CONSTRAINED LANGEVIN DYNAMICS OF POLYPEPTIDE CHAINS

Niels Grønbech-Jensen\(^1\) and Sebastian Doniach

Department of Applied Physics, Stanford University
Stanford, California 94305

Abstract

We have developed an algorithm to compute the trajectory of a polypeptide moving under Langevin Dynamics which incorporates constraints that conserve the the planar geometry of the peptide bonds. We show that for overdamped dynamics the constraints can be implemented at each time step by inversion of a banded matrix. This inversion is computationally very efficient. The forces which are included are those due to the non-bonding interactions between the amino acid atoms, with water put in by a simple dielectric function model. The method can easily be generalized to incorporate explicit water. Because the non-bonding forces are 2-3 orders of magnitude weaker than the bonding forces, we find that the algorithm is stable with time steps on the scale of a thousand times longer than those needed for molecular dynamics simulations. We have tested out the algorithm on simple poly-alanine examples, with extensive runs on 20-alanine. We observe that poly-alanine has rather long-lived meta-stable configurations with partial beta sheet conformations which can live many hundreds of nano-seconds.

1. Introduction

A central problem of the computer simulation of the dynamics of bio-molecules is that of the enormous range of time scales which need to be encompassed. Atomic vibrations occur on sub-pico second time scales while large changes of conformation of even relatively small proteins have time scales ranging anywhere from micro-seconds to seconds.

One approach to overcome some of these problems which has been discussed by a number of authors in the past [1, 2] is to eliminate the very rapid time scales of atomic vibrations by replacing Newtonian dynamics with Langevin dynamics in which the high frequency part of the motion is simply replaced by a noise term with an accompanying friction constant determined by the fluctuation-dissipation theorem. In this work, we have added an additional simplifying step by formulating the dynamics in such a way as to conserve the geometry of the basic peptide bonds in a polypeptide chain, thereby constraining the allowed motion to that of the \(\phi\) and \(\psi\) angles.
\( \psi \) angles at the \( C_\alpha \) hinge points. The formulation is, however, done purely in terms of cartesian coordinates for the individual atoms, with the constraints being put in by a set of forces which orthogonalize the total forces acting on each atom to the constraint directions.

A number of researchers have shown that the slow modes in proteins tend to be overamped [3, 4, 5]. By confining ourselves to over damped Langevin dynamics, we can show that the constraint relations become a set of linear simultaneous equations which we solve at each time step. This is in contrast to the SHAKE algorithm for the application of constraints to under-damped motion in which the presence of the second order acceleration term means that the constraints can only be applied iteratively [6]. We are able to show that the over damped Langevin dynamics can be computed very effectively by inverting a banded matrix at each time step of the simulation. A detailed account of this work may be found in ref [7].

2. Formulation of the Algorithm

Our basic Langevin dynamic equations can be written in the form

\[
\Gamma \frac{d\mathbf{X}}{dt} = -\nabla E + \mathbf{N} + \mathbf{S} \Rightarrow \\
\frac{d\mathbf{X}}{dt} = \Gamma^{-1}\{-\nabla E + \mathbf{N} + \mathbf{S}\}
\]

where \( \mathbf{X} = (x_1, x_2, \ldots, x_n) \) is the cartesian position vector of the atomic coordinates. \( E \) represents the non–convalently bonding forces between the atoms of the peptide. In our initial studies, we do not include the effects of water and simulate these in a very approximate way by means of a dielectric screening function [see below]. \( \Gamma \) represents the friction matrix acting on the individual atoms of the peptide. In general, this will include hydrodynamic effects through the Oseen tensor which will produce frictional correlations between different atoms. In the simplest approach, we replace this by a diagonal matrix \( \Gamma_{ij} = \gamma \delta_{ij} \) in which \( \gamma \) is the friction constant. \( \mathbf{N} \) is a noise-source and \( \mathbf{S} \) represents the constraining forces.

The way the constraints are implemented, which is derived by generalizing the approach of Deutsch and Madden ([8]) is as follows: at each time step of the algorithm the total force on each atom resulting from the non–bonding interactions plus noise is computed. Then, that component of the force which will tend to alter a set of constrained bond lengths is projected out analytically through the constraint forces \( \mathbf{S} \). Angle constraints are put in by combining a number of distance constraints, and planar constraints are implemented using dummy atoms located above the plane. If \( r_{ij} = |\mathbf{x}_i - \mathbf{x}_j| \) is a constrained distance, then by differentiating this with respect to time and inserting Eq. (1) we get:

\[
(\mathbf{x}_k - \mathbf{x}_l) \cdot (\dot{\mathbf{x}}_k - \dot{\mathbf{x}}_l) = 0 \Rightarrow \\
(\mathbf{x}_i - \mathbf{x}_j) \cdot \sum_{ij} \tilde{s}_{ij} = -(\mathbf{x}_i - \mathbf{x}_j) \cdot \sum_j (-\nabla_j E + \tilde{n}_j)
\]

where we have used the simplest possible diagonal friction matrix. Given the positions of the atoms, we can now determine the constraint forces given by \( s_{ij} \). This is done by solving the above set of \( q \) linear equations (Eq. (2)), where \( q \) is the number of constraints in the system. The only \( s_{ij}'s \) are for those \( q \) pairs of atoms for which the distance \( \mathbf{x}_i - \mathbf{x}_j \) is constrained to a given value. Thus the number of non-zero off-diagonal elements on one side of the diagonal of this constraint matrix corresponds to the number of constraints. In the case of poly-alanine, the peptide bond geometry