Coarse-grained protein-protein stiffnesses and dynamics from all-atom simulations

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Motivation

- Connect continuum models to microscopic structures
- Computational efficiency / Physical interpretability
- Description of overdamped dynamics
- (preliminary) Application to real virus: HIV
HIV capsid structure

HIV mature capsid (source structures)

- CTD–NTD linker stiffness (Ganser-Pornillos et al, 2007)
- CTD–CTD dimer bond (Gamble et al, 1997)
- NTD–NTD hexamer bond (Tang et al, 2002; Mortuza et al, 2004)

modified from Wright et al, EMBO J. 26, 2218 (2007)
Simulation details

- NAMD software package
- 1,500,000 steps @ 2fs = 3ns
- 2 domains + 4–7 Å water
Expect bond to be anisotropic: *general* interactions

- Generalize spring to depend on all 6 degrees of freedom
  - $6 \times 6$ stiffness tensor $K$.

- Complication: coordinates have different units
Random walk model

Equation of motion

- Generalized/coarse grained coordinates $x_i$, $i = 1 \ldots N$ ($\sim 6$)

$$\frac{dx}{dt} = \Gamma f(x, t) + \zeta(t)$$

$$\langle \zeta(t) \otimes \zeta(t') \rangle = 2D \delta(t - t')$$

- $\Gamma$ = mobility tensor
- $D$ = diffusion tensor (detailed balance: $D = k_B T \Gamma$)

Expand potential to second order

$$U(x) = U_0 - f_* \cdot (x - x_*) + \frac{1}{2}(x - x_*) K (x - x_*)$$

- $K$ = stiffness tensor
Statics

\[ \frac{dx}{dt} = -\Gamma K(x - x_*) + \zeta(t) \]

**Equipartition theorem**

- If simulation has reached equilibrium (and \( f_* = 0 \)),

\[ x_* = \langle x(t) \rangle \]

\[ k_B T K^{-1} = \langle x(t) \otimes x(t) \rangle - x_* \otimes x_* \]
Statics

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**Equipartition theorem**

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  \[ x_* = \langle x(t) \rangle \]
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Not equilibrated!
Dynamics

\[ \frac{dx}{dt} = -\Gamma K(x - x^*_p) + \zeta(t) \]

**Diffusion tensor**

- At small \(|t' - t|\):
  \[ 2D|t' - t| = \langle [x(t') - x(t)] \otimes [x(t') - x(t)] \rangle \equiv G(t' - t) \]

- Measure correlation functions \(G(\Delta t)\)
- Linear fit at small \(\Delta t\)

**Relaxation matrix**

- Transform coordinates s.t. noise is isotropic \((D_{ij} \rightarrow \delta_{ij})\)
- Transformed stiffness tensor becomes relaxation matrix
  \[ R = \Gamma^{1/2} K \Gamma^{1/2} \]
- Diagonalize to find relaxation times
Trajectories

Time series of linker relaxation modes (smoothed)

- Proteins taken out of biological context: external forces
- Deduce balancing force from drift velocity $\bar{v}$:

$$f_* = -\Gamma^{-1}\bar{v}$$

$\tau_R \sim 1.6\text{ns}$

(normalized position vs. time (ns))

(invalidates itself!)
HIV Simulations

Stochastic Dynamics

Results

Trajectories

**Time series of linker relaxation modes (smoothed)**

- Proteins taken out of biological context: external forces
- Deduce balancing force from drift velocity $\bar{v}$:

$$f_* = -\Gamma^{-1}\bar{v}$$

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<thead>
<tr>
<th>time (ns)</th>
<th>normalized position</th>
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$\tau_R \sim 1.6$ ns

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$\tau_R \sim 0.47$ ns

unforced

forced
Stiffnesses

Individual bonds

- Effective stretching and orientational stiffnesses

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<thead>
<tr>
<th></th>
<th>$K_{\text{stretch}}^{\text{eff}}$ ($k_B T/\text{nm}^2$)</th>
<th>$K_{\text{orient}}^{\text{eff}}$ eigenvalues ($10^3 k_B T$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTD–NTD</td>
<td>12</td>
<td>1.3 2.8 4.5 10 18</td>
</tr>
<tr>
<td>CTD–CTD</td>
<td>9.9</td>
<td>0.21 0.34 1.1 3.9 8.3</td>
</tr>
<tr>
<td>Linker</td>
<td>4.0</td>
<td>0.24 0.40 1.1 2.9 5.5</td>
</tr>
</tbody>
</table>

Entire network

- Assume rigid NTD hexamer and CTD dimer
- Compose multiple linkers
- Lattice constant $a = 4.6\text{nm}$ (cf. 10.7nm expt.)
- Young’s modulus $Y = 5.0\text{GPa}$ (cf. 0.115GPa expt.)
- Accounting for curvature should improve these greatly
Conclusions

- Connect continuum models to microscopic structures
- Measurement of stiffnesses, external forces, diffusion
- Relaxation dynamics give physical timescales for modes
- Validation of simulation run times
- Soon: determine effects of point mutations, ionic strength

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