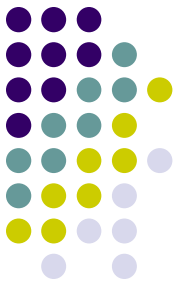


# Readings



- <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=thermodynamics&rid=stryer.section.156#167>
- <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=stability,protein&rid=stryer.section.365#371>
- <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=stryer.section.1687>
- <http://employees.csbsju.edu/hjakubowski/classes/ch331/protstructure/mechdynam2.html>

# Moc/Bio and Nano/Micro

## Lee and Stowell

### Moc/Bio-Lecture 2

---

**Bit O'review**

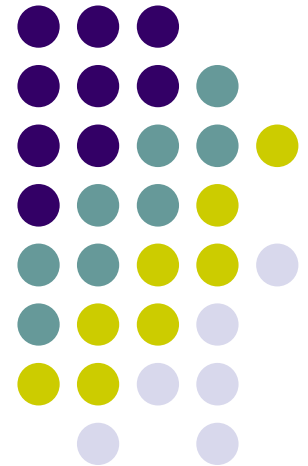
**Thermodynamics of Biomolecules**

**DNA**

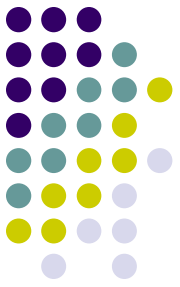
**RNA**

**Proteins**

**Lipids**

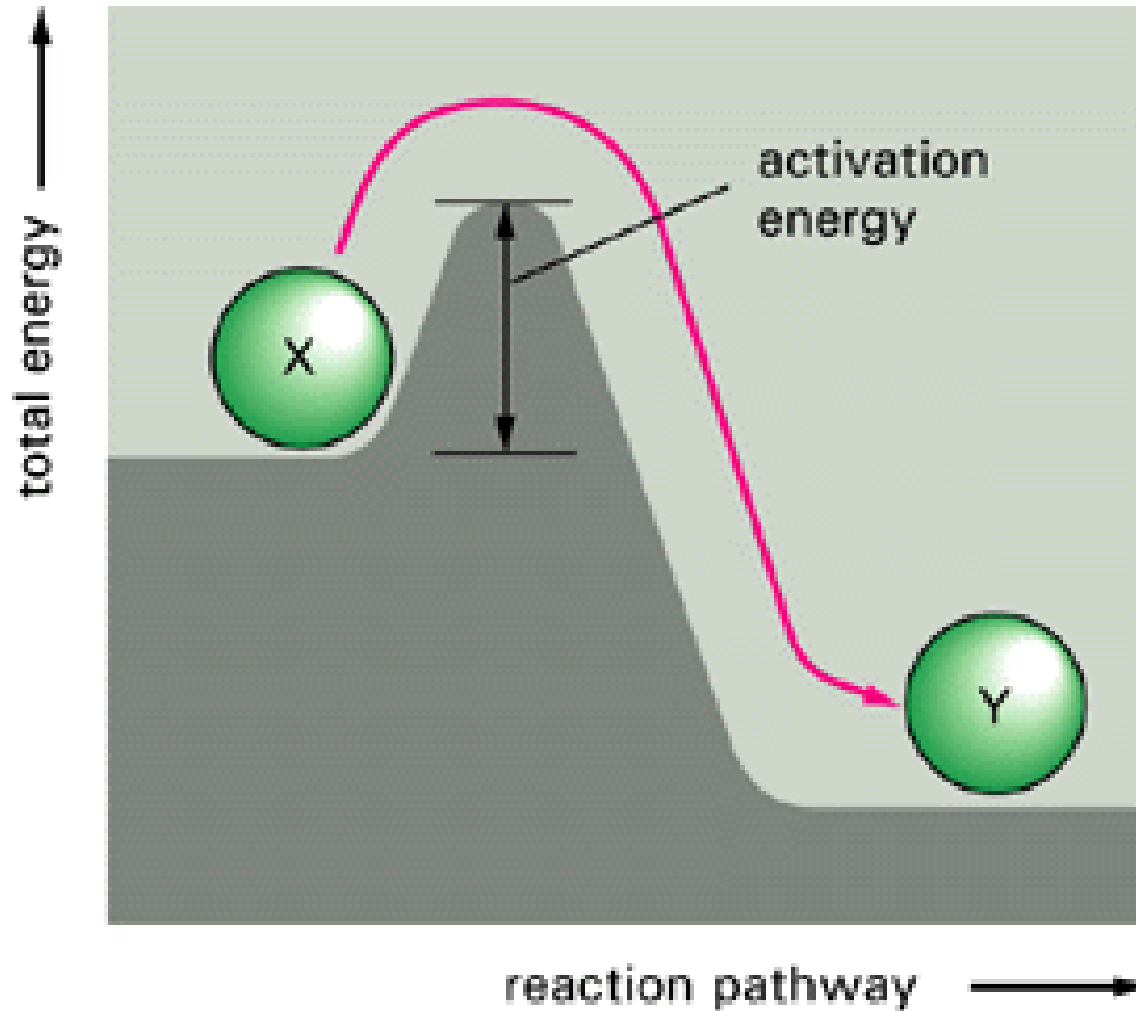
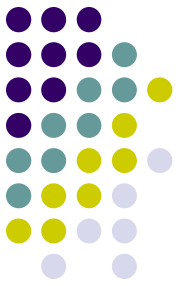


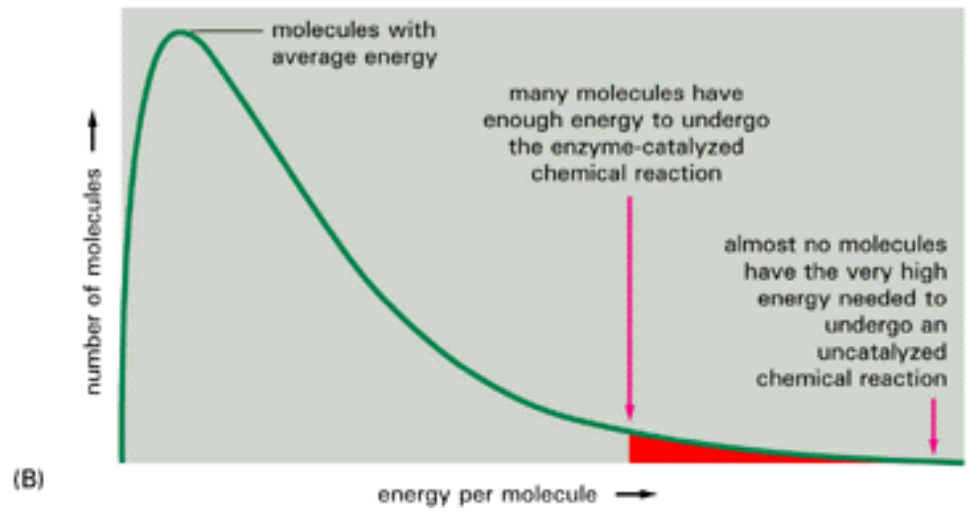
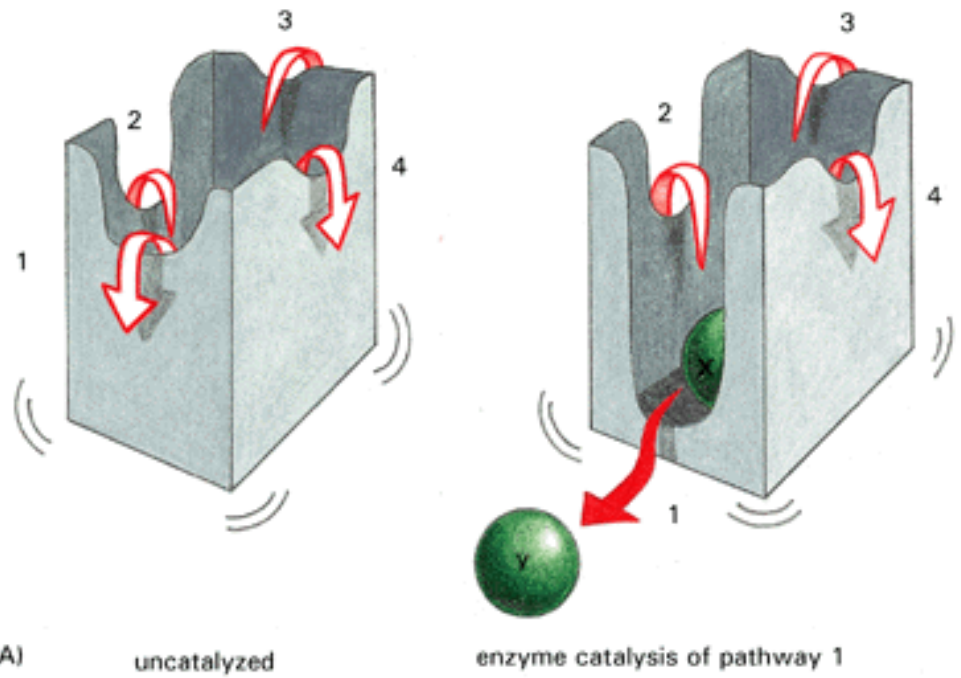
# Biology obeys all the laws of thermodynamics



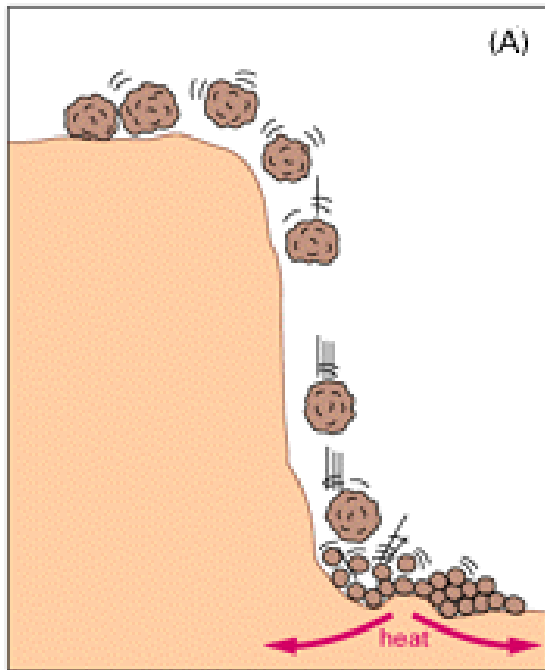
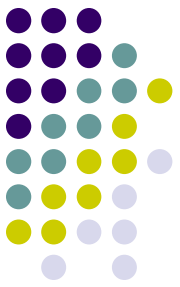
- 1) Energy is Neither Created or Destroyed
- 2) In a closed system the potential energy always decreases (entropy)

# Activation energy

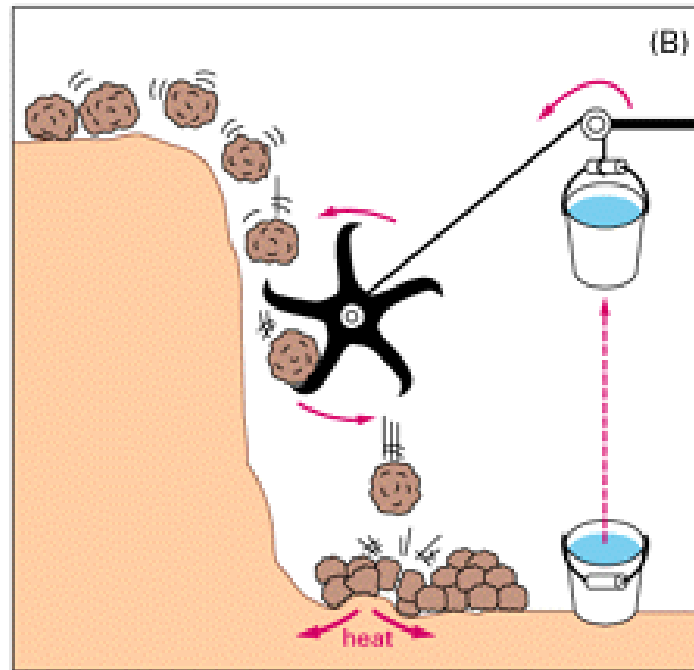




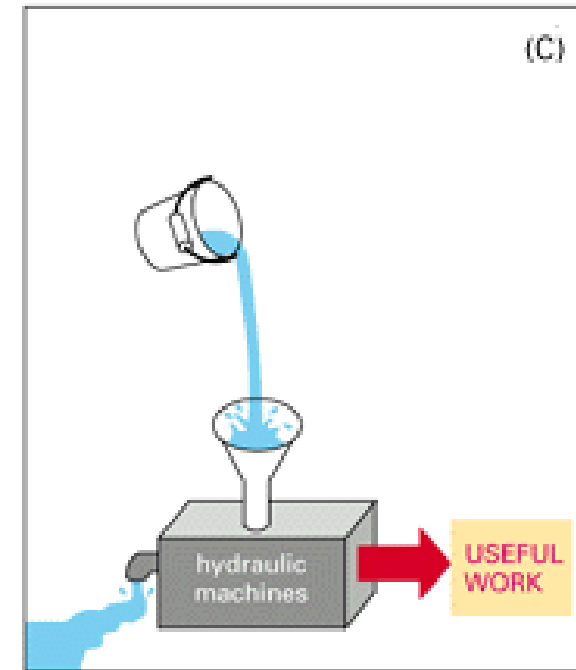
# Performing useful work



kinetic energy transformed into heat energy only

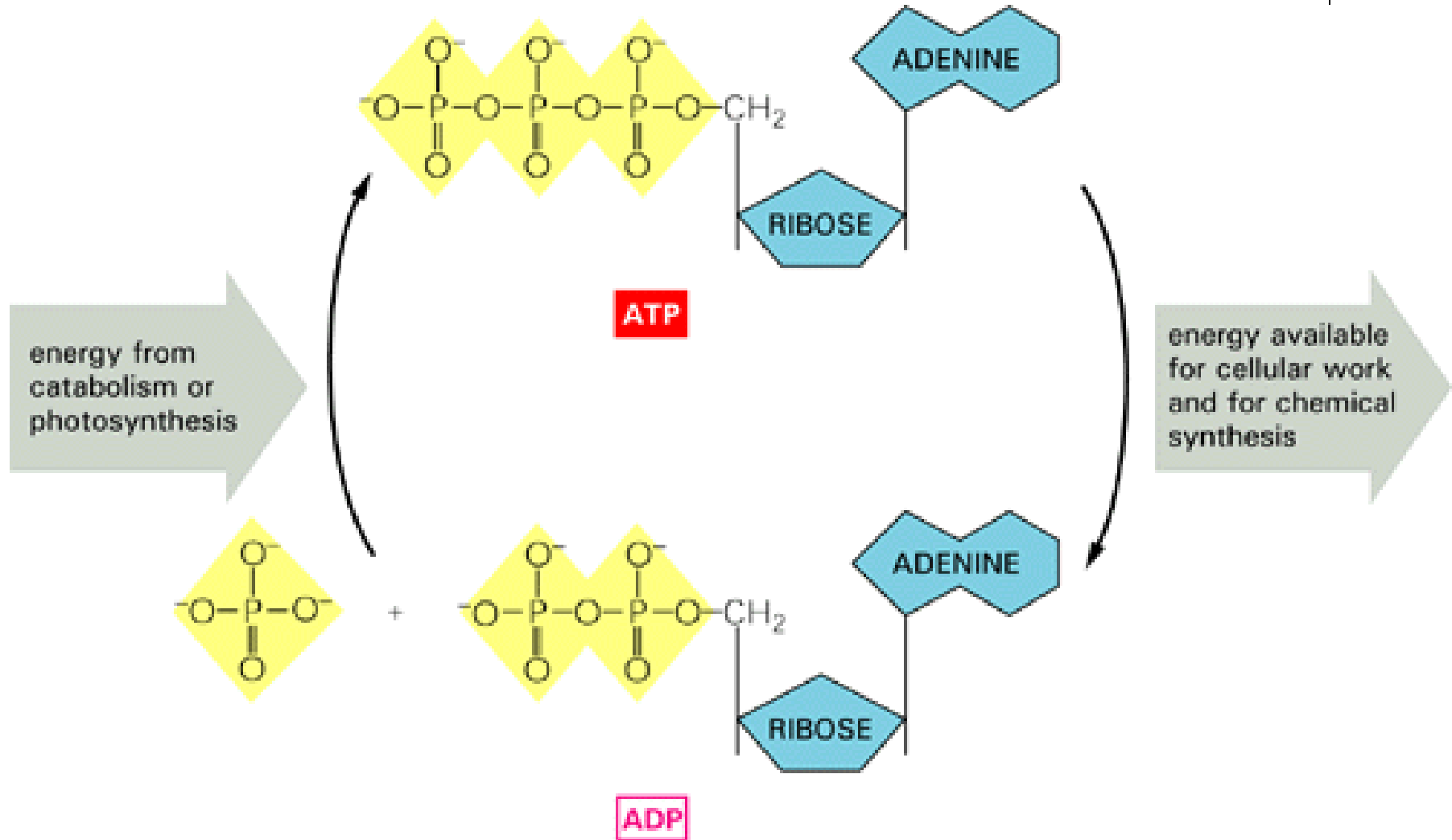
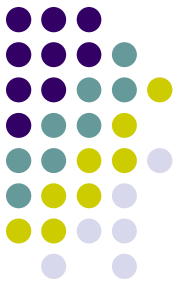


part of the kinetic energy is used to lift a bucket of water, and a correspondingly smaller amount is transformed into heat

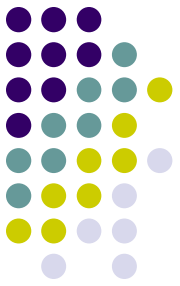


the potential kinetic energy stored in the elevated bucket of water can be used to drive a wide variety of different hydraulic machines

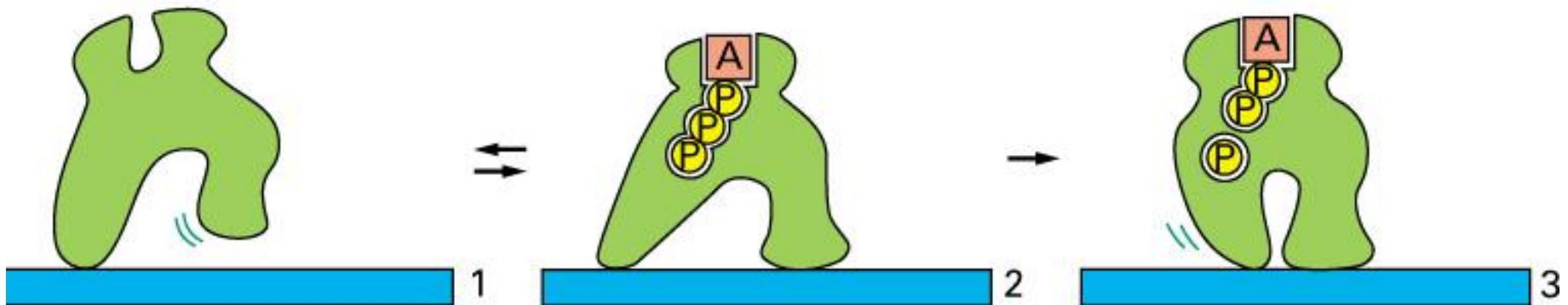
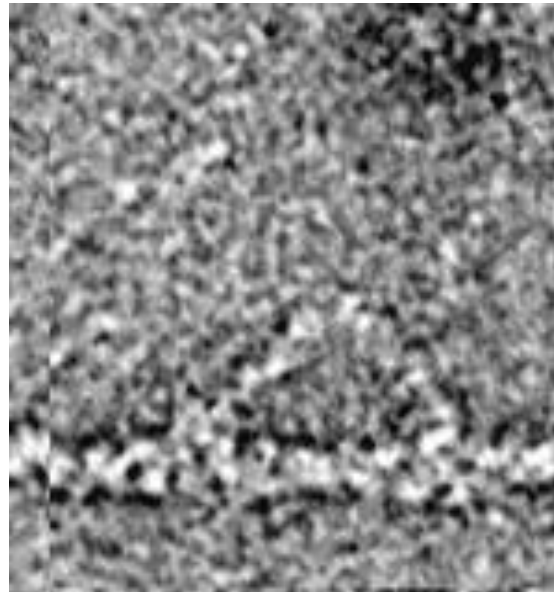
# The currency of the Cell



# Nanomolecular Trains

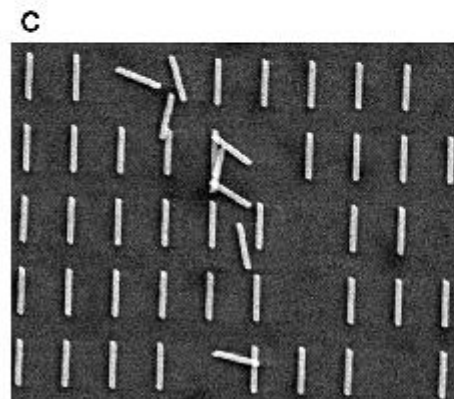
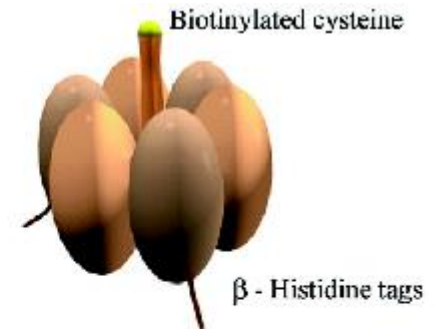
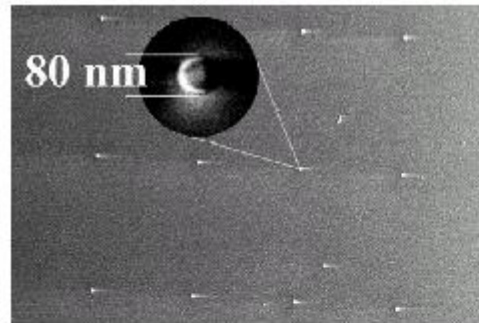
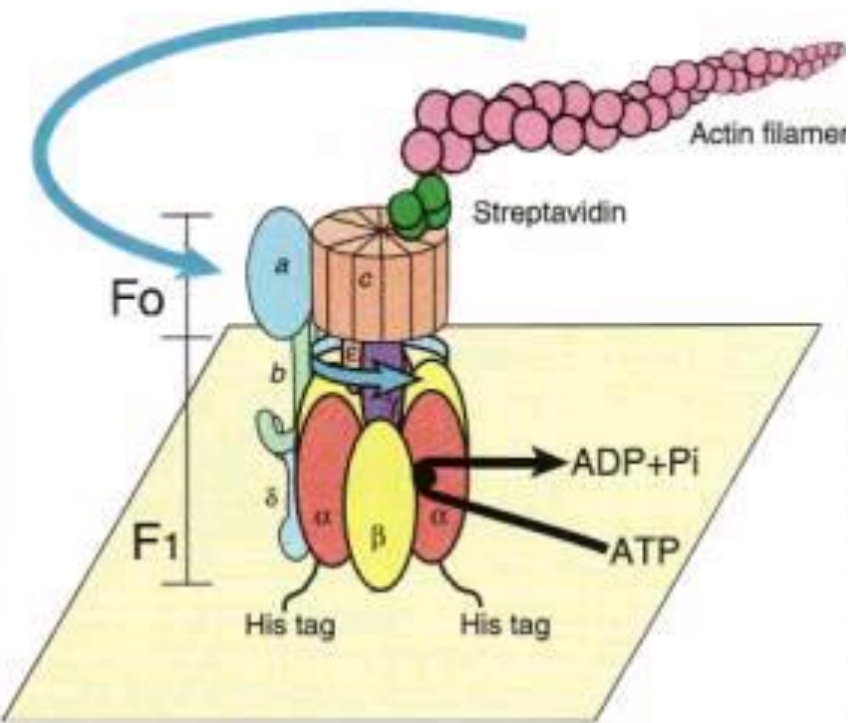
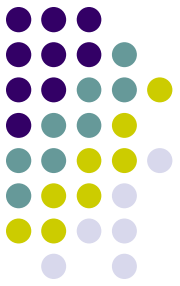


Kinesin  
Step size 8 nm



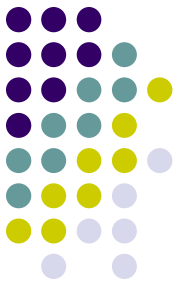


# Nanomolecular rotors



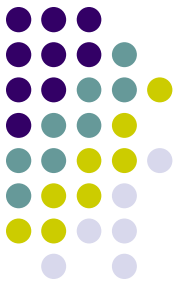
Song et al Science 290, 1554, 2000.

# The order of the cell requires energy



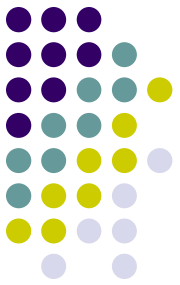
- DNA/RNA synthesis
- Protein synthesis
- Lipid formation (membranes)
- etc

# Stability and Thermo of Biomolecules

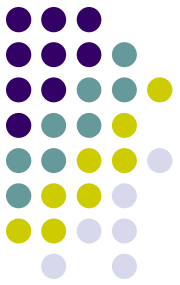


- DNA
  - H-bonding
  - Pi-stacking
  - $T_m$ 's calculated from thermo parameters
- $T_m = \Delta H / (\Delta S + R \ln C_t)$ 
  - $R = 1.987$  eu
  - $\Delta H$  in cal/mol
  - $C_t$  is total molar strand concentration

# DNA energetics



Neighbor Seq	Delta H (kcal/mol)	Delta S (eu)	Delta G (kcal/mol)
AA/TT	-8.4	-23.6	-1.02
AT/TA	-6.5	-18.8	-0.73
TA/AT	-6.3	-18.5	-0.60
CA/GT	-7.4	-19.3	-1.38
GT/CA	-8.6	-23.0	-1.43
CT/GA	-6.1	-16.1	-1.16
GA/CT	-7.7	-20.3	-1.46
CG/GC	-10.1	-25.5	-2.09
GC/CG	-11.1	-28.4	-2.28
GG/CC	-6.7	-15.6	-1.77

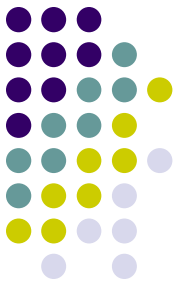


# Example

5'-G-C-T-A-G-C

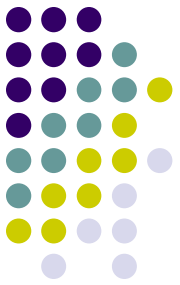
3'-C-G-A-T-C-G

- $\Delta G_t = 2\Delta G(\text{GC/CG}) + 2\Delta G(\text{CT/GA}) + \Delta G(\text{TA/AT})$
- $\Delta H_t = 2\Delta H(\text{GC/CG}) + 2\Delta H(\text{CT/GA}) + \Delta H(\text{TA/AT})$
- $\Delta S_t = 2\Delta S(\text{GC/CG}) + 2\Delta S(\text{CT/GA}) + \Delta S(\text{TA/AT})$
- $T_m = \Delta H_t / (\Delta S_t + R \ln C_t)$



# DNA summary

- Highly specific base pairing
- Nearest neighbor effects only
- GC content governs melting temp



## WORKSHOP MocBio Lecture 2 - MHBS

We learned that the melting temperature of DNA depends on the base content and nearest neighbor effects. What types of forces are responsible for changes due to base content and changes due to neighbor effects?

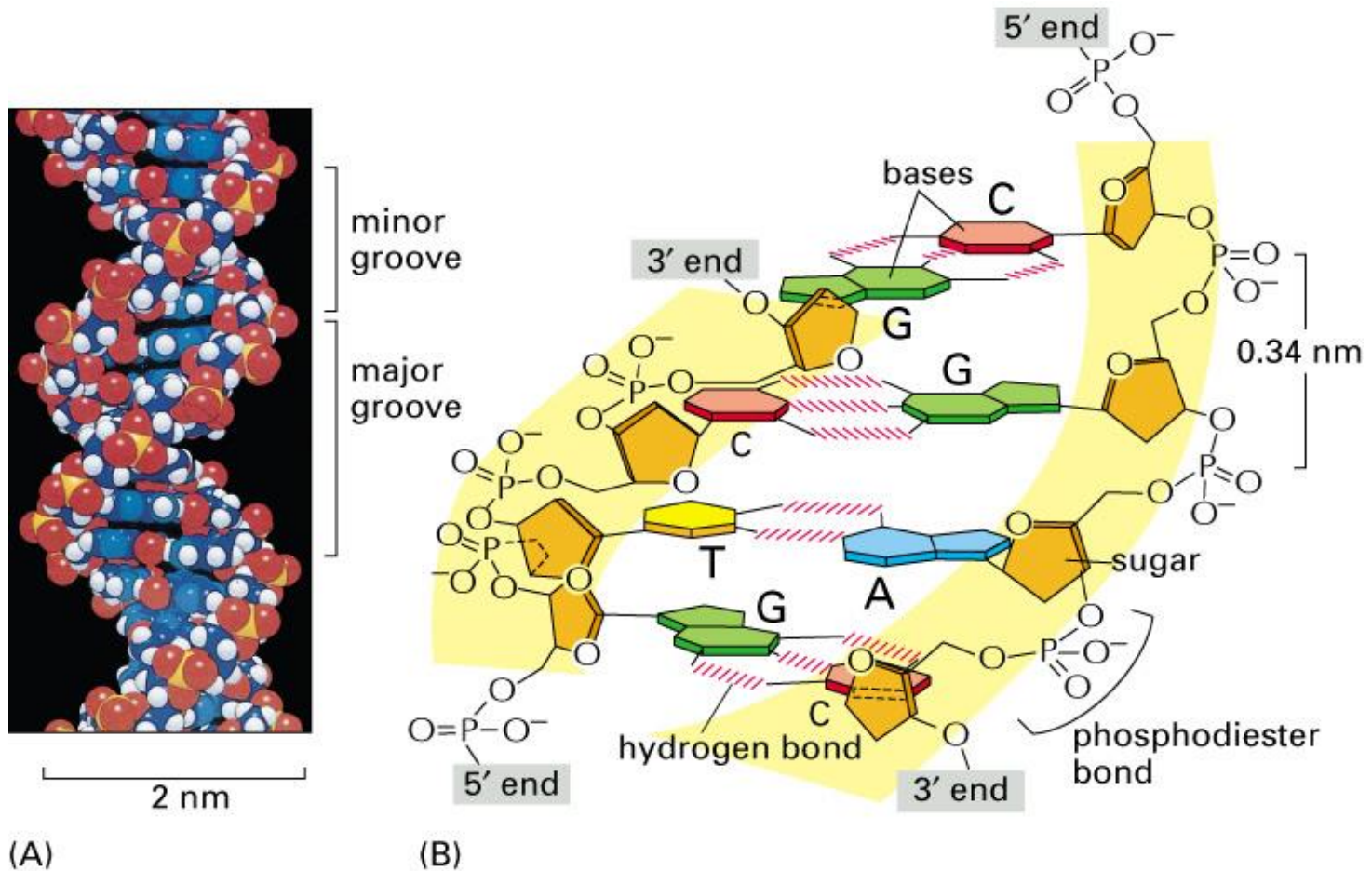


Figure 4-5. Molecular Biology of the Cell, 4th Edition.

# Example: SNP analysis

## Single nucleotide polymorphisms

Looking for mutations that  
correlate with disease

A) Oligonucleotides with  
fluorophores that FRET  
(fluorescence resonance energy  
transfer)

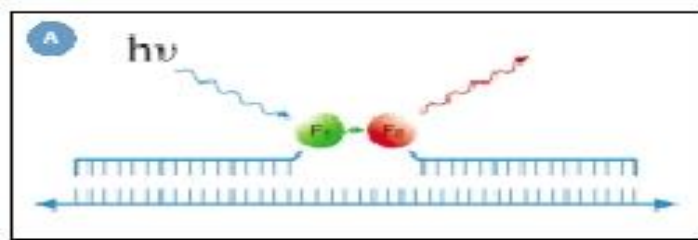


Figure 4A: Hybridization-Probe fluorescent emission by FRET.

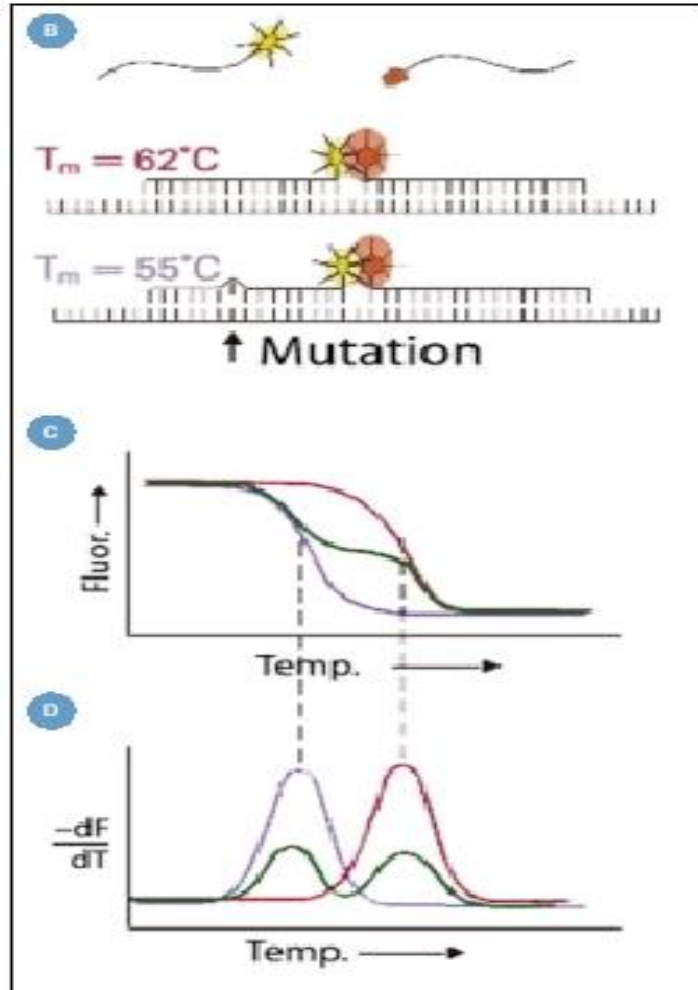
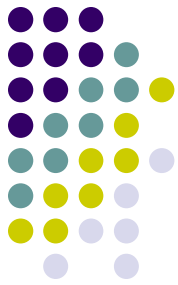


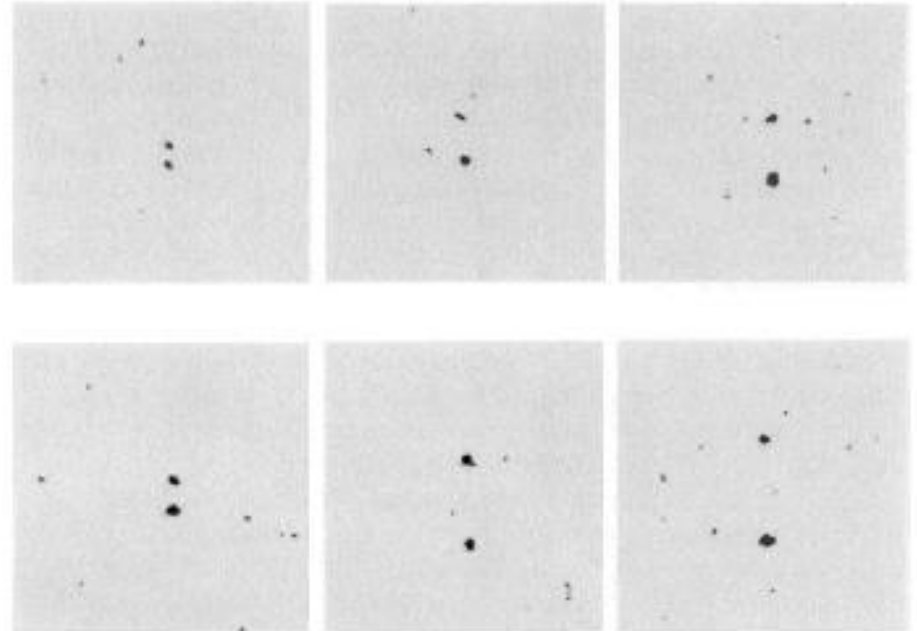
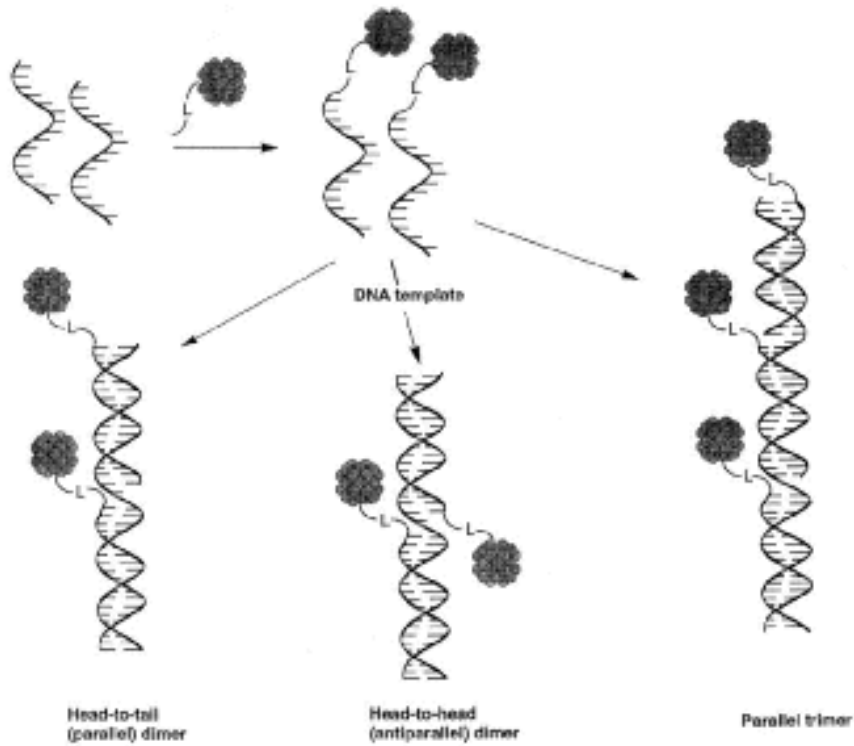
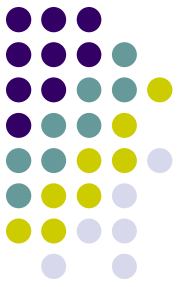
Figure 4: Melting curve analysis using Hybridization Probes.

- homozygous wild-type sample
- homozygous mutant sample
- heterozygous sample

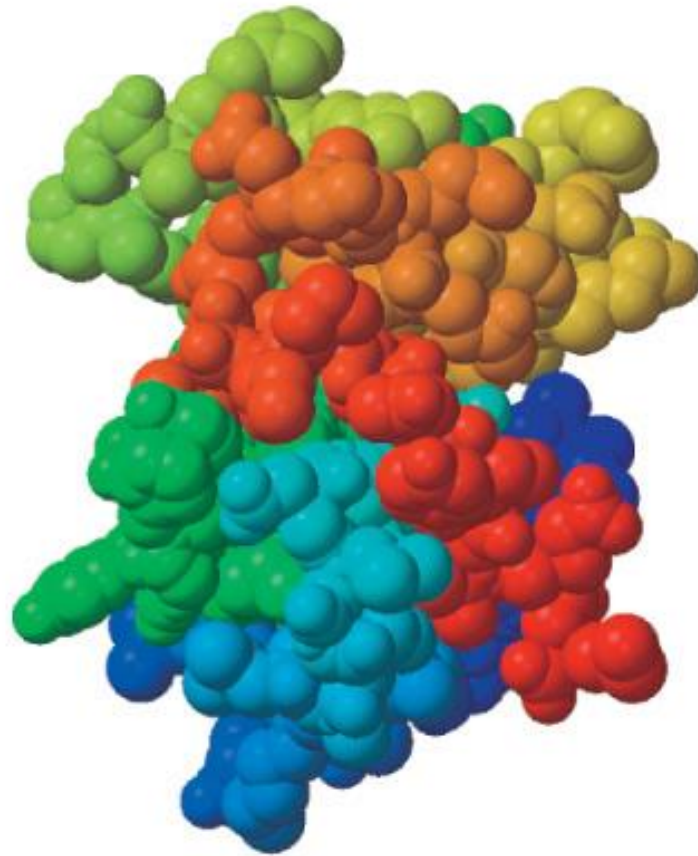
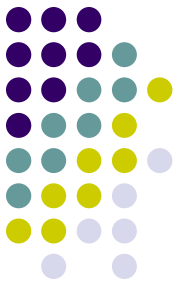




# Example: Gold nanoparticle assembly



# Protein structure and stability



# Peptide bond again

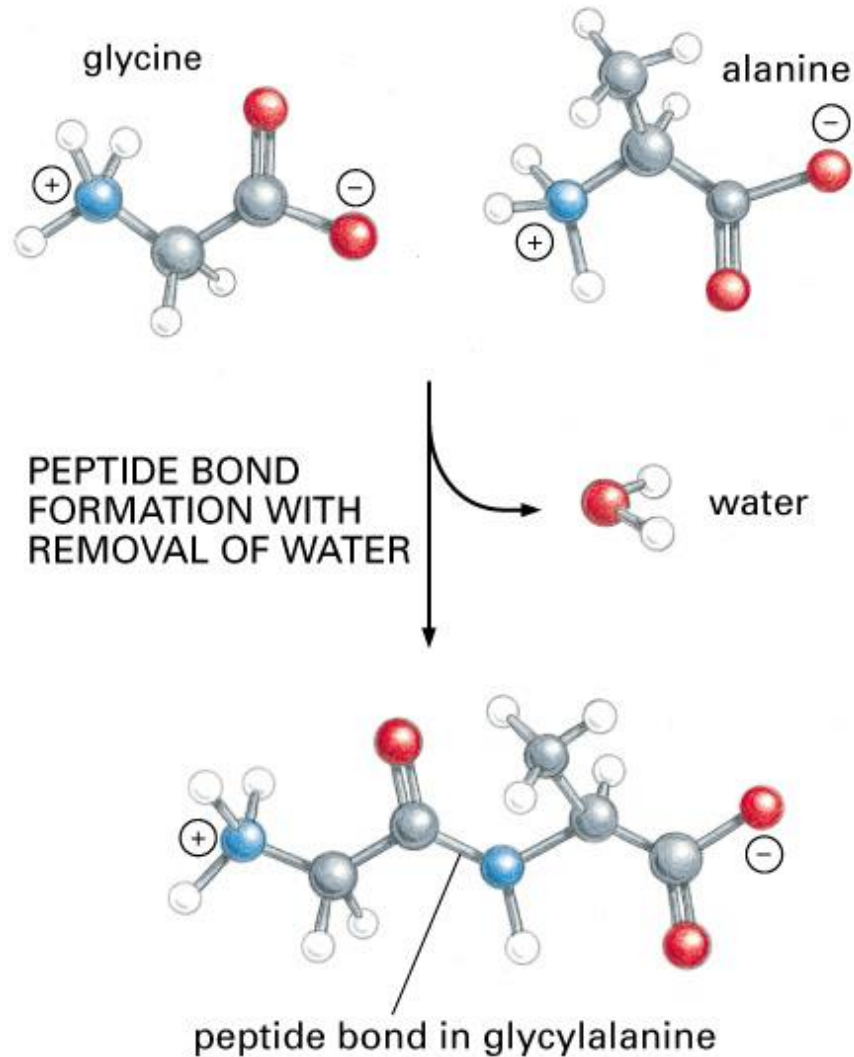
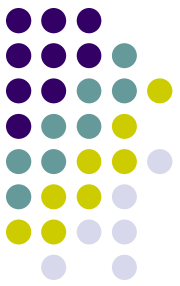


Figure 3-1. Molecular Biology of the Cell, 4th Edition.

# Polypeptide

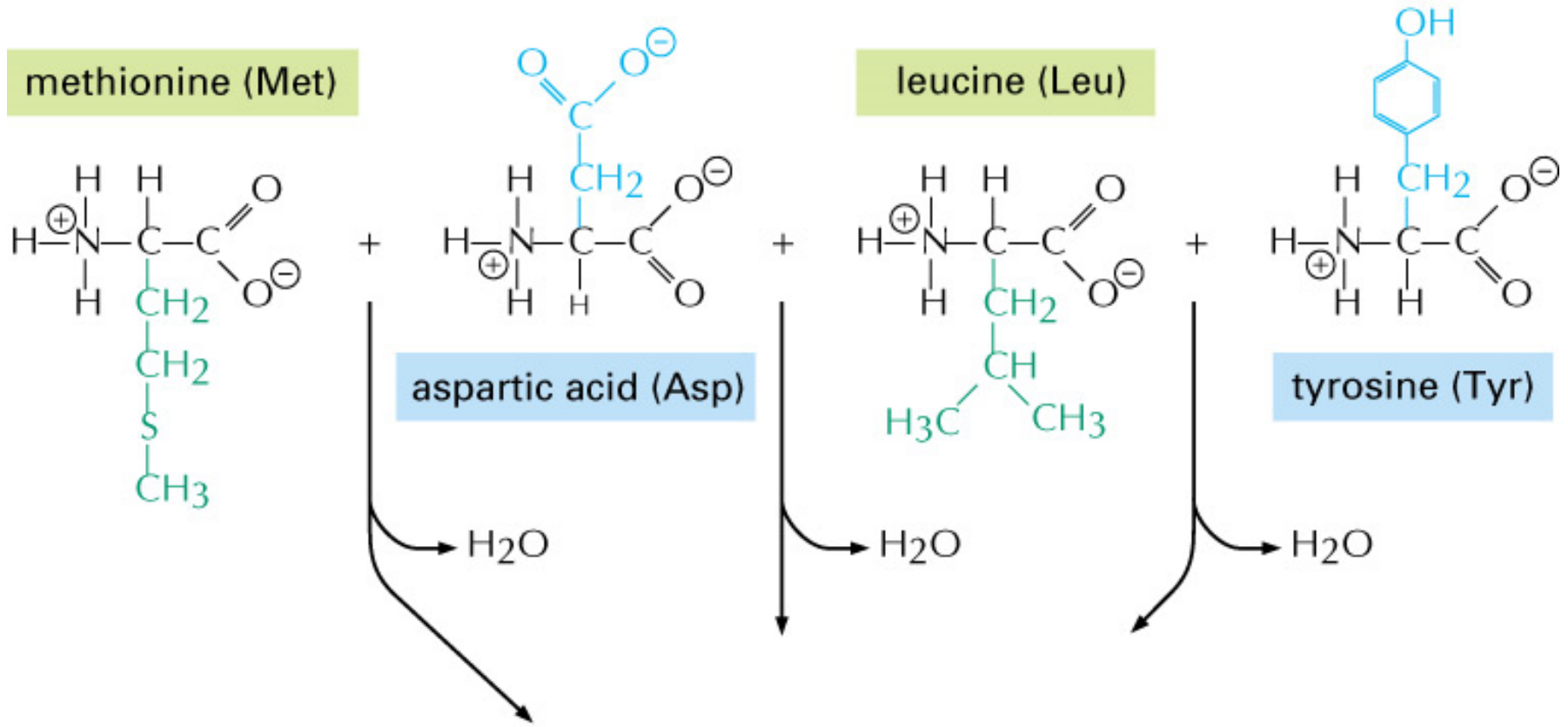
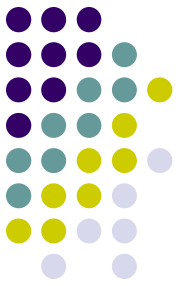
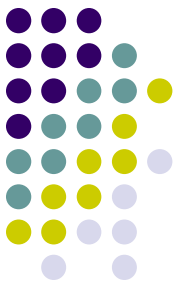
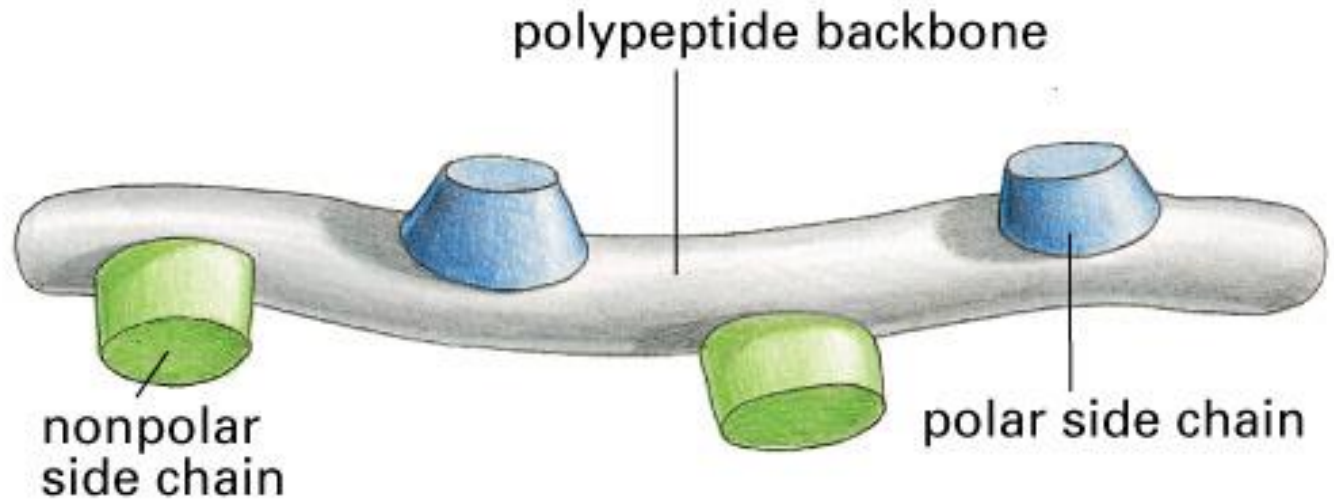


Figure 3-2 part 1 of 3. Molecular Biology of the Cell, 4th Edition.

# And now what?



SCHEMATIC



SEQUENCE



Figure 3–2 part 3 of 3. Molecular Biology of the Cell, 4th Edition.

# Timescales of interest



<b>Motion</b>	<b>Time Scale - log(s)</b>
<b>bond vibration</b>	<b>-14 to -13</b>
<b>proton transfer</b>	<b>-12</b>
<b>hydrogen bonding</b>	<b>-12 to -11</b>
<b>elastic vibration of globular region</b>	<b>-12 to -11</b>
<b>sugar repuckering</b>	<b>-12 to -9</b>
<b>rotation of side chains at surface</b>	<b>-11 to -10</b>
<b>torsional vibration of buried group</b>	<b>-11 to -9</b>
<b>hinge bending at domain interfaces</b>	<b>-11 to -7</b>
<b>water structure reorganization</b>	<b>-8</b>
<b>helix breakdown/formation</b>	<b>-8 to -7</b>
<b>allosteric transitions</b>	<b>-5 to 0</b>
<b>local denaturation</b>	<b>-5 to 1</b>
<b>rotation of medium-sized interior sidechains</b>	<b>-4 to 0</b>

# The route to folded proteins

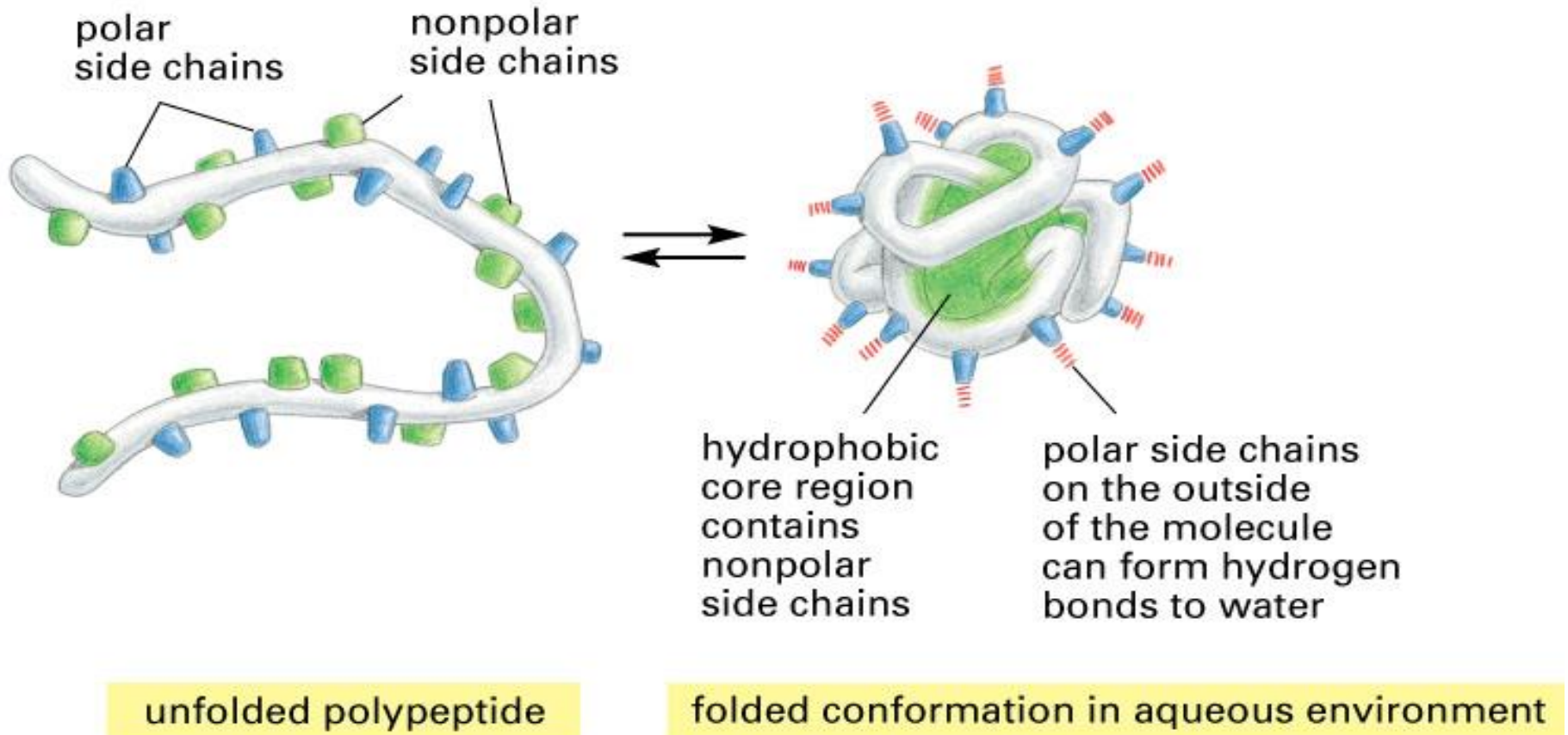
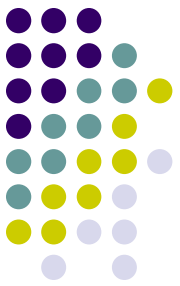
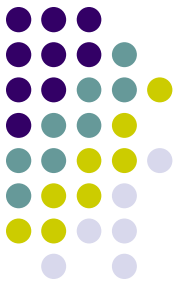


Figure 3–6. Molecular Biology of the Cell, 4th Edition.

# Levinthal's paradox and others



- 100 amino acids
- 2 conformations for each AA
- $10^{30}$  possible conformations
- $10^{-13}$  sec for conformational interconversion
- So  $10^{17}$  sec to sample all conformations
- $\sim 4 \times 10^{16}$  years (age of universe  $\sim 10^{10}$  years)



# Peptide bond

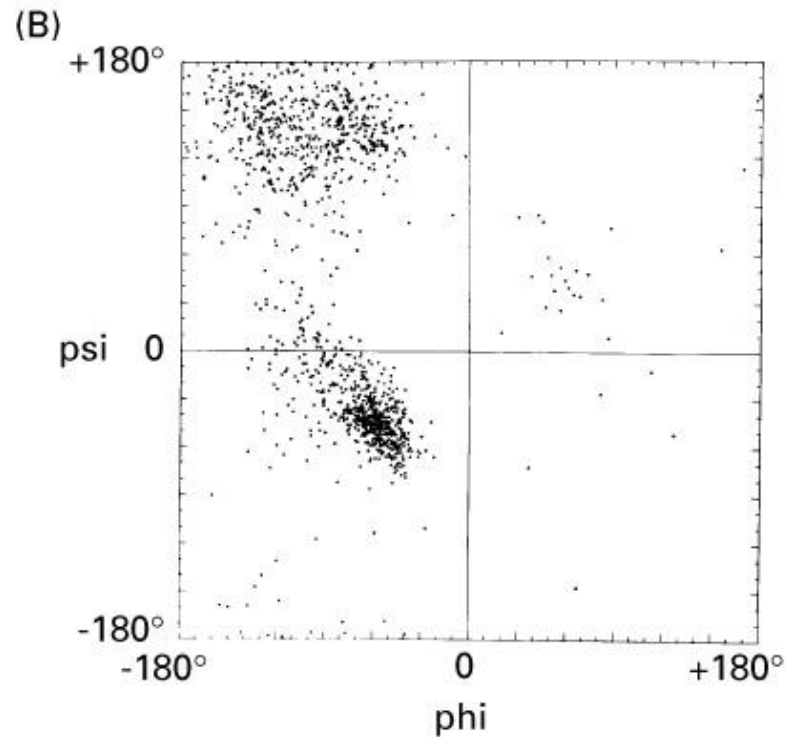
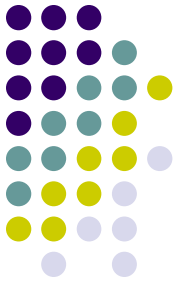
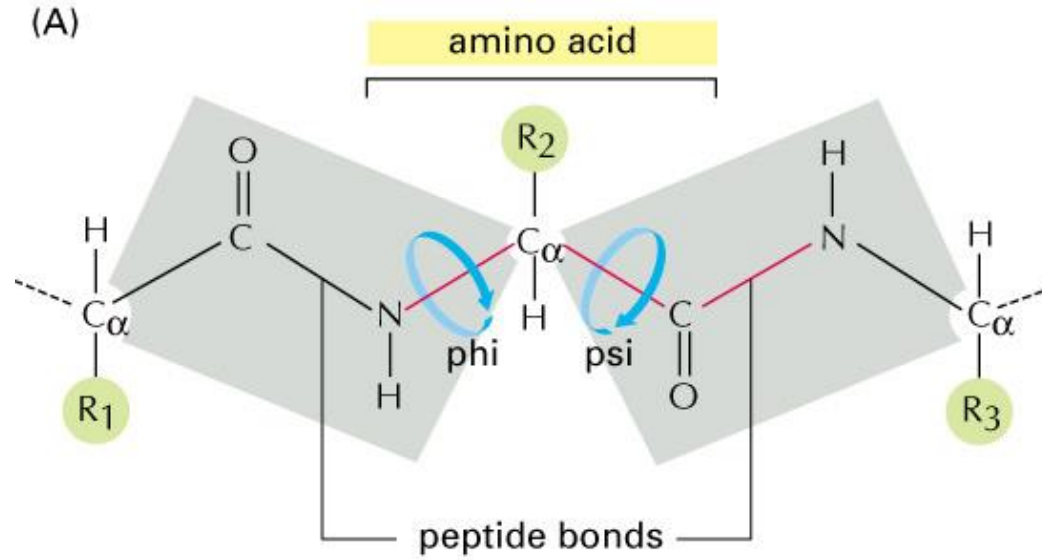
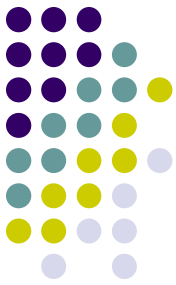


Figure 3-4. Molecular Biology of the Cell, 4th Edition.

Amino acid	$\alpha$ helix	$\beta$ sheet	Turn
Ala	<b>1.29</b>	0.90	0.78
Cys	<b>1.11</b>	0.74	0.80
Leu	<b>1.30</b>	1.02	0.59
Met	<b>1.47</b>	0.97	0.39
Glu	<b>1.44</b>	0.75	1.00
Gln	<b>1.27</b>	0.80	0.97
His	<b>1.22</b>	1.08	0.69
Lys	<b>1.23</b>	0.77	0.96
Val	0.91	<b>1.49</b>	0.47
Ile	0.97	<b>1.45</b>	0.51
Phe	1.07	<b>1.32</b>	0.58
Tyr	0.72	<b>1.25</b>	1.05
Trp	0.99	<b>1.14</b>	0.75
Thr	0.82	<b>1.21</b>	1.03
Gly	0.56	0.92	<b>1.64</b>
Ser	0.82	0.95	<b>1.33</b>
Asp	1.04	0.72	<b>1.41</b>
Asn	0.90	0.76	<b>1.28</b>
Pro	0.52	0.64	<b>1.91</b>
Arg	0.96	0.99	0.88



# Intramolecular forces

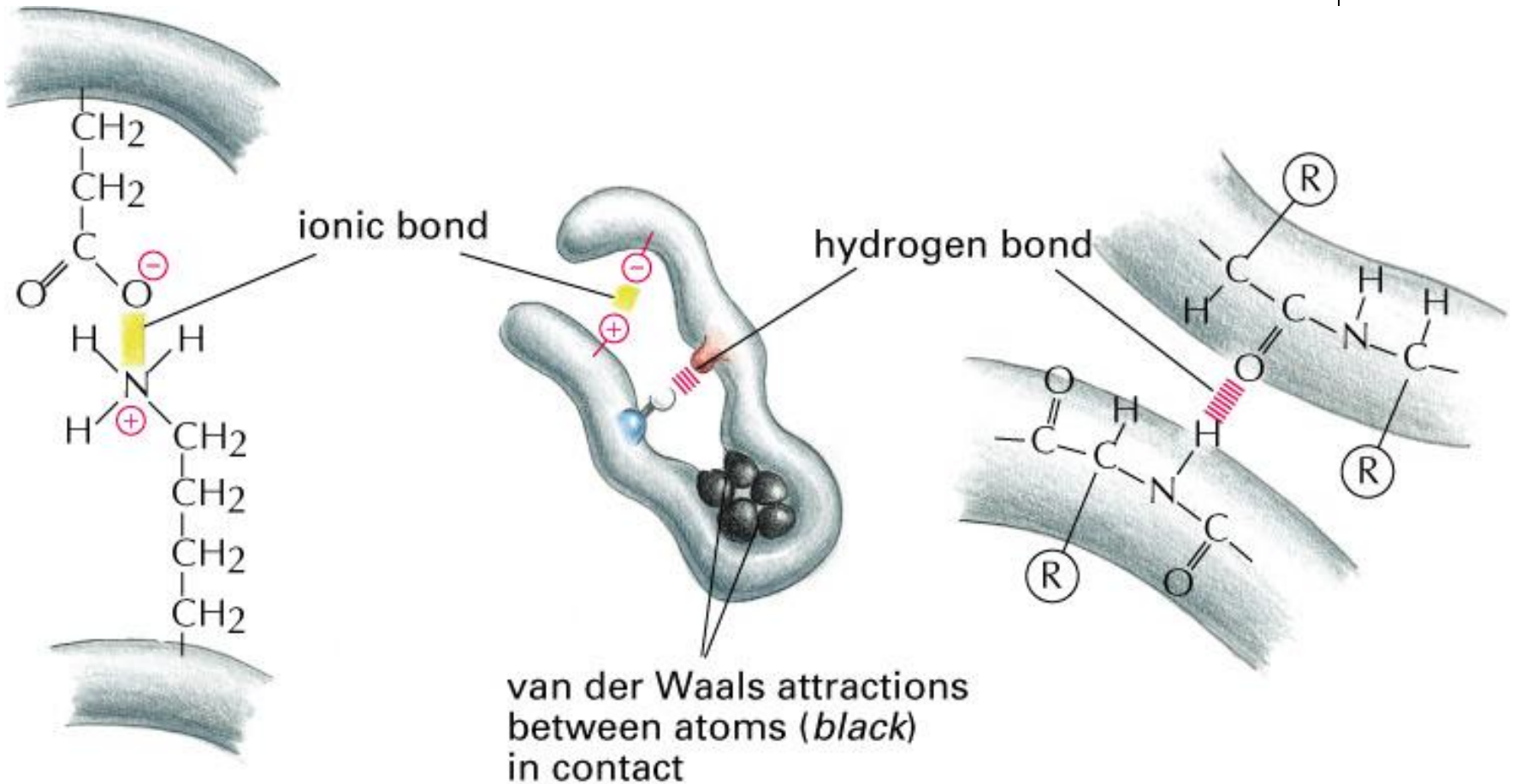
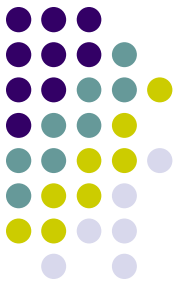
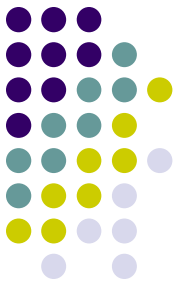
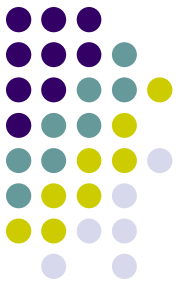


Figure 3-5. Molecular Biology of the Cell, 4th Edition.



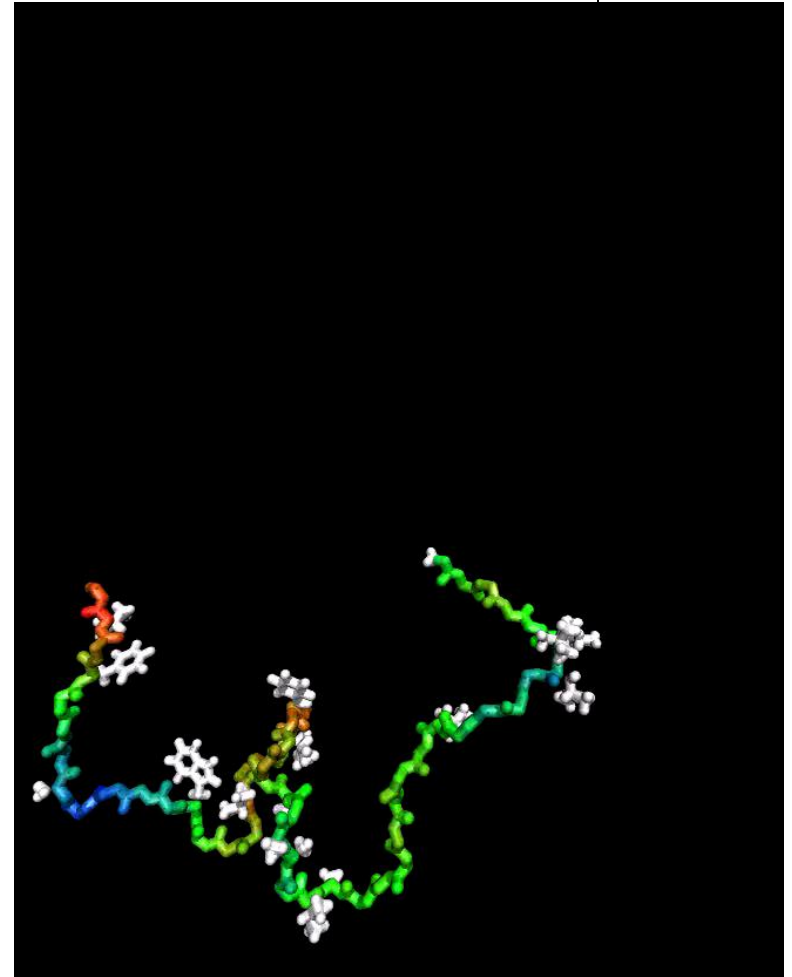
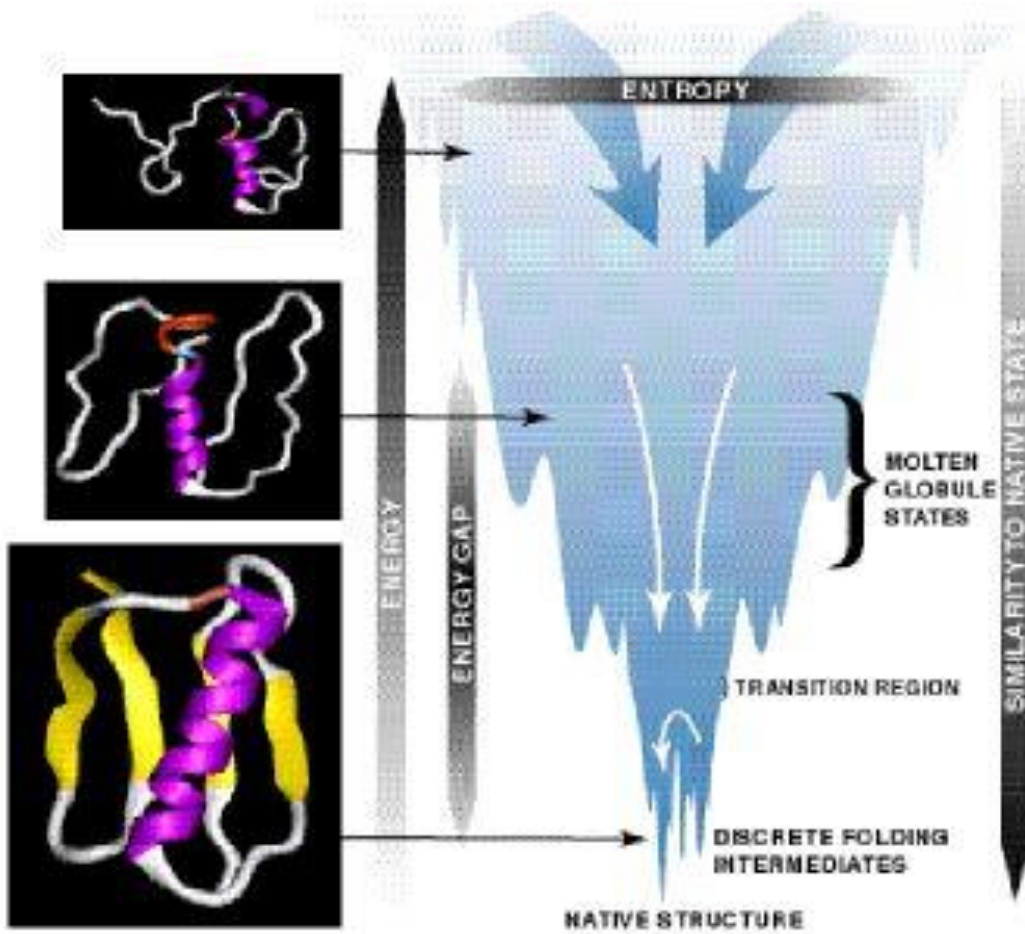
- Ionic interactions
  - $F = (q_1 q_2) / (d^2 \epsilon)$
  - $\epsilon$  the dielectric (water 85)
  - Weak in water  $\ll$  -kcal/mol
- Van der Waales
  - Lennard-Jones potential
  - $F = D_0 [ (R_{eq}/R)^{12} - 2 (R_{eq}/R)^6 ]$
  - 1.3 kcal/mol/CH<sub>2</sub>
- Hydrogen bond
  - Vapor phase about -6 kcal/mol
  - Water about -0.5 to -1.5 kcal/mol
  - $F = D_0 [ 5(R_{eq}/R)^{12} - 6(R_{eq}/R)^6 ] \cos^2 DHA$



# The hydrophobic effect

- Oil in water
  - $\Delta G = \Delta H - T\Delta S$ 
    - Enthalpy of transfer from oil to water is negligible
    - Entropy is largely due to the ordering of water
    - The main driving force in protein folding is entropic
      - But see temperature dependence....

# Cooperatively of Folding

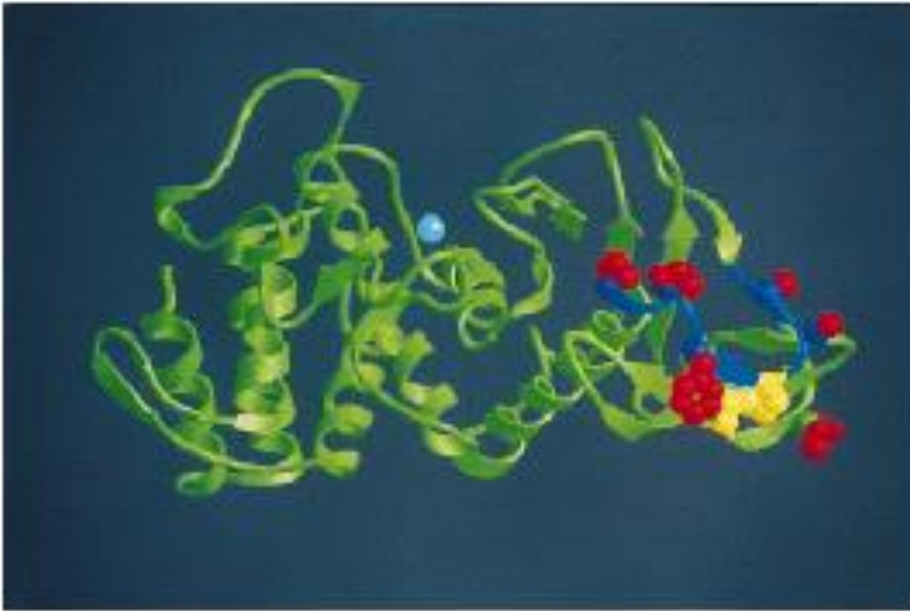
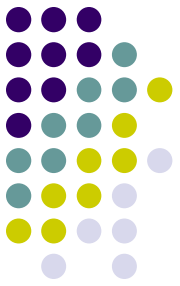




# Protein summary

- H-bond, I-bonds marginal for overall stability
  - Important for secondary conformations
- Van der Waals/ hydrophobic effect drive folding and stability
- Overall stability about 10-12 kcal/mol
- Highly cooperative
- Sequence to fold prediction poor

# Example: Temp Sensitive Enzyme



**Half life at 100C**

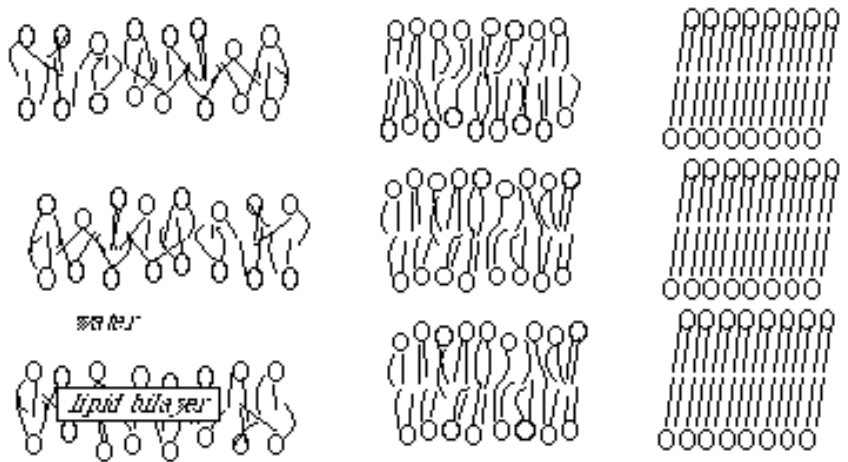
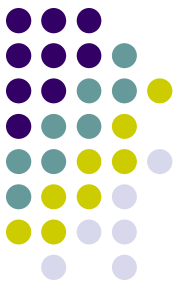
**Native <0.5 min**

**Mutant 170 min**

**Thermolysin like protein**



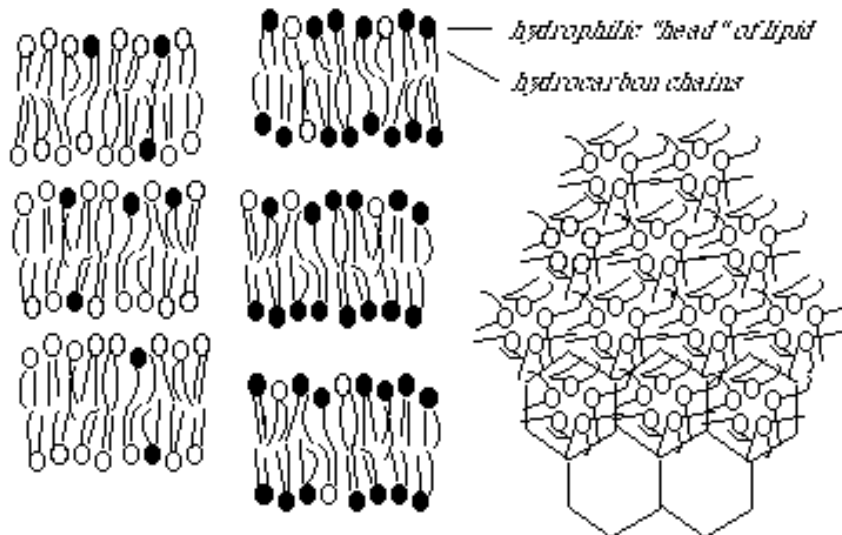
# Lipids and membranes



liquid crystal lamellar phase at high hydration

liquid crystal lamellar phase at lower hydration

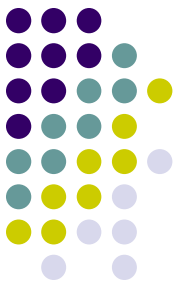
gel phase has lower hydration



phase separation in fluid state  
● is the higher hydrating species

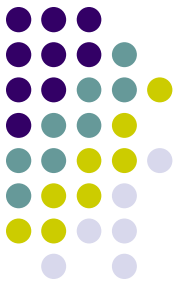
inverted hexagonal phase

# Look familiar



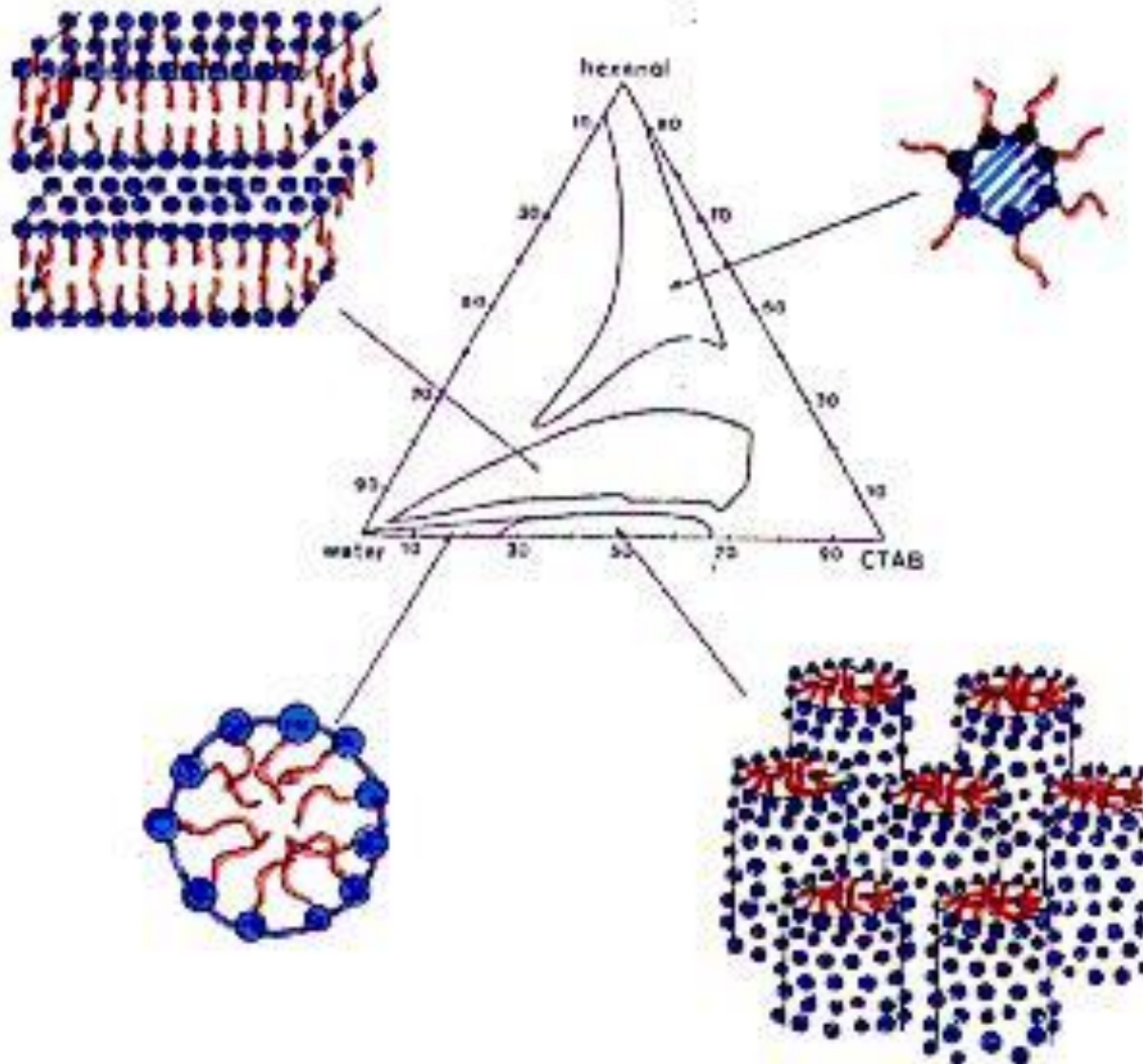
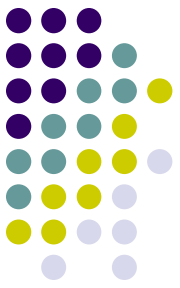
- Ionic interactions
  - $F = (q_1 q_2) / (d^2 \epsilon)$
  - $\epsilon$  the dielectric (water 85)
  - Weak in water  $\ll$  -kcal/mol
- Van der Waales
  - Lennard-Jones potential
  - $F = D_0 [ (R_{eq}/R)^{12} - 2 (R_{eq}/R)^6 ]$
  - 1.3 kcal/mol/CH<sub>2</sub>
- Hydrogen bond
  - Vapor phase about -6 kcal/mol
  - Water about -0.5 to -1.5 kcal/mol
  - $F = D_0 [ 5(R_{eq}/R)^{12} - 6(R_{eq}/R)^6 ] \cos^2 DHA$

# Lipid phases main effectors



- Water content
- Salt concentration
- Small organic molecules
- Temperature
- Nature of the lipid
  - Head group
  - Tail group

# Phase diagram for CTAB



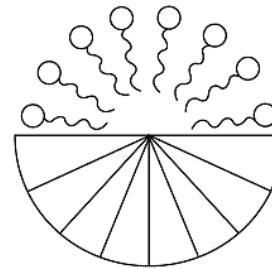
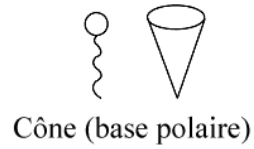
Espèces

Formes

Assemblages

Phase

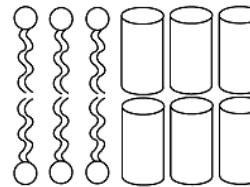
Savon  
Détergents  
Lysophospholipides



Hexagonal I  
(isotrope)



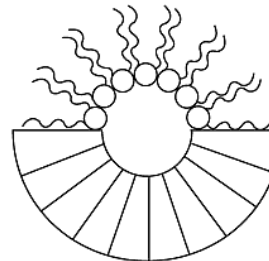
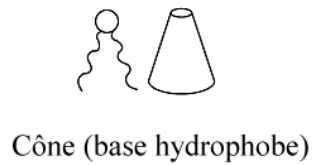
PC, PS, PI, SM  
dicétyl phosphate  
DODAC



Bicouche

Lamellaire  
(cubique)

PE, PA  
Cholestérol  
Cardiolipine  
Lipide A



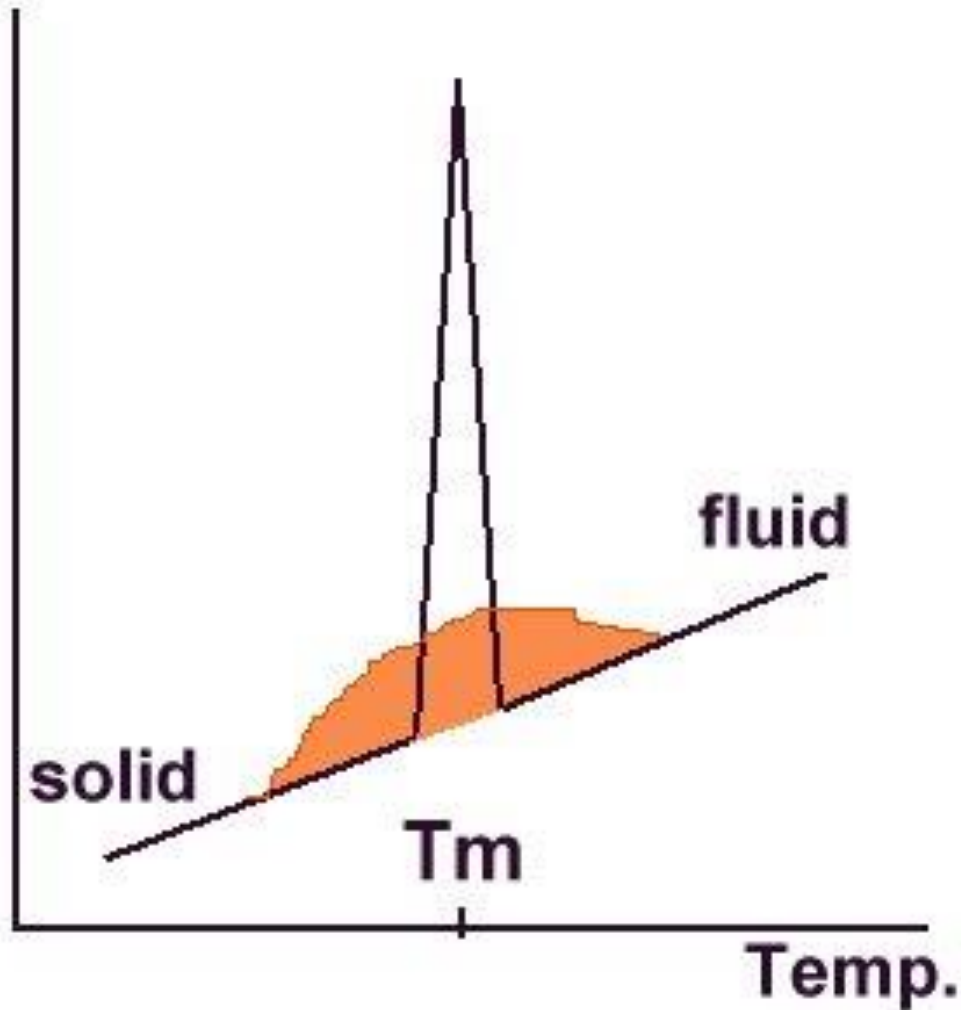
Hexagonal 2

# For each lipid remember the following

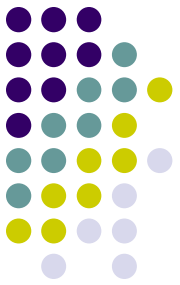


- Below the “melting” temp bilayers are rigid, tightly packed, and immobile
- Above they are flexible and mobile
- The transition temperature is a characteristic of the lipids
- The more pure the lipid system the sharper the transition.

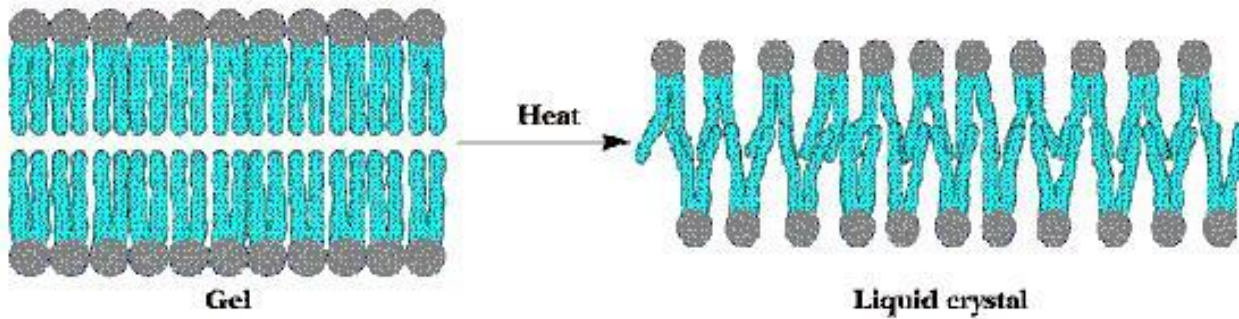
# Effect of cholesterol on phase transition in lecithin vesicles



# Biochemistry 2/e - Garrett & Grisham



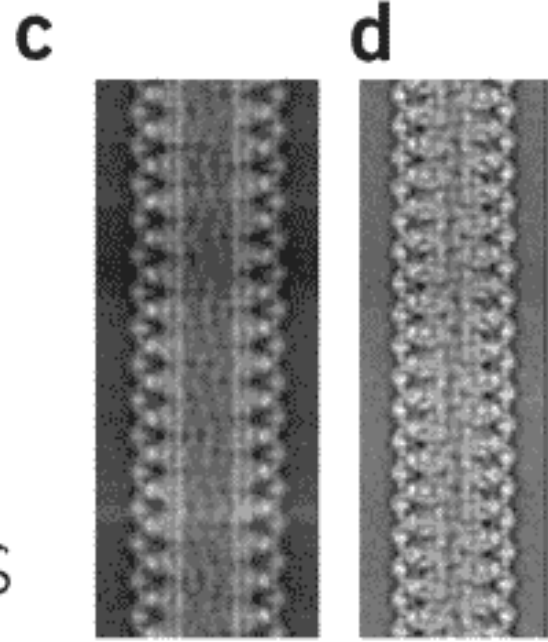
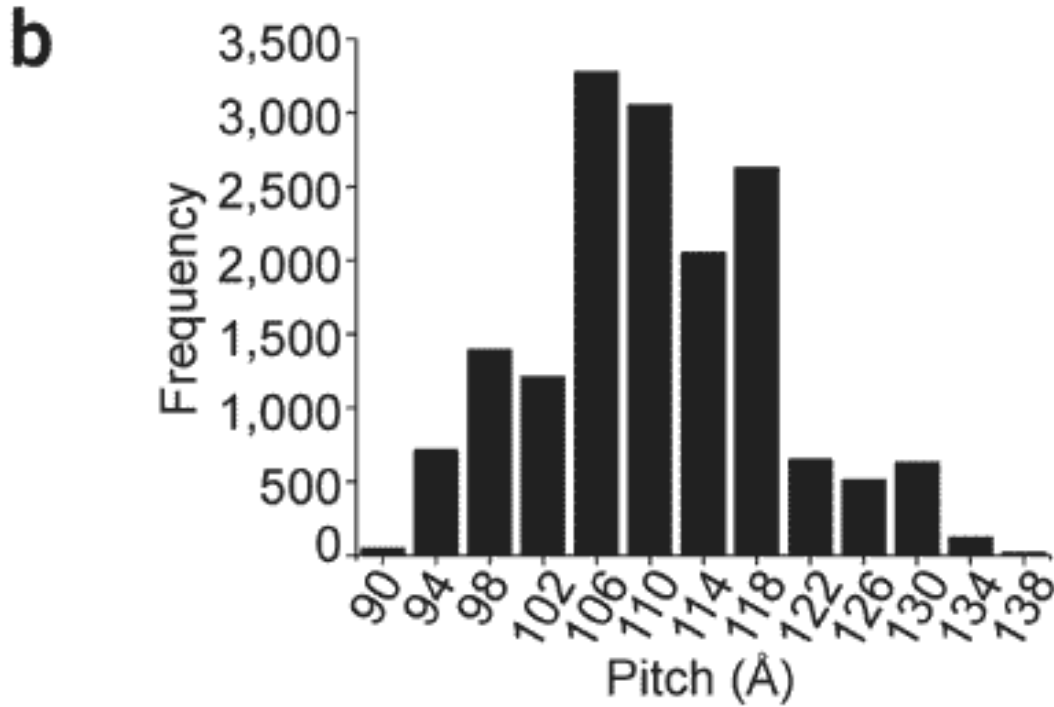
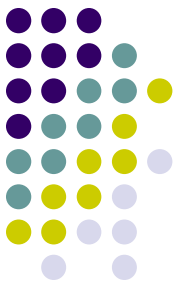
Garrett & Grisham: Biochemistry, 2/e  
Figure 9.12

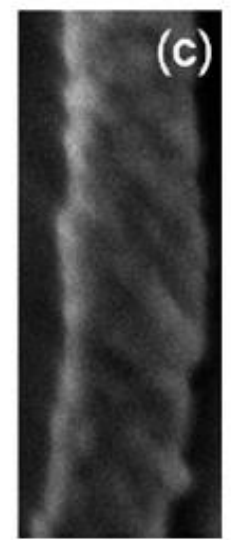
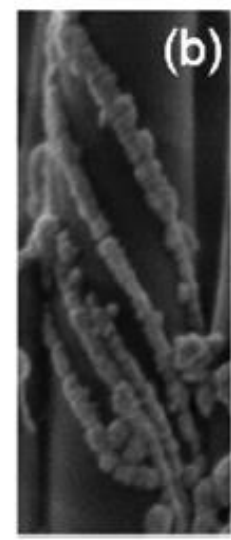
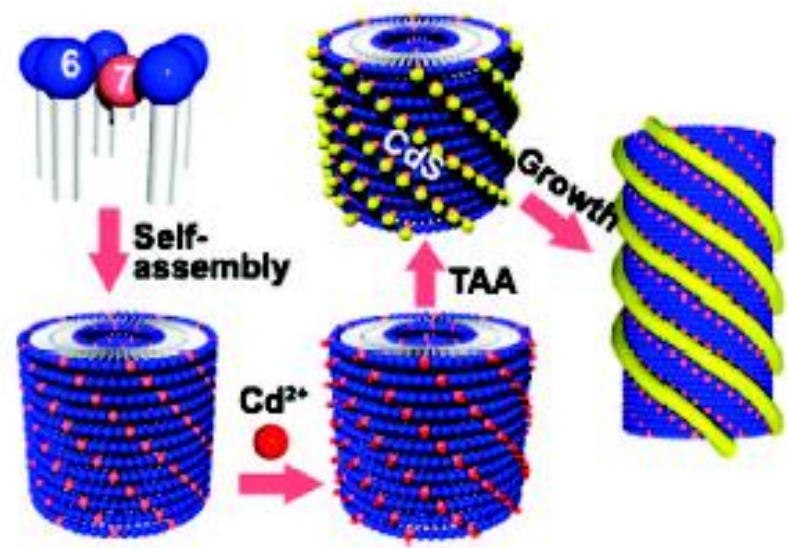
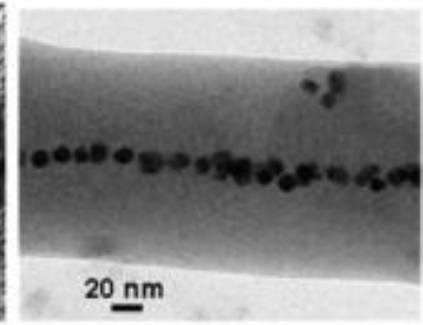
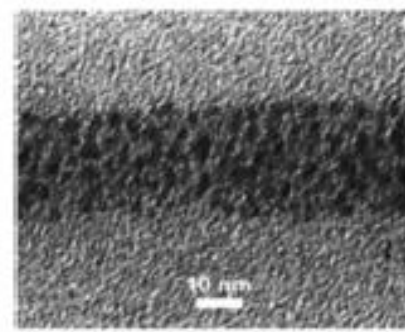
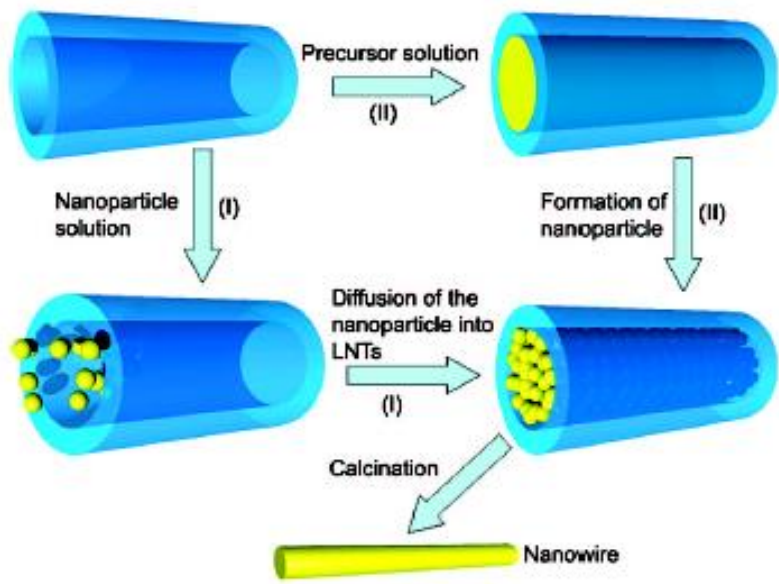


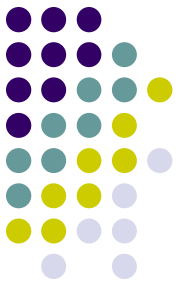
Saunders College Publishing



# Examples: Lipid templates for ordered array assembly







# Lipids summary

- Clear phase transitions
- $T_m$  of phase transition is lipid dependent and environment dependent
- $T_m$  is broadened by addition of other lipids