An efficient hybrid method for modeling lipid membranes with molecular resolution

G.J.A. (Agur) Sevink, M. Charlaganov & J.G.E.M Fraaije
Soft Matter Chemistry Group, Leiden University, The Netherlands

Thanks to: C.D. Chau, A.V. Zvelindovsky, organizers!

Japan, 2010

Universiteit Leiden

Outline

- ✓ Motivation
- ✓ Hybrid CG modeling (ongoing, conceptual)
- ✓ Enhanced sampling (quick)
- ✓ Conclusions/outlook

Japan, 2010

Universiteit Leiden

Motivation

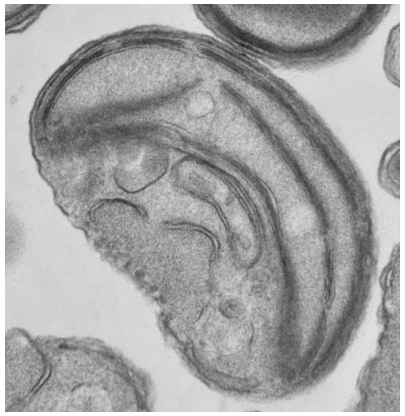
Using/adapting dynamic mesoscopic methodology for block copolymers to simulate life-mimicking (biomematic) structures and structure formation

- Veterinarian
- Biologist
- Physicist
- Mathematician ?

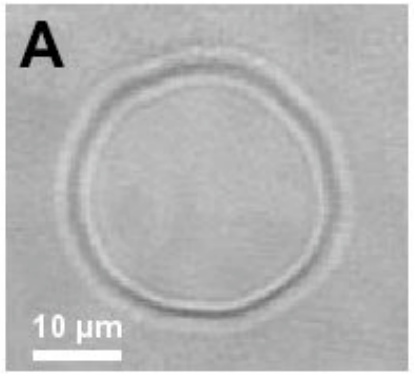
Japan, 2010

Universiteit Leiden

Motivation



reduction



"Cell membrane dynamics essentially lipidic" (100+ simulation papers)

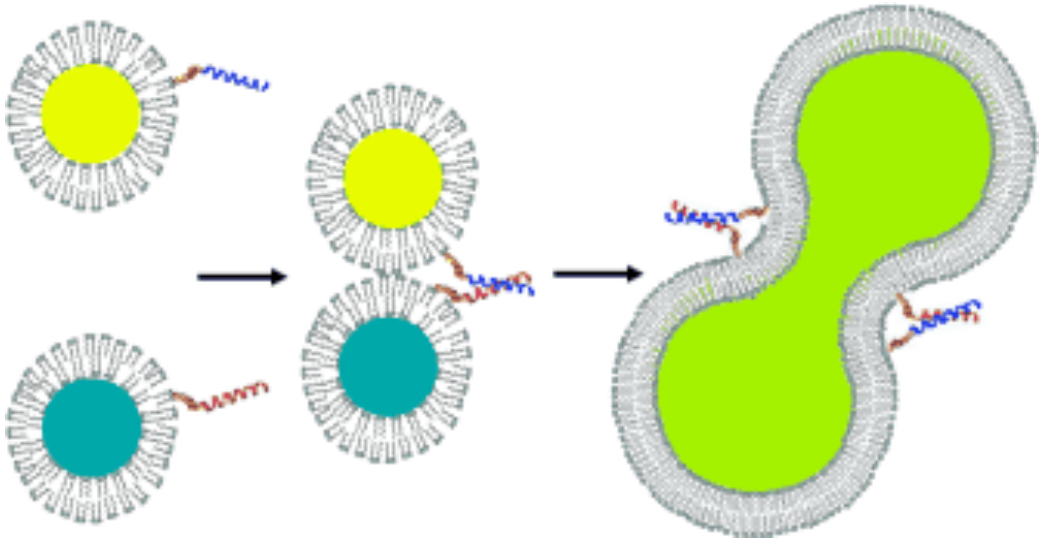
VW Project 2009-2012 'Multiscale hybrid modeling of (bio)membranes' (Schmid, Zvelindovsky, Böker, AS)

Aim: **Realistic** computational modeling of liposome formation, dynamics and (assisted) fusion

Japan, 2010

Universiteit Leiden

Motivation: intriguing experiments in Leiden

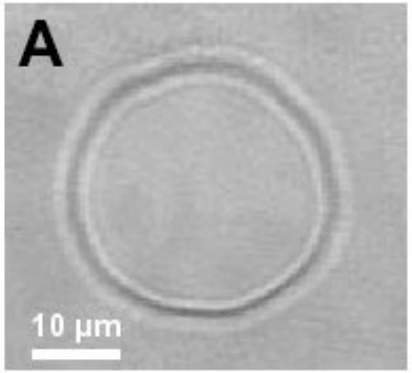


Vesicle fusion induced by coiled-coil motif (short peptide fragments)

Hana Robson Marsden et al, A reduced SNARE model for membrane fusion, Angew. Chem. 2330–2333, 2009.

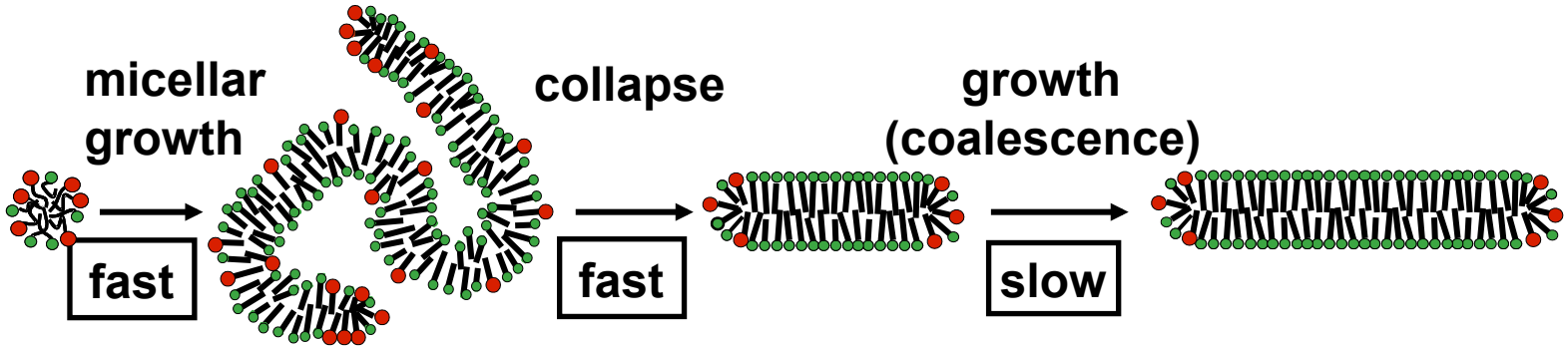
Japan, 2010

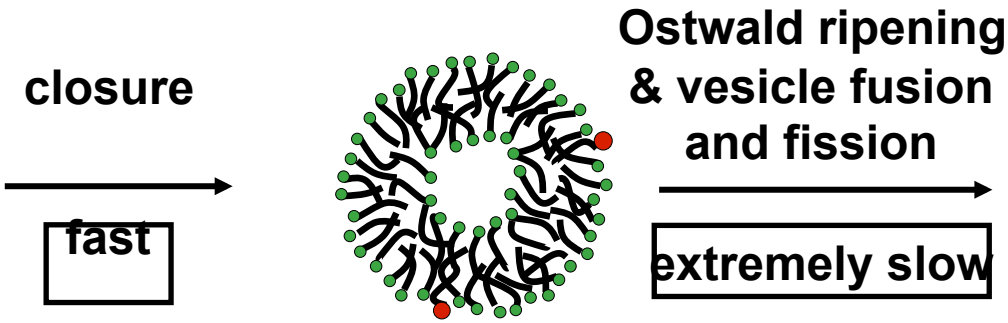
General issues: length and time scales



Nm **and** mm: model for complete vesicle and/or vesicle fusion requires considerable coarse graining

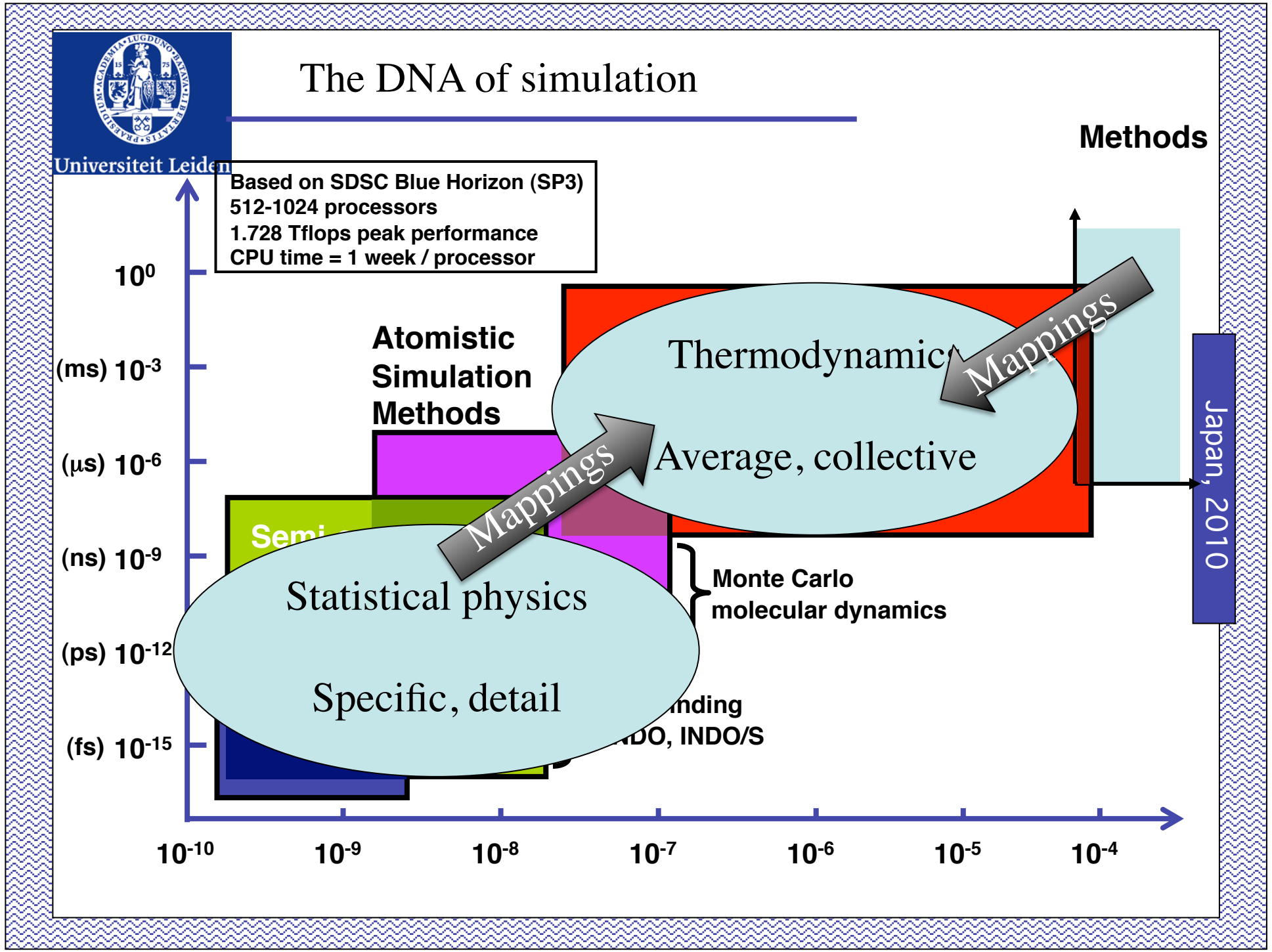
Efficient, realistic, dynamic





J. Leng, S. Egelhaaf, M. Cates (2002) *Europhys. Lett.*

Japan, 2010

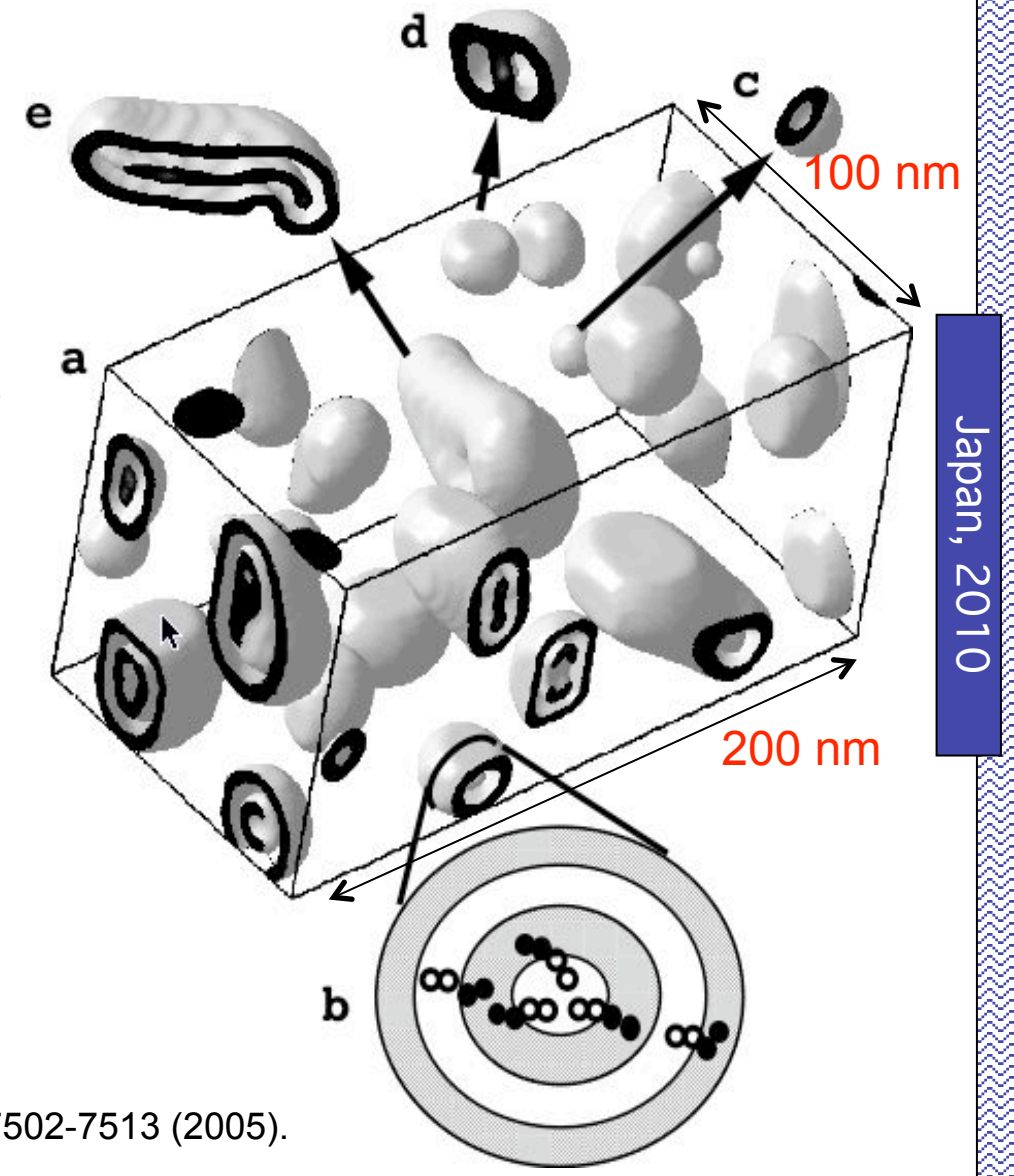

Universiteit Leiden
The DNA of simulation
Methods
Based on SDSC Blue Horizon (SP3)
512-1024 processors
1.728 Tflops peak performance
CPU time = 1 week / processor
10^0
(ms) 10^-3
(μs) 10^-6
(ns) 10^-9
(ps) 10^-12
(fs) 10^-15
Atomistic
Simulation
Methods
Thermodynamic
Average, collective
Mappings
Mappings
Statistical physics
Specific, detail
Monte Carlo
molecular dynamics
Japan, 2010
10^-10
10^-9
10^-8
10^-7
10^-6
10^-5
10^-4

Vesicle formation and fusion (2005)

METHOD: DDFT= mean-field
SCFT+diffusion

20% A_2B_2 in a selective bad solvent

Movie



Japan, 2010

AS., Zvelindovsky A.V. Macromolecules 38 7502-7513 (2005).

Universiteit Leiden

Issues

Beyond block copolymers:

- ✓ How to realistically represent lipids?
- ✓ Increasing complexity?

- ✓ ‘Floppy’ Gaussian chains: onion vesicles
- ✓ Mean-field: concentrated systems

Japan, 2010

Hybrid particle-field model

Aim: flexibility, efficient and realistic liposome simulation

(ongoing work)

Japan, 2010

DDFT: pattern formation dynamics in concentrated BCP

Enthalpic: mean-field interactions (FH)

$$F[\rho_I] = F^{ideal}[\rho_I, U_I] + F^{cohesive}[\rho_I] + \frac{1}{2}\kappa_H \int_V \left(\sum_I \rho_I \right)^2$$

Entropic: Gaussian chains in self-consistent field U

Pressure term, incompressible

$$\frac{d\rho_I(r)}{dt} = M\nabla \cdot \rho_I(r) \nabla \frac{\delta F[\rho, U]}{\delta \rho_I}(r) + \ldots\ldots\ldots + \eta_I(r)$$

noise

local kinetic model

processing conditions

- ✓(quasi)equilibrium behavior, AB, ABC, branced
- ✓Phase transition under external fields (confinement, shear, E, etc)

Japan, 2010

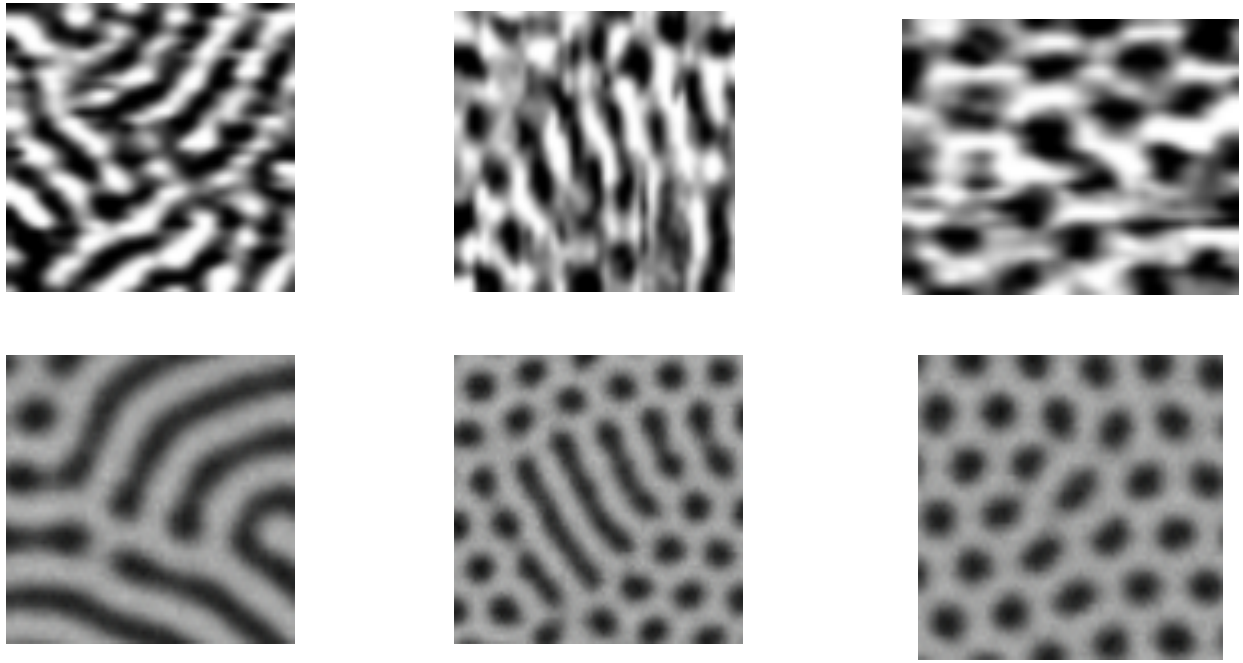
Synergetic validation: flat polymeric ‘membrane’

Structural transition due to thickness reduction : top view

Experiment

$\Delta t^{sim} \sim$ sec

Calculation

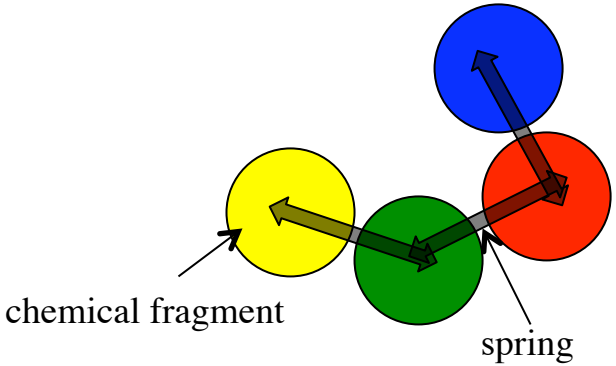


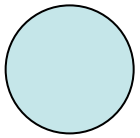
nucleation annihilation splitting

High-speed SFM measurements of membrane dynamics: ~ sec ptf

Japan, 2010

Different representations of constituents

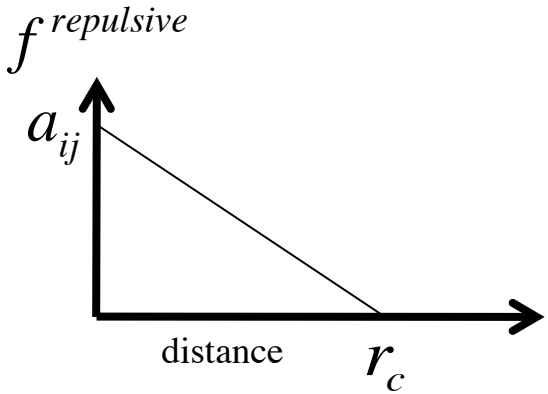




Variable composition

DDFT: Underlying harmonic spring, calculations and interactions field-based

Particles (DPD): Harmonic spring, angle and torsion potentials, soft core repulsive pair potentials



$$a_{ij} = a_{ij}^{0} + \Delta a_{ij}$$

liquid incompressibility

Japan, 2010

Hybrid model

$$F^{hybrid}[\rho_I, \vec{r}_k] = F^{DDFT}[\rho_I] + U^{particles}[\vec{r}_k] + F^{coupling}[\rho_I, \vec{r}_k]$$

$$\sum_{I,k} c_{Ik} \int_V K(\vec{r} - \vec{r}_k)\rho_I(\vec{r})d\vec{r}$$

particles

$$\partial r_k = D_k[f_k^{conserv} - \int_V \sum_I c_{Ik} K(\vec{r} - \vec{r}_k)\nabla\rho_I(\vec{r})d\vec{r}]\partial t + r_k^{random}(t)$$

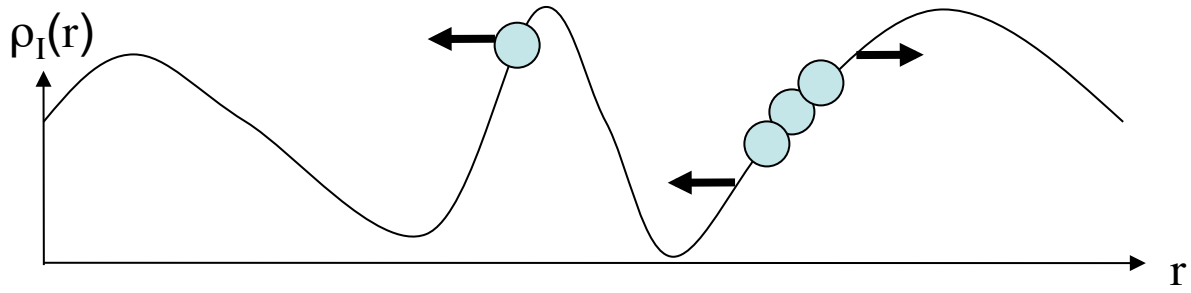
$$\frac{d\rho_I(\vec{r})}{dt} = M\nabla \cdot \rho_I(\vec{r})\nabla[\mu^{DDFT}(r) + \sum_k c_{Ik} K(\vec{r} - \vec{r}_k)] + \eta_I$$

fields

Diffusion, timescales are more or less comparative (coupled update)

Japan, 2010

Physical interpretation



Positive *c*

Coupling force: away from high density field values
Coupling chemical potential: field diffuses away from regions with many particles

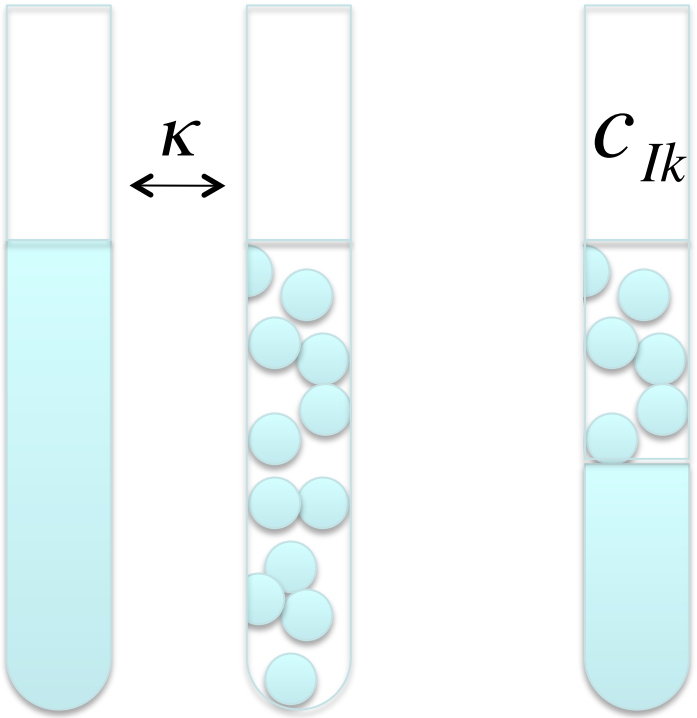
Advantage is possibility to mix different **representations** on CG level for same or different constituents: sparse (particles) + abundant (field)

Mapping: besides FH parameter (χ)/interaction strengths (a) we need compressibility (κ) and coupling (C_{Ik}).

Japan, 2010

Mapping particles and fields: binary system

Determine ‘free’ parameters by requiring thermodynamic consistency for single bead solvent in both representations.



κ : match either pressure or excess chemical potential

c_{Ik} : use field partitioning to determine FH χ and Groot & Warren to convert to soft-core potential strength

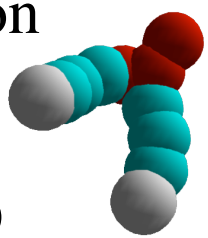
$$\rightarrow c_{Ik} = c_{Ik}(a)$$

Note: *both* particles and fields adapt dynamically

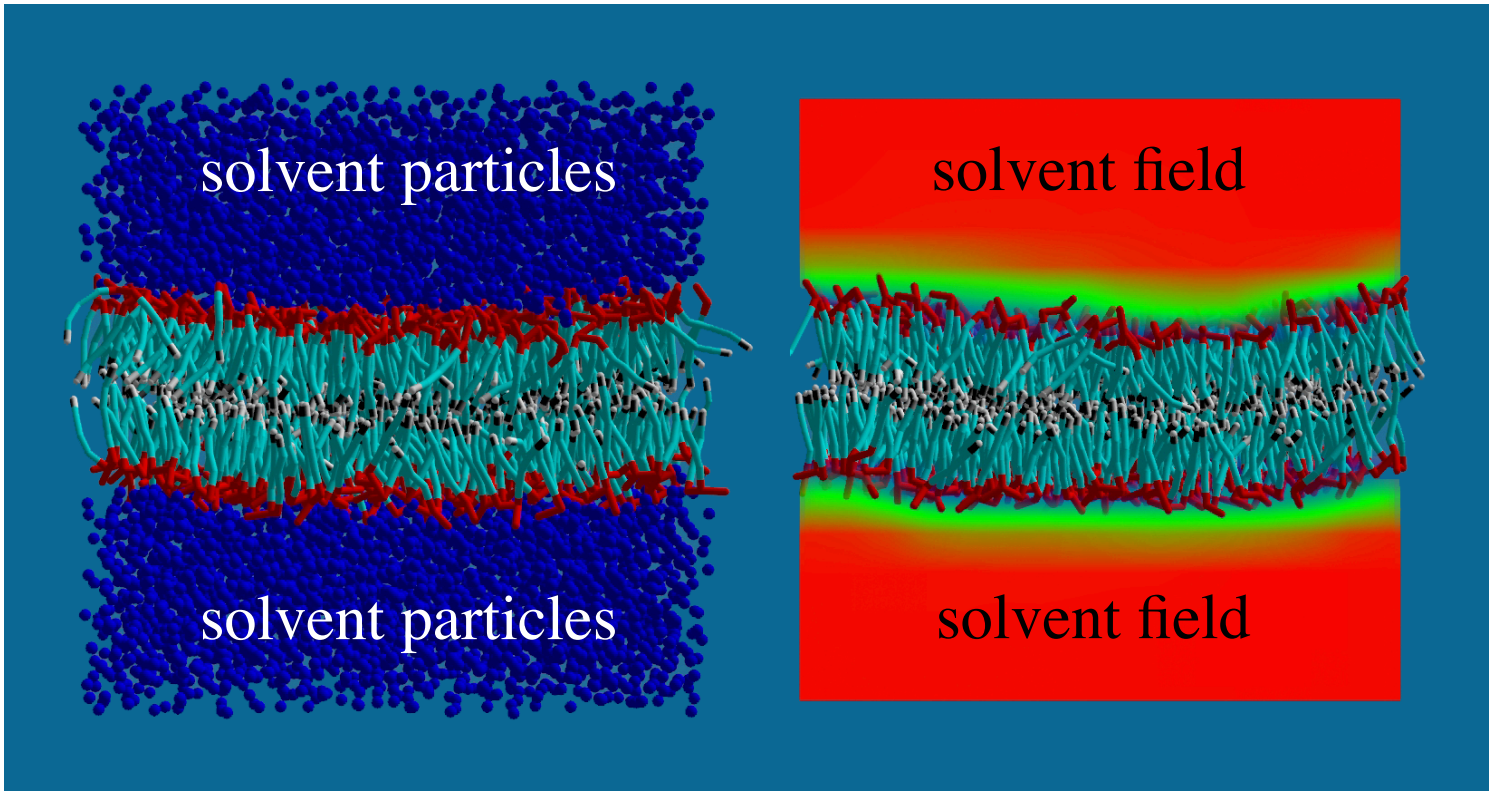
Japan, 2010

Universiteit Leiden

Hybrid vs DPD lipid membrane simulation



Use these values and *realistic* DPD lipid parameters (16^3)



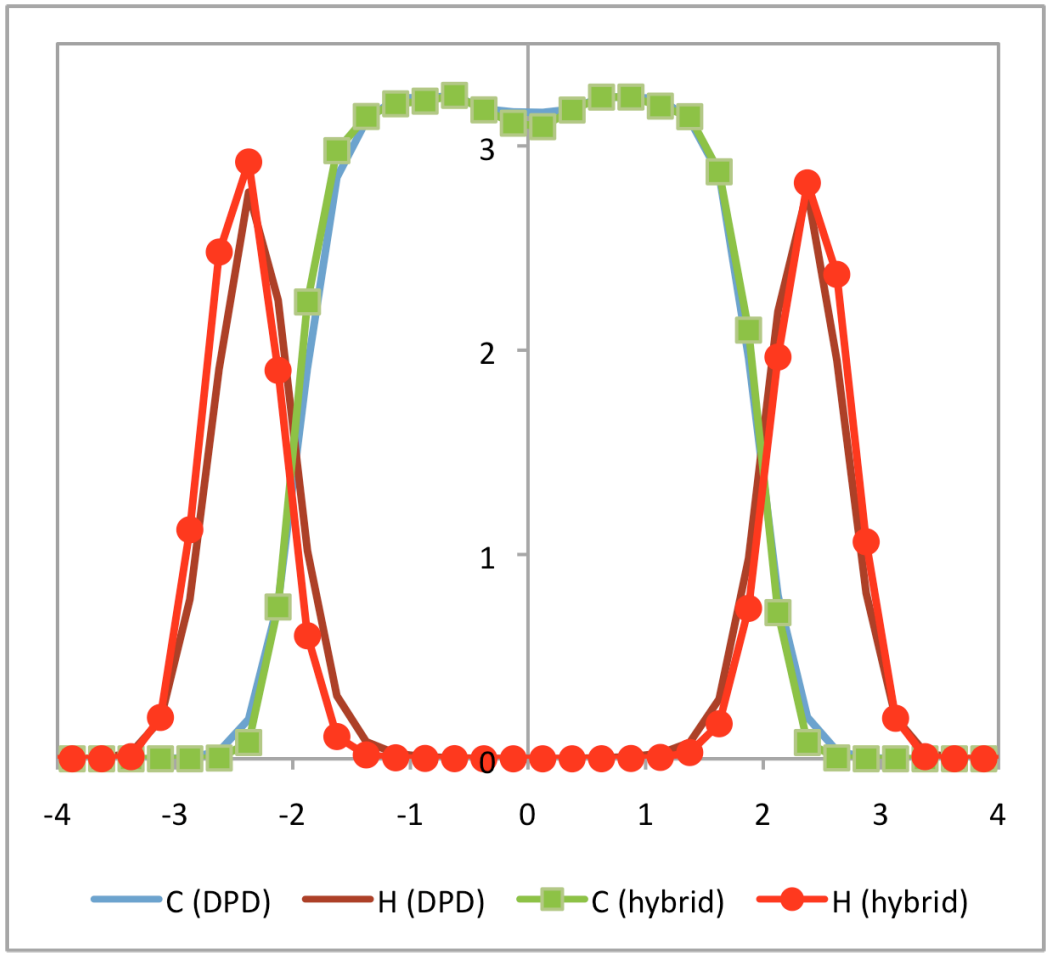
DPD, Shillcock and Lipowky 2002 (realistic)

Hybrid calculation where the solvent is replaced by a field, with the same S&L parameters for the lipid

Japan, 2010

Universiteit Leiden

Hybrid membrane simulation



Averaging over many initial condition and time frames

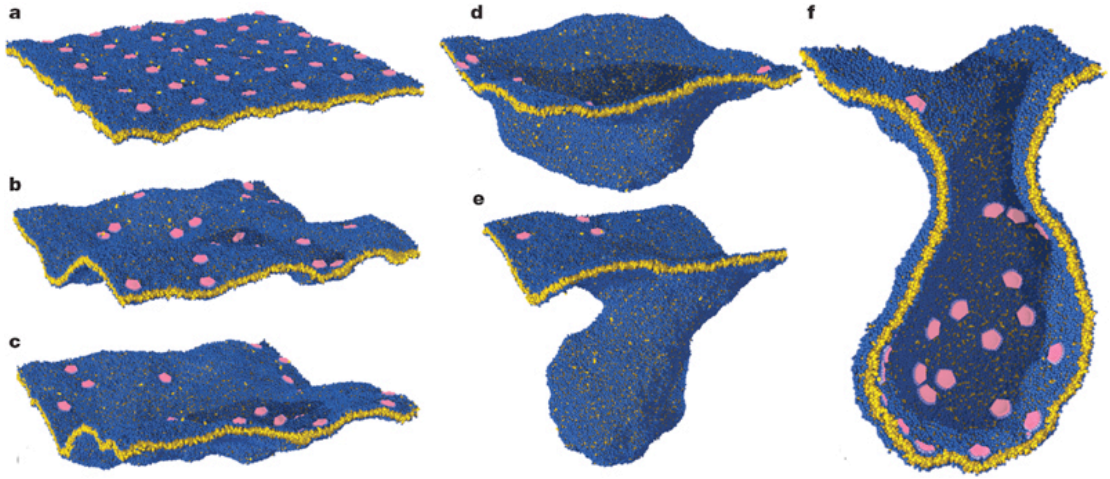
Japan, 2010

Additional benefits: implicit solvent

Preliminary: analytical equilibrium solution for solvent (field) can be converted into an additional potential in particle description

$$(\vec{r}_k^{\,sol}, \vec{r}_k^{\,lipid}) \xrightarrow[mapping]{} (\rho_{sol}, \vec{r}_k^{\,lipid}) \xrightarrow[analytic]{} \vec{r}_k^{\,lipid}$$

$$V \rightarrow A$$



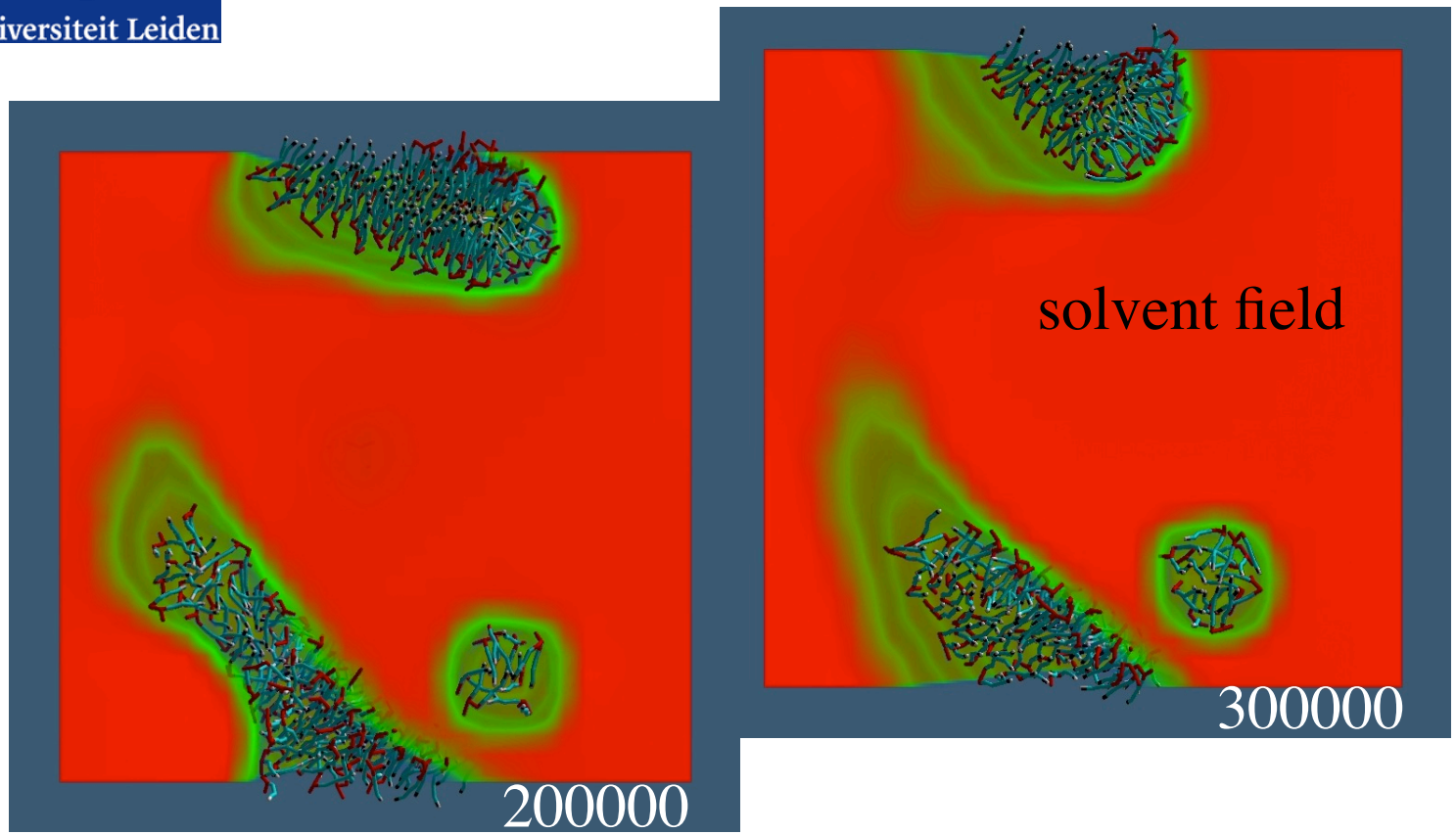
CGMD, implicit solvent

I.R. Cooke, K. Kremer, M. Deserno, Phys. Rev. E, 011506 (2005).

Japan, 2010

Universiteit Leiden

Vesicle formation pathway following quench



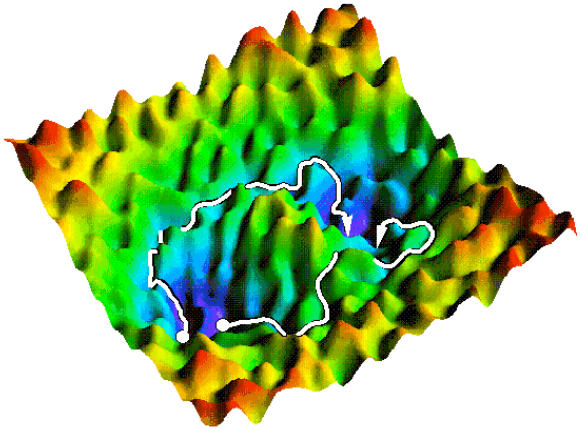
32^3

Diffusion is patient (DPD – O(20000))
Experiments: slow process!

Solution? S-QN: accelerating collective modes

Japan, 2010

Universiteit Leiden



Enhanced sampling:

Accelerating collective modes in a CG particle description

Japan, 2010

Stochastic Quasi-Newton method

Optimization in numerical mathemetics (objective function)

$$\Delta x_k = x_{k+1} - x_k = -\alpha_k \nabla \Phi$$ Steepest descent

$$\Delta x_k = x_{k+1} - x_k = -\alpha_k H^{-1} \nabla \Phi$$ Newton method

Quasi-Newton method $\quad \uparrow B_k$

$$B_k \rightarrow H^{-1}$$

Diffusion in statistical mechanics (potential function)

$$\Delta x_k = -M \nabla \Phi(x_k) \Delta t + \sqrt{2 M k_B T \Delta t}\, \Delta W_k$$

M(x) $\qquad$ $\sqrt{\text{M(x)}}$

Fluctuation-dissipation

Curvature-dependent mobility

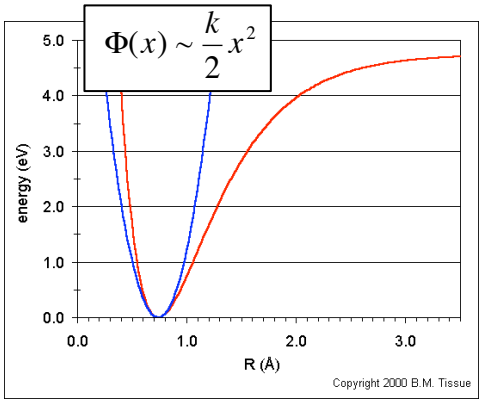
$$M(x) = (\nabla^2 \Phi(x))^{-1}$$

+ spurious drift

Japan, 2010

Stochastic Quasi-Newton method

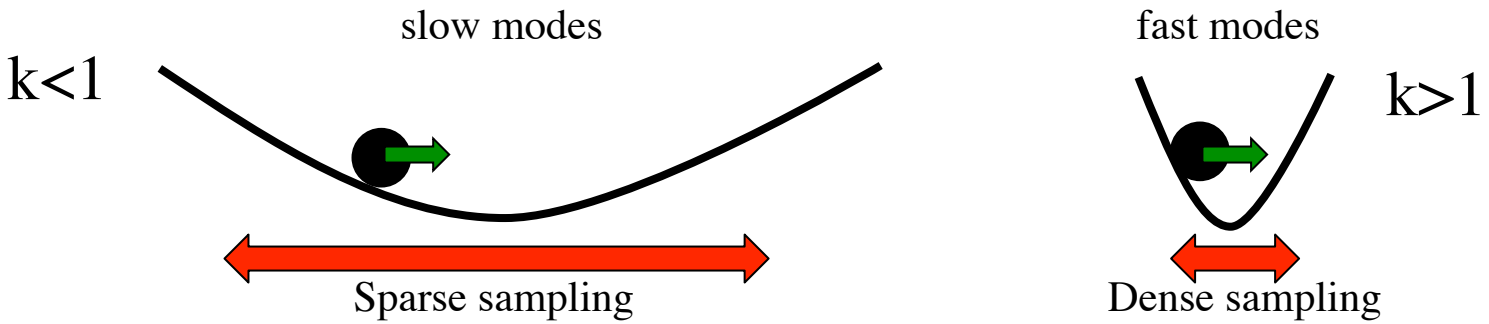
Illustration: 1-D Harmonic oscillator



$$dx = -kxdt + \sqrt{2k_BT}dW(t) \qquad \text{for } M = 1$$

$$dx = -xdt + \sqrt{2\frac{k_BT}{k}}dW(t) \qquad \text{for } M = k^{-1} = (\nabla^2\Phi)^{-1}$$

drift term noise term ~ k^{-1}



Stability analysis: Δt^{max} independent of k

Japan, 2010

Universiteit Leiden

Stochastic Quasi-Newton method

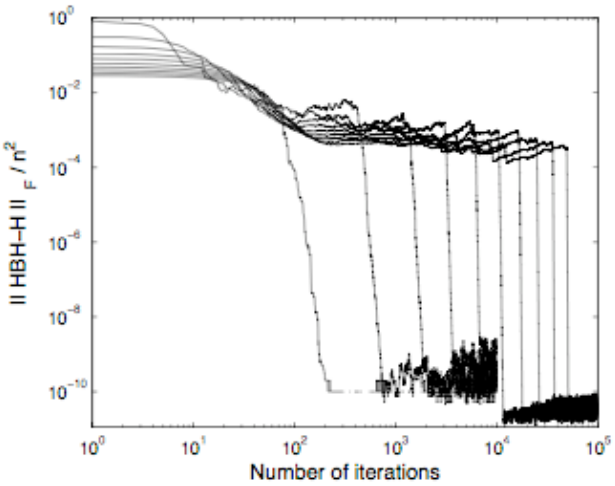
$M(x) = M_k(x_k) = M_k(x_k,\ldots,x_0)$ approximate of $H(x_k)^{-1}$

New factorized update method (equivalent to DFP) for M_{k+1}:

- Hereditary: minimal $\|M_{k+1} - M_k\|_F$
- If M_0 positive definite, M_{k+1} positive definite (√M exists!)
- M_{k+1} is approximate of inverse Hessian (secant condition)
- Efficiency: $M_{k+1} = J_{k+1}J_{k+1}^T \Longrightarrow$ update J_{k+1}

Rouse chain

$M_k \rightarrow H^-$



Additional costs per timestep but

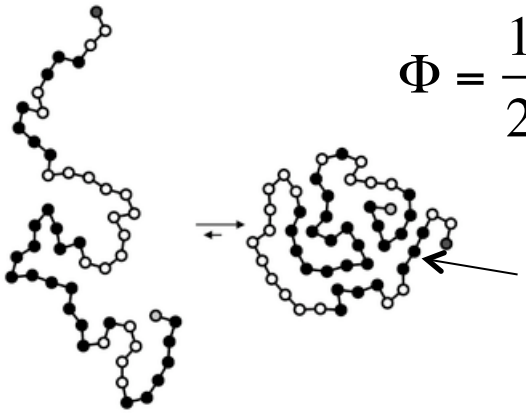
$\Delta t^{SQN} >> \Delta t^{LD}$

Japan, 2010

Stochastic Quasi-Newton method

Analysis for quadratic potential (Rouse chain): *all* modes evolve equally fast (real-space Fourier acceleration)

Minimal model of a protein



$$\Phi = \frac{1}{2}\Phi_{bond} + \frac{1}{2}\Phi_{bending} + \Phi_{dihedral} + \Phi_{LJ}$$

Bead=amino acid (either neutral, hydrophobic or hydrophilic)

Conclusions (S-QN):

✓Enhanced sampling of energy landscape (many inherent states)

✓Hierarchical optimization (bond length, angles, torsions, non bonded)

Generic S-QN method: accelerated but no 'realistic' dynamics

Japan, 2010

Conclusions and outlook

Conclusions:

✓New hybrid model for particle/field mixtures
✓Reuse DPD parameters for CG lipids
✓Possibility of implicit solvent (analytic)
✓Additional sparse constituents can be added as CG particle chains
✓New S-QN method to speed up formation kinetics

To do:

✓Validate membrane material parameters in hybrid model
✓Concise derivation of implicit solvent
✓Implementation and parameterization of SNARE-like CG proteins

Outlook:

✓Large scale simulations
✓Vesicle fusion
✓…

Universiteit Leiden

Thank you for your attention

Questions?

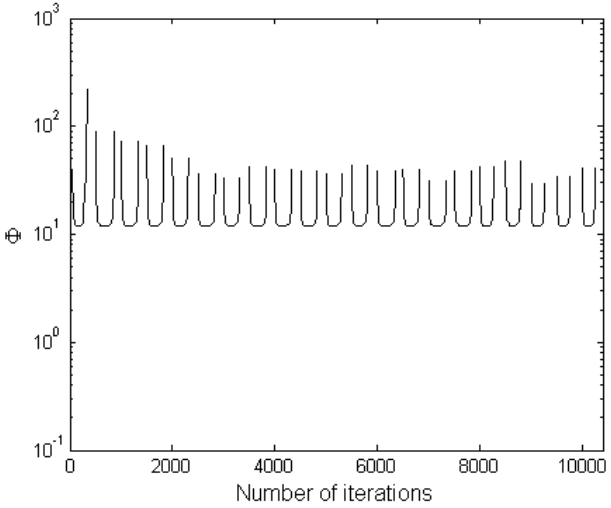
(a.sevink@chem.leidenuniv.nl)

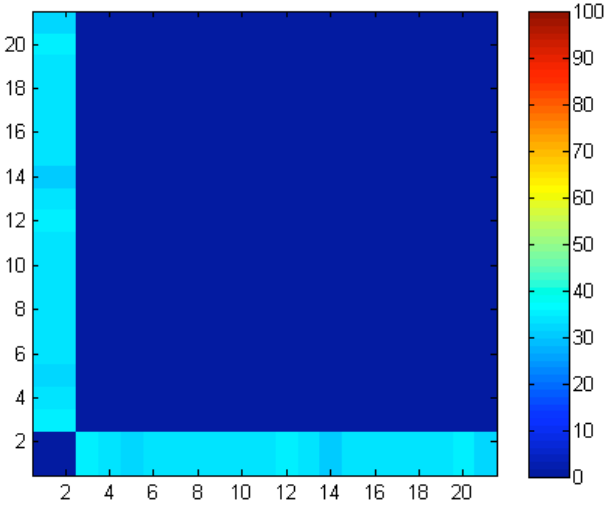
Japan, 2010

Minimal model of a protein (3D): sampling efficiency

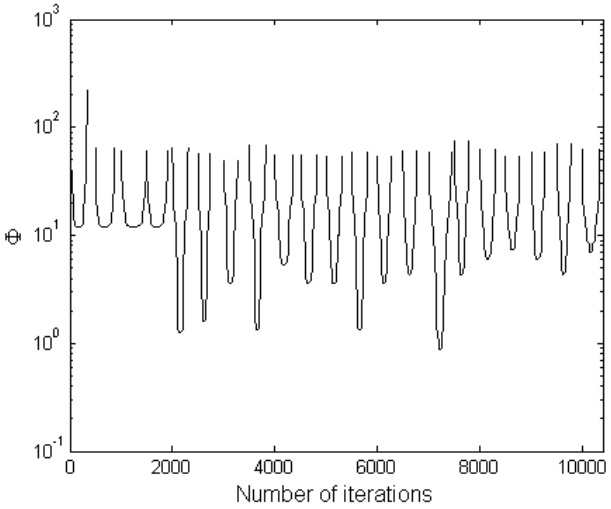
$T > T^{collapse}$

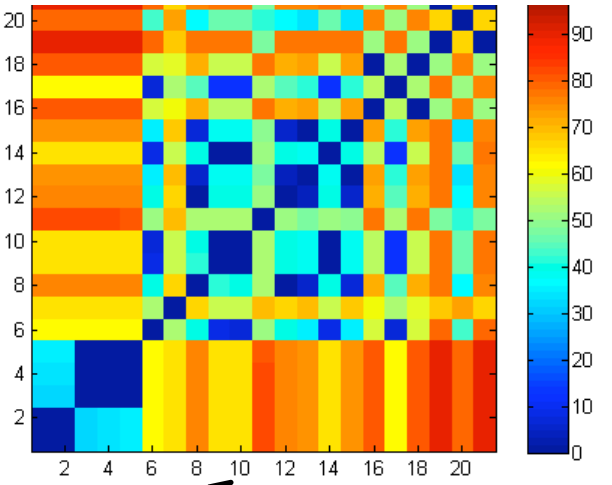
Standard LD (SLD)





One basin





Several basins

Our FSU method

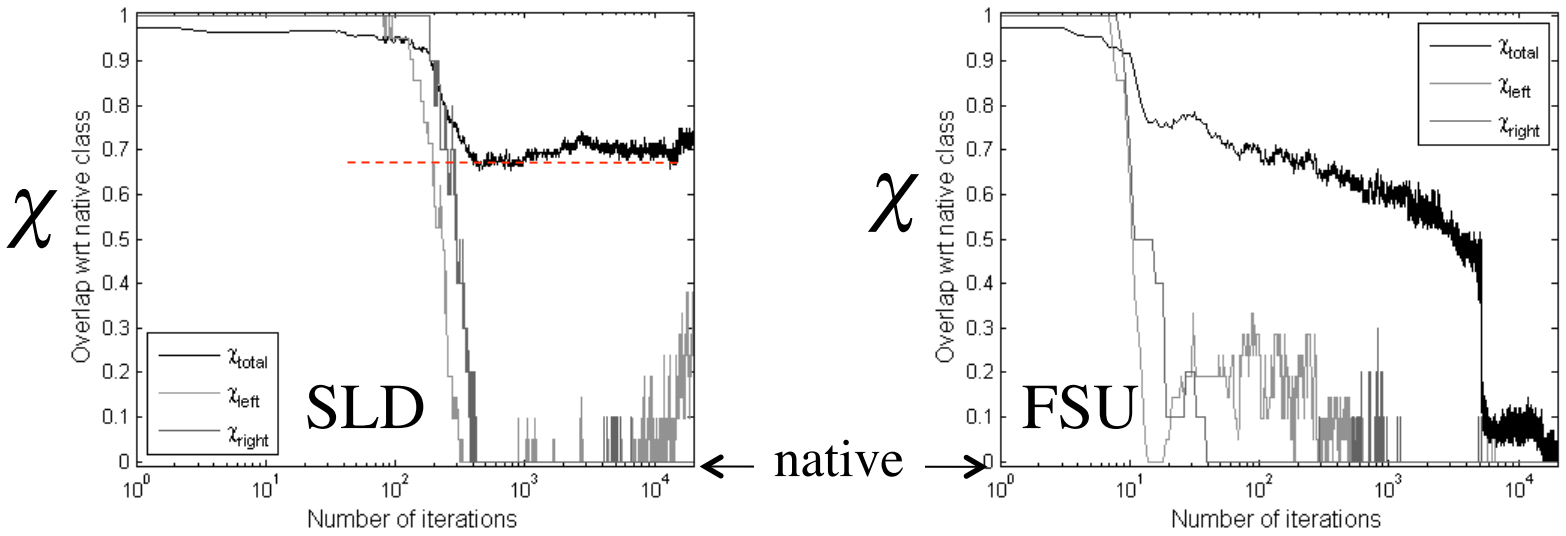
Principles of SQN

'native state'

Minimal model of a protein (3D): mode analysis

$T << T^{fold}$

$LB_8B(NL)_2NBLB_3LB$ Native state: left, turn and right sub-domains



$$\Phi = \frac{1}{2}\Phi_{bond} + \frac{1}{2}\Phi_{bending} + \Phi_{dihedral} + \Phi_{LJ}$$

Equilibration order: bonds, angles, torsions, LJ (even for reduced spring constants)
-> 'soft' RATTLE/SHAKE/LINCS