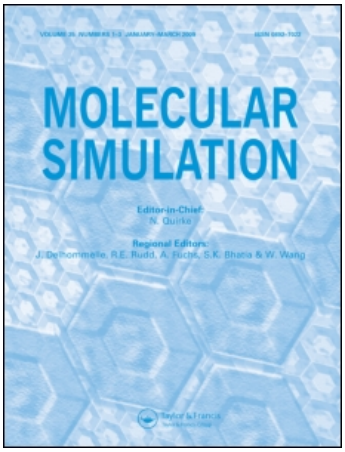

Molecular Simulation
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713644482

Use of the High Directional Monte Carlo Method to Predict the Low Energy Structures of Melittin

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To cite this Article Kim, Tae Kyoung , Yoon, Jeong Hyuk , Shin, Jai Kwang and Jhon, Mu Shik(1995) 'Use of the High Directional Monte Carlo Method to Predict the Low Energy Structures of Melittin', Molecular Simulation, 15: 3, 177 — 187
To link to this Article: DOI: 10.1080/08927029508024053
URL: http://dx.doi.org/10.1080/08927029508024053

Molecular Simulation, 1995, Vol. 15, pp. 177–187
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USE OF THE HIGH DIRECTIONAL MONTE CARLO METHOD TO PREDICT THE LOW ENERGY STRUCTURES OF MELITTIN

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(Received November 1994, accepted April 1995)

A recently developed high directional Monte Carlo sampling procedure is used to predict the low energy conformations of melittin, which is a toxic protein from honey bee venom with 26 amino acid residues. In this procedure, the shape of a potential energy hyper surface is estimated by computing covariance matrices periodically and those matrices are used to generate more important trial conformations of the molecule in Monte Carlo simulations. At the same time, we carry out the vibrational thermalization and simulated annealing successively so as to avoid possible trapping in local energy minima. Several simulations which differ in the starting conformations of the molecule are performed so that we could verify the correct final results. Almost all of the important features in the resultant structures are found to coincide with the previous theoretical and experimental results.

KEY WORDS: Monte Carlo procedure, Sampling function, Covariance matrix, Vibrational thermalization, Simulated annealing, Optimization, Tertiary structure global energy minimum.

INTRODUCTION

Predicting the three dimensional structure of polypeptides and proteins from their primary amino acid sequences is emerging as a most intensive area of research because native three dimensional structures of biomolecules are deeply related to their biological functions. The native conformational state of biomolecules should be approximated by the lowest energy state and therefore the problem of computing the native structure of molecules becomes a multivariate optimization problem on the potential energy surface (PES).

For this reason, multivariate optimization tools for locating the minimum point of the potential energy function are frequently applied to molecular modeling, drug design, mathematical treatment of biological processes, and protein folding problems [1]. However, optimizing the PES has many problems, the most serious of which is the multiple minima problem; in other words, the existence of the huge number of local energy minima which originate in the complexity of PES.

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There have been many attempts to solve the multiple minima problem. One approach is methodological, examples include the build-up procedure [2, 3], a hybrid Monte Carlo method with suitable procedure to increase the sampling efficiency [4–9], relaxing dimensionality to bring down the overestimation of energy barriers between minima [10, 11], using the functional kernels to smooth down the potential energy function [12–15] and the diffusion equation method [16, 17]. Another approach is to improve the computational efficiency by reducing the dimensionality of the PES via lattice models or simplification of force fields to residue-residue parameters [18–22].

None of them is yet regarded as a solution to the problem and furthermore, nobody knows which is the correct approach to take to solve the problem. For our part we have used the recently developed high directional Monte Carlo procedure (HDMC) (which has increased sampling efficiency) so as to effectively accelerate the convergence to the minimum energy conformations of molecules [23–26]. This method utilizes covariance matrices which are computed from the previous history of Monte Carlo walks of some local region on the conformational space to decide where to move. The covariance tensor controls the distribution of individual trial conformations.

This method has successfully located the lowest energy structure of Met-Enkephalin. However, as Shin and Jhon have mentioned in their article [25], the method can underestimate the transition probabilities between local minima. So we have used thermal heating and simulated annealing to relax all degrees of freedom including vibrations so as to compensate for the possible lowering of transition probabilities between metastable states.

The combined method is applied to determine the three dimensional structure of a, 20-residue segment of melittin using CVFF (Consistent Valence Force Field) [27] parameters to describe the pair-wise atomic interactions. It is found that the resulting structures of the HDMC simulations explain almost all of the important structural characteristics of the system within a reasonable amount of computing time.

METHOD

At present, the Monte Carlo method combined with simulated annealing procedure is used as an optimization tool in diverse fields of science. The most important merits of the Monte Carlo method are its flexibility in modeling almost any physical system and an ability to escape from the local minima, in contrast to the common optimization techniques such as steepest descents and conjugate gradients. In this paper, we briefly describe the overall Monte Carlo simulation procedure.

In each step of the Monte Carlo method, a trial conformation (or configuration) is generated by a small random displacement and the change in potential energy, ΔE, is computed. Then, the trial conformation is accepted by the probability of p or rejected by $1 - p$ where

$$p = \min\left[1, \frac{T(\vec{r}|\vec{r}')}{T(\vec{r}'|\vec{r})}\exp(-\beta\Delta E)\right] \tag{1}$$

where $T(\vec{r}'|\vec{r})$ is the joint probability which is usually called as a transition probability. A transition (or movement) will always occur when the movement induces the

decrease in energy and the move to higher energy state is possible when the Boltzmann factor is greater than a random number. Finally, all of those visited states form an ensemble from which we get many sorts of thermodynamic and structural properties.

In practice, $T(\vec{r}'|\vec{r})$ is composed of two philosophically different parts, namely, pure probabilistic transition probability which is called a sampling function and pure energetic one. The former distinguishes the various methods and governs the speed of convergence. Here, we briefly compare the idea in the algorithm of HDMC method with Metropolis Monte Carlo procedure (MMC) [28]. The HDMC method has the same frame in determining whether to move or not by comparing the energy difference between two conformations. But as mentioned above, the feather of the HDMC method that distinguishes it from MMC is in the scheme of sampling a trial conformation. The sampling function of MMC is square mound shaped with a uniform distribution in phase space while that of HDMC resembles the shape of an ensemble distribution function of a given system.

In HDMC simulation, a trial conformation is generated by sampling in the real equilibrium ensemble distribution of a given system. Since the shape of any distribution in phase space can be measured by its covariance matrices, we try to sample a random conformation whose covariance approaches the real distributions of a given system in the phase space. The HDMC sampling function $T_{HDMC}(\vec{r}'|\vec{r})$ can be derived by mathematical formulation as in ref. [25], and is of the form

$$T_{HDMC}(\vec{r}'|\vec{r}) = D(\Sigma)\exp\left(-\frac{1}{2}det\,[(\vec{r}'|\vec{r})^T\Sigma'^{-1}(\vec{r}'|\vec{r})]\right) \tag{2}$$

where

$$D(\Sigma) = \frac{1}{(2\pi)^{N/2}det\,\Sigma} \tag{3}$$

$$\Sigma = \|\sigma'_{ij}\| \tag{4}$$

$$\sigma'_{ij} = (r'_i - r_i)(r'_j - r_j) \tag{5}$$

On the contrary, the sampling function of Metropolis method $T_{MMC}(\vec{r}'|\vec{r})$ can be written by

$$T_{MMC}(\vec{r}'|\vec{r}) = const., \quad \text{if } |r' - r| \leqslant \Delta \tag{6}$$

where Δ is the maximum displacement allowed in the trial move.

The covariance matrix Σ in equation (3) as a guess to the shape of potential energy hyper surface can be calculated from the past history of Monte Carlo walks on some local conformational region. Then a trial conformation is generated by using the HDMC sampling function and is accepted with the same probability of MMC method. By using HDMC sampling function $T_{HDMC}(\vec{r}'|\vec{r})$, the system can be effectively converged to the low energy state because the sampling procedure makes a large move at a smooth and broad potential energy surface and makes a small move at a sharp and narrow potential energy surface.

In order to make the molecule become more flexible and to make them easily escape from metastable states, we combined this HDMC method with simulated annealing

procedure [29]. Monte Carlo procedure generates conformational ensembles weighted by a Boltzmann factor at a given temperature and the temperature is a control parameter by which an ensemble distribution can be changed. By a slow reduction in temperature, the system can be confined in a small region of phase space and finally the system arrives at the global energy minimum state. We applied the temperature annealing from 500 ~ 1000 K to the room temperature using 2 ~ 3% annealing rates. This temperature range and the annealing rate were justified by analyzing the vibrational normal mode frequencies by Shin and Jhon [23]. The temperature of the $(k+1)$th set which is composed of a number of Monte Carlo steps, is given by

$$T^{k+1} = T^k - X_T T^k \tag{7}$$

where X_T is the temperature annealing factor.

When Monte Carlo method is applied to find the minimum energy structure of a molecule, the geometry of the molecule is usually treated as rigid. In other words, bond lengths and bond angles are fixed and only the torsional degrees of freedom are taken into account. Whereas, the global structural movement of large molecules such as folding of protein is a highly cooperative process in which all of the degrees of freedom have to accord in motion to cross over the large energy barriers a rising from non-bonded collision between atoms. Monte Carlo simulation is, however, a stochastic one where the movement occurs randomly without referring to the intrinsic dynamics of a given system. In order to realize the cooperative processes like protein folding during Monte Carlo movement, we periodically relaxed the internal degree of freedom to reduce nonbonded collisions and help to cross over the barrier mainly between two stable secondary structures in proteins which are β-sheet and α-helix [30]. In this vibrational thermalization procedure, we distribute the potential energy to all of the degrees of freedom including internal modes as the same in molecular dynamics (MD) simulation.

Finally, all of the simulational procedures may be summarized as follows. Starting at appropriate conformation, molecular structures are changed by HDMC procedure at some elevated temperature and at some instant, vibrational thermalization is triggered to relax the internal degrees of freedom. And at the same time, temperature is reduced by a constant annealing factor periodically until it reaches the room temperature. These procedures are repeated until the system reaches the equilibrium conformation. The overall procedure is composed of 300 ~ 500 steps of vibrational thermalization (MD) and 20 ~ 30 sets of HDMC simulation where a set is composed of 20 ~ 30 MCS (Monte Carlo steps per variable). This coupled HDMC procedure generally repeats about 30 cycles and the number of total simulation steps is about 12,000 ~ 27,000 MCS and 9,000 ~ 15,000 MD steps.

RESULTS AND DISCUSSION

Melittin is a water soluble membrane binding protein which is a principal component of honey bee venom with 26 amino acid residues with six positive and no negative charges. NMR experimental results indicate that the six C-terminal residues do not influence the conformation of the 20 N-terminal [31]. We simulate the 20-residue

fragment of melittin with sequences as follows;

Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile

The structure of melittin has been investigated by many people under many different conditions [31, 32]. The X-ray structure of tetrameric melittin has been shown to adopt a structure consisting of two helices joined by a hinge. And melittin is known to be unordered or just having a trace of helix in water without salt at neutral pH and at low concentration. But in high protein concentration and/or in a solution with high ionic strength, it adopts a largely helical conformation and aggregates as tetramer. We applied the HDMC method to locate the lowest energy conformation of monomeric melittin in a deprotonated form which mimics the conformation at high pH.

At first, we selected several starting points by refering the general Ramanchandran type contour maps of amino acids

- all the torsion angles of main chain are (−90, 0) which is the saddle point between two secondary structures, α-helix and β-sheet.
- all the torsion angles of main chain are (−90, −30) which is in the region of α-helical domain.
- all the torsion angles of main chain are (−110, 30) which is in the region of β-sheet domain.

In case of the simulation starting at the saddle point between α-helix and β-sheet, the molecule could easily converge to the minimum energy structure which is identical to the previous experimental results. The resultant principal torsion angles are shown in Table 1. And all of the intramolecular energies of the minimum energy structures and

Table 1 Main torsion angle (ϕ, φ) of the lowest energy minimum conformation for Melittin from this work

residue	ϕ	ψ	
Ile (2)	−109.18 (−65.86)	−12.17 (−28.65)	A(A)[a]
Gly (3)	−75.83 (−70.27)	−79.15 (−60.00)	A(A)
Ala (4)	−57.30 (−56.74)	−44.45 (−44.43)	A(A)
Val (5)	−66.68 (−62.28)	−50.93 (−44.42)	A(A)
Leu (6)	−73.25 (−63.11)	−33.24 (−37.03)	A(A)
Lys (7)	−78.03 (−62.60)	−51.09 (−43.83)	A(A)
Val (8)	−73.33 (−61.00)	−43.92 (−49.73)	A(A)
Leu (9)	−69.58 (−53.87)	−37.70 (−35.29)	A(A)
Thr (10)	−56.36 (−73.50)	−36.54 (−19.17)	A(A)
Thr (11)	−75.03 (−75.13)	100.66 (106.30)	C(C)
Gly (12)	151.85 (108.52)	−94.13 (−78.05)	D*(C*)
Leu (13)	−96.12 (−67.87)	−57.24 (−65.12)	A(A)
Pro (14)	−61.13 (−60.19)	−30.97 (−35.76)	A(A)
Ala (15)	−62.38 (−58.49)	−44.45 (−43.70)	A(A)
Leu (16)	−70.67 (−60.47)	−52.79 (−53.97)	A(A)
Ile (17)	−64.82 (−63.41)	−39.02 (−27.17)	A(A)
Ser (18)	−86.48 (−68.24)	−17.37 (−47.68)	A(A)
Trp (19)	−115.34 (−66.34)	20.92 (−50.62)	B(A)

[a].Representation by Zimmermann code

*.Values in parentheses obtained by the simulation of X-ray.

X-ray structure were in the range of 65 ~ 70 kcal/mol., and all of the simulational structures are consistent with the results of experimental [31, 32] and theoretical studies [3, 6]. First of all, hinge region is formed to bridge the two α-helices between Thr-11 and Gly-12. The torsion angle, ϕ, of Gly-12 shows some deviation as if the hinge structure is broken. But, in the refinement simulation starting from X-ray structure, this torsion angle shows large fluctuation with negative value. Also the stability of X-ray structure in a given condition without including explicit water environment was observed by HDMC simulations starting at X-ray conformation itself. The fluctuation of principal torsion angles (ϕ, ψ) is shown in Figure 1.

The structure of melittin shows a slight deviation from the perfect α-helical structure while keeping the structure of hinge segment. And some residues of α-helical domain are partly converted to C or G (β-sheet) structure in terms of the conformational codes of Zimmermann et al. [33]. Melittin fluctuates largely in two terminal parts, Gly residue of hinge part and Leu residue in helix parts. The large fluctuation of two

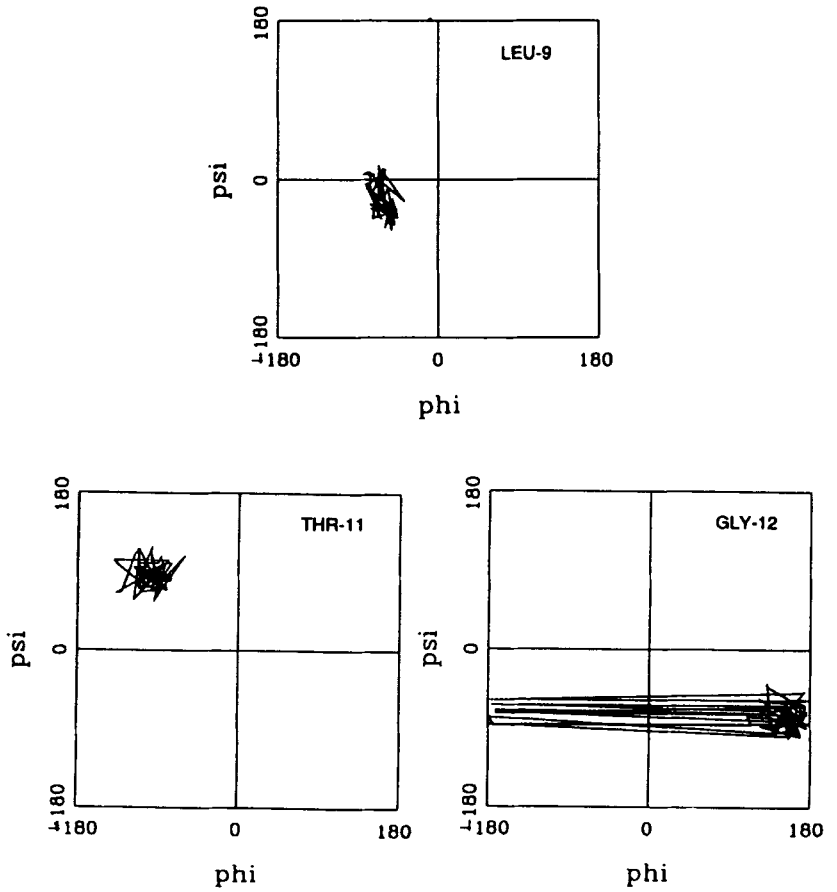

Figure 1 Torsion angle trajectory of main chain of melittin resulted from the simulation starting at X-ray structure by HDMC method at 300 K.

terminal parts might be due to the removal of inter-residue interaction between melittin monomers.

Secondly, in the resultant structures of melittin, there are apparently two α-helical regions connected by a hinge structure. To show the shape of helices, we compare the intra-residue hydrogen bonds of melittin in Table 2. In the simulational structures, the hydrogen bonds between i-th residue and (i + 4)-th residue which represent a characteristic hydrogen bond pair of stable helix, keep the same pattern of typical α-helical structures. Even though there are some deviations in hydrogen bond lengths, all of the hydrogen bond lengths fall within an optimal distance of N – H ··· O, that is 3.0 A°[34]. The resultant structure of melittin is compared with X-ray structure in Figure 2. And the final conformational states of resulting structures which differ in their starting points on the Ramachandran map are shown in Table 3.

For the simulation starting from the torsion angle of (−90, −30), the resultant structure is composed of three structural domains, two α-helical structures and a interhelical hinge region which is the same as the previous results. The Gly residue in hinge part has kept the extended domain as mentioned above, and this can be explained by the large fluctuation of Gly in the simulation starting from X-ray structure.

However, in cases of other starting points of (−110, 30), the final structures have some deviations from the minimum energy structure in detailed distribution of torsion angles of side chains. In case of (−110, 30), the α-helical secondary structure is formed while Leu residue maintains the β-sheet region. However, in X-ray simulation, Leu residue tends to keep the β-sheet structure too. This shows that Leu residue may be strongly stabilized in β-sheet region as well as in α-helix region. The simulational structure starting from this region has higher energy than that of lowest energy structure. There should be a large energy barrier between β-sheet and α-helical region which is not tractable by this type of simulations. Even though HDMC method has succeeded in finding the lowest energy structure of small polypeptides like Met-Enkephalin, there should be some problems involved in extending the size of systems. This means the method in its native form may not be directly applied to predict the minimum energy structure of large molecules greater than melittin. It is generally said that when we are trying to find the lowest energy structure of large molecules such as proteins, the reliability is limited to a rather small molecule of 10-residues without any information about the system. One of the possible solutions to this problem is knowledge-based simulations. In other words, our knowledge about the properties of

Table II Intramolecular hydrogen bond characteristics showing the helix shape of the residues 1–20 of Melittin

residue of hydrogen bond	*hydrogen bond length*
Lys (7) HN – O Gly (3)	2.20
Val (8) HN – O Ala (4)	2.78
Leu (9) HN – O Val (5)	2.72
Leu (13) O – HN Val (17)	1.88
Pro (14) O – HN Ser (18)	2.37
Leu (16) O – HN Trp (19)	2.98

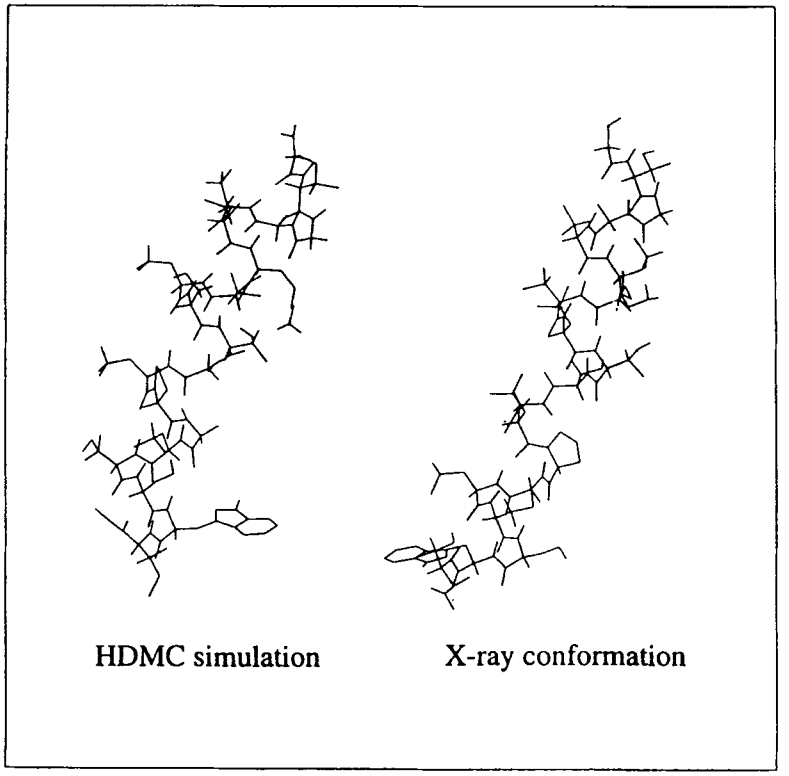

Figure 2 Comparison of the computed lowest energy minimum structure with X-ray of residues 1 ~ 20 of Melittin. Right hand side is X-ray structure and left hand side is the structure resulted from HDMC simulation.

Table III Low energy conformational state for the Melittin obtained by different starting point and condition

Ala (4)	B	A	A
Val (5)	A	A	A
Leu (6)	A	C	A
Lys (7)	A	A	A
Val (8)	A	A	A
Thr (11)	C	A	C
Gly (12)	E	D*	C*
Pro (14)	A	A	A
Ala (15)	A	A	A
Leu (16)	A	C	A
Ile (17)	A	A	A
Ser (18)	A	A	A

*.HDMC-1 is starting at typical α-helical region
*.HDMC-2 is starting at typical β-sheet region

amino acids helps us to increase the reliability of simulations to find the lowest energy conformation of large molecules as in our case, i.e., we have succeeded in reproducing the native structure of melittin by using knowledge-based starting points such as saddle points and α-helical domain.

From the standpoint of reducing the computing time, taking a starting conformation at a saddle point between α-helix and β-sheet is very effective to reduce the negative effects of initial condition. Presumably, the short-range interactions within each residue play a major role in determining the ultimate conformation of each residue in the chain. And when the large globular protein folded, it is essential to introduce long-range interactions to enable the molecule to achieve its proper overall shape. The conventional long-range forces in physical systems are electrostatic Coulomb force and hydrophobic force. In this study, the long range interaction between charges is represented by the electrostatic term using CVFF force field parameters. For the case of hydrophobic forces, we could not introduce them in our simulational frame directly. But fortunately, the hydrophobic interaction was parameterized in a pairwise form depending on the two hydrophobic residues [35]. HDMC method can use this hydrophobic interaction in place of conventional atomic force fields. The long-range interaction also considered as a constraint parameter to lead some possible combination of local fragments. For example, the conformational space of a protein can be divided into several classes characterized by different spatial geometry [36]. We can also use HDMC method as the geometry optimization method of the classes of conformation to find the lowest energy structure. To investigate such a possibility to find the global energy minimum structure of large molecules to its root, further study needs to be continued in the direction of including the environmental effects on protein folding and obtaining the accurate and much simplified force fields.

Acknowledgment

The authors aknowledge the partial support of the Korea Research Centre for Theoretical Physics and Chemistry.

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