Rock climbing: A local-global algorithm to compute minimum energy and minimum free energy pathways

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The calculation of minimum energy or minimum free energy paths is an important step in the quantitative and qualitative studies of chemical and physical processes. The computations of these coordinates present a significant challenge and have attracted considerable theoretical and computational interest. Here we present a new local-global approach to study reaction coordinates, based on a gradual optimization of an action. Like other global algorithms, it provides a path between known reactants and products, but it uses a local algorithm to extend the current path in small steps. The local-global approach does not require an initial guess to the path, a major challenge for global pathway finders. Finally, it provides an exact answer (the steepest descent path) at the end of the calculations. Numerical examples are provided for the Mueller potential and for a conformational transition in a solvated ring system. *Published by AIP Publishing.* [<http://dx.doi.org/10.1063/1.4986298>]

I. INTRODUCTION

Consider a system represented by a coordinate vector x and a potential energy $U(x)$ with two energy minima R and P , which have coordinates x_R and x_P , respectively. The discussion below can be equally applied to a free energy landscape in which x is the vector of the (Cartesian) coarse variables and $U(x)$ is replaced by the potential of mean force, $G(x)$, as we illustrate. We seek a reaction path connecting the two minima, which is defined as the Steepest Descent Path (SDP) in the present manuscript. We denote the path by $x(l)$ where l parameterizes the path. $x(0)$ and $x(L)$ are the vectors of the reactant and product, respectively. If the SDP is unique, it has the lowest energy barrier between the two minima. *The prime challenge that this manuscript addresses is path calculations between two known minima without a need for an initial guess for the path.*

There are many operational definitions for the SDP and we briefly discuss two classes of them. The first class is based on the local environment of the path and the second one is global and considers the whole path. We consider two types of searches for reaction pathways: (i) local and (ii) global. While the classification below is clearly not unique, it is useful in the context of the present manuscript and it provides a simple picture of major directions in reaction path calculations.

- (1) Local searches: A search for saddle points, other minima, and pathways is conducted using information gathered from only one current structure (typically the Hessian matrix, H , and the forces F at a single coordinate set, x , are used). Let q be an eigenvector of H at x with the smallest positive eigenvalue λ . We also call q the softest mode. Let $\lambda - \eta$ be a negative number. We define

a shifted Hessian $H_S = H - \eta \cdot qq^t$ and construct a displacement $\Delta x = H_S^{-1}F$ that goes uphill in the direction of the softest mode q , with displacement size scaled by $\lambda - \eta$ for optimality. The step aims to minimize the energy in all directions with the exception of the softest mode. The energy is maximized along the softest mode. Examples for an algorithm of this type are the study of Cerjan and Miller¹ and numerous investigations by Wales (see a monograph on energy landscapes²).

- (2) Global searches: We are given the positions of two minima, x_R and x_P , and are asked to determine a pathway connecting those two minima, $x(l)$, which is parameterized by $l \in [0, 1]$. By having two coordinate sets to begin with, the process can no longer be characterized as local. An example for a global equation for the minimum energy curve, which was written first in the Locally Updated Planes (LUP) approach,³ and was adopted later by Nudged Elastic Band (NEB)⁴ and the string⁵ approaches, is

$$\begin{aligned} \frac{d}{d\tau}x(l, \tau) &= -\nabla U(x(l, \tau)) \left[I - e(l, \tau)e^t(l, \tau) \right], \\ e(l, \tau) &= \frac{dx(l, \tau)}{dl}. \end{aligned} \quad (1)$$

The fictitious time, τ , is used to quench the path to the steepest descent path. The potential energy is $U(x)$, I is the identity matrix, and $e(l, \tau)$ is the path slope. Given an initial condition (guess) for the path, $x(l, 0)$, the path is propagated as a function of “time.” At the limit of $\tau \rightarrow \infty$, or no more changes in the path as a function of τ , we obtain the steepest descent path.

Equation (1) describes a quenched trajectory of a whole path. We minimize the energy of all the points along the path subject to the constraint that the path starts at the reactants and

ends at the products. Each point along the path feels only the force in the direction perpendicular to the path (the force along the current path is projected out).

When the path does not change as a function of the fictitious time τ , we must have $\frac{dx(l,\tau)}{d\tau} = 0$. Hence, the right-handed side of the equation must be zero as well. We therefore have for the fully-quenched path

$$-\nabla U(x(l,\tau)) \left[I - e(l,\tau) e^l(l,\tau) \right] = 0.$$

The term in the square brackets is a projection operator. We remove from the identity matrix, I , the component that is parallel to the path ($e(l,\tau) \cdot e^l(l,\tau)$). Hence only the force component perpendicular to the path is required to be zero for a stationary path. This requirement is also a definition of the SDP. The asymptotic solution of the quenched equations at the long time limit is the SDP. By consideration of the whole path, $x(l,\tau)$, it is obvious that the equation is not local. In practice, numerical solutions of Eq. (1) necessitate the use of discretization in l and τ . For example, consider the discretization of the path $\{x_1, x_2, \dots, x_L\}$ where $x_1 \equiv x_R$ and $x_L \equiv x_P$ are kept fixed. The LUP³ and later methods built on a similar idea (NEB⁴ and string⁵) optimize the whole path using quenched equations for the discrete set

$$\begin{aligned} \frac{dx_i(\tau)}{d\tau} &= -\nabla U(x_i) \left[I - e_i e_i^l \right], \quad i = 2, 3, \dots, L-1, \\ e_i &\cong \frac{x_{i+1} - x_{i-1}}{|x_{i+1} - x_{i-1}|}. \end{aligned} \quad (2)$$

A time discretization leads to the following global expression of the path refinement:

$$\Delta x_i(\tau) = -\nabla U(x_i(\tau)) \left[I - e_i e_i^l \right] \cdot \Delta \tau, \quad i = 2, 3, \dots, L-1. \quad (3)$$

The discrete equation is non-local and simultaneously couples all structures along the path during the quenching process. To solve Eq. (3), initial conditions $\{x_1, x_2(0), x_3(0), \dots, x_{L-1}(0), x_L\}$ are required. While Eq. (3) is rigorous, the choice of the initial guess will impact, at least, the rate of convergence and the computational efficiency. In practice, the initial choice of the path can impact the final path as well. This is because the refinement process in complex systems and on rough energy landscapes rarely explores the space of all plausible pathways. Hence the choice of the initial conditions can be critical for both, accuracy and efficiency of the calculations. The proposed algorithm of rock climbing avoids the need for an initial guess.

There are also intermediate algorithms that we call local/global. In this class of algorithms, we still use coordinates of the reactants and the products. However, we adjust only one structure at a time instead of optimizing the entire path as discussed above for the global approaches. An example for such an algorithm is the heuristic Targeted Molecular Dynamics (TMD),⁶ which is briefly discussed below.

Consider one realization of TMD using the time dependent restraint $C(t)$. The restraint is added to the regular potential, $U(x)$, during a molecular dynamics run

$$\begin{aligned} C(t) &= \lambda(t) \text{RMSD}(x(t), x_R) + (1 - \lambda(t)) \cdot \text{RMSD}(x(t), x_P), \\ \lambda(t) &= 1 - \frac{t}{t_f}, \end{aligned}$$

where $\text{RMSD}(x, y)$ is the root mean square distance between the vectors x and y . It is computed after an optimal overlap of the two vectors such that their distance is minimal.⁷ The total time of the trajectory is t_f . The function $\lambda(t)$ interpolates linearly between the value of one and zero as a function of time. It therefore biases the MD trajectory at the beginning to the neighborhood of x_R , and as the time progresses to t_f , it biases it to the neighborhood of x_P instead. TMD is widely used in simulations of condensed phase systems and rough energy landscapes because it is simple and requires only a small adjustment to the code compared to regular molecular dynamics runs. In many cases, the one-dimensional restraint is a relatively small perturbation on the system and it produces plausible pathways. TMD trajectories are likely to provide a reasonable starting point for further path and free energy calculations. However, TMD pathways are not rigorous. The resulting path depends on the type of the restraint and on the total length of the trajectory t_f . The rock climbing algorithm, which we propose here, also belongs to the local/global family. Similarly to TMD, an essential component of it is to optimize one structure at a time. In contrast to TMD, the rock climbing has also a global optimization component that provides the exact SDP.

The limitation of local approaches is of path multiplicity. If the system has multiple pathways and saddle points, it is difficult for an automated algorithm to pick up a direction that leads to the desired product. Local approaches are particularly useful when the number of degrees of freedom is relatively small and the energy landscape is reasonably smooth, which reduces the impact of the challenge mentioned above and makes the exhaustive exploration of the energy landscape possible.

Olender and Elber⁸ introduced a functional dubbed W , named scalar work, to compute the SDP, it is defined as

$$W = \int_R^P \sqrt{(\nabla U^t \cdot \nabla U)} \sqrt{d\vec{l} \cdot d\vec{l}}. \quad (4)$$

The value of the true work, W_t , is given by a similar integral, $W_t = - \int_R^P \nabla U^t \cdot d\vec{l}$. The definition in Eq. (4) is the same as the global definition of the reaction coordinate given earlier. It is easy to show that a path that minimizes W is the SDP. Consider the absolute value of the true work

$$\begin{aligned} |W_t| &= \left| \int_R^P \nabla U \cdot d\vec{l} \right| = \left| \int_R^P |\nabla U| \cdot \cos(\theta) \cdot |d\vec{l}| \right| \\ &\equiv |U(P) - U(R)|. \end{aligned} \quad (5)$$

Because W can also be written as $W = \int_R^P |\nabla U| |d\vec{l}|$, we must have $W \geq |W_t|$. W is equal to W_t when $\cos(\theta) = \pm 1$ and has the same sign along the path. Hence, the equality will hold from one stationary point to another. For example, if there is a single saddle point between R and P denoted by D then W is $2U(x_D) - U(x_R) - U(x_P)$ which is the same as $\left| \int_R^D \nabla U \cdot d\vec{l} \right| + \left| \int_D^P \nabla U \cdot d\vec{l} \right|$. Note that the force is antiparallel to the path segment in the

SDP when we progress uphill but is parallel to the path when the system is going downhill.

To compute the path numerically, we discretize the path and use the trapezoidal rule to estimate the line integral,

$$W_d = \sum_{i=1}^n \frac{1}{2} (|\nabla U_i| + |\nabla U_{i-1}|) \Delta l_{i-1,i}. \quad (6)$$

The fixed configuration R is indexed as “0” and configuration P as “ n .” The length element, $\Delta l_{i-1,i}$, is estimated as the distance between two sequential configurations

$$\Delta l_{i-1,i} = \sqrt{(x_i - x_{i-1})^t (x_i - x_{i-1})}. \quad (7)$$

Numerical optimization of a line integral requires adequate representation of the path. The best representation we can get, given a fixed number of points and no prior knowledge on the path curvature, is to distribute the configurations uniformly along the path. This can be achieved by imposing a non-holonomic constraint on the path “velocity” as was done in the string method.⁵ An alternative is to use a penalty function on the distribution of displacement norms.⁹ We define the average displacement along the path

$$\langle \Delta l \rangle = \frac{1}{n} \sum_{i=1}^n \Delta l_{i-1,i} \quad (8)$$

and penalize deviations from the average value by P ,

$$P = \sum_{i=1}^n k (\Delta l_{i-1,i} - \langle \Delta l \rangle)^2. \quad (9)$$

The target function, T , which we optimize in the present manuscript, is a sum of the discrete scalar work defined in Eq. (6) and the penalty of Eq. (9)

$$T = W_d + P = \sum_{i=1}^n \frac{1}{2} (|\nabla U_i| + |\nabla U_{i-1}|) \Delta l_{i-1,i} + k (\Delta l_{i-1,i} - \langle \Delta l \rangle)^2. \quad (10)$$

Minimization of T as a function of all the intermediate configurations, x_i ($i = 1, \dots, n-1$), provides a discrete approximation to the SDP. The coefficient k is chosen such that $k/\langle \Delta l \rangle$ is comparable in magnitude to the norm of the forces, $|\nabla U_i|$, of the system. A very high value of k necessitates the use of small optimization steps. Values of k that are too small will allow significant deviations of the individual displacements from the average and hence a less accurate representation of the path. The minimization requires an initial guess, which in Ref. 9 and later studies¹⁰ we took a straight-line interpolation between the two end points. The initial guess is

$$x_i = x_{i-1} + \frac{x_n - x_{i-1}}{|x_n - x_{i-1}|} \cdot \langle \Delta l \rangle. \quad (11)$$

Equation (11) provides a general and simple set of configurations to start the optimization of T . However, this initial guess may provide highly distorted structures. For example, if we consider the rotation of a benzene ring by 180° , the middle structure of a set of conformations linearly interpolated in Cartesian space will be a “ring” collapsed to a line. It was found in practice that linear interpolation in biological macromolecules is useful only if the reactant and product

conformations are not markedly different. If they are different, significant manual intervention is required to adjust the structures before numerical optimization can begin. This is clearly not ideal and the present manuscript aims to further automate the process of SDP determination with the local/global approach.

The advantage of local approaches^{1,2} is that generating an initial step is easier. We start from a sound configuration and displace it only slightly when generating a new configuration. The disadvantage is that they may “lose” their way if we wish to determine a pathway to a specific product state. By getting lost we mean “unable to determine a path that connects two given minima.” In a local approach, we start with one of the minima and we have no information on the general direction we need to go to find the (given) second minimum. The set of solutions includes all paths with an unknown termination point. This set is larger than the collection of pathways that must end in a second predetermined minimum in the global approach. The method of TMD is an attempt to enjoy both worlds. It is operating on a single structure using straightforward MD that is constrained to end at the product state. Hence TMD simulations cannot get lost. The problem with TMD is that the computed path is not the SDP and the mathematical properties of the path are not clear.

Here we propose a local/global algorithm that produces the exact SDP and benefits from TMD-like features. It constructs one structure at a time, and then it re-optimizes path segments until the complete path is grown. At the least, the new algorithm, which we argue is similar to rock climbing, provides an automated way of generating guesses that are energetically more favorable than guesses generated by linear interpolation or similar procedures.

II. ROCK CLIMBING

In this section, we describe the new algorithm of rock-climbing. Global algorithms that were discussed in the Introduction require an initial guess for the path to be optimized. A straight-line interpolation was frequently used in the past,^{9,10} however, this choice can lead to highly deformed molecular structures with initial conformations that are hard to optimize. The rock climbing algorithm proposes a rigorous path generating approach that exploits information on the two minima without the need to provide an initial guess.

We describe below the implementation of the functional optimization in a local-global algorithm and argue that it is similar to safe rock climbing (also known to professional climbers as top roping). There are several penalty functions that help guide the algorithm to a desired solution and are discussed as well.

A. The path splitting

We re-consider the functional of Eq. (4) that Elber’s group introduce in Ref. 8 and optimize it in an asymmetric fashion, while retaining the global characteristic of the optimization. We break the line integral into two steps

$$W = \int_R^I |\nabla U| dl + \int_I^P |\nabla U| dl. \quad (12)$$

We choose one of the integrals to be investigated accurately and in detail (for illustration, we choose it to be between R and I). The second integral is used to guide the path calculations. More concretely, we write

$$W \cong \int_R^I |\nabla U| dl + \frac{1}{2} (|\nabla U(x_I)| + |\nabla U(x_P)|) \Delta l_{IP}. \quad (13)$$

The second integral is approximated by a trapezoid rule, which is accurate only for small Δl_{IP} . Only $|\nabla U(x_I)|$ and Δl_{IP} of the second integral are functions of the intermediate structure I . Clearly the second “integral” does not provide a lot of information about the path. Nevertheless, it provides a link to the product state and guides the algorithm to the desired final state.

In a similar way to the approach taken in Eq. (10), we discretize the integral of Eq. (13) to obtain a new target function, T_I ,

$$T_I = W_{dl} = \frac{1}{2} \sum_{i=1}^{n_I} [(|\nabla U(x_i)| + |\nabla U(x_{i-1})|) \Delta l_{i-1,i} + k(\Delta l_{i-1} - \langle \Delta l \rangle)^2] + \frac{1}{2} (|\nabla U(x_{n_I})| + |\nabla U(x_P)|) \Delta l_{IP}, \quad (14)$$

where $\langle \Delta l \rangle$ is set sufficiently small to adequately approximate the first integral. In the text below, we will also denote for brevity the configurations that represent the whole path by the vector r ; hence, the target function is $T_I(r)$.

B. A curvature term

We also add a term that helps avoid extreme path curvatures. We define the path curvature by

$$\begin{aligned} \cos(\theta_{i,i-1,i-2}) \\ = (x_i - x_{i-1})^T (x_{i-1} - x_{i-2}) / |x_i - x_{i-1}| |x_{i-1} - x_{i-2}| \\ i = 2, \dots, n_I. \end{aligned} \quad (15)$$

Equation (13) does not significantly penalize configurations that fall backward (e.g., $x_{i+2} = x_i$), which is problematic. Paths that reverse their directions or have extreme curvatures waste intermediate steps, and leave a smaller number of configurations to probe the transition domains (see Ref. 11 for more discussion on path aggregation). We therefore add a local penalty on curvature as $-k' \cdot \cos(\theta_{i,i-1,i-2})$. We write

$$T_{IC} = T_I - \sum_{i=2}^{n_I} k' \cdot \cos(\theta_{i,i-1,i-2}), \quad (16)$$

where k' is a constant coefficient chosen following similar criteria as k .

C. A potential term

The functional that we consider [Eq. (11)] depends only on the forces and not on the value of the potential energy. When the force is zero, it does not contribute to the value of the functional. Therefore, it is not trivial to extend the intermediate structure x_I to a new coordinate if x_I is a stationary point. It is possible to reduce the path resolution and to avoid the saddle point in a first stage of the calculation. However, accurate barrier location is our prime interest, and it is not clear

if a low-resolution path can be efficiently refined at a later stage to produce precise barrier value and location. We therefore add to the target function defined in Eq. (16), a potential energy penalty. The potential penalty is only used near stationary points, in which the force is detected to be about zero. We write

$$T_{ICP} = T_{IC} + \beta \sum_{j \in \text{saddle}} U(x_j) \quad j \leq n_I. \quad (17)$$

To illustrate the importance of the last penalty term, we show the results of a calculation of a path on the Mueller potential¹² with and without the last penalty in Fig. 1.

The parameter values are essentially fixed and are the same in all calculations that we conducted so far. With this fixed choice they have no impact on the final result. They make convergence to the optimal path more accurate and direct. Because constrained or restrained optimization is less efficient than direct optimization, they may make the calculation slower. This is similar however to other leading algorithms in the field as discussed below.

The first parameter determines the strength of the restraint to keep the distances between sequential path configurations to be equal. The parameter should be chosen as high as possible. A similar restraint is used in Ref. 9 and in the NEB method.

FIG. 1. Upper panel: A rock climbing path displayed on the counter lines of the Mueller potential,¹² computed with no potential constraint after 65 iterations. At the saddle point, the path takes a false turn because the absolute force grows mildly in the false direction and is “attractive” (see the lower panel with the counter plot of the norm of the force). Once it reaches a stiff increase in the gradient of the potential energy, the path turns back on itself and continues to the product site. Hence, with sufficiently large number of points, the correct path can be recovered. Lower panel: A map of the norm of the force for the Mueller potential, note the minimum of the force’s norm at the neighborhood of the false path. We also show a correct pathway computed with a potential term with $\beta = 2$.

In the string approach, a constraint with a Lagrange multiplier enforces uniform distribution of points along the path instead of a restraint. The Lagrange multiplier approach conserves the value of the constraints more precisely than the restraints, but it tends to be stiffer and to create additional local minima.

The second parameter is used only when the path curvature is very high and intends to fix situations in which the path is falling back onto itself (e.g., when $x_{i+2} \cong x_i$). It does not affect the value of the action if the path is optimal and guides the calculation to the neighborhood of a correct solution. A related approach is found in the string in which the points are re-distributed along the curve.

The third parameter, that adds the potential as an additional term, is used only in the neighborhood of saddle points to guide the direction of the path. It is the only parameter and restraint that is not used by other approaches. We found it convenient to avoid false pathways as we illustrated in Fig. 1, top. It does not affect the stability of the final functional since it is used when the derivative of the potential is near zero.

Since the formulation of the restraints is similar to what is done in other approaches, the restraints are not making our current procedure more efficient than other related approaches such as the scalar force,⁸ LUP,³ NEB,⁴ or string.⁵ The novelty of our manuscript is the growth procedure of the path while maintaining knowledge on both end points. The growth procedure eliminates the need for an initial guess and as such it is possible to use a variant of rock climbing in other functional

based methods like the MaxFlux.^{13,14} Hence the rock climbing procedure does not come as an alternative to other path algorithms but as a solution to a concrete problem of global approaches.

D. The algorithm

We list below the different steps of the computations

1. **Initiation:** Given initial and final configurations, x_R , and x_P , respectively, we choose an initial small vector displacement δ of a fixed length and optimize the target function for $n_I = 1$, $T(1)$. The initial displacement direction is along the vector connecting the reactant and product positions,

$$T_I(1) = \frac{1}{2} (\nabla U(x_R) + \nabla U(x_R + \delta)) \cdot \delta + \frac{1}{2} (\nabla U(x_R + \delta) + \nabla U(x_P)) \Delta l_{IP}, \quad (18)$$

where the coordinates of the intermediate I are $x_R + \delta$ and are optimized by minimizing the target function as a function of δ ($|\delta| = \text{constant}$). Note that for the first step, there is no need for curvature or potential energy constraints.

2. **Greedy Growth:** To the current $n_I - 1$ set of structures, we add one new conformation using a vector displacement δ , which is along the line connecting x_{n_I-1} and the product conformation, x_P . We then optimize the coordinates of the last point, x_{n_I} , using the target function, $T(2)$,

$$T_{ICP}(2) = \frac{1}{2} \sum_{i=1}^{n_I-1} [(|\nabla U(x_i)| + |\nabla U(x_{i-1})|) \Delta l_{i-1,i} + k(\Delta l_{i,i-1} - \langle \Delta l \rangle)^2] + \frac{1}{2} (|\nabla U(x_{n_I-1})| + |\nabla U(x_{n_I})|) \delta + \frac{1}{2} (|\nabla U(x_{n_I})| + |\nabla U(x_P)|) \Delta l_{IP} - k' |\cos(\theta_{n_I, n_I-1, n_I-2})| + \beta U(x_{n_I}). \quad (19)$$

Note that the last three terms of the target function include most of the terms that depend on the new structure, x_{n_I} , and require evaluation ($\langle \Delta l \rangle$ also depends on the new coordinate). Greedy growth is conducted for K steps before step 3 of path relaxation. The number of steps K is chosen to optimize the calculation. In the present study, global optimization is performed after ten initial greedy growth steps and for every five thereafter in the Mueller potential, while in cyclohexane, it is performed at the end.

3. **Path relaxation:** The complete current path, with the exception of the reactant and product, is relaxed by optimizing the target function $T(3)$. In this step, no new structure is added,

$$T_{ICP}(3) = \frac{1}{2} \sum_{i=1}^{n_I} [(|\nabla U(x_i)| + |\nabla U(x_{i-1})|) \Delta l_{i-1,i} + k(\Delta l_{i,i-1} - \langle \Delta l \rangle)^2] - \sum_{i=2}^{n_I} k' \cdot \cos(\theta_{i,i-1,i-2}) + \frac{1}{2} (|\nabla U(x_{n_I})| + |\nabla U(x_P)|) \Delta l_{IP} + \beta \sum_{j \in \text{saddle}} U(x_j). \quad (20)$$

Interestingly, typical adjustments to the path in this step are not large and can be considered as a refinement.

4. **Convergence test:** If the optimized path of step 3 has $\Delta l_{IP} \approx \langle \Delta l \rangle$, stop and report the final path. If not, return to step 2 of greedy growth to continue path extrapolation until we are sufficiently close to the product state.

Why did we use the analogy and call this algorithm “Rock Climbing”? The algorithm mimics the process of safe rock climbing in which there is a rope attached to the final destination (the product) that guides the climber to the final destination. The rope in our formulation is the term $\frac{1}{2} (|\nabla U(x_{n_I})| + |\nabla U(x_P)|) \Delta l_{IP}$. This term connects the last growing path structure with the structure of the product. The path that we already “climbed” is well marked and understood and is described by the functional value and pathway up to the intermediate point. Note that the initiation and the greedy growth step are similar to TMD. However, retention of the path history and the path refinement of step 3 make the algorithm an exact approach.

III. RESULTS

A. The Mueller potential

The Mueller potential:¹² The Mueller potential was designed as an energy surface that requires rigorous approaches to determine a sensible reaction coordinate. Heuristic methods like adiabatic mapping (e.g., minimizing the energy while keeping an assumed reaction coordinate fixed)

may not work in this case. For example, using the X axis as an adiabatic coordinate cannot capture the change in the direction of the path near the left and top saddle point. As a result, the path of mapping adiabatically X will be discontinuous.

In Fig. 2 we show an illustration of the rock-climbing algorithm on the Mueller potential. As described in Sec. II D, no initial guess is required and the path is built sequentially by an application of a greedy minimization to generate several

FIG. 2. A sequence of events in the rock-climbing algorithm. Each panel describes several local optimizations of a single displacement (greedy growth), which is followed by a global optimization of the path (path relaxation). The changes upon global optimization are small. The final path is shown in the lowest panel.

path displacements. The greedy algorithm is followed by a global optimization of the target function with all configurations up to the current intermediate structure I as variables. In the greedy part of the algorithm, the Matlab function `fmincon` was used. We seek a minimum of $T_{ICP}(2)$ with a maximum of iteration number of 2000. The global optimization of $T_{ICP}(3)$ was conducted with simulated annealing. A Monte Carlo algorithm with Metropolis acceptance-rejection step generates a canonical ensemble for the target function at a given temperature. We consider the change in the target function with an attempted global path displacement dr , which is $\Delta T = T(r + dr) - T(r)$. We then estimate the acceptance probability of the displacement as $P_{acc} = \min[1, \exp(-\beta\Delta T)]$. The steps are repeated while we decreased linearly the annealing temperature, β^{-1} , to find a global minimum of the target function.

B. Cyclohexane

A second more complex example is of a conformational transition in a model cyclohexane molecule embedded in CS_2 liquid [Fig. 3(a)].

The structural change is from the twist-boat to the chair conformation. To avoid overall translation and rotation, we fixed three carbon atoms. In this example, we considered the minimum *free* energy pathway. Instead of the force we used the mean force in the functional optimization. The mean force, $-\nabla G$, is defined as the force on the three atoms of cyclohexane that are allowed to move averaged over all thermal solvent configurations. The number of coarse variables for each image of the system along the path is therefore nine (three atoms, each with three degrees of freedom).

FIG. 3. (a) The cyclohexane in the CS_2 solvation box. (b) Numbering of the carbon atoms on the cyclohexane. The dihedral angles ψ_1 and ψ_2 are measured from atoms 1-2-3-4 and 1-6-5-4, respectively. (c) and (d) Overlapping images of the pathways from twist-boat to chair (see Fig. 4 for more information). The twist-boat configuration is shown in red, the chair is in blue, and a few intermediate steps are shown in red-white-blue scheme. The figures were prepared with the program VMD.¹⁷

The system consists of one cyclohexane solvated in 246 CS_2 molecules, placed in a periodic box of $27 \times 27 \times 27 \text{ \AA}^3$ [Fig. 3(a)]. The simulations were conducted using the NAMD package,¹⁴ with the extended atom model (in which the CH_2 groups are modeled as point masses). The bonded interactions are summarized in Table I. The dihedral stiffness constant is tuned in a way that the transition free energy approximately reproduces the experimental results for the cyclohexane interconversion.¹⁵ The interaction parameters for CS_2 were taken from Ref. 16. The three “fixed” cyclohexane atoms were restrained by springs to their initial locations with a force constant of $2000 \text{ (kcal/mol)/\AA}^2$. The system was equilibrated for 50 ps at 300 K and 1 atm.

To examine the rock-climbing method, first we calculated the entire free energy landscape by running a metadynamics simulation for 20 ns implemented in NAMD^{18,19} with two dihedral angles, ψ_1 and ψ_2 [Fig. 3(b)], as coarse variables and a resolution of 2.5° . The result of this analysis is shown as contour plot in Fig. 4. Moreover, we computed the pathway from twist-boat to chair with the string method with a swarm of trajectories²⁰ starting from a straight line in Cartesian space between reactant and product consisting of 11 points. We used the same coarse variables (coordinates of three atoms) as we used for rock-climbing. At each point on the string path, the coarse variables are constrained by a spring with force constant of $2000 \text{ (kcal/mol)/\AA}^2$ for 200 ps. Then we use the final 150 ps to pull out 300 structures and run short unconstrained trajectories for 12 steps and with a time step of 0.5 fs to find the average drift at each point. After finding the new positions of the entire points, we re-parameterize the path and repeat the procedure for 100 steps. The result is shown in the top panel of Fig. 4.

Two rock-climbing paths were computed starting from both chair to twist-boat and the backwards from twist-boat to chair (represented as path1 and path2 in Fig. 4, respectively). First, a single displacement of length of $0.2 \text{ \AA}$ was added to the current path using the greedy algorithm, and then a global optimization of $T_{ICP}(3)$ was conducted. The parameter β was 10. Note that in this case the global optimization algorithm was applied at the end. For a whole path optimizer, we used a steepest descent method in which the attempted path displacement, dr , is given by $dr = -h \cdot \nabla G$, where $-\nabla G$, the mean force, is computed for the coarse variables. It is an average of forces sampled from an MD trajectory for each path element. The sampling is conducted with constrained coarse variables to provide the mean force at specific locations in coarse space (the solvent CS_2 is allowed to move freely). The step length, h , is adjusted during the calculations for optimality. The displacement is accepted only if $T(r + dr) < T(r)$, otherwise the step h is made smaller. Two different pathways found with this

TABLE I. Bonded interaction parameters used for cyclohexane. The units for energy, length, and angle are kcal/mol, Angstroms, and degrees, respectively.

Interaction	Bond	Angle	Dihedral
	$U_b = k(r - r_0)^2$	$U_\theta = k_\theta(\theta - \theta_0)^2$	$U_\phi = k_\phi[1 - \cos(3\phi - \phi_0)]$
Parameters	$k = 260.0$ $r_0 = 1.526$	$k_\theta = 63.0$ $\theta_0 = 112.4$	$k_\phi = 1.4$ $\phi_0 = 0$

FIG. 4. Top: the free energy landscape for cyclohexane in the two dihedral angles space (ψ_1 and ψ_2 introduced in Fig. 3). Red and violet curves show the computed paths from rock-climbing. The dashed curves correspond to the initial paths before globally optimizing the paths. The yellow dashed and solid lines show the initial and final paths obtained from the string method with swarm of trajectories. Note that in all three paths, the reaction coordinates are Cartesian coordinates of three atoms but for better illustration, two dihedral angles were computed along each path. Bottom: Free energy along each path calculated by Eq. (21). The free energies are calculated from twist-boat to chair for red and yellow curves and from chair to twist-boat for the violet curve.

method, starting from the twisted boat or the chair, are shown schematically in Figs. 3(c) and 3(d).

The free energy profiles are obtained by integrating the mean force along the reaction coordinates for all paths and are shown in the bottom panel of Fig. 4,

$$G = \int_{R(\text{boat})}^x \nabla G \cdot d\vec{l}. \quad (21)$$

According to Fig. 4, there are two distinct pathways with similar free energy values between the reactant and product which both can be captured with rock-climbing. But with the string method, with a straight-line interpolation for an initial path, we end up to only one possible pathway. This is an advantage of the rock climbing algorithm. It is able to pick more than one path in a system with degenerate or almost degenerate pathways by starting from the reactants or the products. Of course, there are more degenerate pathways, and rockclimbing cannot find all of them. However, finding two is a starting point in exploration of path degeneracy.

Another advantage of rock climbing compared to the string method is that it does not require an initial guess. Here we use a linear interpolation for the string as an initial guess. Straight-line interpolations between reactants and

products frequently yield high energy and distorted pathways that are difficult to optimize. Rock climbing is based on an optimization of a functional while LUP³ and the later method of the string⁵ do not. Hence we do not know how to avoid initial guess using rock-climbing like procedure in the LUP and string method.

IV. DISCUSSION

The method of rock-climbing was illustrated above to give adequate results for a “toy” problem: the Mueller potential,¹² and a more complex conformation transition in a solvent. We are currently constructing a minimum free energy pathway for a conformational transition in a protein with the rock-climbing approach. The field of reaction path calculations is rich with whole-path-optimization technologies that provide the exact SDP. This includes approaches from the authors’ laboratory, e.g., LUP,³ and the scalar force⁸ and methods from many other laboratories, for example, a statistical method,²¹ and the widely used the NEB,⁴ and string⁵ methods. The last two are closely related to LUP.³

Another interesting global-local method is the growing string approach,²² in which a string is simultaneously growing in both directions starting from the two corresponding minima. It shares the same philosophy as the present manuscript avoiding a direct global optimization of the path and focuses instead of growing the path. In contrast to the present approach, there is no functional to be optimized which may make the method less stable. Also it is not obvious that two independently grown strings will indeed converge on rough energy landscapes with multiple pathways.

Others have questioned the need for SDP pathways and used alternative definitions of the reaction coordinate. Alternative definitions are clearly possible if they are followed by qualitative and quantitative calculation of mechanisms and rates, which are the true experimental observables. The average potential along the path was used in Ref. 9, and further variations in the functional of the average potential (self-penalty walk) were discussed in Ref. 11. Another definition of a reaction coordinate is based on maximizing the reactive flux¹³ in a continuous²³ or discrete space.^{24,25} Other numerical approaches to compute the SDP globally are possible, for example, by using path acceleration and a Fourier analysis of the path.²⁶ The dominant reaction pathways are another important choice, selecting important pathways from an ensemble of stochastic trajectories.²⁷

The typical definition of a reaction coordinate, as outlined above, is of a curve in space and hyperplanes orthogonal to it at each position along the line. Recent and more elaborate algorithms revisited the use of hyperplanes and define instead general hypersurfaces. One example is of the set of committor surfaces.^{28–30} These general surfaces are defined and computed most elegantly in the context of transition path theory³¹ and were investigated directly from sampled trajectories,^{28–30} in the context of string models,²⁹ and recently also with Milestoning.³²

With such a diverse and large set of tools to compute reaction pathways do we really need yet another approach addressing the same goal? The answer to this rhetoric question

is, of course, “yes,” and the prime motivation is the challenge in identifying an initial guess. The proposed algorithm avoids the need for an initial guess.

The rock-climbing algorithm uses the same functional as the algorithm of scalar work.⁸ However, it optimizes the path differently. The optimization of the functional in the rock climbing algorithm mixes global and local optimizations to obtain the exact SDP. The mixture addresses a significant problem for this type of action-optimization algorithms. The challenge is the generation of an initial guess for the path to be optimized. Linear interpolation between the reactant and product, which we used frequently in the past,^{9,33,34} produced highly distorted intermediate structures that are difficult to optimize. The rock-climbing algorithm generates better initial paths. This is achieved by growing the path locally, by small displacements, and as a result, the attempted extension of the path is of reasonable energy (or free energy). Rock climbing also keeps a global linker to the product state, and therefore guarantees that the system will make it eventually to the product state. The location of the final structure of the path after n steps is difficult to guarantee in a pure local algorithm such as the mode-following approach.^{1,2} The better generation of the initial guess and the retention of the link to the product state are obtained at no cost in accuracy. The final path is the exact SDP.

The algorithm extends the path by one structure and uses a single “rope” to link the last and current conformation with the product. From this perspective, it is similar to the heuristic algorithm of TMD. TMD is used widely because it is simple to implement and use and because it is relevant to experiments that employ external force on the system (called also in this context steered molecular dynamics⁶). However, a major difference between TMD and rock climbing is that rock climbing is an exact procedure while TMD is not. The path in TMD depends on the nature of the assumed reaction coordinate, the rate of pulling to the product and more. Hence, in contrast to other algorithms mentioned above, the mathematical characteristics of the path generated by TMD are not clear. This is not to say that TMD is not useful. TMD paths can be used as an initial guess for further refinement of the path or to sample conformations in reactive place for further evaluation by other techniques.

V. CONCLUSIONS

We introduce and discuss an algorithm to compute the steepest descent path in the energy or free energy space (using a previously determined set of coarse variables). The potential benefit of the algorithm is a mixture of global and local approaches. Information on both the reactant and product is used, which helps guide the path to the desired product. At the same time, the path is grown locally avoiding the problem of highly distorted initial guesses, which is found in more global approaches to compute SDPs. This approach is expected to be mostly useful for computing minimum free energy pathways in a coarse space with a large number of coarse variables (several tens). It is also possible to implement rock climbing in different MD software packages using external scripts. The forces or the mean forces of path configurations are computed

by an external molecular dynamics package, while the script determines the path displacement. Such a procedure in conjunction with the program NAMD¹⁴ was used to optimize the path for cyclohexane.

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- ¹C. J. Cerjan and W. H. Miller, “On finding transition-states,” *J. Chem. Phys.* **75**(6), 2800–2806 (1981).
- ²J. D. Wales, *Energy Landscapes with Applications to Clusters, Biomolecules and Glasses* (Cambridge University Press, Cambridge, 2003).
- ³A. Ulitsky and R. Elber, “A new technique to calculate steepest descent paths in flexible polyatomic systems,” *J. Chem. Phys.* **92**(2), 1510–1511 (1990).
- ⁴H. Jonsson, G. Mills, and K. W. Jacobsen, “Nudged elastic band method for finding minimum energy paths of transitions,” in *Classical and Quantum Dynamics in Condensed Phase Simulations*, edited by B. J. Berne, G. Cicciotti, and D. F. Coker (World Scientific, Singapore, 1998), pp. 385–403.
- ⁵W. E, W. Ren, and E. Vanden-Eijnden, “String method for the study of rare events,” *Phys. Rev. B* **66**(5), 052301 (2002).
- ⁶J. Schlitter, M. Engels, and P. Kruger, “Targeted molecular-dynamics: A new approach for searching pathways of conformational transitions,” *J. Mol. Graphics* **12**(2), 84–89 (1994).
- ⁷W. Kabsch, “Discussion of solution for best rotation to relate two set of vectors,” *Acta Crystallogr., Sect. A: Found. Adv.* **34**, 827–828 (1978).
- ⁸R. Olender and R. Elber, “Yet another look at the steepest descent path,” *J. Mol. Struct.: THEOCHEM* **398**, 63–71 (1997).
- ⁹R. Elber and M. Karplus, “A method for determining reaction paths in large molecules: Application to myoglobin,” *Chem. Phys. Lett.* **139**(5), 375–380 (1987).
- ¹⁰R. Elber, “A milestone study of the kinetics of an allosteric transition: Atomically detailed simulations of deoxy Scapharca hemoglobin,” *Biophys. J.* **92**(9), L85–L87 (2007).
- ¹¹R. Czereminski and R. Elber, “Self avoiding walk between 2 fixed end points as a tool to calculate reaction paths in large molecular systems,” *Int. J. Quantum Chem.* **24**, 167–186 (1990).
- ¹²K. Müller and L. D. Brown, “Location of saddle points and minimum energy paths by a constrained simplex optimization procedure,” *Theor. Chim. Acta* **53**(1), 75–93 (1979).
- ¹³M. Berkowitz, J. D. Morgan, J. A. McCammon, and S. H. Northrup, “Diffusion-controlled reactions: A variational formula for the optimum reaction coordinate,” *J. Chem. Phys.* **79**(11), 5563–5565 (1983).
- ¹⁴J. C. Phillips, R. Braun, W. Wang, J. Gumbart, E. Tajkhorshid, E. Villa, C. Chipot, R. D. Skeel, L. Kale, and K. Schulten, “Scalable molecular dynamics with NAMD,” *J. Comput. Chem.* **26**(16), 1781–1802 (2005).
- ¹⁵D. L. Hasha, T. Eguchi, and J. Jonas, “High-pressure NMR study of dynamical effects on conformational isomerization of cyclohexane,” *J. Am. Chem. Soc.* **104**(8) 2290–2296 (1982).
- ¹⁶D. J. Tildesley and P. A. Madden, “An effective pair potential for liquid carbon disulphide,” *Mol. Phys.* **42**(5), 1137–1156 (1981).
- ¹⁷W. Humphrey, A. Dalke, and K. Schulten, “VMD: Visual molecular dynamics,” *J. Mol. Graphics* **14**(1), 33–38 (1996).
- ¹⁸B. Giovanni, A. Laio, and M. Parrinello, “Equilibrium free energies from nonequilibrium metadynamics,” *Phys. Rev. Lett.* **96**(9), 090601 (2006).
- ¹⁹Y. Wang, C. B. Harrison, K. Schulten, and J. A. McCammon, “Implementation of accelerated molecular dynamics in NAMD,” *Comput. Sci. Discovery* **4**(1), 015002 (2011).
- ²⁰P. C. Albert, D. Sezer, and B. Roux, “Finding transition pathways using the string method with swarms of trajectories,” *J. Phys. Chem. B* **112**(11), 3432–3440 (2008).
- ²¹L. R. Pratt, “A statistical-method for identifying transition-states in high dimensional problems,” *J. Chem. Phys.* **85**(9), 5045–5048 (1986).
- ²²B. Peters, A. Heyden, A. T. Bell, and A. Chakraborty, “A growing string method for determining transition states,” *J. Chem. Phys.* **120**, 7877–7886 (2004).

- ²³P. Metzner, C. Schutte, and E. Vanden-Eijnden, "Transition path theory for Markov jump processes," *Multiscale Model. Simul.* **7**(3), 1192–1219 (2009).
- ²⁴S. Viswanath, S. M. Kreuzer, A. E. Cardenas, and R. Elber, "Analyzing milestoning networks for molecular kinetics: Definitions, algorithms, and examples," *J. Chem. Phys.* **139**(17), 174105 (2013).
- ²⁵E. R. Hernández, C. P. Herrero, and J. M. Soler, "A chain-of-states acceleration method for the efficient location of minimum energy paths," *J. Chem. Phys.* **143**(18), 184104 (2015).
- ²⁶P. Faccioli, M. Sega, F. Pederiva, and H. Orland, "Dominant pathways in protein folding," *Phys. Rev. Lett.* **97**(10), 108101 (2006).
- ²⁷B. Peters, G. T. Beckham, and B. L. Trout, "Extensions to the likelihood maximization approach for finding reaction coordinates," *J. Chem. Phys.* **127**(3), 034109 (2007).
- ²⁸L. Maragliano, A. Fischer, E. Vanden-Eijnden, and G. Ciccotti, "String method in collective variables: Minimum free energy paths and isocommittor surfaces," *J. Chem. Phys.* **125**(2), 024106 (2006).
- ²⁹A. Ma and A. R. Dinner, "Automatic method for identifying reaction coordinates in complex systems," *J. Phys. Chem. B* **109**(14), 6769–6779 (2005).
- ³⁰W. E and E. Vanden-Eijnden, "Transition-path theory and path-finding algorithms for the study of rare events," *Annu. Rev. Phys. Chem.* **61**, 391–420 (2010).
- ³¹R. Elber, J. M. Bello-Rivas, P. Ma, A. E. Cardenas, and A. Fathizadeh, "Calculating iso-committor surfaces as optimal reaction coordinates with milestoning," *Entropy* **19**, 219 (2017).
- ³²R. Elber and A. West, "Atomically detailed simulation of the recovery stroke in myosin by milestoning," *Proc. Natl. Acad. Sci. U. S. A.* **107**, 5001–5005 (2010).
- ³³S. Kirmizialtin, V. Nguyen, K. A. Johnson, and R. Elber, "How conformational dynamics of DNA polymerase select correct substrates: Experiments and simulations," *Structure* **20**, 618–627 (2012).
- ³⁴S. Stepaniants, S. Izrailev, and K. Schulten, "Extraction of lipids from phospholipid membranes by steered molecular dynamics," *J. Mol. Model.* **3**(12), 473–475 (1997).