An Adaptive Multiscale Method for Biomolecular Systems

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Multiscale simulations combine phenomena at various length and time scales and often suffer from reduced numerical precision and integration times dictated by the smallest phenomena modeled. For example, investigators interested in folding patterns of biopolymers may require micro- or milliseconds worth of data, but these phenomena are often driven by even smaller pico- and nanosecond dynamics [1]. A full resolution atomistic model would require small integration steps, often on the order of femtoseconds, to fully capture the "natural" motion of the modeled bodies.

Multiscale modeling methods attempt to address this problem through various approaches: static and dynamic coarse graining [2, 3], serial methods [4], and concurrent methods [5]. The goal of these methods is a reduction in the computation time needed to generate time evolutions. This reduction is achieved by either increasing integration step size or reducing the cost of the forward dynamics.

Our prior works have presented a multiscale method for the continuum regime that allows for bodies at various scales to be modeled together but defined and integrated at the larger scale [6, 7, 8]. A key component of this method is the identification of large active and dissipative forces responsible for high frequency behavior but are not significant contributors to overall response. These forces are eliminated from the dynamics using a scaling factor a_2, allowing resultant accelerations to be significantly smaller. Application of this multiscale method leads to the scaled equation of motion for the general multibody case:

$$M(\mathbf{q})\,\ddot{\mathbf{q}} + C(\dot{\mathbf{q}},\mathbf{q}) + a_2\,\beta\,D(\mathbf{q})\,\dot{\mathbf{q}} = a_2\,\boldsymbol{\Gamma} \tag{1}$$

where M is the mass matrix, $\mathbf{q},\dot{\mathbf{q}}$, and $\ddot{\mathbf{q}}$ are the generalized coordinates and time derivatives, C is the nonlinear accelerations, β is a characteristic damping term, D is a matrix mapping the damping terms, and $\boldsymbol{\Gamma}$ is the generalized active forces.

Scaled system results are then compared to the unscaled case to ensure the scaling procedure did not significantly affect the final predicted states. Testing showed the scaled system better matched empirical data than the unscaled system and generated the results in significantly less time. However, this formulation assumed that the scaling factor - the portion of forces that may be removed - was a constant.

In the modeling of biopolymers, driving forces are often electropotential in nature and can be modeled with a combination of Coulomb and Lennard-Jones terms. More advanced and/or specific potential formulations have been devised [9, 10] and are derivatives of the low-level particle-particle interactions. The forces resulting from these potential interactions decay exponentially with increasing distance and may not always be large enough to satisfy the assumptions made in the derivation of our established multiscale method. However, small but persistent potential attractive forces between two distant bodies can over time produce significant work, resulting in dramatic changes in the order of these forces. Our established multiscale method does not make allowances for active forces whose magnitude changes over several orders. Assuming the contributing forces can be constantly scaled when the magnitudes vary greatly can lead to results inconsistent with the unscaled case.

This work proposes a means of adaptively scaling the portions of the active and dissipative forces that are considered non-contributing. The scaling factor a_2 then becomes a function of time and must be re-evaluated throughout the simulation. As active forces change in magnitude, the scaling factor can be updated to reflect the current state of contribution. The new scaled equation of motion is then:

$$M(\mathbf{q})\,\ddot{\mathbf{q}} + C(\dot{\mathbf{q}},\mathbf{q}) + a_2\,\beta\,D(\mathbf{q})\,\dot{\mathbf{q}} = a_2\,\boldsymbol{\Gamma}_C + a_2^*\,\boldsymbol{\Gamma}_P \tag{2}$$

where a_2^* denotes the time variant scaling factor and the subscripts C and P denote conformational and potential active forces, respectively. It is expected that the conformational and dissipative forces remain significantly large

enough throughout the simulation to justify the constant scaling factor a_2 while the time variant term a_2^* is applied only to the varying potential forces. This approach allows small potential forces to remain unscaled while maintaining the scaling on the remaining large non-contributing forces. Once the potential forces have increased in magnitude significantly, those forces will be similarly scaled. In this manner, the computational savings are conserved and the work done by the potential forces still produces results consistent with the unscaled case.

This adaptive approach does however introduce new problems that must be addressed, such as the effects of scaling potential forces on energy calculation. As the potential energy of an interaction is the anti-derivative of the force, scaling the force also implies that the energy must similarly be scaled. For a constant force scaling, this energy scaling is not a significant problem - the scaled and unscaled systems will simply have differing amounts of energy. Adaptive scaling however leads to discontinuities in the amount of potential energy calculated. In this work, we confirm dynamic consistency in the scaled system by calculating the work done W by both the generalized active and dissipative forces. These work calculations are then combined with the kinetic energy T to show a system wide constant:

$$T - W_\beta - W_C - W_P = constant \tag{3}$$

where the subscripts β, C, and P denote the work done by dissipative, conformational, and potential forces, respectively.

The system selected for testing this proposed adaptive multiscale method is a nanoparticle conjugated with GP1b ligands interacting with endothelial Von Willebrand factor proteins. These nanoparticles have been shown to bind to endothelial cells preferentially over platelets and are a promising scaffold for *in situ* tissue regeneration [11]. As these nanoparticles are carried through the blood plasma, they will naturally come within interaction range of the target proteins, though not necessarily close enough for the potential forces to satisfy the established multiscale analysis. This model then is ideal for testing the adaptive method proposed in this work.

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