Self-Avoiding Walk Between Two Fixed Points as a Tool to Calculate Reaction Paths in Large Molecular Systems

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Abstract

A new computational technique is presented to calculate approximate reaction paths in complex molecules. The method is based on the Gaussian chain approach proposed by Elber and Karplus [1] but avoids some computational difficulties of this technique. It is also more than 10 times faster. The new formulation is quite general and enables empirical interpolation between two types of motions which differ considerably: trapped and ballistic (see also "Note Added in Proof"). We present test results for two model molecules: alanine dipeptide (AD) and isobutyryl-(ala)5-NH-methyl (IAN). The optimization of the chain is very stable and provides an approximate continuous path even if the initial guess is poor.

Introduction

Calculations of reaction paths in large and flexible molecular systems are associated with difficulties which are not present in small molecules. The major new problems which appear as the system size increases are:

1. The existence of a large number of stable configurations and transition states complicates the search for a path between a pair of minima of interest.

2. A number of methods [2] which are very useful for small molecules employ Hessian and related matrices. However, for problems which include more than several tens of atoms the manipulation of these matrices is computationally demanding and cannot be used effectively.

3. In the so-called reaction coordinate or reference coordinate approaches the calculated path may be discontinuous. This may happen if there is no one-to-one mapping between the reference coordinate and the steepest-descent path [3,4].

An attractive approach to the problem is to optimize the complete path at once, rather than to propagate the solution from point to point. In this way the two minima of interest are necessarily connected. Hence, at least difficulty (1) is addressed. In 1953 Onsager and Machlup [5] discussed the path integral formulation of the trajectory of a Langevin particle. Their formulation, though very elegant and having a clear physical interpretation, is difficult to apply computationally. Their functional requires the application of the second derivatives of the potential energy...
which are difficult to deal with in large systems (see also Wolynes [6]). Empedocles (in 1969) [7] proposed (from a completely different point of view) a line integral as an approximation to the reaction coordinate. He assumed a functional form for the path which depends on several parameters to be optimized. The quality of the optimized path depends therefore on the flexibility of the functional form. More recently Pratt [8] proposed to refine Markov chains as an approximation for paths. His formalism is very general, but its computational aspects are unclear. Elber and Karplus [1] proposed a line integral similar to the one proposed by Empedocles. They used a discrete approximation to the integral which is more flexible than the assumed form of Empedocles. Their method was found to be effective even for systems with several thousands atoms. There are however several inherent computational problems in their approach which are addressed and discussed in this article.

Very recently Ulitsky and Elber [9] proposed an optimization algorithm for the complete path which makes it possible to calculate the steepest descent path in flexible polyatomics. It is an important question therefore why we bother to address a problem which is already "solved." The reason is the following: in optimization of complex functions (such as paths in large molecules) an important element of the calculation is the radius of convergence, that is, how close to the solution the initial guess needs to be in order to ensure convergence. The Ulitsky and Elber algorithm, though in principle exact, has a relatively small radius of convergence in large molecular systems. The quality of the initial guess is therefore a painful issue. If a sufficiently good initial guess is not available the Ulitsky and Elber algorithm becomes slow and sometimes does not converge.

The purpose of the present study was to design a method with a large radius of convergence which can provide a sound starting point for refinement to the exact solution. Here we suggest several critical improvements to the Elber and Karplus algorithm which do the job. It is worth emphasizing that the suggested technique addresses all the difficulties mentioned above which makes it a suitable candidate for calculating reaction paths in large molecular systems.

As a side effect, the present results suggest an interpolation between trapped behavior and ballistic motion (see "Note Added in Proof"). This manuscript is organized as follows: in the second section the technique is derived in detail and in the third the computational examples are presented. They include (1) a conformational transition in a dipeptide and (2) a conformational transition in a tetrapeptide (Fig. 1). The performance of the method is examined in the fourth section and conclusions and final remarks are given in the fifth.

**Method**

The following line integral yields the average value of the potential energy \( V(\mathbf{R}) \) along a path \( l(\mathbf{R}) \) [1]

\[
S = \frac{1}{L} \int_{\mathbf{R}_a}^{\mathbf{R}_b} V(\mathbf{R}) \, dl(\mathbf{R})
\]  
(1)
where \( R_a \) and \( R_b \) are the coordinates of the "reactants" and the "products," respectively and \( dl(R) \) is a line element. \( L \) is the length of the path. We assume that the path \( l_{\text{min}}(R) \) which minimizes the functional \( S \) is a reasonable approximation to the reaction coordinate. In general \( l_{\text{min}} \) is not the steepest descent path. In practice the calculated path describes quite well the neighborhood of the transition state and in a number of cases \( l_{\text{min}} \) is very close to the steepest descent path (SDP). \( l_{\text{min}} \) as obtained from the present implementation of Eq. (1) is a good initial guess for SDP calculations and it is also obtained with a fairly large radius of convergence.

We note that using other integrands designed to increase the weight of the barrier in the integral (e.g., replacing \( V(R) \) by \( V^2(R) \)) affects the results only slightly.

We replace the integral by a discretized version

\[
T = \frac{1}{M} \sum_{i=1}^{M} V(R_i) + \text{constraints} \tag{2}
\]

with \( \text{constraints} = \text{CHAIN} + \text{REPRESSION} \) where the \( \text{CHAIN} \) is a constraint which was introduced to keep the distances between successive structures constant.

\[
\text{CHAIN} = \gamma \sum_{i=0}^{M} (d_{i,i+1} - \langle d \rangle)^2 \tag{3}
\]

where \( \gamma \) is a parameter which describes the magnitude of the "attraction" between the monomers.

\[
d_{i,i+1} = |R_{i+1} - R_i|
\]

\[
\langle d \rangle = \left( \frac{1}{M+1} \sum_{i=0}^{M} d_{i,i+1} \right)^{\frac{1}{2}}
\]

\( R_0 = R_a \) is the initial structure (the "reactant") and \( R_{M+1} = R_b \) the final structure (the "product"). Each of the structures \( i = 1, M \) resembles a monomer in a polymer connected by forces given by Eq. (3).

The constraint term which we denoted by \( \text{REPRESSION} \) is repulsion between different monomers. It was included to prevent the aggregation of the polymer.
defined in Eqs. (2) and (3) in the neighborhood of minima. This is a new term which did not exist in the formulation of Elber and Karplus [1]. It increases the sampling of points in the neighborhood of the transition state and it is therefore useful in studies related to the last.

We consider repulsion which decays as a function of distance. Gaussian decay which is scaled by the average distance between sequential points \( \langle d \rangle \) is employed

\[
REPULSION = \rho \sum_{i\neq j+1}^{M+1} \exp \left( -\frac{d_{ij}^2}{\lambda \langle d \rangle^2} \right)
\]

(4)

\( \lambda \) and \( \rho \) are two external parameters which determine the range and the maximal value of the repulsion between "monomers" \( i \) and \( j \). Thus the Gaussian chain (a chain that is allowed to cross itself) of Elber and Karplus algorithm, is currently replaced by a Self Avoiding Walk polymer (or more precisely—Self Penalty Walk). Structures of the SPW chain tend to avoid points in configurational space which are already occupied by other structures. Therefore larger portion of configurational space will be explored by the SPW polymer as compared to the Gaussian chain. This is one of the advantages of the present algorithm. Consider the limit of \( \langle d \rangle \rightarrow 0, M \rightarrow \infty \) and of finite \( \lambda \) and \( L \) in which Eq. (2) should approach an integral. The only pairs of monomers which contribute to the repulsion term are those which are distant of the order of \( \langle d \rangle \) or less. The "volume" of each monomer is of order \( \langle d \rangle^n \) (\( n \) is the number of degrees of freedom) and it goes to zero as \( dI(\mathbb{R}) \) goes to zero. Hence the \( REPULSION \) contribution to the line integral in the limit \( \langle d \rangle \rightarrow 0 \) will include only local chain stiffness. The local stiffness mimics the effect of kinetic energy (see "Note Added in Proof"). A classical trajectory will approach the "ballistic"-stiff behavior (maintaining the direction of motion) for kinetic energies much higher than the energy barriers in the system. Turning off the repulsion between the points yields a trajectory of a particle without inertia or with a diffusive-like motion. Both limits will be demonstrated in the computational example.

For the finite \( \langle d \rangle \) which we employ numerically, an important role is played by both types of repulsions: the local chain stiffness and the repulsion between different portions of the chain that cross.

Cartesian coordinates are most convenient to use in large molecules and therefore we employ them in our study. However the cartesian representation necessitates the elimination of rigid body motions. These motions could affect the distance between the chain structures by applying different rigid body transformations to different monomers. The projection is performed by imposing six linear constraints on each of the monomers of the polymer:

\[
\sum_{j=1}^{N} m_j (r_j - r_i^{(\alpha)}) = 0
\]

\[
\sum_{j=1}^{N} m_j r_j \times (r_j^{(\beta)} - r_j) = \sum_{j=1}^{N} m_j r_j \times r_j^{(\alpha)} = 0
\]

(5)
where \( N \) is the number of atoms, \( m_i \) and \( r_i \) are the mass and the cartesian coordinates of atom \( j \). \( \{ r_{i}^{(k)} \}_{j=1,N} \) are used to define the fixed coordinate system. They are set to the arithmetic average of the reactant and the product coordinates. The monomers are initially oriented by rigid body transformations. The transformations are determined by the requirement that the distance from the monomer to the fixed coordinates will be minimal [10]. During the minimization the rigid body constraints are imposed on the system by the gradient projection technique [3]. This should be contrasted with the penalty function approach employed for the constraints described before. The gradient projection is especially useful when the constraints are linear as is the case with the rigid body motions [3]. Let us denote the constraints in Eq. (5) by \( \{ \sigma_i \}_{i=1,M} \) and the six orthonormal vectors which span the space of the gradient of the constraints by \( \{ e_i \}_{i=1,M} \). To keep the minimization in the subspace which satisfies the \( \sigma \)'s we minimize the function only along the gradient of the target function \(-T\) projected on the subspace which satisfies the constraints, i.e.,

\[
\left\{ \nabla_i T_{proj} = \nabla_i T - \sum_{i=1}^{6} (\nabla_i T \cdot e_i)e_i \right\}_{i=1,M}
\]

where the \( \nabla_i T \) are the gradients of the target function with respect to the coordinates of the \( i \)th monomer. Detailed discussion on the derivation of Eq. (6) and its application to constrained minimization problems is available in Ref. [3b].

To summarize this section: two new features were introduced to the chain algorithm proposed by Elber and Karplus [1]. The first is the repulsion term which made the search for the transition states considerably more efficient and the second is the application of gradient projection technique to eliminate rigid body motions. This modification speeds up the calculations by more than a factor of ten. The numerical properties of the SPW will be demonstrated in the next section.

**Computational Examples**

In order to assess the reliability of the SPW algorithm we investigated conformational changes in two small peptides. The reaction paths for these conformational changes were studied by us extensively in the past. The previous investigations facilitated the analysis of the performance of the chain algorithm. One of the molecules—alanine dipeptide (AD—12 atoms) includes only two soft degrees of freedom (\( \phi, \psi \)) and can be studied by a variety of techniques: for example, adiabatic mapping [11], mode following [2b], constrained optimization [3], and others [9]. The second molecule isobutyryl—(ala)_{3}-NH-methyl (IAN) has 26 atoms and seven soft torsions (three \( \phi \) and four \( \psi \)'s). It is considerably more complex to analyze and to understand. Recently we investigated the connectivity network between the minima of this molecule [3]. We found ca. 140 minima and ca. 500 transition states, demonstrating the inherent complexity of the system and the transition to different glass-like behavior as the peptide size increases. Here we apply the chain algorithm on one of the paths in the network—a path which involves a significant structural change. We consider the transition from a helix to an extended chain conformations
which also includes a number of intermediates. Using previous methods we found it impossible to calculate this reaction coordinate in “one shot.” The stepwise approach which we had to adopt in the past is described in Ref. [3].

The computations were performed using a modified CHARMM program [12]. We added the chain code as a separate head in the above program and used internal calls to obtain the energy and the forces for the atom-atom interactions. The option of distance dependent dielectric “constant” for the electrostatic energy was employed and the 1–4 scaling parameter was set to one. The extended atom model was used in which the CH₃ groups are modeled by spheres. For these small molecules no cutoff for nonbonded interactions was used. The atomic charges for the model molecules were slightly modified compared to the standard data base to ensure system neutrality. They are given in Table I. The target function was optimized by the conjugate gradient algorithm of Powell [13].

<table>
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<tr>
<th>Atom</th>
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Results and Discussion

Alanine Dipeptide

The first question which we addressed is the rate of convergence of the new chain (SPW) as compared to the Elber and Karplus protocol [1]. The new elements in SPW as compared to previous method include the additional REPULSION term, and the rigid body motions are constrained by gradient projection instead of penalty function [3]. The minimization of the set of structures of the chain — \( \{ R_i \}_{i=1}^M \) — is assumed converged if the gradient of the target function \( T \) is smaller than or equal to \( 10^{-3} \) kcal/mol Å. In Figure 2 we examine the number of minimization steps that are required to reach this value of the gradient. In the calculation the number of grid points \( M \) was 20 and the path between minima A and D [Fig. 3(a)] was calculated. The number of minimization steps is machine (computer) inde-
Figure 3(a). Adiabatic $\phi,\psi$ energy map for alanine dipeptide. The angles are given in degrees. The minima are denoted by A to D and the saddle points by T1–T8. The solid lines are the steepest descent paths. The results are taken from Ref. [3b].

pendent and it is therefore a useful measure of the efficiency of the algorithm. The most time consuming part in the calculation is the evaluation of the energies and the gradients of the energies of the different monomers. The number of such evaluations is proportional to the number of minimization steps.

The number of steps required to minimize the Elber and Karplus chain is more than 6000. (The "force constant" for the penalty function on rigid body motions which was defined in [1] was 1000.) The number of steps to reach a minimum in the present chain is at least 10 times smaller and is below 600. The application of the gradient projection technique speeds up the calculations by a factor of approximately 10. Furthermore, currently the accuracy with which the equations for the constraints are solved is limited only by the computer round-off errors.

In Figure 3(a) we show an adiabatic map for alanine dipeptide. The equipotential lines are drawn as a function of the variables $(\phi,\psi)$. It was obtained by fixing the soft degrees of freedom — $(\phi,\psi)$ — and minimizing the energy of the rest of the coordinates. Also shown on the map are the four minima (denoted by A–D) and the eight steepest descent paths connecting those minima which we calculated using
the reference coordinate approach [3]. In the previous study it was difficult to obtain one continuous path connecting minima A and D (though the relevant transition states were identified in a systematic way). This path was finally constructed from two pieces: the path from A to B and the path from B to D. We repeat the calculation of this path using the SPW algorithm for a variety of conditions and test if the SPW algorithm is able to find a continuous path close to the SDP. In the analysis of the SPW parameters we focused on the REPULSION parameter $\rho$. A study of the properties of $\lambda$ is not pursued since it has a similar effect. I.e., larger $\lambda$ (longer range of repulsion) makes the chain stiffer and smaller $\lambda$ makes the chain more flexible. The value of $\lambda$ was set to 2 which after some trial and error seems to be a reasonable choice.

In Figure 3(b) a series of SPW paths calculated for the following values of $\rho$, $\rho = 512, 256, 32, 16, 1, 0$ kcal/mol is shown. The initial guess which was used as a starting point for the path optimization is the “ballistic limit” or a straight line interpolation. For high values of $\rho$ (e.g., $\rho = 512$) the path on the $(\phi, \psi)$ map is close to the initial guess. As $\rho$ becomes lower SPW feels lower penalty and starts to

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Figure 3(b). Dependence of A–D path for alanine dipeptide on $\rho$ parameter ($\lambda = 2$). The steepest-descent path is shown with a thick line. For clarity and ease of comparison the paths are shifted vertically and the contour map [Fig. 3(a)] is omitted.
aggregate at the minima. The lowest minimum in the system is minimum B and it is an intermediate in the path between A and D. This is the spot in which the polymer aggregates at \( \rho = 0 \) ("diffusion limit"—DL). We qualitatively interpret the DL as the case in which the polymer changes its direction very sharply at each step from a monomer to a monomer (strictly speaking the diffusion limit will correspond to the loss of correlation between sequential steps). Note however that the shape of the paths with the different \( \rho \)'s is quite similar in the neighborhood of the transition states even after the aggregation started. Thus it is possible to use these portions of the paths to obtain reasonable estimates for the position of the transition states. This is even in the case of a "collapsed" chain. It is clear however that in the latter case a significant number of structures is not used since a number of structures reside in the minima rather than in the vicinity of the interesting part—the transition state. This is one computational advantage of the repulsion term in the search for saddle points—it prevents aggregation. The repulsion should not be too large, though, to avoid the ballistic limit.

An obvious question to raise is the following: How to choose the values of the repulsion parameters for which the path will be significantly different from the initial straight line guess but still not at the aggregation point (since computationally, the aggregate of structures at a minimum is not useful). In other words, if a reasonable guess to the steepest descent path is of prime interest what is the optimal stiffness of the chain?

A quantitative criterion to determine a reasonable set of parameters for SPW calculations is given below. Consider the following estimate of local curvature of the path: let \( R_i \) be the coordinate set of monomer \( i \), then the cosine of the curvature angle \( \cos(\Theta_i) \) is

\[
\cos(\Theta_i) = \frac{(R_{i+1} - R_i) \cdot (R_{i-1} - R_i)}{|R_{i+1} - R_i| |R_{i-1} - R_i|}
\]

where \( A \cdot B \) is the scalar product of the vectors \( A \) and \( B \) and \(|A|\) is the length of the vector \( A \). For a straight line \( \Theta \) is 180°, for a chain which is going back to where it comes from (one type of an aggregate—\( R_{i+1} = R_{i-1} \)) \( \Theta \) is zero. In particular when the number of monomers is small, the aggregates are characterized by values of \( \Theta \) which are smaller than usual. Hence we should consider paths in which all the \( \Theta \)'s are higher than a cutoff value. The actual value of the cutoff is somewhat arbitrary. As shown below the transition between the "ballistic" and the "trapped" limits is quite sharp which made any choice between \( \Theta \approx 170 \) and \( \Theta \approx 30 \) degrees satisfactory. We adopted 150 degrees. In Figure 4 the minimal angle (maximum curvature) is plotted as a function of the parameter \( \rho \) for paths calculated between minima A and D. \( \rho \) was examined over a broad range from \( 2^{-5} \) to \( 2^{10} \) kcal/mol. The maximum curvature is a sensitive function of \( \log_2(\rho) \) only in a small interval. It has a sharp transition from values which are close to "straight line" (\( \Theta_{\text{min}} \sim 170–180° \)) to the aggregate Gaussian limit (\( \Theta_{\text{min}} \sim 0 \)). At the same time the standard deviation of \( \Theta \) (calculated from the sample of all the angles of a given path) increases rapidly. This "phase transition" takes place at \( \rho \approx 16 \).
In Figure 5 the dependence of the path on the number of points is also examined. Using the "optimal" $\rho$ value ($\rho = 16$ kcal/mol) and setting $\lambda$ to two, the number of points was varied for the A-D path from 5 to 80. Changing the grid from 5 to 40 improves the shape of the path and makes it closer to the SDP. However the attempt to improve the results even further by applying 80 points failed. The local curvature increased significantly at the neighborhood of the minima and the proximity of the transition states was sampled by a number of points smaller than expected according to the study of 40 monomers. Thus the increase in the number of monomers does not necessarily provide a path with a better resolution, since a significant number of structures is "wasted" in the neighborhood of the minima.

With fixed values of $\rho$, $\lambda$ the "local stiffness" of the chain is a constant. The repulsion however is of a shorter range ($\sim \langle d' \rangle$) as the number of points increases. This increases the chain overall flexibility and the ability to form aggregates at the minima.

Another difficulty is associated with the fact that even for a fixed value of chain parameters there can exist a number of local minima for the target function. For example, in Figure 5 it is clear that there are two different local minima for the
The target function corresponding to two different SDP's between A and B (the reader should compare these paths with Figure 3(a). Similar behavior is observed for IAN. This difficulty is inherent to complex molecular systems irrespective of reaction path algorithm used.

**IAN Tetrapeptide**

As noted previously the problem of locating the steepest descent paths in alanine dipeptide can be solved (and was solved) by a variety of techniques. To provide more stringent test on the stability and the radius of convergence of the chain algorithm we consider next a conformational transition in the tetrapeptide IAN. Conformational transitions in this molecule represent a difficult problem which we studied extensively quite recently [3]. Here we consider a single reaction path, between the minimum of the a helix conformation in which all the \((\phi,\psi)\) pairs are in the \((-,-)\) block of the adiabatic map and the extended chain conformation in which the pairs are at \((-,+\) portion of the map [Fig. 3(a)]. Hence the conformational transition requires rotations of at least four dihedral angles. The problem of finding the path between two given minima in this system is nontrivial since the
number of minima and of barriers in the system is at least 138 and 490, respectively [3]. The search for the lowest energy path (with four intermediates) in this complex network requires considerable computational effort [3].

The first study which we pursued is to check if the criterion for "best repulsion parameters" which we developed for alanine dipeptide is still valid for this system. In Figure 6 we plotted the minimum value of $\Theta$ in a minimized path as a function of $\rho$. Also shown in the figure is the standard deviation of $\Theta$ in a path. It is clear from the plot that a sharp transition to an aggregate occurs at $\rho \sim 16$. Hence the criterion which we developed before for the alanine dipeptide case is useful here, too.

We examined in detail the path at $\rho = 32$ which is significantly beyond the aggregation point. The first trial to calculate the path was the optimization of a straight line interpolating between the two extreme minima. The energy profile for this path with 50 monomers is given in Figure 7 and it is quite different from the lowest energy path. The path calculated corresponds to a local minimum of the

![Figure 6](image_url)

**Figure 6.** The minimum angle ($\Theta$) along the path between the helix to the extended chain in LAM. It is plotted as a function of $\rho$. $\rho$ changes from $2^{10}$ to $2^{-3}$. "Phase transition" occurs around $\rho = 16$. The line denoted by $10 \times$ SDEV is ten times the standard deviation of $\Theta$ in a path.
chain which is quite different from the lowest energy path. The chain has a lower minimum close to the SDP which we found by additional search to be described below. We emphasize however, that similarly to the "global minimum" problem of optimizing structures, we have a problem in optimizing a set of structures which forms a chain. By direct minimization (the method which we employed in this study) the minimum closest to the initial guess is found and not necessarily the global minimum. Simulated annealing [13] is one approach which may help. Here we aimed to study in detail the properties of the chain algorithm and therefore a less general (but more efficient) approach was adopted. We note first that this local minimum of the chain is independent of $\rho$, i.e., changing $\rho$ to zero does not change the magnitudes and the properties of the observed transition states, similarly to what we found in alanine dipeptide. To locate a lower energy path we consider path segments which are direct, i.e., without intermediates. This is in the same spirit of Ref. [3]. Structures ($R_i$) along the chain which were candidates for new minima ($V(R_i) < V(R_{i+1})$) were minimized. Let us denote the set of all minima ordered along the chain by $A_i$ ($A_1$ is the reactant and $A_N$ is the product) and by $P_{ij}$ the path connecting minima $i$ and $j$. We proceed by calculating the chains for each
individual path segment between \( \mathcal{A}_i \) and \( \mathcal{A}_{i+1} - (\mathcal{P}_{i+1}) \) (this is different from \([3]\) in which all the \( \mathcal{P}_j \) paths were calculated). The resulting path is practically identical with the SDP and is shown in Figure 7. Another measure of the path quality is shown in Figure 8 in which we examine the variation in the \( \psi \) dihedral angles. These coordinates are the ones with the largest variations along the reaction coordinate. It is evident that the steepest descent path is very close to the path composed of several segments. Also it is clear that the path calculated from the straight line interpolation is quite different. It is interesting that the mechanistic picture of a sequence of isolated rotations around a bond remains true even in the different, higher energy coordinate. We comment that we observed the localizations of the transitions also in previous studies \([3]\).

Figure 8. \( \psi \) angles for the paths described in Figure 7.
We demonstrate finally that there is a local minimum for the whole chain which is close to the SDP. We minimized the complete chain (gathering together all the different segments) using as an initial guess the exact SDP. The calculated path is quite close to the SDP (see Figs. 7 and 8) and the value of the target function is significantly lower than the value which we initially obtained from the optimization of the chain starting from a straight line (60 compared to 140 kcal/mol). Hence it is likely that simulated annealing (or other optimization protocol capable of overcoming barriers and escaping from local minima) can help in finding the lower minimum which is closer to the SDP, even if the starting point is considerably off the target.

Thus computationally two options are available: the first which we adopted here is to find energy minima of structures along the path and to repeat the chain calculations between the energy minima found in a sequential way. The second (which we did not pursue here, but will be pursued in future) is to run a more global search for alternative lower energy minima of the complete chain. The calculation via path segments requires more human time and less computer time.

We finally comment that in contrast to the SPW chain the Ulitsky and Elber algorithm [9] failed to complete this calculation starting from a straight line interpolation and some human intervention was required. This demonstrates the different radius of convergence of the two algorithms.

To summarize we describe the stepwise protocol employed in the search for the path:

1. Start with a relatively stiff chain ($\lambda \sim 2$, $\rho \sim 100 \cdot B$) where $B$ is an estimate for the barrier. The estimate can be quite crude. The initial number of monomers should be relatively small $\sim 10$.
2. Using the obtained path initiate new calculations with a smaller value of $\rho$'s. Monitor the results (using $\Theta$) for the onset of aggregation.
3. Following the criterion for "best repulsion," a path close to the SDP can be obtained using $\rho$ between 2 to 4 times higher than the aggregation threshold.
4. Double the number of the monomers and repeat the calculation with $\rho$ determined by (3). Check for aggregation and changes in the description of the path near the neighborhood of the transition state.
5. Determine if candidates for local minima exist along the chain. If yes, minimize these structures and calculate the chain between the simpler segments.

Conclusions

We presented a new chain algorithm (SPW—Self Penalty Walk) which has a relatively large radius of convergence to stable solutions. It is therefore useful as a generator of initial guesses to exact steepest descent path (SDP) calculations [9]. Two test cases were considered: alanine dipeptide and a tetrapeptide. For both, the chain yields stable solutions which could be manipulated in a systematic way to paths very close to the steepest descent path.

Until now we did not find any example in which the new chain is unstable, a common problem in methods to calculate saddle points and reaction coordinates
in complex molecular systems. We are currently applying this code to a much larger problem (the B to Z transition in DNA) in a straightforward way [14].

We based our protocol on an empirical correlation between "ballistic" and "trapped" limits (the stiff and the flexible chain limits) and we used a transition between the two classes of behavior as a criterion for paths close to the steepest descent path. We pointed out the similarity of the effect of one of the constraints to the effect of kinetic energy.

Acknowledgments

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Note Added in Proof

After this manuscript was accepted for publication we found how to adjust the target function and to choose the parameters, to make the minimization of the spw energy equivalent to optimization of a discretized classical action and therefore to the calculation of a classical trajectory. Hence each of the points corresponds to the position of the system at a specific time. The adjustments are as follows.

(a) Mass weighted coordinates (Q) are employed.

(b) Only the repulsion between monomers i and i + 2 is taken into account (i.e., the sum over j in eq. (4) is modified to include only i + 2).

(c) The individual distances in the repulsion term (d_i) are not scaled by the average distance (\langle d \rangle).

(d) The equidistance constraint is taken in one of the options (N.2.1) between the "real" points and intermediate "ghost" points. The distances are calculated using mass weighted coordinates and the equilibrium distance is set to a fixed value, say d_0. The derivation is as follows: We start with the expression for the modified T

\[ T = \sum_{i=0,2,4,...} V(Q_i) + \text{constraints} \quad \text{(N.1)} \]

where Q_i denotes a mass weighted coordinate vector. As discussed earlier, the constraints include two terms: CHAIN and REPULSION

\[ \text{CHAIN} = \gamma \sum_{i=0,1,2...} (Q_{i,i+1} - d_0)^2 \quad \text{(N.2.1)} \]

It is also possible to use an alternative form for the chain constraint which imposes the conservation of energy (E is the total energy)

\[ \text{CHAIN} = \gamma \sum_{i=1,2...} (Q_{i-1,i+1}^2 - 4\Delta t^2[E - V(Q_i)])^2 \quad \text{(N.2.2)} \]

The second constraint is
\[ \text{REPULSION} = \frac{\rho}{\lambda} \sum_{i=0,2,4...} \exp(-\lambda Q_{i,i+2}^2) \]

where \(Q_{i,j}\) is the distance between two structures \(i\) and \(j\) using mass weighted coordinates

\[ Q_{i,j} = |Q_i - Q_j| \]

Note that using the constraint (N.2.1) the physical points are 0, 2, 4, . . . while the virtual points (1, 3, 5, . . .) are employed in the equidistance constraints to ensure an upper bound for the velocity.

As is shown below the upper bound is given by \(2d_0/\Delta t\). From the formal point of view the equidistance constraint is not really necessary, from the practical point of view this constraint is essential in order to ensure continuous description of the trajectory (polymer).

Consider the limit of small \(\lambda\) in which the REPULSION can be expanded to the first order

\[ \exp(-\lambda Q_{i,i+2}^2) \approx 1 - \lambda Q_{i,i+2}^2 \]  

(N.3)

The target function is now

\[ T = \sum_{i=0,2,4...} (V(Q_i) - \rho Q_{i,i+2}^2) + \frac{M \rho}{\lambda} + \text{CHAIN} \]  

(N.4)

On the other hand, the classical action \(S_{\text{class}}\) is given by

\[ S_{\text{class}} = \int \left( \frac{dQ}{dt} \cdot \frac{dQ}{dt} - V(Q) \right) dt \]  

(N.5)

If \(\rho\) is set to \(1/\Delta t^2\) we can write \(\rho Q_{i,i+2}^2 = (d/Q/dt)^2\). Hence the first two terms in equation (N.4) correspond to a discrete version of \(-S_{\text{class}}/\Delta t\) (\(\Delta t\) is constant). Since the classical trajectory is a stationary point of the functional \(S_{\text{class}}\) (not necessarily a minimum) the minus sign is not important. The third term is a constant and the last term either imposes energy conservation (N.2.1) or enforces an upper bound on the norm of the velocity vector (N.2.2). The norm of the velocity cannot be larger than \((2d_0/\Delta t)\). \(d_0\) can be determined from energy conservation. If the total energy of the system is \(E\), then \(d_0 = \Delta t(E/2)^{1/2}\).

Hence it is possible to use the protocol described in this paper to calculate trajectories with fixed end points or known “reactant” and “products,” a type of computation which is much harder to pursue using initial values techniques to solve the equation of motion.

Bibliography


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