

CS Work in progress

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Coarse-graining, applications and mesoscopic molecular dynamics

Carsten Svaneborg

Institute for Physics, Chemistry, and Pharmacy University of Southern Denmark Campusvej 55, 5320 Odense M

zqex@sdu.dk Http://www.zqex.dk/science



Overview

- Motivation for CG
- Scales / phenomena / methods
- Advantages / Disadvantaged
- Coarse-graining methods / BI
- Examples: lipids
- Dissipative Particle Dynamics
- CS Applications
- Summary

Material properties



Assuming we have a large number of cross-linked polymers, what is the elastic response to deformation?

How can we address this problem with computer simulations?



DNA computation



Assuming we want to carry out a complicated DNA computation operation.

How can we address this problem with computer simulations?



Question



Assuming we have a motile keratocyte.

How can we address this problem with computer simulations?



U.S. National Library of Medicine

Actin





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Problem

Common for these questions are that they address emergent mesoscopic or macroscopic phenomena of the system as a whole, not phenomena particular to molecular or atomic details.

Attacking these questions naively with atomistic detailed models is bound to fail.

Solution

Simplification: Formulate an effective mesoscopic model, that includes the interesting large-scale physics, but which removes uninteresting microscopic details!

Coarse-graining: The process of formulating effective models at larger length scales => hierarchical modelling.

Einstein: Everything should be made as simple as possible, but no simpler.



Advantage



Quantum DNA model Atomistic DNA model Mesoscopic DNA model



Increasing level of detail. Interactions progressively become fundamental, defined ab initio by quantum mechanics.

Disadvantages



Quantum DNA model Atomistic DNA model Mesoscopic DNA model



Complex. Algorithms scales horribly with number of electrons. Hartree-Fock is O(Ne⁴)

Advantage



Quantum DNA model Atomistic DNA model Mesoscopic DNA model



More smooth energy landscapes, faster time steps. Hence an increase size of system, and simulation time that can be studied. MD is O(n) when using cutoff and no charges.

Disadvantage



Quantum DNA model Atomistic DNA model Mesoscopic DNA model



Effective potentials are difficult to derive and dependent on state point. Details are washed out.

Hierarchy (1)



Hierarchy (2)



Fig. 1. Hierarchical length scales for polymeric materials.



A predictive multiscale computational framework for viscoelastic properties of linear polymers Ying Li et al.

Polymer 53 (2012) 5935e5952

Need for CG

Numerous interesting systems has structure on the mesoscopic scale ($nm-\mu m$; $\mu s-ms$).

Examples:

colloidal suspensions / complex fluids (ink, milk, blood, clay, ...),

lipid aggregates / soft condensed matter (liquid crystals, vesicles, membranes)

micro-biological systems (cell organelles, viruses, ...)

These structures are have very complex dynamics! Simulating them at atomistic detail is difficult/ Impossible, hence we need to develop CG models.



red blood cells



Examples

Example of CG





Molecular properties.

- Hydrophobic tail
- Hydrophilic head

Material properties

- Self-assembled structures
- Dynamics



CG models



Ying Li et al. Polymer 53 (2012) 5935



Zun-Jing Wang et al. J. Phys. Chem. B 114, 11207 (2010)



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CG details

How to Coarse-Grain

- Ad hoc method: Invent a model, analyse its behaviour, fit to experiment, improve or reject model.
- Analytical coarse-graining. Integrate out microscopic degrees of freedom.
- Structure-based CG: Utilise the trajectory from an atomistic model to estimate the force field required for a coarse-grained model to produce the same structure at a lower resolution.
- Force-matching CG: During an atomistic simulation we know forces on all atoms, and hence also the net force on a coarse-grained particle. Develop force-field that reproduce this net force such that coarse-grained particles can be simulated directly.

Statistical mechanics (1)

Assume we have a system of N particles and a general interaction potential that depends on the configuration as

 $U(\vec{r_{1,}},\ldots,\vec{r_{N}})$

Probability for particular NVT microstate (Boltzmann):

$$P(\vec{r}_{1},\ldots,\vec{r}_{N}) = Z^{-1} \exp\left(-\beta U\left(\vec{r}_{1},\ldots,\vec{r}_{N}\right)\right)$$
$$Z = \int \exp\left(-\beta U\left(\vec{r}_{1},\ldots,\vec{r}_{N}\right)\right) d\vec{r}_{1}\cdots d\vec{r}_{N}$$

Free energy:

$$F(N, V, T) = -k_B T \ln(Z)$$

Note if we are given microscopic P, we can derive microscopic U:

$$U(\vec{r_{1}},\ldots,\vec{r_{N}}) = -\beta^{-1} \ln P(\vec{r_{1}},\ldots,\vec{r_{N}}) + const$$

Statistical mechanics (2)

Constrained partition function for observable or macrostate:

$$Z(q) = \int \exp\left(-\beta U(\vec{r_{1}}, \dots, \vec{r_{N}})\right) \delta(q - Q[\vec{r_{1}}, \dots, \vec{r_{N}}]) d\vec{r_{1}} \cdots d\vec{r_{N}}$$
$$P(q) = \frac{Z(q)}{\int Z(q) dq}$$

Note, Z(q) is no more than a histogram of the macrostate or obserable q in the equilibrium state.

Note if we know Z(q), we can derive free energy potential for q:

$$U(q, NVT) = -\beta^{-1} \ln [Z(q, NVT)] + const$$

The same applies for partition functions with more arguments $Z(q_{1,}\ldots,q_{P})$

Example: Polymer

Microstates with dist. r when $\langle R_{ee}^2 \rangle$



 $Z(r) = N \exp(-rac{3r^2}{2\langle R_{ee}^2
angle})$

Free energy

$$F(r) = -TS(r) = -k_B T \ln Z(r) = \frac{3k_B T}{2\langle R_{ee}^2 \rangle} r^2 + c$$

Force

$$f(r) = -\frac{\partial F(r)}{\partial r} = -\frac{3k_BT}{\langle R_{ee}^2 \rangle}r$$

CG

Polymer with fixed ends = entropic spring!

Coarse-grained polymer chain, into a single end-to-end distance!

Complex molecules



Statistical mechanics (3)

In general, q can be any (vector of) observables.

Hence we can from any configuration $\vec{r_1}, \dots, \vec{r_N}$

derive a coarse-grained analog

$$\vec{R}_{1,}\ldots,\vec{R}_{M}$$

Where $\vec{R}_{\alpha} = \sum M_{\alpha i} \vec{r}_i$ is the centre of mass of bead alpha

Each bond distance, bond angle, dihedral, ... between CG beads can be stated as a function: $F(\vec{R}_{1},...,\vec{R}_{M})$

The corresponding constrained partition function: $Z(f) = \int \exp(-\beta U(\vec{r_1}, \dots, \vec{r_N})) \delta(f - F[\vec{R_1}, \dots, \vec{R_M}]) d\vec{r_1} \cdots d\vec{r_N}$

and potential

$$U(f, NVT) = -\beta^{-1} \ln [Z(f, NVT)] + const$$

From atomistic model:

Atomistic simulations in NVT ensemble sample microstates as

$$P(\vec{r}_{1},...,\vec{r}_{N}) = Z^{-1} \exp(-\beta U(\vec{r}_{1},...,\vec{r}_{N}))$$

Measure constrained partition function:

$$Z[f] = \int \exp(-\beta U(\vec{r_{1}}, \dots, \vec{r_{N}})) \delta(f - F[\vec{R_{1}}, \dots, \vec{R_{N}}]) d\vec{r_{1}} \cdots d\vec{r_{N}}$$

$$\propto \int P(\vec{r_{1}}, \dots, \vec{r_{N}}) \delta(f - F[\vec{R_{1}}, \vec{R_{M}}]) d\vec{r_{1}} \cdots d\vec{r_{N}}$$

$$= sampled \ histogram \ of \ F[\vec{R_{1}}, \vec{R_{M}}]$$

Boltzmann inversion of sampled histogram:

$$U(f, NVT) = -\beta^{-1} \ln [Z(f, NVT)] + const$$

Review: V. Rühle et al. J. Chem. Theory Comput. 5, 3211 (2009)



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Procedure

- Choose mapping to CG beads
- Perform atomistic simulation
- Sample histograms of bonds, angles, ...
- Smoothen/fit histograms
- Boltzmann invert to obtain potentials
- Run CG simulation with the measured potential.

Note

$$P_r(r) = \frac{H_r(r)}{4\pi r^2}, \quad P_{\theta}(\theta) = \frac{H_{\theta}(\theta)}{\sin \theta}, \quad P_{\varphi}(\varphi) = H_{\varphi}(\varphi)$$

Assume statistical independence of distributions:

$$P(r, \theta, \varphi) = \exp[-\beta U(r, \theta, \varphi)]$$

$$P(r,\theta,\varphi) = P_r(r)P_{\theta}(\theta)P_{\varphi}(\varphi)$$

Correspond to assuming additive potentials

$$U(r, \theta, \varphi) = U_r(r) + U_{\theta}(\theta) + U_{\varphi}(\varphi)$$

$$U_q(q) = -k_{\rm B}T \ln P_q(q), \qquad q = r, \theta, \varphi$$

Iterative Boltzmann inversion

Problem: Small errors in P(r) gives rise to large errors in U(r). Secondly, assumption of statistical independence might be wrong. Both effects can be minimized through iteration:

Initial guess:

$$U(q) = -k_{\rm B}T\ln P(q)$$

Repeat simulations improving CG potential until paircorrelation function matches the reference system:

$$U^{(n+1)} = U^{(n)} + \Delta U^{(n)}$$
$$\Delta U^{(n)} = k_{\rm B} T \ln \frac{P^{(n)}}{P_{\rm ref}} = U_{\rm PMF}^{\rm ref} - U_{\rm PMF}^{(n)}$$

Comparison SPC/E water



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CG summary

- Issues with 3body interactions at high density
- Transferability to other state points (T,N/mu,V/P)
- Just because a CG model can reproduce certain properties other properties might be off (e.g. if they depend on more than the pair-correlation function)
- Dynamics. CG models can easily display dynamics 20-1000x faster than the atomistic simulation. Hence we need to utilize internal clocks rather than simulation time to compare dynamics.
- Allows for simulations of much larger systems for much longer time spans, at the expense of loosing details.

Examples

Coarse-grained lipids



speed-up of three to four orders of magnitude

A Systematically Coarse-Grained Solvent-Free Model for Quantitative Phospholipid Bilayer Simulations Zun-Jing Wang * and Markus Deserno.

J. Phys. Chem. B 114, 11207 (2010)

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Membrane self-assembly



Self-assembly of a bilayer from random distribution

Ira R. Cooke, Kurt Kremer, and Markus Deserno, Membrane Theory and Simulation, MPI Mainz, 2005 metastable sponge phase

Domain formation and budding



Budding induced by domain formation

Ira R. Cooke, Kurt Kremer, and Markus Deserno, Membrane Theory and Simulation, MPI Mainz, 2005

Implicit solvent

Large particles in a solution of small particles execute Brownian motion. Hence the net effect of small/fast degrees of freedom can be coarse-grained into random stochastic kicks and an effective friction.



The end of CG?



Continuum limit

At the very largest length scales, the relevant physics can be described by finite element simulations of Liquids: Navier-Stokes equation Solids: Elasticity theory

New description: System described in terms of fields such as flow velocity, concentration, stress, strain, temperature. Discretized to a mesh. Solved numerically.





Navier Stokes

$$\rho \left(\frac{\partial \mathbf{v}}{\partial t} + \mathbf{v} \cdot \nabla \mathbf{v} \right) = -\nabla p + \nabla \cdot \mathbf{T} + \mathbf{f}$$

V local flow velocity p pressure T deviatoric stress tensor f body force

all of which depends on space and time.

Dissipative Particle Dynamics (DPD)



The DPD thermostat

all interactions among particles are pair-wise and limited (truncated) $\mathbf{F}_i = \sum_{i=1}^{N} \mathbf{F}_{ij}^C + \mathbf{F}_{ij}^D + \mathbf{F}_{ij}^R$ \mathbf{V}_i $\mathbf{F}_{ii}^C = -\boldsymbol{\nabla}\phi_{ii}$ conservative force r_{ij} $\mathbf{F}_{ii}^{D} = -\gamma \omega^{D}(r_{ij}) \left(\mathbf{v}_{ij} \cdot \hat{\mathbf{r}}_{ij} \right) \hat{\mathbf{r}}_{ij} \quad \text{dissipative force}$ $\mathbf{F}_{ii}^{R} = \sigma \omega^{R}(r_{ij}) \xi_{ij} \mathbf{\hat{r}}_{ij}$ random force $\mathbf{r}_{ij} = \mathbf{r}_j - \mathbf{r}_i, \quad r_{ij} = |\mathbf{r}_{ij}|, \quad \mathbf{\hat{r}}_{ij} = \frac{\mathbf{r}_{ij}}{r_{ij}},$ $\mathbf{v}_{ij} = \mathbf{v}_j - \mathbf{v}_i, \quad \omega^R = 1 - \frac{r_{ij}}{r_c}, \quad \omega^D = \left(1 - \frac{r_{ij}}{r_c}\right)^2,$ $\xi_{ij} = -\xi_{ji}$ otherwise random, γ, σ constant

all parameters but the potentials are method parameters

Pep Español, Phys. Rev. E 52(**2**) 1734-1742 (1995)

Hoogerbrugge & Koelman, Europhys. Lett. 19 (1992) 155

The mesoscopic interaction potential

usually, a soft core interaction potential is used:

$$\phi = \begin{cases} \frac{a}{2} \left(r_c - r_{ij} \right)^2 & \text{if } r_{ij} < r_c \\ 0 & \text{otherwise} \end{cases}$$

- simplest potential that generates continuous force between 0 and rc
 - harmonic approximation to any potential around equilibrium



- can be retrieved by averaging molecular dynamics Forrest & Suter, J. Chem. Phys. 102(**18**), 1995 / Lyubartsev et al.

Usually, DPD is performed in *reduced units* where

physical mass and length follow from molecular representation:



How to set *a*? Groot & Warren calibrate to compressibility of water:

$$\frac{1}{k_B T \rho \kappa_T} \bigg|_{\text{sim}} = \left. \frac{1}{k_B T} \frac{\partial P}{\partial \rho} \right|_{\text{sim}} = \left. \frac{1}{k_B T} \frac{\partial P}{\partial n} \right|_{\text{exp}} = \text{const.}$$

pressure-density dependence is given by an EOS (obtained from simulation):

 $P = \rho kT + a\alpha \rho^2 \quad (\alpha = 0.101 + - 0.001)$ ideal excess pressure gas (interactions)



$$--> \kappa^{-1} = 1 + 0.2a\rho/kT = 16$$
 $--> a = 25 kT$

Groot & Warren, J. Chem. Phys. 107 (**11**), 15 (1997) Groot & Rabone, Biophys. J. 81(**2**) 725-736 (2001)

Mixing results from the interplay of internal energy and entropy ...

Calibrate *mutual a*_{ij}'s to Flory-Huggins theory (lattice model for polymer mixtures)

Free energy for polymer mixtures:

$$\frac{\Delta F}{k_B T N} = \chi \phi_A \phi_B + \phi_A \log \phi_A + \phi_B \log \phi_B$$



Integrate the equation of state to obtain free energy.

--> DPD potential: $\chi = (0.231 \pm 0.001)\Delta a$

Groot & Warren, J. Chem. Phys. 107 (**11**), 15 (1997) Groot & Rabone (Biophys. J. 81(**2**) 725-736, 2001)

In the end, the matrix (*aij*) is the main calibration parameter of the DPD method.

Examples: systems of water W and HT surfactants

W H T
25 25 80
H 25 25 80
T 80 80 25



Groot & Warren, J. Chem. Phys. 107 (11), 15 (1997)

Blood flow with DPD simulation



http://www.youtube.com/watch?v=0hibGZi8TWs



DPD summary

- Space and time is coarse-grained
- Conserves local momentum, hence reproduce hydrodynamic behaviour.
- Empirical relation to molecular interactions
- Soft interactions, allowing very long time steps.
- Qualitative rather than quantitative results.

CS applications

Polymer materials



DNA materials



Polymer materials

Microscopic: Atoms, molecules, interactions

Mesoscopic: Structures, dynamics

Macroscopic: Materials, properties







Polymer model

"Hard" beads connected by springs to form chain molecules.



 $\begin{array}{c} \mathbf{3} \\ \mathbf{3} \\ \mathbf{3} \\ \mathbf{1} \\ \mathbf{3} \\ \mathbf{3} \\ \mathbf{1} \\ \mathbf{3} \\ \mathbf{1} \\ \mathbf{3} \\ \mathbf{3} \\ \mathbf{1} \\ \mathbf{3} \\ \mathbf{1} \\ \mathbf{3} \\ \mathbf{3} \\ \mathbf{1} \\ \mathbf{3} \\ \mathbf{3} \\ \mathbf{1} \\ \mathbf{3} \\ \mathbf{1} \\ \mathbf{3} \\ \mathbf{1} \\ \mathbf{3} \\ \mathbf{1} \\ \mathbf{1} \\ \mathbf{3} \\ \mathbf{1} \\ \mathbf{1} \\ \mathbf{3} \\ \mathbf{1} \\ \mathbf$

Dense polymer liquid



$$U_{FENE}(r) = -\frac{kR^2}{2} \log\left[1 - \left(\frac{r}{R}\right)^2\right]$$
$$U_{LJ}(r) = 4\epsilon \left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^6 + \frac{1}{4}\right] \quad \text{for} \quad r < 2^{1/6}\sigma$$

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Polymer materials

Network strained $\lambda = 1, 2, 4$.



~1000000 beads. ~1000 polymer molecules



Polymer materials

Thermal fluctuations of 3 strands.







Dynamics of polymers





Elastic properties



(Some) CG DNA models



Ouldridge, Louis, Doye. JCP **134**, 085101 (2011).



Florescu, Joyeux. JCP **135**, 085105 (2011)



Poland Scheraga, JCP **45**, 1456 (1966). Picture: Jost, Everaers Biophys J. **96**, 1056 (2009)



Savelyev, Papoian. PNAS **107**, 20340 (2010)



Hsu, Sciortino, Starr. PRL **105**, 055502 (2010)



Leunissen, Frenkel. JCP **134**, 084702 (2011)

Dynamic bonding / Directional bonds framework



DNA adapted from Wikipedia

Dynamic bonding / Directional bonds framework



CS. Comp. Phys. Comm. **183**, 1793 (2012). CS, H. Fellermann, S. Rasmussen. DNA18 conference proceedings.

DNA adapted from Wikipedia

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Interactions



Bond + Langevin dynamics





DNA Icosahedron Self-Assembly (implicit solvent)



Construction:







DNA computation (implicit)









Summary

- Coarse-grained molecular dynamics allows phenomena on large time/spatial scales to be simulated and hence studied.
- How to develop coarse-grained force-fields is a very active research field, we are still learning how to do it correctly. E.g. do we want to match structure, dynamics or both?
- Atomistic MD simulations provides insights for developing coarse-grained force fields.

Physics: First CG model



2D ising model. Graphics from http://www.kineticallyconstrained.com/2012/04/renormalisation-group.html

 $T_{RG} = 0 \qquad \qquad T_{RG} = T_c \qquad \qquad T_{RG} \to \infty$

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phase transitions".

It is easy to drown in the details when looking for the big picture, coarse-graining allows us to take a step back, and see the big picture.

