Thermodynamics of hydrogel swelling
Applications of hydrogels in bioengineering

Last Day:	Structure of hydrogels
Today:	bioengineering applications of hydrogels Thermodynamics of hydrogel swelling
Reading:	
Supplementary Reading:	P.J. Flory, 'Principles of Polymer Chemistry,' Cornell University Press, Ithaca, pp. 464-469, pp. 576-581 (Statistical thermodynamics of networks and network swelling) P.J. Flory, 'Principles of Polymer Chemistry,' Cornell University Press, Ithaca, pp. 495-507 (Entropy of polymer-solvent mixing)

Announcements:

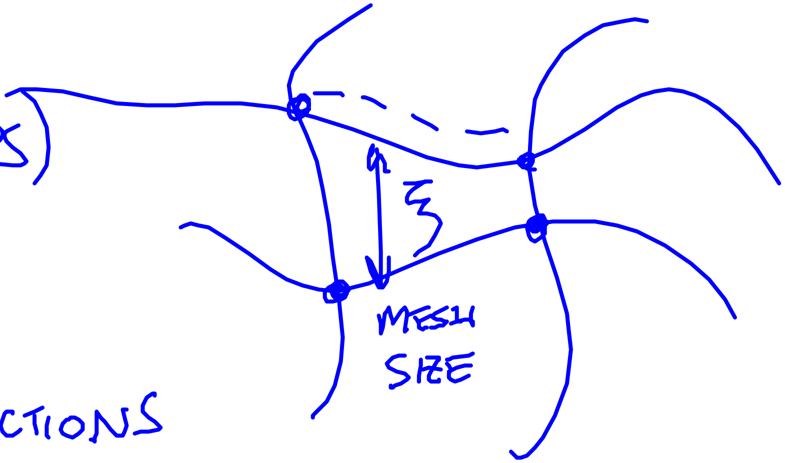
PS 2 DUE 5 pm TODAY (OR TURN IN AFTER CLASS)

PS 3 POSTED LATER TODAY
DUE NEXT THURS.

hydrogels

↳ CROSSLINKED WATER-SWOLLEN POLYMER NETWORK

* COVALENT (COVALENT BONDS)



* PHYSICAL GELS
  - IONIC INTERACTIONS
  - HYDROPHOBIC ASSOCIATIONS / Van der Waals
  - HYDROGEN BONDING
  - (COMBINATIONS)

MOST CRITICAL PARAMETER: SWELLING RATIO. (Q OR S)

$$Q = \frac{V_{POLYMER} + V_{SOLVENT}}{V_{POLYMER}} \longrightarrow \text{DETERMINES } \xi$$

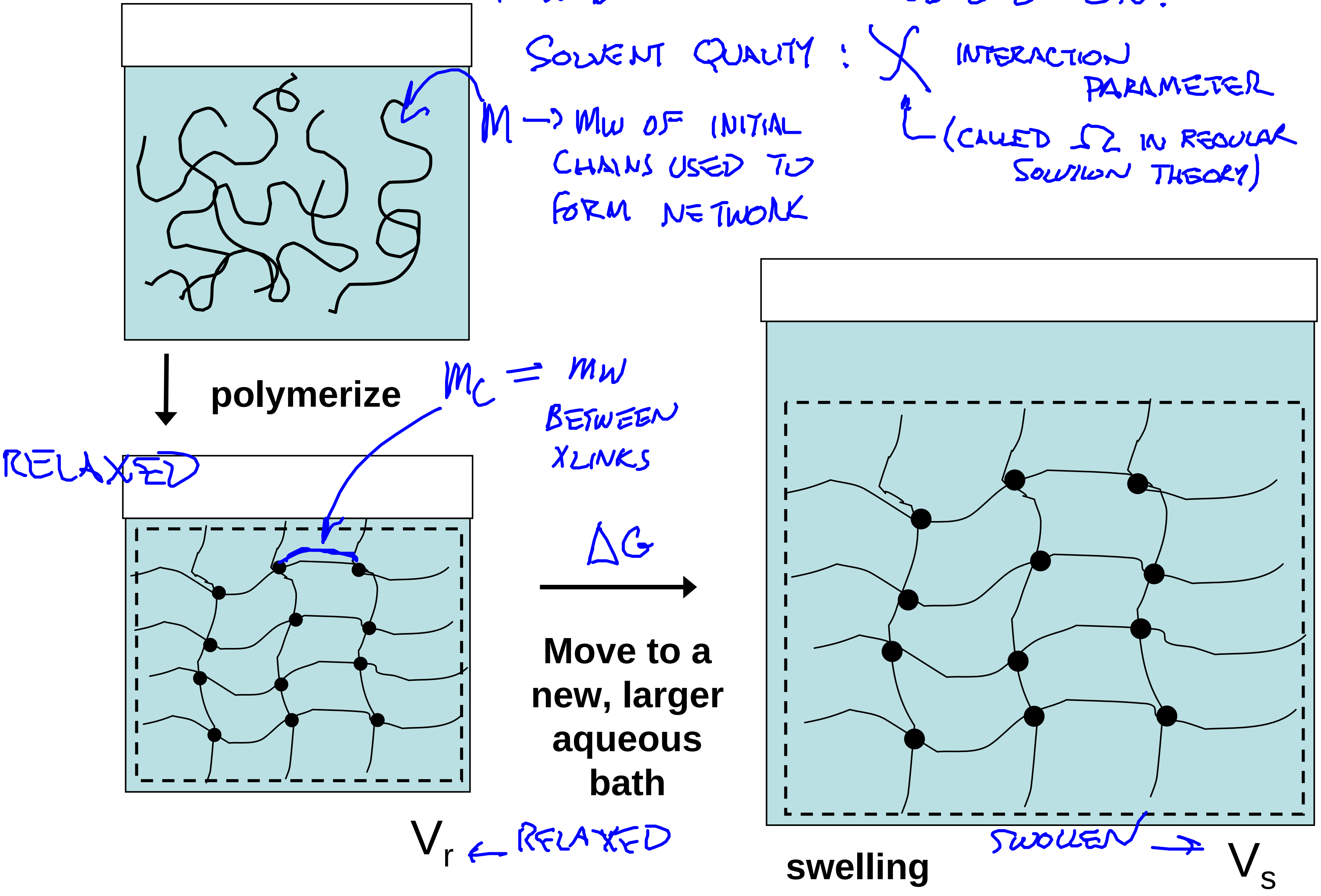
Thermodynamics of hydrogel swelling

HOW DOES SWELLING DEPEND ON:

SOLVENT QUALITY : χ INTERACTION PARAMETER

(CALLED Ω IN REGULAR SOLUTION THEORY)

$M \rightarrow$ MW OF INITIAL CHAINS USED TO FORM NETWORK



polymerize

RELAXED

M_c = MW BETWEEN XLINKS

ΔG

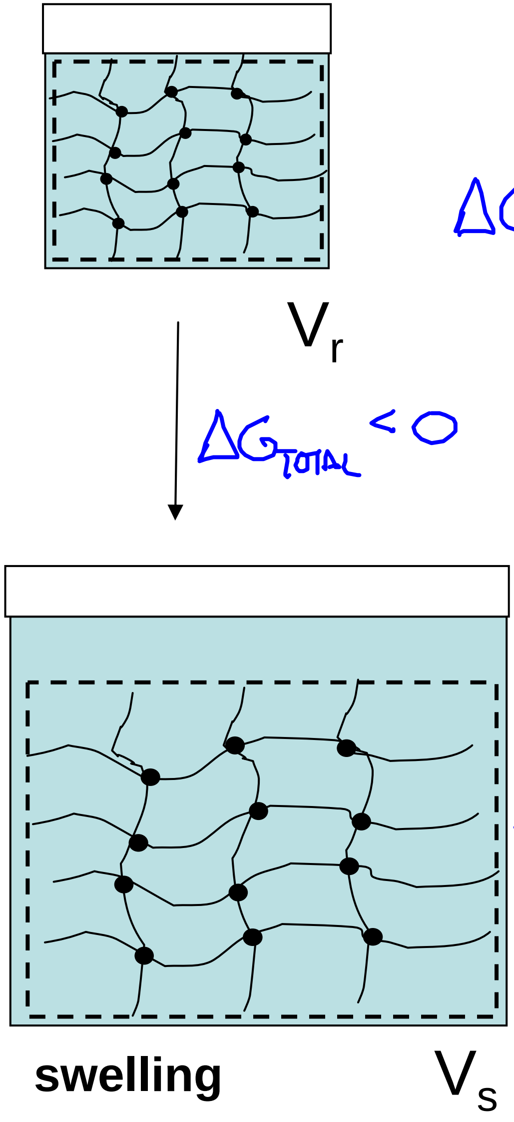
Move to a new, larger aqueous bath

$V_r \leftarrow$ RELAXED

swelling

SWOLLEN $\rightarrow V_s$

Thermodynamics of hydrogel swelling



$\Delta G_{TOTAL} < 0$

Competing driving forces determine total swelling:

$$\Delta G_{TOTAL} = \Delta G_{MIX} + \Delta G_{el}$$

DRIVING SWELLING:

ΔG_{MIX}

- GAIN IN ENTROPY BY MIXING SOLVENT AND POLYMER
- FAVORABLE CONTACTS BETWEEN P + S ALSO POSSIBLE

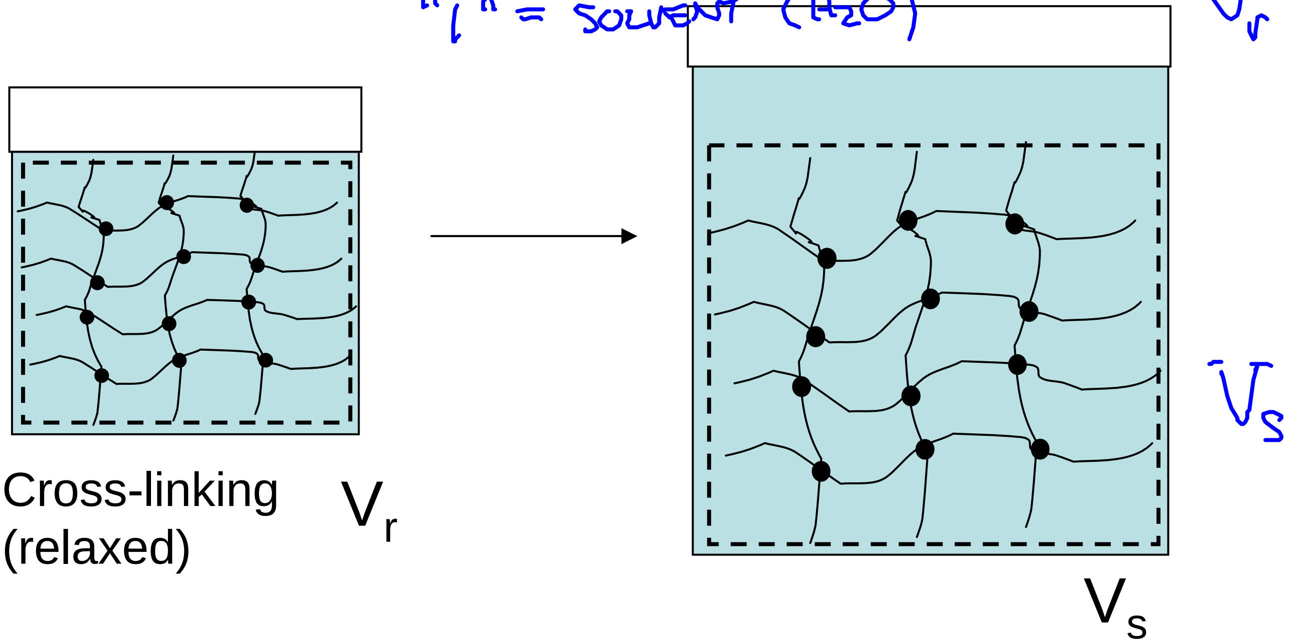
RESISTING SWELLING:

ΔG_{el}

- LOSS IN ENTROPY IN NETWORK CHAINS AS THEY ARE STRETCHED

Description of cross-linked network

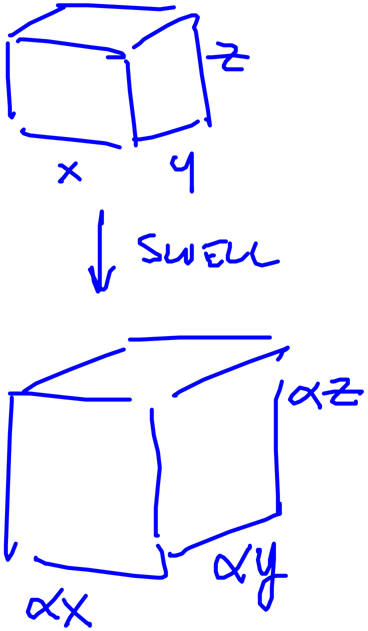
SUBSCRIPTS: "2" = POLYMER
"1" = SOLVENT (H_2O)



Cross-linking (relaxed)

V_r

V_s



Expansion factor: α

ISOTROPIC SWELLING : $\alpha_x = \alpha_y = \alpha_z = \alpha$

$V_{m,1}$ = VOLUME PER MOLECULE

$\alpha_x \alpha_y \alpha_z = \alpha^3 = V_s/Vr = (V_2 + n_1 v_{m,1})/V_r$ swelling

n_1 → # WATER MOLECULES

$\phi_{2,s} = V_2/(V_2 + n_1 v_{m,1})$ volume fraction of polymer in swollen gel

$\phi_{2,r} = V_2/V_r$ volume fraction of polymer in relaxed gel

$Q = \frac{1}{\phi_{2,s}}$

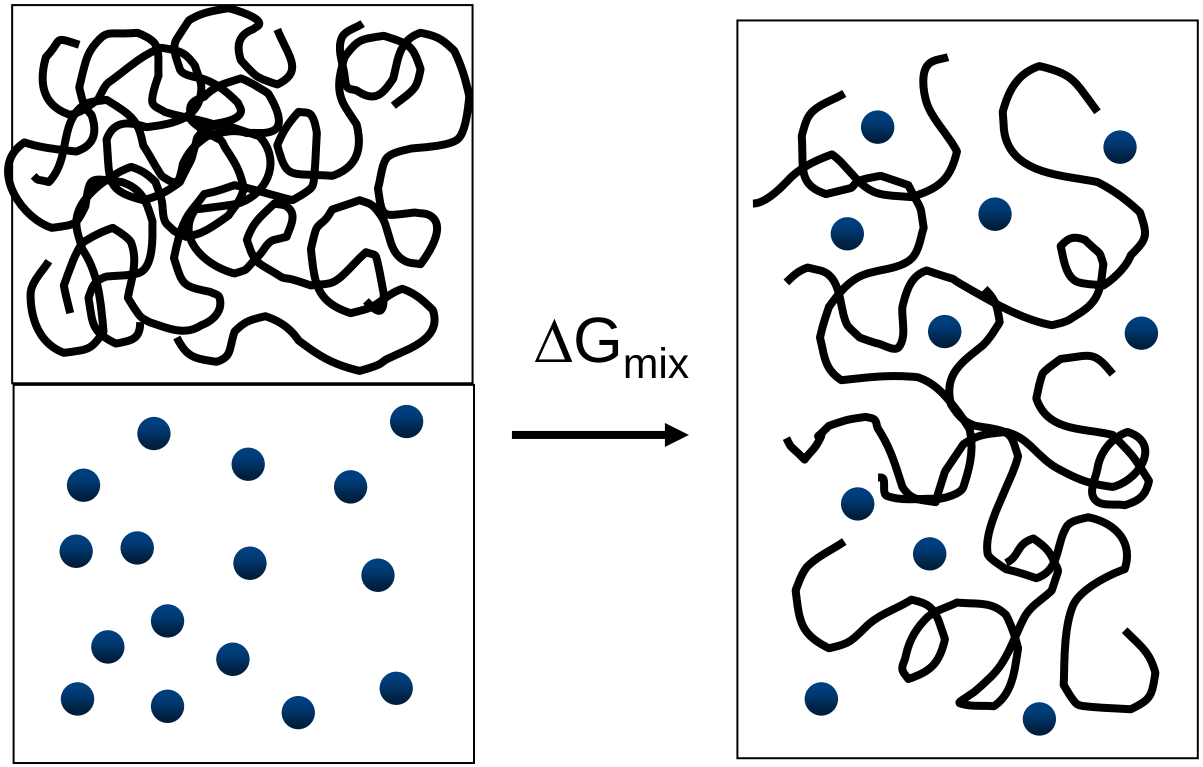
$\frac{V_2}{\text{TOTAL VOL.}}$

Free energy of mixing in the network:

Starting point: thermodynamic description of simple polymer-solvent mixing:

Seek to derive an expression for the free energy of mixing:

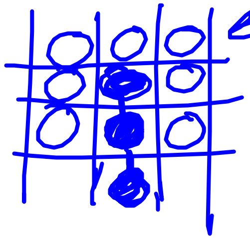
$$\Delta G_{MIX} = \underline{\Delta H_{MIX}} - \underline{T\Delta S_{MIX}} = G_{MIX} - G_{UNMIXED}$$



Free energy of mixing in the network:

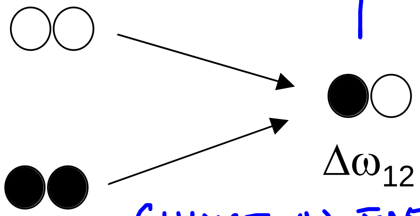
Lattice model description of polymers: (Flory/Huggins)

ENTHALPY OF MIXING:



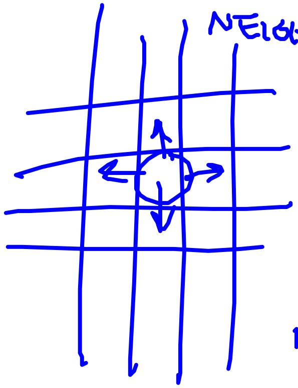
LATTICE OCCUPIED BY EITHER SOLVENT MOLECULES OR POLYMER SEGMENT

Energy of contacts:



CHANGE IN ENERGY ON FORMING A 1-2 CONTACT

z = # NEAREST NEIGHBORS



$$\Delta H_{mix} = \delta \, \Delta\omega_{12}$$

δ = (# 1-2 CONTACTS)

δ = (TOTAL # POLYMER SEGMENTS)(#CONTACTS W/ SOLVENT PER SEGMENT)

$$\delta = (n_2 x)\left[(z)(\phi_{1,s})\right]$$

SEGMENTS PER CHAIN

MEAN FIELD APPROXIMATION

$$n_2 x \phi_1 = n_1 \phi_2$$

$$\delta = z n_1 \phi_{2,s}$$

$$\boxed{\therefore \Delta H_{mix} = z n_1 \phi_{2,s} \Delta\omega_{12}}$$

Free energy of mixing in the network:

Lattice model description of polymers: (Flory/Huggins)

ENTHALPY OF MIXING:

DEFINE INTERACTION PARAMETER χ:

$$\chi \equiv \frac{z \Delta w_{12}}{k_B T}$$

[UNITLESS ENERGY]

BOLTZMANN CONSTANT

$$\therefore \boxed{\Delta H_{mix} = k_B T \, n_1 \phi_{2,s} \chi}$$

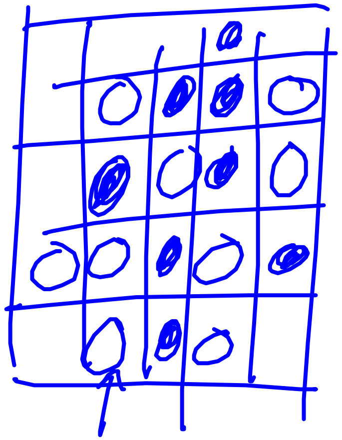
Free energy of mixing in the network:

Lattice model description of polymers: (Flory/Huggins)

ENTROPY OF MIXING: $S = k_b \ln \Omega$

UNIQUE!

CONFIGURATIONS POSSIBLE



A AND B

AND TOTAL

MOLECULES $n = n_A + n_B$

Ω = # WAYS TO FILL LATTICE

STIRLING'S APPROXIMATION:

$$\Omega = \frac{n!}{n_A! \, n_B!} \Longrightarrow \ln N! \approx N \ln N - N$$

$$S = -k_b \left[n_A \ln x_A + n_B \ln x_B \right]$$

x_A = MOLE FRACTION A $= \dfrac{n_A}{n_A + n_B}$

Free energy of mixing in the network:

Lattice model description of polymers: (Flory/Huggins)

ENTROPY OF MIXING:

$$S = k_b \ln \Omega$$

↓

Ω = # STATES

$$\Delta S_{mix} = S_{MIXED} - S_{UNMIXED} = k_b \ln \frac{\Omega_{MIXED}}{\Omega_{UNMIXED}}$$

Image removed due to copyright reasons. Please see: Figure 110 in Flory, P. J. *Principles of Polymer Chemistry.* Ithaca, NY: Cornell University Press, 1953.

$$\Delta S_{MIX} = -k_b \left[n_1 \ln \phi_{1,s} + n_2 \ln \phi_{2,s} \right]$$

↑

FOR A SOLUTION OF POLYMER + SOLVENT

$$\phi_{1,s} = \text{VOLUME FRACTION OF SOLVENT} = \frac{n_1}{n_1 + n_2 X}$$

FOR GEL: $n_2 \cong 0$ (NO FREE POLYMER CHAINS)

$$\boxed{\Delta S_{MIX}^{GEL} \cong -k_b \, n_1 \ln \phi_{1,s}}$$

Free energy of mixing in the network:

Lattice model description of polymers: (Flory/Huggins)

:

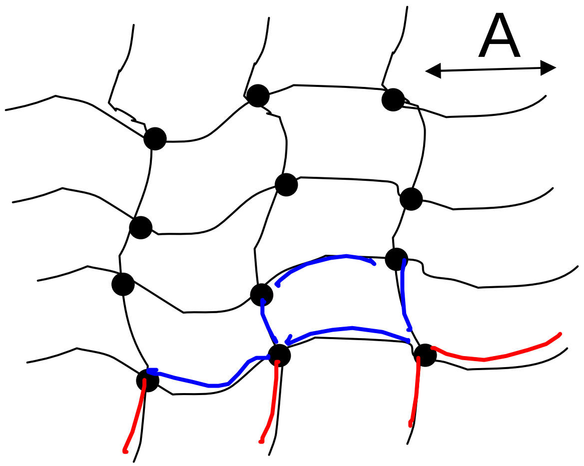
TOTAL FREE ENERGY OF MIXING:

$$\Delta G_{MIX}^{GEL} = \Delta H_{MIX} - T\Delta S_{MIX}$$

$$= k_B T\, n_1 \phi_{2,s} \chi - T\left[-k_b n_1 \ln \phi_{1,s}\right]$$

$$\boxed{\Delta G_{MIX}^{GEL} = k_B T\left[n_1 \ln \phi_{1,s} + n_1 \phi_{2,s} \chi\right]}$$

Description of cross-linked network



Assume cross-links are randomly placed; on average, all are equidistant:

ν = number of subchains in cross-linked network

ν_e = number of **'effective'** subchains: tethered at both ends

M = MW of original chains

M_c = MW of subchains = MW between cross-links

Example: assume polymer chains have a molecular weight M = 4A and each 'subchain' has molecular weight A:

Two useful relationships:

SPECIFIC VOL. OF POLYMER

~~$\nu = V_2/v_{sp,2}M_c$~~

$$\nu = \frac{V_2 N_{AV}}{V_{sp,2} M_C}$$

cm^3

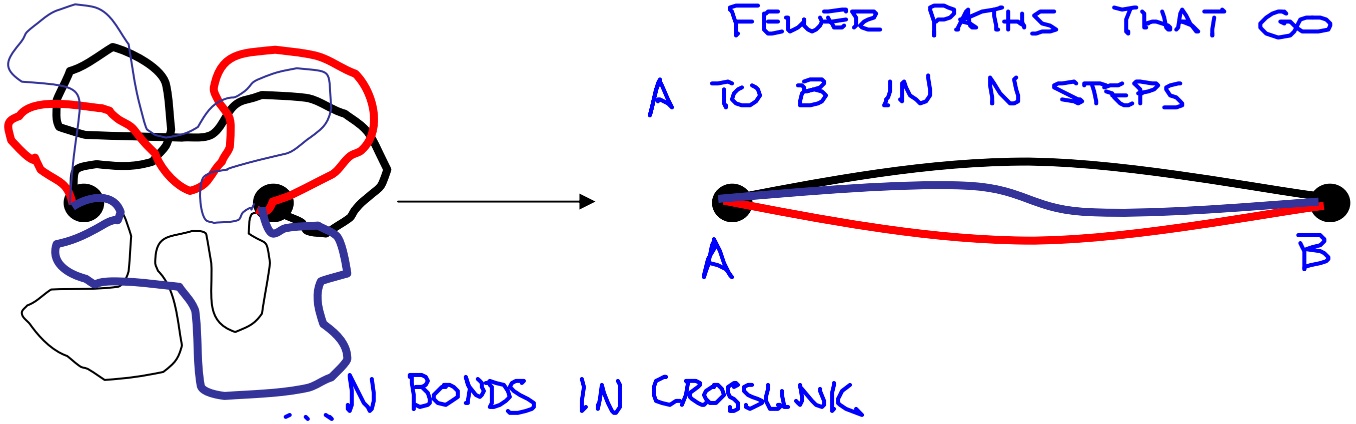
$\frac{cm^3}{g}$

$\frac{g}{mole}$

$\nu_e = \nu(1 - 2(M_c/M))$

Elastic contribution to hydrogel free energy: ΔG_{el} (RUBBER ELASTICITY THEORY)

- Account for entropic retraction force that restrains swelling:



FEWER PATHS THAT GO FROM A TO B IN N STEPS

$\Delta G_{el} > 0$

...N BONDS IN CROSSLINK

$\Delta G_{el} = -T\Delta S_{el}$ (NO ENTHALPIC COMPONENT)

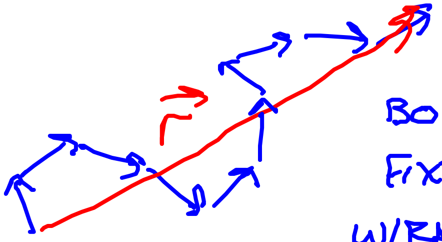
↳ $S = k_b \ln \Omega$

RELAXED STATE

STRETCHED STATE

Elastic contribution to hydrogel free energy: ΔG_{el}

TREAT POLYMER COILS AS "FREELY JOINTED CHAINS":



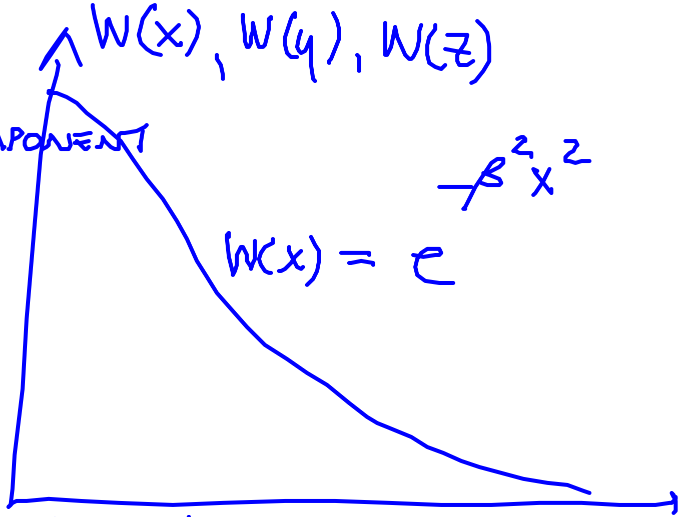
N BONDS OF FIXED LENGTH l W/RANDOM ORIENTATION

PROB. OF A GIVEN x, y, z COMPONENT ~~DISTANCE~~ TO $\vec{r}$

$\vec{r}$ = END-TO-END DISTANCE

$$\underbrace{}$$

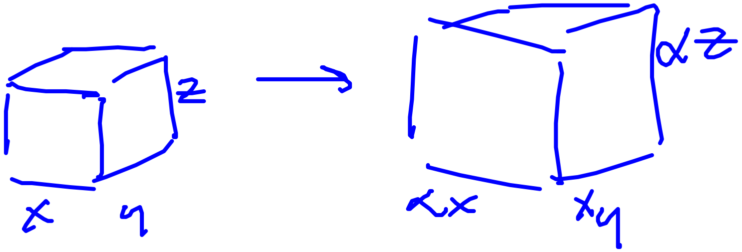
GAUSSIAN DISTRIBUTION FUNCTION FOR END-TO-END DISTANCE



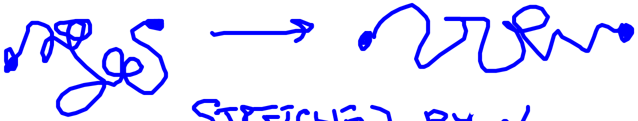
$$W(x) = e^{-\beta^2 x^2}$$

$$\beta \equiv \sqrt{\frac{3}{2}}\,\frac{1}{N^{1/2} l}$$

$W(x)\,W(y)\,W(z) \rightarrow$ DIRECTLY RELATES TO $\underline{\Omega}$



INDIVIDUAL CHAINS <u>MUST</u> UNDERGO SAME DEFORMATION



STRETCHED BY α

Elastic contribution to hydrogel free energy: ΔG_{el}

PROBABILITY THAT A CHAIN HAS $\vec{r}(\alpha x, \alpha y, \alpha z)$ AFTER SWELLING = PROB. THAT CHAIN STARTED w/ $\vec{r}(x,y,z) \propto W(x)W(y)W(z)$ BEFORE SWELLING

$W(x)W(y)W(z)$

↓

Ω IS DETERMINED AS A PRODUCT OF ALL POSSIBLE PROBABILITIES FOR EACH POSSIBLE $\vec{r}$ (SEE FLORY SUPPLEMENTAL READING)

↓

$$\Delta S_{el} = S_{SWOLLEN} - S_{RELAXED} = k_b \ln \frac{\Omega_{SWOLLEN}}{\Omega_{RELAXED}}$$

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

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

Complete expression for the free energy of the gel:

$$\Delta G_{TOTAL} = \Delta G_{mix} + \Delta G_{el} =$$ FREE ENERGY CHANGE AS H_2O ENTERS GEL

CLOSED SYSTEM @ CONSTANT T, P/V : FREE ENERGY IS MINIMIZED AND SYSTEM IS AT EQUILIBRIUM WHEN CHEMICAL POTENTIAL OF H_2O IS THE SAME INSIDE AND OUTSIDE THE GEL:

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

STD STATE

CHEM. POT. IN GEL

$$\mu_1^{\circ} = \mu_1$$

$$\mu_1 \equiv \left(\frac{\partial G}{\partial n_1}\right)_{T,P,n_{i\neq 1}}$$

$$\underbrace{\mu_1 - \mu_1^{\circ}} = 0$$

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

$$\Delta(\mu_1)_{mix} = \left(\frac{\partial \Delta G_{mix}}{\partial n_1}\right)_{T,P,n_2}$$

$$\Delta(\mu_1)_{el} = \left(\frac{\partial \Delta G_{el}}{\partial n_1}\right)_{T,P,n_2}$$

Complete expression for the free energy of the gel:

$$(\Delta\mu_1)_{mix} = \left(\frac{\partial \Delta G_{mix}}{\partial n_1}\right)_{T,P,n_2} = \frac{\partial}{\partial n_1}\left[k_B T\left[n_1 \ln\phi_1 + \chi n_1 \phi_2\right]\right]$$

$$= \frac{\partial}{\partial n_1}\left[k_B T\left[n_1 \ln\phi_1 + \chi \frac{n_1 n_2 x}{n_1 + n_2 x}\right]\right]$$

$$= k_B T\left[\ln(1-\phi_2) + 1 - 1 + \phi_2 + \chi\phi_2 - \chi\phi_2 + \chi\phi_2^2\right]$$

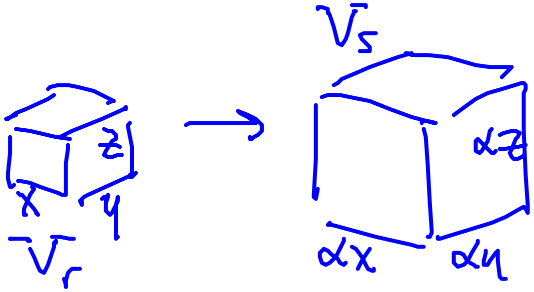
$$\boxed{(\Delta\mu_1)_{mix} = k_B T\left[\ln(1-\phi_2) + \phi_2 + \chi\phi_2^2\right]}$$

Complete expression for the free energy of the gel:

$$(\Delta\mu_1)_{el} = \left(\frac{\partial \Delta G_{el}}{\partial n_1}\right)_{T,P}$$

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

DEPENDENCE ON n_1?



$$\alpha^3 = \frac{\bar{V}_s}{\bar{V}_r} = \frac{\bar{V}_2 + n_1 v_{m,1}}{\bar{V}_r} = \frac{\Phi_{2,r}}{\Phi_{2,s}}$$

$$\therefore (\Delta\mu_1)_{el} = \left(\frac{\partial \Delta G_{el}}{\partial \alpha}\right)_{T,P,n_2} \left(\frac{\partial \alpha}{\partial n_1}\right)_{T,P,n_2}$$

$$\left(\frac{\partial \alpha}{\partial n_1}\right)_{T,P,n_2} = \frac{1}{3}\left(\frac{V_2 + n_1 v_{m,1}}{\bar{V}_r}\right)^{-2/3} \frac{v_{m,1}}{\bar{V}_r} = \frac{v_{m,1}}{3\alpha^2 \bar{V}_r}$$

$$\left(\frac{\partial \Delta G_{el}}{\partial \alpha}\right)_{T,P,n_2} = \frac{3}{2} k_B T \nu_e \left[2\alpha - \frac{1}{\alpha}\right]$$

Complete expression for the free energy of the gel:

$$\therefore (\Delta\mu_1)_{el} = k_B T \nu_e \left(\frac{V_{m,1}}{V_r}\right)\left(\alpha - \frac{1}{2\alpha}\right)\frac{1}{\alpha^2} = k_B T \nu_e \left(\frac{V_{m,1}}{V_r}\right)\left(\frac{1}{\alpha} - \frac{1}{2\alpha^3}\right)$$

$\downarrow$ SUBSTITUTE: $\nu_e = \nu\left(1 - 2\frac{M_c}{M}\right)$

$$(\Delta\mu_1)_{el} = k_B T \nu \left(1 - 2\frac{M_c}{M}\right)\frac{V_{m,1}}{V_r}\left[\left(\frac{\phi_{2,s}}{\phi_{2,r}}\right)^{1/3} - \frac{1}{2}\left(\frac{\phi_{2,s}}{\phi_{2,r}}\right)\right]$$

$$\alpha^3 = \frac{\phi_{2,r}}{\phi_{2,s}}$$

Complete expression for the free energy of the gel:

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

$$k_B T\left[\underbrace{\ln\phi_1 + \phi_{2,s} + \chi\phi_{2,s}^2}_{(\Delta\mu_1)_{mix}} + \underbrace{\nu\left(1-2\frac{M_c}{M}\right)\frac{V_{m,1}}{V_r}\left[\left(\frac{\phi_{2,s}}{\phi_{2,r}}\right)^{1/3} - \frac{1}{2}\left(\frac{\phi_{2,s}}{\phi_{2,r}}\right)\right]}_{(\Delta\mu_1)_{el}}\right] = 0$$

REARRANGE:

$$\boxed{\frac{1}{M_c} = \frac{2}{M} - \frac{v_{sp,2}}{\bar{V}_1}\,\frac{\left[\ln(1-\phi_{2,s}) + \phi_{2,s} + \chi\phi_{2,s}^2\right]}{\phi_{2,r}\left[\left(\frac{\phi_{2,s}}{\phi_{2,r}}\right)^{1/3} - \frac{1}{2}\left(\frac{\phi_{2,s}}{\phi_{2,r}}\right)\right]}}$$

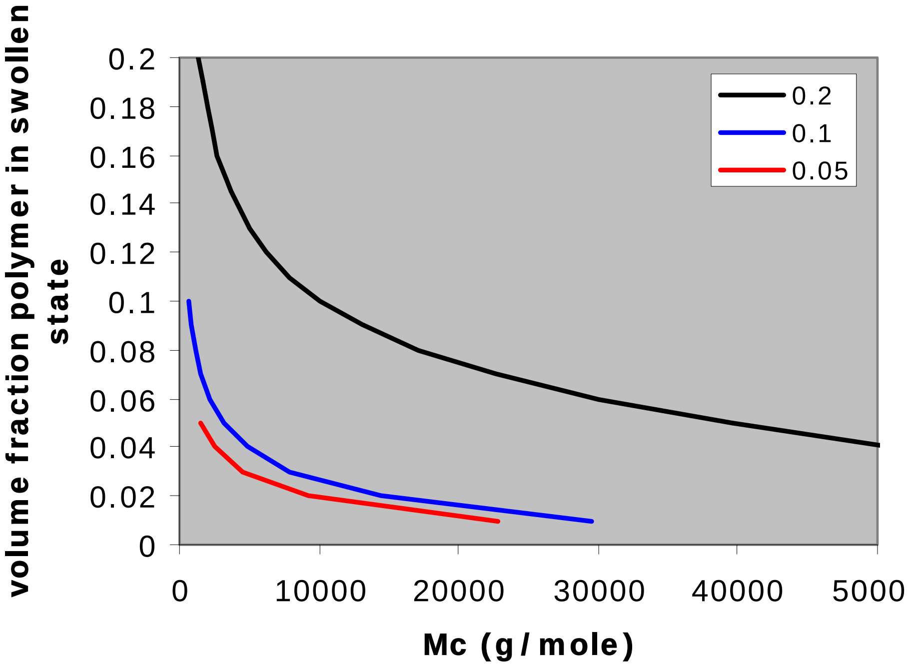
$$\underbrace{\nu = \frac{\bar{V}_2 N_{Av}}{v_{sp,2} M_c}}$$

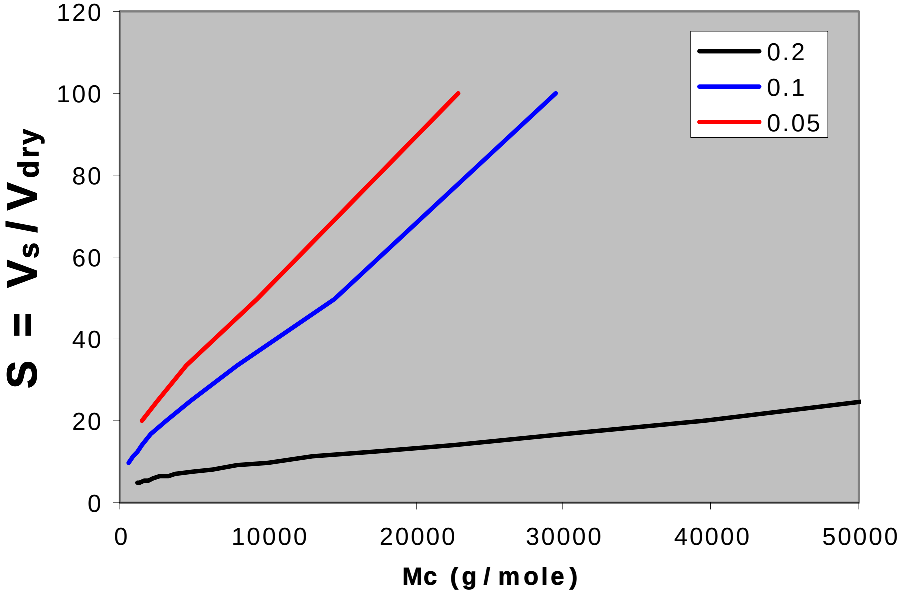
$$\frac{\bar{V}_r}{V_{m,1}\nu} = \frac{v_{sp,2}M_c}{V_{m,1}\phi_{2,r}N_{Av}} = \frac{v_{sp,2}M_c}{\bar{V}_1\phi_{2,r}}$$

↑ MOLAR VOLUME OF SOLVENT

Predictions of Flory/Peppas theory

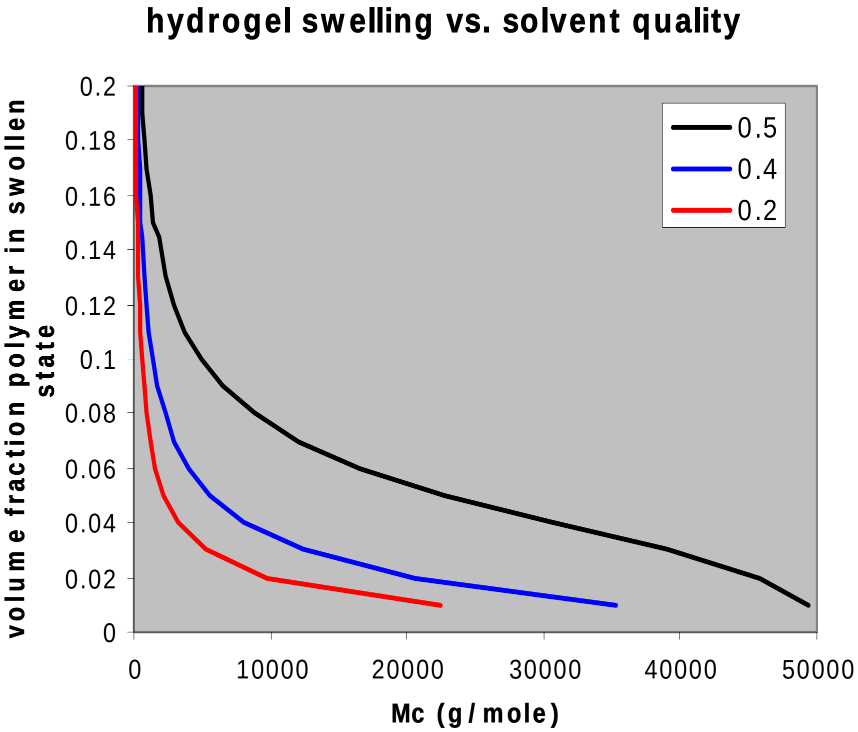
Varying $\phi_{2,r}$:

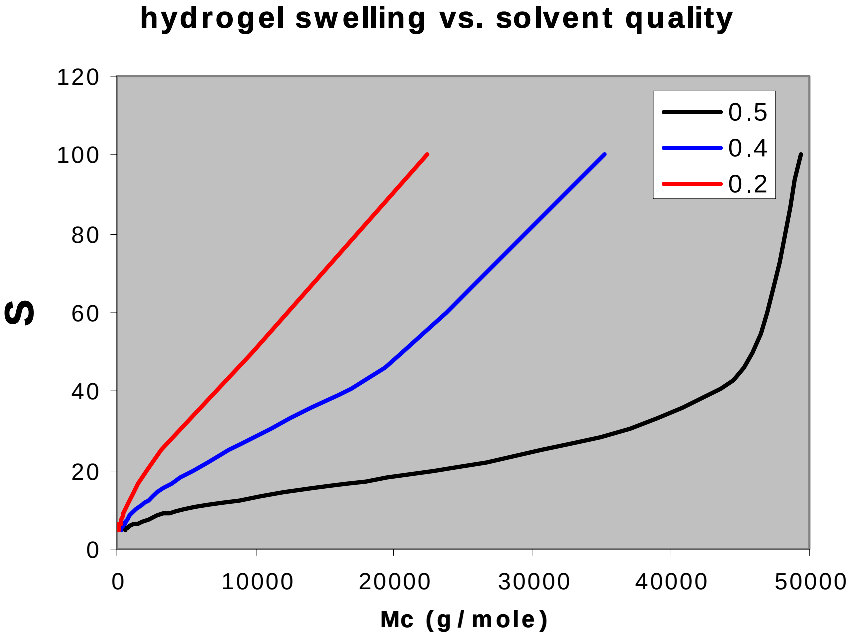




Predictions of Flory/Peppas theory

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)
$v_{m,1}$	molar volume of solvent (water)
$v_{m,2}$	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

Key properties of hydrogels for bioengineering applications:

- EASILY CHEMICALLY MODIFIED
- IN SITU FORMABILITY
  - $h\nu$ UV IRRADIATION
  - ΔT TEMP.
  - CROSSLINKING ENZYMES
  - PRESENCE OF DIVALENT SALTS
- DEGRADABILITY
- RESPONSIVE SWELLING
  - 'SMART' DEVICES
- SOFT TISSUE-LIKE STRUCTURE/PROPERTIES

Further Reading

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2. Flory, P. J. & Rehner Jr., J. Statistical mechanics of cross-linked polymer networks. I. Rubberlike elasticity. *J. Chem. Phys.* **11**, 512-520 (1943).
3. Peppas, N. A. & Merrill, E. W. Polyvinyl-Alcohol) Hydrogels - Reinforcement of Radiation-Crosslinked Networks by Crystallization. *Journal of Polymer Science Part a-Polymer Chemistry* **14**, 441-457 (1976).
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5. An, Y. & Hubbell, J. A. Intraarterial protein delivery via intimally-adherent bilayer hydrogels. *J Control Release* **64**, 205-15 (2000).
6. Brannonpeppas, L. & Peppas, N. A. Equilibrium Swelling Behavior of Ph-Sensitive Hydrogels. *Chemical Engineering Science* **46**, 715-722 (1991).
7. Chiellini, F., Petrucci, F., Ranucci, E. & Solaro, R. in *Biomedical Polymers and Polymer Therapeutics* (eds. Chiellini, E., Sunamoto, J., Migliaresi, C., Ottenbrite, R. M. & Cohn, D.) 63-74 (Kluwer, New York, 1999).
8. Hubbell, J. A. Hydrogel systems for barriers and local drug delivery in the control of wound healing. *Journal of Controlled Release* **39**, 305-313 (1996).
9. Jen, A. C., Wake, M. C. & Mikos, A. G. Review: Hydrogels for cell immobilization. *Biotechnology and Bioengineering* **50**, 357-364 (1996).
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11. Peppas, N. A., Huang, Y., Torres-Lugo, M., Ward, J. H. & Zhang, J. Physicochemical foundations and structural design of hydrogels in medicine and biology. *Annu Rev Biomed Eng* **2**, 9-29 (2000).