

New Space Warping Method for the Simulation of Large-Scale Macromolecular Conformational Changes

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Abstract: A space warping method, facilitating the modeling of large-scale conformational changes in mesoscopic systems, is presented. The method uses a set of “global (or collective) coordinates” that capture overall behavior, in conjunction with the set of atomic coordinates. Application of the space warping method to energy minimization is discussed. Several simulations where the method is used to determine the energy minimizing structures of simple central force systems are analyzed. Comparing the results and behavior of the space warping method to simulations involving atomic coordinates only, it is found that the space warping method scales better with system size and also finds lower minima when the potential energy surface has multiple minima. It is shown that the transformation of $[Ala_{16}]^+$ *in vacuo* from linear to globular is captured efficiently using the space warping method.

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Introduction

Mesoscopic objects, such as macromolecules and viruses, consist of a very large number of atoms. Modeling their conformational changes using all-atom simulations is not feasible in many cases due to computational limitations. They possess a large number of degrees of freedom, making their long-time dynamics complex and difficult to capture.

The distances separating atoms in mesoscopic systems are much larger than the range of interatomic interactions. Thus, many atoms cannot interact directly but rather interact through intervening atoms. For example, an atom on one end of an elongate macromolecule consisting of 10,000 atoms needs a long time to experience the effect of the displacement of an atom at the other end of the molecule. In addition to slowing down simulations, the indirect interaction of atoms leads to the existence of a large number of minima and causes minimization algorithms to find local minima instead of the global minimum.

Another challenge in simulating mesoscopic systems is the multiple time scales characterizing their dynamics. While there are high frequency atomic oscillations, a macromolecule as a whole undergoes large-scale conformational changes. Such changes are difficult to capture because of the limitation on the time step imposed by high frequency vibrations.

Due to the great interest in large systems and long time-scale simulations, there has been a vast amount of work done to address the above problems. The three main approaches to these problems are: reduced variable methods (which will be discussed in the

following few paragraphs because our method lies in this category), multiple time-scale methods,^{1,2} and reaction path optimization.³

The most straightforward reduced variable method is the constrained dynamics approach, where certain degrees of freedom, such as those of high frequency oscillations, are eliminated,⁴ or only a limited number of degrees of freedom, such as those of torsion angles, are used.⁵ More sophisticated algorithms, such as that in ref. 6, divide the molecule into substructures that are modeled at different levels of detail and rigidity.

Normal-mode based dynamics and principal component analysis^{7–10} fall into the category of reduced variable methods as well. Here the number of degrees of freedom of a system is reduced to an “essential subspace,” where only low frequency modes of motion are retained. When these modes are obtained by diagonalizing the Hessian matrix, only small fluctuations around the minimum used to evaluate the matrix can be simulated. The modeling of far-from-equilibrium dynamics needs anharmonic modes (or principal components), which are extracted from the trajectory of the macromolecule. Thus *a priori* knowledge of the system’s trajectory is required.

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In this article, we devise a methodology that accounts for large-scale conformational changes in macromolecules but retains atomic scale detail. We address the problems mentioned above by introducing a set of global (or collective) coordinates that describe overall conformational changes. These global coordinates map every point in space to another point as dictated by the physical principles employed, such as free energy minimization. In order to retain atomic scale detail, however, the coordinates of the atoms in the macromolecule, forming a set of local coordinates, are also used. Our algorithm iterates between local and global coordinates, and is referred to hereafter as the space warping method.

The number of global coordinates in a simulation depends on the transformation used, and, in general, is much less than the total number of degrees of freedom of a mesoscopic object. As shown below, a small number of global coordinates model conformational changes efficiently given that the transformation employed is adequate for the phenomenon of interest.

Unlike other methods, such as constrained dynamics, our approach does not neglect any degrees of freedom of the system. Thus, accuracy need not be compromised for speed. Moreover, our method does not require the system to stay close to a minimum, as limited by normal mode analysis. It accounts for overall conformational changes, and there is no need for *a priori* knowledge of the trajectory, as required by principal component analysis methods.

The article is organized as follows. The general formulation of the method and its application to energy minimization are presented in the "Formulation" section. In "Results and Discussion," we discuss the results of some energy minimization simulations that use the space warping method and analyze its behavior. Concluding remarks, including other possible applications of the method, are presented in the last section.

Formulation

The Mapping

Consider the transformation:

$$\vec{r}' = \sum_n \Gamma_n \vec{f}_n(\vec{r}) \quad (1)$$

Such a transformation maps every point in space (\vec{r}) to a new point (\vec{r}'), and its flexibility depends on the choice of the number and form of the transformation functions $\vec{f}_n(\vec{r})$. The Γ_n 's form a set of global coordinates that determine the actual transformation that takes place in eq. (1).

For example, the linear mapping

$$\begin{aligned} x' &= x_{cm} + \Gamma_0^x + \Gamma_x^x(x - x_{cm}) + \Gamma_y^x(y - y_{cm}) + \Gamma_z^x(z - z_{cm}); \\ y' &= y_{cm} + \Gamma_0^y + \Gamma_x^y(x - x_{cm}) + \Gamma_y^y(y - y_{cm}) + \Gamma_z^y(z - z_{cm}); \\ z' &= z_{cm} + \Gamma_0^z + \Gamma_x^z(x - x_{cm}) + \Gamma_y^z(y - y_{cm}) + \Gamma_z^z(z - z_{cm}) \end{aligned} \quad (2)$$

allows for overall deformations such as expansion and compression, as well as translation and rotation. The Γ_0 's allow for center of mass (x_{cm} , y_{cm} , z_{cm}) translation, Γ_x^x , Γ_y^y , and Γ_z^z allow for scaling, while the rest of the Γ 's allow for rotation about the center of mass. A quadratic mapping, on the other hand, has more flexibility and freedom, allowing for twisting and bending as well.

In particular, a transformation similar to that of eq. (1) can be used to map atomic coordinates from their values at time 0 to their values at some later time t . In this case, let

$$\vec{r}_i(t) = \sum_{n=1}^{N_\Gamma} \Gamma_n(t) \vec{f}_n(\vec{r}_i^0) \quad (3)$$

where \vec{r}_i^0 is the initial position vector of atom i , $\vec{r}_i(t)$ is the position vector of atom i at time t , and N_Γ is the number of global coordinates. Thus, all of the time dependence of the atomic position vectors is in the Γ 's. The transformation functions in eq. (3) should be chosen such that invariant quantities, such as the linear and angular momenta of an isolated system, are preserved during a transformation.

To guarantee the uniqueness of the transformation from \vec{r}^0 to $\vec{r}(t)$, its Jacobian, given by

$$J = \begin{vmatrix} \sum_n \Gamma_n \frac{\partial f_n^x}{\partial x^0} & \sum_n \Gamma_n \frac{\partial f_n^x}{\partial y^0} & \sum_n \Gamma_n \frac{\partial f_n^x}{\partial z^0} \\ \sum_n \Gamma_n \frac{\partial f_n^y}{\partial x^0} & \sum_n \Gamma_n \frac{\partial f_n^y}{\partial y^0} & \sum_n \Gamma_n \frac{\partial f_n^y}{\partial z^0} \\ \sum_n \Gamma_n \frac{\partial f_n^z}{\partial x^0} & \sum_n \Gamma_n \frac{\partial f_n^z}{\partial y^0} & \sum_n \Gamma_n \frac{\partial f_n^z}{\partial z^0} \end{vmatrix} \quad (4)$$

must not pass through zero throughout simulations. Because initially $\vec{r}_i = \vec{r}_i^0$ ($i = 1, 2, \dots, N$) in all simulations, the initial value of the Jacobian is unity. Thus, the Jacobian should remain positive at all times.

For example, the Jacobian of the linear transformation given in eq. (2) must satisfy

$$J_l = \begin{vmatrix} \Gamma_x^x & \Gamma_y^x & \Gamma_z^x \\ \Gamma_x^y & \Gamma_y^y & \Gamma_z^y \\ \Gamma_x^z & \Gamma_y^z & \Gamma_z^z \end{vmatrix} > 0 \quad (5)$$

at all times. In the examples given in the Results and Discussion section, the Jacobian is evaluated numerically to check the validity of the results of the simulations discussed.

Energy Minimization

In this subsection, the global coordinates introduced in the previous section are used for energy minimization. Consider N_a atoms with position vectors $\{\vec{r}_1, \vec{r}_2, \dots, \vec{r}_{N_a}\}$ interacting via a potential energy function $U(\vec{r}_1, \vec{r}_2, \dots, \vec{r}_{N_a})$. Given a set of initial positions, the energy minimizing structure(s) of these atoms can be found by solving the set of steepest descent equations:

$$\frac{dx_i^\alpha}{dt} = -q \frac{\partial U}{\partial x_i^\alpha}, \quad i = 1, 2, \dots, N_a, \alpha = 1, 2, 3 \quad (6)$$

where t is a pseudotime variable, and does not correspond to real time. Different initial conditions will generally lead to different minima, only one of which is the global minimum. For mesoscopic systems, the potential energy surface is complex with many minima, and the numerical solution of eq. (6) may require extensive computational time.

As an alternative, we suggest finding the energy minimizing structure(s) by minimizing the energy of the system with respect to the global coordinates defined in eq. (3). The time evolution of the system is thus found by solving the set of steepest descent equations for the pseudotime evolution of the global coordinates

$$\frac{d\Gamma_n}{dt} = -q'_n \frac{\partial U}{\partial \Gamma_n} = -q'_n \sum_{i=1}^{N_r} \frac{\partial U}{\partial \vec{r}_i} \cdot \frac{\partial \vec{r}_i}{\partial \Gamma_n} = -q'_n \sum_{i=1}^{N_r} \frac{\partial U}{\partial \vec{r}_i} \cdot \hat{f}_n(\vec{r}_i^0), \quad n = 1, 2, \dots, N_\Gamma \quad (7)$$

Although the position of every atom is used in the evaluation of the forces in eq. (7), preserving some atomic scale detail, eq. (7) is a constrained minimization. The form of the transformation functions used restricts the movement of the atoms, resulting in local stresses. For example, the bending of a cylindrical molecule causes a high density of atoms near the point where the molecule bends, creating a configuration that is not energetically favorable.

To release such stresses, the space warping method iterates between minimization with respect to global coordinates and minimization with respect to local coordinates. Large-scale conformational changes are captured using global coordinates [eq. (7)], but then local stresses are released by allowing for local redistributions of atoms [using eq. (6)]. The algorithm alternates between the two sets of coordinates until the solution is obtained.

When the potential energy surface has multiple minima, the actual minimum reached not only depends on initial conditions, but also on the path taken to find the minimum. Thus, it is possible to reach different minima with different methods. In the simulations that we have done so far, the minimum reached using the space warping method is lower than that reached using local coordinates alone whenever the potential energy surface has multiple minima, as discussed in the next section.

Results and Discussion

In this section, several simulations where the space warping method is used are presented. Results and performance are compared to simulations that use local coordinates only (referred to as local-only-simulations). All simulations were performed on an IBM RS/6000 SP machine.

Simple Central Force Test Case

In the systems studied here, atoms interact via a central potential given by

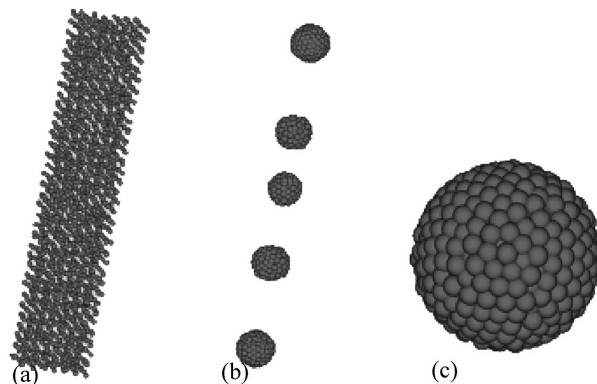


Figure 1. (a) Initial configuration of 1715 atoms. (b) Final configuration determined using local coordinates only, corresponding to a local minimum of the potential energy. (c) Final configuration reached using the space warping method, corresponding to the global minimum of the potential energy or to a minimum that is very close to it.

$$u(r) = \epsilon \left\{ \left(\frac{\sigma^2}{r^2 + \delta} \right)^3 - \left(\frac{\sigma^2}{r^2 + \delta} \right)^{3/2} \right\} \quad (8)$$

where r is the distance between any two atoms and $\delta = 0.01$ is a small number added to the denominator to prevent the potential from diverging at the origin. The parameters σ and ϵ determine the interatomic distance at which the energy has a minimum and the value of the energy at the minimum, respectively. The interaction between any two atoms is cut off at 5 Å. Final conformations shown are at zero temperature.

The transformation used in the space warping simulations discussed below is the linear mapping given by eq. (2). Such a linear transformation is sufficient to capture the overall behavior of the systems studied. The Jacobian for this transformation is evaluated in all simulations to check if it satisfies eq. (5).

Example 1: Collapse of an Elongate Aggregate

This example both illustrates the use of global coordinates in energy minimization and shows how the space warping method scales with system size. To evaluate the scaling and effectiveness of the method, four systems of different sizes (135, 625, 1715, and 6655 atoms) are simulated.

The initial configuration of all systems is rodlike, where atoms are placed on a parallelepiped lattice with some initial random noise to avoid a perfectly regular structure. Each system's evolution towards an energy minimum is simulated using local coordinates only and the space warping method. Figure 1 shows the initial configuration and the energy minimizing configurations found using the two methods for the case of 1715 atoms. The other three systems have similar initial conditions and final structures.

In all cases, the space warping method finds the global minimum or a minimum that is very close to it (because the potential used, like the van der Waals potential, has many minima of comparable energy around the global minimum^{11,12}). The minimum found with the local-only-simulation, on the other hand, is far from the global minimum.

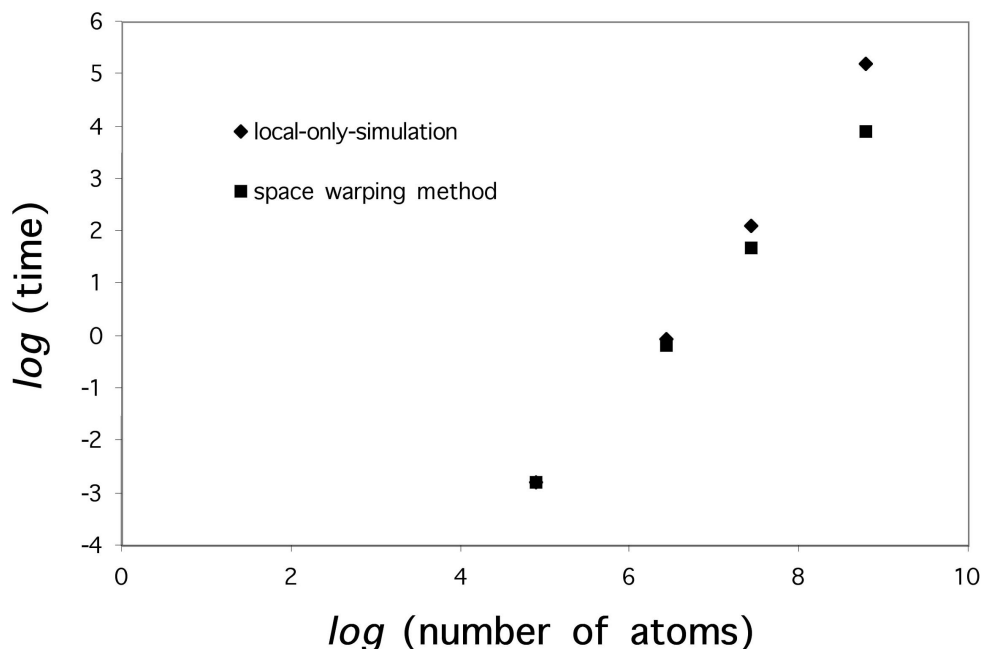


Figure 2. \log_e (simulation time) versus \log_e (number of atoms in the system) for Example 1.

Figure 2 shows the scaling of simulation time with system size. As seen from the slope of the \log_e (time) versus \log_e (number of atoms) graph, the space warping method scales better than the local-only-simulations with system size. Thus, the space warping method not only finds a lower lying minimum, but also requires less time to find it than local-only-simulations need to reach the solution they find.

In Figure 3 we present the time (as a function of system size) that the space warping method needs to reach a structure that has the same energy as that of the equilibrium structure determined with local-only-simulations. Again, the time needed by the space warping method in all cases is less than that of local-only-simulations and the algorithm scales better with the size of the system.

System energy versus number of iterations for the two largest systems studied is shown in Figure 4. Notice how the initial energy drop is much more precipitous in the space warping method simulations than in the local-only-simulations. This initially very large drop in energy is due to the large-scale conformational changes that are handled very efficiently using global coordinates. A disadvantage of van der Waals interactions, however, is that the potential energy surface is very flat around minima. Thus, the energy drop slows down significantly as the solution is approached, reducing the effectiveness of the space warping method.

In Figure 5, system energy versus number of iterations is shown for the first 30 time steps of the simulation of 6655 atoms using the space warping method. The curve illustrates the advantages of using global coordinates and the necessity to iterate between them and local coordinates. The first four dots in the curve are for the first Γ -cycle, where the energy decreases very rapidly. After that, a few local coordinate iterations are needed. In this example, four such iterations are enough to release local stresses and make the configuration ready for another cycle of global coordinates. During

the second Γ -cycle, the energy of the system drops dramatically to a much lower value. After three iterations in this cycle, the system reaches a conformation where no more large-scale conformational changes can take place. From there on, only local coordinates are needed.

To check the validity of our results, the Jacobian for the linear transformation used is monitored in all simulations. Its value as the simulation proceeds for the system of 1715 atoms is shown in Figure 6. It remains positive in this case, as well as in the other

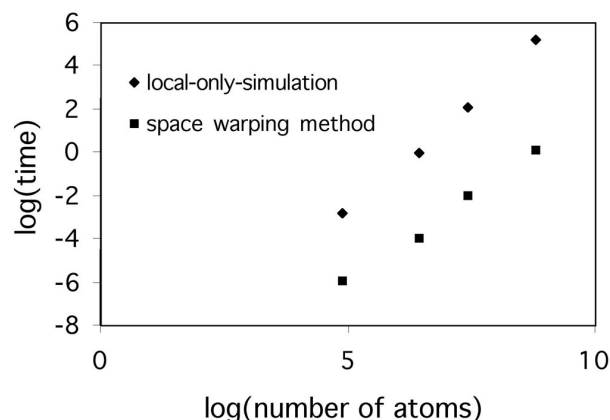


Figure 3. \log_e (t') versus \log_e (number of atoms in the system), where t' is the time the space warping method needs to reach a structure with an energy equal to the energy of the solution found in the local-only-simulation. Notice that while the energies are the same, the configurations obtained by the two simulations are different due to the different evolution paths taken.

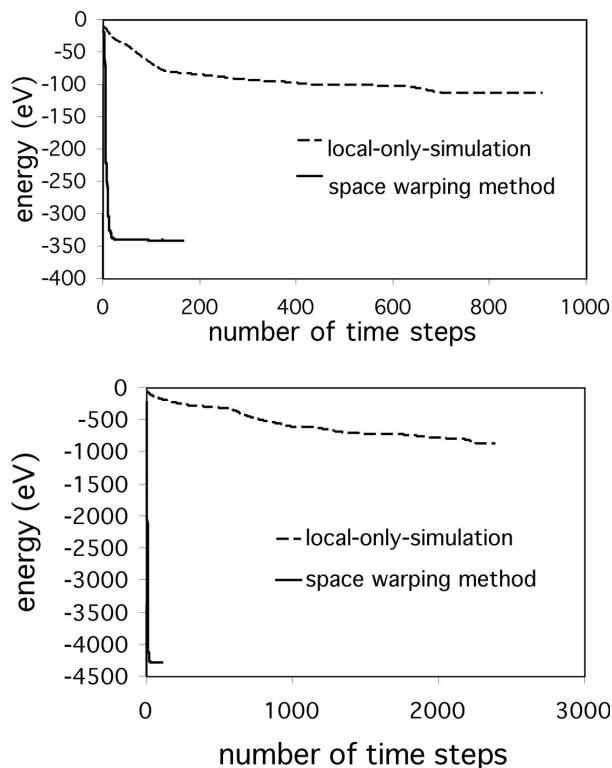


Figure 4. (a) Energy versus number of iterations for 1715 atoms. (b) Energy versus number of iterations for 6655 atoms.

systems, demonstrating the uniqueness of the mapping that takes place.

Example 2: Coalescence of Two Spheres

In this example, two spheres of 625 atoms each are placed in contact, barely touching each other. The system is evolved via a

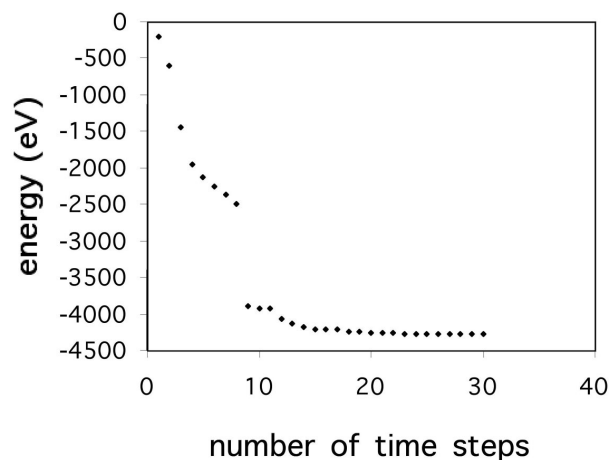


Figure 5. First 30 iterations in the simulation of 6655 atoms using the space warping method.

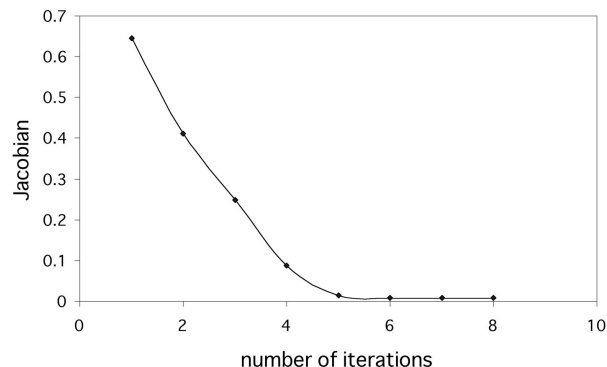


Figure 6. Jacobian versus number of iterations for the first Γ -cycle in the 1715 atom run. Its positive value throughout the cycle demonstrates the uniqueness of the mapping.

local-only-simulation as well as using the space warping method. Both simulations reach the same final spherical structure (with the same energy). The Jacobian of the transformation for the space warping method is evaluated and found to be positive at all times. While the local-only-simulation needs almost 4 h to determine the solution, the space warping method reaches it in 2.5 h only. Although the space warping method reaches the final solution in less time, this particular problem involves significant local small-scale movement, which cannot be captured by global coordinates.

The initial configuration, the intermediate conformation reached after one Γ -cycle, and the final configuration are shown in Figure 7. Notice that the global coordinates compress the system in one direction and expand it in the other two to get closer to the final spherical configuration. System energy versus number of iterations is shown in Figure 8. As in the previous example, the energy drop is more significant using the space warping method, indicating a more efficient route to the final structure.

Example 3: Sphere in an External Potential

This final example shows the simulation of the conformational evolution of a sphere placed in an external potential that has a minimum at $x = 0$ (thus favoring a planar configuration). The initial configuration of 2000 atoms, randomly placed inside a sphere, is shown in Figure 9a. The final configuration obtained, shown in Figure 9b, is a monolayer of atoms in a disk in the yz -plane. This structure is found using both the space warping method and local coordinates only. The Jacobian in the case of the

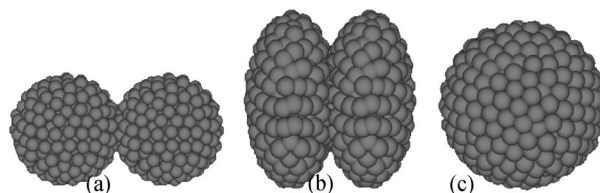


Figure 7. (a) Initial configuration of two spheres in contact. (b) Intermediate structure arrived at after one cycle of global coordinates. (c) Final spherical structure.

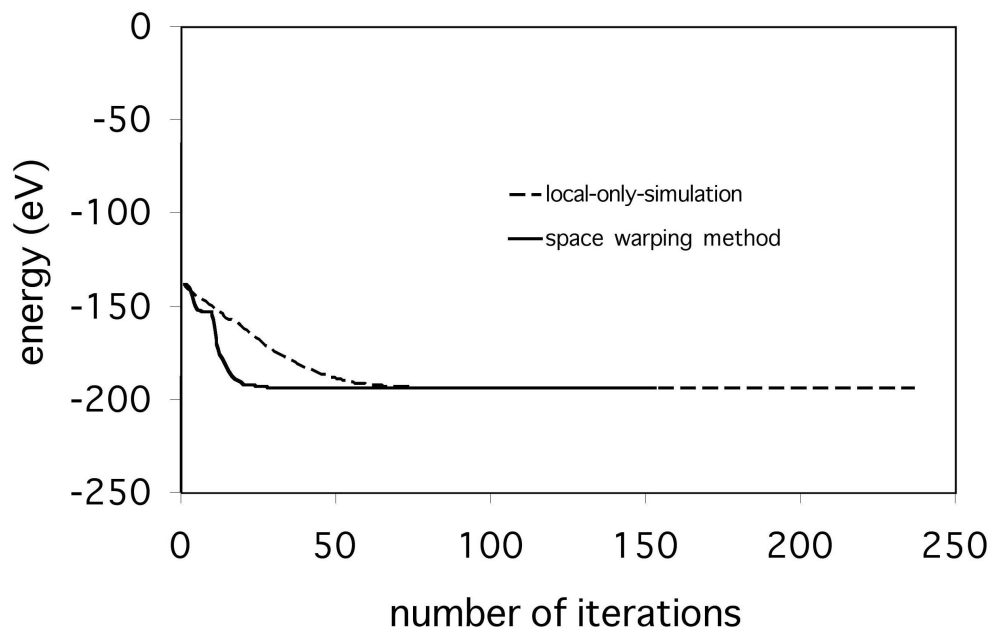


Figure 8. Energy versus number of iterations for the coalescence of two spheres.

space warping method is found to remain positive throughout the simulation.

Figure 10 shows the energy of the system as it evolves toward the minimum. Again, the energy drop is more significant using the space warping method. As for simulation time, the space warping method takes 20.5 h to determine the final configuration, while the local-only-simulation requires 34 h.

Charm22 Polyalanine In Vacuo

In this example we study $[Ala_{16}]^+$ *in vacuo*, a system that has been studied both experimentally¹³ and using molecular dynamics.¹⁴ In these studies, the polypeptide, which has an extra proton at its C-terminus, is observed to prefer a globular conformation, possibly to “solvate” the extra proton through interactions with atoms in

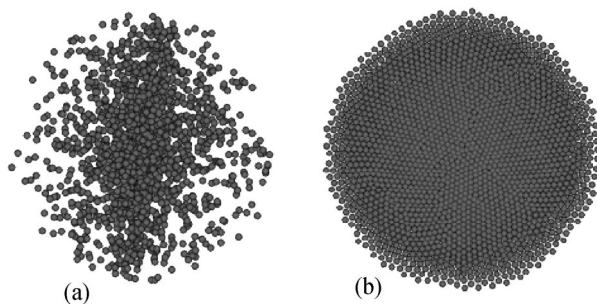


Figure 9. (a) Initial configuration of 2000 atoms placed in an external potential that has a minimum in the yz -plane (which coincides with the plane of the paper). (b) Monolayer of atoms forming the final configuration as viewed from a perspective normal to the yz -plane.

the polypeptide that have negative partial charges. The atoms in our simulation interact via the CHARMM22 force field.¹⁵

In order to overcome energy barriers and reach a low-lying minimum, the system has to be at a finite temperature, where thermal energy is introduced to the system using colored noise. At pseudo-time t , a force of the form

$$F_{\text{rand}} = \sum_{n=0}^{10} A_n \sin(\omega_n t + \phi) \quad (9)$$

where $A_n = A^*/\sqrt{n+1}$ and $\omega_n = 2n\pi/T$, is added to the CHARMM22 force acting on each degree of freedom. In the above formulas, A^* is a measure of the amplitude of the noise (which is proportional to temperature), T is the period of the fundamental mode, and ϕ is a phase assigned randomly to each degree of freedom. In the spirit of simulated annealing, A^* is reduced with time, decreasing the temperature of the system. The exponentially decaying time course of the temperature is designed such that the temperature is negligible by the time the solution is reached.

Starting with a linear configuration of the molecule, as shown in Figure 11a, the system is evolved towards an energy minimizing structure through both a local-only-simulation and a simulation that uses the space warping method. The latter involves global coordinates that correspond to a cubic mapping [which is similar to the mapping in eq. (2) but with quadratic and cubic terms included as well]. Both simulations start at the same temperature and have the same cooling rate. While the molecule stays linear in the local-only-simulation, being trapped in a high-lying minimum, the space warping method finds a globular structure with a much lower energy, as shown in Figure 11b. This structure is globular, as observed experimentally¹³ and obtained in molecular dynamics

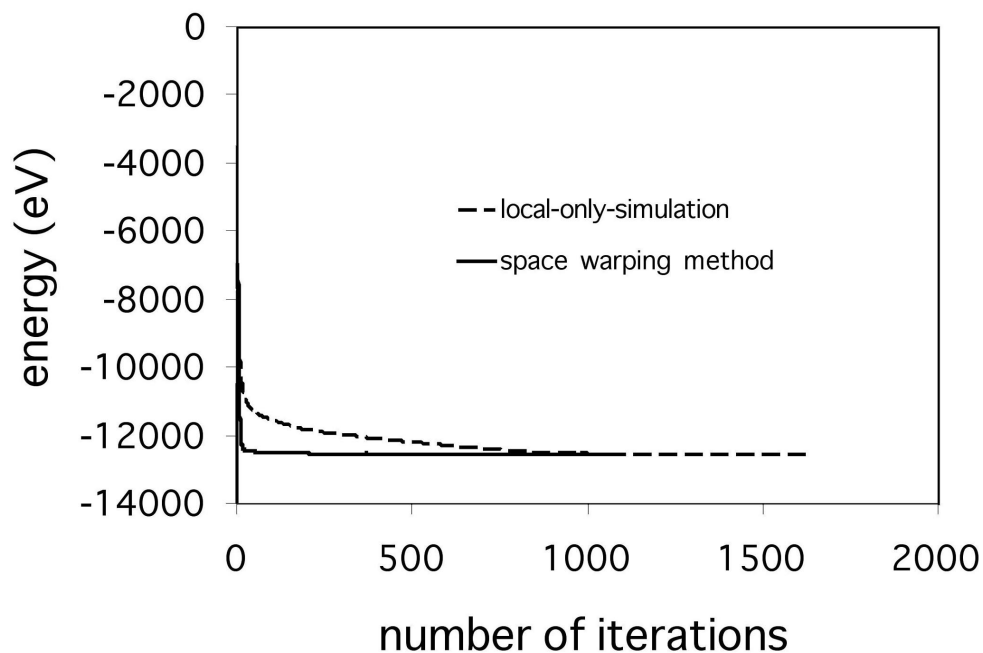


Figure 10. Energy versus number of iterations for a sphere in an external potential.

simulations,¹⁴ and its energy is within $\frac{3}{2}NkT$ of that of a typical configuration generated by molecular dynamics simulations at temperature T .¹⁶

Figure 12 shows the energy of the polypeptide as a function of the number of time steps. Every time step indicated on the x -axis

in the graph corresponds to 50 time steps for the run using the space warping method, and 500 time steps for the local-only-simulation. Notice that the energy of the system, in both cases, initially goes up (due to thermal energy), indicating that the molecule is being kicked out of the basin of attraction of a local

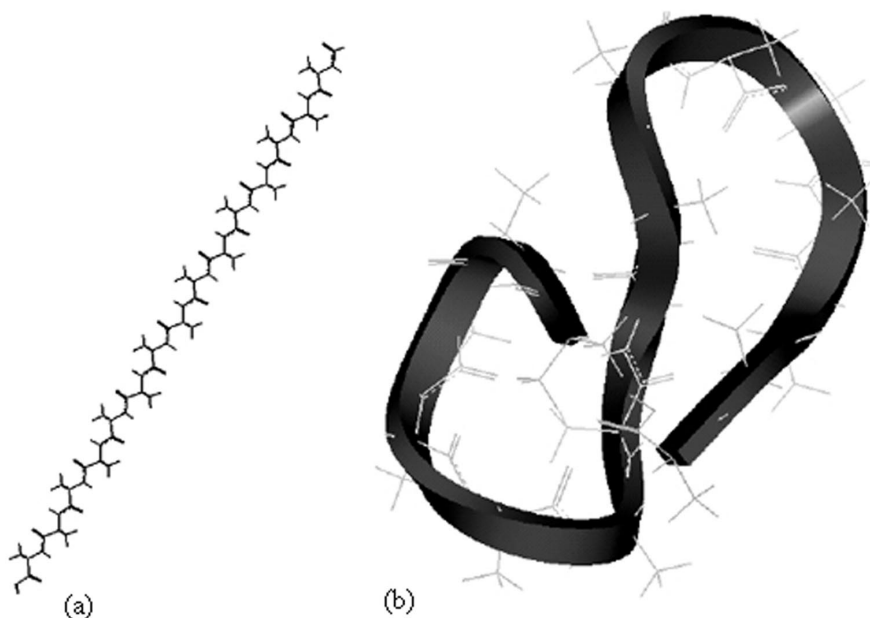


Figure 11. (a) Initial linear configuration of $[Ala_{16}]^+$. System is at a finite temperature. (b) Energy minimizing conformation of $[Ala_{16}]^+$ found using the space warping method. The final globular configuration is at zero temperature.

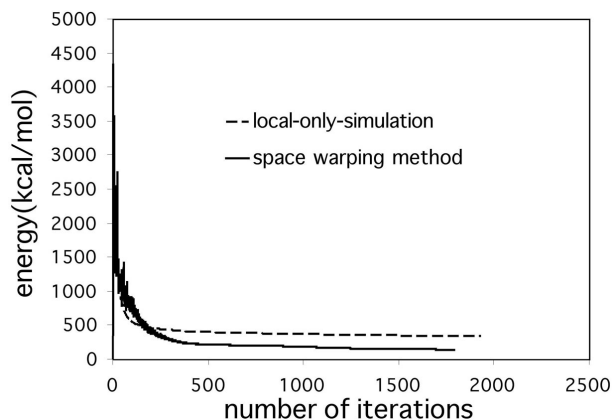


Figure 12. Energy (kcal/mol) of $[Ala_{16}]^+$ versus number of time steps for local-only-simulation and space warping method. Every time step on the x -axis corresponds to 500 in the local-only-simulation, and to 50 in the space warping method.

minimum. However, while the initial temperature and subsequent cooling allow the space warping method to find a low-lying minimum, the molecule in the local-only simulation is trapped in a high-energy local minimum. The local-only-simulation probably needs a much higher initial temperature with a slower cooling rate to find a comparable minimum.

In addition to finding a much lower minimum, the space warping method takes only 3 h to reach this minimum. The local-only-simulation, on the other hand, needs much more CPU time (1 day vs. 3 h in this case). Given the scaling of the space warping method with system size, it is expected that its efficiency and superiority over direct local energy minimization will be even more pronounced for larger polypeptides and proteins. It should be mentioned that we do not yet fully understand the “colored noise” method used to simulate fluctuating thermal forces and the significance of its various parameters and their interplay. We believe that additional insight into its behavior will improve the efficiency of our energy minimization algorithm.

Conclusion

The examples discussed above show that the space warping method is efficient in simulating large-scale conformational changes in macromolecules driven by energy minimization. The method reduces simulation time and scales better than local-only-simulations with system size for the test cases performed. For potential energy surfaces of complex topography, the minima it finds have lower energies than those of minima attained through our local-only-simulations.

An interesting application of the method in the context of energy minimization is to the spanning of potential energy landscapes. Different transformations possess different symmetries and thus might lead to different minima, even when the same initial

configuration is chosen. Thus, the space warping method is useful for finding structures of the same molecule with significantly different morphologies. With the addition of thermal noise, barriers in the potential energy surface are overcome and the space warping method thereby facilitates the search for global minima.

Another application of global coordinates is in molecular dynamics. In this case, Newton’s equations of motion are the starting point for developing time evolution equations for the global coordinates. Small-scale vibrations of atoms are superimposed on the large-scale dynamics of the macromolecule as a whole that is captured by global coordinates. Because the fluctuating forces causing these small-scale atomic vibrations are much weaker than the forces driving the overall dynamics, their effect is included in the Γ equations of motion as a harmonic perturbation. Averaging these forces over all possible small-scale oscillations, we obtain global coordinate dynamics that are renormalized by small-scale atomic vibrations.¹⁷

The space warping method discussed in this article is very general and flexible. Different transformation functions can be used for different systems, optimizing the method’s efficiency in capturing their overall behavior, whether it is used for energy minimization or molecular dynamics. A few global coordinates (\ll number of degrees of freedom of the system) are able to simulate large-scale conformational changes in large systems, a task that is not computationally feasible with most current methods.

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