SimBioMa

Short Visit Scientific Report
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This report is a description of the advancements made during a three-day visit with Giovanni Ciccotti at the University of Rome “La Sapienza”.

The general aim of the short visit was to gain familiarity with each others' work to the extent that we can determine constructive overlap. In collaboration with Christopher Lowe at Universiteit van Amsterdam, I have developed a collection of numerical recipes to calculate constraint forces in molecular dynamics simulations. Prof. Ciccotti is one of the vanguards of the SHAKE method for constrained MD [1], still used thirty years after its development. Furthermore, research in the Ciccotti group retains a focus on constraints. Therefore, the short visit granted us the opportunity to discuss the relationship between our research interests and productive developments in the field.

The specific algorithm developed by Christopher Lowe, Adrian Sutton and myself is MILC SHAKE (Matrix Inverted Linearized Constraints SHAKE) [2], a numerical recipe for calculating constraint forces that exploits the connectivity of the system. When 'bonds' – or, mesoscopic connections when the application is an elastic filament – are connected to at most two nearest neighbors, we refer to the geometry as linear. Systems having this morphology include mesoscopic filaments discretized into many beads, mesoscopic models for polymers, and linear alkanes using the United Atom Model, to name a few. When this geometry is present, the constraint forces can be calculated very quickly using simplified Newton iteration. The most costly step – solving a set of linear equations – is drastically reduced when the geometry is linear because the resultant matrix is tridiagonal, which can be solved efficiently at an order linear cost.

The agenda during the visit focused on two things: the generalization of MILC SHAKE and the combination of constraints and hydrodynamic forces. Although MILC SHAKE is very fast for a linear geometry, nature is frequently not linear. With Christopher Lowe, a few approaches to explore the application of MILC SHAKE to more complicated molecules was explored with great success. The variation of the algorithm was successfully applied to the bile salt taurochenodeoxycholate, a geometry with a four-membered ring, and integrated into Espresso simulation package. The generalized algorithm is essentially MILC SHAKE with one additional step: immediately before one uses a tridiagonal matrix solver during the iterative procedure using simplified Newton iteration, Gaussian elimination is first used to shift the Jacobian into tridiagonal form for a geometry which is not linear. The algorithm then proceeds as normal. Application to various morphologies was discussed, in addition to the possibility of parallelizing our method. Based on preliminary discussions we believe the parallelization should be straightforward.

The second part of the agenda addressed combining constraints and hydrodynamics in a consistent velocity Verlet integration scheme for a model of a mesoscopic elastic filament. The particular form of the fluid force used is Oseen hydrodynamics [3], where the hydrodynamic force is a function of the local filament velocity and the forces acting on each part of the filament (which are used to estimate the local fluid velocity, assuming the fluid is initially at rest). The force is therefore a function of the filament velocity. A modified molecular dynamics integration scheme using Trotter factorization of the Liouville propagator is used to deal with the linear dependence of the local filament velocity.

One unforeseen numerical hurdle involves the form of the force to be inserted into the calculation to estimate the local fluid velocity. The insertion of the SHAKE approximation to the force – known to be a factor on the order of the size of the time step different from the analytical value of the force – leads to the system falling into a numerical trough for the important scenario of

a stiff filament being pushed on one end. The aphysical results from this scenario include constraint forces which differ by more than O(*dt*) from the analytical form of the constraint force (although the constraints are still satisfied throughout the simulation). This may be a pathological example, but it is an important one. The only theoretical results available are in the limit that the fiber experiences very little deformation and for simple scenarios such as a filament moving parallel or perpendicular to its axis until a steady state is reached, the scenario discussed here. The average friction coefficients can then be calculated as a function of the slenderness of the rod. To get around what appears to be a purely numerical problem, the analytical form of the constraint force is inserted into the hydrodynamic force calculation, instead of the SHAKE approximation to the constraint force. The result is numerical stability and physically realistic results.

The initial analytical form used neglected a term dependent upon the square of the relative velocity between two bonded sites. The neglect of this term was justified because only the steady-state configuration and only examples in the limit of negligible deformation were considered, rendering this velocity-dependent term inconsequential. Currently, we would like to apply the model to simulations with complicated energy landscapes (e.g. flagellar motion) where it is possible that this term plays a consequential role. During our visit, we established how to include the velocity term explicitly, using the same methodology used to incorporate a force term linearly proportional to the velocity by using the Trotter factorization of the Liouville propagator.

There are two post-visit tasks that I intend to pursue. The first is to methodically investigate the generalization and parallelization of MILC SHAKE, which we agreed would be a worthwhile body of work whose results, if successful, would form the basis of a nice publication resulting from the short visit grant. The second task is to look into incorporating the velocity squared term into a consistent integration scheme for the mesoscopic filament model, if it indeed cannot be avoided.

1. J.-P. Ryckaert, G. Ciccotti and H.J.C. Berendsen, Numerical integration of the cartesian equations of motion of a system with constraints: molecular dynamics of *n*-alkanes, *J. Comput. Phys.* **23** (1977), pp. 327–341.
2. A.G. Bailey, C.P. Lowe, and A.P. Sutton, Efficient constraint dynamics using MILC SHAKE, *J. Comput. Phys.* **227** (2008), pp. 8949-8959.
3. M.C. Lagomarsino, I. Pagonabarraga and C.P. Lowe, Hydrodynamic induced deformation and orientation of a microscopic elastic filament, *Phys. Rev. Lett.* **94** (2005), p. 148104.