**Action-Derived Molecular Dynamics: from Algorithms to Applications**

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Where transition-pathway search is part of the pleasure.

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**Introduction**

Molecular dynamics (MD) methods are commonly used to study structural, thermodynamic, and kinetic properties of molecular systems. Atomic motions in molecular systems take place on a wide range of time scales. In a molecular dynamics simulation, the equations of motion for all atoms of a system are integrated over a certain period of time. Since the size of time step employed in the integration of the equations of motion is order of fs (10^{-15} sec), the time scale in a practical molecular dynamics is short, typically in the orders of ps (10^{-12} sec) or ns (10^{-9} sec). In many realistic situations, these time scales are not sufficient for the description of the atomic motions. Actually, rare event in the molecular system is not a gradual process but a stochastic process. The precise structure of an activated complex in the chemical reaction is often difficult to determine. Chemical reactions usually involve the activated complex with making and/or breaking of chemical bonds. The reaction pathway is a key object in the understanding of a chemical reaction, in general. Because chemical reaction is extremely complex and general, no computational methods have constantly been applied to the problem, providing new theoretical predictions and deeper insights into the experimental observation. The methods based on the transition-state theory are inefficient for complex systems because it is difficult to design the appropriate reaction coordinates for the chemical reactions, in general. In large
In complex systems, the reaction coordinates are often difficult to define, which limits the scope of the constrained dynamics and/or umbrella sampling procedures.

Passerone and Parrinello (2001) proposed the action-derived molecular dynamics (ADMD) method that explicitly determines the dynamical trajectory of an atomic system for given initial and final conformations with chosen simulation time \( \tau \). Here, initial and final configurations are interchangeable due to the microscopic reversibility, indicating the characteristic feature of the equations of motion. ADMD method is suitable for determining the transition pathway model with a minimum-activation-energy barrier, representing a sampling in trajectory space. The method is especially useful for the case "how systems change (reaction mechanism) during the chemical reactions." This is a contrast to the case "which state is stable?", where thermodynamics is involved. ADMD method does not involve the pre-definition of a reaction coordinate. ADMD is believed to be promising for the general class of multiple time scale simulations, which includes not only infrequent events in condensed matter systems but also slow-mode systems such as the dynamics of biomolecules and polymers and the relaxation in glasses. This web-page is meant to give a comprehensive picture of the ADMD method.

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**Theoretical Background**

ADMD method generates a discretized reaction pathway for a given set of initial and final conformations. ADMD is based on the least action principle (Hamilton's principle). ADMD searching for a transition pathway between two configurations defined precisely before the simulation. The resulting trajectory is not an exact solution of the Newton's equations of motion, but an approximation to the classical pathways. Classical action in a discretized form is not useful in practice. The reason for that is the discretized action is not bounded and the distribution of the extreme condition is depend on the choice of discretization parameter \( \Delta \). Consider an atom of which the trajectory is denoted by a set of vector coordinates, \( \{ q_j \} \). Atomic trajectory of time duration \( \tau \) is represented by a chronological sequence of atomic position vectors. Atomic units (\( \hbar=e=m_e=1 \); a.u. in time = \( 2.4189 \times 10^{-17} \) sec, a.u. in energy = \( \text{hartree} = 2 \times 13.6058 \) eV = 627.50956 kcal/mol, a.u. in length = 0.529177 \( \text{Angstrom} = \text{bohr} = 0.0529177 \) nm, electron rest mass= 1 a.u.) are used in this web-page. The present method employs only Cartesian coordinates which makes it easy to use for a variety of systems. In particular, it is quite useful when the reaction coordinate cannot be represented by a single coordinate or by a combination of a small number of local coordinates. In general, finding these reaction coordinates is not a simple task for a multidimensional system.

\[
S(\{ q_j \}) = \Delta \sum_{j=0}^{P-1} \left[ \frac{\dot{q}_j}{\Delta} \right]^2 - V(q_j) : \text{summation is taken over } j=0,1,2,...,P-1, \Delta = \tau / F, \text{where } j=0 \text{ and } j=P \text{ are the initial and final configurations. One may write down a many-body version of the action as well. Direct application of this discretized action in practice is limited due to the non-analytic nature of the action surface in the pathway space. Extreme condition search is severely depend on the}
\]
choice of $\Delta$.

$$q_j = q_0 + j \frac{\Delta}{\tau} (q_P - q_0) + \sum \left[ a_k \sin \left( \frac{k \pi j \Delta}{\tau} \right) \right] : \text{summation is taken over } k=1,2,3,...,P-1. \text{ Here, } a_k \text{ vectors directly determine the atomic pathway. In a real computation procedure, a fast sine transformation technique can be used.}$$

$$\Theta([q_j], E) = S + \mu \sum (E - E_j)^2 : \text{summation is taken over } j=0,1,2,...,P-1, \text{ where } E_j \text{ stands for a sum of kinetic energy and potential energy at time step index } j. \text{ E is a target energy of the considering system. After an ADMD simulation, one can take the } 3N_{\text{atom}}(P-1) \text{ error variables as shown below:}$$

$$2q_j - q_{j-1} - q_{j+1} - \frac{\Delta^2}{M} \frac{\partial V(q_j)}{\partial q_j} \sim 0 \forall j = 1,2,3,...,P-1. \text{ This mathematical expression is nothing but a Verlet trajectory (}$$

$$q_{j+1} = 2q_j - q_{j-1} - \frac{\Delta^2}{M} \frac{\partial V(q_j)}{\partial q_j} \text{ ) widely used in the conventional molecular dynamics simulations. These are termed by "error variables" in this discussion. The Verlet trajectory has a time-reversal property. The velocities are not needed to compute the trajectories.}$$

$$O([q_j]) = \sum [2q_j - q_{j-1} - q_{j+1} - \frac{\Delta^2}{M} \frac{\partial V(q_j)}{\partial q_j}]^2 : \text{summation is taken over } j=1,2,3,...,P-1. \text{ Elber and his coworkers at Cornell university proposed this object function (also known as Onsager-Machlup action) as a measure of the path quality. Elber and his coworkers used the Onsager-Machlup action in order to find the protein folding pathway models. By the way, two points should be noted in the application of the method: (1) total energy is not conserved along the path. (2) Hessian matrix is required for the minimization procedure. (Calculation of the second derivatives of potential-energy function is time consuming, in general.) For a conservative system, the total energy of the system is unchanged at all time.}$$

$$\Phi([q_j], E; T) = S + \mu \sum (E - E_j)^2 + \nu \left( \langle K \rangle - \frac{3k_B T}{2} \right)^2, \text{ where } <K> \text{ represents average kinetic-energy along the trajectory. The fictitious temperature, } T \text{ is a computational parameter to control the kinetic energy of the system. It turns out that a judicious introduction of the fictitious temperature can improve the path quality in practice. The choice of the parameter does not involve any complex procedure. Here, the coordinate } q_j \text{ in the set of } \{q_j\} \text{ stands for a 3-dimensional vector. An additional summation over all atoms is required for the kinetic-energy control part if a many-body calculation is involved. A procedure is needed to find a set of parameters } \mu' \text{ and } \nu'. \text{ In practice,}$$
one uses the conditions like $\mu > \mu', \nu > \nu'$. One can find a better pathway model (low-activation-energy barrier, fairly and squarely close to Newton's trajectory) assessed on the Onsager-Machlup action if the additional penalty function employed in the pathway optimization procedure.

The quality of atomic trajectories obtained by the proposed ADMD method is significantly improved in terms of the smaller value of Onsager-Machlup action compared to that from the original ADMD method by Passerone and Parrinello. The proposed action is useful for improving path quality and can be used as an atomic trajectory annealing method. This feature was demonstrated by the fact that the path from the proposed ADMD method is also a solution of the original method by Passerone and Parrinello, the difference being only the smaller value of the Onsager-Machlup action. It turns out that ADMD is superior to the nudged elastic band (NEB) in finding low activation-energy barrier between two given states of a complex system. In the case of relatively simple reaction, one can find that the NEB method is working properly.
small width in the probability density distribution of "error variables" (definition for this is shown the text) with an extended action is shown (a.u.=0.529177 Angstrom), indicating an improved 'path quality.' A Stone-Wales defect formation in a C$_{60}$ molecule is the target rare event.

A systematic search for the lowest activation-energy barrier in the ADMD simulation is shown. (a.u. = 2 Ry = 2x13.6058 eV = 627.50956 kcal/mol). The converged pathway calculation is depend on
the initial pathway seed. Here, dot-dashed line (in black) representing total energy is obtained from an ADMD simulation, not from an artificial straight line. Thus, the present energy plot shows that the total-energy conservation is well established along the pathway.

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**Implementation**

Consider a classical N-particle system in which the interactions are described in terms of a many-body potential specifies the microscopic conformation of the system. ADMD application is nothing but a function minimization procedure with 3N(P-1) independent variables and known gradient vector. An MPI based parallelization of ADMD is a natural choice. One can easily obtain about 90% of observed speedup in a typical ADMD application. Object function and its first derivatives can be obtained in a parallel manner. Potential energy and force calculations are time consuming part, hot spot (i.e., object function and its first derivatives) in the ADMD simulations. Basically, one has (P-1) independent atomic configurations. Thus, the number of variables in the ADMD simulation is 3N(P-1), where N stands for the number of atoms.

\[
\frac{\partial \tilde{\Phi}}{\partial \alpha_k} \quad \text{(\emph{sine transformation})}
\]

and \(\tilde{\Phi}\) evaluations are time consuming part in the ADMD simulation.

\[
\{\alpha_k\} \rightarrow \tilde{\Phi}, \left\{\frac{\partial \tilde{\Phi}}{\partial \alpha_k}\right\} \rightarrow \text{new}\{\alpha_k\}
\]

: new trial solution is provided by the LBFGS routine in its iterative call.

One can easily obtain the \(\{q_j\}\) from the \(\{a_k\}\) set through the fast sine transformation. Since the inverse of sine transformation is the \emph{sine} transformation itself with a constant factor. From the evaluations of \(\left\{\frac{\partial \tilde{\Phi}}{\partial q_j}\right\}\), one can obtain the \(\left\{\frac{\partial \tilde{\Phi}}{\partial \alpha_k}\right\}\) through a \emph{fast} sine transformation.

A basic set of MPI routines is employed for a parallel ADMD implementation. Three special techniques are required for an advanced implementation of ADMD. The corresponding links of the computer routines are shown below:

[1] a \emph{fast} sine transformation routine (\textbf{SINET} in the \textbf{GAMS}): It is an important technique when we consider a large value of \(P \sim 1000\). The corresponding CPU time variation is from \(O(P^2)\) to \(O(P \log P)\). (Normalization condition should be tested.)

[2] an \textbf{LBFGS} relaxation routine (for the object-function minimization with gradient calculations) (LBFGS in the Nocedal’s homepage) (LBFGS requires a gradient, not a force.)
[3] In a practical calculation of an atomic trajectory, one needs a procedure to assign the path of each atom of the system under consideration, from the initial to the final configuration. Especially, when dealing with identical particles (as in the C_{60} and C_{120} systems), there is a set of free parameters associated with the relative translational and rotational degrees of freedom between the initial and final configurations. One can use the least-square superposition of two atomic coordinate sets via quaternion method (source code is available on the TINKER Molecular Modeling Package; impose.f). The first coordinate set is fixed while the second one is translated and rotated to provide the best fit. In complex cases, authors introduce an atomic index exchange procedure prior to the ADMD simulation to best superpose the initial atomic positions to the final ones. For this purpose, authors used a simulated annealing method.

A simple description of the algorithm: read two conformations, \( \tau \), and \( P \) -- \( \Delta \) -- setup initial trajectory for each atom (random or input file; sine transformations) -- /\{ object function, 1st derivatives of the object function (time consuming part: parallel job) -- sine transformations -- LBFGS routine call (iterative relaxation in \( \{a_k\} \) ) \}/ -- new trial trajectories, \( \{a_k\} \) by LBFGS -- if object function converged -- print pathway and energies, stop. otherwise, go back to the /\{ \}/

The implementation of the proposed approach to a general system is quite straightforward as in the case of ordinary molecular dynamics simulations, i.e., the only requirement is to evaluate the potential energy and the forces on atoms. The ADMD calculation can be easily and efficiently processed by parallel computation, indicating that the method is useful for studying pathways of complex systems. At each path relaxation step in the object-function minimization procedure, one has to evaluate the potential-energy function and forces for \( (P-1) \) independent atomic configurations. Since these \( (P-1) \) calculations are the most time consuming part of the ADMD simulation, and since they are completely independent of each other, one can easily take advantage of parallel computation with a high parallel efficiency.

The CPU time associated with the relaxation of the path is minimal compared to that of potential energy and forces evaluations. This is due to the characteristic parallel computation-friendly coordinate discretization of the ADMD simulation, in contrast to the opposite case in ordinary molecular dynamics. The implementation of the proposed approach to a general system is quite straightforward as in the case of ordinary molecular dynamics simulations, since the only requirement is to evaluate the potential energy and forces on the atoms.
Action-Derived Molecular Dynamics: from Algorithms to Applications

A flowchart of ADMD method. ADMD simulation is nothing but a function minimization procedure. One of the advantages of the ADMD method is that its calculation can be easily and efficiently parallelized. An LBFGS routine is used for the iterative minimization call. The time consuming part of the ADMD calculation is the multiple evaluations of force and energy. There are (P-1) independent atomic configurations to be determined by the ADMD simulation. For each cycle in the main loop, a new trial pathway is obtained from the LBFGS routine. To reduce a high potential energy fluctuation in
an early stage of the path relaxation, one can simply take \( a_k = 0.0 \) for \( k > k_c \) with a chosen \( k_c \). This type of random seed path setting is physically acceptable one, in general, if one wants to search the probable pathway.

A typical observed speedup in an ADMD simulation is shown. Here, a single node calculation takes about 30 min with a wall-clock time measurement. The observed speedup (wall-clock time of serial execution to wall-clock time of parallel execution) is shown as a function of the number of nodes. A set of MPI routines, communication library, is used for this test. A fast ethernet based PC cluster (Beowulf Project) is employed for this test.
The speedup of parallel ADMD computation is demonstrated by solving the autocatalytic fullerene coalescence. Two $C_{60}$ molecules coalesce into a $C_{120}$ molecule with a catalytic extra carbon atom. This computation was carried out with IBM p690. The computing time on a single CPU was 11,677.4 seconds (wall-clock time). The same computation was also performed using 64 CPUs, and the computing time was 247.0 seconds (wall-clock time). This performance well demonstrates that the action-derived molecular dynamics simulation is a good example for the high-performance computing.
A typical example of the object-function minimization is shown (The vertical axis is in a.u.). Object function consists of discretized action and two penalty functions. Here, a conjugate-gradient (CG) method is used for the object-function minimization. The first penalty function and the second penalty function represent the total-energy conservation restraint and kinetic-energy control restraint, respectively. Discretized action and Onsager-Machlup action are denoted by $S$ and $O$, respectively. A remarkable reduction in the $O$ value at the early stage of the relaxation. A Stone-Wales defect formation in a $C_{60}$ molecule is the target rare event.
A typical distribution of sine expansion coefficients in the atomic trajectory setup is shown. Large amplitudes of low-frequency components are observed in usual ADMD applications. In other words, \( a_k \) with small \( k \)'s make a lot more contribution than \( a_k \) with large \( k \)'s for determining the low-activation pathway. Small number of \( k \) reveals the global nature of the atomic trajectory. Thus, it is inefficient to begin the minimizing procedure with an inclusion of high-\( k \) initial seeds for the \( a_k \) vector set. It is practically advantageous to start the minimization with a relatively small number of \( k \) and then increase the number gradually. This procedure can be interpreted by the application of the one-way multigrid.
algorithm. The number of variables in the ADMD simulation is $3N(P-1)$, where $N$ stands for the number of atoms.

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**Special Features**

Although the Hessian based method for transition-state search is very useful, it is costly because the second derivatives of potential energy are required in the numerical study. Special methods known as dimer, activation-relaxation technique, string, and nudged elastic band are developed for the transition state (TS, activated complex) search with the 1st derivatives of potential energy. The nudged elastic band (NEB) method, developed by Jo'nsson et al. is a heuristic method to search for saddle point, providing the activation-energy barrier and the atomic configuration of the transition state (TS, activated complex). A similar method, string method, is also designed for the study of rare events. NEB and string methods are a significantly advanced version of the boundary value approaches shown in Pratt and Elber's earlier papers. Dimer and Nudged elastic band (NEB) methods are proposed by Jo'nsson group, while string method is proposed by Elber et al. The activation-relaxation technique (ART) developed by Barkema and Mousseau is a method for sampling the energy landscape of activated systems (transition states).

However, these strategies (NEB, string, dimer, and ART) do not take into account of dynamical conditions such as the total-energy conservation and the least action principle. Recent study by Ammal et al. shows that transition states are not necessarily signatures of dynamical transitions even in a simple molecular shape change. A probable pathway to reaction may not cross the saddle point at all. Voter proposed an accelerated version of MD (hyperdynamics) for the study of infrequent events. Chandler group has developed a general computational method for finding the transition pathways for infrequent events. The algorithm requires no preconceived notion of mechanism or transition state. A set of basin of attraction for reactant and product should be defined before the simulation. A simple comparison with other methods (NEB, string, dimer, ART, transition-path sampling, and accelerated MD) is made below. Some molecular dynamics simulations involve an increased temperature of the system, and then overestimating the entropic effect of free energy landscape by facilitating conformational transtions that might not be observed in a low temperature with interest. The accelerated molecular dynamics method ("puddle-skimming") falls into the class of enhanced sampling methods in which the energy barriers are effectively lower, so the system conformational changes between energy minima more rapidly. The "conformational flooding" method (H. Grubmuller) employs an artificial potential that destabilizes the initial conformation and lowers free energy barriers of structural transitions.

The idea to simulate dynamics of atomic systems with optimization of actions has been promoted in the Elber's group. The present ADMD formulation directly searches physically relevant transition pathways for a given set of initial and final conformations. Therefore, the method does not require those assumptions used in the ordinary MD simulations, such as exponential kinetics, and/or an arbitrary identification of the specific conformation. The present approach is shown to be quite effective for obtaining low-energy barrier transition pathways (and/or activated complexes) associated with a general type of chemical reaction.
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<th>ART</th>
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<td>usual integrator</td>
<td>relaxation</td>
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cf. transition state (TS, 1st order saddle point): zero force at each atom + 3 single negative eigenvalue of Hessian matrix (= 3 single imaginary frequency of dynamical matrix) An assembly of atoms, when randomly placed TS, would have an equal probability of forming the reactants and of forming the products.
cf. Arrhenius equation
cf. Hammond Postulate
cf. Ahmed Zewail, Nobel Prize in Chemistry 1999 *For his studies of the transition states of chemical reactions using femtoseconds spectroscopy.*
cf. IRC (intrinsic reaction coordinate): The mass-weighted Cartesian coordinates that connect the TS to reactants and products.
cf. reaction coordinate: Unfortunately, there does not seem to be a rigorous definition of the reaction coordinate, in general. An unfortunate choice of the reaction coordinate may lead to an unfavorable reaction path, which does not pass the transition state region, and may result in substantial overestimation of the activation energy barrier. In practical applications, the reaction coordinate is chosen as a geometrical variable (bond length, bond angle, dihedral angle) or a combination of few variables.
cf. elastic sheet method
cf. Jo’sson group, Henkelman group, Chandler group, Bolhuis Group, Voter group, Wales group, Vanden-Eijnden group
cf. long time dynamics
cf. temperature-accelerated dynamics, parallel replica dynamics
cf. self-guided molecular dynamics
cf. distributed computing: The EON project, folding@home
cf. related computer programs on the web
* D. J. Wales group web-site: doubly nudged elastic band, OPTIM (reaction pathway calculation program), DNEB and NewConnect
* P. Bolhuis' web-site: ransition-path sampling method, transition path sampling web-page (source code)
* N. Mousseau's web-site: activation-relaxation technique web-page (source codes in C and F90)
In a high temperature MD simulation, we frequently observe the conformational change processes related to a set of high energy activation.

**Applications**

ADMD method has been applied successfully to $C_{60}$ formation, $C_{60}$ fusion, surface growth mechanism, protein folding, small molecule isomerization process, and catalytic chemical reactions. Here, we would like to exemplify the problems involved. If we use a short simulation time $\tau$, the corresponding pathway is closely related to a high-energy process. On the other hand, an ADMD simulation with a sufficiently long simulation time $\tau$ will generate the pathway model in which the system stays longer in one or both basins of potential attraction. Thus, the precise value of simulation time $\tau$ ($> \tau^*$) is not a crucial parameter in general. By decreasing the target energy ($E$) of the system, one can sample a low potential-energy-barrier process in transition pathway space. The possible reaction pathway at finite temperature is not unique in general. The reaction pathways should be treated in a manner of an ensemble. However, this type of approach is severely demanding with available computational resources. Therefore, most of ADMD simulations is performed in the local search mode.
ADMD simulation does not require the selection of a reaction coordinate (order parameter). In a typical ADMD application, one takes two local energy-minimum configurations (for simplicity, not for necessity) and try to find a transition pathway. ADMD requires no preconceived knowledge of transition state or transition process. In general, potential-energy surface of the high-dimensional systems are so complex that it is impossible to enumerate all transition pathways. By the way, in usual case, only a set of transition pathways with a low activation-energy is relevant for escaping energy basin. Thus, a systematic target-energy adjustment is very useful in wide areas of application. ADMD simulations open the way for the study of rare events in condensed matter phases. Other applications will follow. Because experiments and static calculations hard to identify specific mechanisms by which products form, the reaction is ideal to study by using ADMD. It is expected that ADMD calculations will continue to increase in their importance and potential to impact challenging problems in theoretical physics, chemistry, biology, and materials science.

Tested 12 independent precursors (energy-minimized configurations) for the C_{60} (Buckyball, Buckminsterfullerene; 0.71 nm in diameter) formation are shown. Each precursor
model consists of 60 carbon atoms. One can introduce an atomic index exchange procedure prior to the ADMD simulation to best superpose the initial atomic positions to the final ones. For this purpose, authors used a simulated annealing method.

For each of pathway calculation the total energy conservation (sum of kinetic energy and potential energy, not shown) is obtained. Calculated potential energy fluctuations along the paths are shown for the 12 precursors. A tight-binding potential is employed for the C-C interatomic interactions. Each of reaction is an exothermic reaction, "reactants → products + energy."
Before an ADMD simulation, a trial pathway should be given. One can use the least-square superposition of two atomic coordinate sets via quaternion method. The first coordinate set is fixed while the second one is translated and rotated to provide the best fit. When $C_{60}$ molecules collide, some of their kinetic energy is converted into potential energy within the colliding $C_{60}$ molecules. If enough energy conversion is found, the old C-C bonds become sufficiently distorted for the colliding molecules to form an activated complex. New C-C bonds can then begin to form.
Since that an initial trial pathway is far from the low activation process, a minimum activation-energy search procedure is required in a real application. For the efficiency, one can use the multigrid method in the relaxation of the atomic trajectories. One-way multigrid method is quite useful for searching a low activation energy process. Slowly varying error components in a trial atomic trajectory is eliminated first in the one-way multigrid algorithm. The Arrhenius equation predicts the rate of a chemical reaction at a certain condition, given the activation energy and chance of successful trial.
SW defect formations in a $C_{60}$ are simulated by ADMD method. Initial, intermediates, and final conformations with the corresponding step indices are shown for two different pathways (with and without exchange). Potential-energy plots, corresponding to each pathway, are shown in the lowest part.

Six snapshots with step indices are shown for the autocatalytic fullerene fusion with exchange. The development of partial density of states associated is also given in the lower part.
Simulated potential-energy variations are shown for five different dynamic pathways of fusion, $C_{60} + C_{60} \rightarrow C_{120}$. One-adatom and two-adatom imply the cases of autocatalytic reaction, and exchange denotes the case that the incoming and outgoing carbon atoms are not identical.
Two different diffusion paths of triangular Cu trimer on Cu(001) surface. Atomic configurations "A" and "C" represent initial configuration and final configuration in the ADMD simulations, respectively. Irrespective of the different colors, spheres stand for the Cu atoms. Periodic boundary conditions are used to simulate the Cu(001) surface structure.
A diffusion path of linear Cu trimer on Cu(001) surface. Atomic configurations "A" and "E" represent initial configuration and final configuration, respectively. Irrespective of the different colors, spheres stand for the Cu atoms. Periodic boundary conditions are used to simulate the Cu(001) surface structure.
Atomistic study of cross slip of a screw dislocation in copper is presented using the ADMD which seeks the most probable dynamic pathway on the potential-energy surface of the atomic system during the cross-slip process. The observed mechanism reveals features of both competing mechanisms postulated in literature, i.e., the Fleischer mechanism and the Friedel-Escaig mechanism. Due to cooperative atomic motions and complex core rearrangement during the process, the activation energies of the current cross-slip mechanism are around 0.5 eV less than the lowest ever reported in corresponding studies using atomistic numerical techniques.
Energy profile of the cross slip with selected intermediate images of core structures along the approximated dynamic pathway. The present calculations were conducted on a parallel Linux cluster using 42 Opteron 1.6 GHz CPUs, and the calculations of above figure took 15 days and involved around $15 \times 10^6$ degrees of freedom.

There are two protein-folding problems in contemporary computational biology. The first one is to predict protein structure from sequence, and the second one is to predict protein folding pathways. Proteins are densely packed with a specific order and shape. The compactness is an essential property of the folded conformations of proteins. However, the dynamics of compaction in the process of protein folding from the extended structures are still poorly understood. Protein-folding is an example of conformational isomerism, where some shapes are stable and functional, but others are not. The dimensionality of a system containing the protein and the water molecules can be reduced when the water molecules are treated implicitly. An understanding of how the protein (and/or the newly synthesized polypeptide chain) is able to fold to its native structure is fundamental to the description of life at a molecular level. The study of protein folding has three aspects: thermodynamics, kinetics, and structure prediction. Obtaining large numbers of independent trajectories is not only a very effective way to use parallel computing technologies but also is required for statistically meaningful results. Unfortunately, it is not yet possible to do statistically meaningful folding simulations of proteins with all-atom models. Understanding protein folding is an important research subject in the post-genomic era. Experimentally speaking, the current spatial and temporal resolution is not sufficiently accurate enough to observe the microscopic protein folding directly at the atomic scale. Computer simulation is a complementary tool that helps to understand kinetic processes and thermodynamic stabilities of protein folding. Nevertheless, direct atomistic folding simulations of proteins have been severely limited by the short time scale accessible with computational methods and resources currently available.
Panel shows initial (C7_{ax}) and final (C7_{eq}) conformations used in the ADMD simulation for alanine dipeptide conformational isomerization. Two backbone dihedral angles, \( \phi \) (C-N-C_{\alpha}-C) and \( \psi \) (N-C_{\alpha}-C-N), major conformational degrees of freedom, are defined following the usual convention. Black, white, red, and blue color balls stand for C, H, O, and N, respectively. These structures possess structural features of the protein backbone, representing suitable models for conformational transitions of proteins. For this reason, these types of structure are investigated extensively to study fundamental issues in conformational isomerization using the spectroscopic experimental tools.
Panels show $R_g$, RMSD, tilde{$N$}, two dihedral angles ($\phi$ and $\psi$), and potential energy along the transition pathway obtained through the ADMD simulation. The additional angle $\theta$ (O-C-N-C$_\alpha$) is the torsional angle. Total-energy conservation is well established along the pathway in the ADMD simulation. The AMBER94 force field is used for the alanine dipeptide conformation. The duration period of conformational isomerization is estimated to be ~480 fs. One thing should be noted here is that the duration time can be changed by total energy of the system. The duration time can become longer than the estimated value if the total energy is closer to the energy barrier, and shorter than the estimated value if the total energy is much higher than the barrier. Thus, the duration time is dependent on the total energy of the system, in general.
Panel shows initial and final conformations used in the ADMD simulation for valine dipeptide conformational isomerization. Two backbone dihedral angles, $\phi$ (C-N-C$_\alpha$-C) and $\psi$ (N-C$_\alpha$-C-N), major conformational degrees of freedom, are defined following the usual convention. Black, white, red, and blue color balls stand for C, H, O, and N, respectively.
Panels show $R_g$, RMSD, $\tilde{N}$, two dihedral angles ($\phi$ and $\psi$), and potential energy along the transition pathway obtained through the ADMD simulation. The additional angle $\theta$ (O-C-N-C$_{\alpha}$) is the torsional angle. Total-energy conservation is well established along the pathway in the ADMD simulation. The AMBER94 force field is used for the valine dipeptide conformation. The duration period of conformational isomerization is estimated to be ~690 fs.
Two panels show initial and final configurations used in the ADMD simulations (a) for an α-helix and (b) for a β-hairpin formation. Black, white, red, and blue colored atoms represent the C, H, O, and N, respectively. A local energy minimization is employed to obtain each configuration.
A detailed analysis of a folding trajectory of the α-helix using the ADMD simulation. Four panels show the evolutions of radius of gyration, RMSD values from the final configuration, the degree of the cooperative atomic motions, the number of contacts, the number of hydrogen bonds, and potential energy as the function of the ADMD step index, j. We observe that (i,i+3) contact forming steps (178 < j < 283), are well separated from (i,i+4) contact forming steps (284 < j < 301), in good agreement with the experimental finding. The appearance of the (i,i+3) contacts precedes the formation of the (i,i+4) contacts. This sequential nature of the contact formation is also in good agreement with other simulation results.
A detailed analysis of a folding trajectory of the $\beta$–hairpin using the ADMD simulation. The same type of analysis on the pathway is made as in above. The first hydrogen bond formation at the central part of the $\beta$–hairpin is found at the steps, $458 < j < 523$. The first the hydrogen bond formation actually initiates a well-defined potential energy decrease (downhill in the potential energy). Thus, in our folding pathway model, once the hydrogen bond forms the remaining folding process is energetically favorable process. This means that after a partial collapse of the peptide with the partial contacts, the system adopts the gradual process associated with the native hydrogen bond formations. In contrast to some simulations, no significant evidence has been found for the compact intermediate structure formations. The present analysis is not consistent with the hydrophobic collapse model in which the folding proceeds by a collapse with downhill in energy. While the first native hydrogen bond forms at the central part of the $\beta$-hairpin, a variation in the contact formation sequence with a similar activation energy barrier (2.93 kcal/mol) is observed. The corresponding contact formation sequence is as follows: \{(5,10)\} -- \{(5,10),(6,9),(6,10)\} -- \{(5,10),(6,9),(6,10),(5,11)\} -- \{(5,10),(6,9),(6,10),(5,11),(7,10)\}. We also find other choices of contact formation sequence with the changes in activation energy. In fact, eight ADMD simulations among our ten ADMD simulations show the first native hydrogen bond formation at the central part of the $\beta$-hairpin. Due to the topological reason, the contact formation is closely related to the formation of the native hydrogen bond formation. Nevertheless, there is a freedom in the contact formation in details, representing the existence of the multiple folding pathways in the $\beta$–hairpin folding. The present formulation is free from common assumptions widely used in MD such as high temperature simulations, a choice of order parameter set, an arbitrary identification of the folded configuration, and/or an exponential kinetics. The present dynamic folding pathway models for both $\alpha$-helix and $\beta$–hairpin formations are consistent with experimental data.
References


