Computergestützte Strukturbiologie
(Strukturelle Bioinformatik)

MD Simulation im Torsionswinkelraum

Sommersemester 2009

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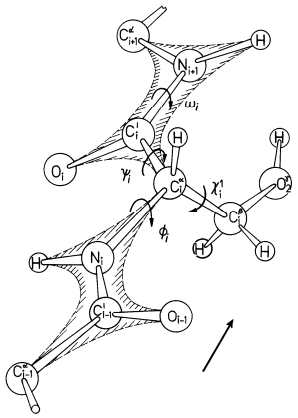
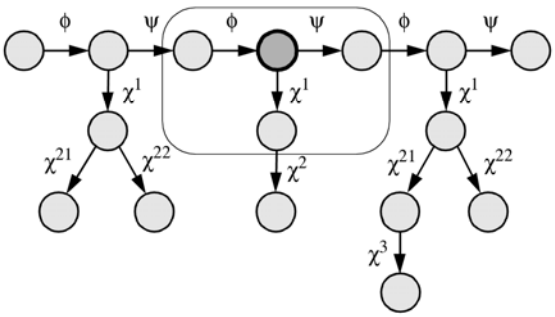
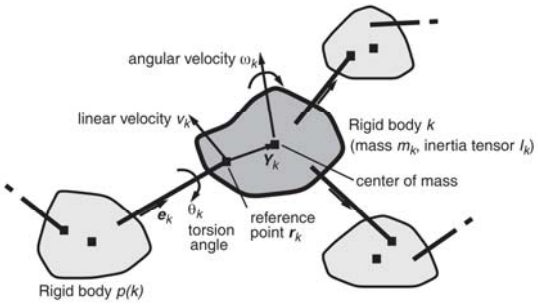
Diederwinkel in Polypeptiden



Tree structure of torsion angles

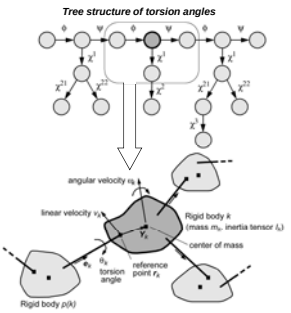


Tree structure with rigid bodies



Torsion angle dynamics algorithm

- **Classical mechanical equations of motion are solved for a system with torsion angles as the only degrees of freedom.**
- **About 10 times less degrees of freedom than in conventional Cartesian space MD.**
- **Fixed bond lengths and bond angles:**
  → no high frequency motions
  → longer integration time-steps
- **Efficient algorithm required!**
- **Amount of computation proportional to system size**



Programs DYANA, CYANA

Jain, Vaidehi, Rodriguez, *J. Comp. Phys.* 106, 258–268 (1993)
Güntert, Mumenthaler, Wüthrich, *J. Mol. Biol.* 273, 283–298 (1997)

Molecular Dynamics

Cartesian space		Torsion angle space
$E_{kin} = \frac{1}{2}\sum_{i=1}^{N} m_i \dot{\mathbf{x}}_i^2$	Kinetic energy	$E_{kin} = \frac{1}{2}\sum_{k,l=1}^{n} M(\theta)_{kl}\dot{\theta}_k\dot{\theta}_l$
diagonal, constant (elements m_i)	Mass matrix M	non-diagonal, non-constant, $n \times n$
$\ddot{x}_i = -\frac{1}{m_i}\frac{\partial E_{pot}}{\partial x_i}$	Accelerations	$M(\theta)\ddot{\theta} = C(\theta, \dot{\theta})$ (n linear equations)
proportional to N	Computational complexity	solving linear system of equations: $\sim n^3$
		exploiting tree structure of the molecule: $\sim n$

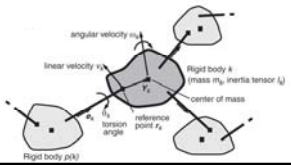
Computation of the kinetic energy

The angular velocity vector $\boldsymbol{\omega}_k$ and the linear velocity $\boldsymbol{v}_k$ of the reference point of the rigid body k are calculated recursively from the corresponding quantities of the preceding rigid body $p(k)$:

$$\boldsymbol{\omega}_k = \boldsymbol{\omega}_{p(k)} + \boldsymbol{e}_k \dot{\theta}_k,$$
$$\boldsymbol{v}_k = \boldsymbol{v}_{p(k)} - (\boldsymbol{r}_k - \boldsymbol{r}_{p(k)}) \wedge \boldsymbol{\omega}_{p(k)}.$$

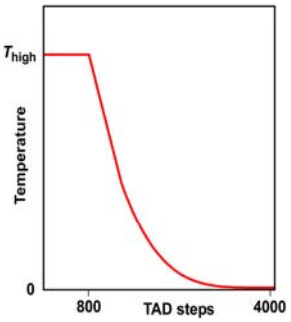
The kinetic energy can then be computed in a linear loop over all rigid bodies:

$$E_{\text{kin}} = \frac{1}{2} \sum_{k=0}^{n} [m_k \boldsymbol{v}_k^2 + \boldsymbol{\omega}_k \cdot I_k \boldsymbol{\omega}_k + 2\boldsymbol{v}_k \cdot (\boldsymbol{\omega}_k \wedge m_k \boldsymbol{Y}_k)]. \qquad [1]$$



Simulated annealing protocol

- Start from random structure
- Use all restraints simultaneously
- Adjustable parameters:
  - start temperature, T_{high}
  - number of TAD steps



Temperature control

Weak coupling to a heat bath is used to control the temperature:

$$\dot{\theta} \leftarrow \dot{\theta} \sqrt{1 + \frac{T^{\text{ref}} - T}{\tau T}}$$

$\dot{\theta}$ torsional velocities
T instantaneous temperature, $T = \frac{2E_{\text{kin}}}{nk_B}$
coupling constant

(Berendsen et al., J. Chem. Phys. 81, 3684–3690, 1984)

Time-step adaption

The same idea is used to adapt the integration time-step, Δt, such as to maintain a user-defined accuracy of energy conservation:

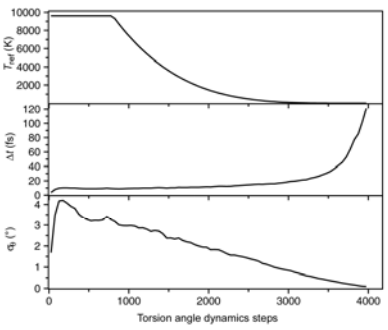
$$\Delta t \leftarrow \Delta t \sqrt{1 + \frac{\varepsilon^{ref} - \varepsilon}{\tau \varepsilon}}$$

ε is the relative change of the total energy, $E = E_{\text{kin}} + E_{\text{pot}}$:

$$\varepsilon = \left| \frac{E(t - \Delta t) - E(t)}{E(t)} \right|$$

Standard protocol: $\varepsilon^{\text{ref}} = 0.005 \ldots 0.0001$, $\tau = 20$

Simulated annealing with torsion angle dynamics



CYANA Computation Time