# Nonlinear instability in multiple time stepping molecular dynamics [*]

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## ABSTRACT

This paper discusses 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 one third and possibly one 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.

## Keywords

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

## 1. INTRODUCTION

Molecular dynamics (MD) is a 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 [5]/r-RESPA [20]/Impulse integrator (hereafter referred to as Impulse), which splits the forces into fast and slow components, and evaluates the former more frequently than the latter. Another approach under active research is called *Multirate* method, which uses large step sizes for the slow components and small step sizes for the fast ones [6, 11]. In this paper we consider MTS integrators only.

A linear instability for Impulse at around half the period of the fastest motion has been identified and explained in previous work [1–3]. Mandziuk and Schlick [14] discovered nonlinear resonances in single time stepping MD integrators. This paper shows additional stability limitations of MTS integrators through the analysis of a nonlinear model problem and through a thorough set of numerical simulations: when constant-energy simulations of Newton's equations of motion are attempted using Impulse, there is nonlinear instability, whose effect is a mild but systematic drift in the energy, when the longest step size is one third and possibly one fourth of the period(s) of the fastest motion(s) in the system, referred to as 3:1 and 4:1 nonlinear instabilities [12]. The predicted instabilities match the observed ones exactly. Though nonlinear instability of multiple time stepping MD simulation of flexible waters was first reported in [7], the current study is more complete and in-depth.

Impulse method with SHAKE [21] constraining (SHAKE-I) is among the several methods that allows larger time steps [8]. SHAKE-I simulation of explicitly solvated biomolecules still exhibit instabilities when outer time steps are greater than 4 fs for long simulations. We show that SHAKE-I suffers from the combined 4:1 and 3:1 nonlinear instabilities.

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 the weak (linear) instability [16]. Thus, the nonlinear instabilities of 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 (the Moore's law) and the desire to simulate longer processes that are of biological relevance and can be experimentally verified, such as the folding of proteins.

## 2. ANALYSIS PROCEDURE

Given here is a procedure for analyzing the stability of a re-

versible symplectic map, which extends the analysis of [17].

## 2.1 Assumptions

Let $y_{n+1} = M(y_n)$ be the map of interest. In the present context $M$ depends on the step size $h$, so we may at times write $M_h(y)$ instead of $M(y)$. Reversible means that $RM(RM(y)) = y$ where $R = \text{diag}(1, -1)$. Most practical reversible symplectic integrators, including simple implicit ones [19], can be expressed as

$$M(y) = RN^{-1}(RN(y)) \qquad (2)$$

where $N(y) = N_{h/2}(y)$ is itself an area-preserving map. It is easily verified that $M(y)$ is indeed reversible. Given here are the stability conditions for this important special case of reversible maps *in terms of the simpler map $N(y)$.*

The analysis is valid only in some neighborhood of a fixed point $y^* = M(y^*)$ of the map. We assume that the Jacobian matrix $M'(y^*)$ is power-bounded, which is necessary for stability. Also assume that $y^* = (q^*, 0)$, which will be the case except possibly for values of $h$ too large to be of practical interest.

## 2.2 Procedure

**Step 1** Express

$$N(y) = N(y^*) + \begin{bmatrix} a_{11} & a_{12} \\ -a_{21} & a_{22} \end{bmatrix} (y - y^*) + O(\|y - y^*\|^2). \qquad (3)$$

For stability it is necessary that either $0 < a_{11}a_{22} < 1$ or $a_{11} = a_{22} = 0$ or $a_{12} = a_{21} = 0$. The symplectic property implies that the determinant $a_{11}a_{22} + a_{12}a_{21} = 1$.

**Step 2** Choose $\alpha \neq 0$, $\beta \neq 0$ so that the map

$$N_Y(Y) = \text{diag}(\alpha, 1/\alpha) \left( N(y^* + \text{diag}(\beta, 1/\beta)Y) - N(y^*) \right) \qquad (4)$$

satisfies

$$N_Y(Y) = \begin{bmatrix} \gamma & \sigma \\ -\sigma & \gamma \end{bmatrix} Y + O(\|Y\|^2) \qquad (5)$$

where $\sigma^2 + \gamma^2 = 1$. This can be done as follows:

$$\alpha = \left( \frac{a_{21}a_{22}}{a_{11}a_{12}} \right)^{1/4}, \qquad \text{if } 0 < a_{11}a_{22} < 1, \qquad (6)$$

$$\beta = \left( \frac{a_{12}a_{22}}{a_{11}a_{21}} \right)^{1/4}, \qquad \text{if } 0 < a_{11}a_{22} < 1, \qquad (7)$$

$$\alpha = \left( \frac{a_{21}}{a_{12}} \right)^{1/2} \beta, \qquad \text{if } a_{11} = a_{22} = 0, \qquad (8)$$

$$\alpha = \left( \frac{a_{22}}{a_{11}} \right)^{1/2} \frac{1}{\beta}, \qquad \text{if } a_{12} = a_{21} = 0. \qquad (9)$$

**Step 3** Express the map $N_Y(Q, P)$ in complex form as

$$N_z(z, \bar{z}) = \mu z + i\mu r(z, \bar{z}), \qquad (10)$$

where $z = Q + iP$, $\mu = \gamma - i\sigma$, and

$$r(z, \bar{z}) = c_1 z^2 + 2\bar{c}_1 z\bar{z} + c_2 \bar{z}^2 + c_3 z^2 \bar{z} + c_4 \bar{z}^3 + \text{U.T.s.} \qquad (11)$$

The U.T.s (unimportant terms) are defined to be the $z^3$ term, the $z\bar{z}^2$ term, and those of degree 4 or more. This can always

be done. Denote $c_j = a_j + ib_j$ where $a_j$ and $b_j$ are real, and define

$$a = 2a_1, \qquad (12)$$
$$c = 2a_2, \qquad (13)$$
$$f = 2a_3 - 12a_1 b_1 + 4a_2 b_2, \qquad (14)$$
$$g = 2a_4 + 4a_2 b_1 + 4a_1 b_2. \qquad (15)$$

**Conclusion** Let $\lambda = \mu^2$.

1. *Third order resonance.* Suppose $\lambda^3 = 1$ but $\lambda \neq 1$. The map is stable at equilibrium if $c = 0$ and $-\sigma f - 3\gamma a^2 \neq 0$, and it is unstable if $c \neq 0$. Hence, the third order resonance is normally unstable.

2. Suppose $\lambda^3 \neq 1$. Let

$$F = -\sigma(4\gamma^2 - 1)f - 3\gamma(4\gamma^2 - 1)a^2 - \gamma(4\gamma^2 - 3)c^2, \qquad (16)$$

$$G = -\sigma(4\gamma^2 - 1)g + 2\gamma ac. \qquad (17)$$

   (a) *Fourth order resonance.* Suppose $\lambda^4 = 1$. The map is stable at equilibrium if $|G| < |F|$, and it is unstable if $|G| > |F|$.

   (b) Suppose $\lambda^4 \neq 1$. The map is stable at equilibrium if $F \neq 0$.

## 3. APPLICATION TO IMPULSE

We apply the analysis procedure just outlined to a nonlinear model problem to obtain the nonlinear stability conditions on Impulse.

### 3.1 The map

Consider the nonlinear model problem with the following potential energy:

$$U(q) = \underbrace{\frac{1}{2}\Omega^2 q^2}_{\text{oscillate}} + \underbrace{\frac{1}{2}Aq^2 + \frac{1}{3}Bq^3 + \frac{1}{4}Cq^4}_{\text{kick}} + O(q^5), \qquad (18)$$

where the splitting between the oscillate and kick step for Impulse is done as indicated.

The discretization of this problem using the first half of Impulse is given by:

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

$$p_0^+ = p - \frac{h}{2}(Aq + Bq^2 + Cq^3) + O(q^4), \qquad (19)$$

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

$$\begin{bmatrix} q_{1/2} \\ p_{1/2} \end{bmatrix} = \begin{bmatrix} c' & \frac{s'}{\Omega} \\ -\Omega s' & c' \end{bmatrix} \begin{bmatrix} q \\ p_0^+ \end{bmatrix}. \qquad (20)$$

### 3.2 Main result

Let $\lambda = \mu^2$, where $\mu = \gamma - i\sigma$ 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. [18].

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 Impulse is unstable in practice. This instability is confirmed by the numerical results in Section 4.

2. **Fourth order resonance.** Suppose $\lambda = e^{-i\pi/2}$. 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, 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.

### 3.3 Discussion

Implications of the stability condition for 4:1 resonance can be assessed by considering two particles separated by a distance $r$ for which the fast force is harmonic and the slow force is electrostatic [12]. The stability condition is only satisfied either if the two particles are oppositely charged or if the 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 a switching function. The stability condition for 4:1 resonance is not satisfied for typical switching functions.

## 4. NUMERICAL EXPERIMENTS

We perform numerical experiments with flexible waters and a constrained solvated protein using the Impulse integrator. These correspond to widely used protocols in simulations of biological macromolecules. All simulations use the CHARMM force field [13]. The first system contains only 141 TIP3P waters [9] (423 atoms), 10 Å of radius with shortest period around 10 fs. The latter system is the 2mlt proteins [4] solvated in a 58 Å× 38 Å× 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.

### 4.1 Normal modes of the model systems

Power spectrum analysis of the time history of the energy of the MD simulation is a powerful tool, among several others, to reveal the characteristic frequencies of the normal modes of the system, which forms the basis of correlating the time step related nonlinear instabilities with one or many of the normal modes. Note that different step sizes of the inner-most integrator result in different effective frequencies of the fastest motions. The numerical periods and errors are shown in Table 1.

### 4.2 Measuring instabilities

We use the *"Percent Relative Drift of Total Energy,"* $D_{\rm rel}$, as a metric to measure the instabilities [8], which is given as follows:

$$D_{\rm rel} = 100bL/K, \tag{21}$$

**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 ($\Delta t$[fs], $\delta t$[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) |

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. We define the error bars as two times the *"Percent Relative Root Mean Square Deviation,"* $\delta_{\rm rel}$, as follows to measure the goodness of the linear curve fit:

$$\delta_{\rm rel} = \frac{100}{K}\sqrt{\sum_{i=1}^{N}(y_i - \tilde{y}_i)^2/N}, \tag{22}$$

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 $t_i$.

### 4.3 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 K. Each simulation has a length of 500 ps. Numerical results clearly reveal the step-size-related, nonlinear instabilities.

The first system was minimized using 10000 steps of conjugate-gradient minimization, then equilibrated for 100 ps at 300 K, using NAMD2.3 [10]. We ran the simulations using PROTOMOL, an experimental component-based framework for high performance MD and stochastic simulations [15]. PROTOMOL's modular design allows easy prototyping of complex methods. It is freely available at http://www.nd.edu/~lcls/protomol. The shortest periods of the system are obtained using the Fourier analysis of the energy history: about 10 fs for bond stretching (see the first row in Table 1, the first spike in Fig. 1) and 18 fs for angle bending (the second spike in Fig. 1). The instabilities associated with outer step sizes are plotted in Fig. 2. It is clear that in the neighborhood of $\Delta t = 3.33$ 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 $\Delta t = 2.4$ fs. Note that simulations may become unstable even for step sizes larger than those just exciting the nonlinear instabilities, *e.g.* the last few data points in Fig. 2 with $\Delta t > 3.3363$ fs.

We show the details of the total energy drift by plotting the block-averaged total energy output versus time to visualize the nonlinear instabilities for simulations of flexible waters at room temperature, see Figs. 3 and 4.

The second system was minimized using 30000 steps of conjugate-gradient minimization, then equilibrated for 200 ps at 300 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. Similarly, the shortest periods of the system are obtained as shown in Fig. 5. The energy drift for different step sizes is shown in Fig. 6. PME is used for the Coulomb force evaluation. Simulations with outer time step greater than 4 fs are unstable with noticeable energy drift. With smaller time steps, the simulations
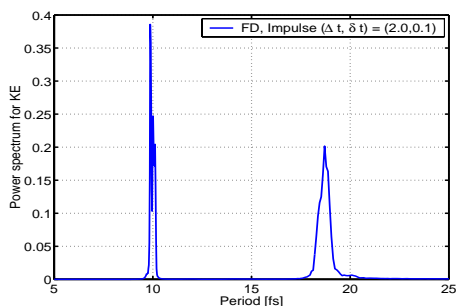
**Figure 1:** The periods of the fastest normal modes from a $200\,\text{ps}$ simulation of the same system with inner time step of $0.1\,\text{fs}$ at $300\,\text{K}$.
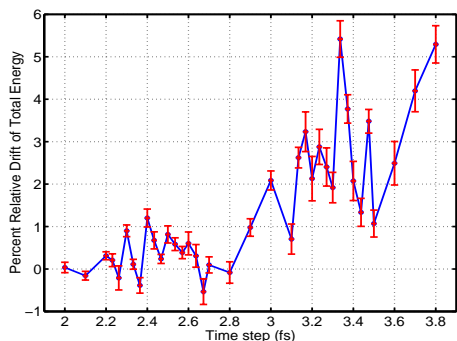


**Figure 2:** Energy drift for Impulse applied to a 20Å-diameter sphere of flexible water at about $300$ K. Each point represents a **500 ps MD simulation** with an outer step size $\triangle t$ given by the x-axis, and an inner step size $\delta t$ equal or very close to $0.1$ fs. The peaks at step sizes of $2.40\,\text{fs}$ and $3.33\,\text{fs}$ 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 $\triangle t > 3.3363\,\text{fs.}$)

are stable without any noticeable energy drift, *e.g.*, SHAKE-I with outer time step of 3 fs and inner time step of 1 fs is stable with total energy drift of $0.06 \pm 0.04\%$. It is hard to make any specific identification of nonlinear resonance from the unstable simulations 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.

## 5. DISCUSSION

In protein simulations, there are possibly several other factors that may also contribute to instability [12]. Examples include difficulties in matching the cutoff radii for the short-/intermediate-/long-range forces for Coulomb interactions in Ewald splitting; group switching functions, and many others related to the arbitrary potential breakup. 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.
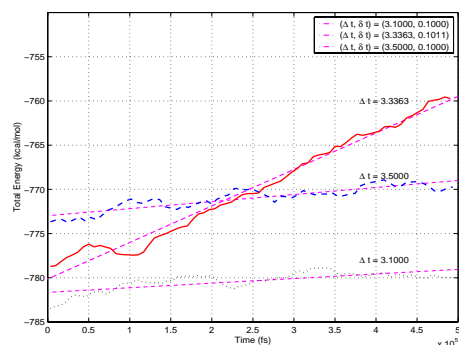


**Figure 3:** Block-averaged drift of total energy for $500$ ps of molecular dynamics simulation of $10\,\text{Å}$ radius of water using Impulse at $300\,\text{K}$. The percent relative drift of total energy of the three simulations is $0.70\%$, $5.42\%$ and $1.07\%$ for $\Delta t = 3.10\,\text{fs}$, $\Delta t = 3.33\,\text{fs}$ and $\Delta t = 3.50\,\text{fs}$, respectively. The curves have been shifted for clarity: the curve with $\Delta t = 3.33\,\text{fs}$ is shifted by $5.0\,\text{kcal/mol}$, and the curve with $\Delta t = 3.50\,\text{fs}$ is shifted by $10.0\,\text{kcal/mol}$. This shows evidence of the 3:1 nonlinear instability due to resonance.
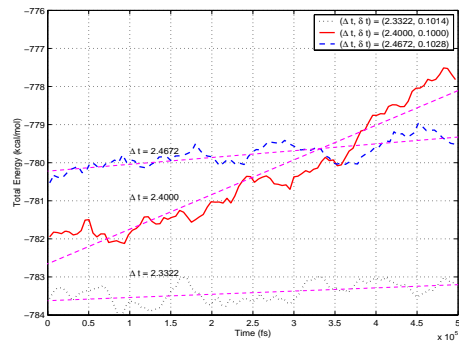


**Figure 4:** Same as in Fig. 3 except that it shows evidence of a possible 4:1 resonance. The percent relative drift of total energy of the three simulations is $0.11\%$, $1.20\%$ and $0.24\%$ for $\Delta t = 2.33\,\text{fs}$, $\Delta t = 2.40\,\text{fs}$ and $\Delta t = 2.47\,\text{fs}$, respectively. The curves have been shifted for clarity: the curve with $\Delta t = 2.40\,\text{fs}$ has been shifted by $1.5\,\text{kcal/mol}$, and the curve with $\Delta t = 2.47\,\text{fs}$ is shifted by $3.0\,\text{kcal/mol}$.

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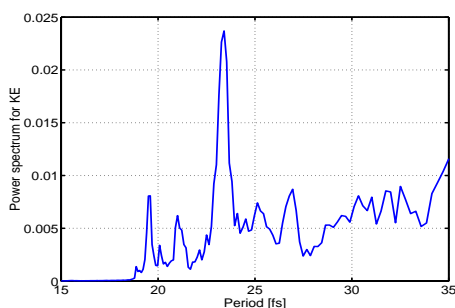
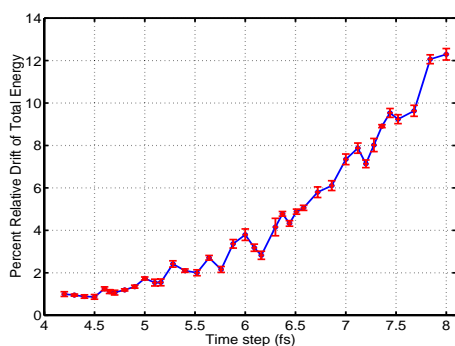**Figure 5:** The periods of the fastest normal modes from a $200\,\mathbf{ps}$ simulation of the same system with inner time step of $1\,\mathbf{fs}$ at $300\,\mathbf{K}$.



**Figure 6:** Energy drift for Impulse applied to the explicitly solvated 2mlt system, at $300\,\mathbf{K}$. Each point represents a $500\,\mathbf{ps}$ MD simulation with a step size $\Delta t$ given by the x-axis, and an inner step size $\delta t$ in the range of $0.82$ to $1\,\mathbf{fs}$. 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.

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