Why coarse-graining?

If you haven’t figured that out by now, you should ask for your money back.

No, seriously.

Why coarse graining?
Why coarse-graining?

Efficiency

Insight
Efficiency

Does that mean just “bigger systems”? 

No. Not just.

All-atom lipid bilayer
20nm × 20nm, 1024 lipids, 10ns

What if we want a boxlength of $L=200$nm?
How does computing effort scale with $L$?

\[
\text{effort} \sim L^2 \times L^4 \sim L^6
\]

Amount of material
Equilibration time
Efficiency

20nm $\rightarrow$ 200nm

$10^6 \approx 2^{20}$

20 doublings of computer power!

20 x 2 years (Moore’s law)

40 years

I’ll be retired by then!

(best case scenario)
Efficiency

Stated differently:

The amount of material scales with the membrane area $A$. Using a domain decomposition scheme, this can (in the best case) be compensated by increasing the number of processors proportional to $A$.

But the simulation time towards equilibration scales like $A^3$. This still leaves an uncompensated factor of $A^2$ that you must do more work or have faster chips or better ideas.
Coarse graining cannot just help you to look at much bigger systems. It can help you to get well equilibrated data for somewhat bigger systems.

If someone offers you 1000 times more computational power, you should make your membrane length ~3 times bigger and simulate it for ~100 time longer!
Coarse graining cannot just help you to look at much bigger systems. It can help you to get well equilibrated data for somewhat bigger systems.

(Unfortunately, the latter doesn’t look as obviously sexy.)

(Is it better to have non-equilibrated data of an impressively big or complex system, or to rather have equilibrated data of a system that is not accurate or big enough?)
“The purpose of computation is insight, not numbers.”

Richard W. Hamming (1915-1998)
Assume that there’s some biophysical problem that can only be solved by sifting through many Terabytes of all-atom simulation trajectories. This of course might happen!

But if it does, how much have we understood of the problem, after we have done the simulation?

As scientists we ought to be curious about how many Terabytes of detail we can throw away before we begin to model the system. Because our brains are finite.

(Engineering, on the other hand, might be a whole different issue. Numbers often matter!)
Coarse graining is the art of throwing such supposedly unnecessary detail away.

(In fact, I believe that Physics is the art of throwing unnecessary detail away)

It’s an art.
There’s no sure-fire way of getting it right.

You throw the wrong stuff away, you’re doomed!

Well, not really: If you make sure that your simulation is correct, then you have a falsifiable result! So you’re scientific!
Today:

I’ll illustrate a way to treat the mesoscopic regime in an efficient and insightful way. (OK, that’s a tall order.)

- Generic top-down bead-spring
- solvent free
- only pair forces
- robust & physically meaningful

I.R. Cooke, K. Kremer, M. Deserno, Phys. Rev. E 72, 011506 (2005);
Today:


Today:

Physics based? 
Definitely Yes!

But is there room for physical reasoning or physics-based effects in biology?

I think: Definitely Yes!

I.R. Cooke, K. Kremer, M. Deserno, Phys. Rev. E 72, 011506 (2005);
Why is “solvent free” good?

membrane ↔ surface

solvent ↔ bulk

Unless you’re careful, you might end up simulating a finite size effect!
Example

membrane  surface

solvent  bulk

16,000 DPD lipids 4 beads per lipid.
64,000 degrees of freedom for lipids.

But in total 1,536,000 particles in box!

96% of simulation time spent with solvent!
(They had a good reason for doing this. But do you, too?)

M. Laradji & P.B. Sunil Kumar
Difficulties

Implicit solvent models are incredibly common and useful in polymer physics.

Why has it taken so long for them to appear in the field of membrane research?

Polymers don’t first have to self assemble!

One needs additional cohesion to make the lipids come together.

Fluidity has proven to be the major challenge.
Difficulties

Implicit solvent models are incredibly common and useful in polymer physics.

Why has it taken so long for them to appear in the field of membrane research?

Polymers don't first have to self-assemble! One needs additional cohesion to make the lipids come together.

Fluidity has proven to be the major challenge.

Weak attraction $\Rightarrow$ gas phase

No fluid phase in between?!?

Strong attraction $\Rightarrow$ solid (gel) phase

Fluidity has proven to be the major challenge.
Our model

Link three beads

\[ V_{\text{bond}}(r) = -\frac{1}{2}k_{\text{bond}} r_\infty^2 \log \left[ 1 - \left( \frac{r}{r_\infty} \right)^2 \right] \]

Make lipid stiff

\[ V_{\text{bend}}(r_{13}) = \frac{1}{2}k_{\text{bend}} (r_{13} - 4\sigma)^2 \]

Nonbonded

\[ V_{\text{rep}}(r) = 4\epsilon \left[ \left( \frac{r_c}{r} \right)^{12} - \left( \frac{r_c}{r} \right)^6 + \frac{1}{4} \right] \Theta(r_c - r) \]

\[ V_{\text{attr}}(r) = \begin{cases} \frac{-\epsilon}{\cos^2 \frac{\pi (r-r_c)}{2w_c}} , & r < r_c \\ -\epsilon \cos^2 \frac{\pi (r-r_c)}{2w_c} , & r_c \leq r \leq r_c + w_c \\ 0 , & r > r_c + w_c \end{cases} \]
Overall phase behavior

Long-ranged attractions “save” the system some entropy!

I.R. Cooke, K. Kremer, M. Deserno, Phys. Rev. E 72, 011506 (2005);
Overall phase behavior


Long-ranged attractions “save” the system some entropy!

Shape of CG potential is qualitatively important!

I.R. Cooke, K. Kremer, M. Deserno, Phys. Rev. E 72, 011506 (2005);
Self assembly
Properties

Are these things really lipid membranes?
Bending modulus

Fluctuation spectrum from continuum theory

\[ E = \int dA \left\{ \frac{1}{2} \kappa K^2 + \sigma \right\} \approx \frac{1}{2} \int dx \, dy \left\{ \kappa (\nabla^2 h)^2 + \sigma (\nabla h)^2 \right\} \]

total curvature  
surface tension  
“linearized Monge gauge”
Bending modulus

Fluctuation spectrum from continuum theory

\[ E = \int dA \left\{ \frac{1}{2} \kappa K^2 + \sigma \right\} \approx \frac{1}{2} \int dx \, dy \left\{ \kappa (\nabla^2 h)^2 + \sigma (\nabla h)^2 \right\} \]

total curvature \hspace{1cm} \text{surface tension} \hspace{1cm} \text{“linearized Monge gauge”}

Fourier expansion and equipartition theorem

\[ \langle |h_q|^2 \rangle = \frac{k_B T}{L^2 \left[ \kappa q^4 + \sigma q^2 \right]} = \frac{k_B T}{L^2 \kappa} q^{-4} \]

determine bending modulus!

zero surface tension
Bending modulus

Fluctuation spectrum from continuum theory

\[ \langle |h_q|^2 \rangle \]

- **q^{-2}**
- **q^{-4}**

- **tension**
- **bending**
- **protrusions...**

\[ \sqrt{\sigma / \kappa} \quad 1/d \]
Bending modulus

Fluctuation spectrum from continuum theory

simulate at zero tension

simulate big systems

beware of spectral mesh damping!

$\langle |h_q|^2 \rangle$

$\sqrt{\sigma / \kappa}$

$1 / d$

$q^{-2}$

$q^{-4}$
Bending modulus

However...

- Equilibration time of Fourier modes scales like $q^{-4}$ (remember?)
- Large bending modulus ($\kappa$) from small perturbation ($kT$) $\rightarrow$ small signal!
- Result relevant for strong bending?

\[ h(x) = h_q e^{i qx} \quad \rightarrow \quad K = -h''(x) = h_q q^2 e^{i qx} \]

\[ \langle K^2 \rangle = \langle |h''(x)|^2 \rangle = q^4 \langle |h_q|^2 \rangle = \frac{k_B T}{L^2 \kappa} \]

\[ \bar{R} = \frac{1}{\langle K^2 \rangle^{1/2}} = \sqrt{\frac{\kappa}{k_B T}} \quad L \simeq 3 \ldots 5 \quad L \]
Bending modulus

However...

- Equilibration time of Fourier modes scales like $q^{-4}$ (remember?)
- Large bending modulus ($\kappa$) from small perturbation ($kT$) $\Rightarrow$ small signal!
- Result relevant for strong bending?

Maybe we need an alternative technique?
Bending modulus

...from actively bent membranes

first implementation:
Enforce large undulation mode, measure constraining force.

Simpler way: Stretch a membrane tether!

Bending modulus

...from actively bent membranes

Energy: \[ E = \frac{\kappa}{2} \times \frac{1}{R^2} \times A \]

Force: \[ F = \left( \frac{\partial E}{\partial L} \right)_A = \cdots = \frac{2\pi \kappa}{R} \]

Bending modulus: \[ \kappa = \frac{FR}{2\pi} \approx \frac{F}{2\pi} \]

what about fluctuations?

Bending modulus
...from actively bent membranes

Results:
Within the limits of our resolution no stiffening (or softening) of the membrane at (very!) large curvatures is observed.

Result from fluctuation analysis
Stretching modulus

Stretching modulus

Simple theory for this:

Farago, JCP, 2003; Tolpekina/den Otter/Briels, JCP 2004; Cooke/Deserno, JCP 2005

Membrane stretching plus line energy

\[ E = \frac{1}{2} M \left( \frac{A - A_S - \pi R^2}{A_S} \right)^2 + 2\pi \gamma R \]

rescaling of energy:

\[ \lambda^3 = \frac{\gamma A_S}{\pi M} , \quad \tilde{R} = \frac{R}{\lambda} , \quad B = \frac{A - A_S}{\pi \lambda^2} \]

equilibrium condition for pore radius:

\[ \tilde{R}^3 - B \tilde{R} + 1 = 0 \]

Only one length scale, only one dimensionless driving parameter!
Three fitting parameters:

- zero tension area
- stretching modulus
- line tension

but you cannot tune the jump height!

Line tension

However, if all you want is the line tension, there’s a simpler way of doing this:

Simulate a periodically half-connected bilayer in a box.

Stress tensor will be imbalanced precisely by twice the line tension!
Line tension

However, if all you want is the line tension, there’s a simpler way of doing this:

\[ \Pi_{xx} = P \]

\[ \Pi_{yy} = P - 2\gamma / L_x L_z \]

\[ \gamma = \frac{1}{2} L_x L_z (\Pi_{xx} - \Pi_{yy}) \]

(Notice that \( P = 0 \) in the solvent free case!)
Vesicles

After having measured bending rigidity and line tension, we can make a prediction about the size of certain vesicles.


Sonicate vesicle solution, rip vesicles into bits and pieces! These (flat!) pieces will merge and grow bigger. At what point will they again close up and form vesicles?

Why would they close up in the first place?
Vesicles

After having measured bending rigidity and line tension, we can make a prediction about the size of certain vesicles.

\[ E_{\text{pancake}} = 2\pi R \gamma \]

\[ E_{\text{vesicle}} = 4\pi (2\kappa + \bar{\kappa}) \]
After having measured bending rigidity and line tension, we can make a prediction about the size of certain vesicles.

\[ E_{\text{curvature}} = \frac{1}{2} \kappa \left( \frac{1}{R_1} + \frac{1}{R_2} \right)^2 + \bar{\kappa} \frac{1}{R_1} \cdot \frac{1}{R_2} \]

\[ E_{\text{vesicle}} = 4\pi R^2 \cdot \left[ \frac{1}{2} \kappa \left( \frac{1}{R_1} + \frac{1}{R_2} \right)^2 + \bar{\kappa} \frac{1}{R_1} \cdot \frac{1}{R_2} \right] \]

\[ = 4\pi \left[ 2\kappa + \bar{\kappa} \right] \]
Vesicles

After having measured bending rigidity and line tension, we can make a prediction about the size of certain vesicles.

\[
\begin{align*}
E_{\text{pancake}} &= 2\pi R \gamma \\
E_{\text{vesicle}} &= 4\pi (2\kappa + \bar{\kappa})
\end{align*}
\]

Energies are equal, if

\[
R_{\text{pancake}} = \frac{2(2\kappa + \bar{\kappa})}{\gamma}
\]

(real stability analysis: \(2 \rightarrow 4\))
Vesicles

What values do we expect?

\[ \kappa \approx 20 k_B T \approx 80 \text{pN nm} \]

\[ \kappa \approx -\kappa \quad \gamma \approx 10 \text{pN} \]

\[ R_{\text{pancake}} = \frac{4(2 \kappa + \kappa)}{\gamma} \approx \frac{4\kappa}{\gamma} \approx \frac{320 \text{pN nm}}{10 \text{pN}} \approx 32 \text{nm} \]

Very little is known about this value!

This is then also the diameter of the vesicles we expect to find!
Vesicles

What values do we expect?

\[ \kappa \approx 20 \, k_B T \approx 80 \text{pN nm} \]

\[ \bar{\kappa} \approx -\kappa \quad \gamma \approx 10 \text{pN} \]

\[
R_{\text{pancake}} = \frac{4 (2\kappa + \bar{\kappa})}{\gamma} \approx \frac{4\kappa}{\gamma} \approx \frac{320 \text{pN nm}}{10 \text{pN}} \approx 32 \text{nm}
\]

Very little is known about this value!
How we measure $\bar{\kappa}$

The energy of a partially curved patch can be calculated as:

$$\frac{\Delta E(x, \xi)}{8\pi \kappa + 4\pi \bar{\kappa}} = \Delta \tilde{E}(x, \xi) = x + \xi \left[ \sqrt{1 - x} - 1 \right]$$

$$x = (Rc)^2$$

$$R = \sqrt{\frac{A}{4\pi}}$$

$$\xi = \frac{\gamma R}{2\kappa + \bar{\kappa}}$$
How we measure $\bar{\kappa}$

$\Delta \tilde{E}$

$\xi = 0, 1, 1.5, 2$
How we measure $\bar{\kappa}$

This is called the “splitting probability”...

...and it can be calculated *analytically* if the energy barrier is known!
How we measure $\bar{\kappa}$

\[ \xi \approx 1.5 \]

\[ \xi = \frac{\gamma R}{2\kappa + \bar{\kappa}} \]
Applications
Protein-induced budding

Membrane-curving proteins can attract and drive membrane vesiculation


Intuitive, but no physical justification!
Protein-induced budding

Interaction potential from linearized theory
(spherical caps, radius \(a\), detachment angle \(\alpha\))

\[
U(R) = 2\pi \sigma a^2 \alpha^2 \left[ K_0 \left( \frac{R}{\lambda} \right) + \left( \frac{a}{\lambda} \right) K_2 \left( \frac{R}{\lambda} \right) \right]
\]

[T.R. Weikl, M.M. Kozlov, W. Helfrich, PRE 57, 6988 (1998)]

characteristic decay length: \(\lambda = \sqrt{\kappa/\sigma}\)

\[
\sigma = 0 \Rightarrow U(R) = 8\pi \kappa \alpha^2 \left( \frac{a}{R} \right)^4
\]


This is always repulsive!
Protein-induced budding

many caps
("contact lens")

36 curved caps, ~50000 lipids, 160nm side-length, total time ~1ms
no lateral tension
no explicit interaction between caps


Some observations:
- Caps attract collectively
- Attractive pair-forces exist?
- No crystalline structure
- Cooperative vesiculation
- No “scaffolding”
- 50-100nm length scales
- Several milliseconds
Protein-induced budding

Blood and Voth, PNAS 103, 15068 (2006)
Protein-induced budding


Blood and Voth, PNAS 103, 15068 (2006)
Protein-induced budding


Lipid A-B–mixtures

\[ W_{AB} < W_{AA} = W_{BB} \]

B.J. Reynwar & M. Deserno,
Biointerphases 3, FA118 (2009)
Lipid A-B–mixtures

\[ \mathcal{W}_{AB} < \mathcal{W}_{AA} = \mathcal{W}_{BB} \]

B.J. Reynwar & M. Deserno,
Biointerphases 3, FA118 (2009)
Lipid A-B–mixtures +proteins

Composition-induced protein aggregation

B.J. Reynwar & M. Deserno,
Biointerphases 3, FA118 (2009)
Lipid A-B–mixtures +proteins

Pair potentials can be fitted by simple ground state theory.

B.J. Reynwar & M. Deserno, Biointerphases 3, FA118 (2009)
Peptide-induced pore formation

Antimicrobial Peptide
“magainin”

Peptide-induced pore formation

Example above:

Peptides:

\[ P^m_n \text{ - peptide} \]

Example above: \[ P^2_8 \]

Peptide-induced pore formation

### Peptide-induced pore formation

Let us now look at this system consisting of many of these peptides.

<table>
<thead>
<tr>
<th>Binding strength</th>
<th>$k_BT=1.7$</th>
<th>$k_BT=1.9$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_6^2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>stray</td>
<td>stray</td>
</tr>
<tr>
<td>1.6</td>
<td>bound</td>
<td>bound/inserted</td>
</tr>
<tr>
<td>1.7</td>
<td>inserted</td>
<td>inserted</td>
</tr>
<tr>
<td>1.8</td>
<td>inserted</td>
<td>inserted</td>
</tr>
</tbody>
</table>

| $P_8^2$          |            |            |
| 1.4              | stray      |            |
| 1.5              | bound      |            |
| 1.6              | inserted   |            |
| 1.7              | inserted   |            |
| 1.8              | inserted   | inserted   |

Peptide-induced pore formation

...of a peptide which *alone* does *not* insert within 25000τ


- Stronger joint perturbation
- Sliding in very efficient

\[ c) \rightarrow g) \ 3000\tau \]
Peptide-induced pore formation

$w_c = 1.5$

$P_8^0$ → $P_8^1$ → $P_8^2$ → $P_8^3$

No peptide attraction

Some peptide attraction

$P_6^2 \quad w_c = 1.6$

Lipid curvature effects

The model of Israelachvili, Mitchell and Ninham


\[ P = \frac{V}{LA} \]

- \( V \) = lipid volume
- \( L \) = lipid length
- \( A \) = lipid head area

packing parameter
Lipid curvature effects

The model of Israelachvili, Mitchell and Ninham


\[ P = \frac{V}{LA} \]

- \( V \) = lipid volume
- \( L \) = lipid length
- \( A \) = lipid head area

packing parameter
Lipid curvature effects

50:50 mixture

Simple model gives:

\[ E = \frac{1}{2} M (K - K_\ell)^2 \]

\[ S = \text{ideal gas} \]

\[ \ln \frac{\phi_{\text{out}}}{\phi_{\text{in}}} = \frac{2MK_\ell}{k_B T} K \]

Density of big headed lipids in the outer monolayer

Density of big headed lipids in the inner monolayer

Linear in bilayer curvature!

Lipid curvature effects

50:50 mixture

Simple model gives:

\[ \ln \frac{\phi_{\text{out}}}{\phi_{\text{in}}} = \frac{2M(K - K_{\ell})}{k_B T} K \]

Density of big headed lipids in the outer monolayer

Density of big headed lipids in the inner monolayer

Linear in bilayer curvature!

Lipid curvature effects

For realistic membrane curvatures the effect is not enough to drive sorting!

That's small!

Tian & Baumgart, Biophys. J. 96, 2676 (2009)