

SOME MULTIPLE-TIME-SCALE PROBLEMS IN MOLECULAR DYNAMICS

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Abstract: Many physical problems, particularly in chemical and biological systems, involve processes that occur over widely varying time scales. Such problems have motivated the development of new methods for treating multiple-time-scale problems in molecular dynamics (MD). Methods have been developed for determining the vibrational frequencies and normal modes of large systems in full and reduced conformational space. A method is given for quasiharmonic analysis and reduced quasiharmonic analysis.

Key Words: Molecular Dynamics Simulation, Normal Mode Analysis, Quasiharmonic Analysis, Hamiltonian Systems, Symplectic Integration Methods

INTRODUCTION

Molecular dynamics (MD) simulation and harmonic analysis are among the main theoretical methods of investigation of the dynamic properties of biological macromolecules, such as proteins. MD simulation is a technique in which the classical equation of motion for all the atoms of a molecule is integrated over a finite period of time. The resulting trajectory is used to compute the time-dependent properties of the system. Harmonic analysis is a direct way of analyzing vibrational motions. The harmonicity of the potential function is a basic assumption in the normal mode approximation used in harmonic analysis. This is known to be inadequate in the case of proteins, because anharmonic effects, which MD has shown to be important in protein motion, are neglected. When anharmonic effects are incorporated, quasi harmonic analysis may be applied. In this method, MD simulation is used to obtain effective modes of vibration from the atomic fluctuations about an average structure. These modes include the anharmonic effects neglected in a normal mode calculation [1-3]. Harmonic analysis also proved useful in developing an efficient Split Integration Symplectic Method (SISM) for MD simulation employing an order of magnitude longer time step than can be used by other methods of the same order and complexity. The technique, derived in terms of the Lie algebraic language, is based on the splitting of the total Hamiltonian of the system into two parts, each of which can either be solved exactly or more conveniently than by using

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standard methods. The individual solutions are then combined in such a way as to approximate the evolution of the original equation for a time step, and to minimize errors. The SISM has been tested on a variety of examples. In all cases the SISM possess long term stability and the ability to take larger time steps [4, 5]. What we present here is a description of the various techniques to perform harmonic analysis of large systems.

MATERIALS AND METHODS

The steps involved in normal mode determination procedure and analysis can be summarized as follows:

- (a) Select an appropriate model and parameters which define the potential surface.
- (b) Starting from the crystal structure, minimize to find a new structure that is near the crystal structure that has a small energy gradient.
- (c) Generate the second derivative matrix of the energy with respect to Cartesian displacements (in compressed form).
- (d) The eigenvector equation is set up for solution with a method adapted for large systems.
- (e) All eigenvalues and desired eigenvectors are found by matrix diagonalization.
- (f) Optionally, refine the computed eigenvalues and eigenvectors by processing through the original second derivative matrix.
- (g) Analyze the normal modes and frequencies, i.e. process the results.

Reduced basis normal mode analysis techniques allow the study of motions of interest in the harmonic limit. The reduction of the problem can be viewed as either the removal of unwanted motion through the use of constraints, or as the inclusion of desired motion.

Quasiharmonic analysis is a method for obtaining effective modes of vibration from fluctuations calculated by an MD simulation. The underlying principle is that an effective force field can be calculated from atomic fluctuations relative to the average dynamic structure that yields the same fluctuation matrix as that obtained from a normal mode calculation. Because the fluctuation matrix is inversely proportional to the effective force constant matrix, they have common eigenvectors corresponding to the quasiharmonic modes of vibration. They may or may not be similar to the normal modes, since anharmonic effects are implicitly included. Quasiharmonic modes can be analyzed in the same way as normal modes and the comparison of the results with those from harmonic approximation calculations for the same system is straightforward.

Reduced basis quasiharmonic analysis represents a way of studying modes of vibration from dynamic fluctuations for problems of a large size. The method presented is similar to reduced basis normal mode analysis with the important

difference that in the reduced basis quasiharmonic calculation there is no Hessian; instead there is a fluctuation (covariance) matrix.

RESULTS AND DISCUSSION

The modes presented here include the lowest modes of Bovine Pancreatic Trypsin Inhibitor (BPTI). BPTI, a small globular protein which consists of 58 amino acids, is the most widely used "test case" for normal mode calculations, and it plays the role of the "hydrogen atom" of protein dynamics.

Figure 1 displays a blueprint of the procedures used for performing harmonic analysis of large systems, in particular, proteins. This schematism is for the protein BPTI and was done with the CHARMM Program [6]. The starting point for the calculations was to begin with known X-ray coordinates. All heavy atoms and all polar hydrogens are explicitly represented. Nonpolar hydrogens are expressed in an extended atom representation.

Several methods for performing large-scale harmonic analysis for the minimized X-ray structure of BPTI were employed to obtain vibrational frequencies and normal modes of vibration in full and on a reduced basis. Different truncation schemes – shift, switch, and no cutoff – were used to truncate nonbonding interactions, and two different dielectric constants – rdie and cdie – were employed to examine the effects of the electrostatic interactions. Additionally, the effect of different parameter sets used for calculation of the potential function was examined.

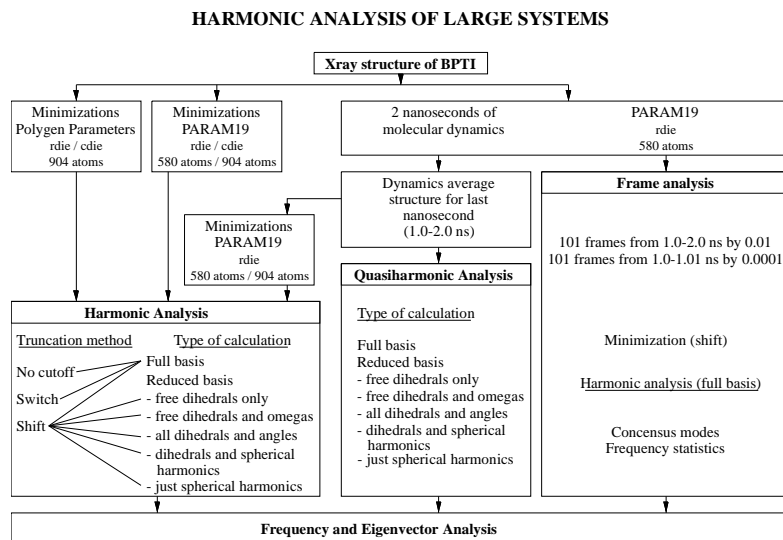


Fig.1 Schematism of procedures for performing harmonic analysis of large systems.

A two-nanosecond MD simulation of BPTI, starting from the energy minimized X-ray structure, was carried out using the polar hydrogen atom model in a pseudovacuum in a constant energy ensemble at room temperature. From the last nanosecond of the MD simulation, where there were no major structural changes, the average structure of BPTI was determined.

The use of a single molecular system and a consistent Hamiltonian allowed the direct comparison of the results from all the presented methods. From this comparison, insight into the details of the interplay between harmonic and anharmonic motion could be obtained.

For this model of BPTI, at 300 K, only 42% of the behavior was attributed to harmonic motion, and 58% was attributed to substate jumping and other anharmonic motion. This may indicate that normal mode analysis is incomplete for the comprehensive examination of protein behavior. However, normal mode analysis is known to be important in the dynamics of large systems because, through the combination of methods, it provides an insight into the dynamics and flexibility of large molecular systems.

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