# Hydrogel Biomaterials: Structure and thermodynamics

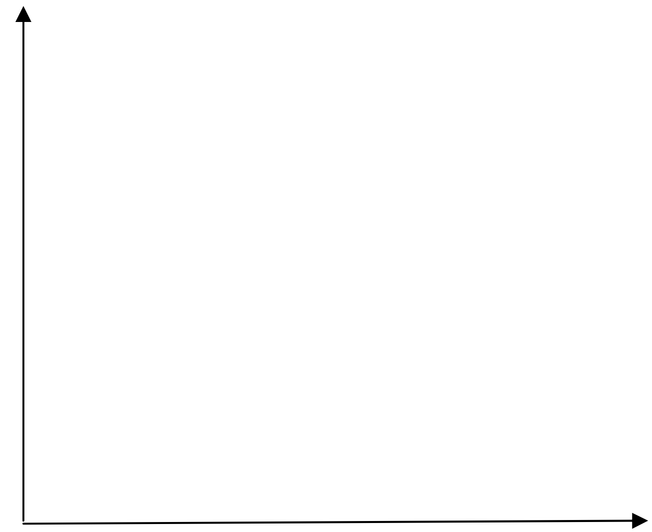
**Last Day:** programmed/regulated/multifactor controlled release for drug delivery and tissue engineering

**Today:**
Finish discussion of programmed release materials
Structure of hydrogels, basic chemistry of covalent hydrogels
Physical properties of hydrogels for biomedical applications

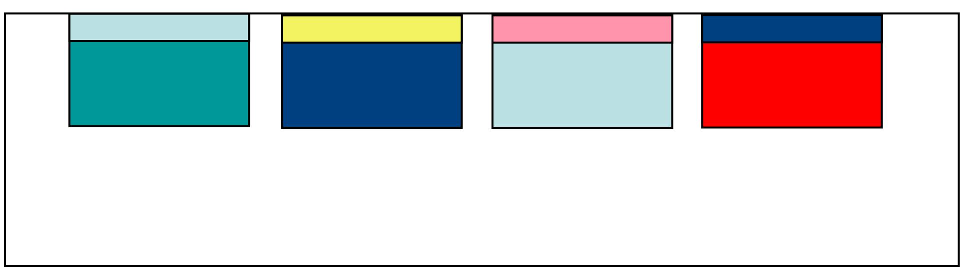
**Reading**: N.A. Peppas et al., 'Physicochemical foundations and structural design of hydrogels in medicine and biology,' *Annu. Rev. Biomed. Eng.*, **2**, 9-29 (2000).

## Announcements:

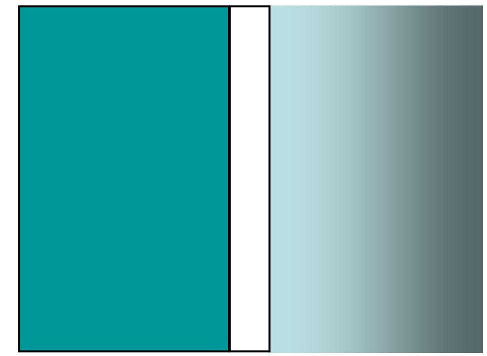
# Biodegradable programmed burst release chips



Richards-Grayson, A. C., I. S. Choi, B. M. Tyler, P. P. Wang, H. Brem, M. J. Cima, and R. Langer. "Multi-pulse Drug Delivery from a Resorbable Polymeric Microchip Device." *Nature Materials* 2 (2003): 767-772.



# Biodegradable programmed burst release chips



# Controlled release in tissue engineering/regenerative medicine

**Nerve TE paradigms:**

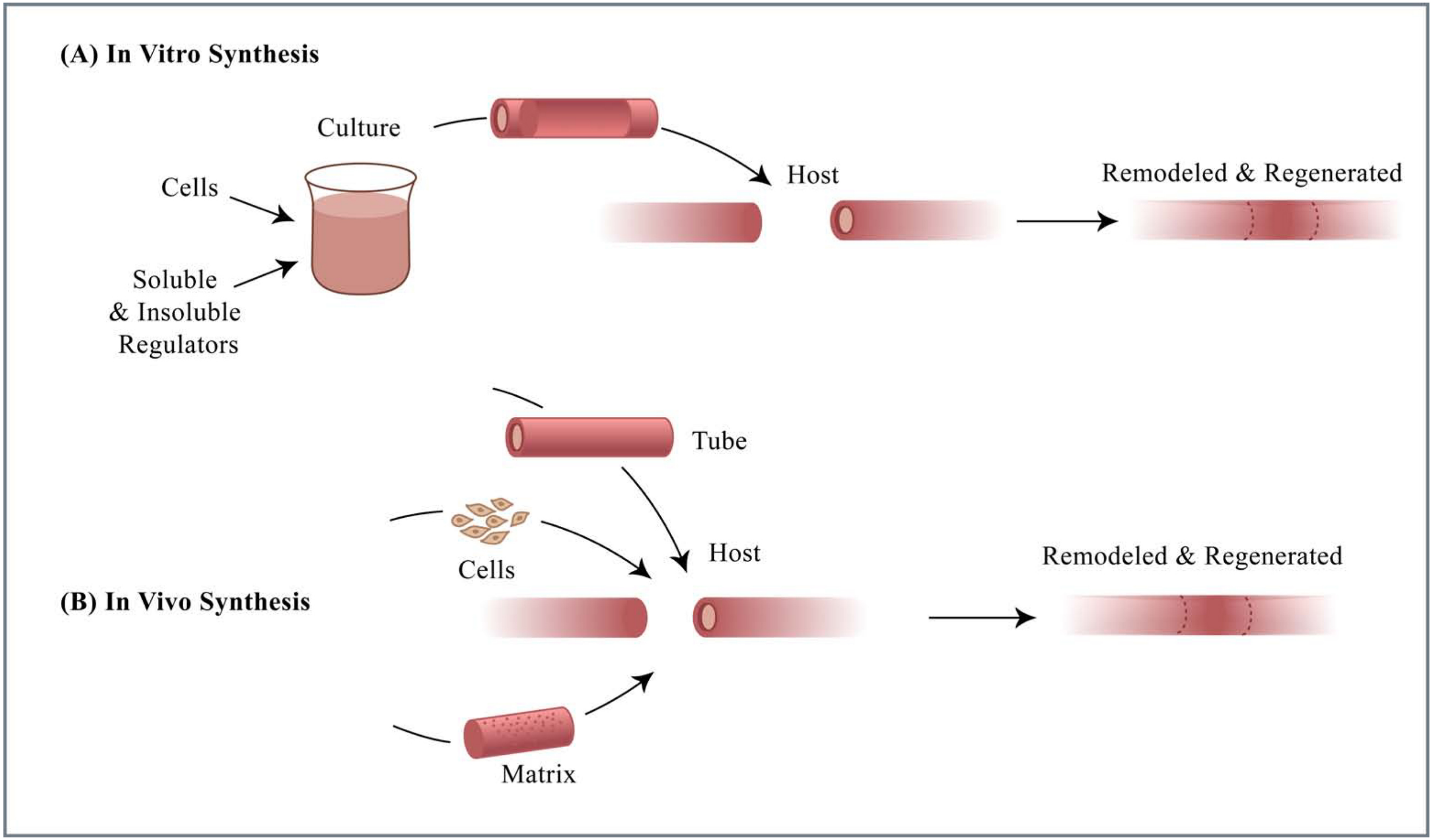



Figure by MIT OCW.

# Controlled release in tissue engineering/regenerative medicine

**Skin TE paradigms:**

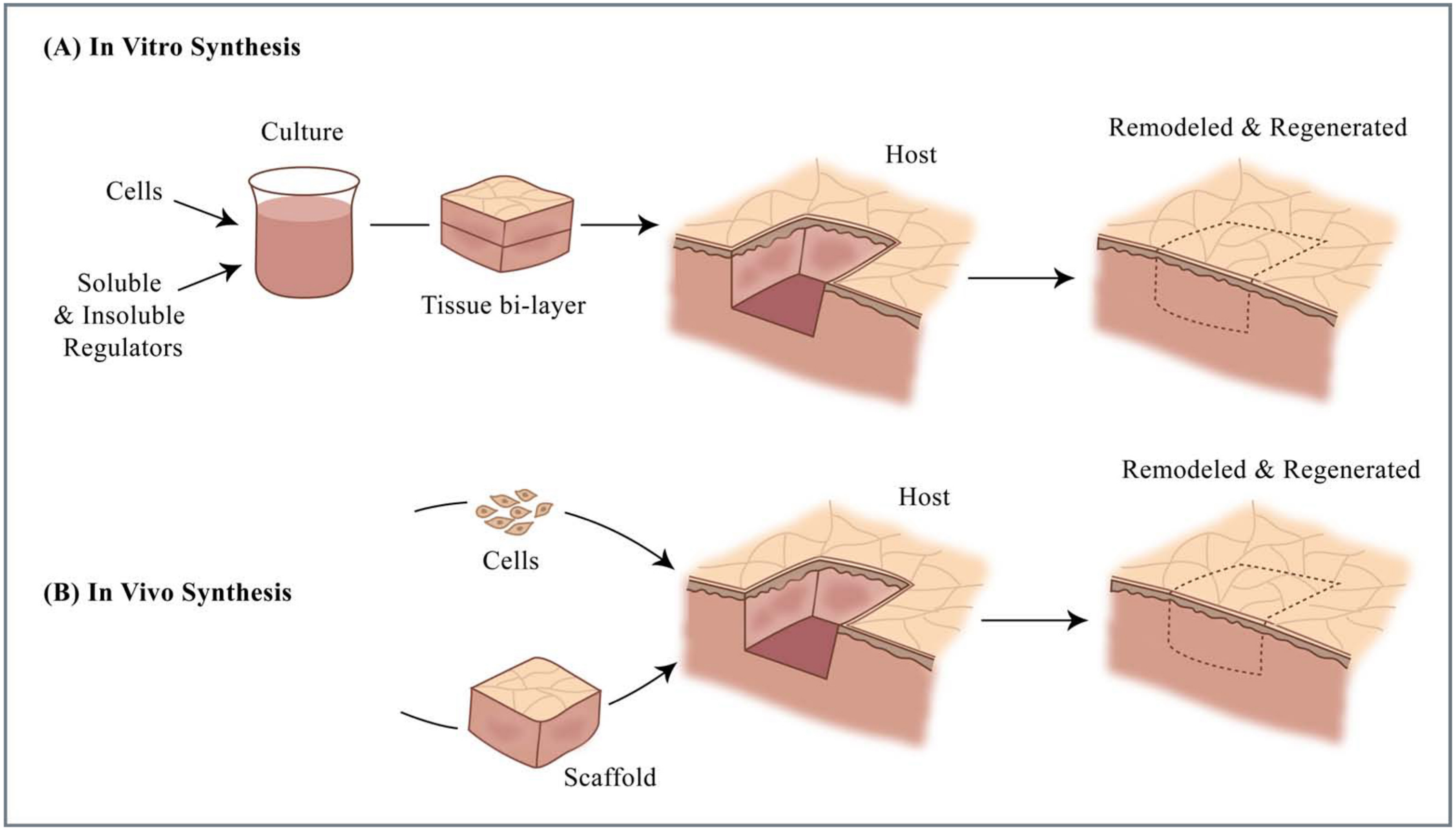
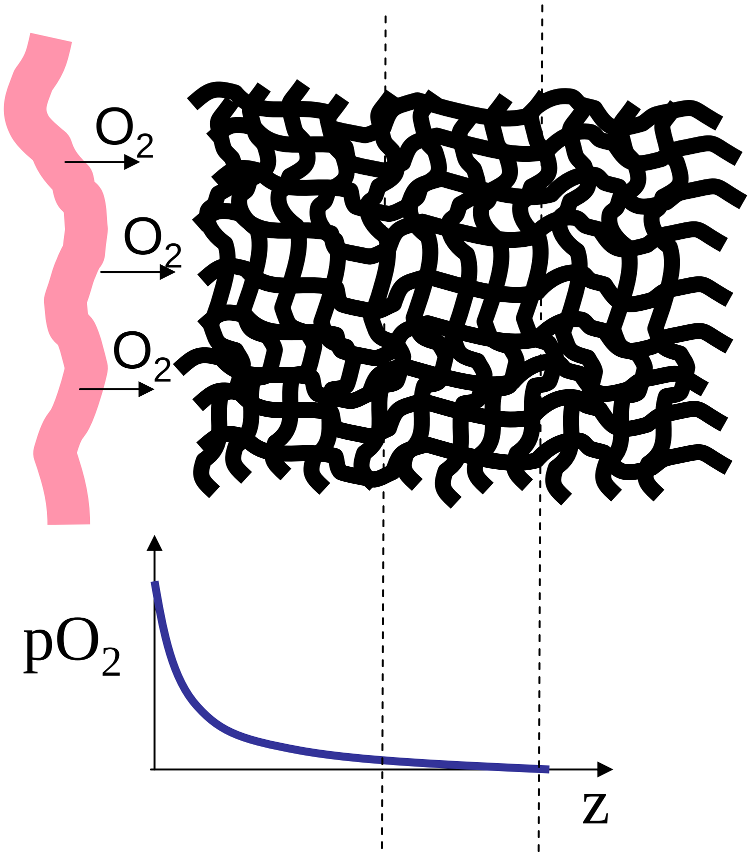



Figure by MIT OCW.



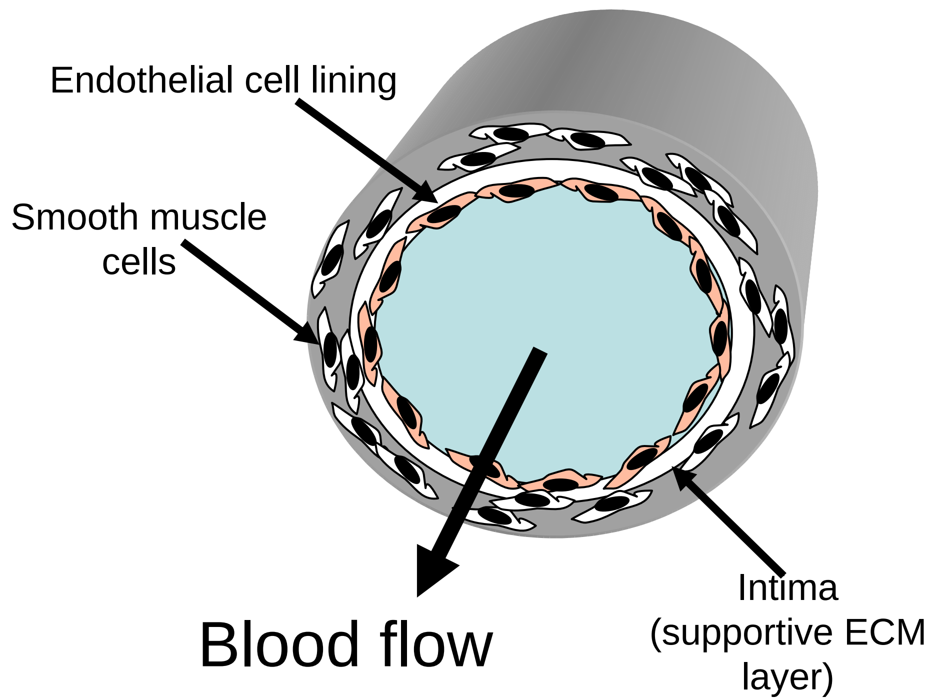
(I. Yannas)

# Challenge of providing blood supply to macroscopic engineered tissues



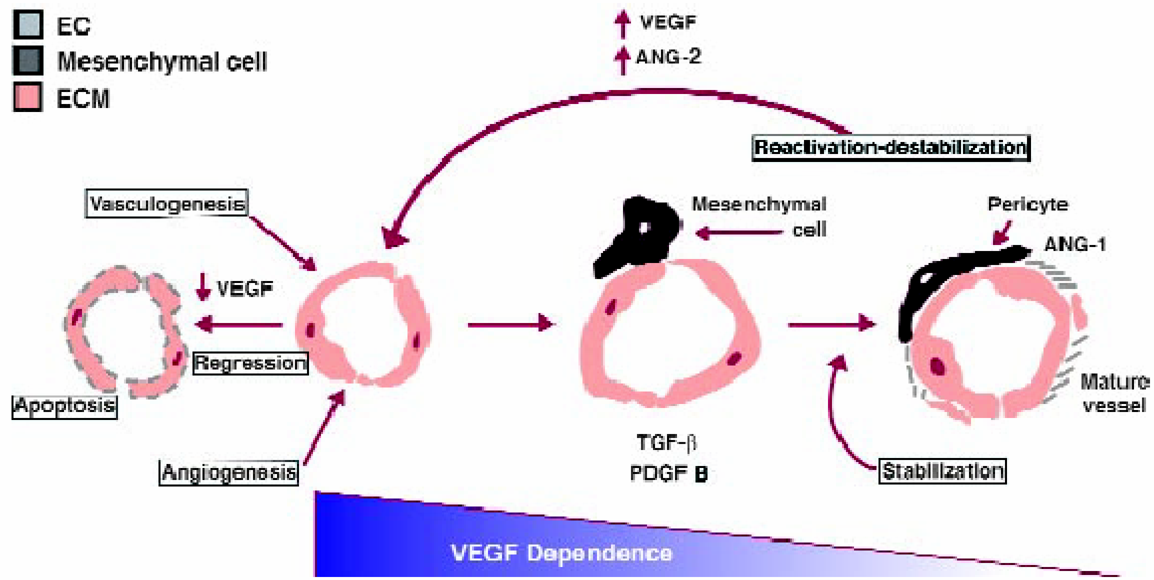

Extensive cell death
in center of construct

**blood vessel structure:**



# Case study: controlled release of multiple cytokines from a TE scaffold to drive angiogenesis

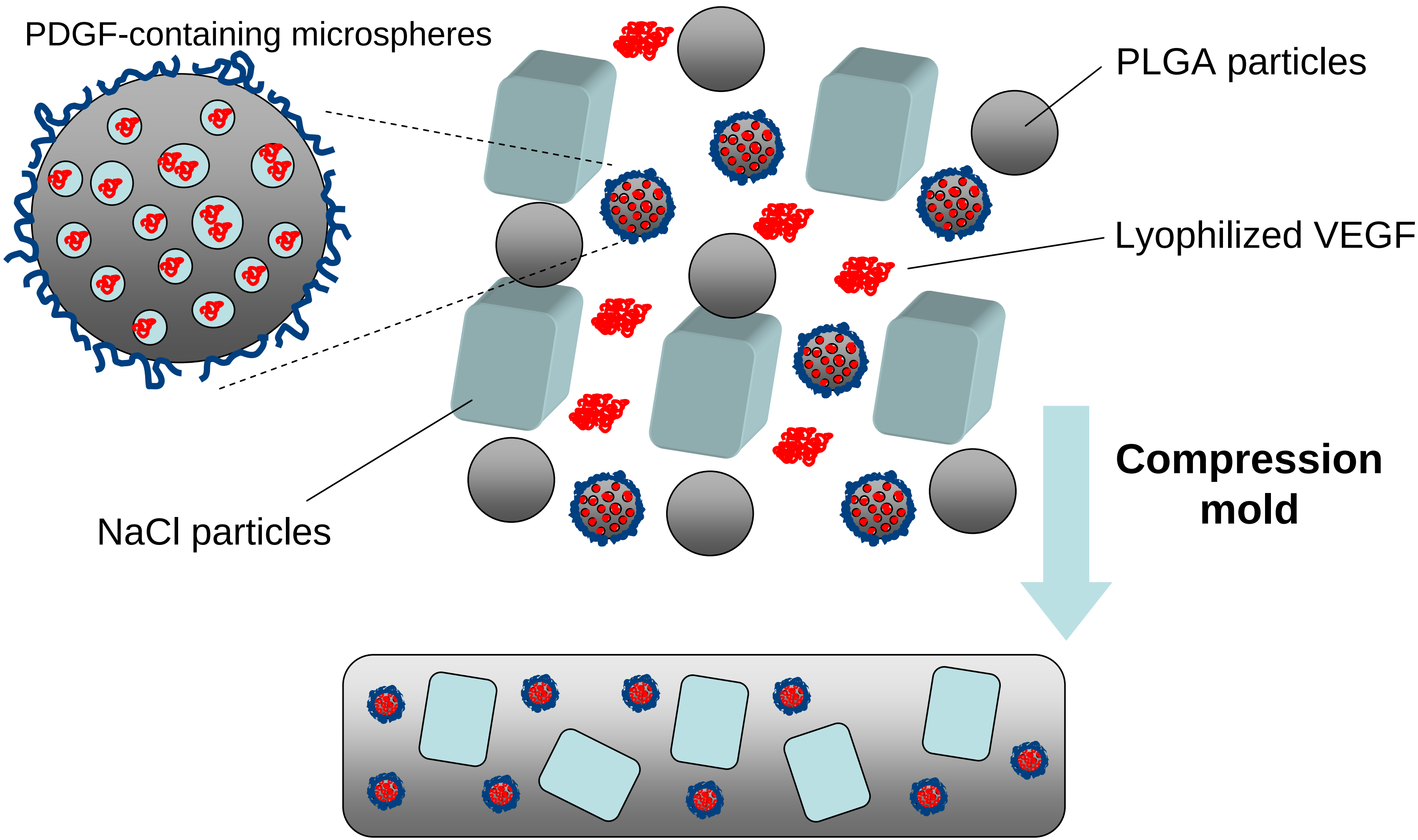
**Figure 1**
Vessel maturation: vessel development proceeds from a stage of growth-factor dependence where loss of a survival factor leads to apoptosis. Vessel stabilization is marked by investment with mural cells, local activation of TGF-β, and basement membrane production. The angiopoietins are clearly implicated, though their precise roles are yet to be determined.



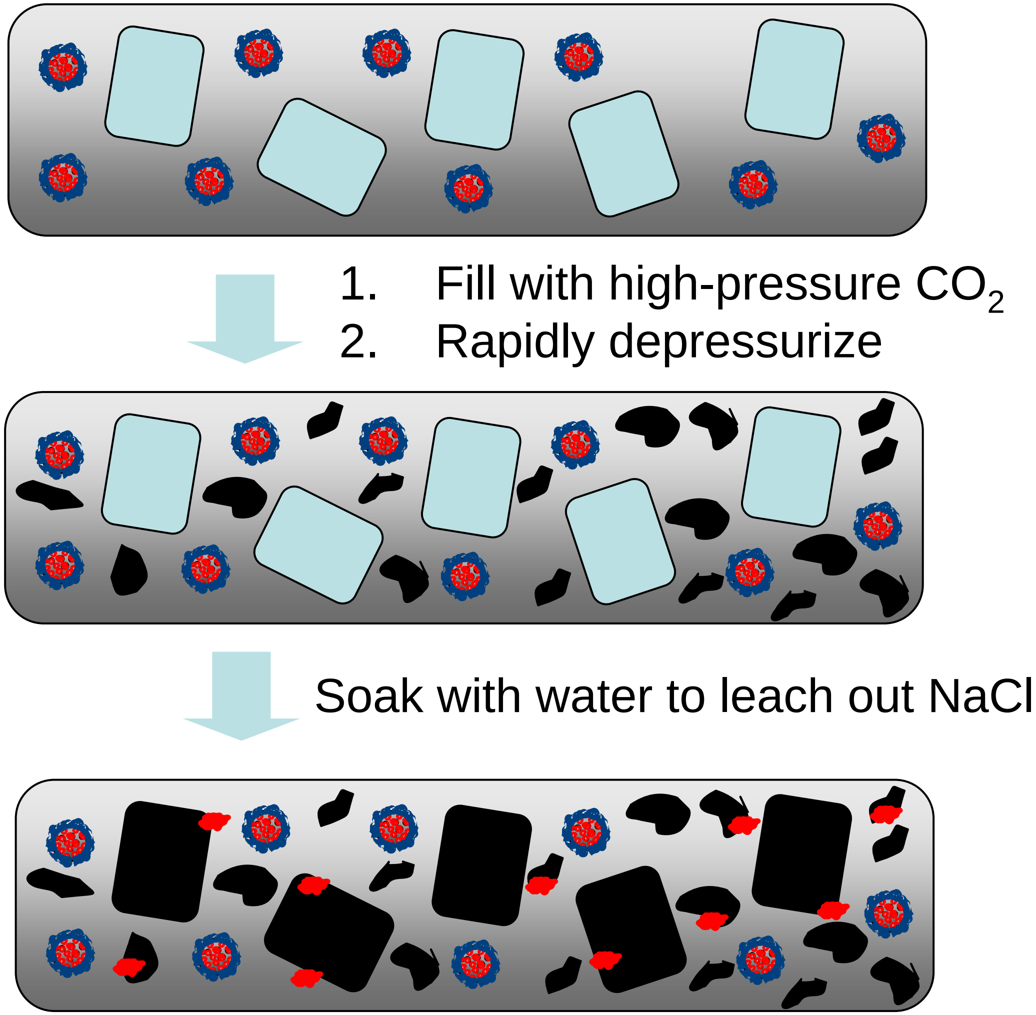

**Steps in angiogenesis:**

1. VEGF (vascular endothelial growth factor)
   - -attracts endothelial cells, induces proliferation
   - -induces tube formation
2. PDGF (platelet-derived growth factor)
   - -attracts smooth muscle cells, stabilizes new vessels

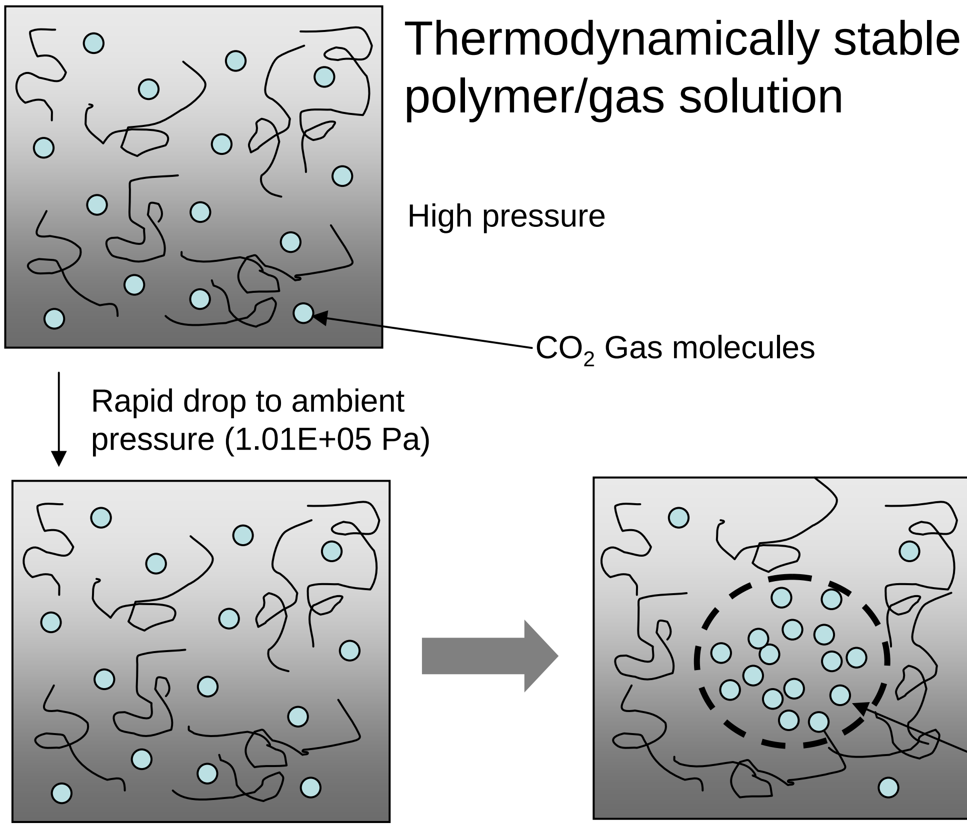
# Fabricating dual-factor delivery microstructures



# Fabricating dual factor-delivery microstructures



# Gas nucleation by generating thermodynamic instability in polymer/gas solution



Thermodynamically stable polymer/gas solution

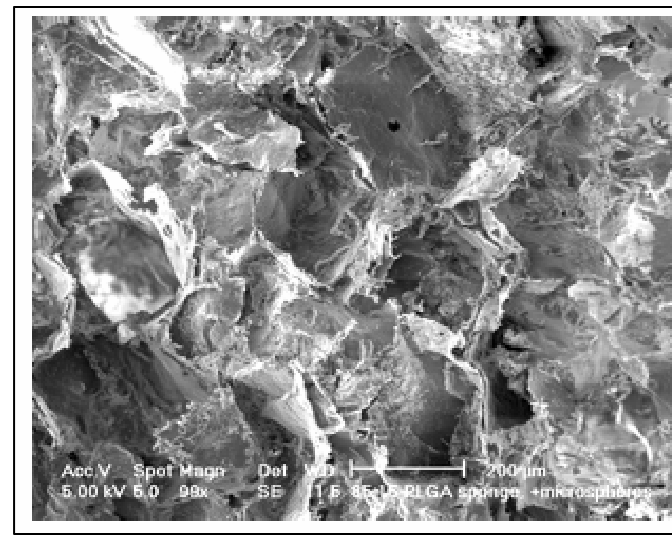
High pressure

$CO_2$ Gas molecules

Rapid drop to ambient pressure (1.01E+05 Pa)

unstable

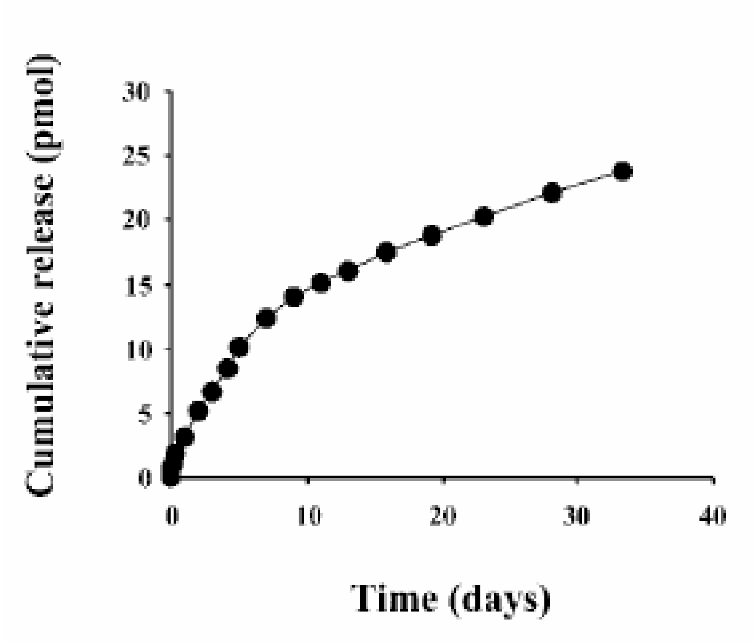
stable



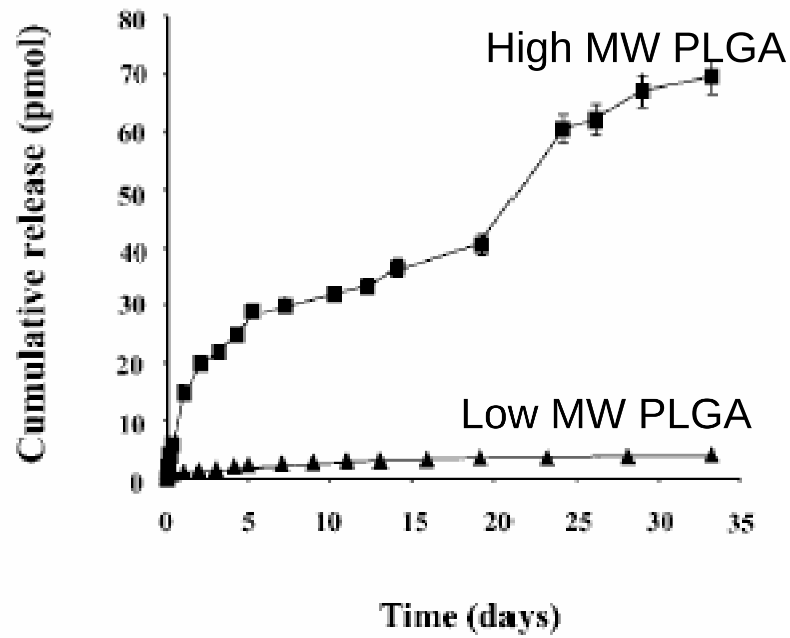
Gas bubble creates void in polymer matrix

# Release of cytokines from scaffolds

**VEGF release**




**PDGF release**




***In vivo* experiments:**

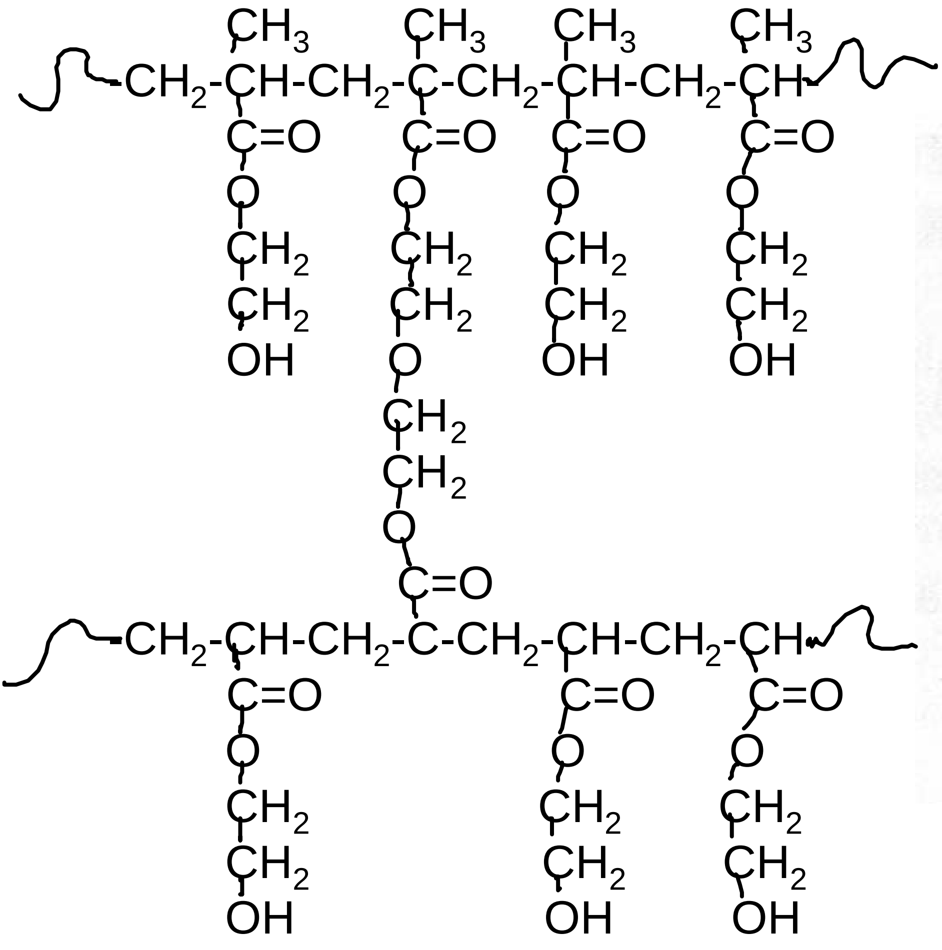
Scaffolds implanted subcutaneously (under skin) of Lewis rats

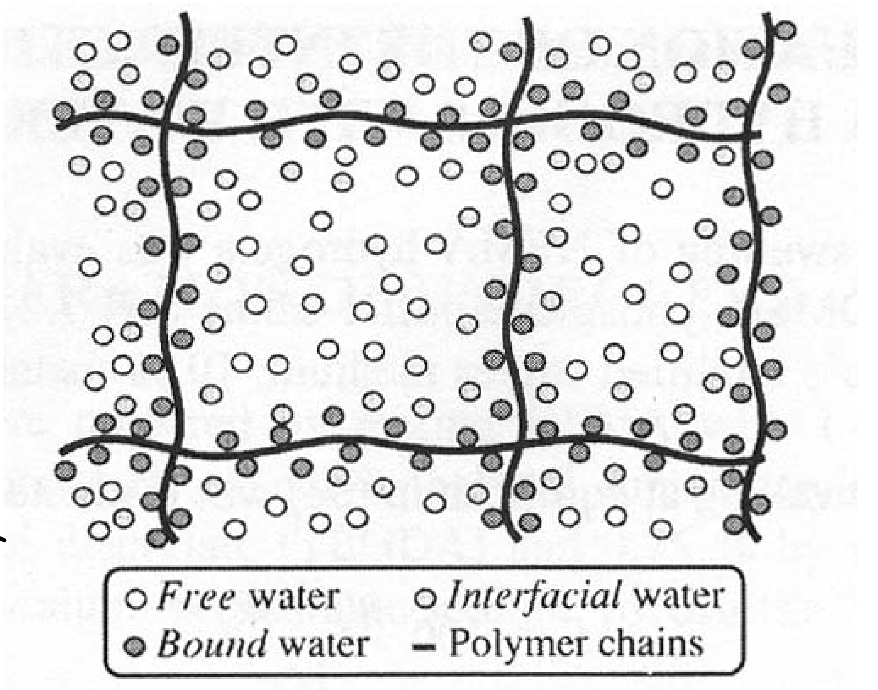
1) Compared bolus injection of free cytokines with release from scaffolds
2) Compared dual cytokine delivery from scaffolds with single factor delivery

# II. HYDROGELS

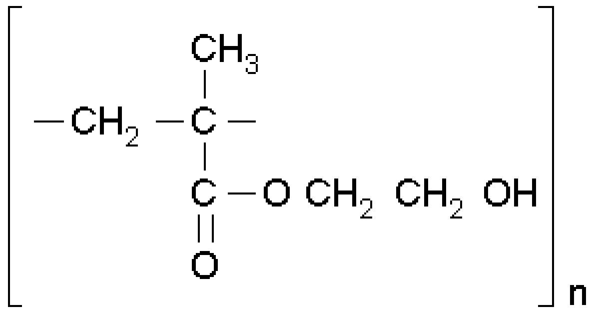
# The structure of hydrogels

# Structure of hydrogels

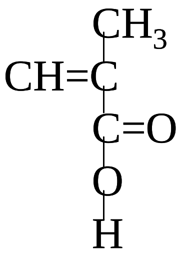




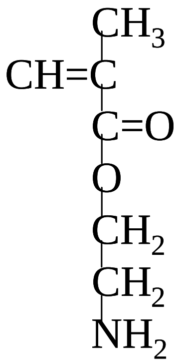
# Representative monomers used for biological applications



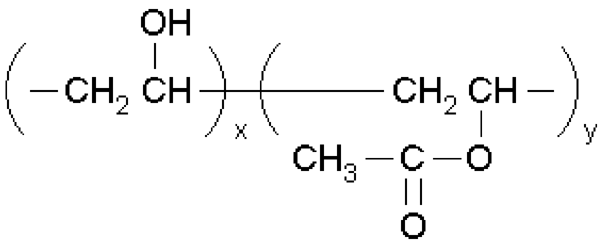
Hydroxyethyl methacrylate



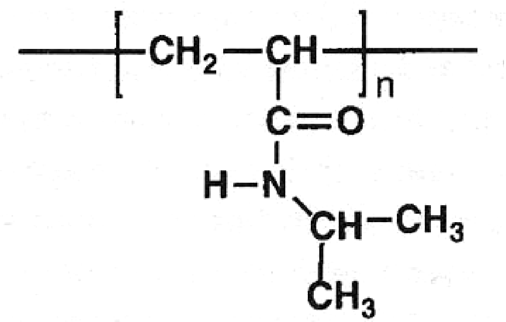
Methacrylic acid



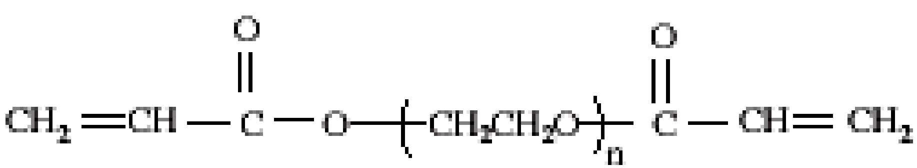
2-aminoethyl methacrylate



Poly(vinyl alcohol)



N-isopropylacrylamide



Poly(ethylene glycol) diacrylate

# Common biomedical hydrogel components

Table removed due to copyright reasons.
Please see:
Table 1 in Peppas, N. A., Y. Huang, M. Torres-Lugo, J. H. Ward, and J. Zhang. "Physicochemical Foundations and Structural Design of Hydrogels in Medicine and Biology." *Annu Rev Biomed Eng* 2 (2000): 9-29.

# Bonding in hydrogels

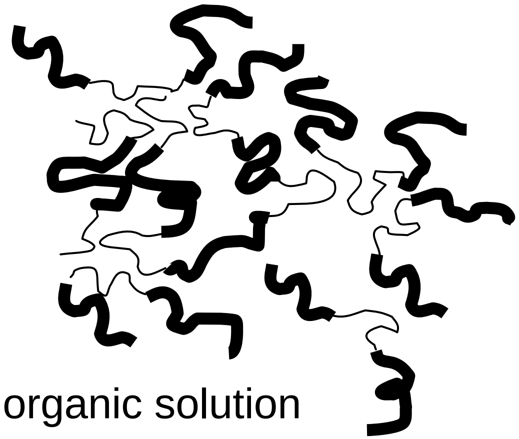
- Covalent
- Ionic
- Hydrogen bonding
- Polypeptide complexation (e.g., coiled coils)
- Hydrophobic effect

# Covalent hydrogel structure

Typical covalent hydrogel synthesis:

Interpenetrating networks:

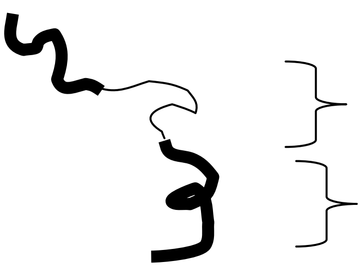
# Physical gels: example- Hydrophobic interactions in physical gels



organic solution

Physical gels are formed by *noncovalent* cross-links

***Example blocks:***



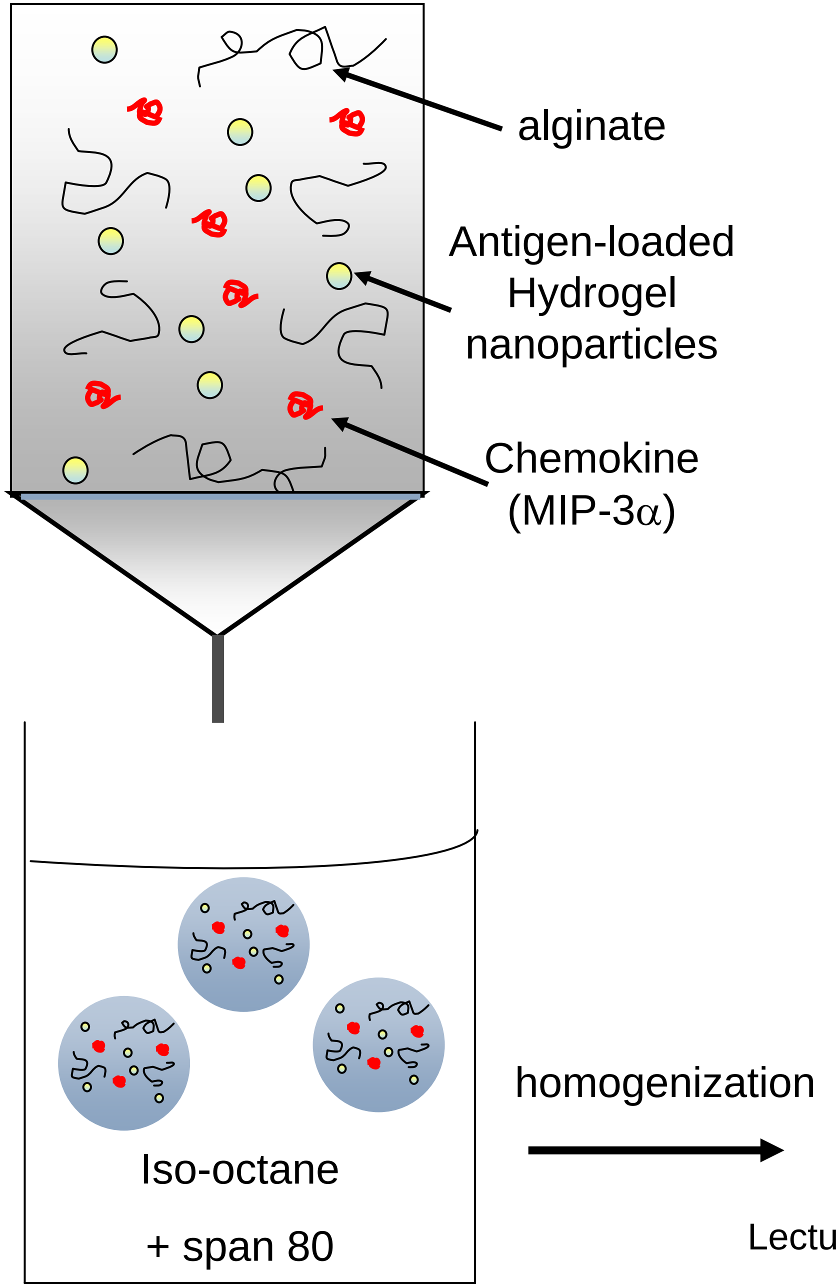
Hydrophilic B blocks — Poly(ethylene glycol) (PEG)

Hydrophobic A blocks — Poly(propylene oxide) (PPO), Poly(butylene oxide) (PBO)

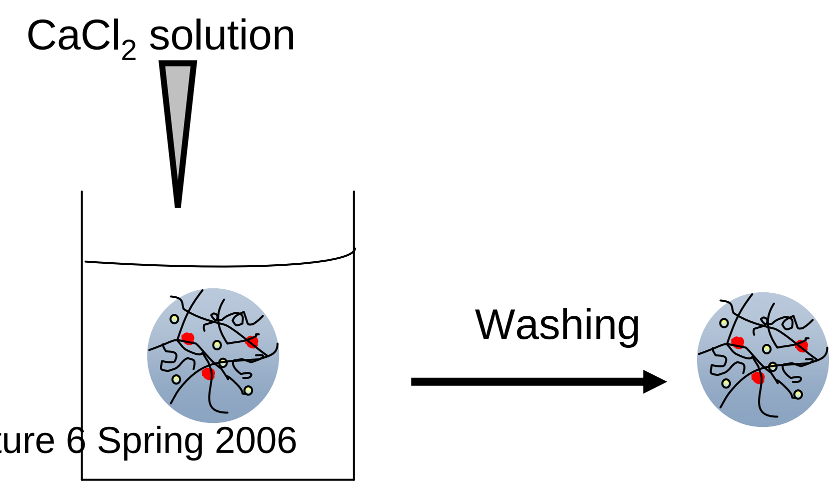
# Physical gels: ionically-crosslinked gels

alginate

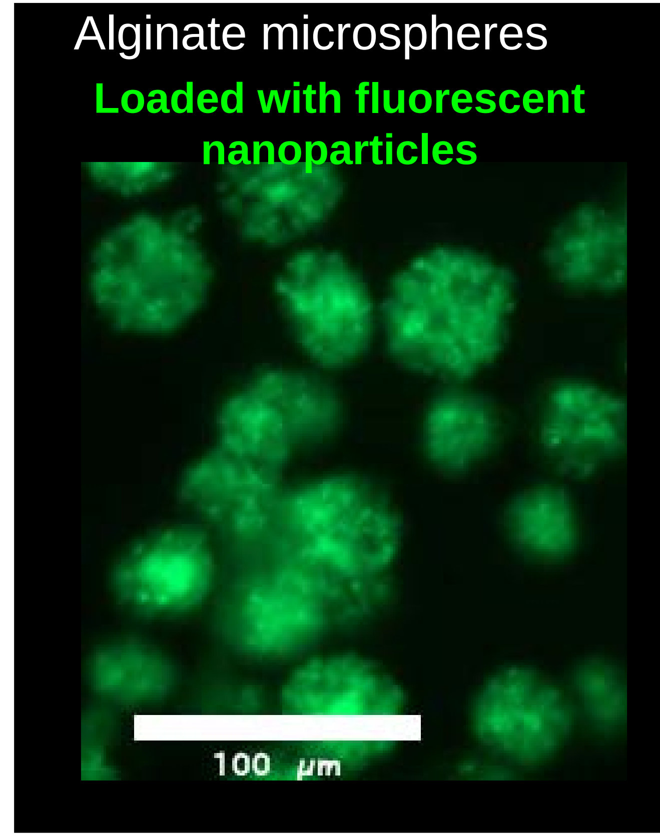
Images removed due to copyright restrictions.
Please see:
Rees, D. "Polysaccharide Shapes and Their Interactions - Some Recent Advances." *Pure Appl Chem* 53 (1981): 1-14. http://www.iupac.org/publications/pac/1981/pdf/5301x0001.pdf



alginate
Antigen-loaded
Hydrogel
nanoparticles
Chemokine
(MIP-3α)
Iso-octane
+ span 80
homogenization

$CaCl_2$ solution
Washing

Alginate microspheres
Loaded with fluorescent
nanoparticles
100 μm

# Key properties of hydrogels for bioengineering applications:

# Further Reading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2. An, Y. & Hubbell, J. A. Intraarterial protein delivery via intimally-adherent bilayer hydrogels. *J Control Release* **64**, 205-15 (2000).
3. 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).
4. Elisseeff, J. et al. Photoencapsulation of chondrocytes in poly(ethylene oxide)-based semi-interpenetrating networks. *Journal of Biomedical Materials Research* **51**, 164-171 (2000).
5. Jen, A. C., Wake, M. C. & Mikos, A. G. Review: Hydrogels for cell immobilization. *Biotechnology and Bioengineering* **50**, 357-364 (1996).
6. Anseth, K. S. & Burdick, J. A. New directions in photopolymerizable biomaterials. *Mrs Bulletin* **27**, 130-136 (2002).
7. 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).
8. Hennink, W. E. et al. in *Biomedical Polymers and Polymer Therapeutics* (eds. Chiellini, E., Sunamoto, J., Migliaresi, C., Ottenbrite, R. M. & Cohn, D.) 3-18 (Kluwer, New York, 2001).
9. Flory, P. J. & Rehner Jr., J. Statistical mechanics of cross-linked polymer networks. II. Swelling. *J. Chem. Phys.* **11**, 521-526 (1943).
10. Flory, P. J. & Rehner Jr., J. Statistical mechanics of cross-linked polymer networks. I. Rubberlike elasticity. *J. Chem. Phys.* **11**, 512-520 (1943).
11. 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).
12. Flory, P. J. *Principles of Polymer Chemistry* (Cornell University Press, Ithaca, 1953).