Drug Delivery: Molecular Simulations

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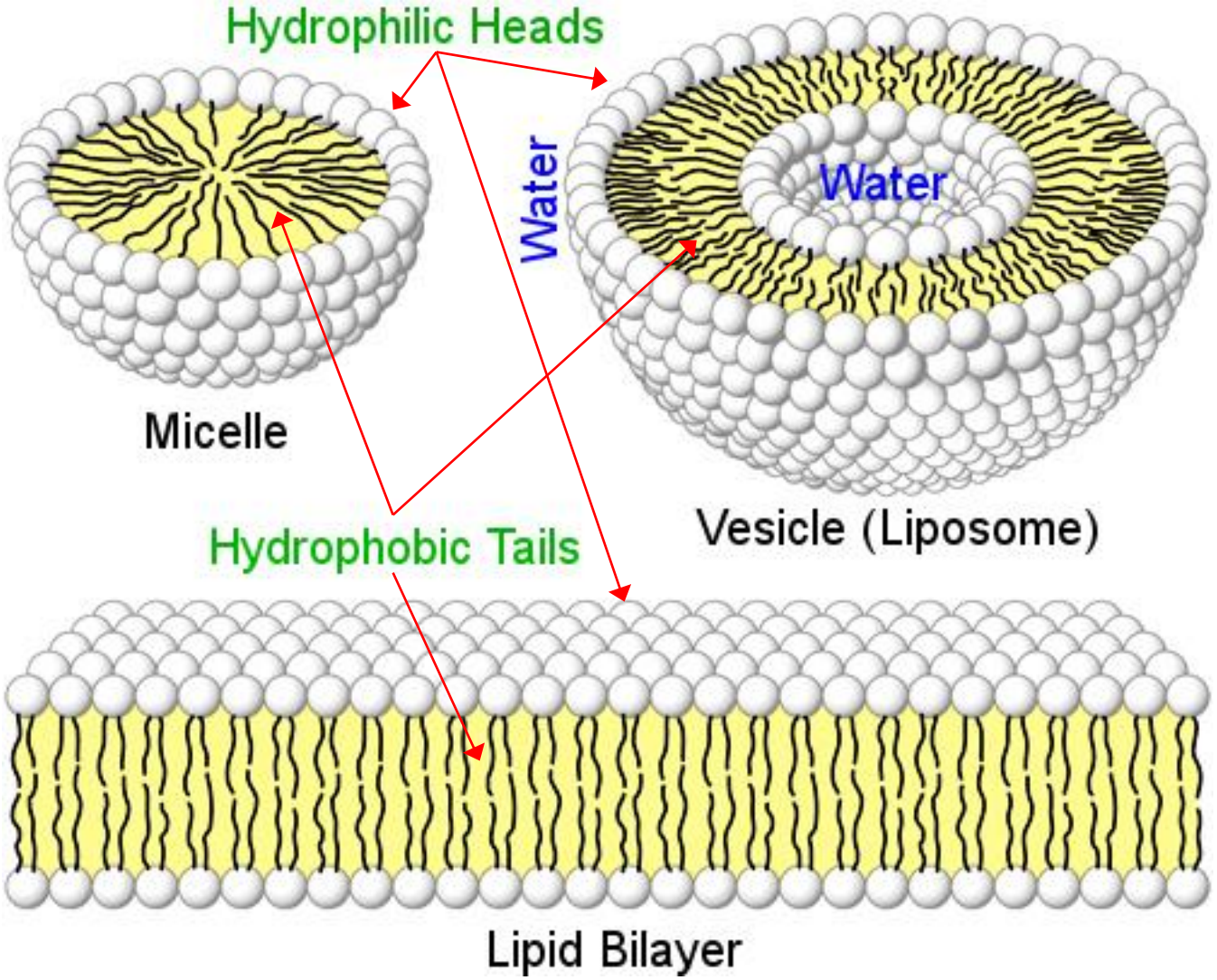
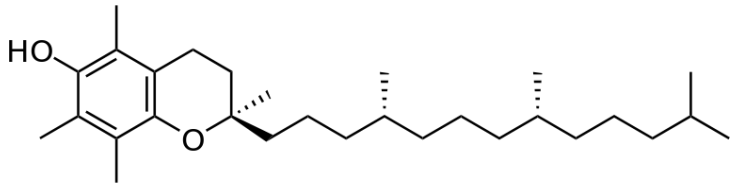
Bilayers, Vesicles, Micelles



Drug Delivery

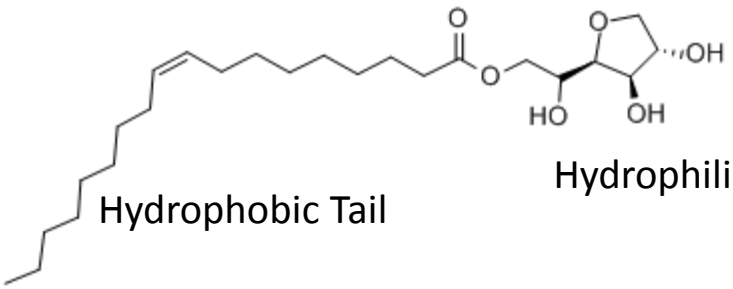
- Potential drug delivery vehicles
  - Span 80 nonionic Vesicles (Niosomes)
  - Bile salt micelles
    - Sodium cholate
  - poly(lactic-*co*-glycolic acid) (PLGA)
    - Nanoparticles that break down to release contents

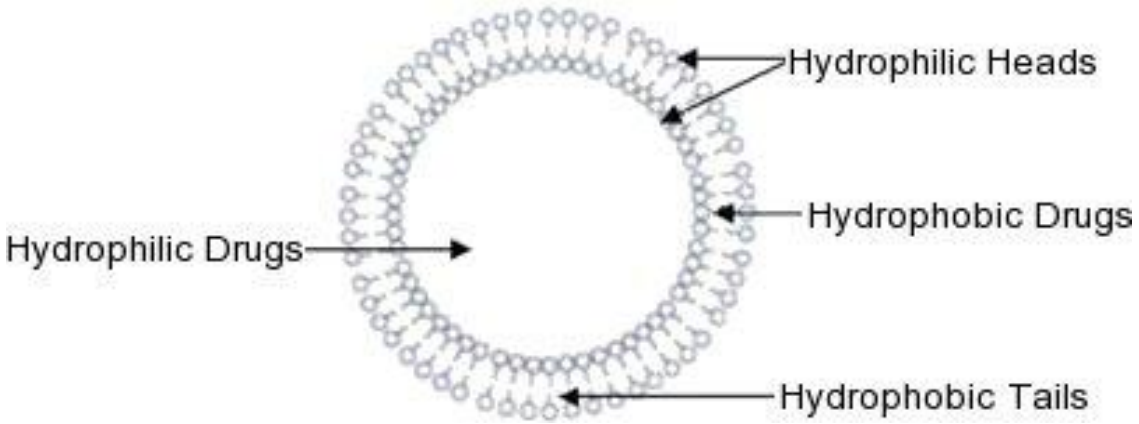
- Drug (Hydrophobic)
  - α-tocopherol (Vitamin E)



Span 80 Niosomes

Span 80 (Sorbitan, mono-(9Z)-9-octadecenoate)

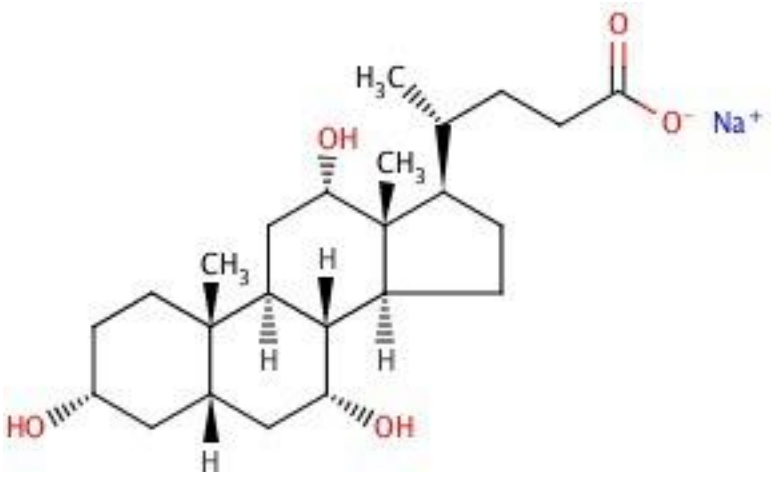




Bile Salt Micelles

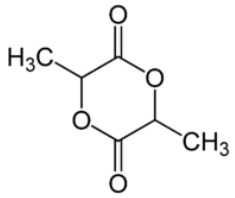
- Bile salts
  - Emulsification of fats in the intestine
  - Rings region similar to cholesterol
  - Rings region is hydrophilic on one face and hydrophobic on the other
  - Form micelles with on the order of 10 molecules

- Sodium Cholate
  - Carboxylic acid group

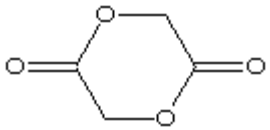


PLGA Nanoparticles

- Biodegradable
- Copolymer
  - Lactide

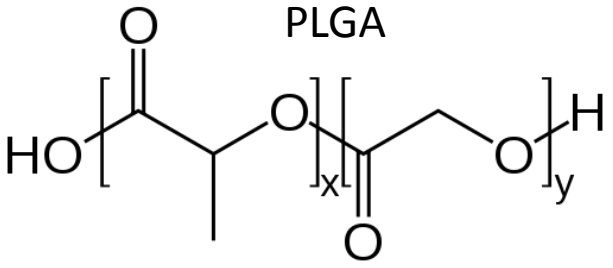


  - Glycolide



- Chain of esters

PLGA



- *O*(100) nm diameter nanoparticles
  - Cristina Sabliov, Carlos Astete

Molecular Dynamics Simulations

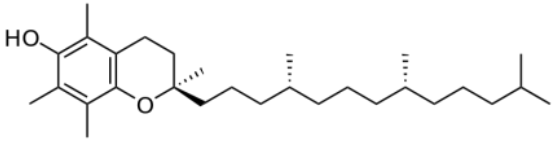
- Analytical potential energy function to describe interactions between atoms/sites

$$V = \sum_{\text{bonds}} k_b (b - b_0)^2 + \sum_{\text{angles}} k_\theta (\theta - \theta_0)^2 + \sum_{\text{dihedrals}} k_\phi [1 + \cos(n\phi - \delta)]$$
$$+ \sum_{\text{impropers}} k_\omega (\omega - \omega_0)^2 + \sum_{\text{Urey-Bradley}} k_u (u - u_0)^2$$
$$+ \sum_{\text{nonbonded}} \epsilon \left[\left(\frac{R_{\min_{ij}}}{r_{ij}} \right)^{12} - \left(\frac{R_{\min_{ij}}}{r_{ij}} \right)^{6} \right] + \frac{q_i q_j}{\epsilon r_{ij}}$$

Bonded interactions

- Integrate Newton's equations of motion
  - Modify dynamics for NVT, NPT, etc. or external forces (non-equilibrium)

Simulations: Vitamin E + Bilayer



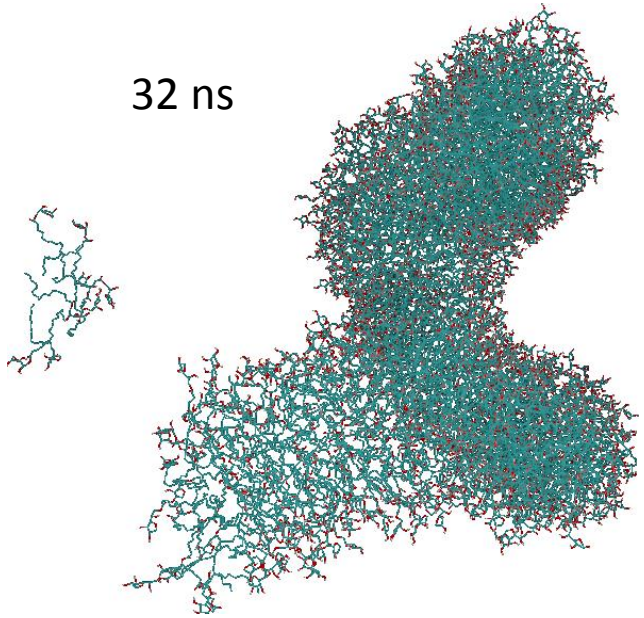
- Potential of mean force or PMF (free energy) as a function of the distance of the head from the bilayer center
  - 64 DMPC, 2 Vitamin E, 4890 water
  - NPT: 1 bar (semi-isotropic), 323 K
  - Umbrella sampling: harmonic bias potentials
    - 47 windows
  - Two vitamin E (4.7 nm apart)
    - Run until two PMF curves converge, gives uncertainty estimate

$$A^i(d) = -kT \ln\left[P^i_{bias}(d)\right] - U^i_{bias}(d) + F^i$$

$$U^i_{bias}(d) = k^i_{bias}(d - d^i_{ref})^2$$

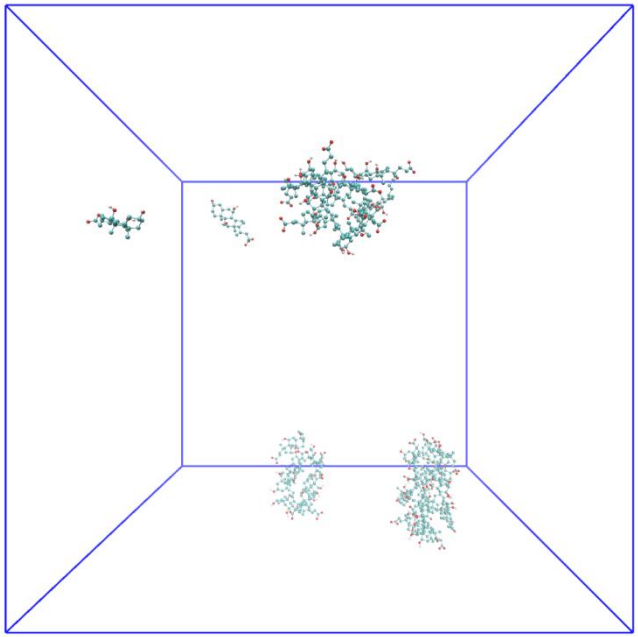
Simulations: Span 80

- GROMOS 53a6 potential energy parameters developed by Bhupender Thakur and Kumuditha Ratanayake
- Simulation of 1000 Span 80 molecules randomly distributed in 111,358 water molecules (Jieqiong Lin)
  - NPT: 1 bar, 360 K



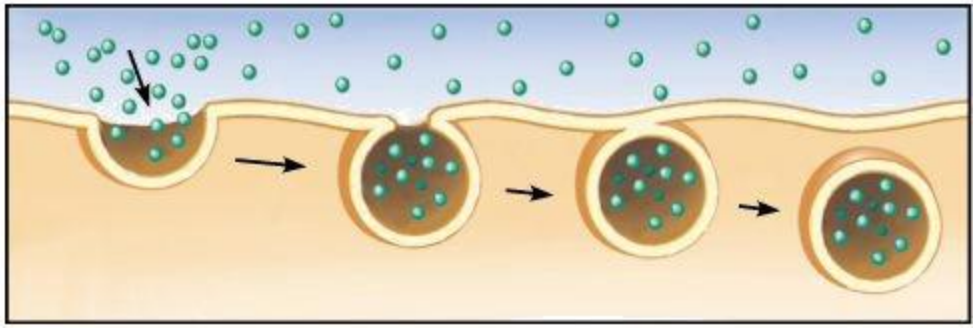
Simulations: Bile Salts

- Jieqiong Lin
- Potential energy parameters for rings region from cholesterol, carboxylic acid tail from Automated Topology Builder
- 31 cholate ions, 77 sodium ions, 46 chloride ions, and 16000 water molecules
  - NPT: 1 bar, 310 K



Simulations: PLGA

- PLGA particles must be taken up into cells by endocytosis



- Cell membranes are negatively charged
  - Negatively charged PLGA particles will be repelled
  - Positively charged modified PLGA may stick to bilayers