A PENALTY FUNCTION METHOD FOR CONSTRAINED MOLECULAR DYNAMICS SIMULATION

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Abstract. We propose a penalty-function method for constrained molecular dynamics simulation by defining a quadratic penalty function for the constraints. The simulation with such a method can be done by using a conventional, unconstrained solver only with the penalty parameter increased in an appropriate manner as the simulation proceeds. More specifically, we scale the constraints with their force constants when forming the penalty terms. The resulting force function can then be viewed as a smooth continuation of the original force field as the penalty parameter increases. The penalty function method is easy to implement and costs less than a Lagrange multiplier method, which requires the solution of a nonlinear system of equations in every time step. We have first implemented a penalty function method in CHARMM and applied it to protein Bovine Pancreatic Trypsin Inhibitor (BPTI). We compared the simulation results with Verlet and Shake, and found that the penalty function method had high correlations with Shake and outperformed Verlet. In particular, the RMSD fluctuations of backbone and non-backbone atoms and the velocity auto correlations of C_α atoms of the protein calculated by the penalty function method agreed well with those by Shake. We have also tested the method on a group of argon clusters constrained with a set of inter-atomic distances in their global energy minimum states. The results showed that the method was able to impose the constraints effectively and the clusters tended to converge to their energy minima more rapidly than not confined by the constraints.

Key Words. Constrained molecular dynamics, Verlet algorithm, Shake algorithm, Lagrange multipliers method, penalty function method.

1. Introduction

Molecular dynamics simulation can be used to study many different dynamic properties of proteins, but a long sequence of iterations has to be carried out even for small protein motions due to the small time step (1.0e-15sec) required [23]. The bonding forces are among those causing fast protein vibrations that require small time steps to integrate, but they may be replaced by a set of bond length constraints, to increase the step size and hence the simulation speed [12]. Several Lagrange multiplier types of methods have been developed for constrained molecular dynamics simulation. However, in all these methods, the multipliers have to

be determined in every time step by solving a nonlinear system of equations so that the new iterate can satisfy the constraints [3]. Depending on the number of constraints, the additional computational cost can be large, given the fact that the force field calculation in every time step is at most $O(n^2)$, while the solution of the nonlinear system of equations may require $O(m^3)$, where n is the number of particles in the system and m the number of constraints.

In this paper, we propose a so-called penalty function method [18] for constrained molecular dynamics. In this method, a special function is defined so that the function is minimized if the constraints are satisfied. By adding such a function in the potential energy function, the constraints can then be removed from the system, and the simulation can be carried out in a conventional, unconstrained manner. The advantage of using a penalty function method is that it is easy to implement, and does not require solving a nonlinear system of equations in every time step. The disadvantage of the method is that the penalty parameter, i.e., the parameter used to scale the penalty function, is hard to control and in principle, needs to be large enough for the penalty function to be truly effective, which on the other hand, may cause numerical instabilities when used in simulation [10]. It may also arguably be a disadvantage that the penalty function method only forces the constraints to be satisfied approximately but not completely. In any case, the method may possibly be used as an alternatively and computationally more efficient approach for constrained molecular dynamics simulation than the Lagrange multiplier types of methods.

We have first implemented a penalty function method in CHARMM [7] and tested it on protein Bovine Pancreatic Trypsin Inhibitor (BPTI) by following a similar experiment done by Gunsteren and Karplus in [12] for the Shake algorithm [22]. In this implementation, we removed the bond length potentials from the potential energy function and introduced the corresponding bond length constraints. For each of the bond length constraints, we constructed a quadratic penalty function and inserted it into the potential energy function. For each different type of bond, we also scaled the corresponding penalty function with the force constant of the bond so that the resulting function had the same form as the original bond length potential if without multiplied by the penalty parameter. In this way, the resulting force field becomes simply a continuation of the original force field as the penalty parameter changes continuously from 1 to a value > 1. We conducted a simulation on BPTI with the penalty function method, and compared the results with Verlet and Shake, and found that the penalty function method had a high correlation with the Shake and outperformed the Verlet. In particular, the root-mean-square-deviations (RMSD) of the backbone and non-backbone atoms and the velocity auto correlations of the C_α atoms of the protein calculated by the penalty function method agreed well with those by Shake. Note again that the penalty function method requires no more than just applying a conventional, unconstrained simulation algorithm such as the Verlet algorithm to the potential energy function expanded with additional penalty terms for the bond length constraints.

We have also tested the penalty function method on a group of argon clusters with the equilibrium distances for a selected set of molecular pairs as the constraints. Here by the equilibrium distances we mean the distances for the pairs of argon molecules when the clusters are in their global energy minimal states. We generated these distances by using the global energy minimal configuration of the clusters published in previous studies [19]. A penalty function was constructed for each of the constraints and incorporated into the potential energy function of the cluster. The simulation was then conducted by using a conventional, unconstrained