Hybrid particle-field molecular dynamics for biological systems

Hyllerås seminar

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Biological scale

- Complex organism
- Organ
- Tissue
- Cell
- Organelle
- Atom
- Molecule
- Macromolecule
- Macromolecular complex

Scale:
- Organ: $10^{-4}$ m
- Tissue: $10^{-2}$ m
- Cell: $10^{-6}$ m
- Organelle: $10^{-8}$ m
- Atom: $10^{-10}$ m
Coarse-graining

\[ Z = \int d\Gamma \, e^{-\beta H(\Gamma)} \]

\[ Z \simeq \int d\Gamma_{\text{CG}} \, e^{-\beta H(\Gamma_{\text{CG}})} \]

- Fewer degrees of freedom
- Speedup of dynamics
The hybrid particle-field method

\[ H(\{r\}) = H_0(\{r\}) + W[\{\phi(r)\}] \]

Particle-particle-Hamiltonian \hspace{1cm} Density-field interaction-energy

\[ \sum_{i<j} V_{ij} \]

\[ \sum_i V_k(r_i) \]

\[ F_i = -\nabla_i V_k(r_i) \]

\{r\} \equiv \{r_1, \ldots, r_N\}, particle positions.

\{\phi\} \equiv \{\phi_1, \ldots, \phi_M\}, particle-type number densities.
Computation of forces

1) Linear interpolation:
\[ \{ \mathbf{r} \} \rightarrow \{ \phi_{nml} \} \]

2) Finite-differences:
\[ \{ \phi_{nml} \} \rightarrow \{ \nabla \phi_{nml} \} \rightarrow \{ \nabla V_{nml} \} \]

3) Force interpolation:
\[ \{ \nabla V_{nml} \} \rightarrow \mathbf{F}_i \]
Implementation and parallelization

Distribute particles

Compute $V_k$ and $\nabla V_k$

Interpolate and integrate forces

$t = t + \Delta t$
corresponds to update frequency $\delta t$?

Yes

No communication

Excellent scaling for small and large systems!

Interaction energy: Polymer-theory

\[ W[\phi] = \int d\mathbf{r} \frac{1}{2\rho_0} \left( \sum_{k\ell} \tilde{\chi}_{k\ell} \phi_k(\mathbf{r}) \phi_\ell(\mathbf{r}) + \frac{1}{\kappa} \left( \sum_\ell \phi_\ell(\mathbf{r}) - \rho_0 \right)^2 \right) \]

- **Mixing**
  \[ \tilde{\chi}_{k\ell} > 0 \rightarrow Likes \ not \ to \ mix \]
  \[ \tilde{\chi}_{k\ell} \leq 0 \rightarrow Likes \ to \ mix \]

- **Compressibility**
  \[ \kappa \sim 0 \rightarrow incompressible \]
  \[ \kappa \gg 0 \rightarrow very \ compressible \]

**Net effect**

\[ V_k(\mathbf{r}) = \frac{1}{\rho_0} \left( \sum_\ell \tilde{\chi}_{k\ell} \phi_\ell(\mathbf{r}) + \frac{1}{\kappa} \left( \sum_\ell \phi_\ell(\mathbf{r}) - \rho_0 \right) \right) \]

\( \rho_0 \): density-parameter related to the volume per bead.
Hybrid Particle-Field Model for Conformational Dynamics of Peptide Chains

\[ H = H_0(\{r\}) + W[\rho(r)] \]

S.L Bore et al., JCTC, 2018
Previous work

Cα-representation

Reconstruction of dipole
Two-bead model

\[ V(\gamma, \phi) = V(\gamma) + V(\phi) ? \]

4-Alanine

\[ \rightarrow V(\gamma, \phi) = \frac{1}{2} k(\phi) (\gamma - \gamma_0(\phi))^2 + V_{\text{prop}}(\phi, \lambda) \]
Propensity potential

Boltzmann Inversion

Desired PMF $\rightarrow$ PMF $\rightarrow$ Propensity potential $\rightarrow$ Actual PMF

- $-1 \leq \lambda < 0 \implies$ Helical
- $0 < \lambda < 1 \implies$ Extended
- $\lambda = 0 \implies$ Random

\[
V_{\text{prop}}(\phi, \lambda) = \frac{1}{2} \left( (|\lambda| - \lambda) V_\alpha(\phi) + (|\lambda| + \lambda) V_\beta(\phi) + (1 - |\lambda|) V_0(\phi) \right)
\]
### Phase-diagram: homo-poly-peptide

<table>
<thead>
<tr>
<th>$\tilde{\chi}_{k\ell}$</th>
<th>CB</th>
<th>$H_2O$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB</td>
<td>0</td>
<td>$\alpha$</td>
</tr>
<tr>
<td>$H_2O$</td>
<td>$\alpha$</td>
<td>0</td>
</tr>
</tbody>
</table>

The phase-diagram illustrates the stability of different peptide conformations as a function of $\lambda$ and $\alpha$. The conformations include:

- **i:** Random coil
- **ii:** $\alpha$-helix
- **iii:** $\beta$-hairpin
- **iv:** Extended
- **v:** Helix-coil-helix
- **vi:** $\beta$-floor/helix
- **vii:** Helical bundle

The diagram shows the transition regions between these conformations for peptide lengths of 15 aa, 30 aa, and 60 aa. The color gradient indicates the probability of each conformation, with darker colors representing higher probability.
HP-model

<table>
<thead>
<tr>
<th>$\tilde{\chi}_{k\ell}$</th>
<th>$C_{BP}$</th>
<th>$C_{BH}$</th>
<th>$H_2O$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{BP}$</td>
<td>0</td>
<td>$\alpha$</td>
<td>0</td>
</tr>
<tr>
<td>$C_{BH}$</td>
<td>$\alpha$</td>
<td>0</td>
<td>$\alpha$</td>
</tr>
<tr>
<td>$H_2O$</td>
<td>0</td>
<td>$\alpha$</td>
<td>0</td>
</tr>
</tbody>
</table>

$\alpha$-part: PHPPHHPPHPPHHPHPH

$\beta$-part: PHPHPHPHPHPHPHHPH

HP-polymer interacting with membrane

\[ \lambda = -0.25 \]

\[ \lambda = -0.50 \]

\[ \lambda = -0.75 \]

Outlook

- Parametrization: Toy-model $\rightarrow$ 20 amino-acids
  - Chemical specific $\tilde{\chi}_{k\ell}$-parameter
  - Strategies for modeling $V(\phi, \gamma)$
  - Machine-learning?
  - New PhD-student Manuel Carrera

- Electrostatics
  - Particle-field method for electrostatics

- Application of current model
  - Tsudo Yamanaka, Yamagata University, Japan
Electrostatics in Hybrid particle-field

\[ \nabla \left( \epsilon(r) \nabla \psi(r) \right) = -\rho(r) \]

H.B. Kolli et al. JCTC, 2018

S.L. Bore et al., JCTC, 2018
Electrostatic screening: Atomistic vs coarse-grained

Atomistic molecular dynamics:
- Charges are resolved
- Screening is modeled directly

Coarse-grained molecular dynamics:
- Charge resolution is lost
- Screening modeled indirectly

Idea: \[ \nabla \cdot (\epsilon(\mathbf{r}) \nabla \psi(\mathbf{r})) = -\rho(\mathbf{r}) \] (Generalized Poisson equation)
External potential in a density dependent dielectric

Electrostatic interaction energy:

\[
W_{\text{elec}}[\{\phi(r)\}] = \frac{1}{2} \int \mathrm{d}r \frac{D(r) \cdot D(r)}{\epsilon(r)},
\]

\(\{\phi\}\) : number densities. \(D\) : displacement field. \(\epsilon\) : permittivity.

Potential felt by particles of type \(K\):

\[
V_{\text{ext},K}(r) = \left( \frac{\delta W_{\text{elec}}}{\delta \phi_K(r)} \right) = \int \mathrm{d}r' \frac{\delta W_{\text{elec}}}{\delta D(r')} \frac{\delta D(r')}{\delta \phi_K(r)} + \frac{\delta W_{\text{elec}}}{\delta \epsilon(r)} \frac{\partial \epsilon(r)}{\partial \phi_K(r)} q_K \psi(r)
\]

\(\psi\) : electrostatic potential. \(E\) : electrostatic field \((E = -\nabla \psi = \epsilon D)\).
Modelling: density dependence of the dielectric

Density weighted average:

$$\epsilon(\{\phi(r)\}) = \sum_{K}^{M} \frac{\epsilon_K \phi_K(r)}{\phi_0(r)},$$

$\epsilon_K$: dielectric of particle type $K$. $\phi_0$: local total particle density.

Potential felt by particle of type $K$:

$$V_{\text{ext},K}(r) = q_K \psi(r) - \frac{1}{2} \epsilon_K - \frac{\epsilon(r)}{\phi_0(r)} |E(r)|^2,$$

Forces on particle of type $K$:

$$F_K = -\nabla V_{\text{ext},K}(r) = q_K E(r) + \frac{1}{2} \nabla \left( \frac{\epsilon_K - \epsilon(r)}{\phi_0(r)} |E(r)|^2 \right).$$
Force computation and molecular dynamics

Compute $\rho_{lmn}$ & $\epsilon_{lmn}$

Solve GPE

Compute forces $F_i$

New positions

Partitioning of ions (1)

Ions in a phase separated oil/water mixture of $\epsilon_o$ and $\epsilon_w$. ($RT \times \chi_{ow} = 30 \text{ kJ mol}^{-1}$)

Distribution coefficient:

$$D_{o/w} = \frac{c_o}{c_w}$$

$c_0$ and $c_w$: concentration of ions within each phase.
Partitioning of ions (2)

\[ D_{o/w} = f(c, P_{o,w}^\pm, P_{o,w}^{ip}, K_w) \]

\( c \): concentration of ions.

Born theory of ions:

\[ \log P_{o/w}^\pm = \gamma \left( \frac{1}{\epsilon_w} - \frac{1}{\epsilon_o} \right) \]

\( \epsilon_o \): dielectric constant of the solvent.

\( K_w \): ionization constant of water.

\( D_{o/w} \): partition coefficient of ions between oil and water.

\( P_{o/w}^{ip} \): ionization potential of water.

\( P_{o/w}^\pm \): partition coefficient of ions between oil and water.

\( K_o \): dissociation constant of oil.
Outlook

- Implementation
  - Parallel version
  - Improve on accuracy

- Application
  - Antonio De Nicola: Charged lipids
  - Ken Schafer: Molecular packing of SDS
  - Victoria Ariel Bjørnestad

![Small angle scattering diagram](image)

Exp. vs sim.
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