Molecular dynamics simulation

addendum

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May 11, 2016

Dèja vu – energy

$$E(R^N) =$$

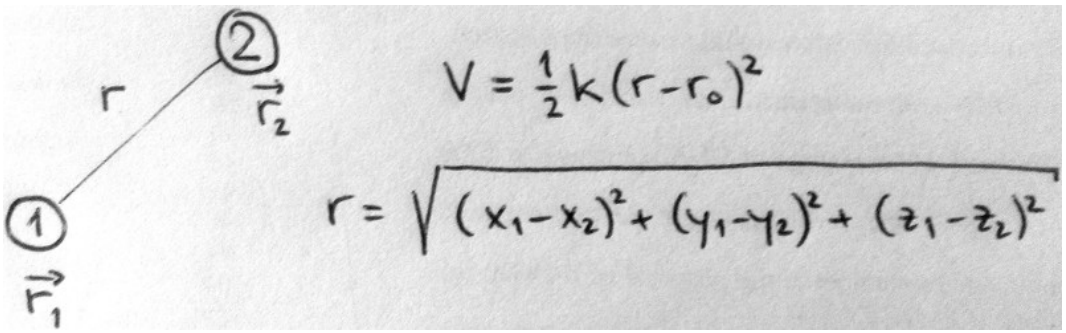
$$= \frac{1}{2}\sum_i k_i(r_i - r_i^0)^2 + \frac{1}{2}\sum_j k_j^{\vartheta}(\vartheta_j - \vartheta_j^0)^2 + \frac{1}{2}\sum_n V_n \cdot \cos\left[n\omega - \gamma_n\right]$$

$$+ \sum_i^N \sum_{j=i+1}^N \left\{ 4\varepsilon_{ij}\left(\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right) + \frac{1}{4\pi\varepsilon_0}\frac{q_i q_j}{r_{ij}} \right\}$$

Dèja vu – forces

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

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



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

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

$$\dot{r} = \frac{\partial H}{\partial p} = \frac{p}{m} \rightarrow p = m\dot{r} \rightarrow \dot{p} = m \cdot \ddot{r}$$

$$\dot{p} = -\frac{\partial H}{\partial r} = -\frac{\partial V}{\partial r} = F$$

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

Verlet – normal form

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

$r(t-\Delta t)$? 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 – alternatives

. . . with improved numerical behavior:

- Velocity Verlet

$$\begin{aligned} r(t+\Delta t) &= r(t) + v(t)\cdot\Delta t + \tfrac{1}{2}a(t)\cdot\Delta t^2 \\ v(t+\Delta t) &= v(t) + \tfrac{1}{2}\big(a(t)+a(t+\Delta t)\big)\cdot\Delta t \end{aligned}$$

- leap-frog

$$\begin{aligned} v(t+\tfrac{1}{2}\Delta t) &= v(t-\tfrac{1}{2}\Delta t) + a(t)\cdot\Delta t \\ r(t+\Delta t) &= r(t) + v(t+\tfrac{1}{2}\Delta t)\cdot\Delta t \end{aligned}$$

Constraint dynamics

Dynamics of large flexible (bio) molecules
- complex combination of different motions

High frequency modes of motions – bond stretch / angle bend
- rather uninteresting, no need for exact description

Lower frequency modes – dihedrals and larger
- conformational changes, important, must be treated properly

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Time step – directed by the highest-frequency modes involved
Idea – keep the bonds (or, additionally, angles) fixed,
and leave other modes of motion untouched
– introduce constraints

Constraint dynamics

Constraint

- requirement that the system is required to meet
- example: a bond has length of d exactly: $|\vec{r}_{12}|^2 = d^2$
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Restraint

- additional energy contribution in the force field
- example: using NMR-estimated distance of atoms j and k,
  $V_{\text{rest}} = \frac{1}{2} k_{\text{rest}} (r_{jk} - r_{\text{NMR}})^2$
- imposes an energy penalty on any deviation,
  but still r_{jk} is allowed to deviate from r_{NMR}
- the affected mode still contributes $\frac{1}{2} kT$ to kinetic energy

Constraint dynamics

Introduce additional forces $\vec{G}$ on atoms,
which keep the bond lengths and optionally angles fixed:

$$m_i \ddot{\vec{r}}_i = \vec{F}_i + \vec{G}_i$$

Technique:

- integrate eqns of motion for one step with 'normal' forces $\vec{F}$, but for now without considering $\vec{G}$
- determine the forces $\vec{G}$ required to satisfy constraints
- correct the new atom positions

Constraint dynamics

Example: 3-atomic molecule, bonds 1–2 and 2–3 fixed, angle is free

Eqns of motion:

$$\begin{aligned} m_1 \ddot{\vec{r}}_1 &= \vec{F}_1 + \vec{G}_1 \\ m_2 \ddot{\vec{r}}_2 &= \vec{F}_2 + \vec{G}_2 \\ m_3 \ddot{\vec{r}}_3 &= \vec{F}_3 + \vec{G}_3 \end{aligned}$$

Constraints to be fulfilled:

$$\begin{aligned} \chi_{12} &= r_{12}^2 - d_{12}^2 = 0 \\ \chi_{23} &= r_{23}^2 - d_{23}^2 = 0 \end{aligned}$$

Constraint dynamics

Lagrangian mechanics provides the constraint forces, generally:

$$\vec{G}_a = \frac{1}{2}\lambda_{12}\nabla_a\chi_{12} + \frac{2}{3}\lambda_{23}\nabla_a\chi_{23}$$

with so-far undetermined Lagrange multipliers λ

$\vec{G}$ must be directed along bonds and obey Newton'd 3rd law:

$$\begin{aligned}
\vec{G}_1 &= \lambda_{12}\vec{r}_{12} \\
\vec{G}_2 &= -\lambda_{12}\vec{r}_{12} + \lambda_{23}\vec{r}_{23} \\
\vec{G}_3 &= -\lambda_{23}\vec{r}_{23}
\end{aligned}$$

Constraint dynamics

Modified integrator eqn:

$$\vec{r}_i(t+\Delta t) = \vec{r}'_i(t+\Delta t) + \Delta t^2/m_i \cdot \vec{G}_i$$

Insert the previously obtained constraint forces

$$\begin{aligned}
\vec{r}_1(t+\Delta t) &= \vec{r}'_1(t+\Delta t) + \Delta t^2/m_1 \cdot \lambda_{12}\vec{r}_{12} \\
\vec{r}_2(t+\Delta t) &= \vec{r}'_2(t+\Delta t) + \Delta t^2/m_2 \cdot (-\lambda_{12}\vec{r}_{12} + \lambda_{23}\vec{r}_{23}) \\
\vec{r}_3(t+\Delta t) &= \vec{r}'_3(t+\Delta t) + \Delta t^2/m_3 \cdot (-\lambda_{23}\vec{r}_{23})
\end{aligned}$$

Subtract eqns I–II and II–III to obtain the lengths to be fixed

Constraint dynamics

$$
\begin{aligned}
\vec{r}_{12}(t+\Delta t) &= \vec{r}'_{12}(t+\Delta t) + \\
&+ \Delta t^2 (m_1^{-1} + m_2^{-1}) \cdot \lambda_{12} \vec{r}_{12} - \Delta t^2 m_2^{-1} \cdot \lambda_{23} \vec{r}_{23} \\
\vec{r}_{23}(t+\Delta t) &= \vec{r}'_{23}(t+\Delta t) - \\
&- \Delta t^2 m_2^{-1} \cdot \lambda_{12} \vec{r}_{12} + \Delta t^2 (m_2^{-1} + m_3^{-1}) \cdot \lambda_{23} \vec{r}_{23}
\end{aligned}
$$

- take square modulus of both sides of eqns ($|\vec{r}_{12}|^2, \ldots$)
- apply constraints, $|\vec{r}_{12}|^2 = d_{12}^2, \ldots$
- obtain a set of quadratic eqns for λ_{12} and λ_{23}
- solve, perhaps in a linearized form and iteratively
- obtain the final new coordinates from (previous slide)

$$\vec{r}_1(t+\Delta t) = \vec{r}'_1(t+\Delta t) + \Delta t^2 / m_1 \cdot \lambda_{12} \vec{r}_{12}$$

SHAKE

Large (bio)molecule – large number of constraints n_c
Set of eqns – solution requires inversion of an $n_c \times n_c$ matrix
– possibly time-consuming

SHAKE – an alternative algorithm:

- process the constraints one by one
- satisfying one constraint may violate another
  $\rightarrow$ iterative procedure necessary
- run until all constraints are met within a preset tolerance
- angle constraints – re-formulate as bond constraints (rigid Δ)

Similar algorithms exist for other integrators,
e.g. RATTLE for velocity Verlet, to treat velocities

LINCS, SETTLE

LINCS – yet another constraint algorithm

- resets bond lengths after an unconstrained integration step
- non-iterative, no expensive matrix operations
- faster and more stable than SHAKE
- available for bond constraints and isolated angle constraints

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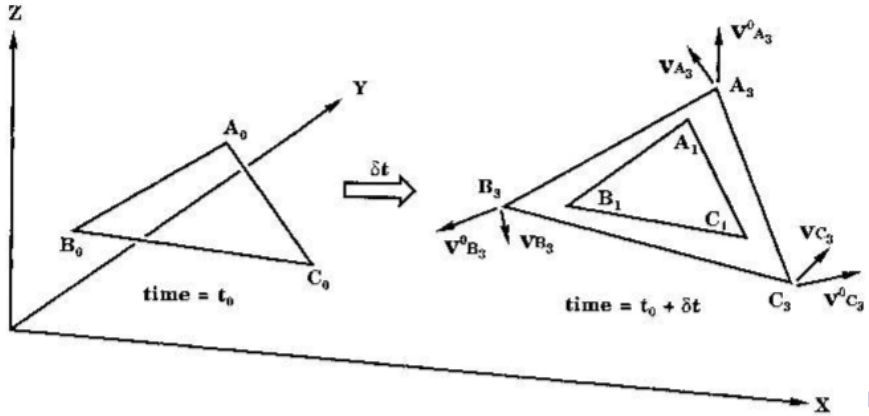
SETTLE – specialized algorithm for rigid triangles – H_2O

- 3 bond constraints for a molecule with 3 atoms
- analytical, non-iterative solution of SHAKE+RATTLE
- fulfills constraints exactly ($\rightarrow$ no tolerance values needed)
- faster than SHAKE $\rightarrow$ useful for molecules in aqueous solution



Constraint dynamics

Condition

- no coupling between the constrained and unconstrained modes of motion

Usual choices

- bonds with hydrogen
  - Δt may be increased from 1 to 2 fs
- all bonds
- all bonds + all angles
  - looks absurd, but may be a good idea for proteins

Restrained molecular dynamics

Additional contributions in the eqn for total (potential) energy

- 'penalty' for deviation from a desired value of a coordinate
- generates additional force
- still, the coordinate *may* deviate from the desired value

position restraints, angle restraints, distance restraints, orientation restraints and dihedral restraints

Position restraints

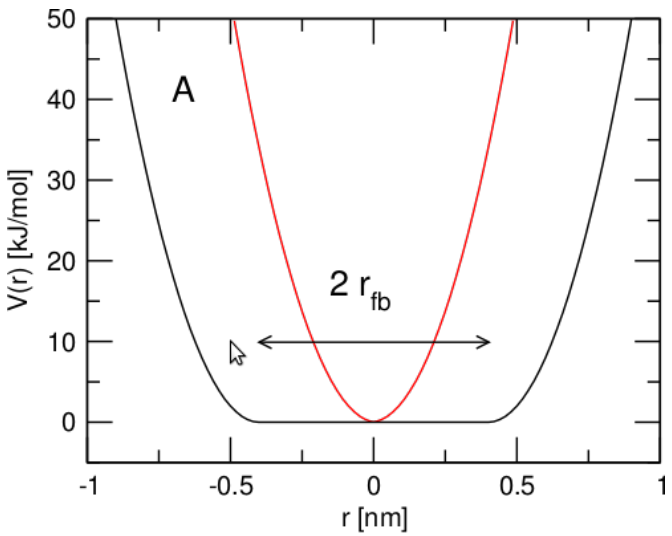
distance of an atom from a fixed reference position $\vec{R}_i$:

$$V_{\text{posres}} = \frac{1}{2} k_{\text{posres}} \left| \vec{r}_i - \vec{R}_i \right|^2$$

- to restrain e.g. the protein during equilibration
  while the solvent is free to move
  – prevent any unwanted drastic rearrangements
- to restrain the surroundings of a region of interest
  whenever there is not enough info on the surroundings
  – the region of interest is simulated without restrains

Flat-bottomed position restraints

- no energy penalty up to a certain distance r_{fb} from the reference position
- restraints the atom to a volume rather than to a point

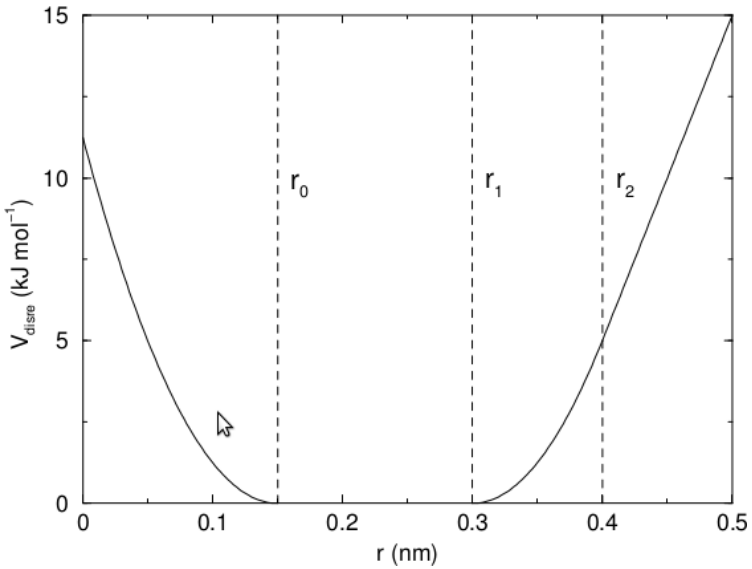


$$r = \left| \vec{r}_i - \vec{R}_i \right|$$

$$V_{\text{fb}} = \begin{cases} \frac{1}{2} k_{\text{fbpr}} (r - r_{\text{fb}})^2 & \text{if } r > r_{\text{fb}} \\ 0 & \text{if } r < r_{\text{fb}} \end{cases}$$

Distance restraints

- penalty according to the distance between two atoms
- often – impose experimental restraints on molecular motion
  e.g. from NMR or diffraction experiments
- MD – tool for structure refinement using NMR data
- optionally time- or ensemble-averaging



$$r = |\vec{r}_i - \vec{r}_j|$$

$$V_{\mathrm{dr}} = \begin{cases} \frac{1}{2} k_{\mathrm{dr}} (r_0 - r)^2 & \text{if } r < r_0 \\ 0 & \text{if } r_0 < r < r_1 \\ \frac{1}{2} k_{\mathrm{dr}} (r - r_1)^2 & \text{if } r_1 < r < r_2 \\ \frac{1}{2} k_{\mathrm{dr}} r (r_2 - r_1) + c & \text{if } r > r_2 \end{cases}$$

Restraints – further ideas

- angle restraints – angle between two bonds
- dihedral restraints
- orientation restraints – angle of two vectors
- time averaging for distance restraints
  – so that fluctuations are not damped
- averaging over multiple pairs of atoms
  – due to the nature of NMR data