INTERNATIONAL JOURNAL OF
NUMERICAL ANALYSIS AND MODELING
Volume 10, Number 4, Pages 920–942

THE SOLUTION OF THE BOUNDARY-VALUE PROBLEMS FOR THE SIMULATION OF TRANSITION OF PROTEIN CONFORMATION

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Abstract. Under certain kinetic or thermodynamic conditions, proteins make large conformational changes, formally called state transitions, resulting in significant changes in their chemical or biological functions. These dynamic properties of proteins can be studied through molecular dynamics simulation. However, in contrast to conventional dynamics simulation protocols where an initial-value problem is solved, the simulation of transition of protein conformation can be done by solving a boundary-value problem, with the beginning and ending states of the protein as the boundary conditions. While a boundary-value problem is generally more difficult to solve, it provides a more realistic model for transition of protein conformation and has certain computational advantages as well, especially for long-time simulations. Here we study the solution of the boundary-value problems for the simulation of transition of protein conformation using a standard class of numerical methods called the multiple shooting methods. We describe the methods and discuss the issues related to their implementations for our specific applications, including the definition of the boundary conditions, the formation of the initial trajectories, and the convergence of the solutions. We present the results from using the multiple shooting methods for the study of the conformational transition of a small molecular cluster and an alanine dipeptide, and show the potential extension of the methods to larger biomolecular systems.

Key words. Macromolecular modeling, protein folding and misfolding, molecular dynamics simulation, initial-value problems, boundary-value problems, finite difference methods, multiple shooting methods

1. Introduction

Under certain kinetic or thermodynamic conditions, proteins make large conformational changes, formally called state transitions, resulting in significant changes in their chemical or biological functions. Of various types, protein folding or misfolding may be those of the most important conformational transitions of proteins. Folding accounts for the whole process of a one-dimensional polypeptide chain folding into a stable three-dimensional protein. The process can be considered as the protein making a conformational transition, or a series of conformational transitions, from an arbitrary state to its native state [36]. Instead, misfolding, as the word implies, is a process that the protein folds to a nonnative state, either from an arbitrary state or its native state. Proper folding is necessary for a protein to assume its normal function, while misfolding often leads to an abnormal protein. The latter could alter the normal behaviors of a biological system and cause complex diseases [32].

The dynamic properties of proteins can be studied through molecular dynamics simulation. A conventional molecular dynamics simulation protocol solves an initial-value problem for the equation of motion defined for the molecule, with the positions and velocities of the atoms in the molecule as the initial conditions

Received by the editors May 2, 2012.
2000 *Mathematics Subject Classification.* 65K10, 65L05, 65L10, 65L80, 90C30, 92B05.
This research was supported partially by the NIH/NIGMS grant R01GM081680 and the Institute of Mathematics and Its Applications with funds provided by the NSF of America.

[38]. Such a procedure can be used to track protein conformational transitions, but the simulation has to be carried out for a very long time to make it possible for the expected transition to occur. Alternatively, the conformational transition of a molecule can be formulated more naturally as a boundary-value problem, with the beginning and ending positions of the atoms in the molecule as the boundary conditions. This latter approach has been adopted by several research groups [35, 16, 4, 8, 20]. However, an accurate solution to the boundary-value problem has not been fully developed.

In this paper, we study the solution of the boundary-value problems for the simulation of transition of protein conformation using a standard class of numerical methods called the multiple shooting methods. We describe the methods and discuss the issues related to their implementations for our specific applications, including the definition of the boundary conditions, the formation of the initial trajectories, and the convergence of the solutions. We present the results from using the multiple shooting methods for the study of the conformational transition of a small molecular cluster and an alanine dipeptide, and show the potential extension of the methods to larger biomolecular systems.

2. Classical Simulation

A protein is composed of a sequence of amino acids. The neighboring amino acids in the sequence are connected by strong chemical bonds and form an amino acid chain called a polypeptide. The polypeptide chain, once generated in the cell, quickly folds into a three dimensional structure and then becomes a live and functional protein (see Figure 1). The folding of a protein has been one of the most fundamental yet challenging scientific problems in the past several decades. Today, it is still unclear why and how a given sequence of amino acids can fold into a specific three dimensional protein, and it is still not possible to predict the folding pathway and the folded structure for an arbitrarily given protein [9, 30].

A protein may misfold to a "wrong" structure and lose its normal function. This may happen when the folding process makes a "wrong" turn or the native structure unfolds to another structure under certain conditions [14, 37]. The study of protein misfolding is as difficult as the study of protein folding. Many important diseases are in fact caused by or related to protein misfolding. For example, the well-known mad cow disease is believed to be the result of the misfolding of the prion protein, which damages the neuron cells in the brain [1, 32] (see Figure 2).

Both folding and misfolding can be viewed as special types of conformational transitions: During folding, a protein changes its conformation from an initial state to the native state. During misfolding, a protein makes a conformational transition from an initial (and perhaps the native) state to a misfolded state. In either case, the process can be considered as a transition of protein conformation between two conformational states. Without loss of generality, we assume that the two states correspond to two energy minima of the protein. Then, the problem of finding a folding or misfolding pathway is to find a conformational trajectory from one energy minimum to another in the protein conformational space.

A protein conformation (or structure) is difficult to determine experimentally. The tracking of a conformational trajectory is certainly even harder. Theoretically, it may be approached through molecular dynamics simulation, which basically tries to follow the conformational changes along the trajectory based on the known physical interactions in the protein. Mathematically, a system of equations, defined by the Newton's Second Law of Motion for the atoms in the protein, needs to be