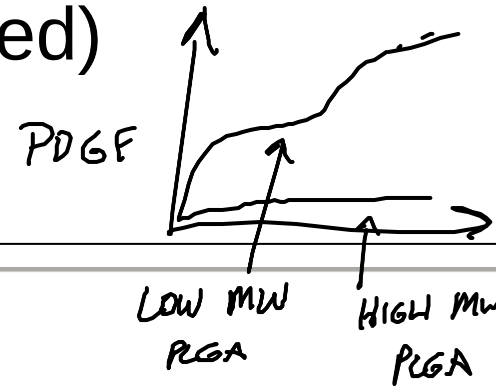
Hydrogel thermodynamics (continued)
Physical hydrogels



Last Day: bioengineering applications of hydrogels
thermodynamics of hydrogel swelling

Today: Structure, physical chemistry, and thermodynamics of physical gels

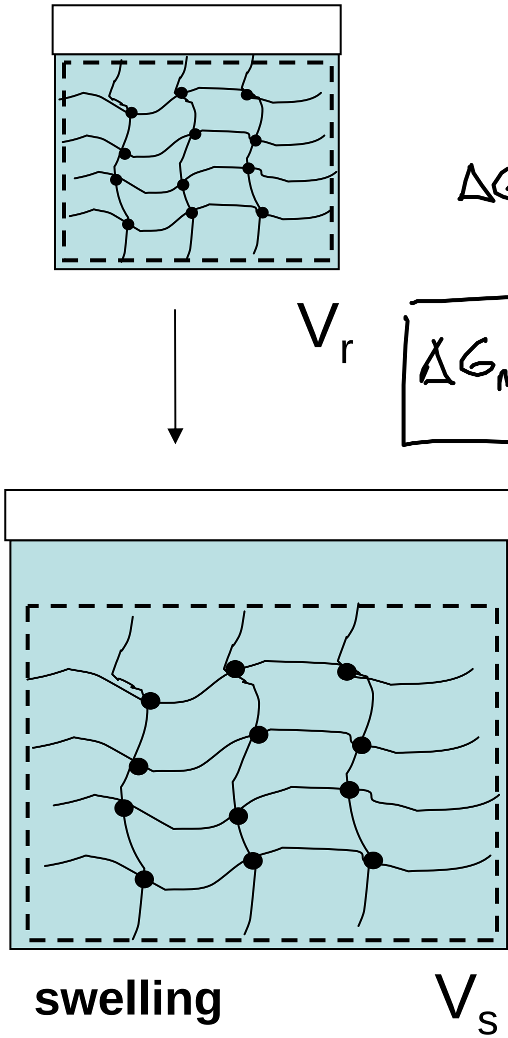
Reading: L.E. Bromberg and E.S. Ron, 'Temperature-responsive gels and thermogelling polymer matrices for protein and peptide delivery,' *Adv. Drug Deliv. Rev*., **31**, 197 (1998)

D. Chandler 'Interfaces and the driving force of hydrophobic assembly,' *Nature* **437**, 640-647 (2005)

Announcements: PS 3 DUE THURSDAY 5 pm
PS 2 SOLUTIONS POSTED

Thermodynamics of hydrogel swelling:

Peppas-Merrill theory (derived from Flory-Rehner theory of elastic gels)



Competing driving forces determine total swelling:

$$\Delta G_{mix} = k_B T \left[\underbrace{n_1 \ln \phi_{1,s}}_{-\Delta S_{mix}} + \underbrace{n_1 \phi_{2,s} \chi}_{\Delta H_{mix}} \right]$$

$\boxed{\Delta G_{mix} < 0 \text{ OVERALL}}$

$-\Delta S_{mix}$: < 0 FAVORS MIXING

ΔH_{mix}: > 0 IF $\chi > 0$ (WEAKLY RESISTS MIXING)

TYPICAL VALUE: $\chi_{PEO-H_2O} \simeq 0.4$

$$\Delta G_{el} = -T\Delta S_{el} = \frac{3}{2} k_B T \nu_e \left[\alpha^2 - 1 - \ln \alpha \right]$$

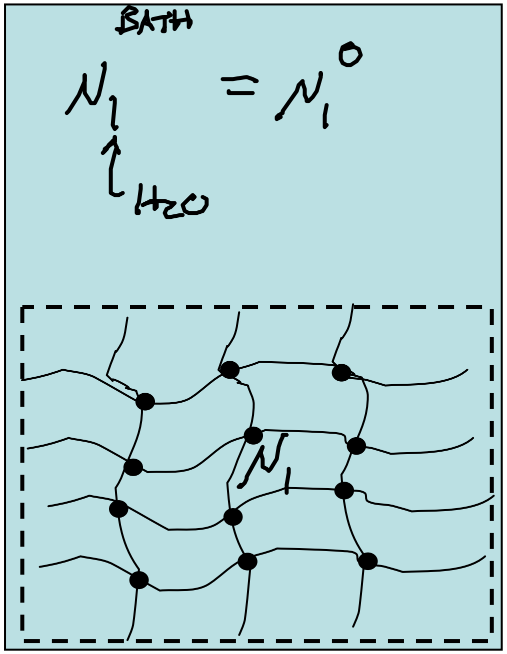
ν_e: # EFFECTIVE NETWORK CHAINS

α: EXPANSION COEFFICIENT

$$\alpha = \left(\frac{V_s}{V_r} \right)^{1/3}$$

$\boxed{\Delta G_{el} > 0 \text{ OVERALL}}$

Chemical potential requirement for equilibrium in the gel:



REQUIREMENT FOR EQUILIBRIUM:

$$\mu_1^{BATH} = \mu_1$$

$$\mu_1 - \mu_1^0 = 0$$

$$\Delta\mu_1 = 0 \quad \text{FOR EQUILIBRIUM}$$

$$(\Delta\mu_1)_{mix} + (\Delta\mu_1)_{El} = 0$$

$$\Delta\mu_1 \equiv \left(\frac{\partial \Delta G}{\partial n_1}\right)_{T,P,n_2}$$

Governing equation for equilibrium:

$$(\Delta\mu_1)_{mix} + (\Delta\mu_1)_{el} = 0$$

M_C MW BETWEEN XLINKS

$$\frac{1}{\boxed{M_C}} = \frac{2}{\boxed{M}} - \frac{v_{sp,2}}{V_1\phi_{2,r}}\left[\frac{\ln(1-\boxed{\phi_{2,s}}) + \phi_{2,s} + \chi\phi_{2,s}^2}{\left(\frac{\phi_{2,s}}{\boxed{\phi_{2,r}}}\right)^{1/3} - \frac{1}{2}\left(\frac{\phi_{2,s}}{\boxed{\phi_{2,r}}}\right)}\right]$$

MASTER SWELLING EQ'N FOR PEPPAS-MERRILL (DERIVED FROM FLORY-REHNER)

$\square$ = PARAMETERS I CHOOSE

SWELLING RATIO $Q = \frac{V_{SWOLLEN}}{V_{DRY}} = \frac{1}{\phi_{2,S}}$

Example application of Flory-Rehner/Peppas-Merrill theory:

SUPPOSE WE WERE FORM A CROSSLINKED DEXTRAN HYDROGEL.

WE START W/ PHYSICAL CONSTANTS:

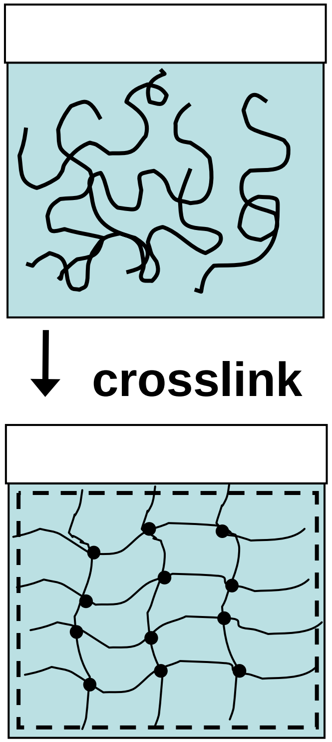
FIXED BY CHOICE OF MATERIALS SYSTEM

- $v_{sp,2} = 0.62\ cm^3/g$ DEXTRAN SPEC. VOLUME
- $\bar{V}_1$ = MOLAR VOLUME OF H_2O = $18\ cm^3/mole$
- χ = DEXTRAN-H_2O INTERACTION PARAM. = 0.65

CONTROLLED BY SYNTHESIS

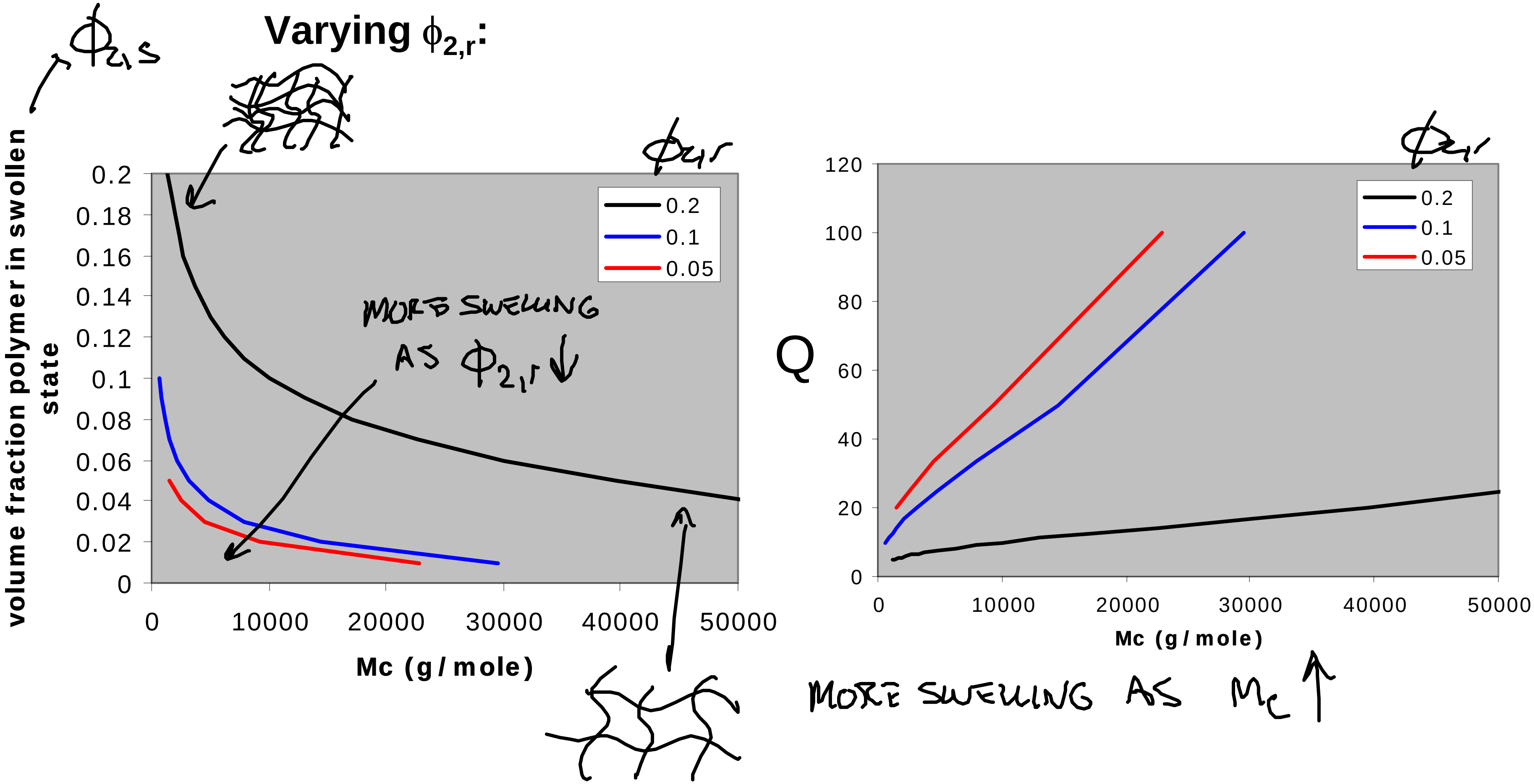
- M = MW OF INITIAL CHAINS
- M_c = MW BETWEEN XLINKS
- $\Phi_{2,r}$ = VOL. FRACTION OF POLYMER IN XLINKING STEP

$\Phi_{2,r}$



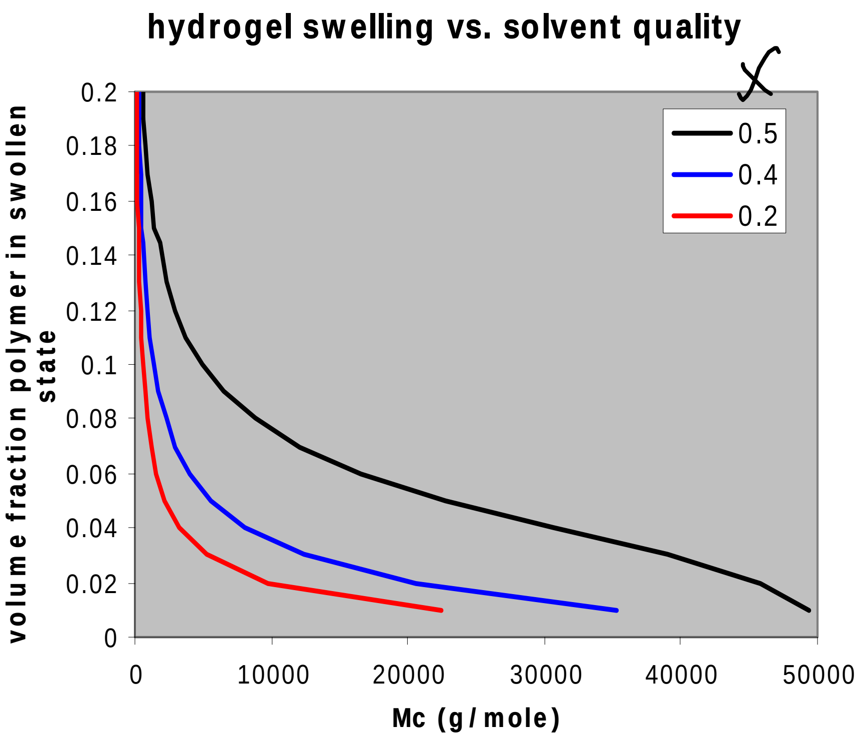
Predictions of Flory/Peppas theory

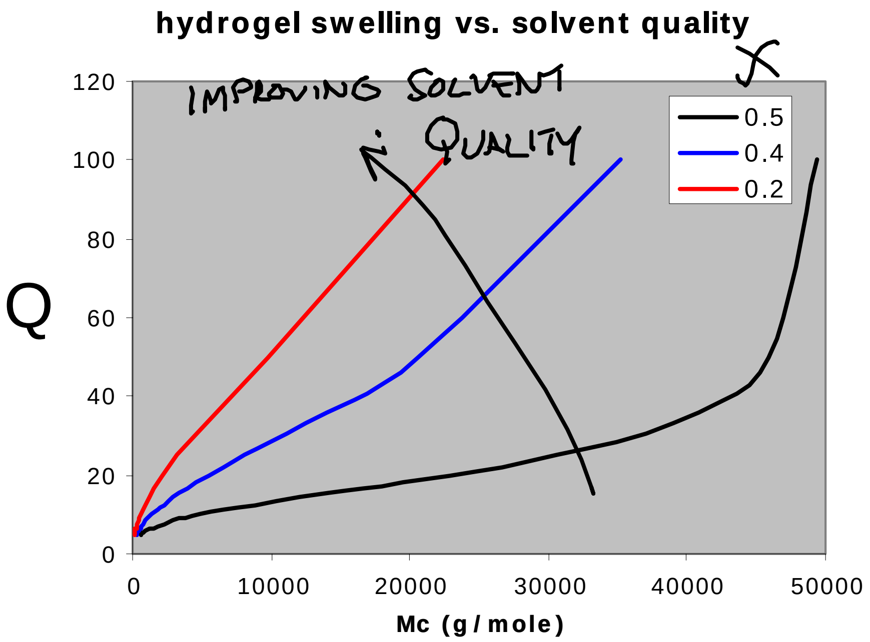
Varying $\phi_{2,r}$:



Predictions of Flory/Peppas theory

Varying χ:





Model parameters

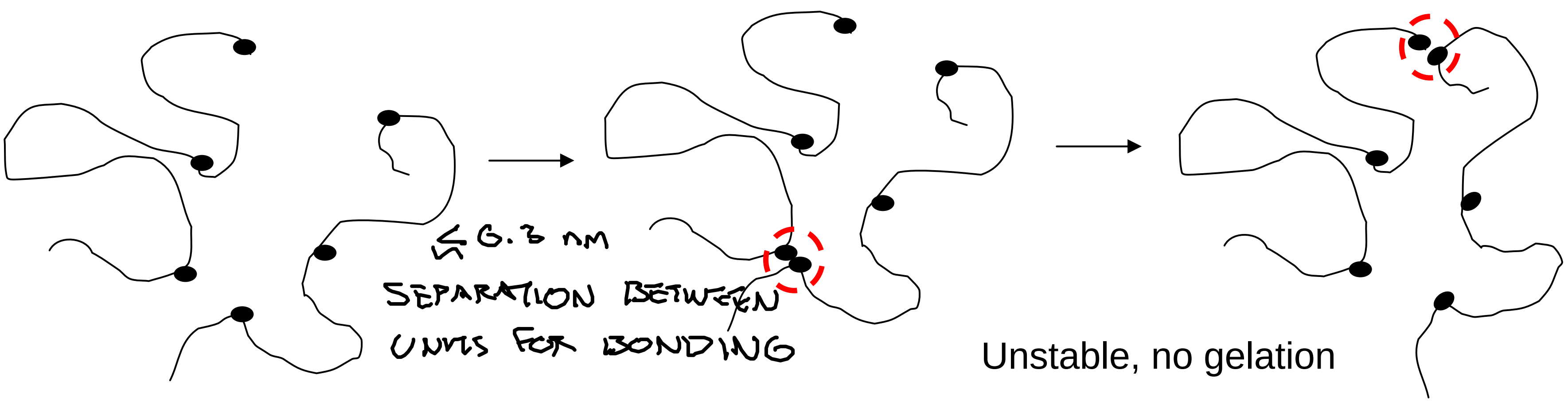
μ_1^{bath}	chemical potential of water in external bath (= μ_1^0)
μ_1	chemical potential of water in the hydrogel
μ_1^0	chemical potential of pure water in standard state
Δw_{12}	pair contact interaction energy for polymer with water
z	model lattice coordination number
x	number of segments per polymer molecule
M	Molecular weight of polymer chains before cross-linking
M_c	Molecular weight of cross-linked subchains
n_1	number of water molecules in swollen gel
χ	polymer-solvent interaction parameter
k_B	Boltzman constant
T	absolute temperature (Kelvin)
$v_{m,1}$	MOLECULAR ~~molar~~ volume of solvent (water) CM³/MOLECULE
$v_{m,2}$	MOLECULAR ~~molar~~ volume of polymer
$v_{sp,1}$	specific volume of solvent (water)
$v_{sp,2}$	specific volume of polymer
V_2	total volume of polymer
V_s	total volume of swollen hydrogel
V_r	total volume of relaxed hydrogel
ν	number of subchains in network
ν_e	number of ‘effective’ subchains in network
ϕ_1	volume fraction of water in swollen gel
$\phi_{2,s}$	volume fraction of polymer in swollen gel
$\phi_{2,r}$	volume fraction of polymer in relaxed gel

Bonding in physical hydrogels

NON-COVALENT BOND STRENGTHS IN H_2O:

	KCAL/MOLE	
HYDROPHOBIC INTERACTIONS (VdW)	~0.1	COMPETITION W/ H_2O
IONIC	~3	
H-BONDS	~1	

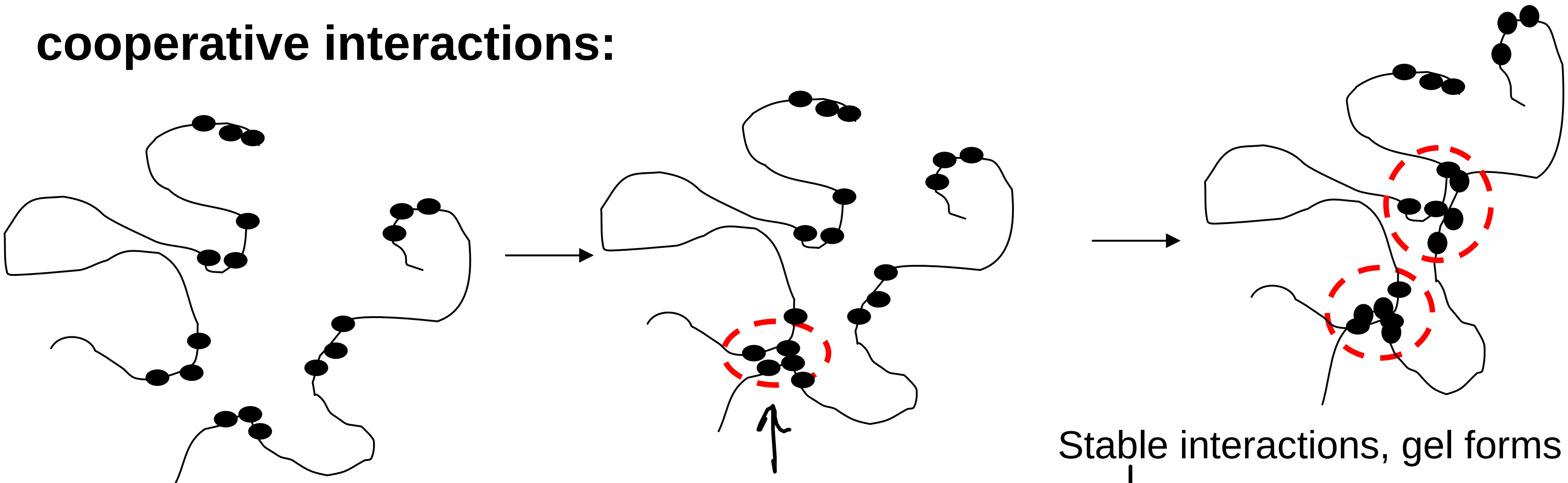
non-cooperative interactions:



Bonding in physical hydrogels

* MOLECULAR SEQUENCE OF CHAINS DICTATES OUTCOME

cooperative interactions:



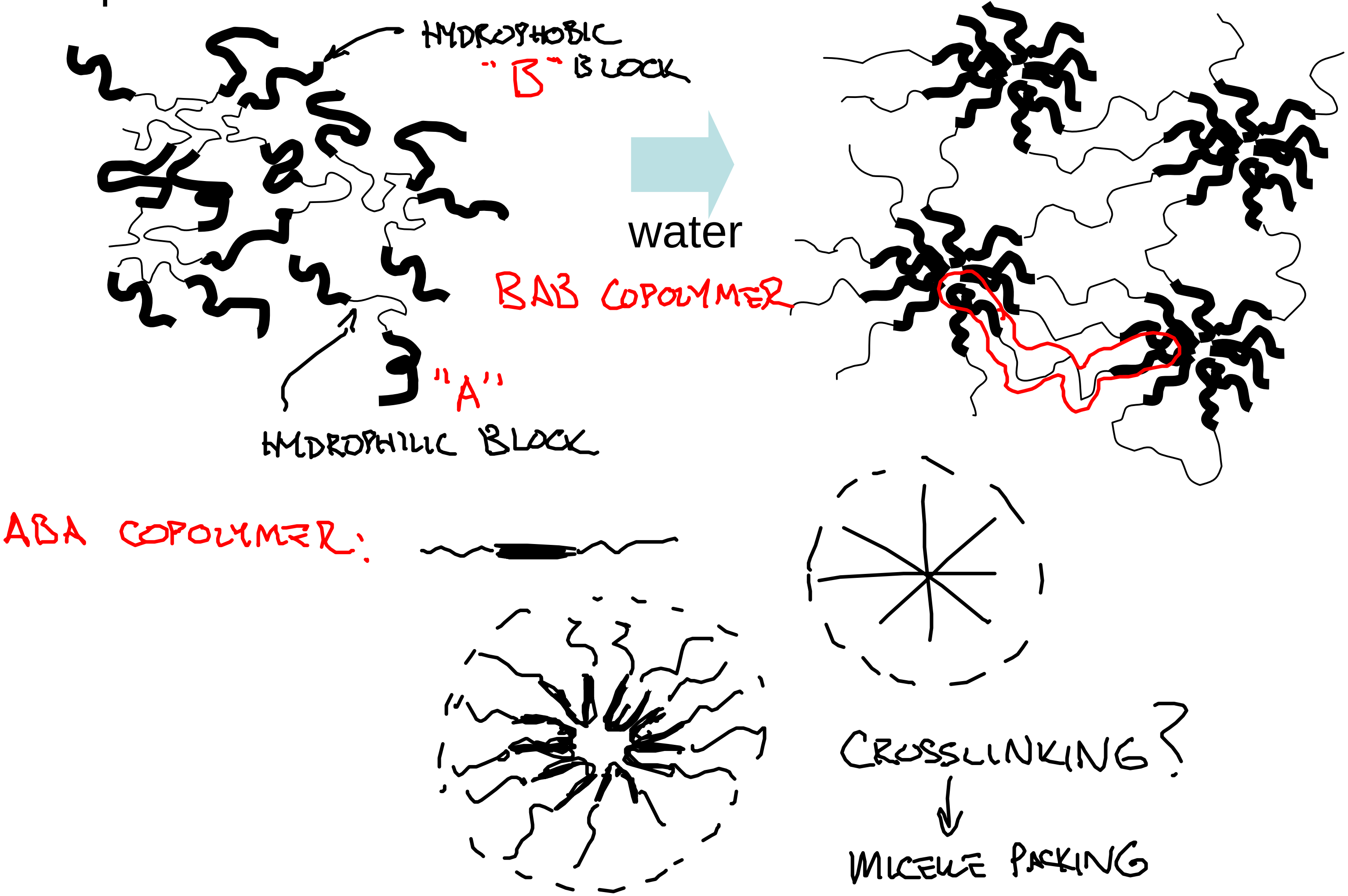
LOWERED ENERGY BARRIER FOR SUBSEQUENT BONDS FOLLOWING INITIAL CONTACT

Stable interactions, gel forms

FAVORED BY 'BLOCKY' STRUCTURES

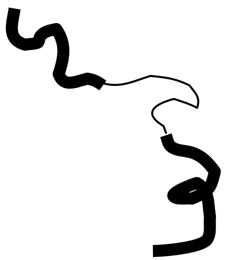
Gelation via hydrophobic associations

Block sequence controls self-assembled structures formed:



Chemical structure of associative copolymers used in bioengineering

Example blocks:

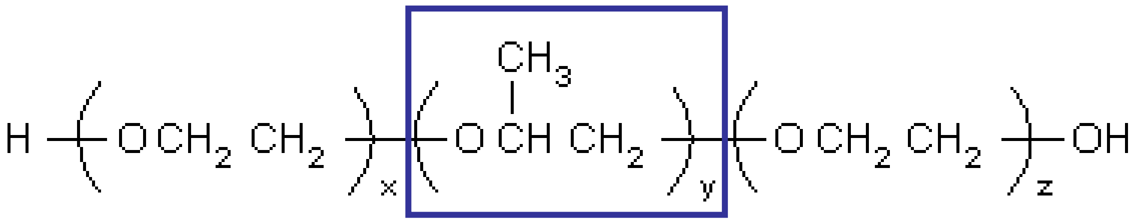


Hydrophilic B blocks

Poly(ethylene glycol) (PEG)

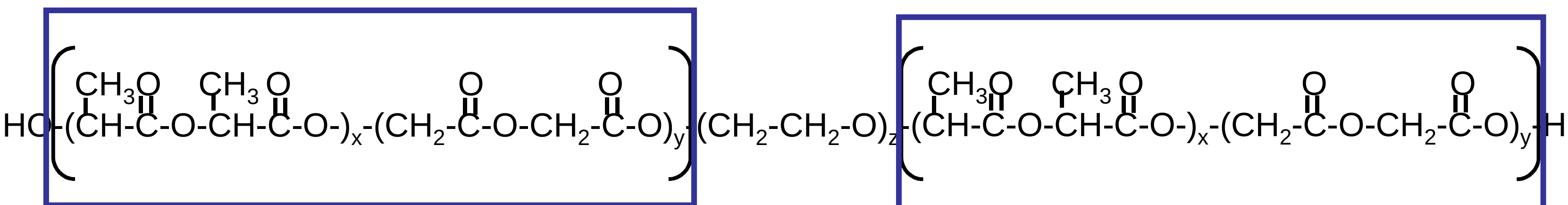
Hydrophobic A blocks

Poly(propylene oxide) (PPO)
Poly(butylene oxide) (PBO)



PEO PPO PEO

PLURONICS

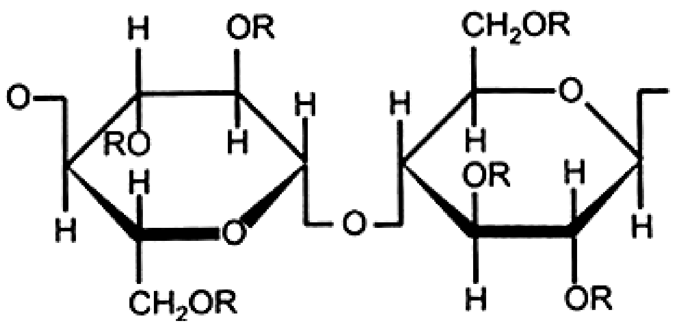


PLGA PEG PLGA

Gelation via hydrophobic associations

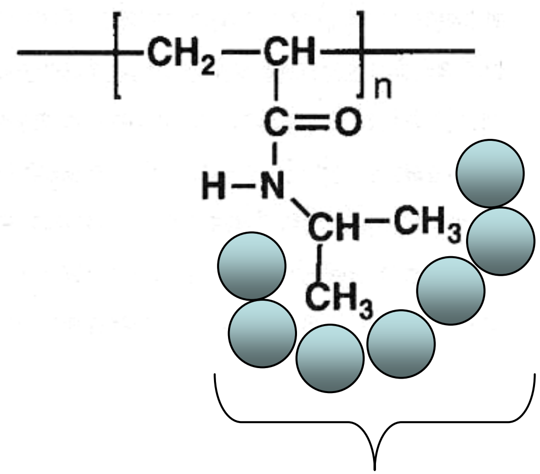
MIXED POLAR/NONPOLAR GROUPS GIVE GELS AT ELEVATED TEMPERATURE, WHERE NONPOLAR GROUPS DEHYDRATE

Hydroxypropylmethyl cellulose



$R = -CH_2-\underset{OH}{CH}-CH_3$, $-CH_3$, or $-H$

Poly(N-isopropylacrylamide)



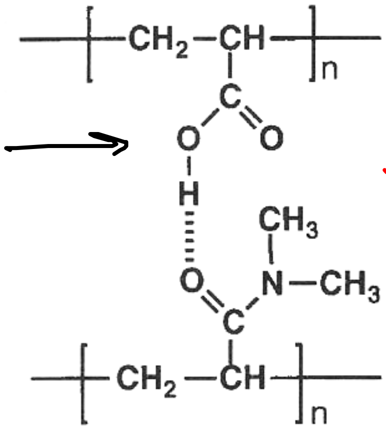
ordered water molecules
(minimize water-hydrophobe contacts)

Dehydration allows water to disorder (*entropically-driven*)

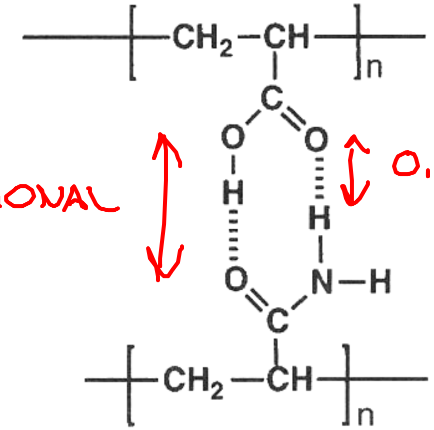
$$\Delta S = S_{dehydrated} - S_{hydrated} > 0$$

Hydrogen-bonded hydrogels

CARBOXYLIC ACIDS

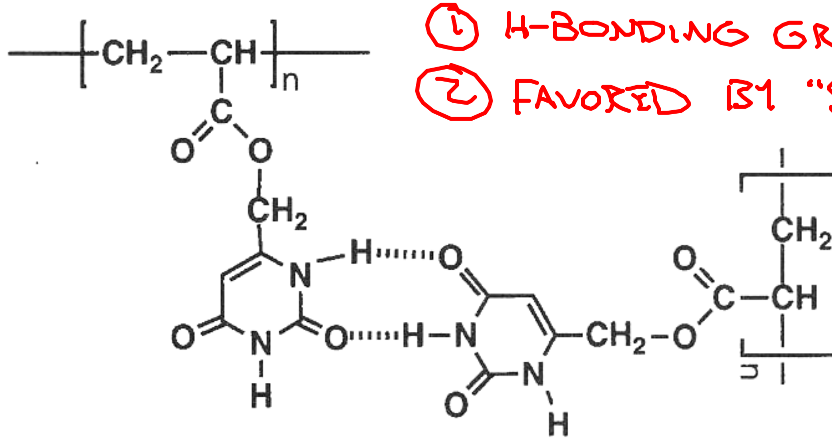


DIRECTIONAL



0.3 nm

(c)

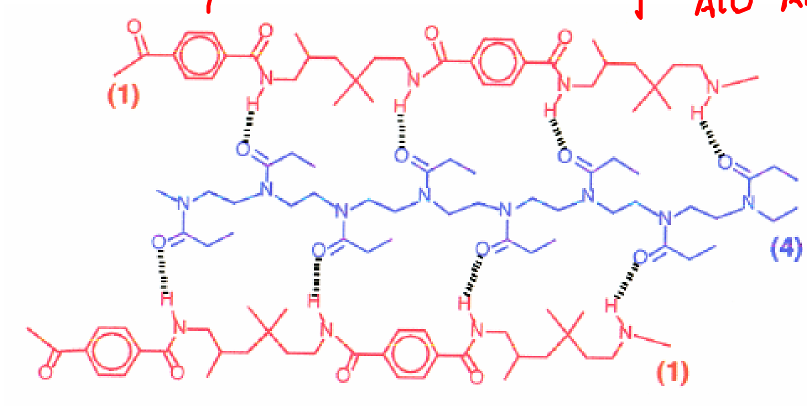


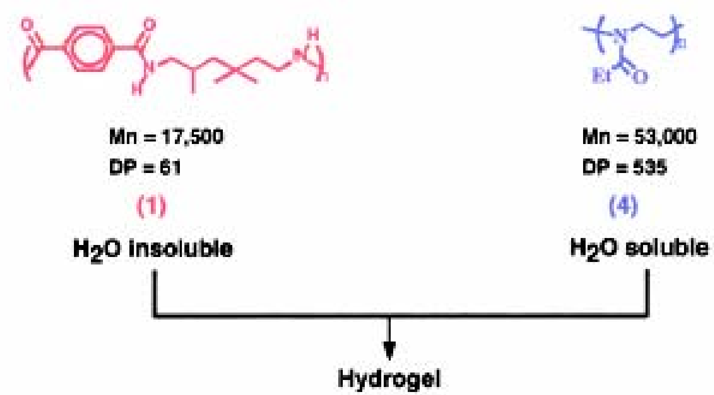
GEL FORMATION W/ H-BONDERS:

1. H-BONDING GROUPS AS BLOCKS
2. FAVORED BY "STIFF" BACKBONES

ORIENT THE DONOR/ACCEPTOR GROUPS

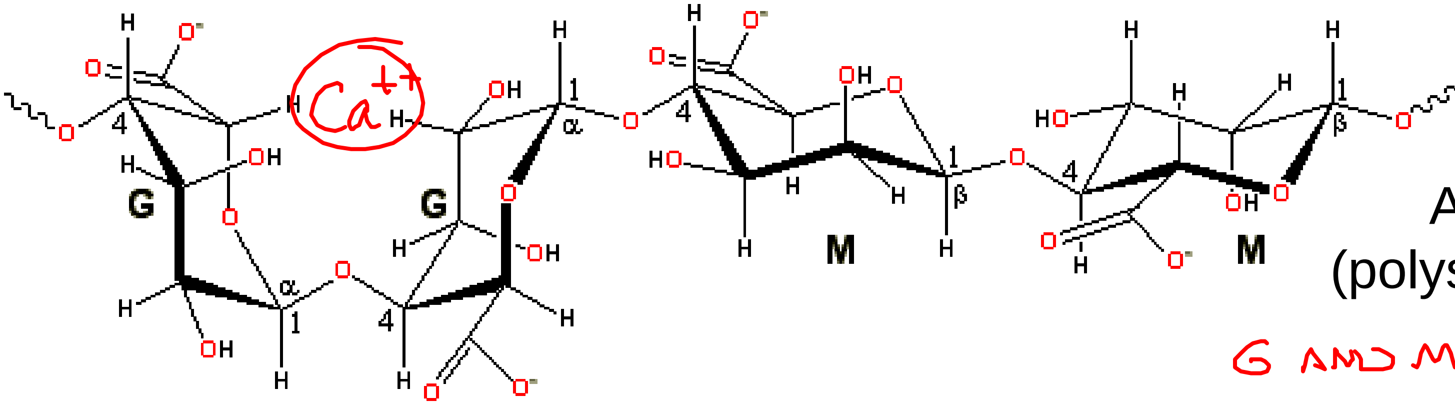
RIGID SEGMENTS IN BACKBONE
AID ALIGNMENT OF H-BONDING UNITS





Figures 4 and 5 in Percec, V., T. K. Bera, and R. J. Butera. *Biomacromolecules* 3 (2002): 272-9.

Ionically-bonded hydrogels

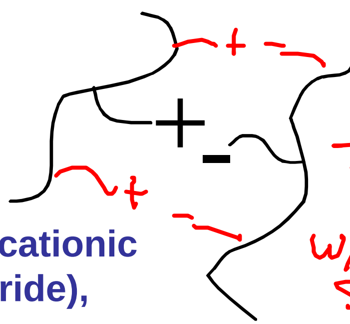


Alginate
(polysaccharide)

G AND M BLOCKS

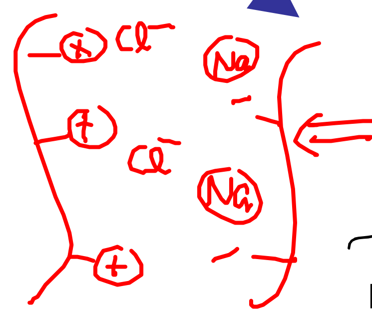
+ cationic polymer

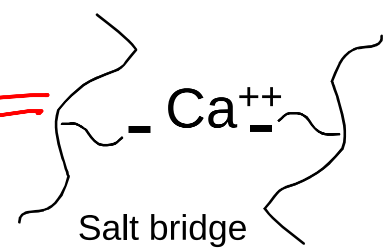
+ divalent cations



EXCHANGE
W/IONS IN
SOLUTION

e.g. chitosan (cationic polysaccharide), polylysine



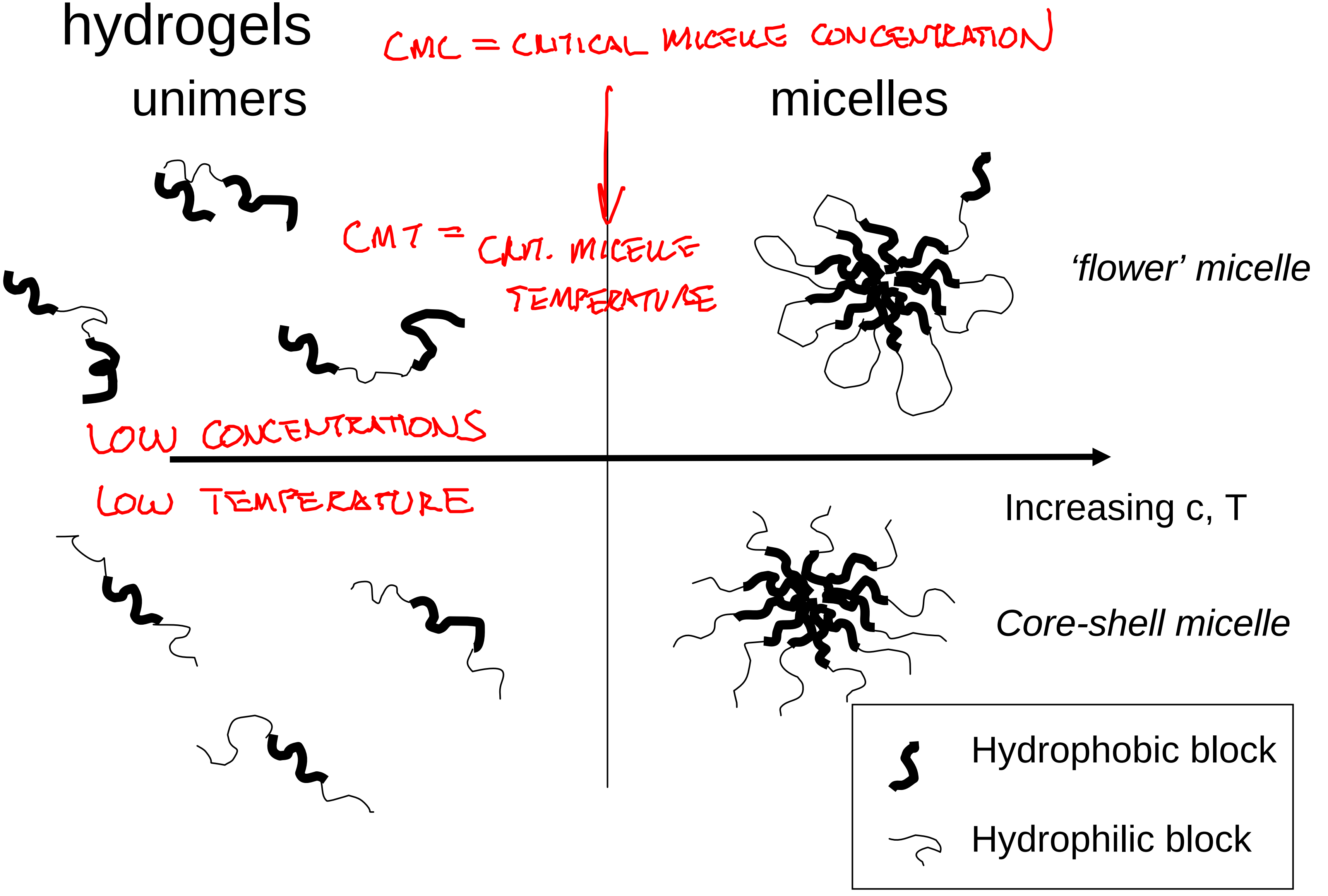


Salt bridge
Divalent cations

Combined non-covalent interactions example: coiled-coil peptide gels

Figure 1 in Wang, C., R. J. Stewart, and J. Kopecek. "Hybrid Hydrogels Assembled From Synthetic Polymers and Coiled-coil Protein Domains." *Nature* 397 (1999): 417-20.

Structure of associating block copolymer hydrogels

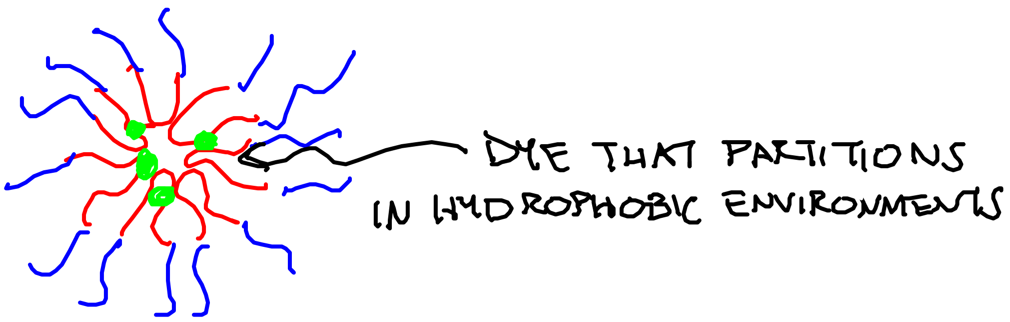


Formation of micelles

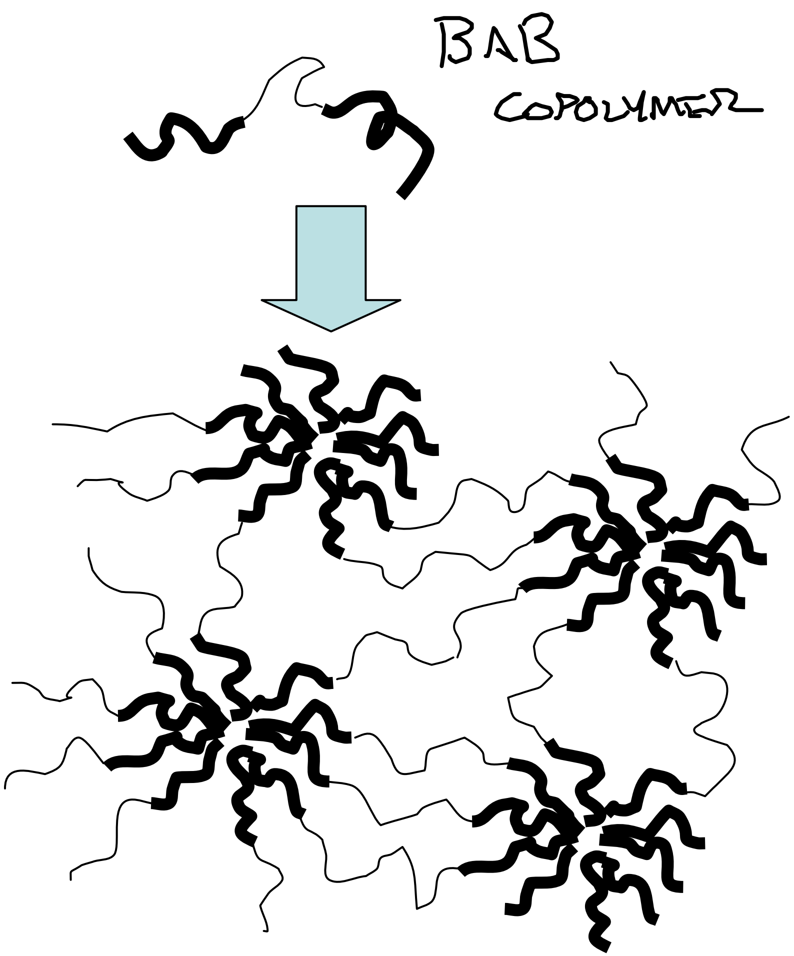
Experiments by Hatton group at MIT:

PEO-PPO-PEO micellization at different temperatures measured by adding a hydrophobic dye that absorbs UV light when bound in a hydrophobic environment (e.g. micelle core) but not free in solution

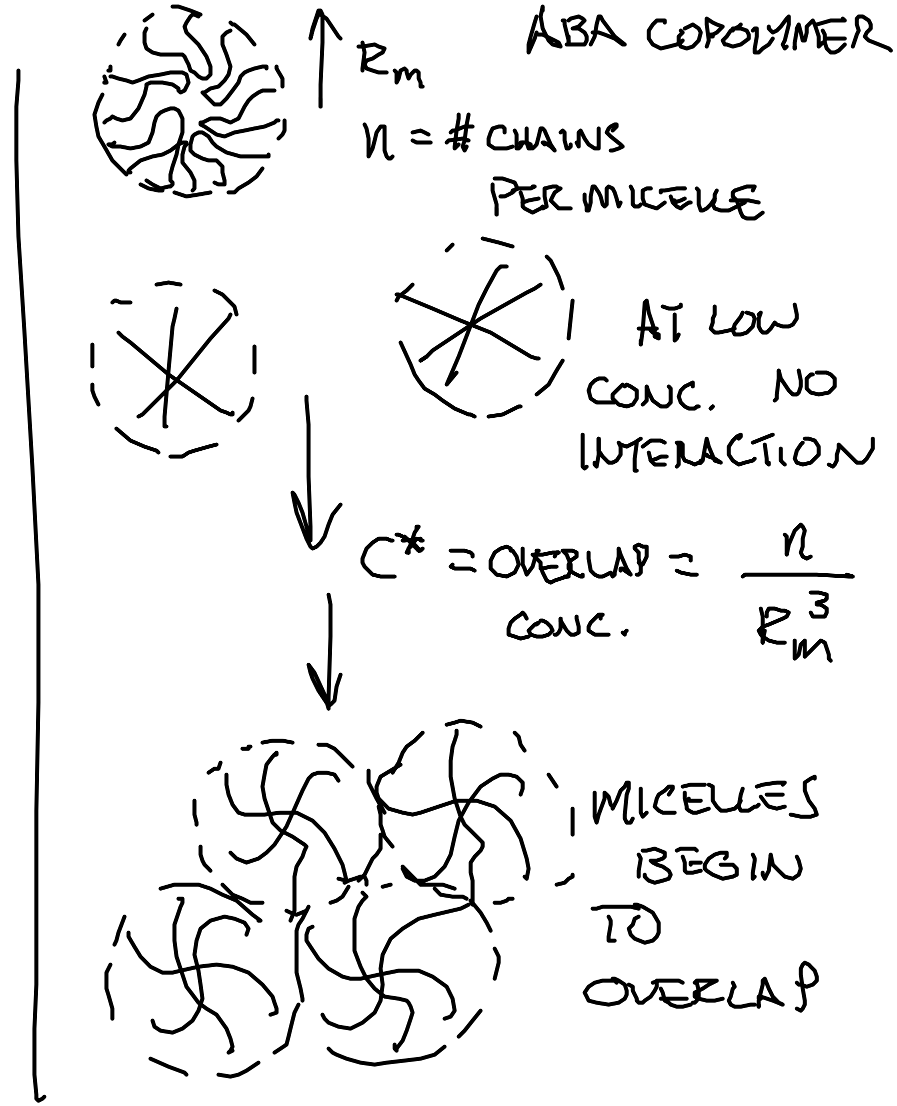
Figure 3 in Alexandridis, P., J. F. Holzwarth, and T. A. Hatton. *Macromolecules* 27 (1994): 2414-2425.



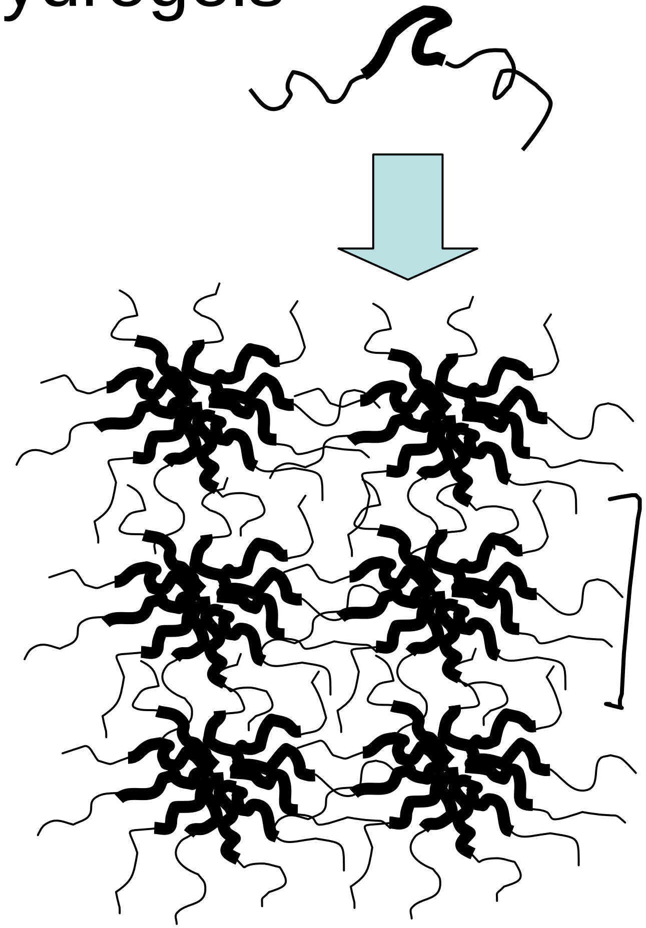
Structure of associating block copolymer hydrogels



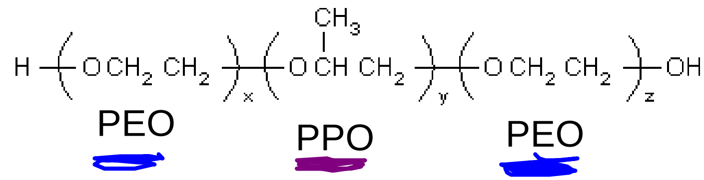
Intermicelle physical cross-links



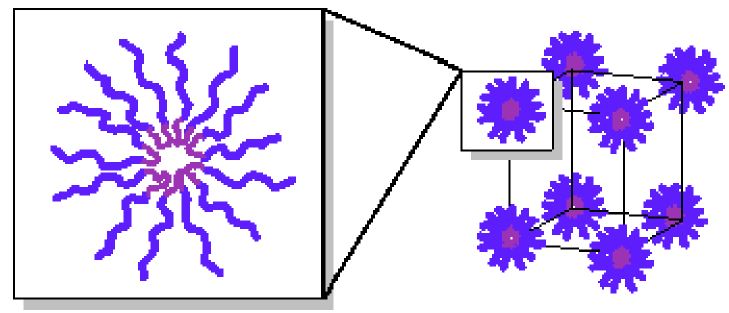
Structure of associating block copolymer hydrogels

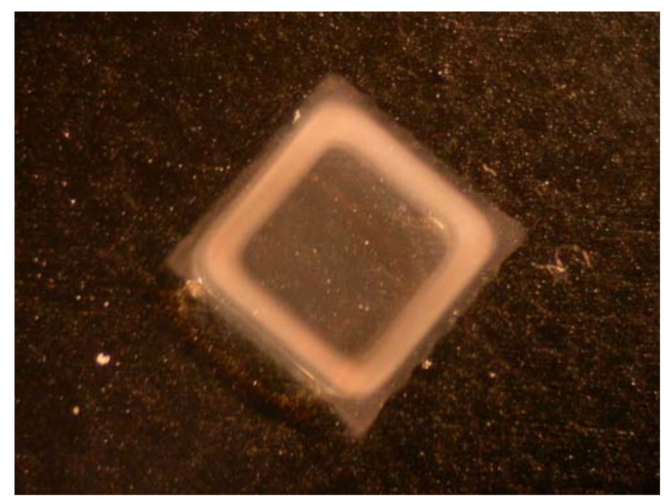


PACK AS HARD SPHERES



micelle (spherical)





Entanglement and H-bonding between packed micelle coronas

Structure of associating block copolymer hydrogels

Figures 19 and 20 in Chu, B. and Z. Zhou. *Nonionic Surfactants: Polyoxyalkylene Block Copolymers*. Edited by V. M. Nace. New York, NY: Marcel Dekker, 1996, pp. 67-143.

Block length determines gel structure

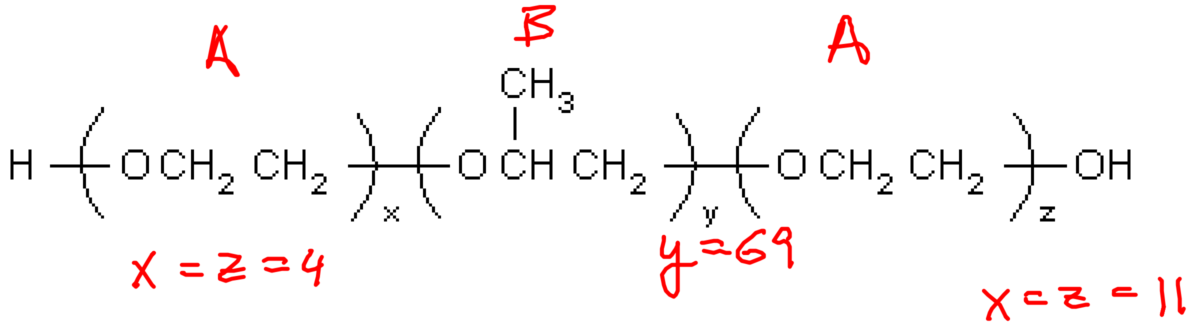
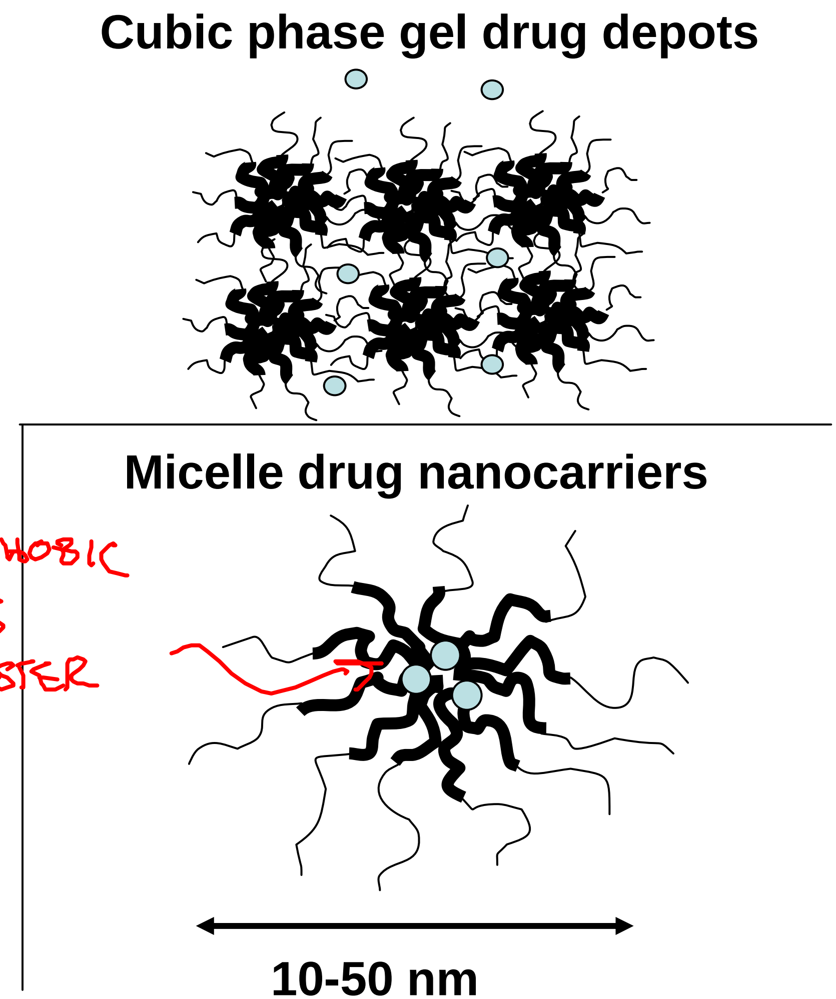


Figure 14 in Chu, B. Z. Zhou. *Nonionic Surfactants: Polyoxyalkylene Block Copolymers.* Edited by V. M. Nace. New York, NY: Marcel Dekker, 1996, pp. 67-143.

Relation between structure and applications in bioengineering



HYDROPHOBIC
DRUGS
SEQUESTER

Figure 1 in Zhang, L., D. L. Parsons, C. Navarre, and U. B. Kompella. *J Control Release* 85 (2002): 73-81.

Thermodynamics of hydrophobic association

UCST: ENTROPY FAVORS MIXING
WHILE ΔH RESISTS MIXING

$\Delta G_{mix} = \Delta H - T\Delta S$

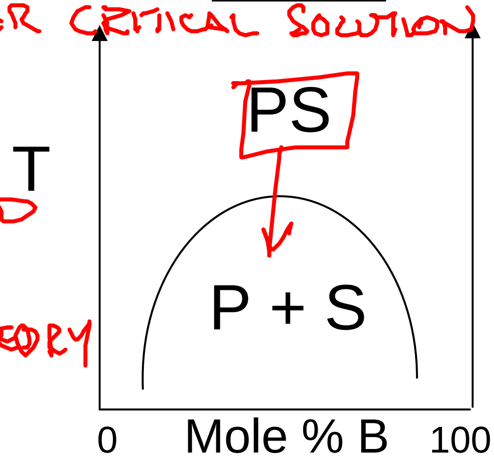
LCST: ENTHALPY FAVORS MIXING
(STRONG SPECIFIC INTERACTIONS)
ENTROPY DISFAVORS MIXING

LOWER CST

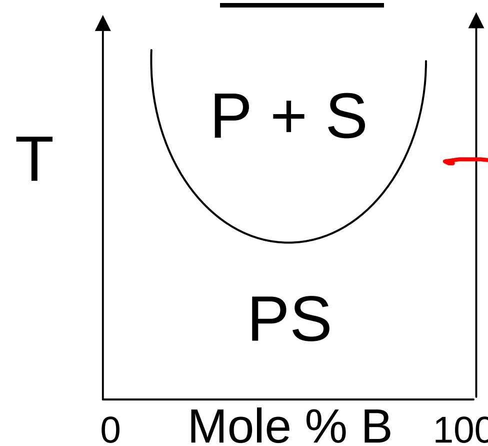
UCST

UPPER CRITICAL SOLUTION TEMP.

PREDICTED BY FLORY THEORY (χ)



LCST



ANALOGOUS TO PLURONIC SELF-ASSOCIATION

PS = polymer solution
P + S = two-phase region: polymer-rich, polymer-poor
(ΔH TYPICALLY ONLY WEAKLY DEPENDENT ON T)

Thermodynamics of hydrophobic association

CLOSED ASSOCIATION MODEL: $nU \rightleftharpoons M$

UNIMERS (U)

MICELLES (M) → (n CHAINS)

$$K_{eq} = \frac{C_m}{C_u^n}$$

(C = TOTAL CONC. OF POLYMER $= nC_m + C_u$)

DEFINE: $X_{2,CMC}$ AS X_2 WHEN $\frac{\partial C_u}{\partial C} = 0.5$

X → MOLE FRACTION

$$\Delta \bar{G}^\circ = \left(\mu_{2,0}^{MIC} - \mu_{2,0}^{UNI}\right) = \text{FREE ENERGY CHANGE PER MOLE TO } U \to M = \Delta \bar{H}^\circ - T\Delta \bar{S}^\circ$$

$$\boxed{\Delta \bar{G}^\circ = -RT \ln K_{eq} \simeq RT \ln X_{CMC}}$$

EMPIRICALLY DETERMINED

$$\Delta \bar{H}^\circ = R \left(\frac{\partial \ln X_{CMC}}{\partial (1/T)}\right)_{P} = \frac{\partial \ln X_2}{\partial (1/T_{CMT})}$$

Determination of thermodynamic driving force for triblock self-assembly

Figure 6 and Table 4 in Alexandridis, P., J. F. Holzwarth, and T. A. Hatton. *Macromolecules* 27 (1994): 2414-2425.

Further Reading

1. Wang, C., Stewart, R. J. & Kopecek, J. (1999) *Nature* **397,** 417-20.
2. Guenet *Thermoreversible Gelation of Polymers and Biopolymers*, New York).
3. Shah, J. C., Sadhale, Y. & Chilukuri, D. M. (2001) *Adv Drug Deliv Rev* **47,** 229-50.
4. Landau, E. M. & Rosenbusch, J. P. (1996) *Proc Natl Acad Sci U S A* **93,** 14532-5.
5. Ron, E. S. & Bromberg, L. E. (1998) *Adv Drug Deliv Rev* **31,** 197-221.
6. Percec, V., Bera, T. K. & Butera, R. J. (2002) *Biomacromolecules* **3,** 272-9.
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9. Salem, A. K., Rose, F. R. A. J., Oreffo, R. O. C., Yang, X., Davies, M. C., Mitchell, J. R., Roberts, C. J., Stolnik-Trenkic, S., Tendler, S. J. B., Williams, P. M. & Shakesheff, K. M. (2003) *Advanced Materials* **15,** 210-213.
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11. Zhang, L., Parsons, D. L., Navarre, C. & Kompella, U. B. (2002) *J Control Release* **85,** 73-81.
12. Jeong, B., Bae, Y. H., Lee, D. S. & Kim, S. W. (1997) *Nature* **388,** 860-2.
13. Chu, B. & Zhou, Z. (1996) in *Nonionic Surfactants: Polyoxyalkylene Block Copolymers*, ed. Nace, V. M. (Marcel Dekker, New York), pp. 67-143.
14. Chu, B. (1995) *Langmuir* **11,** 414-421.
15. Alexandridis, P., Holzwarth, J. F. & Hatton, T. A. (1994) *Macromolecules* **27,** 2414-2425.