What Makes Molecular Dynamics Work?

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Statement of application problem

$$\Gamma = \begin{bmatrix} q \\ p \end{bmatrix}, \qquad \frac{\mathrm{d}}{\mathrm{d}t}\Gamma = J\nabla H(\Gamma), \qquad J = \begin{bmatrix} 0 & I \\ -I & 0 \end{bmatrix}$$

Chaotic.

Concern: discretization errors overwhelm numerical trajectories in long time integrations. Frenkel and Smit (2002) speculates that shadowing may provide the justification but concludes by saying

that there is clearly still a corpse in the closet. We believe this corpse will not haunt us, and we quickly close the closet.

Aim

Characterize and design suitable numerical integrators,

but first

Define the computational goal.

In a nutshell …

Coping with chaos

Incorporate uncertainty stochastically,
1. in initial conditions

$$\Gamma(0) = \text{random values},$$

(2. in boundary conditions

$$\frac{\mathrm{d}}{\mathrm{d}t}\Gamma = J\nabla H(\Gamma) + \text{random terms})$$

and compute expected values for some "observable" $A(\Gamma(t))$:
typically calculate an ensemble $\{\Gamma_{(\nu)}(t)\}$ and use

$$\frac{1}{N_{\text{trials}}} \sum_{\nu=1}^{N_{\text{trials}}} A(\Gamma_{(\nu)}(t)).$$

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Sensitivity (condition, robustness)

Are statistical properties sensitive to perturbations in H?

Crisanti, Falcioni, and Vulpiani, *Physica A* (1989)

"…the evolution law of chaotic dynamical systems ….
In spite of the short predictability time tp on a single trajectory
we found that the statistical properties are not sensitive to
small changes in the evolution law …. This feature holds also
for correlation functions at a delay larger than tp."

Summary

- It is standard to incorporate randomness into MD and it is appropriate to require only accurate expectations.

- Clever numerical experiments show the value of being symplectic.

- Symplectic integrators are useful because they conserve energy well and preserve volume in phase space.

Outline

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Molecular dynamics

Typically, molecular dynamics is not dynamics
    but a method for generating random numbers.

Sometimes, molecular dynamics is dynamics
    but often not the calculation of a real trajectory.

Classical biomolecular dynamics

5–500 million steps

10–100 million flops/step

use of a 32-processor cluster is representative

`folding@home` is extreme:
   200,000 desktops over the Internet
   e.g., 200 yr. of CPU time to do 700 μsec. of simulation

the world's 2 fastest computers are MD simulators

Classical atomistic model

$H(q, p) = \frac{1}{2} p^\mathsf{T} M^{-1} p + U(q)$ where $U(q)$ is a sum of

$\mathcal{O}(N)$ few-body potentials for covalent bonded forces,

$\mathcal{O}(N^2)$ 2-body potentials for nonbonded forces, e.g.,

$$U^{\mathrm{el}}(\vec{r}_1, \vec{r}_2, \ldots, \vec{r}_N) = \frac{1}{2} \sum_{i=1}^{N} \sum_{j=1}^{N}{}' \frac{Z_i Z_j}{4\pi\varepsilon_0 |\vec{r}_j - \vec{r}_i|}$$

where the primed sum omits i and those atoms covalently interacting with i. The forces: $\vec{F}_i^{\mathrm{el}} = -\nabla_i U^{\mathrm{el}}(\cdots)$.

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 II. Transient simulations

III. Steady-state simulations

IV. Numerical integrators for steady state

 V. Numerical integrators for transients

VI. Importance of being symplectic

Liouville equation

Consider random initial conditions *only*:

$$\Gamma(0) = \text{random with prob. density } \rho_0(\Gamma), \qquad \frac{\mathrm{d}}{\mathrm{d}t}\Gamma = J\nabla H(\Gamma).$$

Define
$$\rho(\Gamma, t) = \text{p.d.f. for } \Gamma(t).$$

Then

$$
\begin{aligned}
\rho(\Gamma, 0) &= \rho_0(\Gamma), \\
\rho_t + \nabla \cdot (\rho J \nabla H) &= 0, \qquad \text{(Liouville equation)}
\end{aligned}
$$

a linear hyperbolic PDE, for which $\Gamma(t)$ is a characteristic.

Transient simulations

To describe the value of a time-dependent quantity $A(\Gamma(t))$, a time-dependent ρ-weighted average is used:

$$\mathsf{E}[A(\Gamma(t))] = \int A(\Gamma)\rho(\Gamma, t)\mathrm{d}\Gamma.$$

This might be calculated as

$$\mathsf{E}[A(\Gamma(t))] \approx \frac{1}{N_{\text{trials}}} \sum_{\nu=1}^{N_{\text{trials}}} A(\Gamma_{(\nu)}(t)),$$

which requires an ensemble of, say, 10 to 10 000 dynamical trajectories with random initial conditions.

An example: conformational dynamics

Let q-space be partitioned as $A + B + C$ (states or conformations).
Consider the calculation of

$$\Pr(q(t) \in B \mid q(0) \in A)$$

given a distribution for $\Gamma(0)$.
That is, calculate

$$\iint 1_B(q)\rho(q, p, t)\, \mathrm{d}q\, \mathrm{d}p$$

where

$$1_X(q) \overset{\mathrm{def}}{=} \begin{cases} 1, & q \in X, \\ 0, & q \notin X. \end{cases}$$

A specific example

Flow of water through aquaporin (membrane protein)

<div align="right">Tajkhorshid et al., *Science* (2002)</div>

Very occasionally a water molecule colored **yellow**
traverses the channel:

command-L

produced with VMD, Theoretical and Computational Biophysics Group

Another example: time correlation functions

The velocity is $v = M^{-1}p$ and its autocorrelation function is

$$\frac{\mathsf{E}[v(t)^\mathsf{T}v(0)]}{\sqrt{\mathsf{E}[v(t)^\mathsf{T}v(t)]}\sqrt{\mathsf{E}[v(0)^\mathsf{T}v(0)]}}$$

assuming that $\mathsf{E}[v(t)] = 0$.

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Steady state

Setting $\rho_t = 0$ gives

$$\nabla H \cdot J \cdot \nabla \rho = 0,$$

which is satisfied for

$$\rho(\Gamma) = \text{function}(H(\Gamma)),$$

e.g., the Boltzmann distribution

$$\rho(\Gamma) = \mathrm{e}^{-H(\Gamma)/k_{\mathrm{B}}T} \bigg/ \int \mathrm{e}^{-H(\Gamma)/k_{\mathrm{B}}T} \mathrm{d}\Gamma.$$

models a system of constant volume kept in an environment of constant temperature T where k_{B} is Boltzmann's constant.

Approach to steady-state

Can $\rho(\Gamma, t) \to$ steady-state for a linear hyperbolic PDE?

Rate of convergence? exponential? power law?
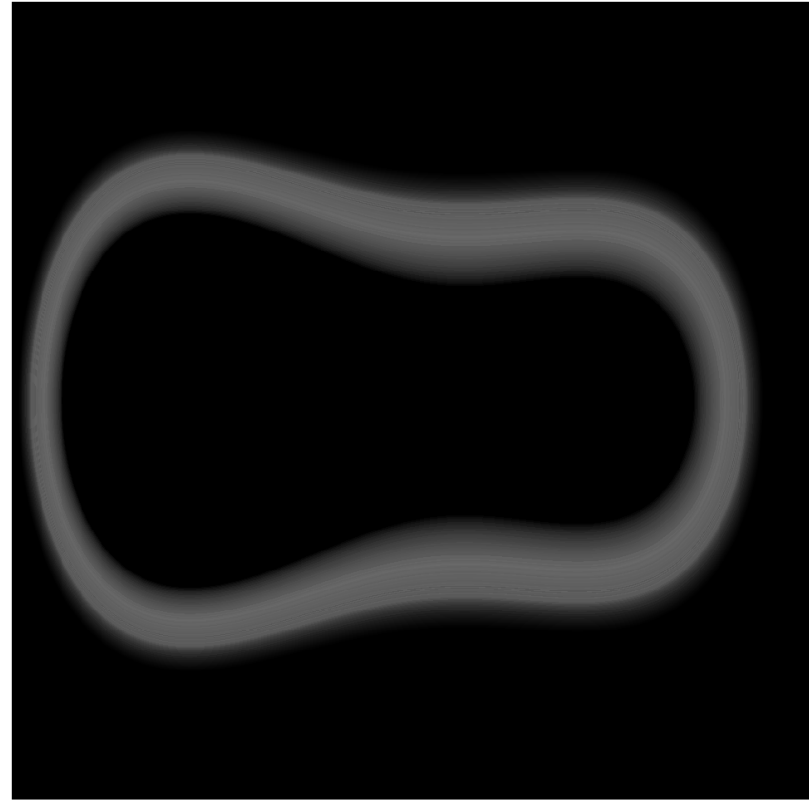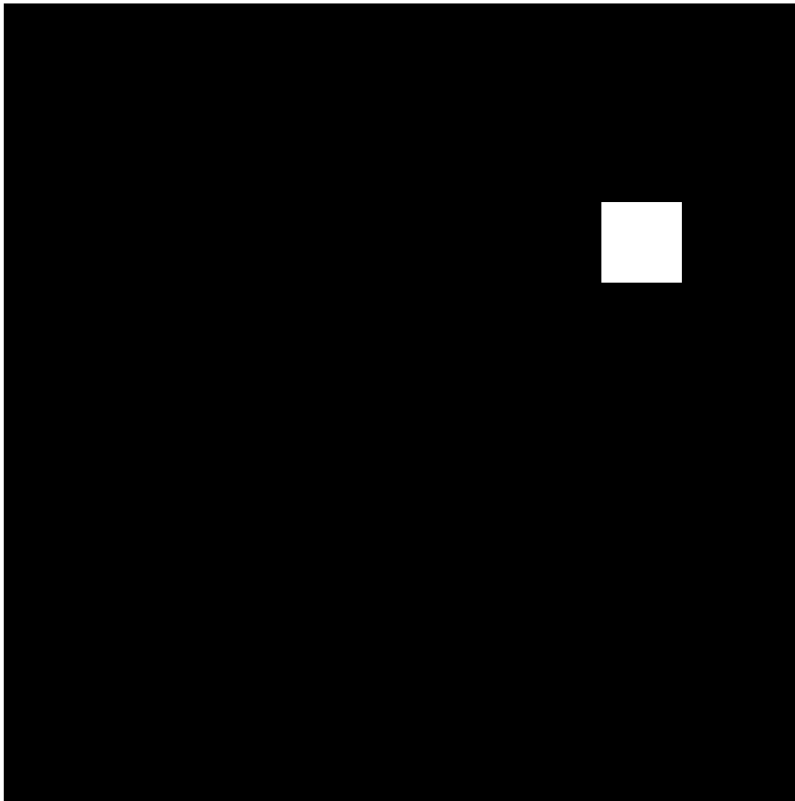
If so, ...

Steady state density

For simplicity, assume that $H(\Gamma)$ is the only conserved quantity.

Given a distribution $\rho_0(\Gamma)$, we smear it out uniformly in each shell, $E \leq H(\Gamma) \leq E + \mathrm{d}E$, of equal energy to get a density $\overline{\rho_0}$, which is a function only of $H(\Gamma)$. Formally,

$$\overline{\rho_0}(\Gamma) = \frac{\int \delta(H(\Gamma') - H(\Gamma))\rho_0(\Gamma')\mathrm{d}\Gamma'}{\int \delta(H(\Gamma') - H(\Gamma))\mathrm{d}\Gamma'}.$$

Example of steady state density

$$H(q,p) = \frac{1}{8}(q^2 - 1)^2 + \frac{1}{8}(q + 1) + \frac{1}{2}p^2$$

Mixing

Convergence occurs if the dynamics is *mixing*,

$$\rho(\Gamma, t) \overset{\text{weak}}{\rightarrow} \overline{\rho_0}(\Gamma) \quad \text{as } t \to +\infty,$$

i.e.,

$$\lim_{t \to +\infty} \int A(\Gamma)\rho(\Gamma, t)\mathrm{d}\Gamma = \int A(\Gamma)\overline{\rho_0}(\Gamma)\mathrm{d}\Gamma$$

for any smooth $A(\Gamma)$.

$$\text{e.g.,} \sin tx \overset{\text{weak}}{\rightarrow} 0 \quad \text{as } t \to +\infty,$$

Animation of mixing

Hénon-Heiles Hamiltonian

$$H(q,p) = \tfrac{1}{2}(p_1^2 + p_2^2) + \tfrac{1}{2}(q_1^2 + q_2^2 + 2q_1^2 q_2 - \tfrac{2}{3}q_2^3)$$

with 14130 initial values uniformly distributed
   in a sphere of radius 0.0045
     on the energy surface $H(q,p) = 1/8$.
1000 steps of dynamics with step size 0.125
   projected onto the two position variables.

command-L

Ergodicity

If the dynamics is *ergodic*,

$$\frac{1}{t} \int_0^t \rho(\Gamma, t')\, \mathrm{d}t' \to \overline{\rho_0}(\Gamma) \quad \text{as } t \to +\infty.$$

The existence of the limit is guaranteed by a theorem of Birkhoff; its value is the essence of ergodicity.

Steady-state simulations

In most applications, only $\rho(\Gamma)$ is needed
  and equations of motion are not essential.
To describe the value of an "observable" $A(\Gamma)$, such as
temperature, a ρ-weighted average is used:

$$\mathsf{E}[A(\Gamma)] = \int A(\Gamma)\rho(\Gamma)\mathrm{d}\Gamma.$$

This might be calculated as

$$\mathsf{E}[A(\Gamma)] \approx \frac{1}{N_\mathrm{trials}} \sum_{\nu=1}^{N_\mathrm{trials}} A(\Gamma_{(\nu)}),$$
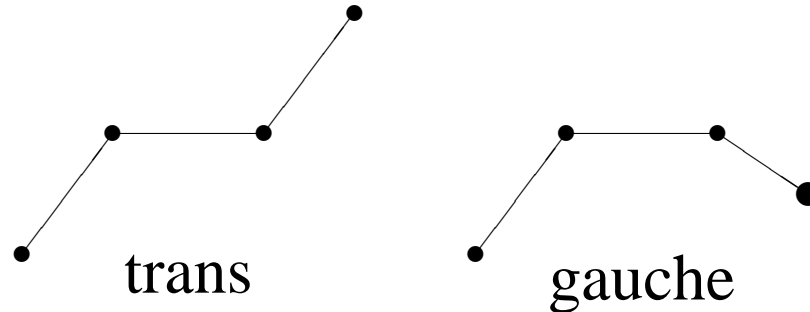
which requires random sampling of phase space.

Representative "observables"

- structure determination: most probable conformations

- free energy differences: relative probabilities of two states

- potentials of mean force: relative probabilities of differing values ξ' of a reaction coordinate $\xi(q)$:

$$\iint \delta(\xi(q) - \xi')\rho(q, p)\mathrm{d}q\mathrm{d}p.$$

Conformations

trans   gauche

- clusters of configurations

- better still, regions of configuration space such that transitions between them are rare (Schütte, Deuflhard)

- more conveniently, dihedral angle ranges and occurrences of hydrogen bonds (strong noncovalent associations)

Sampling methods

Use a stochastic (or deterministic!) ergodic Markov chain to generate Γ_1, Γ_2, ... having the desired distribution:

- Monte Carlo methods are unbiased: well designed moves are needed or hybrid Monte Carlo can be used.

- Molecular dynamics with stochastic terms can be used.

- Molecular dynamics with extended Hamiltonians can be used if ergodic.

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What is needed for steady state

A numerical integrator $\Gamma^{n+1} = \Psi(\Gamma^n)$, Γ^n "$\approx$" $\Gamma(n\Delta t)$, generates approximate densities $\rho^n(\Gamma)$.
for steady state, what is desired is some result like

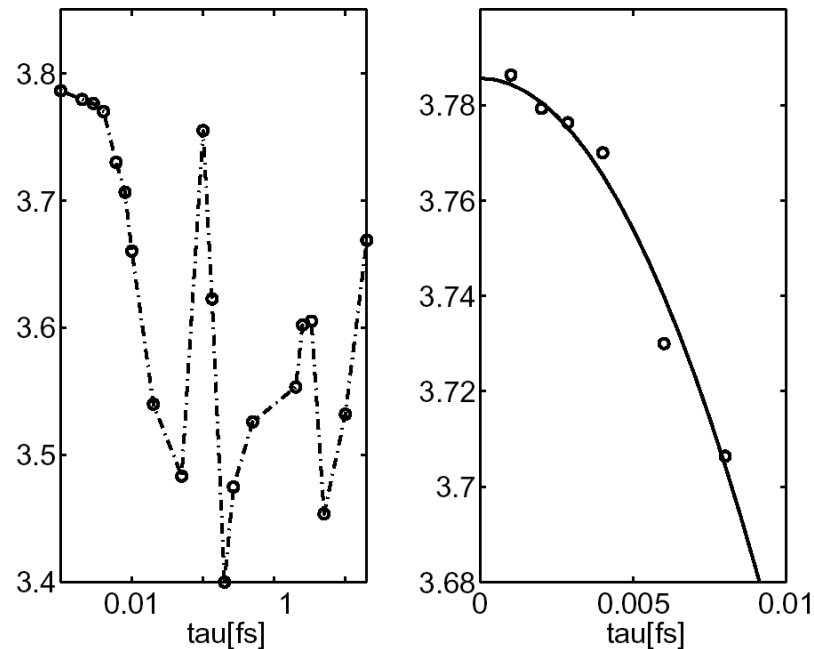$$\rho_{\Delta t}(\Gamma) = \rho(\Gamma) + O(\Delta t^k)$$

where

$$\frac{1}{t}\int_0^t \rho(\Gamma, t')\, \mathrm{d}t' \to \rho(\Gamma) \quad \text{as } t \to +\infty,$$

$$\frac{1}{N}\sum_{n=1}^N \rho^n(\Gamma) \to \rho_{\Delta t}(\Gamma) \quad \text{as } N \to +\infty,$$

and $\rho^0(\Gamma) = \rho(\Gamma, 0)$.

Example

average length of butane vs. step size

Deuflhard,
Dellnitz,
Junge &
Schütte
(1996,1999)

The choppy behavior is hardly consistent with an asymptotic expansion for $\rho_{\Delta t}(\Gamma)$ in powers of Δt.

Necessary conditions

- near conservation of energy on long time intervals

- near preservation of phase space volume: An integrator $\Gamma^{n+1} = \Psi(\Gamma^n)$ is *volume preserving* if

$$\det \partial_\Gamma \Psi(\Gamma) = 1.$$

  Indeed, one can show that ergodicity requires preservation of phase-space volume.

- small local error for Ψ.

Are these sufficient?

Steady state—some numerical evidence

Tupper(2002) creates problems for which we know analytically the distribution of $A(\Gamma)$ on most of phase space and uses this to test the accuracy of numerical integrators:

- The symplectic Euler method produces accurate results even for large step sizes.

- The Euler method with a projection on each step to exactly conserve energy produces miserable results.

- The projected backward Euler method produces good results only for small step sizes.

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What is needed for transients

Is there an analytical trajectory that shadows a numerical trajectory Γ^n? Probably not.

However, all we need is weak accuracy:

$$\mathsf{E}[A(\Gamma^n)] \approx \mathsf{E}[A(\Gamma(n\Delta t))] + \mathcal{O}(\Delta t^k).$$

or, equivalently, that $\rho^n(\Gamma) = \rho(\Gamma, n\Delta t) + \mathcal{O}(\Delta t^k)$ in the weak sense.

Importance of mixing

Long-time accuracy of numerical solutions of the Liouville
equation would seem to require that
    it have the character of a parabolic PDE,
which is to say that
    the ODE have the character of a stochastic DE.
The mixing property gives it this character.

Transients—some numerical evidence

Tupper(200x) constructs a parameterized Hamiltonian system which is arbitrarily close to a Gaussian process for which is known the exact time correlation function for the position and uses this to test the accuracy of numerical integrators for moderately long time periods:

- The symplectic Euler method accurately calculates time correlation functions even for large step sizes.

- The symplectic Euler method with energy projection produces inaccurate results for practical step sizes.

Is accuracy possible for long time periods?

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Importance of being symplectic

The integrator Ψ is symplectic if

$$(\partial_\Gamma \Psi(\Gamma))^\top J \partial_\Gamma \Psi(\Gamma) = J.$$

- exact preservation of phase space volume

- near conservation of energy for very long times

If (and only if) Ψ is symplectic, there exists a shadow (or modified) Hamiltonian $H_{\Delta t}(\Gamma)$ for which
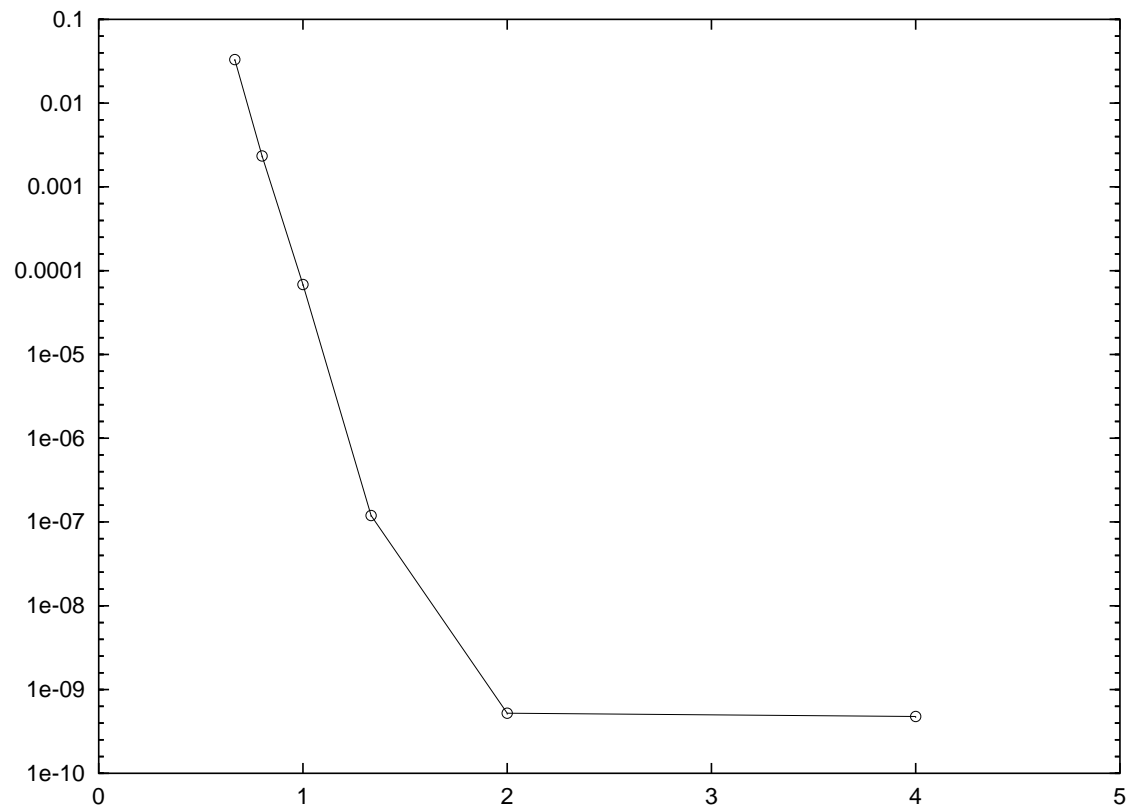
$$H_{\Delta t}(\Gamma^n) - H_{\Delta t}(\Gamma^0) = \mathcal{O}(\mathrm{e}^{-c/\Delta t}) \quad \text{for time } n\Delta t \leq \mathrm{e}^{c/\Delta t}.$$

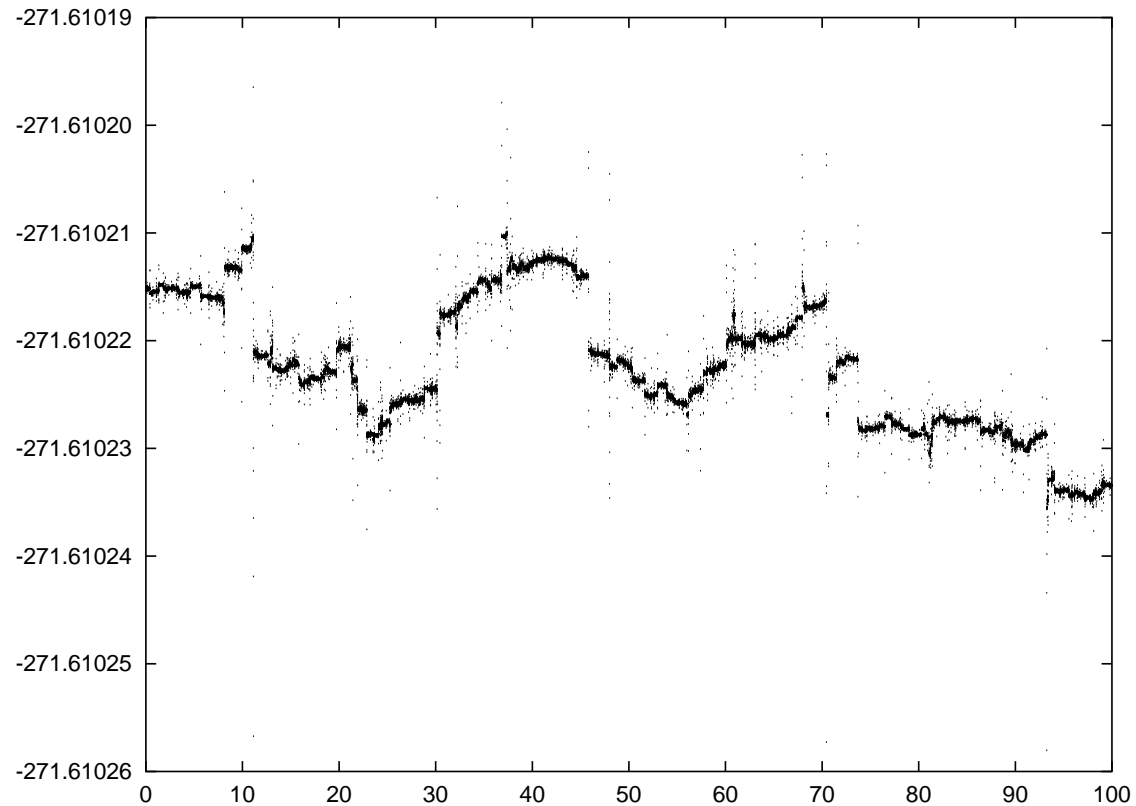# Energy conservation for molecular dynamics

Conservation of shadow Hamiltonian implies that energy fluctuates but does not drift.

Example of a 24th order shadow Hamiltonian for a 100 ps simulation of 125 flexible TIP3P water molecules.

Fluctuation range vs. $1/\Delta t$

Shadow Hamiltonian vs. time for $\Delta t = 1$ fs

Summary

- It is standard to incorporate randomness into MD and it is appropriate to require only accurate expectations.

- Clever numerical experiments show the value of being symplectic.

- Symplectic integrators are useful because they conserve energy well and preserve volume in phase space.

Further remark

Rigorous results are beyond reach. Making progress is possible only by patching together

- limited theoretical results, and

- conjectures supported by experimental results.