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A Markov Chain Sampling Method for Conformational Energy Optimization of Peptides

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***Abstract*— The Markov chain sampling is a powerful tool for the optimization of complicated objective functions. It is introduced in order to more efficiently search the domain of the objective function. In many applications these functions are deterministic and randomness. The maximum statistic converge to the maximum point of probability density which establishing links between the Markov chain sampling and optimization search. This statistical computation algorithm demonstrates convergence property of maximum statistics in large samples and it is global search design to avoid on local optimal solution restrictions. We have developed and implemented a Markov chain sampling to determine the best energy minimum for oligopeptides. Our test molecule was Met-enkephalin, a pentapeptide that over the years has been used as a validation model for many global optimizers. The test potential energy function was ECEPP/3. The results indicate that the proposed optimization search is an efficient algorithm for conformational searches.**

***Index Terms*— Markov chain, protein structure prediction, protein folding, conformational space search**

I. INTRODUCTION

The computational identification of the low energy structures of a peptide from its sequence alone has been a problem of major interest for many years. It is not an easy task even for small peptides, due to the multiple-minima problem and combinatorial explosion. A number of conformational search algorithms have been developed in the past for this purpose. We have developed an algorithm that addresses this problem. Peptides are short polymers made up of a few to a few tens of amino acids. Many of these have meaningful roles in biochemistry and biophysics. Some sequences of peptides have a clear tendency to form well-defined three-dimensional structures, that is, to fold. Peptides are also useful as model systems for much larger peptide chains known as proteins. The naturally occurring three dimensional structure of a protein, its "tertiary structure," is believed to be uniquely determined by its "primary structure," the sequence of amino acids of which the protein is composed. Anfisen [1] in his "thermodynamic hypothesis" proposes that the native state of a protein is the structure that minimizes the free energy. By definition, such a state would be at the global minimum of free energy relative to all other states accessible on that time scale. Thus, the conformational search, or folding, can be posed as an optimization problem. Conformational search of peptide molecules, to a first approximation, can be thought of as the problem of finding the 3D molecular structure that corresponds to the lowest local minimum of an appropriate mathematical function describing the potential energy of the system. Computer simulations are often used to carry out this task. A major concern in computer simulations is to obtain a set of low-energy conformations with biological significance; that is, finding those conformations that are near the thermodynamic native state. Folding a protein from only a knowledge of its amino acid sequence is a formidable task. Because it is computationally impossible to test all possible conformations to determine the global minimum, it is necessary to develop methods that can land upon a global minimum without testing all conformational possibilities. This is a challenging optimization (minimization) task. In many cases the detailed properties of the potential function to be minimized are not known. Even if the function is differentiable, one can often encounter non-convex surfaces, and the local properties of the function can be different in the different search regions, i.e., the basins can have different size or depth, the smoothness can vary, etc. Many different force fields for proteins have been designed as a summation of a set of potential energy contributions. Among the most used ones are: ECEPP [2], MM2[3], ECEPP/2 [4], CHARMM [5], DISCOVER [6], AMBER [7], GROMOS87 [8], MM3 [9], and ECEPP/3 [10]. Most of these have a large number of local minima. In general, protein folding with any force field is a NP-hard problem [11] where the time needed to locate the lowest minimum grows exponentially when the number of variables grows linearly. A major challenge in this type of global optimization problems is that there is no clear mathematical basis for efficiently reaching the global minimum, thus finding the latter in an accurate and speedy way is of general interest. To reduce the size of the problem one takes advantage of the fact that under biological conditions some internal motions of protein molecules occur on a time scale much smaller than others. Experimentally, the average values of covalent bond distances and covalent bond angles are fairly constant, and lead to the assumption that conformational changes observed in the dihedral angles could fully determine the overall shape of the protein molecule. Thus, if one specifies the position of all atoms in the protein molecule as a function of its internal coordinates, under the assumption of constant bond lengths and bond angles, the problem drastically reduces the number of its degrees of freedom. Although the size of the problem can be reduced when the energy function is written in terms of torsional angles, it is known that in this form the energy function is no longer partially separable, meaning that it is no longer much less expensive to reevaluate the energy if only a few variables change than if they all change. To overcome this effect, a number of workers have devised interesting stochastic and non-stochastic methods, which impose constrains and bias the search towards the region where the global minimum could be found. Among stochastic methods employed to predict oligopeptide 3D structures are Monte Carlo with minimization (MCM) [12a, 12b], simulated annealing (SA) [13], threshold accepting (TA) [14], free energy Monte Carlo

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with minimization (FMCM) [15], multi-canonical ensemble (ME)[16], conformational space annealing (CSA) [17], and genetic algorithms18 (GA) [18]. Among non-stochastic methods we find molecular dynamics with minimization (MDM) [19], dynamic programming (DP) [20], the diffusion equation method (DEM) [21a], the mean-field technique (MFT) [22], and a global optimization procedure known as _BB [23]. In this article we take an approach to minimize the ECEPP/3 [10] energy function based on tabu search (TS) [24], a stochastic optimizer developed to treat complex combinatorial optimization tasks. Our test molecule is that of Met-enkephalin, a pentapeptide that has been used as a validation model for many global optimizers, and because its lowest energy conformation for the potential energy function ECEPP/3 is known [23]. We first present the problem we are dealing with in a mathematical fashion, then we discuss the general principle of the proposed sampling algorithm and explain how to use this algorithm for conformational search. Finally, we present our computational results.

Protein Conformational Search Problem

As indicated above, the conformation of a protein with a sequence of N_{res} amino acid residues in the peptide chain can be described by a set of dihedral angles ϕ_i, ψ_i, ω_i, where i = 1,…,N_{res} on the backbone, plus a set of dihedral angles χ_i^j, i = 1,…, N_{res}, j = 1,…, J_i, where J_i denotes the dihedral angles of the side group on the i-th residue. If one wishes to allow capping of the peptide, then one has to include two more sets of dihedral angles. One could be defined as φ_k^N, k = 1,…, K^N for those dihedral angles on the amino end group, and the other could be defined as φ_k^C, k = 1,…,K^C for those dihedral angles on the carbonyl end group. In this paper the complete ECEPP/3 [10] force field was used. This force field is built upon the assumptions that the bond lengths and angles are at their equilibrium values, and that the resulting function is in reality a conformational energy surface made of a summation over interactions of types 1–4 and higher. These interactions take into account electrostatic, nonbonded, hydrogen bond, and torsional energies, plus other empirical terms that take into account a loop closing potential in the case that the peptide has intramolecular disulfide bonds, and fixed conformational energies for the propyl and hydroxypropyl residues. A condensed description of the ECEPP/3 force field could be written as:

$$U = U_{elec} + U_{nonb} + U_{hb} + U_{tor} + U_{loop} + U_{S-S}$$

Where

$$U_{elec} = \sum_i \sum_{i \neq j} 332.0_{q_i q_j} / Dr_{ij}$$

$$U_{nonb} = \sum_i \sum_{i \neq j} FA / r_{ij}^{12} - C / r_{ij}^{6}$$

$$U_{hb} = \sum_h \sum_x A'_{hx} / r_{hx}^{12} - B_{hx} / r_{hx}^{10}$$

$$U_{tor} = \sum_k (U_0 / 2.0)(1 \pm \cos n_k \theta_k)$$

$$U_{loop} = \sum_l B_l \sum_{i=1}^{i=3} (r_{il} - r_{i0})^2$$

$$U_{S-S} = \sum_s A_s (r_{4s} - r_{40})^2$$

All constants are estimated by fitting of experimental data [10]. Given these definitions, the potential energy minimization problem can be summarized as follows:

minimize $U(\phi_i, \psi_i, \omega_i, \chi_i^j, \varphi_k^N, \varphi_k^C)$

subject to the particular constrains:

$$-180° \le \phi_i, \psi_i < +180°, i = 1,..., N_{res}$$

$$-10° \le (\omega_i - 180°) \le +10°, i = 1,..., N_{res}$$

$$-180° \le \chi_i^j \le +180°, i = 1,..., N_{res}, j = 1,..., J^i$$

$$-180° \le \varphi_k^N, \varphi_k^C \le +180°, k = 1,..., K^N, k = 1,..., K^C$$

The most important points in the implementation of a bee swarm optimization to our particular application are: the search space *X*, the cost function *f*. The cost function *f* (*x*) is the empirical energy function ECEPP/3, which is designed to work in angle space *X*, while keeping bond length and bond angle values constant, and where no solvent effects are included.

II. Markov Chain Monte Carlo

Markov chain Monte Carlo methods are a class of sample-generating techniques by controlling how a random walk behaves. It attempts to directly draw samples from some complex probability distribution based on constructing a Markov chain that has the desired distribution as its equilibrium distribution. The state of the chain after a large number of steps is then used as a sample of the desired distribution. The quality of the sample improves as a function of the number of steps. Usually it is not hard to construct a Markov chain with the desired properties. The more difficult problem is to determine how many steps are needed to converge to the stationary distribution within an acceptable error. The Markov chain Monte Carlo has become a powerful tool for Bayesian statistical analysis, Monte Carlo simulations, and potentially optimization with high nonlinearity. There are many ways to choose the transition probability, and different choices will result in different behaviour of Markov chain. In essence, the characteristics of the transition kernel largely determine how the Markov chain of interest behaves, which also determines the efficiency and convergence of Markov chain Monte Carlo sampling. There are several widely used sampling algorithms, such as Metropolis-Hasting Algorithm [25] and Gibbs Sampler [26].

A. Metropolis-Hastings Sampling Algorithm

The basic idea of Markov chain Monte Carlo methods is to construct a Markov chain with the specified stationary distribution, namely $\pi(\theta)$, then run the chain with full length till the sample chain value close enough to its stationary distribution. Then take stationary chains as the samples of $\pi(\theta)$ and make variety of statistical inference based on these samples. The most popular Markov chain Monte Carlo sampling method is Metropolis-Hastings algorithm, which means sampling starts from another easily known reversible Markov chain *Q*, and obtain the new Markov chain by comparing. It generates a random walk using a proposal density and a method for rejecting proposed moves.

To draw samples from the target distribution, we let $\pi(\theta) = \beta \cdot p(\theta)$, where β is a normalizing constant which is either difficult to estimate or not known. We will see later that the normalizing factor β disappear in the expression of acceptance probability. The Metropolis-Hastings algorithm essentially expresses an arbitrary transition probability from state θ to ϕ as the product of an arbitrary transition kernel $q(\theta,\phi)$ and a probability $\alpha(\theta,\phi)$. That is,

$$P(\theta,\phi) \equiv P(\theta \to \phi) = q(\theta,\phi)\alpha(\theta,\phi)$$

Here q is the proposal distribution function, while $\alpha(\theta,\phi)$ can be considered as the acceptance rate from state θ to ϕ, and can be determined by

$$\alpha(\theta,\phi) = \min\left\{\frac{\pi(\phi)q(\phi,\theta)}{\pi(\theta)q(\theta,\phi)},1\right\} = \min\left\{\frac{p(\phi)q(\phi,\theta)}{p(\theta)q(\theta,\varphi)},1\right\}$$

The essence of Metropolis-Hastings algorithm is to first propose a candidate θ^*, then accept it with probability α. That is, $\theta_{t+1} \leftarrow \theta^*$ if $\alpha \geq u$ where u is a random value drawn from an uniform distribution in [0, 1], otherwise $\theta_{t+1} \leftarrow \theta_t$. It is straightforward to verify that the reversibility condition is satisfied by the Metropolis-Hastings kernel

$$q(\theta,\phi)\alpha(\theta,\phi)\pi(\theta) = q(\phi,\theta)\alpha(\phi,\theta)\pi(\phi),$$

for all θ, ϕ. Consequently, the Markov chain will converge to a stationary distribution which is the target distribution $\pi(\theta)$.

In a special case, when the transition kernel is symmetric is its arguments, or $q(\theta,\phi) = q(\phi,\theta)$, for all θ, ϕ, then the acceptance rate $\alpha(\theta,\phi)$ become

$$\alpha(\theta,\phi) = \min\left\{\frac{p(\phi)}{p(\theta)},1\right\},$$

And the Metropolis-Hastings algorithm reduces to the classic Metropolis algorithm. In this case, the associated Markov chain is called as symmetric chain. In a special case when $\alpha = 1$ is used, that is the acceptance probability is always 1, then the Metropolis-Hastings degenerates into the classic widely used Gibbs sampling algorithm. However, Gibbs sampler becomes very inefficient for the distributions that are non-normally distributed or highly nonlinear.

B. Random Walk and Levy Flight

A random walk is a random process which consists of taking a series of consecutive random steps. The sum of each consecutive step which is a random step drawn from a random distribution forms a random walk. It means the next state will only depend on the current existing state and the transition from the existing state to the next state. This is typically the main property of a Markov chain. If the step size obeys the Gaussian distribution, the random walk becomes the Brownian motion. In theory, as the number of steps increases, the central limit theorem implies that the random walk should approaches a Gaussian distribution. If the step size obeys other distribution, we have to deal with more generalized random walk. A special case is when the step size obeys the Levy distribution, such a random walk is called a Levy flight or Levy walk. Levy flight is a random walk whose step length is drawn from the heavy-tailed Levy distribution often in terms of a simple power law formula. It is worth to point out that a power law distribution is often link to some scale free characteristics, and Levy flights can thus show self-similarity and fractal behaviour in the fight patterns.

III. MARKOV CHAIN SAMPLING FOR OPTIMIZATION SEARCH

A simple random walk can be considered as a Markov chain. In a probability distribution, the largest density area is mostly tending to be sampled. So the sampling density function should converge to the maximum point of maximum probability if the sample is sufficiently large. Thus establishing links between the function maximum value and sampling extreme statistics. We can use Markov chain Monte Carlo to simulate a sample of this distribution. And the optimal will appear most frequently in the sample. That is, the optimal state will have the greatest probability.

Suppose that we are interested in exploring solutions x that minimize an objective function $f(x) \in \mathrm{R}$, where $x = (x_1,..., x_n) \in R^n$. That is, if we want to find the minimum of an objective function $f(x) \in \mathrm{R}$ at $x = x^*$ so that $f^* = f(x^*) \leq f(x)$. We can convert it to a target distribution for a Markov chain

$$\pi(x) \propto e^{-\beta f(x)}$$

where $\beta > 0$ is a parameter which act as a normalized factor. β should be chosen so that the probability is close to 1 when $x \to x^*$. At $x = x^*$, $\pi^* = \pi(x^*) \geq \pi(x)$. This often requires that the formulation of $f(x)$ should be non-negative, which means that some objective functions can be shifted by a large constant $\mathrm{C} > 0$ if necessary. Then, a Markov chain is constructed to sample $\pi(x)$. Typically, the solutions in the vicinity of the global minimum of $f(x)$ are most likely to be drawn in the sampling process. Therefore, Markov chain Monte Carlo can also be used for optimization purposes. To design a Markov chain with stationary distribution $\pi(x)$, the maximum point in finite sampling from distribution $\pi(x)$ will be sufficiently close to the maximum point of $f(x)$ in the feasible region. When the transition kernel is symmetric is its arguments, or $q(y, x_t) = q(x_t, y)$, then the acceptance rate $\alpha(x_t, y)$ become

$$\alpha(x_t, y) = \min\left\{1, \frac{\pi(y)q(y, x_t)}{\pi(x_t)q(x_t, y)}\right\} = \min\left\{1, \frac{\pi(y)}{\pi(x_t)}\right\}$$

The proposed Markov chain sampling for optimization search algorithm is:

(1) Start with x_0, at $t = 0$, $x_0^* = x_0$

(2) Propose a new solution y

(3) Drawn u from the uniform distribution $U(0,1)$

(4) Compute $\alpha(x_t, y) = \min\left\{1, \frac{\pi(y)}{\pi(x_t)}\right\}$

(5) Take $x_{t+1} = \begin{cases} y & u \leq \alpha \quad \text{(with probability} \quad \alpha) \\ x_t & u > \alpha \quad \text{(with probability} \, 1\text{-}\alpha) \end{cases}$

(6) Take $x_{t+1}^{*} = \begin{cases} x_t^{*} & f(x_t^{*}) > f(x_{t+1}) \\ x_{t+1} & f(x_t^{*}) \le f(x_{t+1}) \end{cases}$ . . . . . .

Repeat (2) to (6). If the iteration times are large enough, then x_t^{*} will convergence to the maximum point of the objective function $f(x)$ in distribution. We can see from the problem analysis above that the key points of Markov chain sampling method are designing of general probability density function $\pi(x)$ and uniform sampling from conditional constraint region.

In order to solve an optimization problem, we can search the solution by performing a random walk starting from a good initial but random guess solution. However, to be computationally efficient and effective in searching for new solutions, we can keep the best solutions found so far, and to increase the mobility of the random walk so as to explore the search space more effectively. We can find a way to control the walk in such a way that it can move towards the optimal solutions more quickly, rather than wander away from the potential best solutions. These are the challenges for the most metaheuristic algorithms. The same issues are also important for Monte Carlo simulations and Markov chain sampling techniques. An important link between Markov chain and optimization is that some heuristic or metaheuristic search algorithms such as simulated annealing use a trajectory-based approach. They start with some initial random solution, and propose a new solution randomly. Then the move is accepted or not, depending on some probability. It is similar to a Markov chain. In fact, the standard simulated annealing is a random walk. Simulated annealing is a probabilistic method for finding global minimum of some cost function introduced by Kirkpatrick et al. [27]. It searches local minimum, and finally stays at the global minimum given enough time. This sampling method was originally extended from Metropolis Algorithm [28] by implanting a temperature function *T*. *T* is used to control the difficulty for the stochastic sampler to escape from a local minimum and reach the global optimal for a non-optimal state. Algorithms such as simulated annealing which use a single Markov chain may not be very efficient. In practice, it is usually advantageous to use multiple Markov chains in parallel to increase the overall efficiency. In fact, the algorithms such as particle swarm optimization can be viewed as multiple interacting Markov chains, though such theoretical analysis remains almost intractable. The theory of interacting Markov chains is complicated and yet still under development. However, any progress in such areas will play a central role in the understanding how population- and trajectory-based metaheuristic algorithms perform under various conditions.

In addition, a Markov chain is said to be ergodic or irreducible if it is possible to go from every state to every state. Furthermore, the use of a uniform distribution is not the only way to achieve randomization. In fact, random walks such as Levy flights on a global scale are more efficient. On the other hand, the track of chaotic variable can travel ergodically over the whole search space. In general, the chaotic variable has special characters, i.e., ergodicity, pseudo-randomness and irregularity. To enrich the searching behavior and to avoid being trapped into local optimum, chaotic sequence and a chaotic Levy flight can be incorporated in the meta-heuristic search for efficiently generating new solutions. In the paper [29], we presented synergistic strategies for meta-heuristic optimization learning, with an emphasis on the balance between intensification and diversification. We showed some promising efficiency for global optimization. Interestingly, it can be viewed to link with optimization search and Markov chain sampling under appropriate conditions.

IV. Simulation Results

Met-enkephalin has 24 dihedral angles, that according to our definition of a space search means that a set of 24 variables will be optimized. In the following table, we show our results of the best low-energy conformations of Met-enkephalin using the proposed global optimization method.

Tyr	ϕ	-83.5
	ψ	155.8
	ω	-177.2
	χ_1	-173.2
	χ_2	79.4
	χ_3	-166.4
Gly	ϕ	-154.3
	ψ	86.0
	ω	168.5
Gly	ϕ	82.9
	ψ	-75.1
	ω	-170.0
Phe	ϕ	-136.9
	ψ	19.1
	ω	-174.1
	χ_1	58.9
	χ_2	94.6
Met	ϕ	-163.5
	ψ	161.2
	ω	-179.8
	χ_1	52.9
	χ_2	175.3
	χ_3	-179.8
	χ_4	58.6
Energy		-11.707

V. Conclusion

Protein function is related to its structure. In order to predict the protein structure computationally, protein must be represented in favorable representation. An efficient energy function should be used to calculate the protein energy, and then a conformational search algorithm must be applied to find the lowest free energy conformation. To this end, an energy function is used to calculate its energy and a conformational search algorithm is used to search the conformational search space to find the lowest free energy

conformation. Markov chain Monte Carlo is a family of simulation methods, which generate samples of Markov Chain processes. In this paper, we set up a framework of Markov chain sampling to search the protein conformational search space. The proposed algorithm was able to find the lowest free energy conformation of Met-enkephalin using ECEPP/3 force fields.

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