Molecular Dynamics: Artifacts of Quantization

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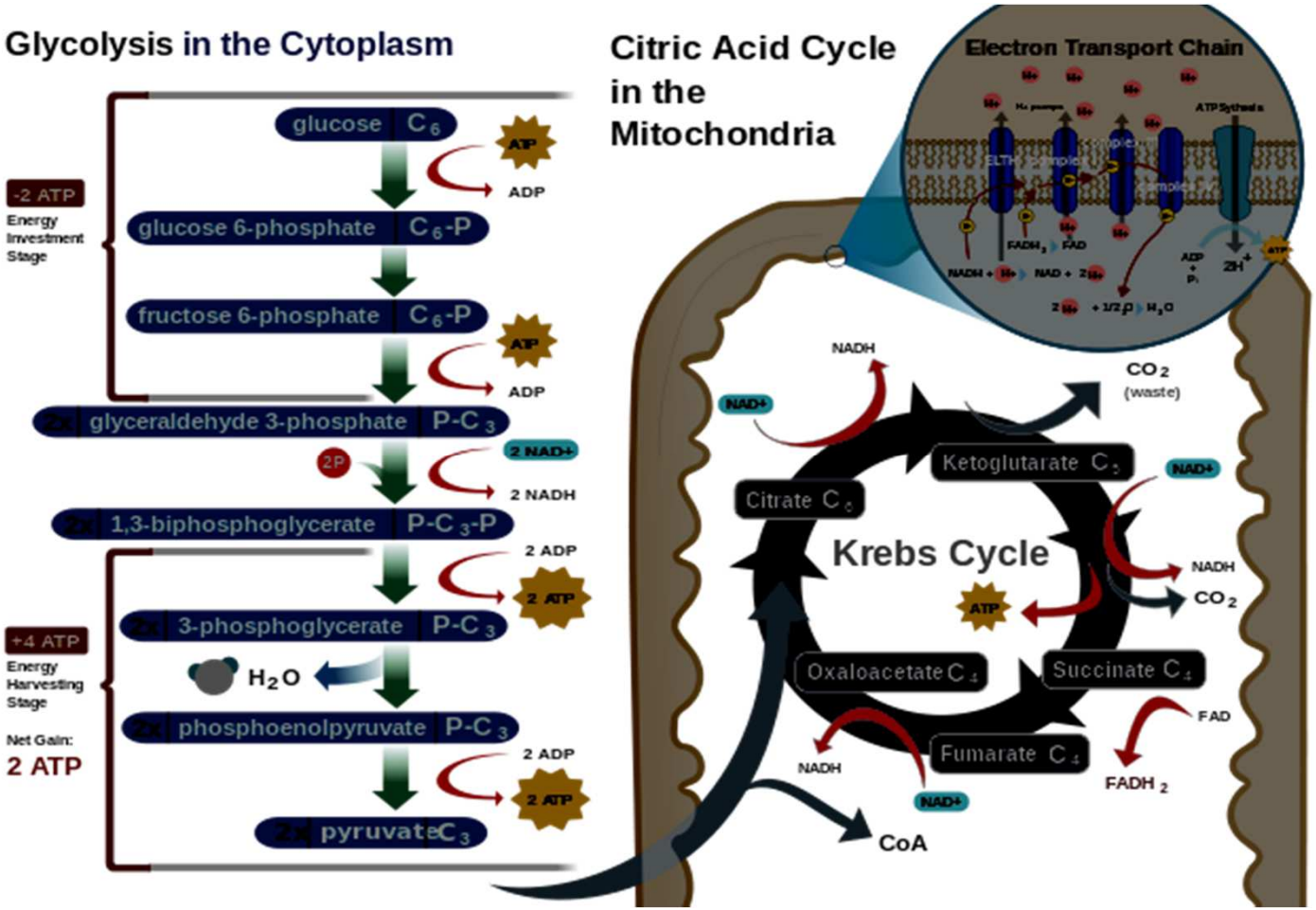
Molecular Dynamics Code is Often Used to Study Biomolecules

- YouTube Videos On Molecular Dynamics:
  - http://www.youtube.com/watch?v=lLFEqKl3sm4 (first minute)
  - http://www.youtube.com/watch?v=vN4RKPNOsEc (38:00, for about a minute)

Complex I begins conversion of NADH to ATP



Can use MD to explore Questions About Complex I

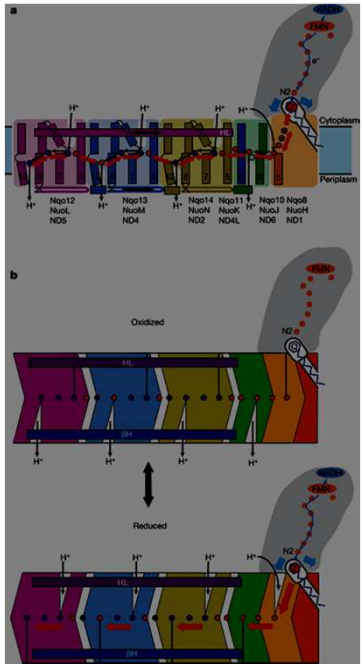
What to the water channels look like?

What are the pKa's of relevant residues?

What are the consequences of changing the redox states?

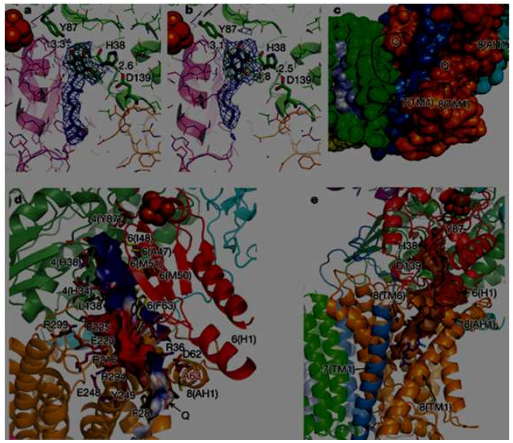
Does Quinol w/ oxidized N2 have a higher free energy than Quinone w/ reduced N2?

Does this alternate state also have an minimal energy state that switches water channel direction?



R Baradaran *et al. Nature* **000**, 1-6 (2013) doi:10.1038/nature11871

Compare against crystallographic waters and Dowser-like program that has been tested on many crystal structures.



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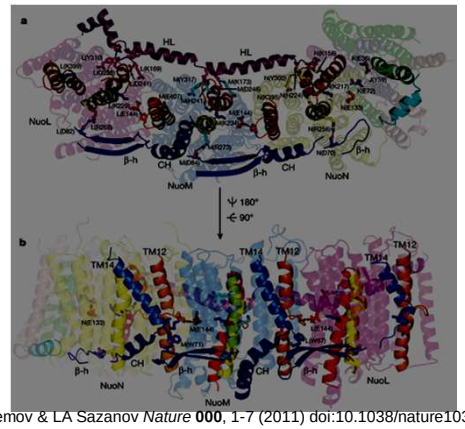


RG Efremov & LA Sazanov *Nature* **000**, 1-7 (2011) doi:10.1038/nature10330

How does the horizontal helix H-L interact with lipids in the membrane?

What are the forces on the connecting units H-L and β-H?

Gromacs Follows the following scheme

(i) Compute accelerations: $a = F_i(t)/m_i$, where F is the force disregarding constraints.
(ii) Update and scale velocities: $v' = \lambda(v + a\Delta t)$.
(iii) Compute new unconstrained coordinates: $r' = r + v'\Delta t$.
(iv) Apply SHAKE to coordinates: SHAKE($r' \rightarrow r''$; r).
(v) Correct velocities for constraints: $v = (r'' - r)/\Delta t$.
(vi) Scale coordinates and box: $r = \mu r''$; $b = \mu b$.

$$\lambda = \left[1 + \frac{\Delta t}{\tau_t}\left\{\frac{T_0}{T(t - \frac{1}{2}\Delta t)} - 1\right\}\right]^{1/2}, \qquad \mu = \left[1 + \frac{\Delta t}{\tau_p}\beta\{P(t) - P_0\}\right]^{1/3}.$$

GROMACS: A message-passing parallel molecular dynamics implementation, H.J.C. Berendsen, D. van der Spoel, R. van Drunen, Computer Physics Communications 91 (1995) 43-56

Non-Bonded Forces

$$\boldsymbol{F}_i = -\boldsymbol{F}_j = -\frac{\partial V(r_{ij})}{\partial r_{ij}} \frac{\boldsymbol{r}_{ij}}{r_{ij}} .$$

- *short-range repulsion:* $V(r) = C_{12}/r^{12}$ or $V(r) = A \exp(-Br)$,
- *dispersion interaction:* $V(r) = -C_6/r^6$,
- *Coulomb interaction* $f q_i q_i / r$,

GROMACS: A message-passing parallel molecular dynamics implementation, H.J.C. Berendsen, D. van der Spoel, R. van Drunen, Computer Physics Communications 91 (1995) 43-56

Bonded Forces

Covalent Bonds: $V(r) = \frac{1}{2}k_b(r - b)^2$

Covalent Bonds Angles: $V(r_1, r_2, r_3) = \frac{1}{2}k_\theta(\theta - \theta_0)^2$

Dihedral Angles: $V(r_1, r_2, r_3, r_4) = \frac{1}{2}V_0[1 + \cos(n\phi - \phi_0)]$

Optional 1-4: $C_{12}/r^{12} - C_6/r^6$

Alternative: $V(\phi) = \sum_{n=0}^{5} a_n \cos^n \phi$

Improper Dihedral Angles: Similar to dihedral but meant to keep things in plane

Distance restraining potential: To match experimental distances

External forces, eg. Position restraints: $V = \frac{1}{2}\sum_i k_i(r_i - r_i^0)^2$

In later versions more forms of potentials are allowed in addition to harmonic:
Cubic, and Morse potentials in particular

GROMACS: A message-passing parallel molecular dynamics implementation, H.J.C. Berendsen, D. van der Spoel, R. van Drunen, Computer Physics Communications 91 (1995) 43-56

Want to analyze artifacts of going from Continuous to Discrete

- Molecular dynamics simulations simulates a continuous time, and continuous variable system, evolving according to Newton's Laws, with a discrete time quantized (IEEE floating point) variable system following some algorithm.

$$\underline{m}\ddot{\underline{x}}(t)=\underline{f}(\underline{x}(t)) \rightarrow (\underline{x}^{n+1},\underline{v}^{n+1},\underline{f}^{n+1})= \mathcal{A}(\underline{x}^{n},\underline{v}^{n},\underline{f}^{n}),$$ Time-step is implicit

*Magnetism, is not a factor in cases I care about, so no velocity dependence
*Dissipation and noise are not handled well in this formalism, need to work on this
*Bit representations, floating point or even fixed would generate too much data
**In biological systems, if units are picked properly, should not have much dynamic range

Strömer-Verlet Algorithm Used in Many Codes

Velocity Explicit Verlet Implementation

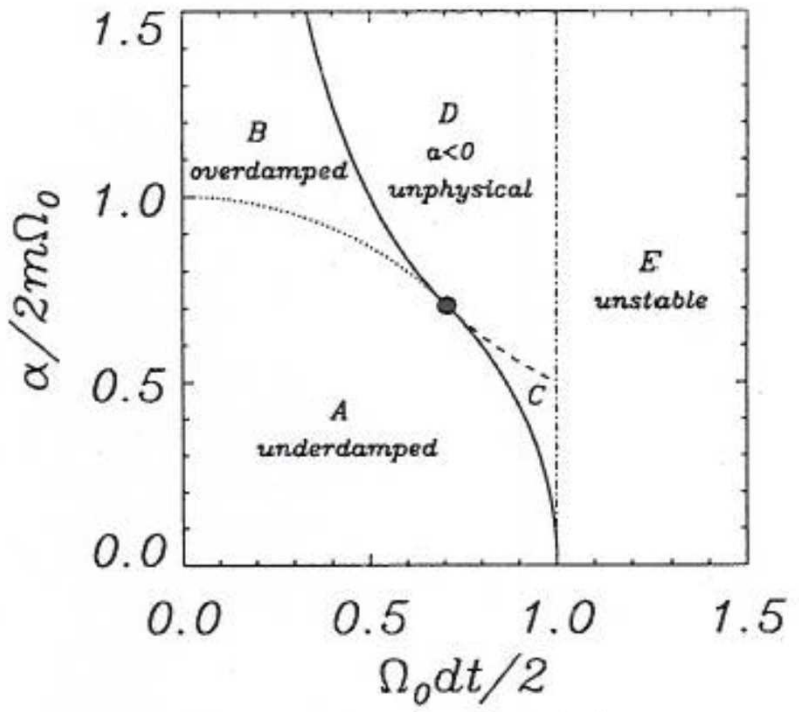
$$r^{n+1} = r^n + v^n dt + \frac{dt^2}{2m} f^n, \quad (1)$$

$$v^{n+1} = v^n + \frac{dt}{2m}(f^n + f^{n+1}). \quad (2)$$

Provably Equivalent to Position-Verlet and Leap Frog Implementations

A simple and effective Verlet-type algorithm for simulating Langevin Dynamics, Neils Gronbach-Jensen, Oded Farago, Molecular Physics 2013

Strömer-Verlet Algorithm Has A Simply Described Stable Region



A simple and effective Verlet-type algorithm for simulating Langevin Dynamics, Neils Gronbach-Jensen, Oded Farago, Molecular Physics 2013

Stability of Explicit Runge-Kutta Methods Is Not as Straight-Forward

Süli, Endre; Mayers, David (2003), *An Introduction to Numerical Analysis*, Cambridge University Press, ISBN 0-521-00794-1.

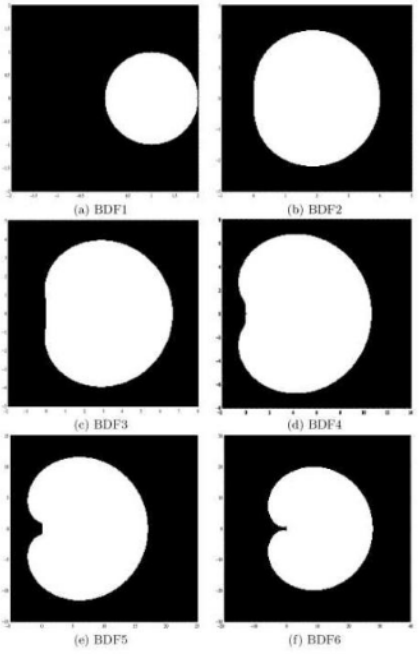


Fig. 12.5. Absolute stability regions in the complex plane for k-step Backward Differentiation Formulae, $k = 1, 2, \ldots, 6$. In each case the region of absolute stability is the set of points in the complex plane outside the white region. In each case, the region of absolute stability contains the whole of the negative real axis.

$$\dot{y} = f(t, y), \quad y(t_0) = y_0$$

$$y_{n+1} = y_n + \tfrac{1}{6}h\left(k_1 + 2k_2 + 2k_3 + k_4\right)$$
$$t_{n+1} = t_n + h$$

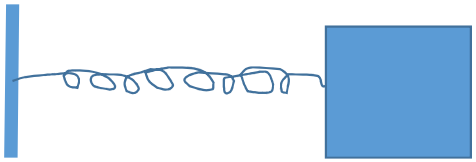
$$k_1 = f(t_n, y_n),$$
$$k_2 = f(t_n + \tfrac{1}{2}h, y_n + \tfrac{h}{2}k_1),$$
$$k_3 = f(t_n + \tfrac{1}{2}h, y_n + \tfrac{h}{2}k_2),$$
$$k_4 = f(t_n + h, y_n + hk_3).$$

http://en.wikipedia.org/wiki/Runge%E2%80%93Kutta_methods

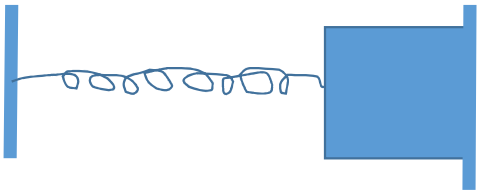
*Absolute Stability however doesn't make sense for Verlet

Will Simulate Two Simple Systems

1) Harmonic Oscillator – expecting fairly boring results



2) Harmonic Oscillator bouncing against a hard-wall



*Need to add damping and noise to get something more interesting

Need a way to Compare Methods

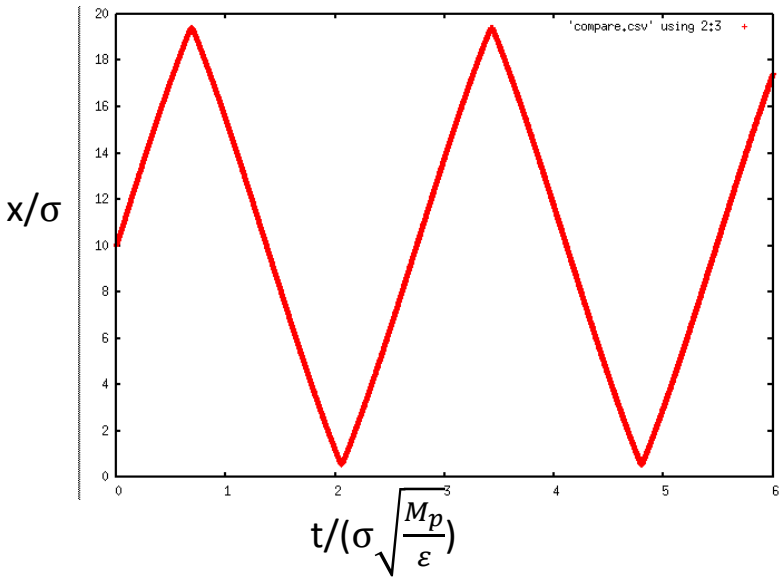
- Need good way to evaluate performance of different methods that will work for both different algorithms, and different systems
- Qualitative: Look at how phase space changes with increasing time step. Look at how return maps for positions and velocity change over time.
- Quantitative: Time averaged phase-space “separation” (same initial conditions) as a function of time step.
- Create Bifurcation diagram of above with time-step as a parameter
- More involved: Look at information measures of generated symbols from generating partitions of simulations at differing time steps.
- Computational measures—run-time, flops, memory usage, cycles

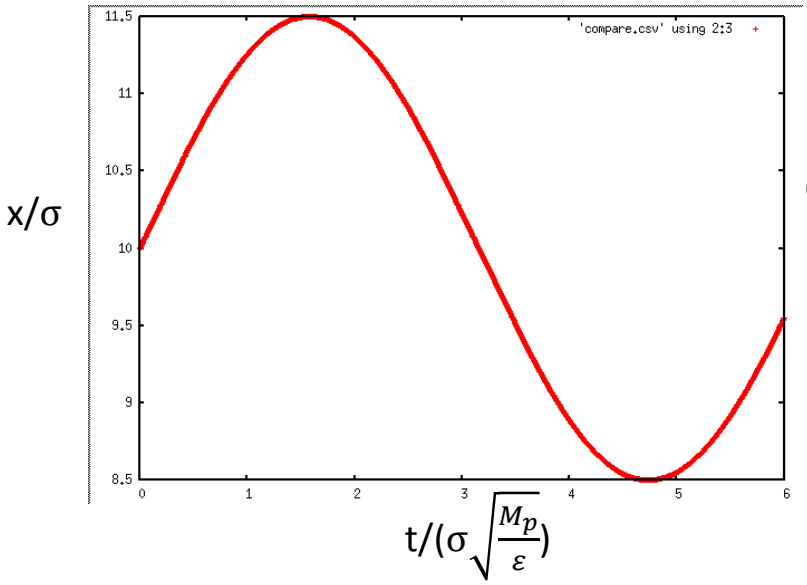
How to Create Generating Partitions

- Start of with a binary alphabet and some decision point based on position of mass. Try also with velocity of mass, and acceleration of mass.
- Sweep the decision point to see what generates the highest entropy rate.

Both Verlet and RK4 methods give same results for small time steps and centered HO

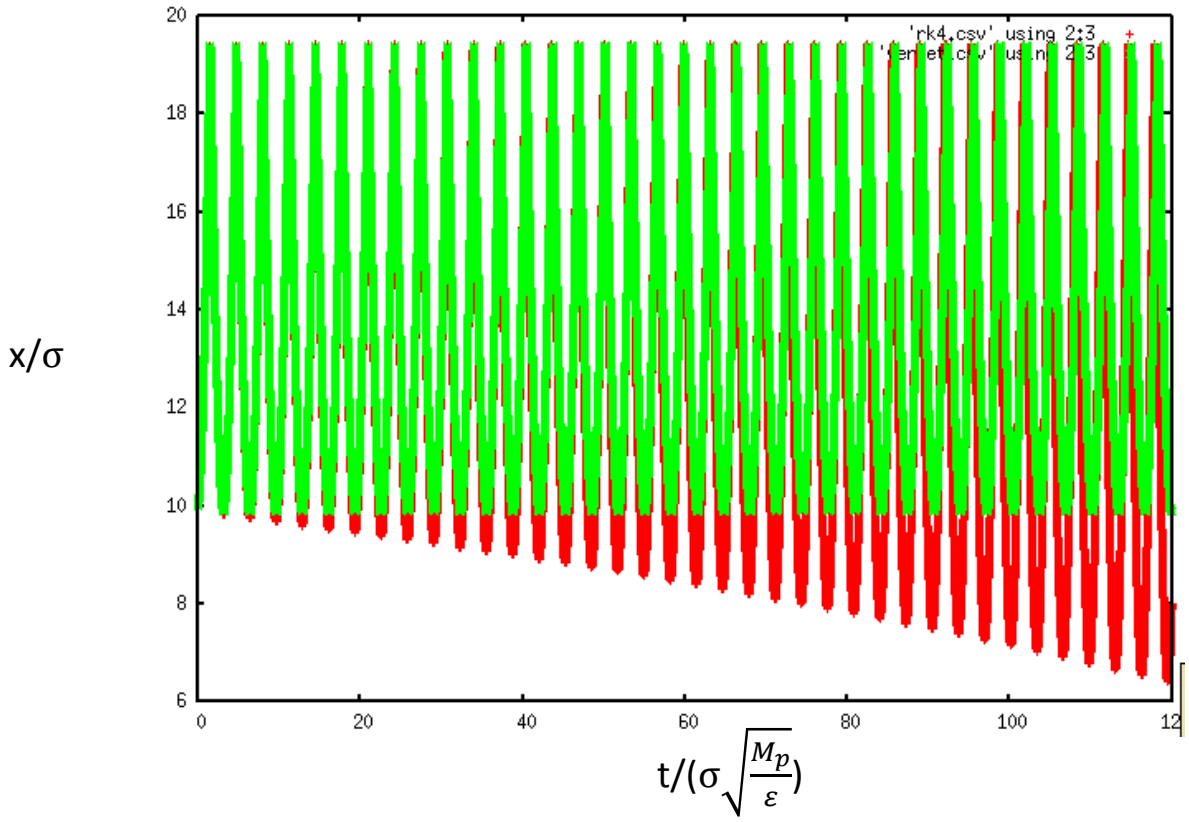
- Implemented a harmonic oscillator confined to a box. Idea is to be able to increase initial velocity to switch between harmonic oscillator case and harmonic oscillator bouncing against walls (Verlet & RK4).





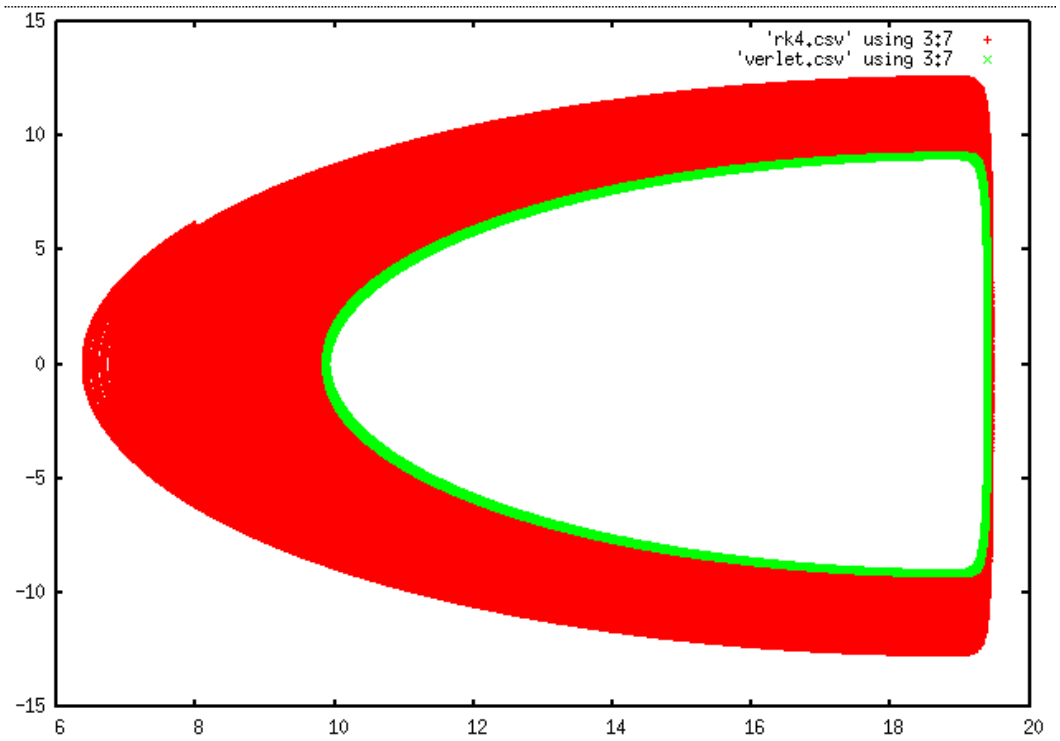
dt=6e-7 ($\sigma\sqrt{\frac{M_p}{\varepsilon}}$)

If Equilibrium is Shifted closer to a wall, and time step increased, RK4 starts to Diverge



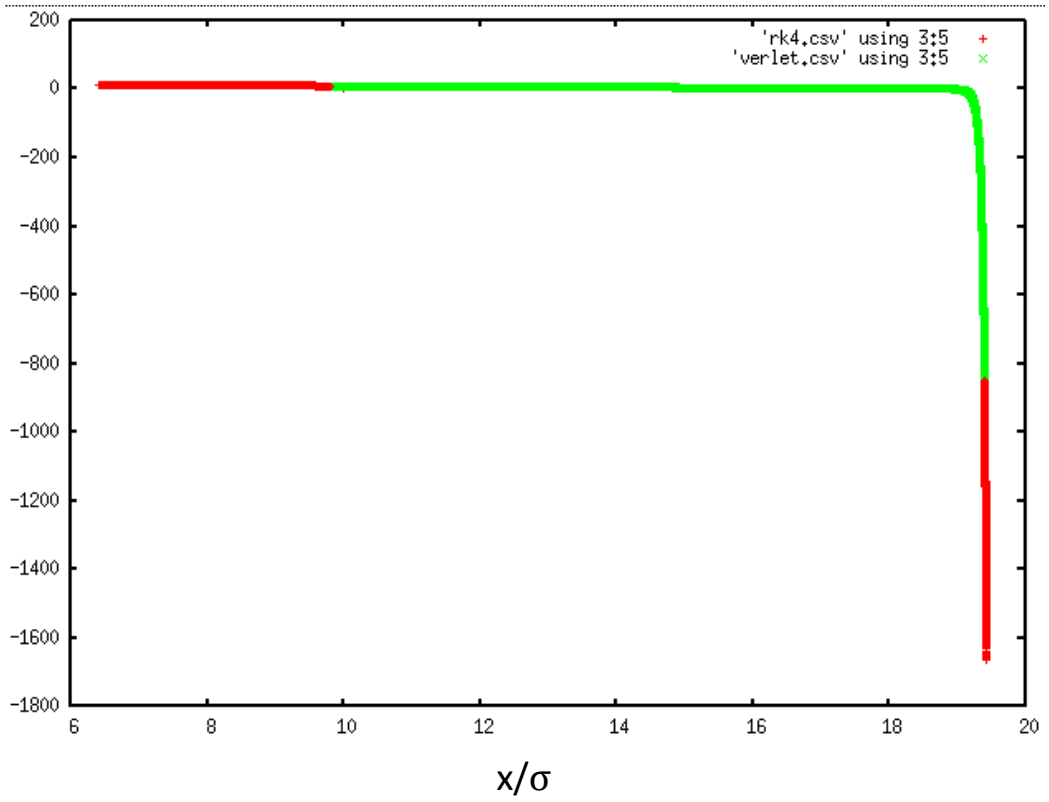
dt=1.2e-4 (σ$\sqrt{\frac{M_p}{\varepsilon}}$)

Phase Space Also Diverges in a Bit



dt=1.2e-4 ($\sigma\sqrt{\frac{M_p}{\varepsilon}}$)

As does Force vs. Position



dt=1.2e-4 ($\sigma\sqrt{\frac{M_p}{\varepsilon}}$)