Nonlinear instability in multiple time stepping molecular dynamics *

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Abstract

This paper uncovers additional stability limitations of multiple time stepping (MTS) integrators for molecular dynamics (MD) that attempt to bridge time scales. In particular, it is shown that when constant-energy (NVE) simulations of Newton's equations of motion are attempted using the Verlet-I/r-RESPA/Impulse, there are nonlinear instabilities when the longest step size is a third and possibly a fourth of the period(s) of the fastest motion(s) in the system. This is demonstrated both through the analysis of a nonlinear model problem and through a thorough set of numerical simulations.

Key words. Long molecular dynamics simulations, multiple time stepping, Verlet-I/r-RESPA/Impulse, linear instability, nonlinear instability

1 Introduction

Molecular dynamics (MD) is the computer approach to statistical mechanics. It is widely used for biomolecular simulations. Starting with the atomic coordinates, the molecular connectivity and force field parameters, trajectories are computed by solving Newton's equations of motion, *i.e.*, the system of ODEs given by

$$\dot{\mathbf{q}} = \mathbf{M}^{-1}\mathbf{p}, \quad \dot{\mathbf{p}} = -U'(\mathbf{q}), \tag{1}$$

where $\mathbf{q}$ is the position vector, $\mathbf{p}$ is the momentum vector, $U(\mathbf{q})$ is the potential energy, $-U'(\mathbf{q})$ is the force, and $\mathbf{M}$ is the mass matrix.

A severe limitation in the ability of these simulations is given by the great range of time scales in biological systems, which span fifteen orders of magnitude. In an attempt to bridge the time scale gap, multiple time stepping (MTS) integrators have been introduced and have been an area of active research for more than a decade. The prototypical algorithm is the Verlet-I [1]/r-RESPA [2]/Impulse integrator, which splits the forces into fast and slow components, and evaluates the former more frequently than the latter.

A linear instability for Verlet-I/r-RESPA/Impulse at around half the period of the fastest motion has been identified and explained in previous work [3–8]. Mandziuk and Schlick [9] discovered nonlinear resonances in single time stepping MD integrators. This paper uncovers additional stability limitations of MTS integrators: it is shown that when constant-energy (NVE) simulations of Newton's equations of motion are attempted using the MTS integrator Verlet-I/r-RESPA/Impulse, there is nonlinear instability, whose effect is a mild but systematic drift in the energy, when the longest step size is a third and possibly a fourth of the period(s) of the fastest motion(s) in the system, referred to as 3:1 and 4:1 nonlinear instabilities [10]. This is demonstrated both through the analysis of a nonlinear model problem and through a thorough set of numerical simulations. The predicted instabilities match the observed ones exactly.

Constrained dynamics simulations of explicitly solvated biomolecules using Impulse with SHAKE [11] or RATTLE [12] as the inner-most integrator still exhibit instabilities when outer time steps are greater than 4 fs for long simulations. This paper also shows that simulations

using Verlet-I/r-RESPA/Impulse with SHAKE as the inner-most integrator suffer from the 4:1 and 3:1 nonlinear instabilities too.

Increasing computer power requires stricter stability properties. An early example of this phenemenon was Milne's algorithm which was an efficient method until the use of electronic computers revealed the unfortunate long term effects of weak (linear) instability [13,14]. Thus, the nonlinear instabilities of Verlet-I/r-RESPA/Impulse that are reported and analyzed in this paper are likely to be very significant in long MD simulations due to the tenfold increase in computer power every five years [15] and the desire to simulate longer processes that are of biological relevance and that can be experimentally verified, such as the folding of proteins.

2 Nonlinear Stability Analysis of Multiple Time Stepping Integrators

2.1 The map

Assume a nonlinear model problem with potential energy given by

$$U(q) = \underbrace{\frac{1}{2}\Omega^2 q^2}_{\text{oscillate}} + \underbrace{\frac{1}{2}Aq^2 + \frac{1}{3}Bq^3 + \frac{1}{4}Cq^4}_{\text{kick}} + O(q^5), \tag{2}$$

where the splitting between the oscillate and kick step for Verlet-I/r-RESPA/Impulseis done as indicated.

The discretization of this problem using the first half of Verlet-I/r-RESPA/Impulse is given by:

$\frac{1}{2}$ kick:

$$p_0^+ = p - \frac{h}{2}(Aq + Bq^2 + Cq^3) + O(q^4), \tag{3}$$

$\frac{1}{2}$ oscillate: Let $s' = \sin\frac{h\Omega}{2}$ and $c' = \cos\frac{h\Omega}{2}$, we have

$$\begin{bmatrix} q_{1/2} \\ p_{1/2} \end{bmatrix} = \begin{bmatrix} c' & \frac{s'}{\Omega} \\ -\Omega s' & c' \end{bmatrix} \begin{bmatrix} q \\ p_0^+ \end{bmatrix}. \tag{4}$$

2.2 Main result

Let $\lambda = \mu^2$, where $\mu = \gamma - \mathrm{i}\sigma$ in which

$$\gamma = \begin{cases} \left(1 - \frac{h}{2}\frac{s'}{\Omega c'}A\right)^{1/2} c', & c' \neq 0, \\ 0, & c' = 0, \end{cases}$$

and

$$\sigma = \begin{cases} \left(1 + \frac{h}{2}\frac{c'}{\Omega s'}A\right)^{1/2} s', & \frac{s'}{\Omega} \neq 0, \\ 0, & \frac{s'}{\Omega} = 0. \end{cases}$$

We assume that either $-(s')^2 < \frac{hs'c'}{2\Omega}A < (c')^2$, or $\frac{s'}{\Omega} = A = 0$ or $c' = A = 0$. These assumptions are necessary to avoid linear instability at half the shortest period, cf. [4].

Applying the procedure for analyzing the stability of a reversible symplectic map outlined in [10], which extends the analysis of [16], to the above nonlinear model problem, we obtain the nonlinear stability conditions on multiple time stepping algorithms:

1. **Third order resonance.** Suppose $\lambda^3 = 1$ but $\lambda \neq 1$. The map is stable at equilibrium if $B = 0$ and $C \neq 0$, and it is *unstable if* $B \neq 0$. This condition for stability is as stringent

for MTS as it is for leapfrog, and thus Verlet-I/r-RESPA/Impulse is unstable in practice. This instability is confirmed by the numerical results in Section 3.

2. **Fourth order resonance.** Suppose $\lambda = \mathrm{e}^{\mathrm{i}\pi/2}$. The map is stable at equilibrium if $C < 0$ or $C > 2hB^2s'c'/\Omega$. It is unstable if $0 < C < 2hB^2s'c'/\Omega$. Thus, Verlet-I/r-RESPA/Impulse may or may not be stable at the fourth order resonance. This fourth order resonance is observed in our numerical experiments, although our experiments are not conclusive regarding whether this is an unstable nonlinear resonance.

2.3 Discussion

Implications of the stability condition for 4:1 resonance can be a assessed by considering two particles separated by a distance r for which the fast force is harmonic and the slow force is electrostatic [10]. The stability condition is only satisfied either if the two particles are oppositely charged or if cutoffs are being chosen to yield reasonable accuracy. Neglected is the fact that in simulations of liquids, where particles can move closer together, the slow potential is defined as the product of the actual potential times times a switching function. The stability condition for 4:1 resonance is not satisfied for typical switching functions.

3 Numerical Experiments

Unstable resonances manifest themselves in the neighborhood of a certain step size: There is a definite range of step sizes that cause unbounded energy drift, even if the neighboring step sizes are stable. Examples of this resonance phenomenon are presented in [5].

We perform numerical experiments with flexible waters and a constrained solvated protein using the Verlet-I/r-RESPA/Impulse integrator. These correspond to widely used protocols in simulations of biological macromolecules. All simulations use the CHARMM force field [17]. The first system contains only 141 TIP3P waters [18] (423 atoms), 10 Å of radius with shortest period around 10 fs (symmetric and anti-symmetric O-H bond stretching). The latter system is the 2mlt proteins [19] solvated in a 58 Å$\times$ 38 Å$\times$ 25 Å box of rigid waters (total 5143 atoms including 868 atoms in the proteins), SHAKE-constraining the bonds of polar hydrogens in the proteins and the bonds and angles in waters. The periods of the remaining fastest modes are in the range of 18 to 24 fs, which correspond to the H-X-H angle bending (where X represents a non-hydrogen atom) and C=C stretching. The justification of freezing the almost decoupled high frequency stretching can be found in Ref. [20].

3.1 Normal mode analysis for the model systems

Normal mode analysis of the systems of interest forms the basis of correlating the time step related nonlinear instabilities with one or many of the normal modes. Power spectrum analysis of the time history of the energy of the simulation is a powerful tool, among several others, to reveal the characteristic frequencies of the normal modes of the system. Not surprisingly, the size of the inner time step of the MTS integrators used in the MD simulations affects the accuracy of the frequencies (and thus periods and wave-numbers) of the fastest motions. The periods and errors are shown in Table 1. The method of nonbonded force evaluation generally does not affect the accuracy of the frequencies of the fastest motions.

Table 1: The periods for symmetric and asymmetric bond stretching in a droplet of flexible water obtained via normal mode analysis of enery output from simulations (each 200 ps long).

Integrator (Δt[fs], δt[fs])	Period [fs]	Error ($\%$)
Impulse (2.0, 0.1)	(9.87, 10.07)	($-$, $-$)
Impulse (2.0, 1.0)	(9.71, 9.91)	(1.63, 1.50)
Leapfrog ($-$, 2.0)	(9.12, 9.33)	(7.65, 7.35)

3.2 Measuring instabilities

We use the *"Percent Relative Drift of Total Energy,"* $D_{\rm rel}$, as a metric to measure the instabilities [21], which is given as follows:

$$D_{\rm rel} = 100bL/K, \tag{5}$$

where b is the slope of the linear curve fit of the block-averaged total energy, L is the simulation length, and K is the average kinetic energy throughout the simulation. For a fixed simulation length, the bigger the value of $D_{\rm rel}$, the more unstable the simulation goes. In order to measure the goodness of the linear curve fit, we define the error bars as two times the *"Percent Relative Root Mean Square Deviation,"* $\delta_{\rm rel}$, which is given as follows:

$$\delta_{\rm rel} = \frac{100}{K}\sqrt{\sum_{i=1}^{N}(y_i - \tilde{y}_i)^2/N}, \tag{6}$$

where N is the number of data points of the block-averaged total energy, y_i is the block-averaged total energy at time t_i, $\tilde{y}_i$ is the value of the fitted straight line at t_i.

3.3 Numerical results

We perform simulations of the flexible water system, and the solvated 2mlt system SHAKE-constraining all the bonds of polar hydrogens in the protein and the waters. All simulations are at $300\,\mathrm{K}$. Each simulation has a length of $500\,\mathrm{ps}$. Numerical results clearly reveal the step-size-related, nonlinear instabilities.

For the first system, it was minimized using 10000 steps of conjugate-gradient minimization, then the system was equilibrated for $100\,\mathrm{ps}$ at $300\,\mathrm{K}$, using NAMD2.3 [22]. We ran the simulations using PROTOMOL, an experimental component-based framework for MD simulations [23, 24]. PROTOMOL, whose modular design allows for easy prototyping of complex methods, is freely available at `http://www.nd.edu/~lcls/protomol`. The instabilities associated with outer step sizes are plotted in Fig. 1. It is clear that in the neighborhood of $\Delta t = 3.33\,\mathrm{fs}$ there is an 3:1 unstable resonance that manifests itself in an unmistakable drift at that step size. A milder 4:1 resonance occurs at around $\Delta t = 2.4\,\mathrm{fs}$. Note that simulations may become unstable even for step sizes larger than the ones that just excite the nonlinear instabilities, *e.g.* the last few data points in Fig. 1 with $\Delta t > 3.3363\,\mathrm{fs}$.

For the second system, it was minimized using 30000 steps of conjugate-gradient minimization, and then the system was equilibrated for $200\,\mathrm{ps}$ at $300\,\mathrm{K}$, SHAKE-constraining the bonds of polar hydrogens in the protein, the O-H bonds and H-O-H angles in waters, then we ran the simulations, all using NAMD2.5. The results are shown in Fig. 2. PME is used for Coulomb force evaluation. Simulations with outer time step greater than $4\,\mathrm{fs}$ are unstable. It is hard to make any specific identifications of nonlinear resonance just from these figures

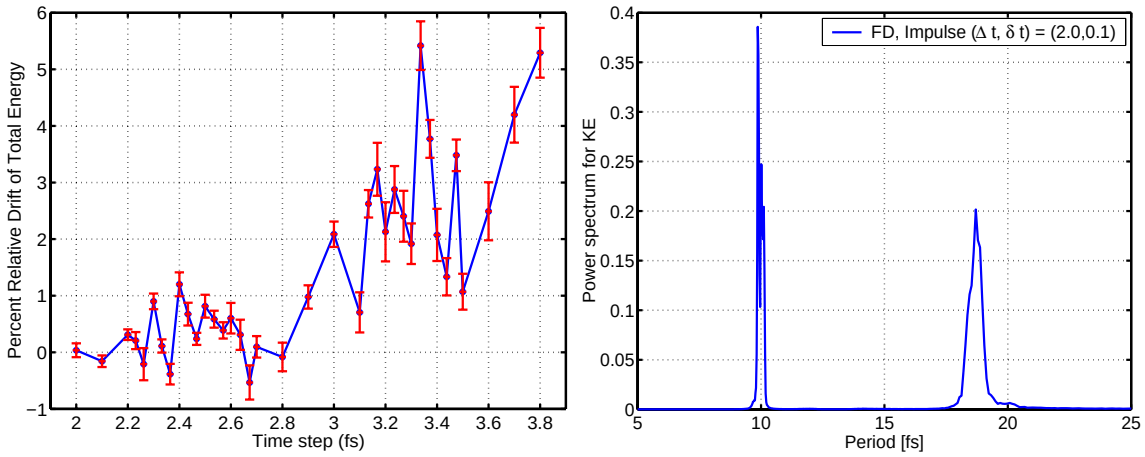

Figure 1: On the left: Energy drift for Verlet-I/r-RESPA/Impulse applied to a 20Å-diameter sphere of flexible water at about 300 K. Each point represents a 500 ps MD simulation with an outer step size Δt given by the x-axis, and an inner step size δt equal or very close to 0.1 fs. **The peaks at step sizes of** 2.40 fs **and** 3.33 fs **show evidence of 4:1 resonance and 3:1 instability.** This figure also shows that we may get instability even for longer step sizes in the neighborhood of nonlinear resonances (the last few data points with $\Delta t > 3.3363$ fs. On the right: The periods of the fastest normal modes from a 200 ps simulation of the same system with inner time step of 0.1 fs (at 300 K).

because the remaining modes are continuous. Most likely these drifts correspond to the combined effects of 4:1 and 3:1 resonances associated with the remaining modes including angle bending, C=C stretching, and some of the non-bonded interactions.

4 Discussion

In protein simulations, there are possibly several other factors that may also contribute to instability. Examples include difficulties in matching the cutoff radii for the short-/intermediate-

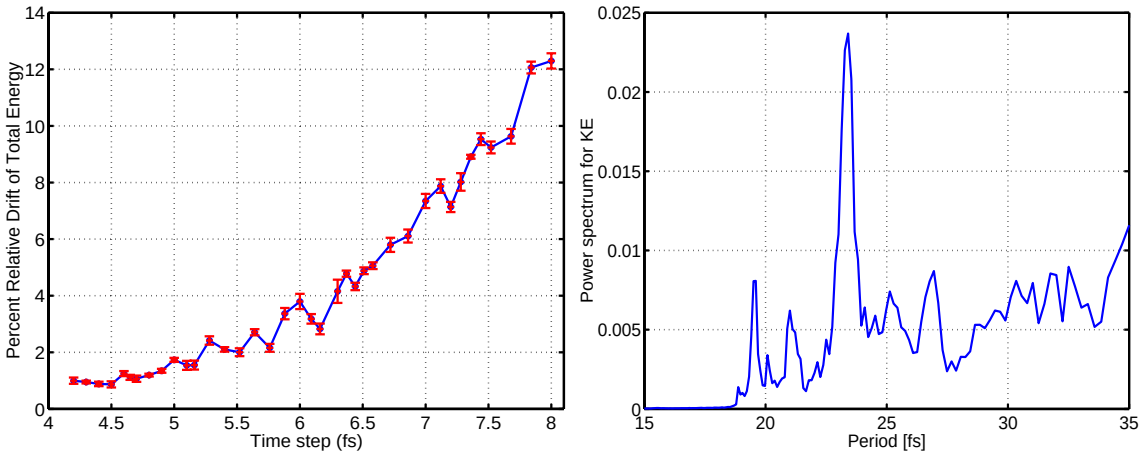

Figure 2: On the left: Energy drift for Verlet-I/r-RESPA/Impulse applied to the explicitly solvated 2mlt system, at 300 K. Each point represents a 500 ps MD simulation with a step size Δt given by the x-axis, and an inner step size δt in the range of 0.82 to 1 fs. On the right: The periods of the fastest normal modes from a 200 ps simulation of the same system with inner time step of 1 fs (at 300 K). It is hard to make any specific identifications of nonlinear resonance just from these figures because the remaining modes are continuous. Most likely these drifts correspond to the combined effects of 4:1 and 3:1 resonances.

/long-range forces for Coulomb interactions in Ewald splitting [25–27]; group switching functions, *e.g.*, when the group radii (intermediate or long) matches a critical distance between two neighboring groups and many others related to the arbitrary potential breakup [28]. Nonetheless, the step size related nonlinear instabilities should not be neglected. In particular, although 4:1 nonlinear instability could be eliminated by designing a switching function that satisfies certain inequality condition, 3:1 nonlinear instability is a general phenomenon. In some applications, accuracy limits the time step, but in the important cases shown here, the time step is limited by stability.

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