Finding dominant reaction pathways via global optimization of action

Juyong Lee
Laboratory of Computational Biology,
National Heart, Lung, and Blood Institute (NHLBI),
National Institutes of Health (NIH), Bethesda, Maryland 20892, U.S.A.

In-Ho Lee
Korea Research Institute of Standards and Science, Daejeon 34113, Republic of Korea

InSuk Joung and Jooyoung Lee
School of Computational Sciences, Korea Institute of Advanced Study, Seoul 02455, Korea

Bernard R. Brooks
Laboratory of Computational Biology,
National Heart, Lung, and Blood Institute (NHLBI),
National Institutes of Health (NIH), Bethesda, Maryland 20892, USA

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Abstract

We present a new computational approach to sample multiple reaction pathways with fixed initial and final states through global optimization of the Onsager-Machlup action using the conformational space annealing method. This approach successfully samples not only the most dominant pathway but also many other possible paths without initial guesses on reaction pathways. Pathway space is efficiently sampled by crossover operations of a set of paths and preserving the diversity of sampled pathways. The sampling ability of the approach is assessed by finding pathways for the conformational changes of alanine dipeptide and hexane. The benchmarks demonstrate that the rank order and the transition time distribution of multiple pathways identified by the new approach are in good agreement with those of long molecular dynamics simulations. We also show that the folding pathway of the mini-protein FSD-1 identified by the new approach is consistent with previous molecular dynamics simulations and experiments.

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Finding multiple reaction pathways between two end states remains a challenging problem in computational biophysics [1]. For this purpose, performing a long-time molecular dynamics (MD) simulation is a commonly used approach. Despite recent progress in the methodologies of MD, this approach still suffers from a timescale problem. Many biological reactions such as protein folding and conformational transitions occur in the microsecond or millisecond ranges, which are hard to be performed with conventional computers. In addition, MD simulations starting from one end state are not guaranteed to reach the other end state of interest. Thus developing an efficient computational method to find multiple possible reaction pathways connecting two end states is necessary. There are currently no methods that can efficiently produce the multiple dominant pathways connecting two well-defined end point states in a complex system. The objective of this work is to present such a method. Other approaches using a conformational driving force do not sample alternatives. Methods that are robust, such as transition path sampling [2 3], are very expensive to use for complex systems with and multiple steps and barriers.

Various chain-of-state methods have been suggested based on the assumption that a dominant transition pathway between two states follows the minimum energy pathway [4 6]. The limitations of these methods are that they do not consider the dynamics of a system and find only the nearest local minimum solution from a given initial pathway [1]. Alternative methods based on the principle of least action have been suggested [7 13]. Passerone and Parrinello suggested the action-derived molecular dynamics (ADMD) method based on the combination of classical action and a penalty term that conserves the total energy of a system [11 12]. To enhance the convergence of ADMD calculations, Lee et al. introduced a kinetic energy penalty term based on the equipartition theorem [13 16]. Although ADMD yields physically relevant pathways, it has two practical limitations [13 17]: i) it strongly depends on the initial guess of a pathway; and ii) it cannot identify the most dominant pathway when there are multiple pathways because the classical least action principle is an extremum principle.

For diffusive processes, the second problem can be avoided by using the Onsager-Machlup (OM) action $S_{OM}$ [8 18 23]. Onsager and Machlup showed that the relative probability to observe a pathway with an OM action of $S$ is proportional to $e^{-S/k_BT}$ where $k_B$ is the Boltzmann constant and $T$ is a temperature. Thus the most dominant pathway corresponds to the one that minimizes $S_{OM}$ and the same result can be obtained by solving the Fokker-
Planck equation [24–26]. This property recasts the problem of finding dominant pathways into a global optimization problem. However, finding the global minimum of $S_{OM}$ is a numerically challenging task because the minimization of $S_{OM}$ requires the second derivatives of a potential function, which are computationally expensive, at best, and wholly unavailable for many quantum mechanical energy surfaces.

In this work, we propose an efficient computational method that finds not only the most dominant pathway but also multiple suboptimal pathways without second derivative calculations. For global optimization of $S_{OM}$, we used an efficient global optimization method called conformational space annealing (CSA) based on a combination of genetic algorithm, simulated annealing, and Monte Carlo minimization [27, 28]. The CSA method has been demonstrated to be extremely efficient in solving various global optimization problems including finding low energy conformations of Lennard-Jones clusters [29], protein structure prediction [28–34], multiple sequence alignment [35], and community detection in networks [36–38]. We extend the CSA approach to examining pathways, preserving all features that make it robust and efficient, by applying it to sets of entire pathways represented as a chain-of-states. From benchmark simulations using alanine dipeptide, we observed that our method finds multiple transition pathways, which are consistent with long-time Langevin dynamics (LD) simulations. In addition, the rank order statistics and transition time distributions of the multiple transition pathways are in good agreement with those of the LD results. We will call the method Action-CSA.

Here, we briefly review the theoretical background behind Action-CSA. If a system with $N$ atoms with a potential energy $V$ follows the overdamped Langevin dynamics,

$$\gamma m \ddot{x} = -\frac{\partial V}{\partial x} + \mathbf{R}, \quad (1)$$

where $m$ is a diagonal mass matrix, $x$ is a $3N$ dimensional coordinate vector, $\gamma$ is collision frequency, and $\mathbf{R}$ is a Gaussian random force, the relative probability of finding a final state $x_f$ at a time $t$ from an initial state $x_i$ via diffusive trajectories $x(t)$ is determined by using the path integral approach and OM action $S_{OM}[x(t)]$ [18, 19]:

$$P(x_f|x_i; t) = \int_0^t Dx(t) \exp\left(-\frac{S_{OM}[x(t)]}{k_B T}\right), \quad (2)$$

where $Dx(t)$ indicates that the integration runs over all possible pathways $x(t)$. This relationship suggests that if the $S_{OM}$ values of all physically accessible pathways are obtained,
one can determine the relative populations of multiple pathways. Thus, $S_{OM}$ is a proper target objective function of global optimization. The generalized OM action of a pathway $x(t)$ is defined [18, 19, 39, 40]:

$$S_{OM}[x(t)] = \frac{\Delta V}{2} + \frac{1}{4\gamma} \int_0^t d\tau \left\{ [\gamma m \dot{x}(\tau)]^2 + \|\nabla V[x(\tau)]\|^2 - 2k_B T \nabla^2 V[x(\tau)] \right\},$$  \hspace{1cm} (3)

where $\Delta V = V(x_f) - V(x_i)$. The last term is related to trajectory entropy connected with fluctuations [40-42] and was not presented in the original work by Onsager and Machlup because the harmonic potential was considered [18, 19]. Note that the minimization of $S_{OM}$ using analytic local minimization algorithms requires third derivatives. This makes the direct global optimization of $S_{OM}$ hard to be applied to detect transition pathways of biomolecules with all-atom force fields due to the complexity of implementation and high computational cost. For numerical calculations based on a chain-of-state representation, the OM action should be discretized. The method uses the second-order discretization of the symmetric OM formula, which uses only gradients for $S_{OM}$ calculations [43]:

$$S_{OM}[x(t)] = \frac{\Delta V}{2} + \sum_{i=0}^{P-1} \frac{\Delta t}{4\gamma} \left\{ \frac{\gamma m(x_{i+1} - x_i)}{\Delta t} \right\}^2 + \frac{\|\nabla V(x_i)\|^2}{2} + \frac{\|\nabla V(x_{i+1})\|^2}{2}$$

$$- \frac{\gamma m(x_{i+1} - x_i)}{\Delta t} [\nabla V(x_{i+1}) - \nabla V(x_i)],$$  \hspace{1cm} (4)

where $P + 1$ is the number of replicas, $\Delta t$ is a time step between successive replicas, and $t = P\Delta t$ is the total transition time. This formula is superior to the direct implementation of Eq. (3) since it requires only the first derivatives of $V$ to evaluate $S_{OM}$.

Here, we describe the application of CSA to optimize $S_{OM}$. In general, a pathway is represented as a chain of $P - 1$ replicas with $N$ atoms for each replica leading to $3N(P - 1)$ total degrees of freedom. Each replica is represented by a sequence of $3N - 6$ internal dihedral angles and 6 net translational/rotational degrees of freedom. An Action-CSA calculation starts with a set of random pathways on a pathway space. Subsequently, the actions of the random pathways should be locally optimized. We call this set of pathways a bank, and update conformations in the bank during the Action-CSA calculation. As stated previously, direct minimization of $S_{OM}$ using analytic gradients is computationally challenging.

For a computationally feasible local action optimization, we optimized a pathway using
a modified action from ADMD instead of using $S_{OM}$. The discretized classical action is defined:

$$S_{\text{classical}}[\mathbf{x}(t)] = \sum_{i=0}^{P-1} L_i(x_i) \Delta t = \sum_{i=0}^{P-1} \left[ \frac{m(x_i - x_{i+1})^2}{2\Delta t^2} - V(x_i) \right] \Delta t. \quad (5)$$

Physically accessible pathways correspond to the stationary points of $S_{\text{classical}}$. Finding such pathways is a computationally difficult task because $S_{\text{classical}}$ is not bounded; $S_{\text{classical}}$ can be minimized or maximized, and the stationary points of $S_{\text{classical}}$ can be minima, maxima or saddle points. Another practical problem is that the total energies of pathways satisfying the stationary condition $\delta S_{\text{classical}} = 0$ may not be conserved \[11\]. To find pathways that satisfy the principle of least action and conserve total energies, a modified action with a penalty term restraining total energy was suggested \[11\]:

$$\Theta(x_i; E) = \mu_A S_{\text{classical}} + \mu_E \sum_{i=0}^{P-1} (E_i - E)^2$$

$$= \mu_A \sum_{i=0}^{P-1} \left[ \frac{m(x_i - x_{i+1})^2}{2\Delta t^2} - V(x_i) \right] \Delta t + \mu_E \sum_{i=0}^{P-1} \left\{ \left[ \frac{m(x_j - x_{j+1})^2}{2\Delta t^2} + V(x_j) - E \right] \right\}, \quad (6)$$

where $E$ is a targeted total energy of a system, $\mu_A$ and $\mu_E$ are the weighting parameters of the classical action, and the restraint term for energy conservation. The minimization of $\Theta[x(t); E]$ requires only the first derivatives of $V$.

We call the set of locally optimized initial random pathways using $\Theta[x(t); E]$ the first bank. The first bank remains the same throughout the optimization and is used as the reservoir of partially optimized pathways to enhance the diversity of pathway search. A copy of the first bank is generated and called a bank. The conformations in the bank are updated during a calculation while the size of the bank is kept constant. By using the pathways included in the first bank and the bank, new trial pathways are generated by performing crossover and random perturbation operations. For a crossover operation, two pathways, a seed pathway from the bank and a random pathway either from the bank or the first bank, are selected and random parts of two selected configurations are swapped. For a random perturbation, a certain number of degrees of freedom of a seed pathway, up to 5% of total degrees of freedom, were randomly changed. The generated trial pathways are
locally optimized using $\Theta[x(t); E]$ to remove any possible artifacts generated by the crossover
and the random perturbation operations. However, after local minimizations, the bank was
updated by comparing the $S_{OM}$ values of the existing pathways and the new ones instead of
$\Theta[x(t); E]$.

A key feature of CSA is a sophisticated bank-update procedure that prevents a search
being trapped in local minima during the optimization and keeps the diversity of the bank.
For a newly obtained configuration $\alpha$, the distances between $\alpha$ and the existing ones in the
bank are calculated. If the distance $D$ between $\alpha$ and its closest neighbor is less than a cutoff
distance $D_{cut}$, only the better configuration in terms of the objective function is selected.
If $D > D_{cut}$, $\alpha$ is considered a new configuration and it replaces the worst configuration in
the bank. At initial stages of a calculation, $D_{cut}$ is kept large for wider sampling. As the
calculation proceeds, it gradually decreases for a refined search near the global minimum.
The bank keeps updating until no pathway with a lower $S_{OM}$ is found. In this work, a
distance between two pathways was measured by the Fréchet distance [44]. More details on
a general CSA procedure are described elsewhere [27, 29, 33, 35].

To verify that Action-CSA successfully finds multiple transition pathways and allows
one to determine the rank order of the pathways based on their optimized $S_{OM}$ values,
we applied our method to investigate the conformational transition of alanine dipeptide
from $C7_{eq}$ to $C7_{ax}$ in the vacuum. Here, we used the polar hydrogen representation in the
PARAM19 force field [45] and dielectric constant was set to 1.0 [46]. We performed Action-
CSA simulations with different transition times, $t$ in Eqs. (4) and (6), ranging from 0.2 ps
to 2.0 ps with an interval of 0.1 ps. The numbers of replicas were adjusted with $t$ to keep
the time step between replicas $\Delta t = 5$ fs. All simulations were performed at temperature $T$
= 350 K with a collision frequency $\gamma = 1.0$ ps$^{-1}$. The reference total energy $E$ in Eq. (5)
was obtained by adding the initial potential energy $V(x_i) = -43.3$ kcal/mol and a kinetic
energy of 12.5 kcal/mol estimated by $3Nk_B T/2$ with the number of atoms $N = 12$. The
weighting parameters $\mu_A$ and $\mu_E$ in Eq. (5) were set to $-1.0$ and $1.0$, respectively. For
comparison purposes, we performed 500 $\mu$s LD simulations of alanine dipeptide under the
same condition and counted the number of the $C7_{eq} \rightarrow C7_{ax}$ transitions.

Now we will show that the Action-CSA identifies not only the most dominant pathway
but also multiple possible pathways. We identified 8 different pathways for the $C7_{eq} \rightarrow C7_{ax}$
transition by clustering all pathways sampled from the Action-CSA simulations (Figure 1A).
From the $S_{OM}$ values obtained with different transition times (Figure 1B), it is clear that the pathway that passes barrier B has the lowest $S_{OM}$ values along all transition times tested, which indicates that it is the most dominant pathway regardless of transition time. This is consistent with the LD simulation results. To compare the Action-CSA result with LD, we performed 5000 independent 100 ns LD simulations amounting to 500 $\mu$s trajectories (Table I). From the simulations, we observed 1350 transitions from $C7_{eq}$ to $C7_{ax}$ and categorized them by finding the nearest neighbor from the 8 pathways obtained with CSA. Among them, the pathway that crosses barrier B was identified as the most dominant one with all transition times. This demonstrates that Action-CSA correctly identified the minimum OM action pathway and that it matches the most dominant pathway observed in LD simulations.

| Path ID | Frequency |
|---------|-----------|
| Path1   | 1183      |
| Path2   | 116       |
| Path3   | 25        |
| Path4   | 7         |
| Path5   | 4         |
| Path6   | 4         |
| Path7   | 10        |
| Path8   | 1         |

In addition, it is also identified that the Action-CSA simulations can provide information on the transition times of various pathways. Until $t < 0.8$ ps, the pathway that crosses barrier C (Path2) has the second lowest $S_{OM}$ and the lowest $S_{OM}$ value was observed at 0.4 ps. These are consistent with the LD results in which all 118 transitions that crossed barrier C occurred within 1.1 ps and their most probable transition time was 0.7 ps (the inset of Fig 1B). However, when $t > 0.8$ ps, Path3, which passes the fully extended conformation region $(\Phi, \Psi) = (-180^\circ, 180^\circ)$ and barrier A and B becomes the pathway with the second lowest $S_{OM}$. From the LD simulations, when $t > 0.9$ ps, 25 pathways similar to Path3 were
FIG. 1. Upper panel: eight different pathways for the $C_7_{\text{eq}} \rightarrow C_7_{\text{ax}}$ transition and the potential energy surface for the $\Phi$ and $\Psi$ angles with the PARAM19 force field (in units of kcal/mol). Potential energy barriers are labeled in order of their heights (from A to F). Lower panel: the $S_{\text{OM}}$ values of 6 pathways for the $C_7_{\text{eq}} \rightarrow C_7_{\text{ax}}$ transitions of alanine dipeptide along different transition times.
identified, which makes them the second dominant pathway. These results demonstrate that the profile of $S_{OM}$ values is consistent with the distributions of transition times obtained from the LD simulations. Note that the most probable transitions times observed from the LD simulations are longer than the minimum action transition times obtained from the CSA simulations. This is because high-frequency motions due to thermal fluctuations are filtered out in the minimum action pathways [1, 8, 9]. This means that the dwell time is well filtered out in the simulation, where a physically sufficient sampling time is assumed.

The second example is finding possible pathways for the conformational change of hexane from the all-gauche(-) (g-g-g-) to the all-gauche(+) state (g+g+g+). We assessed the sampling ability of Action-CSA by investigating how many pathways are found. If we assume that dihedral angles do not cross a high barrier around the cis state, all possible transition pathways between the two all-gauche states can be enumerated (Table II). For this reaction, there exist 44 possible pathways in total. If the symmetries of dihedral angles and atomic order are considered, all 44 pathways can be categorized into 14 unique pathway types. We repeated the Action-CSA calculation of the reaction 40 times by using 200 trial pathways consisting of 100 replicas and a transition time of 3 ps.

In all simulations, the 6 lowest action pathways, C+C+, C-C-, T+C+, T+C-, C+M+, and C+M-, were found consistently. The other higher action pathways except for the highest action pathway, M+XM-, were found in at least 29 out of 40 CSA simulations. Only M+XM- was found in 9 simulations. On average, a single CSA simulation sampled 12 out of 14 unique path types and 26 out of 44 possible pathways. These results show that Action-CSA assuredly samples a number of lowest action, most dominant, pathways. The majority of the remaining pathways with higher actions can also be found with a tendency that relatively lower action pathways are more likely to be found. The sampling ability of Action-CSA can be improved by using a larger bank size. The potential energy landscape of the C+C+ pathway corresponding to the least $S_{OM}$ shows that hexane crosses 6 energy barriers (Fig. 2).

The third example is finding the folding pathway of FSD-1, a 28-residue mini-protein that has been widely investigated as a model system for studying protein folding [15, 47–51]. Folding pathways of FSD-1 from the fully extended conformation to the native structure were represented by using 100 replicas, a total folding time of 10 ps, and a temperature of 300 K. The protein was represented by the PARAM19 force field [45] and solvation effects were considered using the FACTS implicit solvent model [52].
The characteristics of the identified lowest action folding pathway are consistent with experiments where the N-terminal $\beta$-hairpin is more flexible than the C-terminal $\alpha$-helix. A comparison of the RMSD values indicates that the $\alpha$-helix folds first. Afterward, the folding of $\beta$-hairpin and the formation of hydrophobic core occur concurrently (the upper panel of Fig. 3). The potential energy landscape of FSD-1 folding shows that the potential energy decreases quickly after the 80th step suggesting that the step may be the transition state of folding (the lower panel of Fig. 3). The conformation at the 80th step shows that the helix is almost formed while the C-terminal region is not folded and the hydrophobic core is partially exposed, which is similar to transition states observed in previous conventional MD simulations.

In conclusion, we demonstrated that efficient global optimization of Onsager-Machlup action reveals multiple reaction pathways successfully. In this work, we introduced a new computational method that samples not only the most dominant pathway but also other possible pathways by optimizing Onsager-Machlup action using the CSA method. The advantages of our method over existing pathway sampling methods are the fact that it
samples multiple pathways regardless of the quality of initial guesses on pathways; it requires only the calculation of first derivatives; and its sampling ability is not limited by high energy barriers separating pathways, which is a major limiting factor of previous MD-based pathway sampling methods in exploring pathway space [20, 22, 26, 54]. In addition, we identified that the profile of minimum Onsager-Machlup actions found with different transition time parameters provide kinetic information on pathways. In terms of implementation, Action-
CSA calculation is massively parallel because the local minimization of each trial pathway is independent of each other. Thus, pathway samplings for larger systems are readily possible with help of a large cluster system.

### TABLE II: List of 14 unique pathway types and 44 non redundant pathways for conformational change of hexane from g-g-g- to g+g+g+.

| Unique path type | Non redundant path |
|------------------|--------------------|
| C+C+             | g-g-g- → tg-g- → tg-t → ttt → tg+t → tg+g+ → g+g+g+  |
|                  | g-g-g- → g-g-t → tg-t → ttt → tg+t → g+g+t → g+g+g+  |
| C+C-             | g-g-g- → g-g-t → tg-t → ttt → tg+t → tg+g+ → g+g+g+  |
|                  | g-g-g- → tg-g- → tg-t → ttt → tg+t → g+g+t → g+g+g+  |
| T+C+             | g-g-g- → tg-g- → tg-t → ttt → tg+g+ → ttt → g+g+g+  |
|                  | g-g-g- → g-g-t → tg-t → ttt → g+tt → g+g+t → g+g+g+  |
|                  | g-g-g- → g-g-t → g-tt → ttt → tg+t → g+g+t → g+g+g+  |
|                  | g-g-g- → tg-g- → ttg- → ttt → tg+t → g+g+t → g+g+g+  |
| T+C-             | g-g-g- → g-g-t → tc-t → ttt → ttg+ → ttt → g+g+g+  |
|                  | g-g-g- → tg-g- → tg-t → ttt → g+tt → g+g+t → g+g+g+  |
|                  | g-g-g- → g-g-t → g-tt → ttt → tg+t → g+g+t → g+g+g+  |
|                  | g-g-g- → tg-g- → ttg- → ttt → tg+t → g+g+t → g+g+g+  |
| C+M+             | g-g-g- → tg-g- → tg-t → ttt → ttg+ → g+tg+ → g+g+g+  |
|                  | g-g-g- → g-g-t → tg-t → ttt → g+tt → g+tg+ → g+g+g+  |
|                  | g-g-g- → g-tg- → ttg- → ttt → tg+t → g+g+t → g+g+g+  |
|                  | g-g-g- → g-tg- → g-tt → ttt → tg+t → g+g+t → g+g+g+  |
| C+M-             | g-g-g- → g-g-t → tg-t → ttt → ttg+ → g+tg+ → g+g+g+  |
|                  | g-g-g- → tg-g- → tg-t → ttt → g+tt → g+tg+ → g+g+g+  |
|                  | g-g-g- → g-tg- → g-tt → ttt → tg+t → g+g+t → g+g+g+  |
|                  | g-g-g- → g-tg- → ttg- → ttt → tg+t → g+g+t → g+g+g+  |
| T+T+             | g-g-g- → tg-g- → ttg- → ttt → ttg+ → ttt → g+g+g+  |
|                  | g-g-g- → g-g-t → tg-t → ttt → g+tt → g+g+t → g+g+g+  |
| T+T-             | g-g-g- → tg-g- → ttg- → ttt → g+tt → g+g+t → g+g+g+  |
|          | g-g–g → g-g–t → g–tt → ttt + tg–t → g+g+g+ |
|----------|-----------------------------------------------|
| T+M+     | g-g–g → g-g–t → g–tt → ttt + g+tt → g+tg+ → g+g+g+ |
|          | g-g–g → tg–g → ttg–t → ttt + g+tt → g+tg+ → g+g+g+ |
|          | g-g–g → gt–g → g–tt → ttt + g+tt → g+tg+ → g+g+g+ |
| T+M-     | g-g–g → g-g–t → g–tt → ttt + g+tt → g+tg+ → g+g+g+ |
|          | g-g–g → tg–g → ttg–t → ttt + g+tt → g+tg+ → g+g+g+ |
|          | g-g–g → gt–g → g–tt → ttt + g+tt → g+tg+ → g+g+g+ |
| M+M-     | g-g–g → g–tg–t → g–tt → ttt + g+tt → g+tg+ → g+g+g+ |
|          | g-g–g → g–tg–t → g–tt → ttt + g+tt → g+tg+ → g+g+g+ |
| T+XT-    | g-g–g → g–tg–t → g–tt → ttt + g+tt → g+tg+ → g+g+g+ |
|          | g-g–g → tg–g → ttg–t → g+tt → g+tg+ → g+g+g+ |
| TXM      | g-g–g → g–tg–t → g–tt → g–tt + gc–tg+ → g+g+g+ |
|          | g-g–g → g–tg–t → g–tt → g–tt + gc–tg+ → g+g+g+ |
| M+XM-    | g-g–g → g–tg–t → g–tt → g–tt + gc–tg+ → g+g+g+ |
|          | g-g–g → g–tg–t → g–tt → g–tt + gc–tg+ → g+g+g+ |
|          | g-g–g → g–tg–t → g–tt → g–tt + gc–tg+ → g+g+g+ |

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* Co-corresponding author: [jlee@kias.re.kr](mailto:jlee@kias.re.kr)
† Co-corresponding author: [brb@nih.gov](mailto:brb@nih.gov)
[1] R. Elber, The Journal of Chemical Physics 144, 060901 (2016).
[2] C. Dellago, P. G. Bolhuis, F. S. Csaika, and D. Chandler, Journal of Chemical Physics 108, 1964 (1998).
[3] P. G. Bolhuis, D. Chandler, C. Dellago, and P. L. Geissler, Annual Review of Physical Chemistry 53, 291 (2002).
[4] R. Czerminski and R. Elber, International Journal of Quantum Chemistry 186, 167 (1990).
[5] G. Henkelman, B. P. Uberuaga, and H. Jónsson, Journal of Chemical Physics 113, 9901 (2000).
[6] W. E, W. Ren, and E. Vanden-Eijnden, Physical Review B 66, 5 (2002).
[7] R. E. Gillilan and K. R. Wilson, Journal of Chemical Physics 97, 1757 (1992).
[8] R. Olender and R. Elber, The Journal of Chemical Physics 105, 9299 (1996).
[9] R. Elber, J. Meller, and R. Olender, The Journal of Physical Chemistry B 103, 899 (1999).
[10] R. Elber and D. Shalloway, The Journal of Chemical Physics 112, 5539 (2000).
[11] D. Passerone and M. Parrinello, Physical Review Letters 87, 108302 (2001).
[12] D. Passerone, M. Ceccarelli, and M. Parrinello, Journal of Chemical Physics 118, 2025 (2003).
[13] I.-H. Lee, J. Lee, and S. Lee, Physical Review B 68, 064303 (2003).
[14] I.-H. Lee, S.-Y. Kim, and J. Lee, Chemical Physics Letters 412, 307 (2005).
[15] I.-H. Lee, S.-Y. Kim, and J. Lee, The Journal of Physical Chemistry. B 116, 6916 (2012).
[16] I.-H. Lee, S.-Y. Kim, and J. Lee, International Journal of Molecular Sciences 14, 16058 (2013).
[17] R. Crehuet and M. J. Field, Physical Review Letters 90, 089801; author reply 089802 (2003).
[18] L. Onsager and S. Machlup, Physical Review 91, 1505 (1953).
[19] S. Machlup and L. Onsager, Physical Review 91, 1512 (1953).
[20] P. Eastman, N. Grønbech-Jensen, and S. Doniach, Journal of Chemical Physics 114, 3823 (2001).
[21] D. M. Zuckerman and T. B. Woolf, Physical Review. E, Statistical, nonlinear, and soft matter physics 63, 016702 (2000).
[22] H. Fujisaki, M. Shiga, and A. Kidera, Journal of Chemical Physics 132, 134101 (2010).
[23] H. Fujisaki, M. Shiga, K. Moritsugu, and A. Kidera, The Journal of Chemical Physics 139, 054117 (2013).
[24] P. Faccioli, M. Sega, F. Pederiva, and H. Orland, Physical Review Letters 97, 108101 (2006).
[25] M. Sega, P. Faccioli, F. Pederiva, G. Garberoglio, and H. Orland, Physical Review Letters 99, 118102 (2007).
[26] S. Beccara, T. Skrbic, R. Covino, and P. Faccioli, Proceedings of the National Academy of Sciences U.S.A. 109, 2330 (2012), arXiv:1111.3518v1.
[27] J. Lee, H. Scheraga, and S. Rackovsky, Journal of Computational Chemistry 18, 1222 (1997).
[28] J. Lee, A. Liwo, and H. Scheraga, Proceedings of the National Academy of Sciences U.S.A. 96, 2025 (1999).
[29] J. Lee, I.-H. Lee, and J. Lee, Physical Review Letters 91, 080201 (2003), arXiv:0307690 [cond-mat].
[30] P. J. Steinbach, Proteins: Structure, Function and Genetics 57, 665 (2004).
[31] K. Joo, J. Lee, S. Lee, J.-H. Seo, S. J. Lee, and J. Lee, Proteins 69, 83 (2007).
[32] J. Lee, K. Joo, Kim, Seung-Yeon, and J. Lee, Journal of Computational Chemistry 29, 2479 (2008).
[33] K. Joo, J. Lee, J.-H. Seo, K. Lee, B.-G. Kim, and J. Lee, Proteins: Structure, Function, and Bioinformatics 75, 1010 (2009).
[34] J. Lee, J. Lee, T. N. Sasaki, M. Sasai, C. Seok, and J. Lee, Proteins: Structure, Function, and Bioinformatics 79, 2403 (2011).
[35] K. Joo, J. Lee, I. Kim, S. J. Lee, and J. Lee, Biophysical Journal 95, 4813 (2008).
[36] J. Lee, S. P. Gross, and J. Lee, Physical Review E 85, 056702 (2012).
[37] J. Lee and J. Lee, PLOS ONE 8, e60372 (2013).
[38] J. Lee, S. P. Gross, and J. Lee, Scientific Reports 3, 2197 (2013).
[39] K. L. C. Hunt and J. Ross, The Journal of Chemical Physics 75, 976 (1981).
[40] A. B. Adib, The Journal of Physical Chemistry. B 112, 5910 (2008), arXiv:0712.1255.
[41] K. R. Haas, H. Yang, and J. W. Chu, Journal of Physical Chemistry Letters 5, 999 (2014).
[42] K. R. Haas, H. Yang, and J. W. Chu, Journal of Physical Chemistry B 188, 8099 (2014).
[43] T. F. Miller and C. Predescu, Journal of Chemical Physics 126, 144102 (2007).
[44] H. Alt and M. Godau, International Journal of Computational Geometry & Applications 05, 75 (1995).
[45] E. Neria, S. Fischer, and M. Karplus, The Journal of Chemical Physics 105, 1902 (1996).
[46] R. J. Loncharich, B. R. Brooks, and R. W. Pastor, Biopolymers 32, 523 (1992).
[47] S. Jang, S. Shin, and Y. Pak, Journal of the American Chemical Society **124**, 4976 (2002).

[48] H. Lei and Y. Duan, Journal of Chemical Physics **121**, 12104 (2004).

[49] H. Lei, S. G. Dastidar, and Y. Duan, Journal of Physical Chemistry B **110**, 22001 (2006).

[50] C. Wu and J. E. Shea, PLoS Computational Biology **6**, e1000998 (2010).

[51] H. Lei, Z. X. Wang, C. Wu, and Y. Duan, Journal of Chemical Physics **131**, 165105 (2009).

[52] U. Haberthür and A. Caflisch, Journal of Computational Chemistry **29**, 701 (2008).

[53] J. A. Feng, J. Kao, and G. R. Marshall, Biophysical Journal **97**, 2803 (2009).

[54] D. H. Mathews and D. A. Case, Journal of Molecular Biology **357**, 1683 (2006).