Coarse grained modeling: applications in polymers and biological systems

Presented by
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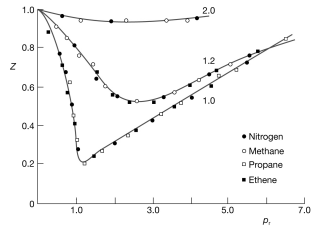
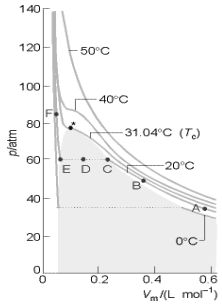
Experimental data of Z for different gases



- Z for different gases at the same reduced variables (T_r and P_r) are the same. Chemical identity disappears.

Universal behavior near the critical point

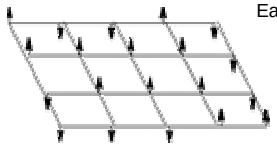


Isotherm for CO_2 gas

$(\rho_L-\rho_g)\sim(T-T_c)^m$

The exponent *m* is universal

Ising model for phase transition

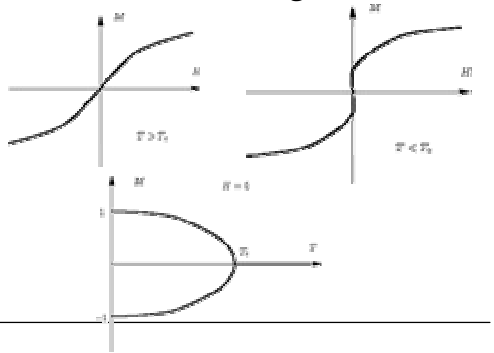


Each lattice site has a spin s_i

$$\sigma_i = \begin{cases} 1, & \text{"up"} \\ -1, & \text{"down"} \end{cases}$$

$$\mathcal{H} = -H\sum_i \sigma_i - \frac{J}{2}\sum_{(i,j)} \sigma_i\sigma_j$$

Phase transition in Ising model



Polymers as long chains

$-CH_2-CH_2-CH_2-CH_2-$ Poly(ethylene)

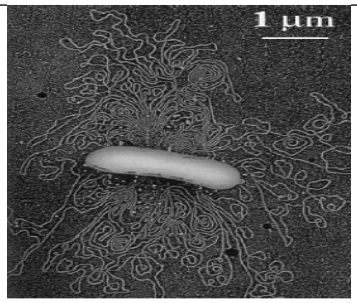
$-CH_2-\underset{\bigcirc}{CH}-CH_2-\underset{\bigcirc}{CH}-$ Poly(styrene)

$-CH_2-\underset{Cl}{CH}-CH_2-\underset{Cl}{CH}-$ Poly(vinyl chloride)

Number of monomer units in the chain $N >> 1$.

For synthetic macromolecules usually N =10^2~10^4

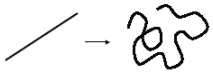
Name	Molecular Formula	Melting Point (°C)	Boiling Point (°C)	State at 25°C
methane	CH_4	-183	-164	gas
ethane	C_2H_6	-183	-89	
propane	C_3H_8	-190	-42.8	
butane	C_4H_{10}	-138	-0.5	
pentane	C_5H_{12}	-130	36	
hexane	C_6H_{14}	-95	69	
heptane	C_7H_{16}	-91	98	
octane	C_8H_{18}	-57	125	
nonane	C_9H_{20}	-51	151	liquid
decane	$C_{10}H_{22}$	-30	174	
undecane	$C_{11}H_{24}$	-25	196	
dodecane	$C_{12}H_{26}$	-10	216	
eicosane	$C_{20}H_{42}$	37	343	
triacontane	$C_{30}H_{62}$	66	450	solid



Electron microscope picture of bacterial DNA partially released from its native shell (source: *Dictionary of Science and Technology*, Christopher Morris ed., San Diego, CA: Academic Press, 1992)

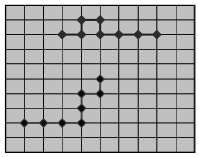
Physical properties of polymers are governed by three main factors

- Number of monomers in the chains, N, ($N>>1$)
- Monomers units are connected in the chain
  - They do not have the freedom of independent motion (unlike systems of disconnected particles, e.g. low molecular weight of gases and liquids).
- Polymer chains are flexible especially in solution or in melt



Coarse-grained models for polymers

Freely jointed chains

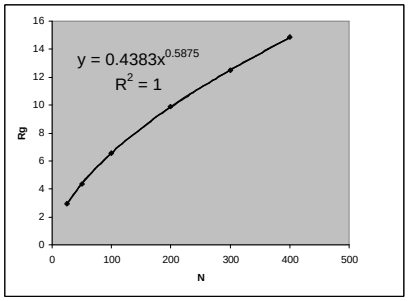


Random Walks (RW) or Self-avoiding Random Walks (SAW) on the lattice

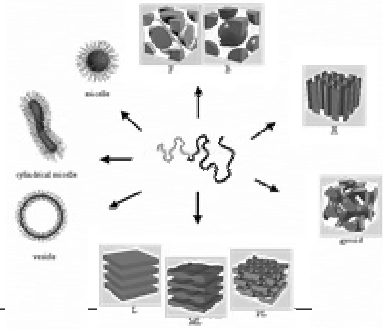
How does polymer size scales with N?

- If you treat polymer long chain as random walk (monomer overlaps are allowed), one would predict the size $R_g \sim N^{1/2}$
- When monomer overlaps are disallowed (also called excluded volume interaction), $R_g \sim N^{\nu}$, ν is the Flory's exponent. (ν=3/5 in three-dimension, ¾ in two-dimension, 1 in one-dimension).
- The determination of this exponent is from through the numerical data from computer simulations.

R_g variation with N in our lattice models



Self-assembly of block copolymers



A little bit about simulation algorithm

- Lattice SAW of diblock copolymers $N_A N_B$
- Empty lattice sites are treated as solvents, S
- Pair-wise interaction energy $E_{AS}=E_{AB}>0$, all other pair-wise interactions are zero.
- Start with a randomly placed polymers, equilibrate it by "reptation moves" with "Metropolis rule", i.e. accepting a "proposed move" with a probability of *P*

$$P = \min(\mathbf{1}, \exp(-\frac{\Delta E}{k_B T}))$$

Determination of CMC

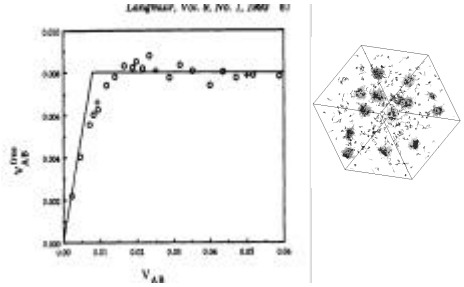


Figure: Plot of concentration of free diblock copolymers versus total concentrations of diblock copolymers (Wang et al. *Langmuir*, 9, 66-70 (1993))

Slow equilibration of micelles

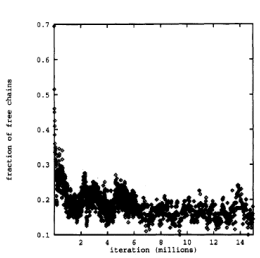


Figure 3. Fraction of free chains during a simulation on a 44^3

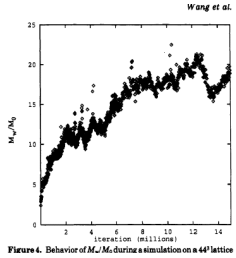


Figure 4. Behavior of M_w/M_0 during a simulation on a 44^3 lattice

Experimental measurement of slow chain exchange

Macromolecules **1995,** *28,* 904−911

Exchange of Chains between Micelles of Labeled Polystyrene-*block*-poly(oxyethylene) As Monitored by Nonradiative Singlet Energy Transfer

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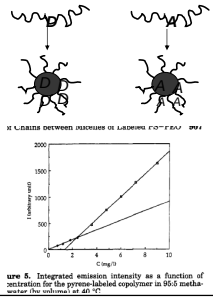
Received May 19, 1994; Revised Manuscript Received November 16, 1994®

ABSTRACT: The dynamics of the exchange of chains between micelles formed by diblock copolymers in dilute solution in a selective solvent has been studied using fluorescence measurements. The samples are polystyrene-*block*-poly(oxyethylene) with a single fluorescent label (either naphthalene or pyrene) covalently attached at the junction between the blocks. The critical micelle concentration (cmc) of each sample can be determined from the concentration dependence of the integrated emission intensity, provided the cmc is high enough to permit detection. In order to study the kinetics, micelles of the two differently labeled samples were first prepared at the same concentration, solvent, and temperature, but in two different containers. The contents of the containers were then mixed, and the efficiency of nonradiative singlet energy transfer from naphthalene to pyrene was measured as a function of time. The time dependence of the intensity of the emission from naphthalene can be fitted to a sum of two exponentials, with time constants that differ by at least an order of magnitude. Activation energies are somewhat smaller for the faster process than for the slower process, but in both cases they are on the order of 10^2 kJ mol^{-1} under the conditions where they can be measured. We have not been able to account for this result with a kinetic scheme that assumes the exchange of chains between the micelles takes place exclusively via the population of free chains. This difficulty suggests that an additional mechanism for the exchange of chains may be active.

Experimental Results



ure 5. Integrated emission intensity as a function of centration for the pyrene-labeled copolymer in 95:5 metha-

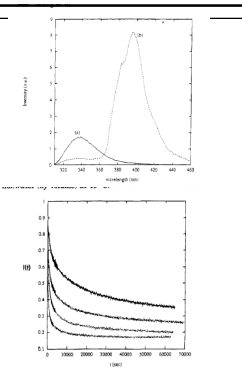


Figure 6. Normalized fluorescence emission at 338 nm in 90: 10 methanol:water when the total concentration of copolymer is 0.129 g L^{-1} and α = 0.5. The temperature is 25, 30, 35, and 40 °C, respectively, from top to bottom.

after mixing preequilibrated samples of the naphthalene-

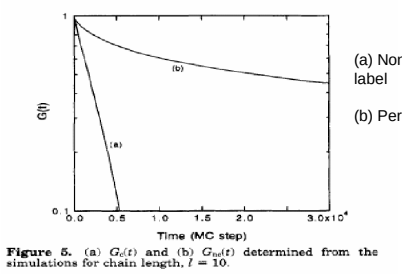
Exchange of adsorbed polymers

- Experiments monitored displacement of Hydrogenated PMMA by Deuterated PMMA through reflectance FT-IR (exchange process)
- Measured Exchange kinetics is highly non-exponential. Some can be fitted to stretched-exponential decay, $\exp(-(t/\tau)^{1/2})$
- Exchange rate, τ_{exch} increases with M.W. of polymers dramatically.

Dynamic Monte Carlo

- Start with a well-equilibrated system, monitor exchange of polymers between adsorbed states and non-adsorbed states as a function of "simulation time"
- Simulation time is defined in Monte Carlo Steps. One Monte Carlo step refers to one cycle of proposed moves for all polymer beads.
- When using correct "move" algorithm, simulation relaxation time for a polymer chain $\tau \sim N^2$, Diffusion of polymer chains, $D \sim 1/N$, all give "expected" behavior for polymers in solutions.

Relaxation of label concentrations on the surface



(a) Non-permanent label

(b) Permanent label

Figure 5. (a) $G_c(t)$ and (b) $G_{nc}(t)$ determined from the simulations for chain length, $l = 10$.

Wang et al, Macromolecules, 1995, 28, 7061

A simple kinetic model

$$\frac{d\Gamma(t)}{dt} = -k_d\Gamma(t) + k_a(\Gamma_s)\, C(z,t)|_{z=0}$$

$$D\frac{\partial^2 C(z,t)}{\partial^2 z} = \frac{\partial C(z,t)}{\partial t}$$

Solutions:

$$\frac{\Gamma(t)}{\Gamma_0} = \frac{1}{(\alpha_2 - \alpha_1)}[\alpha_2 f(\alpha_1 t^{1/2}) - \alpha_1 f(\alpha_2 t^{1/2})]$$

$$f(w) = \mathrm{erfc}(w)\exp(w^2)$$

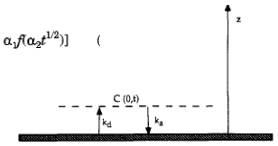
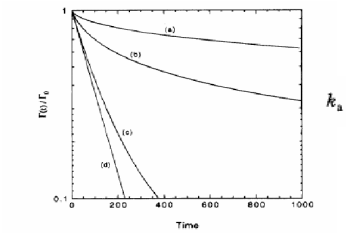


Figure 1. Schematic drawing of the exchange kinetics under consideration

Sample calculated solutions



$$k_a = k_d\Gamma^{eq}/C^{eq} = k_dQ$$

Figure 2. Sample calculations of $\Gamma(t)/\Gamma_0$ with $k_d = 0.01$ time^{-1}, $k_a = 0.02$ (length/time): (a) $D = 0.001$ length^2/time, $Q^2k_d/4D = 10$; (b) $D = 0.01$ length^2/time, $Q^2k_d/4D = 1$; (c) $D = 1.0$ length^2/time, $Q^2k_d/4D = 0.1$; (d) simple exponential decay function, $\exp(-k_dt)$.

Testing of the solutions

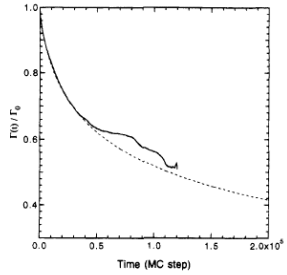


Figure 6. Solid line: $G_{nc}(t)$ determined from the simulation for $l = 20$. Dashed line: Calculated according to (8) using parameters tabulated in Table 1 for $l = 20$.

Mapping of real polymers to coarse-grained models

- For a real polymer, one can determine characteristic ratio, C_∞ based on : $\langle R^2 \rangle = C_\infty n l_0^2$ either using Rotational Isomeric State Theory or from experiments
- For polyethylene, $C_\infty = 6.7 \pm 0.3$, $l_0 = 1.53$Å
- To map it to lattice polymers, use two conditions: $\langle R^2 \rangle = 1.5Na^2 = C_\infty n l_0^2$, and $Na = n l_0$, this leads to $a = 6.834$Å, *if n=10,00 (M_w=14000 g/mol), N=223*

Coarse-grained modeling of proteins

- The earliest use of lattice models for proteins probably is in the study of protein folding (Skolnick et al.)
- Each residue is represented by a bead on the lattice. The simplest type of protein to consider is the H-P model (i.e. only two types of beads, hydrophilic and hydrophobic beads).
- The advantage of using lattice model is fast relaxation, capable of sampling "all" conformations. Sometime it is called "ab initio" method

Elastic Network Model

VOLUME 77, NUMBER 9 PHYSICAL REVIEW LETTERS 26 AUGUST 1996

Large Amplitude Elastic Motions in Proteins from a Single-Parameter, Atomic Analysis

Monique M. Tirion*
Department of Membrane Research and Biophysics, Weizmann Institute of Science, Rehovot 76100, Israel
(Received 22 April 1996)

Normal mode analysis (NMA) is a leading method for studying long-time dynamics and elasticity of biomolecules. The method proceeds from complex semiempirical potentials characterizing the covalent and noncovalent interactions between atoms. It is widely accepted that such detailed potentials are essential to the success of NMA's. We show that a single-parameter potential is sufficient to reproduce the slow dynamics in good detail. Costly and inaccurate energy minimizations are eliminated, permitting direct analysis of crystal coordinates. The technique can be used for new applications, such as mapping of one crystal form to another by means of slow modes, and studying anomalous dynamics of large proteins and complexes. [S0031-9007(96)01063-0]

PACS numbers: 87.15.By, 87.15.He

Tirion, M. M. Phys. Rev. Lett. 1996, 77, 1905

She replaces this complicated force-field with

$$E_p = \frac{1}{2}\sum_{\text{bonds}} K_b(b - b_0)^2 + \frac{1}{2}\sum_{\text{angles}} K_\theta(\theta - \theta_0)^2 + \frac{1}{2}\sum_{\text{dihedrals}} K_\phi[1 + \cos(n\phi - \delta)] + \sum_{\text{nonbonded pairs}}\left[\frac{A}{r^{12}} - \frac{B}{r^6} + \frac{q_1 q_2}{Dr}\right]. \quad (1)$$

with a simple Hookean pairwise potential between atoms

I replace the habitual detailed potentials, such as the one in Eq. (1), by the Hookean pairwise potential (between atoms a and b):

$$E(\mathbf{r}_a, \mathbf{r}_b) = \frac{C}{2}(|\mathbf{r}_{a,b}| - |\mathbf{r}^0_{a,b}|)^2. \quad (3)$$

Here $\mathbf{r}_{a,b} \equiv \mathbf{r}_a - \mathbf{r}_b$ denotes the vector connecting atoms a and b, and the zero superscript indicates the given *initial* configuration. Thus, the usual minimization of the potential energy is eliminated.

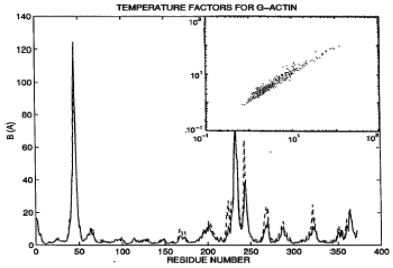


FIG. 3. Comparison of theoretical temperature factors, B, obtained with the L79 potential (dashed curve) and the potential of Eq. (1), for the G-actin::ADP:Ca^{++} system. The contributions of the 30 slowest modes are included. The inset shows the scatter plot of the two data sets: the standard potential along the ordinate, and the current simplified potential along the abscissa.

- Bahar and Jernigan further coarse grained the protein structure to one site per amino acid, and applied the Hookean Potential between residues within a cut-off distance. They obtained very insightful results.

Biophysical Journal Volume 78 April 2000 2093–2106

Proteins with Similar Architecture Exhibit Similar Large-Scale Dynamic Behavior

O. Keskin,* R. L. Jernigan,† and I. Bahar*†
*Chemical Engineering Department and Polymer Research Center, Bogazici University, and TUBITAK Advanced Polymeric Materials Research Center, Bebek 80815, Istanbul, Turkey, and †Molecular Structure Section, Laboratory of Experimental and Computational Biology, Division of Basic Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892-5677 USA

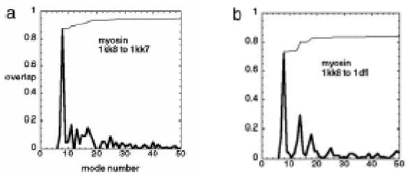
VOLUME 80, NUMBER 12 PHYSICAL REVIEW LETTERS 23 MARCH 1998

Vibrational Dynamics of Folded Proteins: Significance of Slow and Fast Motions in Relation to Function and Stability

Ivet Bahar, Ali Rana Atilgan, Melik C. Demirel, and Burak Erman
Polymer Research Center, Bogazici University, and TUBITAK Advanced Polymeric Materials Research Center, Bebek 80815, Istanbul, Turkey
(Received 10 November 1997)

Keskin, Jernigan, Bahar, Biophys. J. 2000, 78, 2093
Bahar, Atilgan, Demirel, Erman, Phys. Rev. Lett., 1998, 80, 2733

- This elastic network model is extremely useful to predict the "possible" conformational change of proteins. It is much faster and efficient that "atomic detailed" normal mode analysis.



One single slow mode contribute 80% of known conformational change of myosin

Zhang and Doniatch, PNAS, 2003, 100, 13253

doi: 10.1016/S0022-2836(02)00135-3 available online at http://www.idealibrary.com on IDEAL J. Mol. Biol. (2002) 318, 733–747

JMB

The Mechanism and Pathway of pH Induced Swelling in Cowpea Chlorotic Mottle Virus

Florence Tama and Charles L. Brooks III*

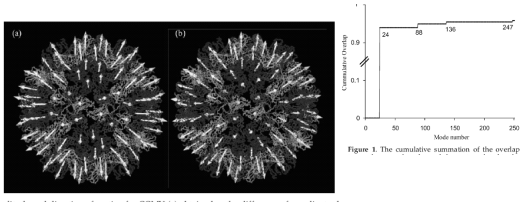


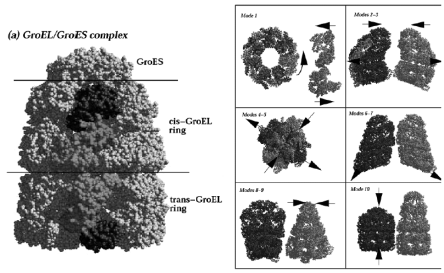
Figure 1. The cumulative summation of the overlap

Tama and Brooks, J. Mol. Biol., 2002, 318, 733-747

Biochemistry **2002**, *41*, 491−501

Molecular Mechanisms of Chaperonin GroEL−GroES Function

O. Keskin,[‡,⊥,⊥] I. Bahar,*[,‖] D. Flatow,[‡] D. G. Covell,[§] and R. L. Jernigan[‡]



Keskin, Bahar, Flatow, Covell, Jernigan, Biochemistry, 2002, 41, 491

Tama, Valle, Frank, Brooks, PNAS, 2003, 100,9319

Dynamic reorganization of the functionally active ribosome explored by normal mode analysis and cryo-electron microscopy

Florence Tama*, Mikel Valle†, Joachim Frank†,*, and Charles L. Brooks, III*,‡

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Global ribosome motions revealed with elastic network model

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Wang, Rader, Bahar, Jernigan, J. Struct. Biol., 2004, 147, 302-314

Justification of its success and challenges

- The slow "global" motions of the proteins are not very sensitive to the local "chemical" specific interactions between atoms, rather it is the packing of the proteins determine its "cooperative" motions. So the coarse-grained modeling works well for this purpose.
- Elastic network model is extremely useful for studying motions of large biological assembly
- Challenges are how to correlate the motions predicted to the function of the assembly.