Molecular dynamics simulation

how to get things moving

Marcus Elstner and Tomáš Kubař

2018, April 27 & May 4

Motivation

Consider a (bio)molecule in aqueous solution
at ambient conditions

- structure is varying
- interactions are varying (H-bonds)
- the energy of the system is fluctuating
- description with a single, static structure – meaningless
- an interesting process may be going on ☺
- then, multiple ‘structures’ may be relevant

State of the system

- (micro)state of a system:
  positions $\vec{r}_i$ and momenta $\vec{p}_i$ of all the atoms
- configuration space – $3N$-dimensional space of coordinates
- phase space – $6N$-dim. space of coords and momenta $\{\vec{r}_i, \vec{p}_i\}$
- trajectory in phase space – sequence of points $\{\vec{r}_i(t), \vec{p}_i(t)\}$
  passed by the system in course of time

State of the system

example – 1D harmonic oscillator:

time course of coordinate and of velocity

$$\begin{aligned} r(t) &= a \cdot \cos[\omega t] \\ v(t) &= -a\omega \cdot \sin[\omega t] \end{aligned}$$

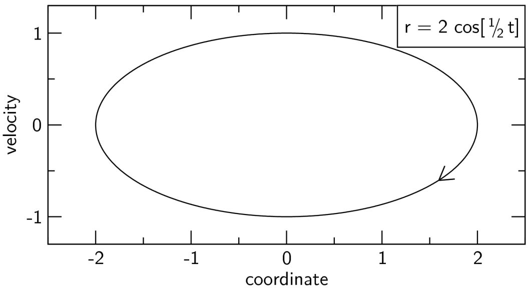
plot of velocity vs. coordinate – in 2D phase space:

elliptic trajectory

$$\left(\frac{x(t)}{a}\right)^2 + \left(\frac{v(t)}{a \cdot \omega}\right)^2 = 1$$

State of the system

Example – 1D harmonic oscillator:

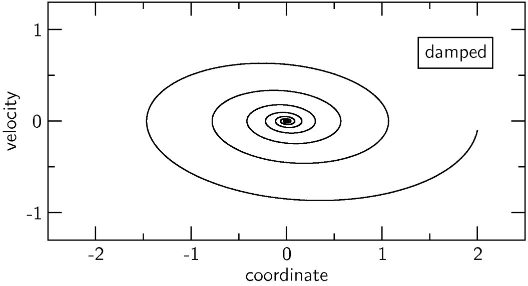


$$E_{\text{tot}} = E_{\text{kin}} + E_{\text{pot}} = \frac{1}{2} m\omega^2 a^2$$

conservative system – total energy remains conserved (constant)

State of the system

Example – 1D harmonic oscillator:

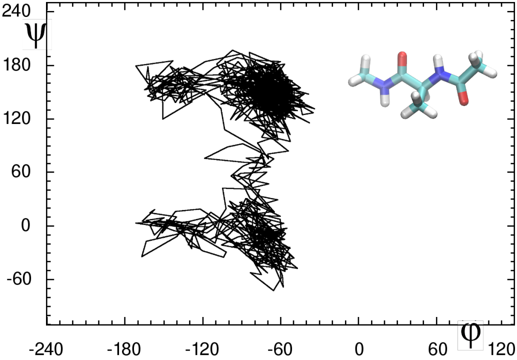


with friction or other damping

- the total energy of the system is decreasing

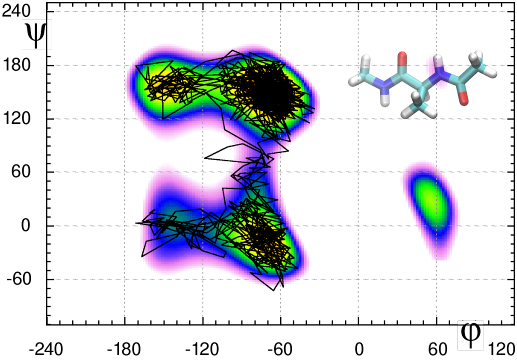
State of the system

Example – alanine dipeptide in aqueous solution:
config. space of dihedral angles $\varphi - \psi$ (Ramachandran plot)



State of the system

Example – alanine dipeptide in aqueous solution:
config. space of dihedral angles $\varphi - \psi$ (Ramachandran plot)



Thermodynamic properties

Back to the molecule in solution:

MD simulation – we generate a trajectory in phase space
for some time → snapshots $\{\vec{r}_i(t_k), \vec{p}_i(t_k)\}$,
evaluate energy in time instants t_k $(k = 1, \ldots, M) \rightarrow E_k$
and calculate the average:

$$\langle E \rangle_t = \frac{1}{M} \sum_{k=1}^{M} E_k$$

generally – we obtain the average value of the property of interest,
over all observed structures

to obtain the change of the property in a reaction:
we do this for the product and for the reactant,
obtain averages for both states and subtract them

Thermodynamic properties

we obtain the trajectory by doing an MD simulation
– a good idea, but still there are issues:

- Do we have enough snapshots? – all relevant conformations?
- How do we consider experimental conditions – temperature?
- Suppose we know the structure of the reactant.
  How do we get the structure of the product?
  or even the whole reaction path?
- Does the average of energy provide useful information?
  What about free energies / entropy?

Thermodynamic properties

Characteristics of (bio)molecular simulations:

- it is easy to derive the total energy – force field
- not so easy to make proper use of the energy function
  to get the thermodynamic properties right
- it is all about thermodynamics
  in possible contrast to quantum chemistry

Thermodynamic properties

time average for energy and other properties of interest:

$$\langle A \rangle_t = \frac{1}{t_1 - t_0} \int_{t_0}^{t_1} A(t)\,\mathrm{d}t$$

experimental sample – huge number of molecules,
all relevant conformations of molecule/solvent are present
– thermodynamic ensemble

How many molecules in the ensemble are found in $\{\vec{r}_i, \vec{p}_i\}$?
→ phase-space density (per volume unit) $\rho(\vec{r}, \vec{p})$
→ ensemble average can be calculated:

$$\langle A \rangle_e = \frac{\int A \cdot \rho(\vec{r}, \vec{p})\,\mathrm{d}\vec{r}\,\mathrm{d}\vec{p}}{\int \rho(\vec{r}, \vec{p})\,\mathrm{d}\vec{r}\,\mathrm{d}\vec{p}}$$

Thermodynamic properties

experiment – ensemble average is always measured
simulation – a single molecule – time average available

simulation – system is considered ergodic
 – passes through all points of phase space
 constituting the real ensemble
 provided the simulation is long enough
 – implies:

$$\langle A \rangle_t = \langle A \rangle_e$$

the topic of sampling, danger of undersampling

Déjà vu – energy

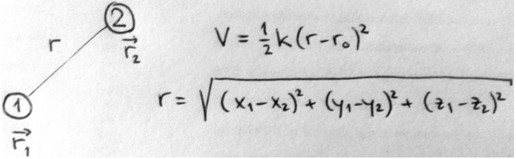
$$E(R^N) =$$

$$\begin{aligned} &= \frac{1}{2}\sum_i k_i (r_i - r_i^0)^2 + \frac{1}{2}\sum_j k_j^\vartheta (\vartheta_j - \vartheta_j^0)^2 + \frac{1}{2}\sum_n V_n \cdot \cos\left[n\omega - \gamma_n\right] \\ &+ \sum_i^N \sum_{j=i+1}^N \left\{ 4\varepsilon_{ij} \left(\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6} \right) + \frac{1}{4\pi\varepsilon_0}\frac{q_i q_j}{r_{ij}} \right\} \end{aligned}$$

Déjà vu – forces

$$V = V(r_{ij}) + V(r_{ik}) + V(r_{il}) + \ldots$$

$$F_i^x = -\frac{\partial V}{\partial x_i} = -\frac{\partial V(r_{ij})}{\partial r_{ij}} \frac{\partial r_{ij}}{\partial x_i} - \frac{\partial V(r_{ik})}{\partial r_{ik}} \frac{\partial r_{ik}}{\partial x_i} - \frac{\partial V(r_{il})}{\partial r_{il}} \frac{\partial r_{il}}{\partial x_i} - \ldots$$



$$V = \frac{1}{2}k(r-r_0)^2$$

$$r = \sqrt{(x_1-x_2)^2+(y_1-y_2)^2+(z_1-z_2)^2}$$

$$\vec{F}_1 = -k(r_{12} - r_0) \cdot \frac{\vec{r}_{12}}{r_{12}}$$

Equations of motion

total energy – Hamilton function (Hamiltonian):

$$H = T + V = \frac{1}{2}\frac{p^2}{m} + \frac{1}{2}kr^2$$

equations of motion in Hamilton's formalism:

$$\dot{r}_i = \frac{\partial H}{\partial p_i} \qquad \dot{p}_i = -\frac{\partial H}{\partial r_i}$$

leading to ordinary differential eqn (ODE) of 2nd order

$$\begin{aligned} \dot{r} &= \frac{\partial H}{\partial p} = \frac{p}{m} \rightarrow p = m\dot{r} \rightarrow \dot{p} = m \cdot \ddot{r} \\ \dot{p} &= -\frac{\partial H}{\partial r} = -\frac{\partial V}{\partial r} = F \end{aligned}$$

$$m \cdot \ddot{r} = F$$

Equations of motion

example – harmonic oscillator: $H = \frac{1}{2}\frac{p^2}{m} + \frac{1}{2}kr^2$

$$\begin{aligned} \dot{r} &= \frac{\partial H}{\partial p} = \frac{p}{m} \\ \dot{p} &= -\frac{\partial H}{\partial r} = F = -k \cdot r \end{aligned}$$

equation of motion:

$$m \cdot \ddot{r} = -k \cdot r$$

- We will use the same concept – considering x, y, z of all of the atoms instead of r, and taking forces from the ‘long equation’
- Hamilton / Lagrange formalisms are more general
  - other coordinates than x, y, z of atoms may be used
  - internal coordinates ...

Relevant differential equations

1st-order ODE

- generally: $\dot{x} = f(x, t)$
- example: $\dot{x} = -k \cdot x$
- solution: $x(t) = A \cdot \exp\left[-k \cdot t\right]$
- e.g. radioactive decay, dynamics of populations

Relevant differential equations

2nd-order ODE:

- $\ddot{x} = f(x, \dot{x}, t)$
- example: eqn of motion of harmonic oscillator $\ddot{x} = -\frac{k}{m} \cdot x$
- with linear damping: $\ddot{x} = -\zeta \cdot \dot{x} - \frac{k}{m} \cdot x$
- reduction of 2nd-order ODE to two 1st-order ODEs by introducing velocity v:

$$\begin{aligned} \dot{x} &= v \\ \dot{v} &= -\zeta \cdot v - \frac{k}{m} \cdot x \end{aligned}$$

these ODEs have to be solved numerically

(Too) simple numerical solution

$$\ddot{r} = f(r, t)$$

common trick – Taylor expansion ($\Delta t = t - t_0$):

$$r(t) = r(t_0) + \dot{r}(t_0) \cdot \Delta t + \frac{1}{2}\ddot{r}(t_0) \cdot \Delta t^2 + \ldots$$

Euler method – 1st-order approximation:

$$r(t) \approx r(t_0) + \dot{r}(t_0) \cdot \Delta t$$

Numerical integration starts at time t_0 – we make a step Δt:

$$\begin{aligned} a(t_0) &= -\frac{F}{m} \\ r(t_0 + \Delta t) &= r(t_0) + v(t_0) \cdot \Delta t \\ v(t_0 + \Delta t) &= v(t_0) + a(t_0) \cdot \Delta t \end{aligned}$$

Verlet – normal form

Euler method – too large numerical error $\mathcal{O}(\Delta t^2)$
more accurate integration is needed

Verlet method:
Taylor expansion up to 2nd order,
derivation from two virtual steps, forwards and backwards:

$$\begin{aligned} r(t+\Delta t) &= r(t) + \dot{r}(t)\cdot\Delta t + \frac{1}{2}\ddot{r}(t)\cdot\Delta t^2 \\ r(t-\Delta t) &= r(t) - \dot{r}(t)\cdot\Delta t + \frac{1}{2}\ddot{r}(t)\cdot\Delta t^2 \end{aligned}$$

add both equations – eliminate the velocity $\dot{r}$:

$$\begin{aligned} r(t+\Delta t) &= 2\cdot r(t) - r(t-\Delta t) + \ddot{r}(t)\Delta t^2 \\ \ddot{r}(t) &= a(t) = \frac{F(t)}{m} = -\frac{1}{m}\frac{\partial V}{\partial r}(t) \end{aligned}$$

Verlet – normal form

$$r(t+\Delta t) \;=\; 2\cdot r(t) - r(t-\Delta t) + \ddot{r}(t)\Delta t^2$$

strange – not only $r(t)$ and $a(t)$ needed, but also $r(t-\Delta t)$?
no problem – information equivalent to velocity, so that initial conditions may be converted:

$$r(t_0-\Delta t) = r(t_0) - v(t_0)\cdot\Delta t$$

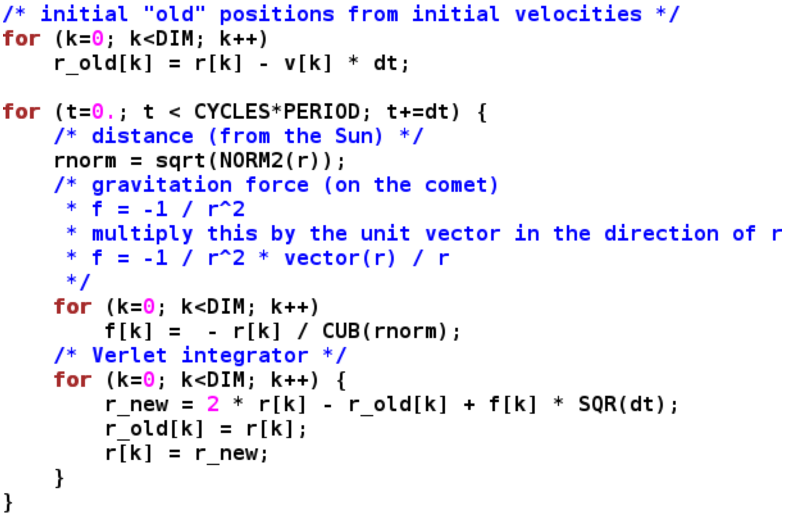
velocities – not in there explicitly, but may be obtained:

$$\dot{r}(t) = v(t) = \frac{r(t+\Delta t) - r(t-\Delta t)}{2\cdot\Delta t}$$

(Verlet normal form)

Verlet – normal form

program for ‘astronomic’ simulations: $(\vec{F} = -1/r^2 \cdot \vec{r}/r)$



```
/* initial "old" positions from initial velocities */
for (k=0; k<DIM; k++)
    r_old[k] = r[k] - v[k] * dt;

for (t=0.; t < CYCLES*PERIOD; t+=dt) {
    /* distance (from the Sun) */
    rnorm = sqrt(NORM2(r));
    /* gravitation force (on the comet)
     * f = -1 / r^2
     * multiply this by the unit vector in the direction of r
     * f = -1 / r^2 * vector(r) / r
     */
    for (k=0; k<DIM; k++)
        f[k] =  - r[k] / CUB(rnorm);
    /* Verlet integrator */
    for (k=0; k<DIM; k++) {
        r_new = 2 * r[k] - r_old[k] + f[k] * SQR(dt);
        r_old[k] = r[k];
        r[k] = r_new;
    }
}
```

Detailed balance

In equilibrium, this condition holds:
The rate of transitions from state i to state j
is the same as from j to i, on average.

In the other words: the flux of probability from state i to state j
is exactly balanced by the probability flux from j to i:

$$p_{i\to j} \cdot \rho_i^{\mathrm{eq}} = p_{j\to i} \cdot \rho_j^{\mathrm{eq}}$$

The probability ρ depends on the ensemble
(which in turn depends on the conditions):

- isolated system – microcanonical ensemble:
  principle of equal a priori probabilities, $\rho_i^{\mathrm{eq}} = \rho$
- closed system – canonical ensemble: $\rho_i^{\mathrm{eq}} \propto \exp[-\beta E_i]$

Any MD algorithm/implementation shall observe detailed balance!

Velocity Verlet

another, equivalent formulation

- positions calculated first using velocities

$$r(t+\Delta t) = r(t) + v(t)\cdot\Delta t + \frac{1}{2}a(t)\cdot\Delta t^2$$

- forces (→ accelerations) calculated in new positions,
  and new velocities obtained as

$$v(t+\Delta t) = v(t) + \frac{1}{2}\big(a(t) + a(t+\Delta t)\big)\cdot\Delta t$$

- next calculation of positions $r\dots$

MD is started with the knowledge of r_0 and v_0
in every step, $r(t+\Delta t)$ is calculated first
so that $a(t+\Delta t)$ can be updated, to get $v(t+\Delta t)$

Velocity Verlet

VV – better numerical precision than normal Verlet

numerical problem of normal Verlet

- – adding a small but important term $\ddot{r}(t_0)\Delta t^2$ to a large term calculated as difference: $2r(t) - r(t - \Delta t)$
- – large relative uncertainty

desirable – use an algorithm that is mathematically equivalent but does not require to perform potentially problematic calculations

Leap-frog

yet another equivalent formulation, similar to VV

– r and v are evaluated in an alternating fashion:

$r(t)$, $v(t+\frac{1}{2}\Delta t)$, $r(t+\Delta t)$, $v(t+\frac{3}{2}\Delta t)$, $r(t+2\Delta t)$ ...

- velocities at $t+\frac{1}{2}\Delta t$ are obtained first:

$$v(t+\tfrac{1}{2}\Delta t) = v(t-\tfrac{1}{2}\Delta t) + a(t)\cdot\Delta t$$

- then, positions are updated at $t+\Delta t$:

$$r(t+\Delta t) = r(t) + v(t+\tfrac{1}{2}\Delta t)\cdot\Delta t$$

So, accelerations have to be calculated at t, $t+\Delta t$, $t+2\Delta t$...
from forces, and positions are needed to compute forces
– in fact, positions have to be known at the same t that we need a

Initial conditions

To start the MD
– the positions r_0 and the velocities v_0 have to be specified
First step – calculations of forces at r_0 to get accelerations a_0
Then – the integrator may provide r (and v) at time $t_0 + \Delta t$

To obtain a trajectory over a time interval T,
we perform M steps
– we have to evaluate the forces on all atoms $M = T/\Delta t$ times

Computational cost of the calculation of forces
determines how many steps we can afford to make

Δt – crucial parameter

Numerical issue:

- we neglect contributions in Δt^3 and higher orders $\rightarrow$ error per step in the order of Δt^3 ($\mathcal{O}(\Delta t^3)$)
- keep the step short $\rightarrow$ make the error small
- disadvantage: we may need too many steps to simulate certain time T
- trade-off: Δt too long $\rightarrow$ too large error
  dynamics may deviate, momentum may not be conserved…

Δt – crucial parameter

Chemical issue:

- fastest motion – hydrogen atoms, period around 10 fs
- rule of thumb – stable integration with $\Delta t \leq$ fastest period (much more relaxed than in ‘astronomic’ simulations ☺)
- practically, Δt of 1 fs is used (2 fs with special treatment)

→ 1M calculations of forces needes for a trajectory of 1 ns
large systems – multi-ns simulations routinely, μs possible

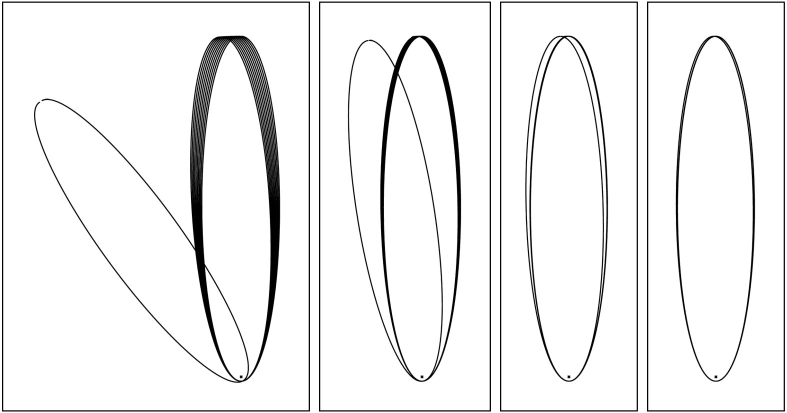
Δt – astronomic test

static heavy object (star) + moving light object (comet)
+ gravity ($F = -1/r^2$) → dynamics with Verlet integrator
gravity – inverse-square law much like Coulomb between atoms
exact trajectory – periodic along an ellipse with star in 1 focus

simulation – four different values of the time step:
1×10^{-5}, 2×10^{-5}, 5×10^{-5} and 10×10^{-5} of the orbital period
→ 100k, 50k, 20k and 10k steps per period – mmore than in MD

Δt – astronomic test

first 10 orbits are shown, and then the 100th shown again



credit for the idea: Jiří Kolafa, Prague

Δt – astronomic test

shortest step – reasonable trajectory, small deviation
2nd-longest step – error becomes evident
longest step – large deviation

important – trajectory is precessing (ellipse is ‘rotating’),
but it remains elliptic whatever the time step is
constant remain also total energy and orbital period
– consequence of reversibility of Verlet:
if we reverse the course of time ($\Delta t \rightarrow -\Delta t$),
we will simulate towards initial conditions of the trajectory

generally – energy in Verlet fluctuates (with longer step),
but it does not drift

Verlet or something better?

Verlet – very approximative yet still routinely used for MD
why? – because it is efficient – why?

- forces on atoms (→ accelerations) calculated only 1× per step
- no higher derivatives of positions are involved

more accurate methods to integrate ODEs are available, and
are used in some applications, if improved accuracy is required

straightforward – involve extra terms from Taylor expansion
– hardly ever done, there are other ways to improve accuracy. . .

Gear: predictor–corrector

- provides solution correct to an order of choice
- new positions are calculated (predicted) from Taylor expansion
  using a certain number of previous steps
- then, forces ($\rightarrow$ accelerations)
  are calculated in the predicted positions
- accelerations used to make correction of positions
- additional computational effort, decreased efficiency
- accuracy may be improved significantly, longer step possible
- still, only 1 calculation of forces per step

Gear: predictor–corrector

nth-order Gear integrator:
coords of all atoms $\vec{r}$ and their derivatives up to the order of $n-1$:

$$R = \begin{pmatrix} \vec{r} \\ \dot{\vec{r}} \cdot \Delta t \\ \ddot{\vec{r}} \cdot \frac{1}{2}\Delta t^2 \\ \dddot{\vec{r}} \cdot \frac{1}{6}\Delta t^3 \end{pmatrix}$$

for the 4th-order method

initialization: $\vec{r}$ and $\dot{\vec{r}}$ from init. conditions, $\ddot{\vec{r}}$ calculated from forces
– 1 calculation of forces required at start
higher derivatives may be set to zero

Gear: 1: prediction

MD step at time t starts with prediction
of coordinates+derivatives at time $t + \Delta t$:

$$R_{\mathrm{p}}(t + \Delta t) = \begin{pmatrix} 1 & 1 & 1 & 1 \\ 0 & 1 & 2 & 3 \\ 0 & 0 & 1 & 3 \\ 0 & 0 & 0 & 1 \end{pmatrix} \cdot R(t)$$

- the matrix contains binomial coefficients
- the calculation passes a polynomial of order $n - 1$
  through the previous n points of the trajectory
  (at t, $t - \Delta t, \ldots t - (n-1)\Delta t$)
  and generates a point on this polynomial after Δt
- prediction may be good for continuous force functions
- no calculation of force up to this point!

Gear: 2: error

next, we calculate the error of the prediction:
we obtain the force at the predicted position,
and compare it with the force predicted in step 1 → error

$$E = \frac{1}{2}\left(\frac{\vec{f}(\vec{r}_{\mathrm{p}})}{m} - \ddot{\vec{r}}_{\mathrm{p}}\right)\Delta t^2$$

E – vector with as many components as the vector of coordinates
(every coordinate with its derivatives has ‘its own’ error)

Gear: 3: correction

Finally, using the error E, we calculate the corrected coordinates and derivatives as

$$R(t+\Delta t) = R_{\mathrm{p}}(t+\Delta t) + E \cdot \begin{pmatrix} a_0 \\ a_1 \\ a_2 \\ a_3 \end{pmatrix}$$

coefficients $a_0,\ a_1 \ldots a_{n-1}$

– estimated to prevent the accumulation of integration errors

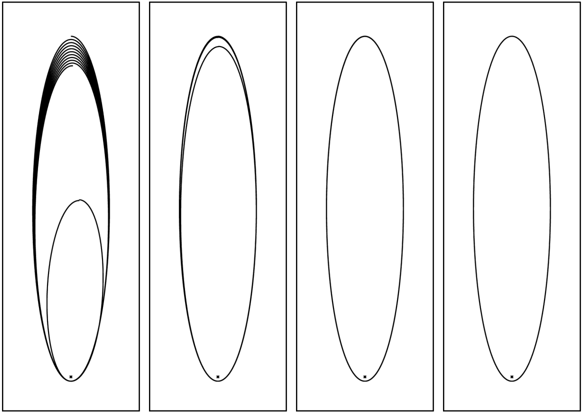
– may be looked up in tables

– for 4th-order method for 2nd-order ODE and forces not depending on velocities:

$a_0 = \frac{1}{6}$, $a_1 = \frac{5}{6}$, $a_2 = 1$ and $a_3 = \frac{1}{3}$

Gear – astronomic test

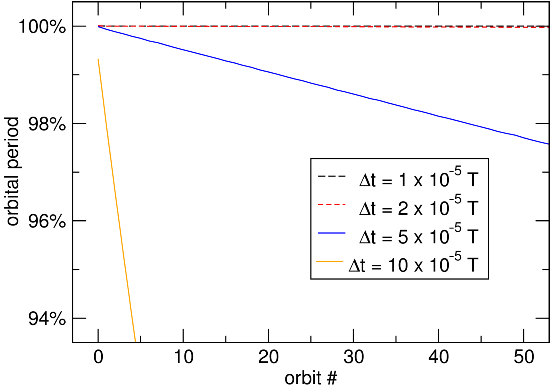
$\Delta t = 10 \times 10^{-5}$, 5×10^{-5}, 2×10^{-5} and 1×10^{-5} of correct period



Gear – astronomic test

- Gear may provide more accurate trajectories than Verlet,
  with the same Δt
- perfect trajectories with the two shortest time steps
  (Verlet showed deviations even with the shortest step)
- incorrect behavior with the second-largest step,
  just wrong with the longest one
- different character of deviation than with Verlet:
  the elliptic trajectory of the comet is getting ‘shorter’,
  rather than precessing
- important: the orbital period is becoming shorter,
  and total energy is decreasing

Gear – astronomic test



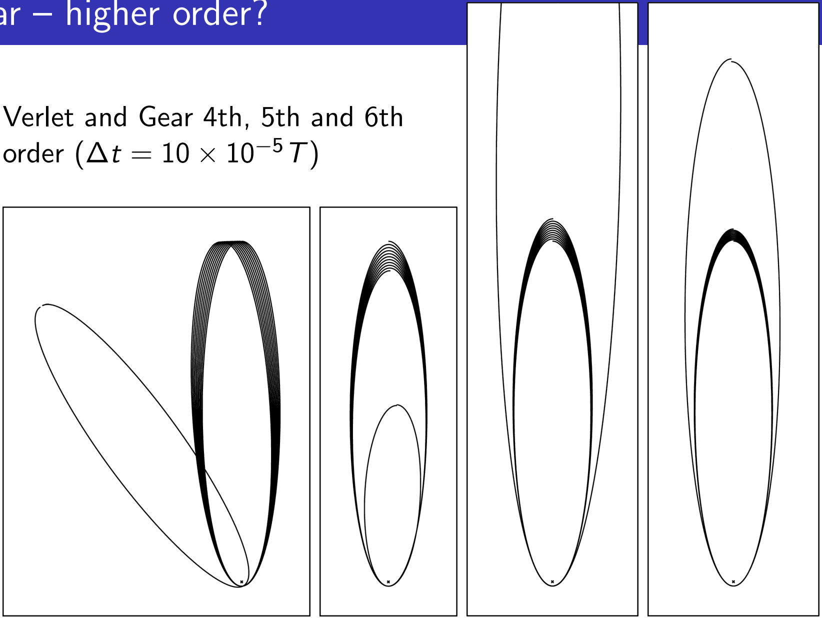
general observation:

- energy will decrease or increase (drift) in the simulation
- this may be negligible with longer step / higher-order Gear

Gear: not reversible, does not conserve energy.

Gear – higher order?

Verlet and Gear 4th, 5th and 6th order ($\Delta t = 10 \times 10^{-5} T$)



Gear – higher order?

note: Verlet corresponds to 3th-order Gear formally
higher derivatives in calculation improve the results only slightly
– the drift of energy is slower but still unsatisfactory

general observations:

- when making the step shorter,
  results of higher-order methods will improve faster
- when making the time step longer,
  higher-order methods are more prone to fail completely
  while lower-order methods are more robust
- higher-order integrators are a good choice
  if accurate trajectories are desired
- lower-order or Verlet integration is sufficient for applications
  with 'weaker' requirements – typically, MD

Runge–Kutta integration

Runge–Kutta methods – numerical integrators of 1st-order ODEs
classical 4th-order method RK4:

- 4 calculations of the derivative in every step
- points at which the derivative is calculated
  - chosen depending on the previous calculations,
  - the first is done at the start of the integration step

$$\begin{aligned} g_0 &= \dot{r}\left(r(t)\right) \\ g_1 &= \dot{r}\left(r(t) + \tfrac{1}{2} g_0 \Delta t\right) \\ g_2 &= \dot{r}\left(r(t) + \tfrac{1}{2} g_1 \Delta t\right) \\ g_3 &= \dot{r}\left(r(t) + g_2 \Delta t\right) \end{aligned}$$

We calculate the value of the function at time $t + \Delta t$
using a weighted average of the obtained derivative values:

$$r_{n+1} = r_n + \tfrac{1}{6}\left(g_0 + 2g_1 + 2g_2 + g_3\right) \cdot \Delta t$$

the RK4 method

derivative of y is calculated at points m_0, m_1, m_2 and m_3

calculated derivatives $g_0, \ldots g_3$ are shown as arrows

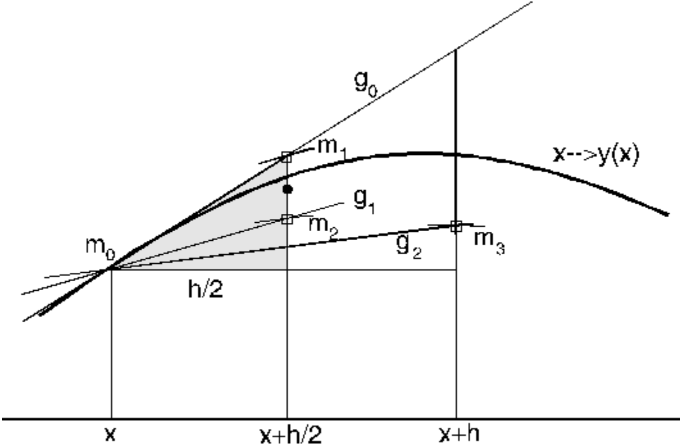


image downloaded from `www.hsg-kl.de`

the RK4 method

- actually predictor–corrector with 4 predictions per step
- 4 calculations of the derivative needed per step
- error per step reduced to $\mathcal{O}(\Delta t^5)$ – 4th-order method
- solves 1st-order ODEs much like the Euler method does
- to solve Newton eqns of motion (2nd-order ODEs)
  - eqns are converted to system of two 1st-order eqns
  - positions and velocities of atoms are propagated:

$$\begin{aligned}\dot{\vec{r}} &= \vec{v}\\ \dot{\vec{v}} &= \frac{\vec{f}}{m}\end{aligned}$$

the RK4 method

Can RK4 be used directly somewhere in computational chemistry?
Yes! Let us propagates a time-dependent Schrödinger equation
– 1st-order ODE for the wave function Ψ of the system:

$$\frac{\partial \Psi}{\partial t} = -\frac{i}{\hbar}\hat{H}\Psi$$

- we express Ψ as linear combination of suitable basis functions:
  $\Psi = \sum_m c_m \varphi_m$
- Hamiltonian is a matrix of elements between basis functions:
  $H_{mn} = \left\langle \varphi_m \middle| \hat{H} \middle| \varphi_n \right\rangle$
- we calculate the derivative with matrix multiplication as $H \cdot \Psi$