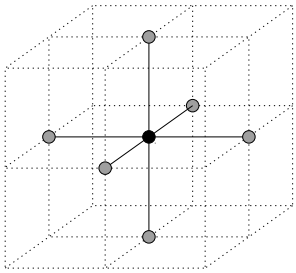
	Proteins	RNA
Full Backbone	N-C_α-C	P-$O_{5'}$-$C_{5'}$-$C_{4'}$-$C_{3'}$-$O_{3'}$
Coarse-grain	C_α or μ	$C_{1'}$, N, P or μ

where in the RNA coarse-grain model, the user can select among the carbon $C_{1'}$- or nitrogen N-atom, both adjacent to the glycosidic bond, the backbone phosphorus or the center of mass of the nucleotide, denoted by μ.

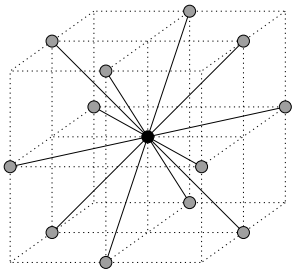
Lattices

`LocalMove` supports the cubic and face-centered cubic (FCC) lattice. The latter, well-known to crystallographers as one of the *Bravais* lattices, has contact number 12, meaning that each lattice point has 12 immediate neighbors; see Figure 2. Covell and Jernigan have shown that the FCC lattice is the most appropriate 3D lattice

(a) Cubic lattice



(b) Face-centered cubic lattice



(c) Numbers of self-avoiding walks on FCC

Size	Number
1	12
2	132
3	1,428
4	15,108
5	157,812
6	1,635,396

Figure 2: **Neighbors of a point under various lattice models**: (left) 3-dimensional cubic lattice, (middle) 3-dimensional face-centered cubic lattice, (right) Numbers of self avoiding walks of various sizes on FCC. The FCC lattice can be represented as the set of all integral coordinates (x, y, z), such that $(x+y+z) \bmod 2 = 0$. If $p = (x, y, z)$ and $q = (a, b, c)$, then p, q are immediate neighbors if $|x-a|+|y-b|+|z-c| = 0 \bmod 2$, and $|x-a|, |y-b|, |z-c| \leq 1$. Note that immediate neighbors on the FCC lattice are at Euclidean distance $\sqrt{2}$ from each other, hence comparisons with PDB data are made after normalization that ensures unit distance between successive monomers.

for fitting protein C_α-atoms as a self-avoiding walk; i.e. `cRMS` values are smaller for the FCC than for the cubic, body-centered cubic and tetrahedral lattices.

Algorithm

Simulated annealing

`LocalMove` implements the Monte-Carlo Markov Chain (MCMC) algorithm, as well as simulated annealing, and the user can set an initial temperature, terminal threshold temperature and temperature scaling factor c (i.e. temperature is periodically decreased by $T = c \cdot T$). Alternatively, a **greedy descent** (no Metropolis step) and a **Fixed Metropolis probability** strategy are implemented.

Three strategies are implemented in `LocalMove` to choose an initial self-avoiding configuration: **Random**, a random 3D self-avoiding walk is generated; **Straight line**; **Rounded (greedy)**. By rounding, we mean a greedy, iterative procedure to place the next monomer (or atom) of a growing chain on the closest lattice point to the previous monomer (or atom), while guaranteeing a self-avoiding walk. If this strategy does not produce a self-avoiding walk, which sometimes happens, then

`LocalMove` chooses a random self-avoiding walk as the initial on-lattice conformation.

`LocalMove` performs *local* k-monomer moves, generalizing the move set of Šali et al. (14). Given a current self-avoiding walk $p_1, \ldots, p_n$, `LocalMove` randomly chooses positions i, j, and replaces the intermediate k-monomer walk $p_{i+1}, \ldots, p_{j-1}$, where $k = j - i - 1$, by a different k-monomer walk $p'_{i+1}, \ldots, p'_{j-1}$ having the same vector difference. Three types of strategies are proposed regarding *self-avoidance*: **Strict**, where the self-avoidance of the resulting walk is tested in linear time and the move is rejected if the test is failed; **Local**, where only a subset of points adjacent to the insertion point are tested; **None**, where self-avoidance is not enforced. depending of the option. The relevant parameters handled by `LocalMove` for such moves are the **local move size**, the **self-avoidance strategy** and the **strategy for picking a new local move at random**.

`LocalMove` simulations can be stopped for some of the different following reasons: Either a limit temperature is bypassed during the simulated annealing; a distance threshold is reached; the maximal number of steps have been performed; or the simulation is *stalled* for too long, leaving few hope for improvement. In the latter, the required improvement over a user-defined period of time can be either **relative** or **absolute**.

Additional features

In addition to the features described above, our webserver gives its user the possibility to **follow in realtime** the lattice fitting process. After the beginning of the lattice fitting process, the user's browser is redirected to a webpage featuring an experiment player based on the popular JMol. Additionally, an email is sent to the user, featuring an **unique identifier** for the ongoing experiment. Through entering this identifier at any time during or after completion of the experiment, the user can access its results or follow its progress. Results are kept until about one week after the end of the experiment, and are then deleted. Even if such is the case, the user is proposed to **repeat the experiment**, using the same parameters or is allowed to modify them in a **prefilled version of the webserver form**. This allows for a quick and easy modification of an already run experiment.

Finally, `movies` can be generated automatically after the lattice fitting process is over. To that purpose, snapshots of the molecule are rendered using `PyMol` each 500 steps of the Monte-Carlo algorithm, and assembled using `FFMpeg`.

Results

Preliminary results are given in Tables 1 and 2, to compare `LocalMove` (greedy strategy, rounded initial conformation, self-avoiding walk test for intermediate conformations) with the method of Reva et al. (15) (optimal parameters A=10, $T \approx 0.1$ – see p. 7 of (15)). Although the method of Reva et al. is clearly superior for cubic lattice fits, it is not publicly available. In contrast, `LocalMove` provides acceptable approximate lattice representations for cubic and face-centered cubic lattices, for various coarse grain and backbone models of both protein and RNA.

Tables 1 and 2 respectively list the best scores and average scores for cubic lattice fits of 17 protein chains of various sizes. Scores for the method of Reva et al. (15) are values of RMS in lattice units, while those of `LocalMove` are values of RMSDc in lattice units – i.e. pdb files are scaled to have distance 1.0 between successive monomers (or atoms) when superimposing structures. RMS, as measured in (15), is approximately the same as RMSDc; however there is a technical difference, explained as follows. In Reva's method, a cubic orthonormal lattice is projected onto the C_α-trace of a protein, self-consistent field is approximated, followed by dynamic programming. It is unclear from (15) whether the (stochastic) cubic orthonormal lattice is defined from any 3 randomly chosen orthogonal basis vectors emanating from origin $(0, 0, 0)$, or whether the origin is randomly chosen as well. In contrast, given the C_α traces $p_1, \ldots, p_n$ and $q_1, \ldots, q_n$, BioPython computes RMSDc by superimposing the centers of mass, then computing optimal rotation matrix to return the C_α-trace $r_1, \ldots, r_n$ obtained by $q_1, \ldots, q_n$ by the computed translation and rotation. The value of RMSDc is then $\sqrt{\sum_{i=1}^{n} ||p_i - r_i||^2/n}$.

To illustrate the stability of our approach, we ran `LocalMove` on all RNA models/chains found in the NDB. Namely, we fit the backbone atoms $O_{5'}$,P,$O_{3'}$,$C_{5'}$, $C_{4'}$, $C_{3'}$ on the FCC lattice. We rescaled the resulting models and superimposed them with the original NDB backbone data, normalized so that adjacent atoms were at distance $\sqrt{2}$, the distance between adjacent lattice points in the FCC lattice. Superimposition was performed using Biopython `http://biopython.org/`. After removal of 17 spurious values the `cRMS` values obtained when superimposing the 1735 on-lattice RNA models/chains on (normalized) backbone data from the NDB, we obtain mean `cRMS` is 0.554169 with standard deviation 0.145392. Similarly, we obtained `LocalMove` fits of backbone atoms (N,C_α, C) of monochain proteins from PDBselect25 (20), a nonredundant protein database, where pairwise sequence identity is at most 25%. When on-lattice fits were superimposed on original (normalized) backbone off-lattice data from PDBselect25, the `cRMS` had mean of 0.612181 and standard deviation of 0.161009.

For these experiments with both NDB and PDBselect25, `LocalMove` was run for 1 million steps, using the greedy (Monte Carlo with zero probability for Metropolis moves) strategy with at most 3-monomer moves. In this case, the greedy strategy

pdbID	size	Reva	greedy RMSD 4	greedy RMS 4	fixed RMSD 4	anneal RMSD 4
1epg	53	0.573	0.731	0.795	0.819229	0.63175
2ovo	56	0.612	0.634	0.895	0.901008	0.556876
1acb:I	63	0.630	0.751	1.059	1.034372	0.620289
2ctx	71	0.666	0.842	1.164	1.065386	0.723368
1fkf	107	0.658	0.658	0.767	1.15722	0.686337
3sic	107	0.654	0.720	0.877	1.169239	0.655475
1cdp	108	0.653	0.644	0.798	0.761084	0.757177
2trx	108	0.678	0.682	0.919	0.87416	0.868124
1hmd	113	0.628	0.908	1.494	0.797958	0.79189
1ppa	121	0.670	0.817	1.747	0.924893	0.917508
1rat	124	0.698	0.955	1.186	1.493441	1.26029
2aza	129	0.703	0.740	0.869	1.743398	0.699028
1ifb	131	0.736	0.801	0.980	1.185644	0.733953
1myg	153	0.683	1.273	1.347	0.871547	0.870891
2fcr	173	0.693	0.711	1.036	0.972334	0.975169
1fdl	218	0.714	0.791	1.169	1.348602	0.891129
7tim:A	247	0.718	0.886	1.108	1.110148	1.106702
RMSDc	122	0.669	0.797	1.071	1.072	0.809
Time	-	-	76.240	66.830	70.39	128.18

Table 1: Comparison of best scores out of 100 runs. Scores are RMS for the optimized method of Reva et al. (15) (A=10,$T \approx 0.1$, shells 1,2), while remaining scores are RMSDc using various strategies with `LocalMove`. (See text for distinction between RMS and RMSDc.) Four strategies of `LocalMove` are displayed, in order from left to right: greedy method to minimize RMSDd, greedy method to minimize RMS, Monte Carlo with fixed probability of 20% in Metropolis step to minimize RMSDd, Monte Carlo with simulated annealing to minimize RMSDd. For each strategy of `LocalMove`, the maximum number of monomers moved is 4, and the intitial self-avoiding walk is determined by rounding if possible. In the simulated annealing, initial temperature $T = 10$, stopping temperature $T = 0.1$, temperature scaling factor $c = 0.95$, (artificial) Boltzmann constant $k = 4.699 \times 10^{-5}$. Reva et al. (15) study the effect of parameters A, T and number of shells on the accuracy and time of their method. Accuracy in this table is given for $A = 10$, $T \approx 0.1$ taking first and second shells, for which Reva et al. report a run time of approximately 30 sec. Average `LocalMove` run time in seconds for each of the four strategies is respectively 76.24, 66.83, 70.39, and 128.18. (Shorter run times with less accuracy found when minimizing RMSDc instead of RMSDd, and when maximum number of monomers moved is 3, rather than 4.

pdbID size Reva	Greedy RMSD 4	Greedy RMS 4	Anneal RMSD 4	Fixed RMSD 4
1epg 53 0.682	1.435	1.358	0.807	0.873
2ovo 56 0.691	0.713	0.824	0.675	0.942
1acb:I 63 0.707	0.767	0.951	0.744	1.071
2ctx 71 0.762	0.798	0.897	0.960	1.094
1fkf 107 0.784	0.852	0.996	0.807	1.195
3sic 107 0.757	0.761	0.900	0.768	1.193
1cdp 108 0.699	0.953	1.086	0.770	0.807
2trx 108 0.744	0.694	0.801	0.895	0.899
1hmd 113 0.709	0.946	1.117	0.799	0.832
1ppa 121 0.722	0.855	0.856	0.955	0.960
1rat 124 0.773	0.986	1.192	1.587	1.507
2aza 129 0.789	1.012	1.771	0.846	1.767
1ifb 131 0.802	1.108	1.203	0.824	1.200
1myg 153 0.724	0.772	0.962	0.874	0.891
2fcr 173 0.749	1.160	1.516	0.981	0.995
1fdl 214 0.863	0.921	1.082	1.087	1.358
7tim:A 247 0.761	0.954	1.193	1.111	1.117
Average 122 0.748	0.923	1.100	0.911	1.100

Table 2: Comparison of average scores out of 100 runs, for method of Reva et al. (15) and the four strategies of `LocalMove`, as explained in Table 1.

attempts to minimize `dRMS`; i.e. `LocalMove` accepts a randomly proposed k-monomer move, for $k \leq 3$, provided that the `dRMS` score of the proposed move is lower. The initial on-lattice structure determined by *rounding*. We allow early termination when relative improvement is less than 0.01%; i.e. after every 15,000 steps, if the relative difference between best score and that of an ancestor 15,000 steps prior to current step is less than 0.0001, (recall that score means `dRMS`) then computation terminates. Technically, this means that we compute whether $\frac{s_0 - s_1}{s_0} < 0.0001$, where s_0 denotes the ancestor score 15,000 steps before, and s_1 denotes the current move.

Discussion

In this paper, we present a new web server, `LocalMove`, capable of determining approximate on-lattice fits of protein and RNA 3-dimensional conformations on the cubic and the face-centered cubic lattice. `LocalMove` returns the PDB file of the approximate on-lattice fit, and interactively displays a dynamic movie of 3-dimensional images of intermediate conformations during the computation. In Tables 1 and 2, we benchmark `LocalMove` against what appears to be the only publicly available data set for previous on-lattice fits. To the best of our knowledge, no other method is publicly available to compute on-lattice fits of protein and RNA molecules. Reva's

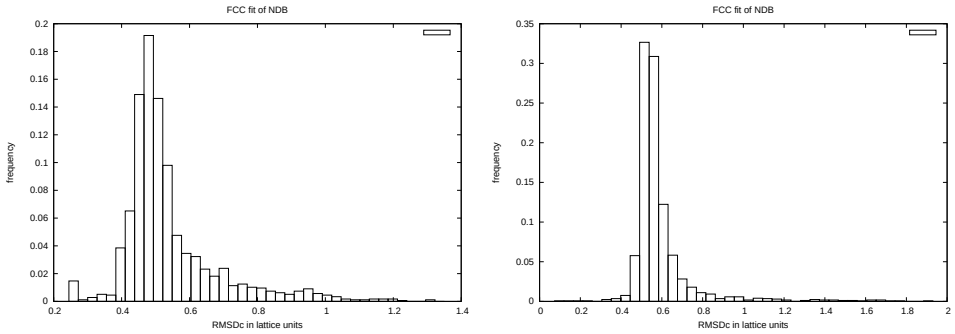


Figure 3: *(Left)* Distribution of `cRMS` for `LocalMove` best on-lattice fits for the *backbones* ($O_{5'}$,P,$O_{3'}$,$C_{5'}$, $C_{4'}$, $C_{3'}$) of 1735 RNA models/chains from the NDB, superimposed with the (normalized) NDB files. Statistics for RMSDc: mean is 0.554169, standard deviation is 0.145392, both measured in lattice units. *(Right)* Distribution of `cRMS` for `LocalMove` best on-lattice fits for the *backbone* (N,C_α,C) of 1733 (monochain) proteins from PDBselect25 (20), a nonredundant protein database (pairwise, proteins have at most 25% sequence identity), superimposed with the (normalized) original PDB files. Statistics for RMSDc: mean is 0.612181, standard deviation is 0.161009.

method and most of the earlier methods handle only the cubic lattice, known not to be optimal for biopolymer folding, while `LocalMove` handles cubic and FCC lattices with a variety of coarse grain and backbone models for both protein and RNA.

We believe that the new server, `LocalMove`, as well as our previous 3-dimensional RNA motif detection server, `DIAL`, described in Ferrè et al. (21), will contribute to better detection and classification of RNA motifs, essential ultimately for predicting tertiary structure, catalytic sites and function of RNA.

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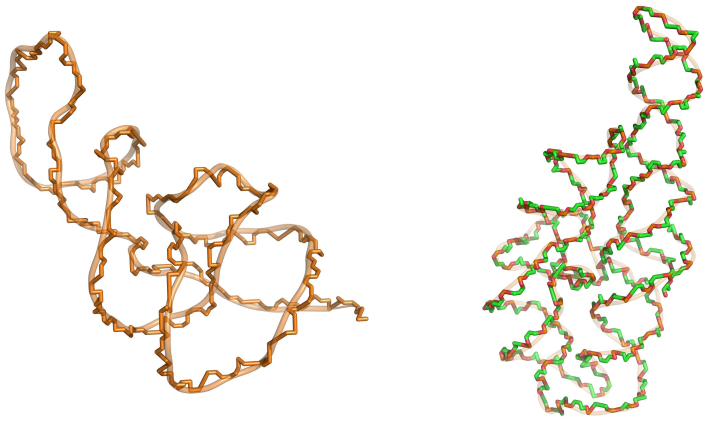

Figure 4: FCC lattice fits for the full backbone of two ribozymes models (PDB IDs 1SJ3:R and 1GID:A) superimposed with their original models.

of Šali et al. (14); `MoCaPro` is not publicly available and cannot perform the computations supported by `LocalMove`.

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References

[1] Abe, H. and Go, N. May 1981 Noninteracting local-structure model of folding and unfolding transition in globular proteins. II. Application to two-dimensional lattice proteins. *Biopolymers.* **20**, 1013–1031.

[2] Lau, K. and Dill, K. A. (1989) A lattice statistical mechanics model of the conformational and sequence spaces of proteins. *Journal of the American Chemical Society* **22**, 3986–3997.

[3] Hart, W. E. and Istrail, S. C. (1996) Fast protein folding in the hydrophobic-hydrophilic model within three-eighths of optimal. *J. Comput. Biol.* **3**, 53–96.

[4] Kihara, D., Lu, H., Kolinski, A., and Skolnick, J. (2001) TOUCHSTONE: An *ab initio* protein structure prediction method that uses threading-bases tertiary restraints. *Proc. Natl. Acad. Sci. USA* **98(18)**, 10125–10130.

[5] Dokholyan, N. V., Buldyrev, S. V., Stanley, H. E., and Shakhnovich, E. I. (1998) Discrete molecular dynamics studies of the folding of a protein-like model. *Fold. Des.* **3**, 577–587.

[6] Berman, H. M., Battistuz, T., Bhat, T. N., Bluhm, W. F., Bourne, P. E., Burkhardt, K., Feng, Z., Gilliland, G. L., Iype, L., Jain, S., Fagan, P., Marvin, J., Padilla, D., Ravichandran, V., Schneider, B., Thanki, N., Weissig, H., Westbrook, J. D., and Zardecki, C. June 2002 The Protein Data Bank. *Acta Crystallogr. D. Biol. Crystallogr.* **58**, 899–907.

[7] Manuch, J. and Gaur, D. R. February 2008 Fitting protein chains to cubic lattice is np-complete. *J. Bioinform. Comput. Biol.* **6**, 93–106.

[8] Godzik, A., Kolinski, A., and Skolnick, J. (1993) Lattice representations of globular proteins: How good are they? *Journal of Computational Chemistry* **14**, 1194–1202.

[9] Rabow, A. A. and Scheraga, H. A. (1993) Lattice neural network minimization. Application of neural network optimization for locating the global-minimum conformations of proteins. *J. Mol. Biol.* **232**, 1157–68.

[10] Rykunov, D. S., Reva, B. A., and Finkelstein, A. V. (1995) Accurate general method for lattice approximation of three-dimensional structure of a chain molecule. *Proteins: Structure, Function, and Genetics* **22**, 100–109.

[11] Park, B. H. and Levitt, M. (1995) The complexity and accuracy of discrete state models of protein structure. *J. Mol. Biol.* **249**, 493–507.

[12] Reva, B. A., Rykunov, D. S., Olson, A. J., and Finkelstein, A. V. (1995) Constructing lattice models of protein chains with side groups. *J. Comput. Biol.* **2**, 527–35.

[13] Huang, X. Fitting protein chains to lattice using integer programming approach M.sc. thesis School of Computing Science, Simon Fraser University January 2007.

[14] Sali, A., Shakhnovich, E., and Karplus, M. May 1994 How does a protein fold? *Nature* **369**, 248–251.

[15] Reva, B., Finkelstein, A., Rykunov, D., and Olson, A. (1996) Building self-avoiding latice models of proteins using a self-consistent field optimization. *PROTEINS: Structure, Function and Genetics* **26**, 1–8.

[16] Reva, B. A., Rykunov, D. S., Finkelstein, A. V., and Skolnick, J. (1998) Optimization of protein structure on lattices using a self-consistent field approach. *J. Comput. Biol.* **5**, 531–538.

[17] Metropolis, N., Rosenbluth, A., Rosenbluth, M., Teller, A., and Teller, E. (1953) Equation of state calculations by fast computing machines. *J. Chem. Phys.* **21**, 1087–1092.

[18] Clote, P. and Backofen, R. (2000) Computational Molecular Biology: An Introduction, John Wiley & Sons, 279 pages.

[19] Berman, H. M., Olson, W. K., Beveridge, D. L., Westbrook, J., Gelbin, A., Demeny, T., Hsieh, S. H., Srinivasan, A. R., and Schneider, B. September 1992 The nucleic acid database. A comprehensive relational database of three-dimensional structures of nucleic acids. *Biophys. J.* **63**, 751–759.

[20] Hobohm, U. and Sander, C. (1994) Enlarged representative set of protein structures. *Protein Science* **3**, 522.

[21] Ferre, F., Ponty, Y., Lorenz, W. A., and Clote, P. July 2007 DIAL: a web server for the pairwise alignment of two RNA three-dimensional structures using nucleotide, dihedral angle and base-pairing similarities. *Nucleic. Acids. Res.* **35**, W659–W668.

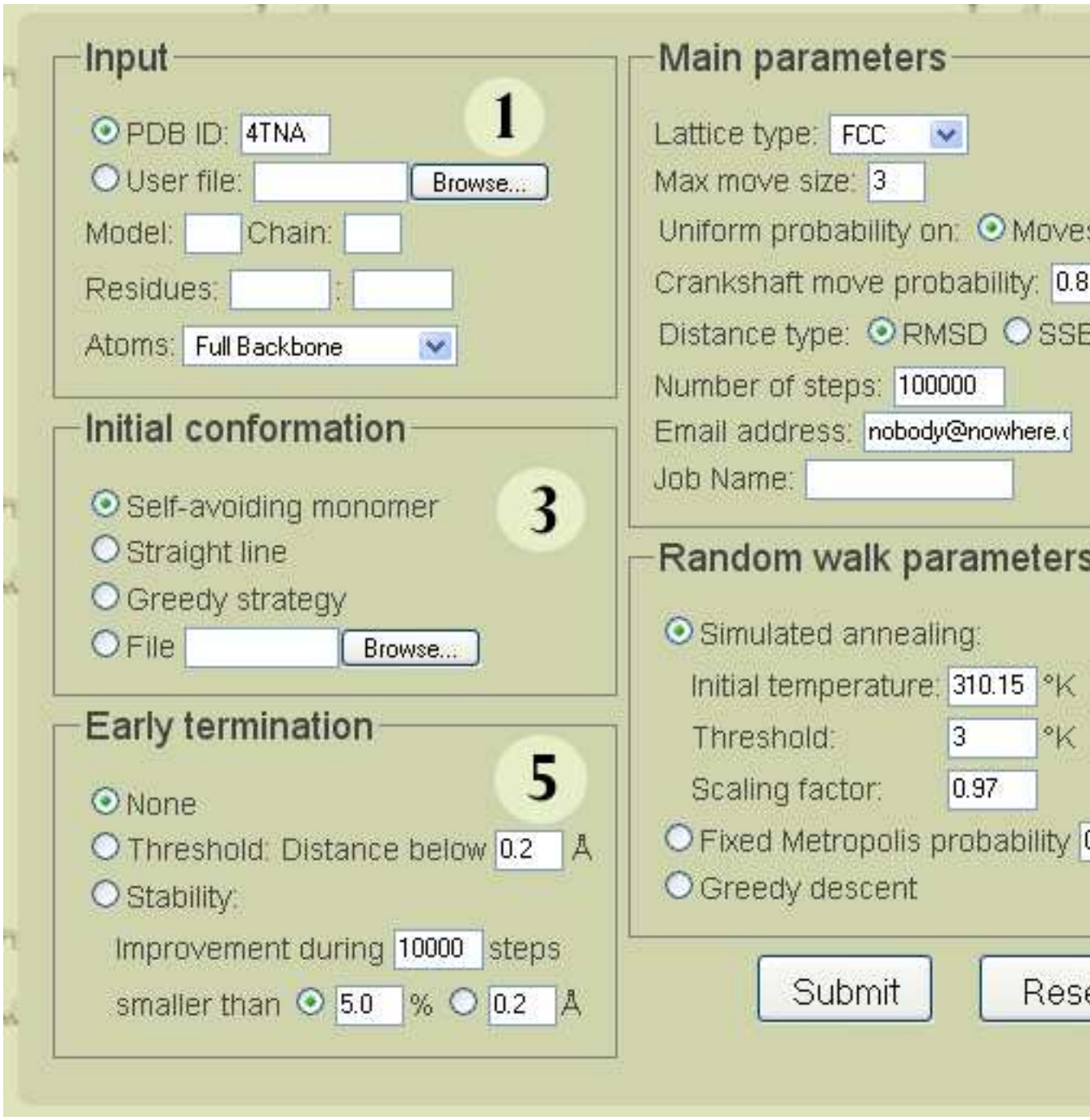

Figure 5: Screen shot of `LocalMove` web server.