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

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

Constraint dynamics

Constraint

- condition that the system is required to meet
- example: a bond has length of d exactly: $|\vec{r}_{12}|^2 = d^2$
- the associated mode of motion does not contain any energy

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

Formally:

Introduce additional (artificial) 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:

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

The math is somewhat complex...

Constraint dynamics – details 1

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:

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

Constraint dynamics – details 2

Lagrangian mechanics provides the constraint forces, generally:

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

with so-far undetermined Lagrange multipliers λ

conditions for $\vec{G}_a$:

- must be directed along bonds (to only affect the bond length)
- must obey Newton's 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 – details 3

Modified eqn for the Verlet integrator:

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

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
$\rightarrow$ obtain 2 conditions, from which
2 unknowns λ_{12} and λ_{23} can be determined

Constraint dynamics – details 4

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

- take square modulus of both sides of eqns ($|\vec{r}_{12}|^2$, ...)
- apply constraints, $|\vec{r}_{12}|^2 = d_{12}^2$, ...
- 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:

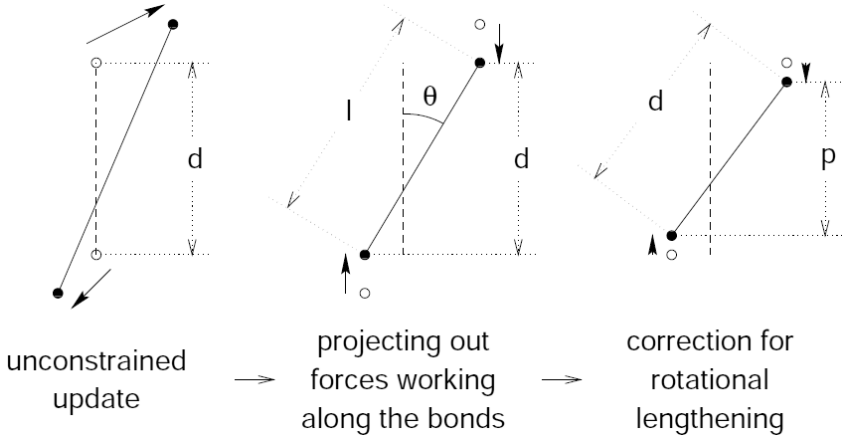
- process the constraints one by one
- satisfying one constraint may violate another
  $\rightarrow$ iterative procedure necessary
- run until all constraints are met within a preset tolerance
- angle constraints – re-formulate as bond constraints (rigid Δ)

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

LINCS

yet another constraint algorithm

- resets bond lengths after an unconstrained integration step
- non-iterative – always 2 steps:

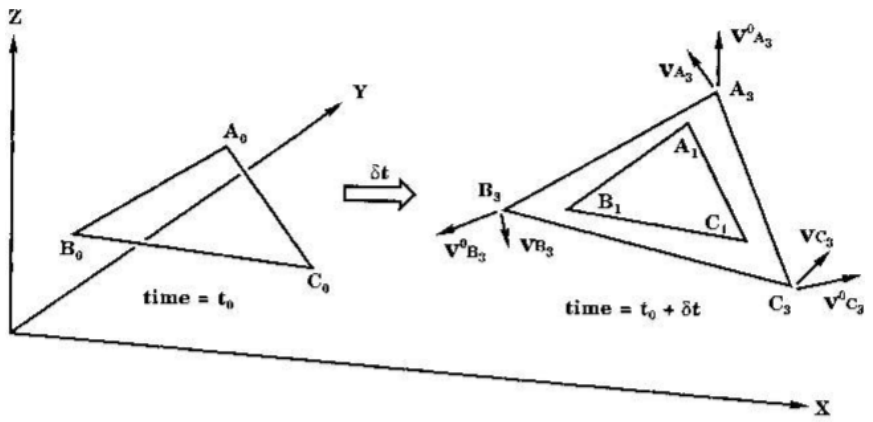


- no expensive matrix operations
- faster and more stable than SHAKE
- available for bond constraints and isolated angle constraints

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
  - may look absurd, but is often 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 reference value, and fluctuate

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

Position restraints

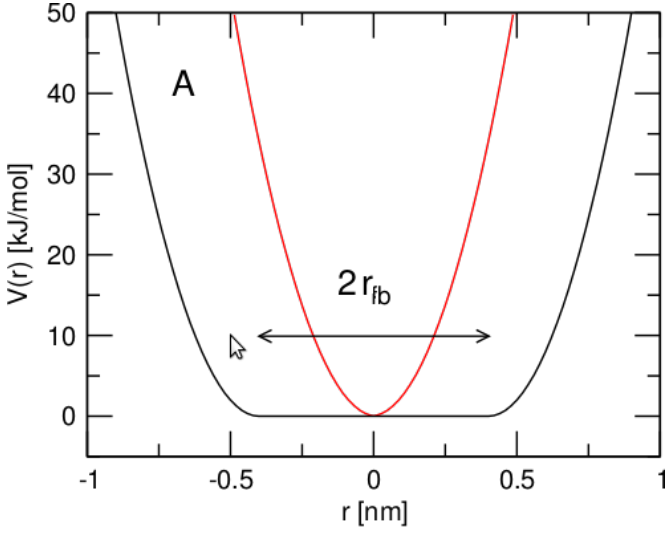
distance of an atom from a fixed reference position $\vec{R}_i$:

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

- 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

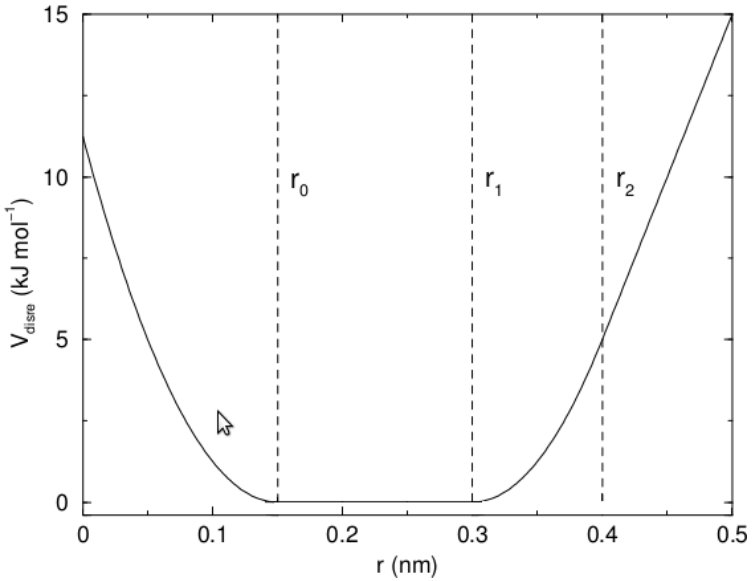


$$r = \left| \vec{r}_i - \vec{R}_i \right|$$

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

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