SANTA CLARA UNIVERSITY

INTRODUCTION TO WEARABLES AND IMPLANTABLES

SCU BIOENGINEERING
M.Mobed-Miremadi
7/13/2016

REFERENCES

- ***Biomaterials Science, 2nd Edition, An Introduction to Materials in Medicine;*** **ISBN-10:** 0123746264
- Please click on hyperlinks

EXAMPLE OF CUTTING EDGE WEARABLE AND IMPLANTABLES

PROFUSA

MAGMARIS

BIVACOR

KIDNEY

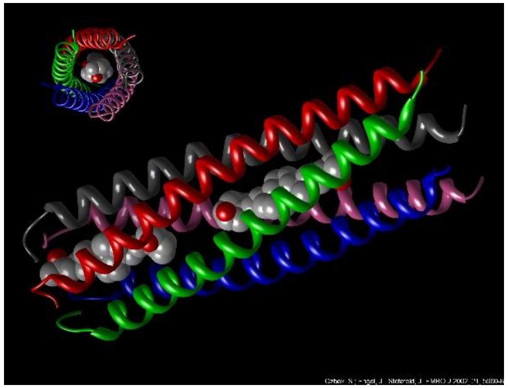
STRECHABLE ELECTRONICS

DEBIOTECH

BIOMATERIALS+
BIO/MICRO-FABRICATION+
MINIATURIZATION+
BIOCOMPATIBILITY+ ….
= *Wearables and Implantables*

SMART POLYMERS

Biomaterials

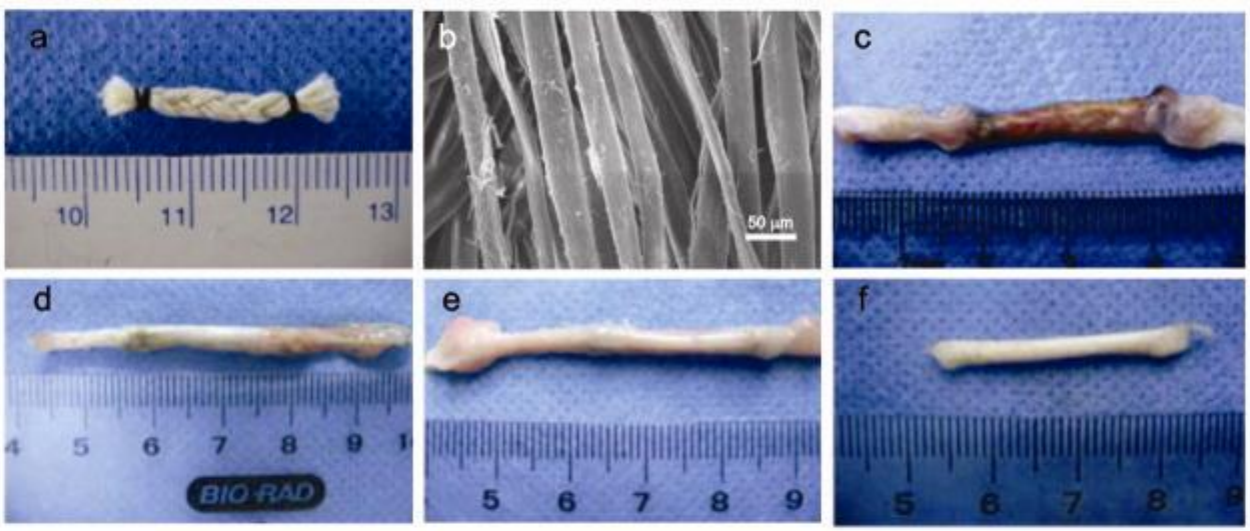


http://engineering.nyu.edu/files/pressrelease/COMPcc_blackBG_color_600dpi_4inx3in.jpg

0:01 / 1:14

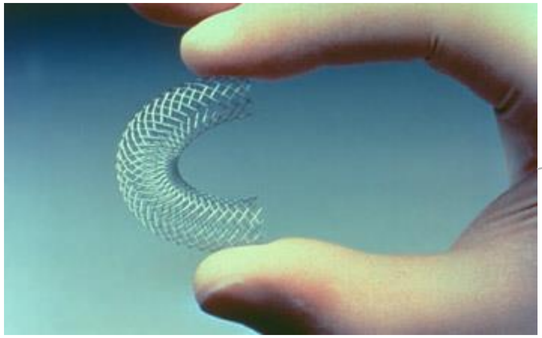
Light-Activated Glue for A Broken Heart

http://www.youtube.com/watch?v=iaZhJuxPNpA



http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3631569/

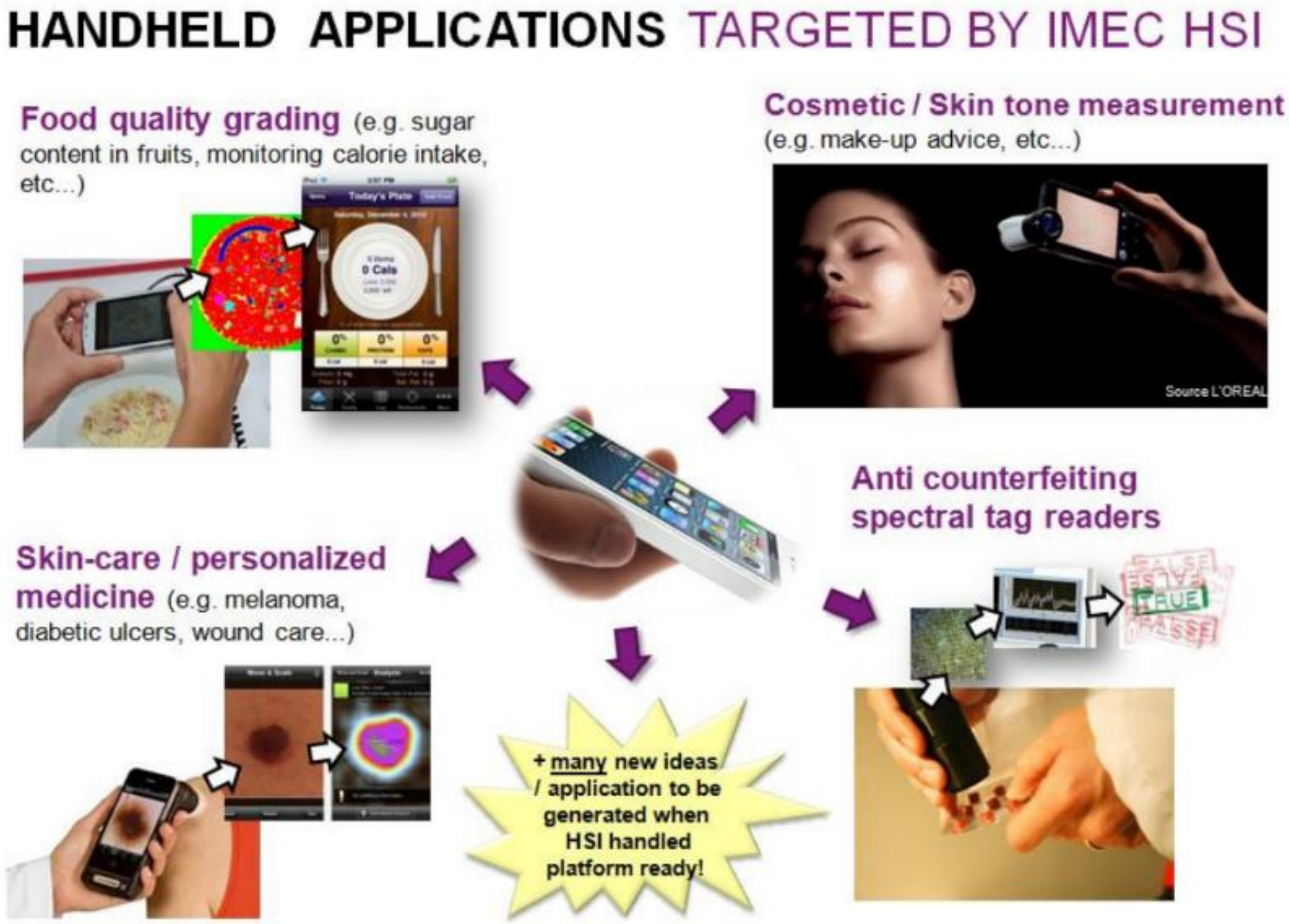
Bio-Medical Devices



http://virchicago.com/carotid-artery-blockage/

Bio-Signals

Hyperspectral Imaging



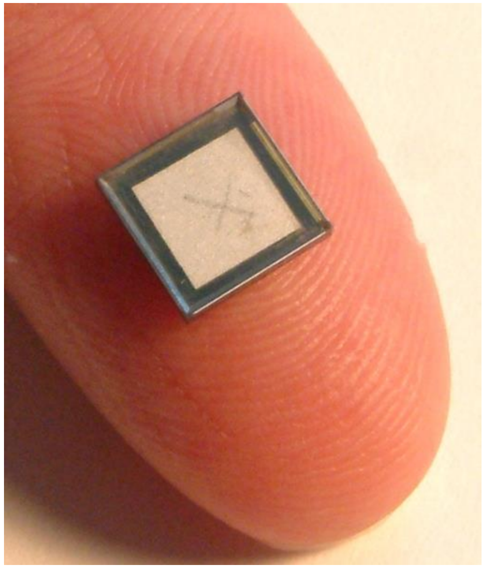
http://sites.ieee.org/scv-mems/files/2014/01/TSensors-1-22-14_final.pdf

Bio-Diagnostics and Bio-MEMS

miniaturized total chemical analysis systems (μTAS)

Bio-Chip and Micro Device Development

Miniaturized



http://djhurij4nde4r.cloudfront.net/images/images/000/121/043/fullsize/99058.Drug_Delivery_Infusion_Micropump.m.jpg?1390576193

BIOCOMPATIBILITY TESTING MATRIX

Nelson Laboratories Tests for Consideration

[Based on ISO 10993-1:2003(E) and FDA G95-1 Guidelines]

Device Categories			Biological Effect									
			Initial								Other[4]	
Body Contact		Contact Duration A- Limited [≤ 24 hrs] B- Prolonged [>24 hrs to ≤30 days] C- Permanent [>30 days]	Cytotoxicity	Sensitization	Irritation	Systemic Toxicity	Subacute (Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity
Surface Devices	Skin	A	■	■	■							
		B	■	■	■							
		C	■	■	■							
	Mucosal Membranes	A	■	■	■							
		B	■	■	■	◊	◊		◊			
		C	■	■	■	◊	■	■	◊		◊	
	Breached or Compromised Surfaces	A	■	■	■	◊						
		B	■	■	■	◊	◊		◊			
		C	■	■	■	◊	■	■	◊		◊	
External Communicating Devices	Blood Path, Indirect[3]	A	■	■	■	■				■		
		B	■	■	■	■	◊			■		
		C	■	■	◊	■	■	■	◊	■	■	■
	Tissue[1] /Bone/Dentin Communicating	A	■	■	■	◊						
		B	■	■	■	■	■	■	■			
		C	■	■	■	■	■	■	■		■	■
	Circulating Blood[3]	A	■	■	■	■		◊[2]		■		
		B	■	■	■	■	■	■	■	■		
		C	■	■	■	■	■	■	■	■	■	■
Implant Devices	Tissue/Bone	A	■	■	■	◊						
		B	■	■	■	■	■	■	■			
		C	■	■	■	■	■	■	■		■	■
	Blood[3]	A	■	■	■	■	■		■	■		
		B	■	■	■	■	■	■	■	■		
		C	■	■	■	■	■	■	■	■	■	■

[1] "Tissue includes tissue fluids and subcutaneous spaces.

[2] For all devices used in extracorporial circuits.

[3] Pyrogenicity/Materials Mediated should be considered.

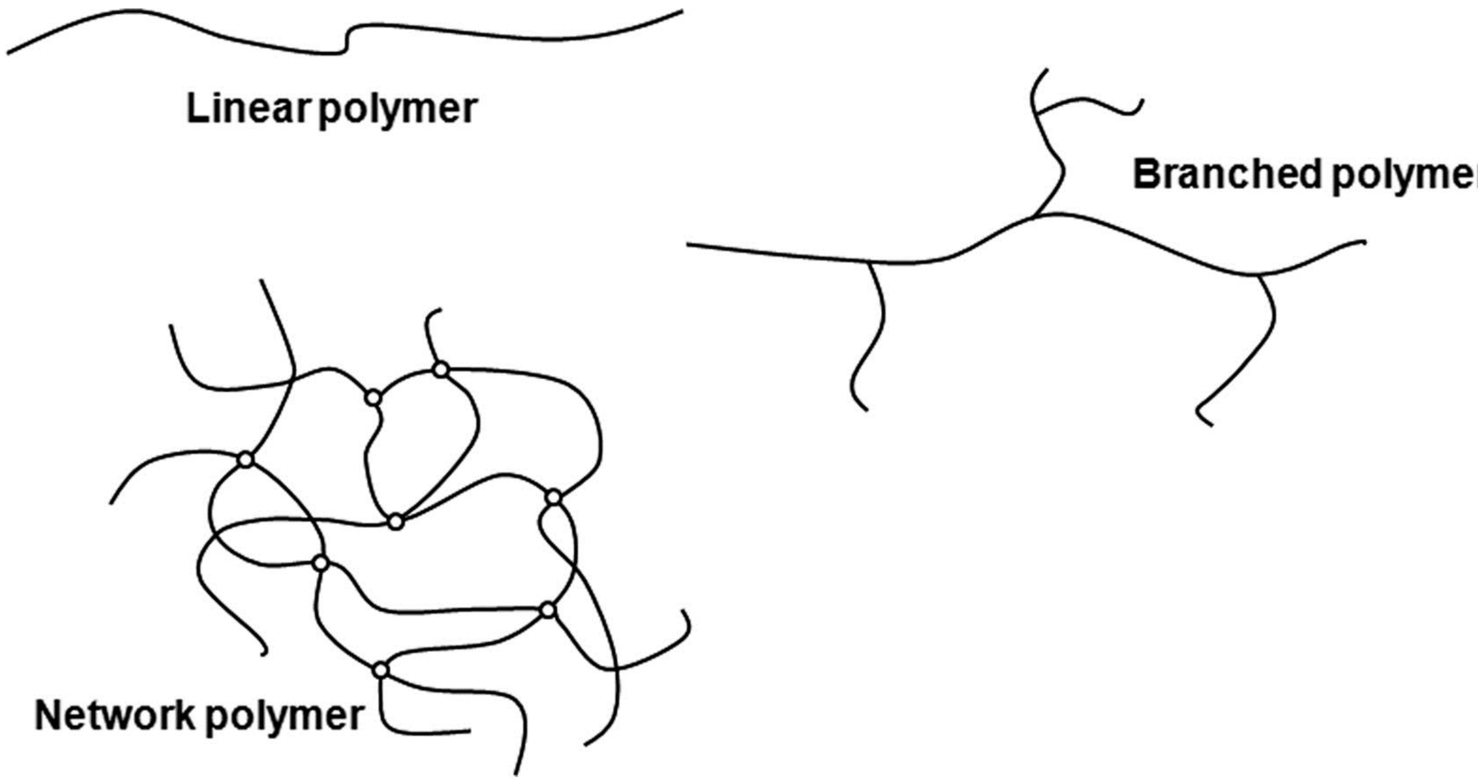
[4] Supplemental tests for consideration

■- ISO Evaluation Tests for Consideration

◊- Additional tests which the FDA considers may be applicable

For additional information or a price quote contact
sales@nelsonlabs.com

FOCUS: POLYMERS
SPECIFICALLY HYDROGELS


Linear polymer
Branched polymer
Network polymer

WHY POLYMERS?

- Weaker than metal and ceramics because chains are linked by London, Van Der Waal, H-bonding and dipole-dipole interactions.
- Less brittle than ceramics and biocompatibility can be inferred by functional groups
- Chemical resistance (PVC)
- Optical properties (contact lenses)
- Inert with a wide range of transition temperatures (PE and PP for food storage and refrigeration
- Light weight
- Sterilizable

………

Main Categories of Synthetic Polymers:

- **Plastics:**
  - Thermoplastics – can be remelted (reversible phase transitions)

  Ultrasonic welding: eg. PMMA, Polyamide (Nylons, PA), PLLA,Polystyrene.

  - Thermosetting Plastics – can not be remelted

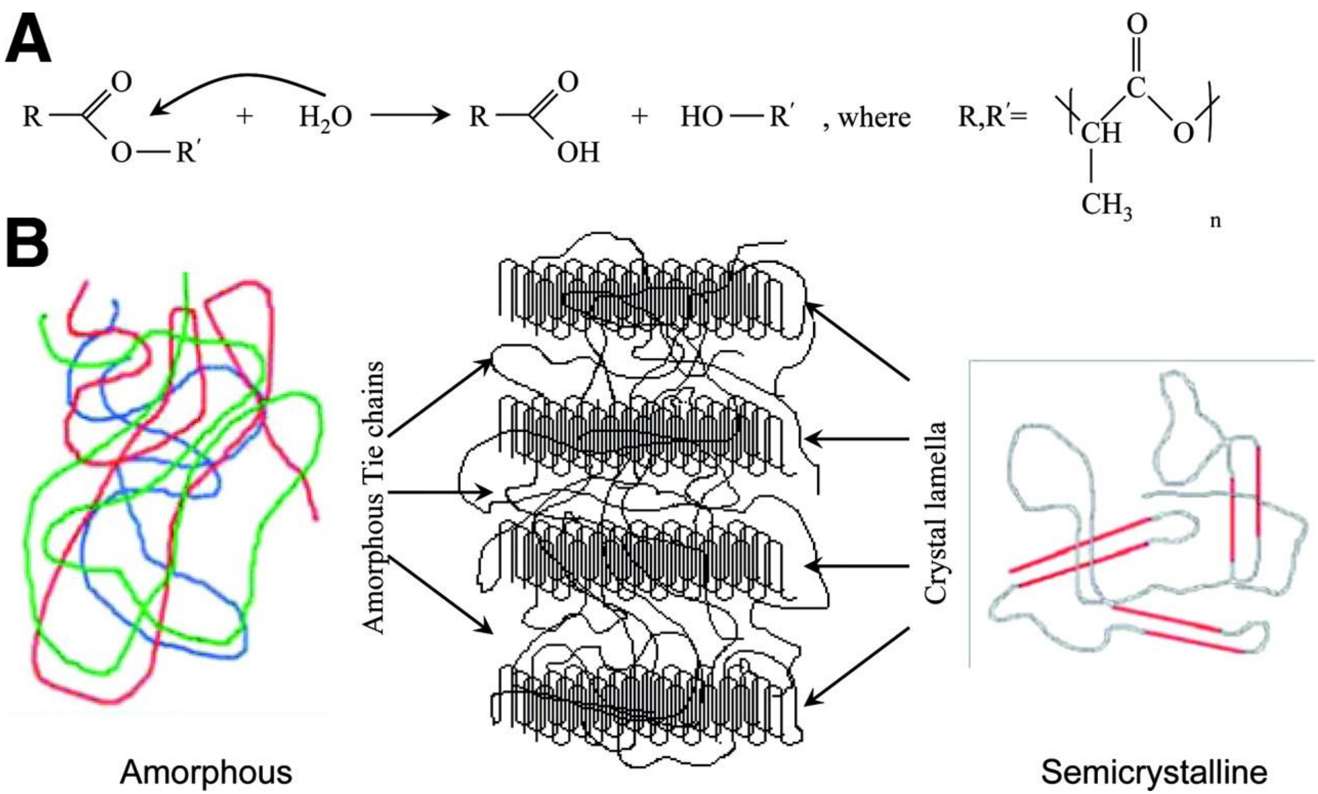
  Strong but brittle, Polyurethanes, Silicones

- **Elastomers:**

  Thermosets and thermoplastic

  Extremely flexible (mostly thermosets)

  Isoprene, Nitrile



A, Reaction pathway for hydrolytic degradation of the PLA family of polymers.
B, Schematic presentation of amorphous polymer (left), semicrystalline structure of the PLLA with crystal lamella (crystalline polylactide) interconnected by amorphous tie chains binding the lamellae together (middle), and semicrystalline polymer (right).

http://circ.ahajournals.org/content/123/7/779/F1.expansion.html

-----AAAAAAAAAAAAA------

Homopolymer

-----AAAABBBBBAAAA------

Block copolymer

-----AABABBBAABBAB------

Random copolymer

B
B
B
B
B
B
-----AAAAAAAAAAAAA------

Graft copolymer

-----ABABABABABABA------

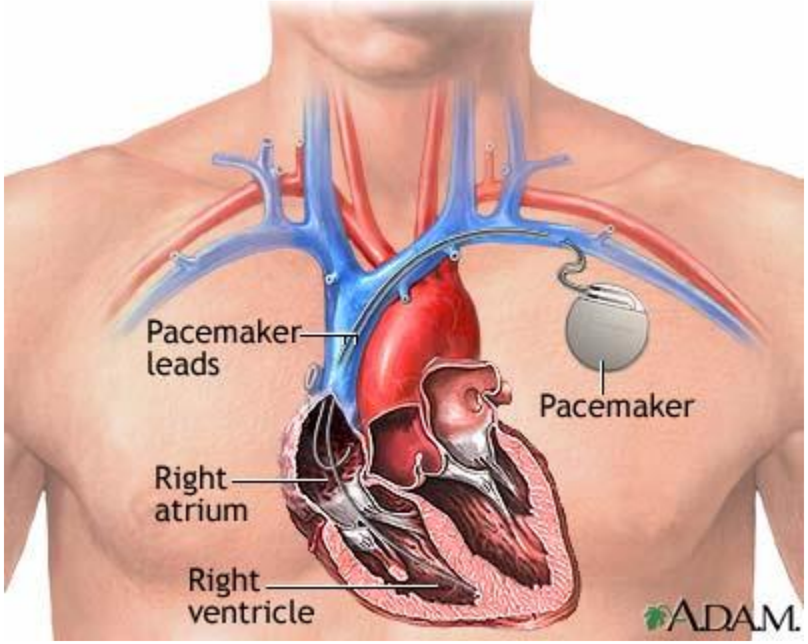
Alternating copolymer

POLYMERS IN MEDICINE

http://www.techreleased.com/blog/your-life-could-depend-on-plastics/

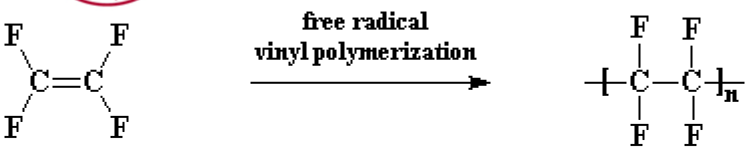
http://bonesmart.org/joints/is-the-plastic-used-in-knee-implants-and-hip-implants-safe/

http://www.theplasticsurgerycenter.com/implants.html



http://health.allrefer.com/pictures-images/pacemaker.html

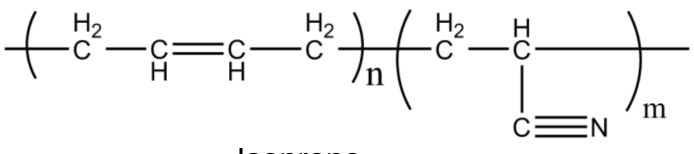
PTFE



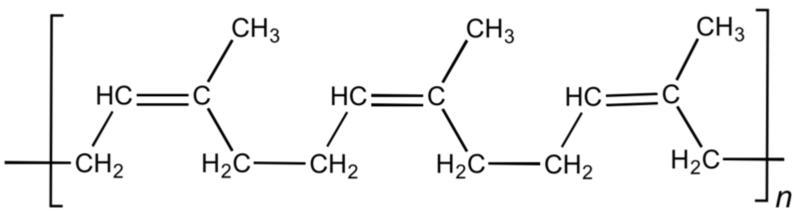
tetrafluoroethylene

polytetrafluoroethylene

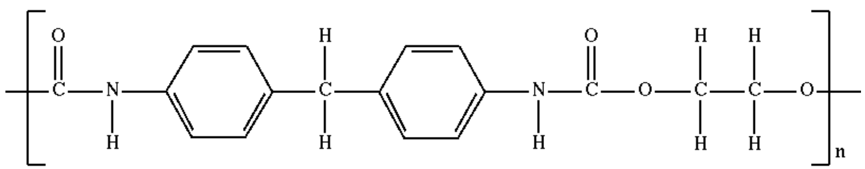
Nitrile



Isoprene



Polyurethane



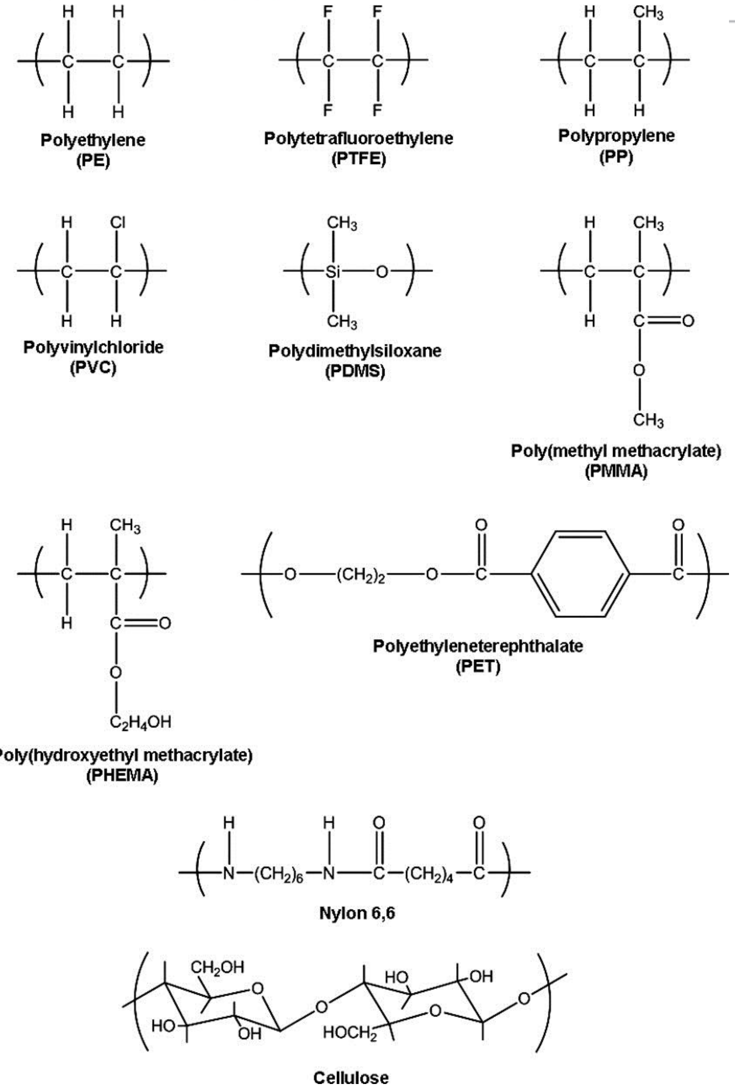


Figure 8.03

Polymer	Application
UHMWPE	Knee, hip & shoulder joints
Silicone	Finger Joints
Polylactic acid, polyglycolic acid,nylon	Sutures
Polymethyl methacrylate (PMMA)	Bone Cement, Contact Lenses
Acetal, polyethylene,polyurethane	Pacemakers
(PTFE), PVC	Blood Vessels
Hydrogels	Ophtalmology, Artificial Organs
Polydimethyl siloxane, polyurethane	Facial Prostheses

Degradation of Polymers & Hydrogels

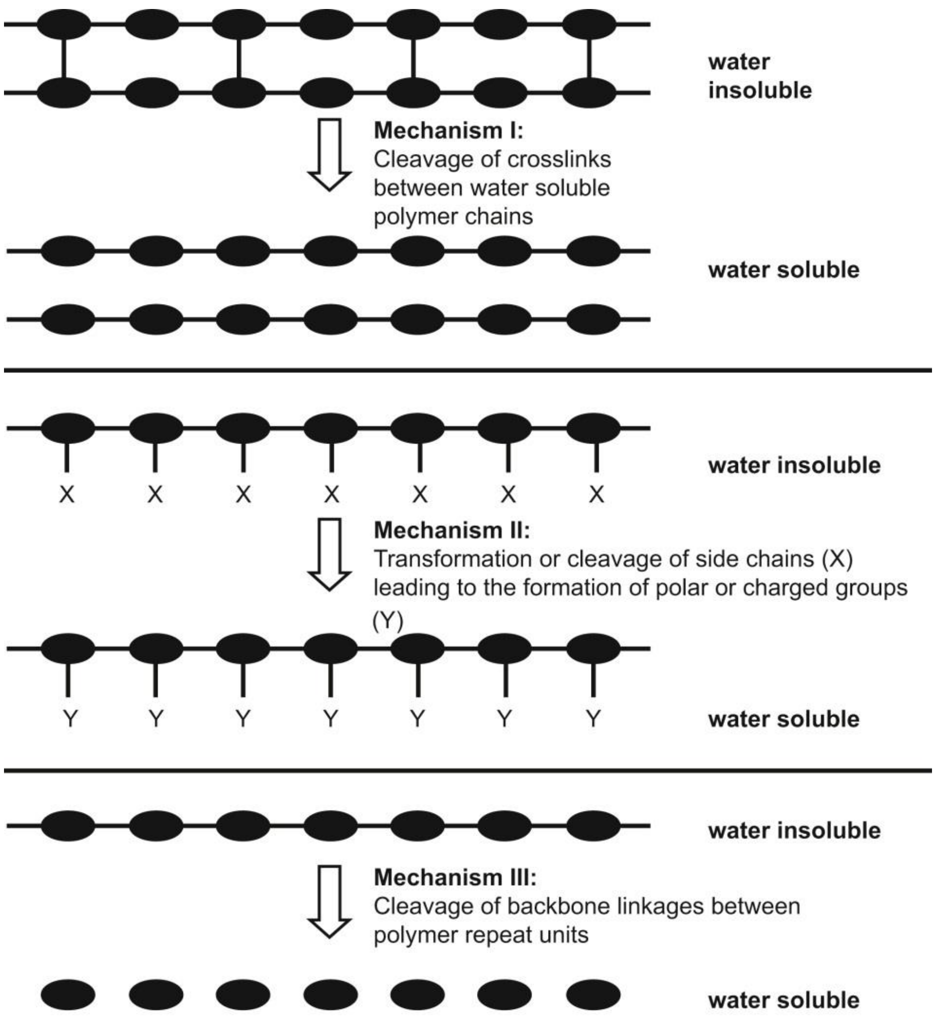
- **Degradation** (Chemical): Classical definition is a cleavage of covalent bonds.
For Bioengineers this could mean hydrolysis, oxidative/reductive, photodegradation and enzymatic mechanisms.

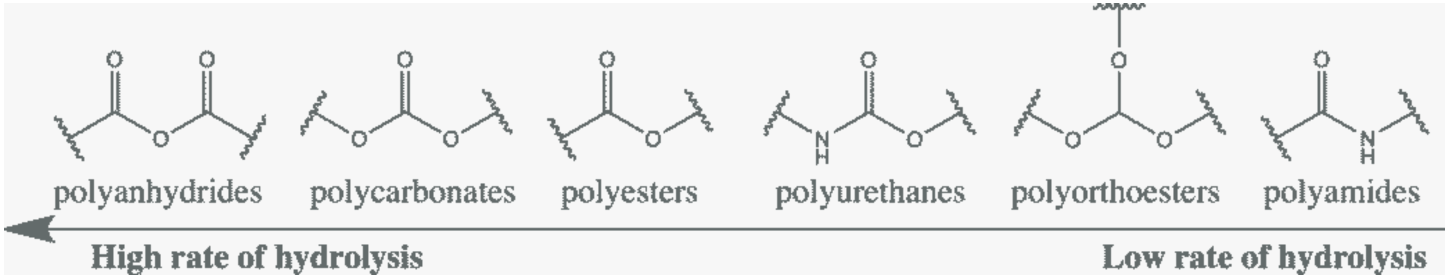
- **Erosion** (Physical): Loss of mass
Equivalent to degradation, ablation, dissolution, mechanical wear.
pH and Temperature (physical conditions) are very important.

- Official definition of **biodegradation** “enzymatic hydrolysis.
For example, initial degradation of PLA stents is not biodegradation it is dissolution

- **Bio-erosion** is chemical and physical:
Physical dissolution consists of water insoluble chain becoming water soluble this could have been initiated by backbone cleavage and vice-versa.

- **Bio-absorption** and **Bio-resorption** processes are referred to as material removed through cellular activity (i.e. phagocytosis).


water
insoluble
Mechanism I:
Cleavage of crosslinks
between water soluble
polymer chains
water soluble
water insoluble
X X X X X X X
Mechanism II:
Transformation or cleavage of side chains (X)
leading to the formation of polar or charged groups
(Y)
Y Y Y Y Y Y Y
water soluble
water insoluble
Mechanism III:
Cleavage of backbone linkages between
polymer repeat units
water soluble


O
O
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N
H
O
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O
O
N
H
polyanhydrides
polycarbonates
polyesters
polyurethanes
polyorthoesters
polyamides
High rate of hydrolysis
Low rate of hydrolysis

CLASSIFICATION OF HYDROGEL-BASED DEGRADABLE MEDICAL IMPLANTS

1) **Temporary support device:** Temporary mechanical support until tissue gains it s strength
Sutures [PGA, Dexon]; vascular grafts, bone fixation devices.
http://www.medicaldevice-network.com/contractors/biotechnology/degradable-solutions-ag/

2) **Temporary barrier: Prevention of post-surgical adhesions**
"Artificial skin" products used in burns and deep skin lesions.
SINUFOAM: https://www.youtube.com/watch?v=5ZLQp6-nWJA

3) Implantable drug delivery devices/injectable polymer-drug depot system/Tissue scaffolding
PLA, PGA, Alginate, liquid-crystals (liposomes)

HYDROGELS

Properties of Hydrogels

- Water insoluble 3D polymeric chain of networks.
- Swellable
- Porous
- Sterilizable
- Biocompatible

BIOMIMETIC SOFT TISSUE

Properties of Hydrogels

- One ore more highly electronegative atoms resulting in charge asymmetry and H-bonding.
- Porous and hydrophiic, water content may constitute 10%-95% of the total weight by volume.

Xerogels

- Dried Hydogels
- Usually cross-linked and optically clear.
- Slow diffusion of water through the pores and swelling enables release of trapped compounds.

Hydrogel Classification

- Neutral
- Anioninc
- Cationic
- Ampholytic
- Amorphous
- Semi-crystalline
- Hydrogen-bonded hydrogels

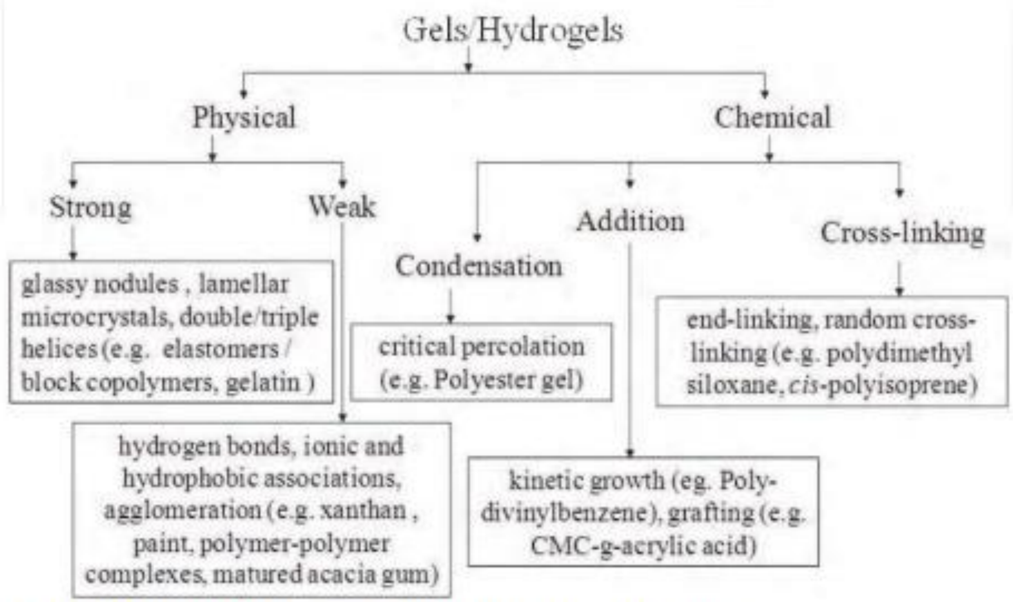


Fig. 1. Classification of gelation mechanism and relevant examples.

1.2 Classification of hydrogel

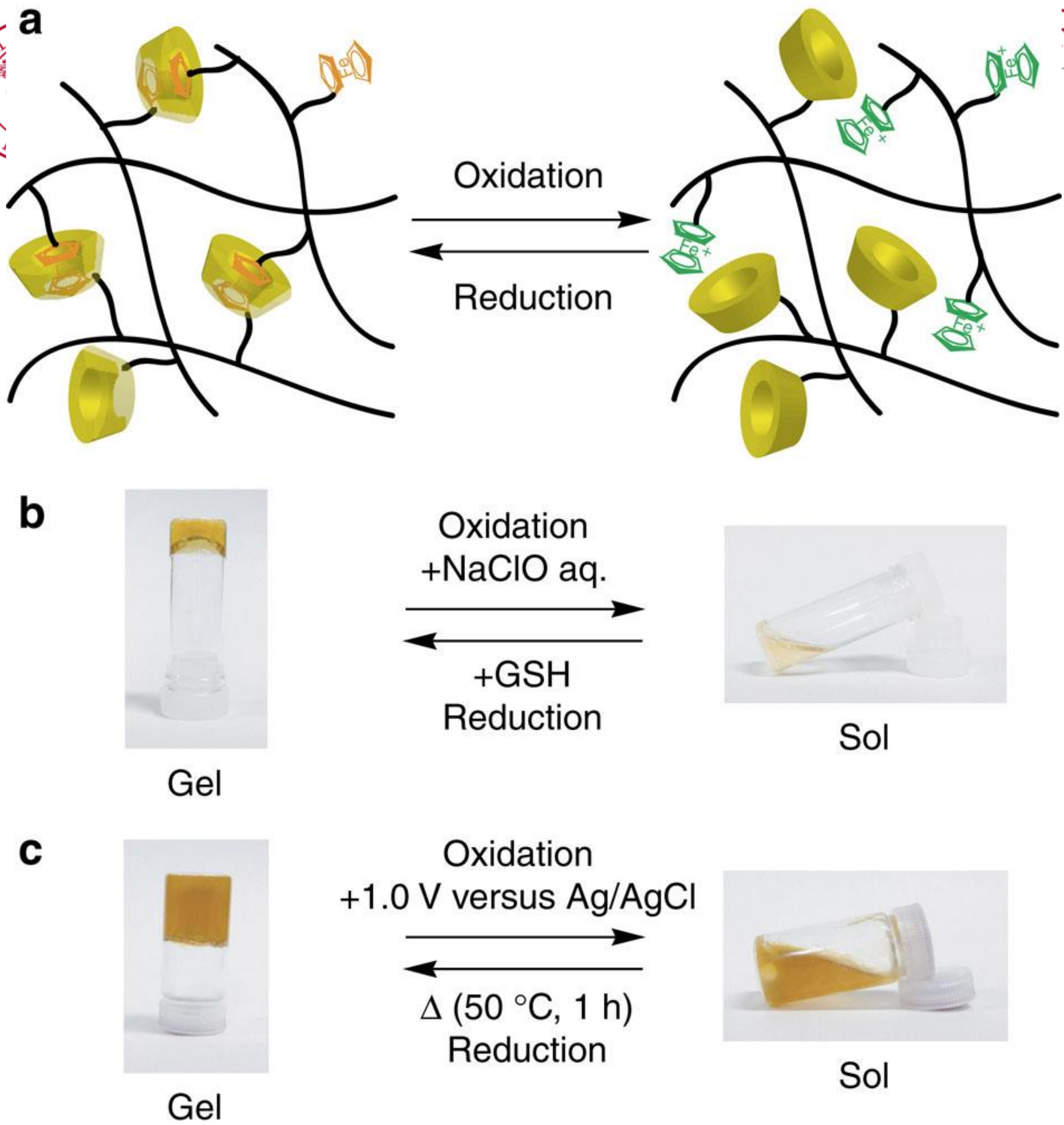
Hydrogels are broadly classified into two categories:

Permanent / chemical gel: they are called 'permanent' or 'chemical' gels when they are covalently cross-linked (replacing hydrogen bond by a stronger and stable covalent bonds) networks (Hennink & Nostrum, 2002). They attain an equilibrium swelling state which depends on the polymer-water interaction parameter and the crosslink density (Rosiak & Yoshii, 1999).

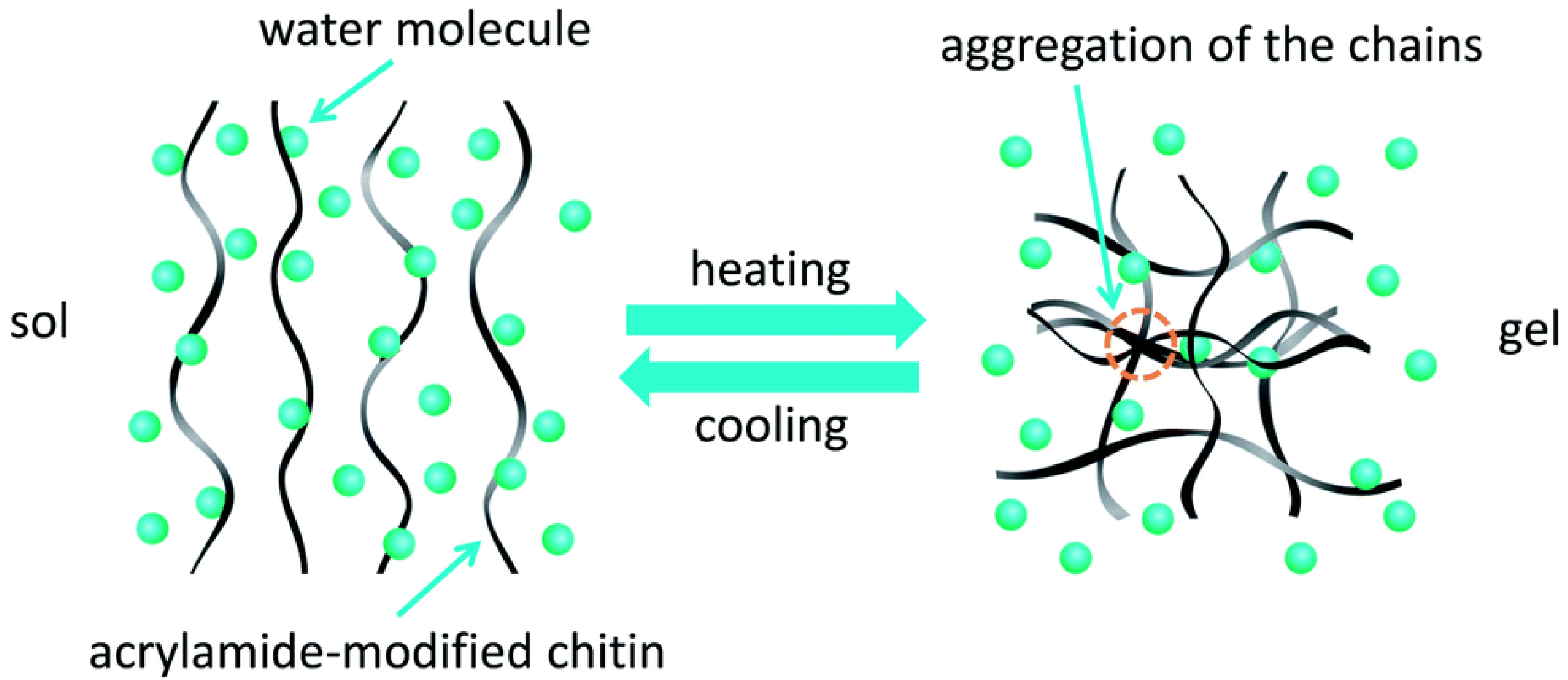
Reversible / physical gel: they are called 'reversible' or 'physical' gels when the networks are held together by molecular entanglements, and / or secondary forces including ionic, hydrogen bonding or hydrophobic interactions. In physically cross-linked gels, dissolution is prevented by physical interactions, which exist between different polymer chains (Hennink & Nostrum, 2002). All of these interactions are reversible, and can be disrupted by changes in physical conditions or application of stress (Rosiak & Yoshii, 1999).

Source: http://cdn.intechopen.com/pdfs-wm/17237.pdf

SMART HYDROGELS



http://www.nature.com/ncomms/journal/v2/n10/fig_tab/ncomms1521_F3.html



http://pubs.rsc.org/en/content/articlelanding/2014/tb/c4tb00067f#!divAbstract http://www.gizmag.com/electrically-charged-hydrogel-soft-robotics/28576/

SOFT ROBOTICS and IONOPRINTING

BIOFABRICATION

PHOTOLITHOGRAPHY

JOVE

3D-Bioprinting

ORGANONOVO

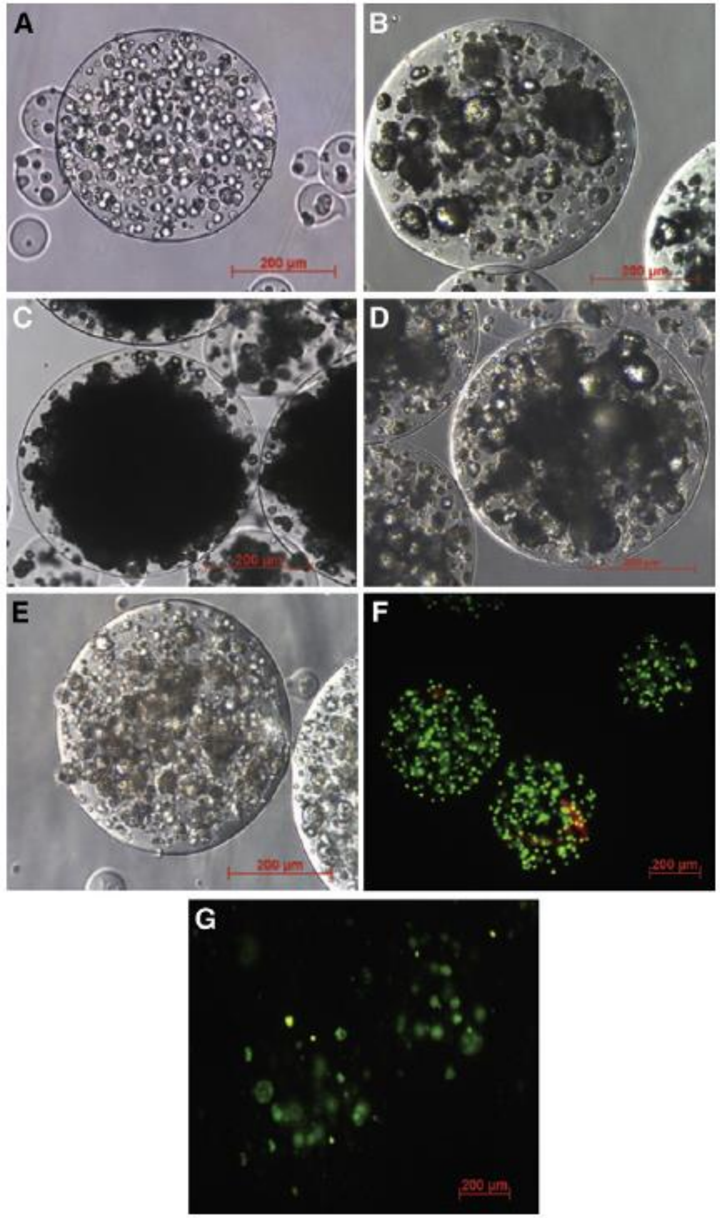


Fig. 4. Encapsulated mESC retrieved from the peritoneal cavity of BALB/c mice were encapsulated as single cells on day 0 (A). Capsules retrieved at one month (B), two months (C), and three months (D) have formed aggregates in contrast to being single cells prior to transplantation. The same occurred during culture in vitro after one week (E). Retrieved capsules were also assessed for viability using fluorescent microscopy. Viable cells stain green (6-CFDA) and dying cells red (PI) prior to transplantation (F) and two months posttransplantation (G). Reproduced, with permission, from [91]. © 2006 Lippincott Williams and Wilkins.

MWCO of different Artificial Cell Membranes

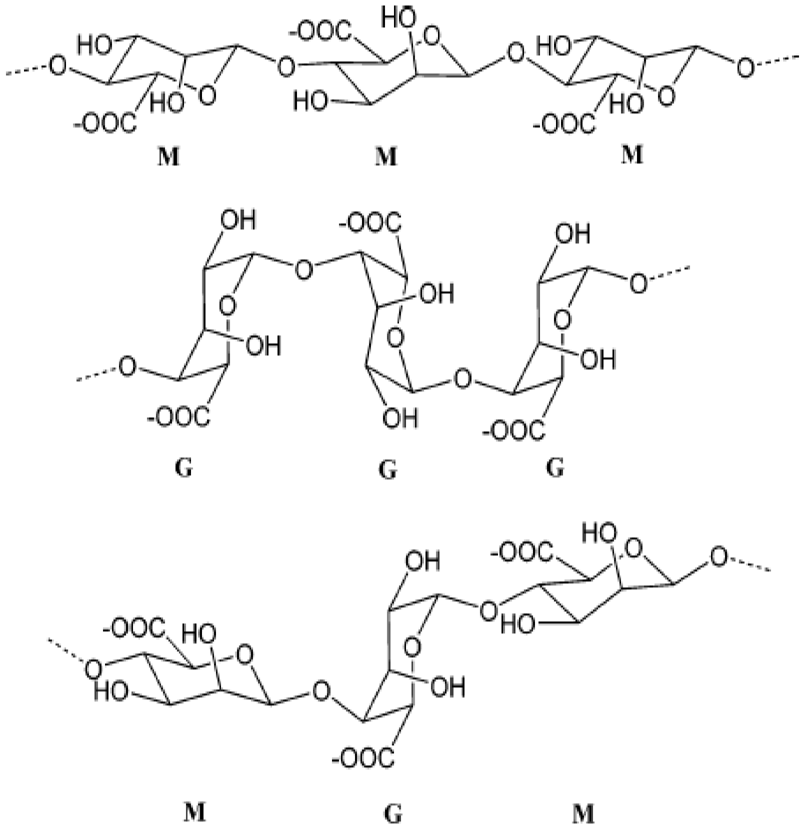
Membrane Type	***Application***	***Diffusing Molecule***	***MW***	***Stokes Radius (nm)***
Liposomes	Drug Delivery	Oxygen	16	0.2
	Blood Subtitutes	Carbon Dioxide	44	0.3
		Urea	60	0.3
Lipid-Complexed Polymer	Inborn Errors for Metabolism	Creatinine	113	0.4
	Drug Delivery	Phenylalanine	147	0.4
		Glucose	180	0.4
Cellulose Nitrate and Polyamide	Hemoperfusion	Beta-endorphin	3,438	1.1
		Insulin	5733	1.3
		IL-beta	17000	1.9
Alginate-Polylysine-Alginate (1.5%-2% alginate-based)	Regenerative Medicine	Super Oxide Dismutase	31,187	2.3
	Oral Delivery of Genetically Engineered Bacteria	TNF	51000	2.7
		Albumin	66248	3.0
Hollow Fiber Filter	Liver Support System	Transferrin	81,000	3.2
		Ig-D	160,000	4.0
		Ig-E	190,000	4.2

SOCIETAL MOTIVATION

- Prevalence of Coronary Heart Disease (2010): 11.8% of the American population (http://www.cdc.gov/nchs/fastats/heart.htm).
- Prevalence of Chronic Kidney Disease (2010): 10% of the American population (kidney.niddk.nih.gov/kudiseases/pubs/kustats/)
- The World Health Organization in its annual report states that 10 percent of the deaths in the low-income countries and about 15 percent of the deaths in the high income countries are due to injuries and blood loss. The current survey evaluated the wound management market in just United States alone at $7.4 billion in 2009, almost three times its value in 2002 (http://www.idataresearch.net/idata/report_view.php?ReportID=822)

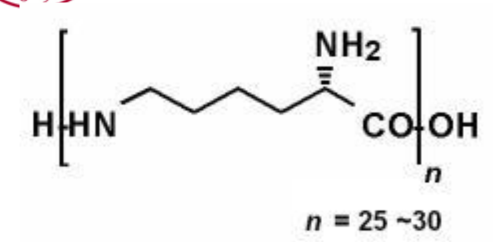
SUSTAINABLE WATER-BASED CHEMISTRY

BASE MATERIAL: ALGINATE



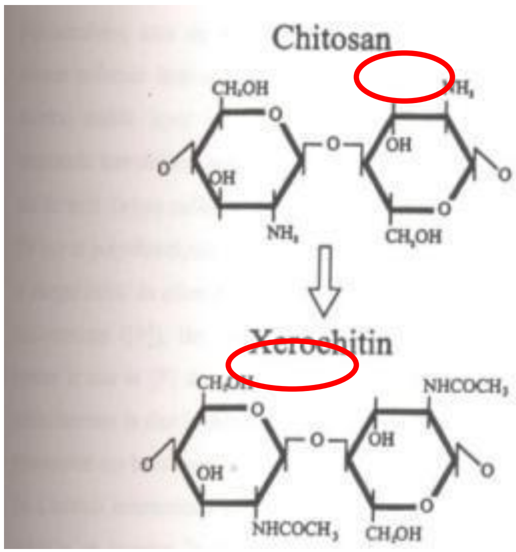
An anionic copolymer of various MWs (degrees of polymerization) , comprised of β-D-mannuronic acid (M-block) and (1→4)-linked α-L-guluronic acid (G-block) units arranged in non-regular blockwise pattern of varying proportion of GG, MG and MM blocks.

POLYCATIONS



• For polylysine (polycationic) molecular weight determination (intrinsic viscosity) is important because of the polyelectrolyte effect.

OR



- (Xero)-Chitin confers rigidity to the exoskeleton of all Arthropods.
- Chitin and its derivative are considered as stiff chains.

- Chitosan, a cationic polyelectrolyte is commercially available and characterized by its degree of de-acetylation.

$$[\eta] = \lim_{c \to 0} \frac{\eta_{sp}}{c} \equiv \lim_{c \to 0} c^{-1} \ln \eta_{rel}$$

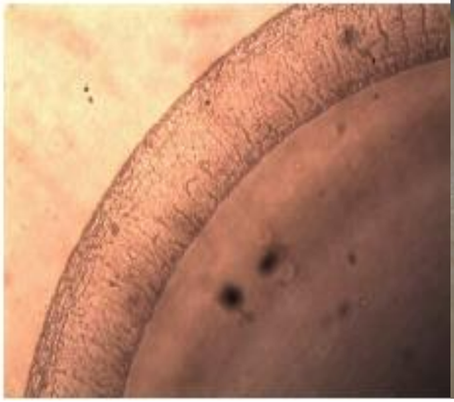
$$[\eta] = KM^{a}$$

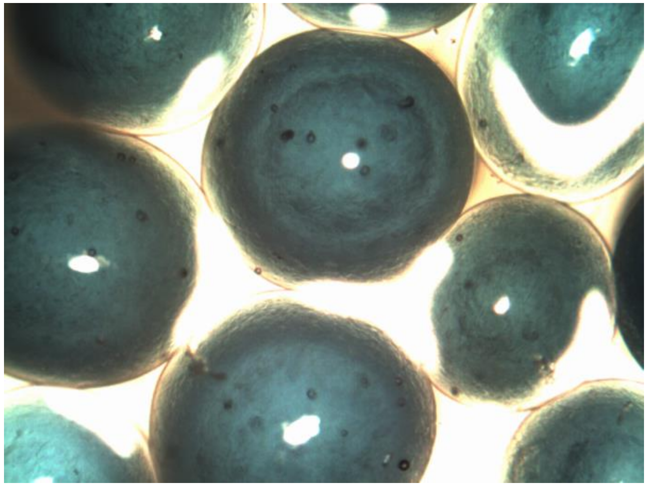
→ d.p≈15

ALGINATE
the Miracle Bio Polymer

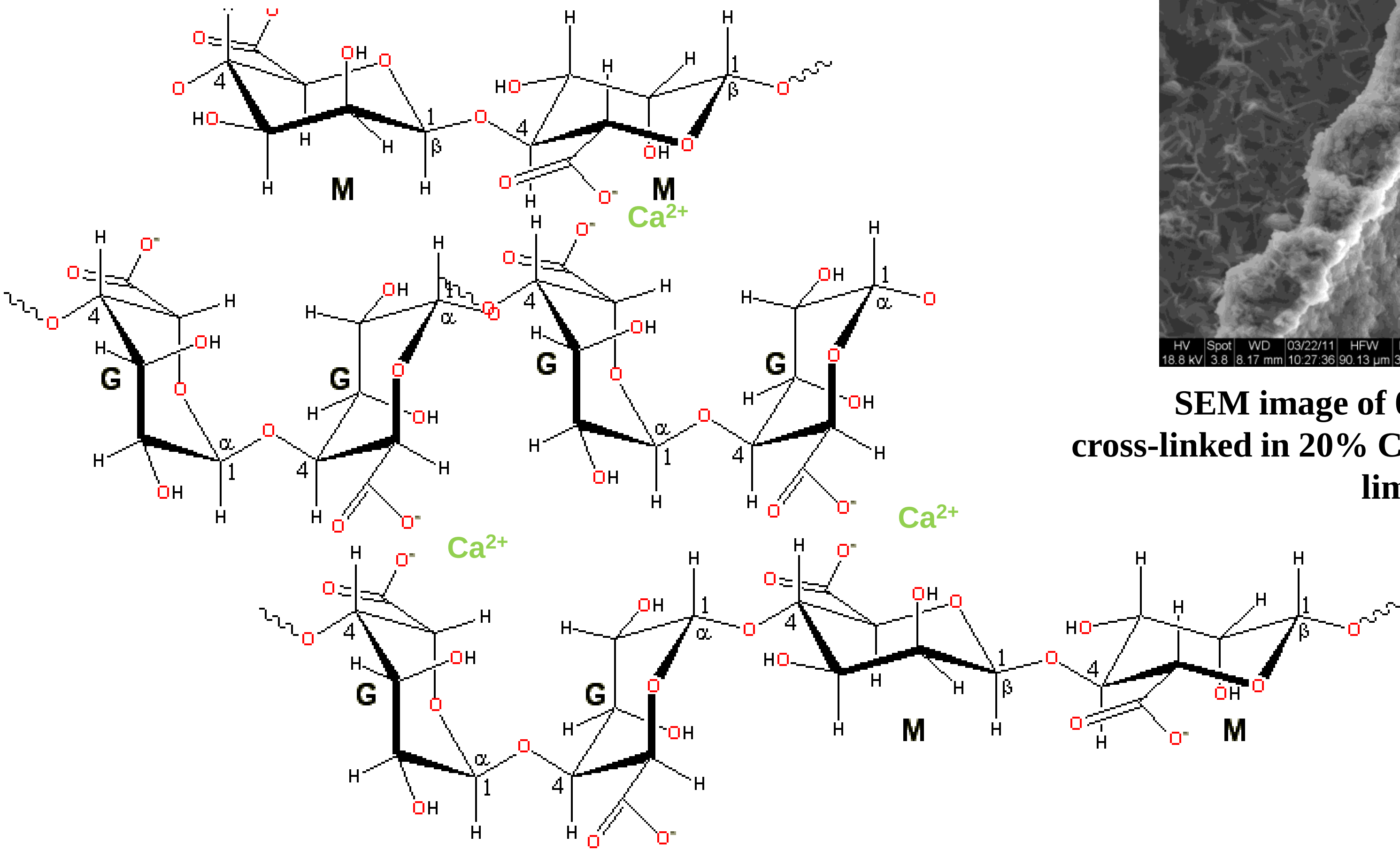
- Economical ($0.44/g)
- Biocompatible
- Biodegradable
- Viscoelastic once cross-linked
- Sterilizable

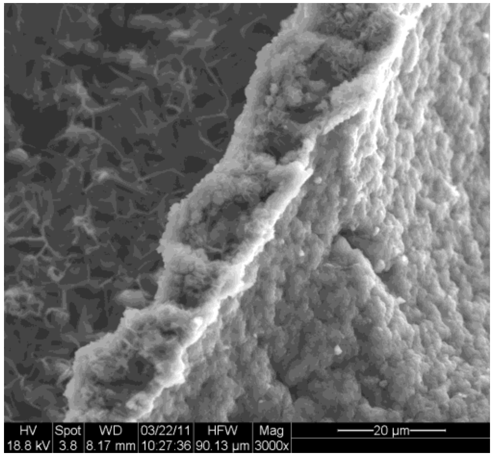
Bio-Printing and Alginate Structure Fabrication Involves Cross-Linking





CROSS-LINKING ALGINATE USING DIVALENT IONS





SEM image of 0.5% Alginate cross-linked in 20% $CaCl_2$ membrane/co limit

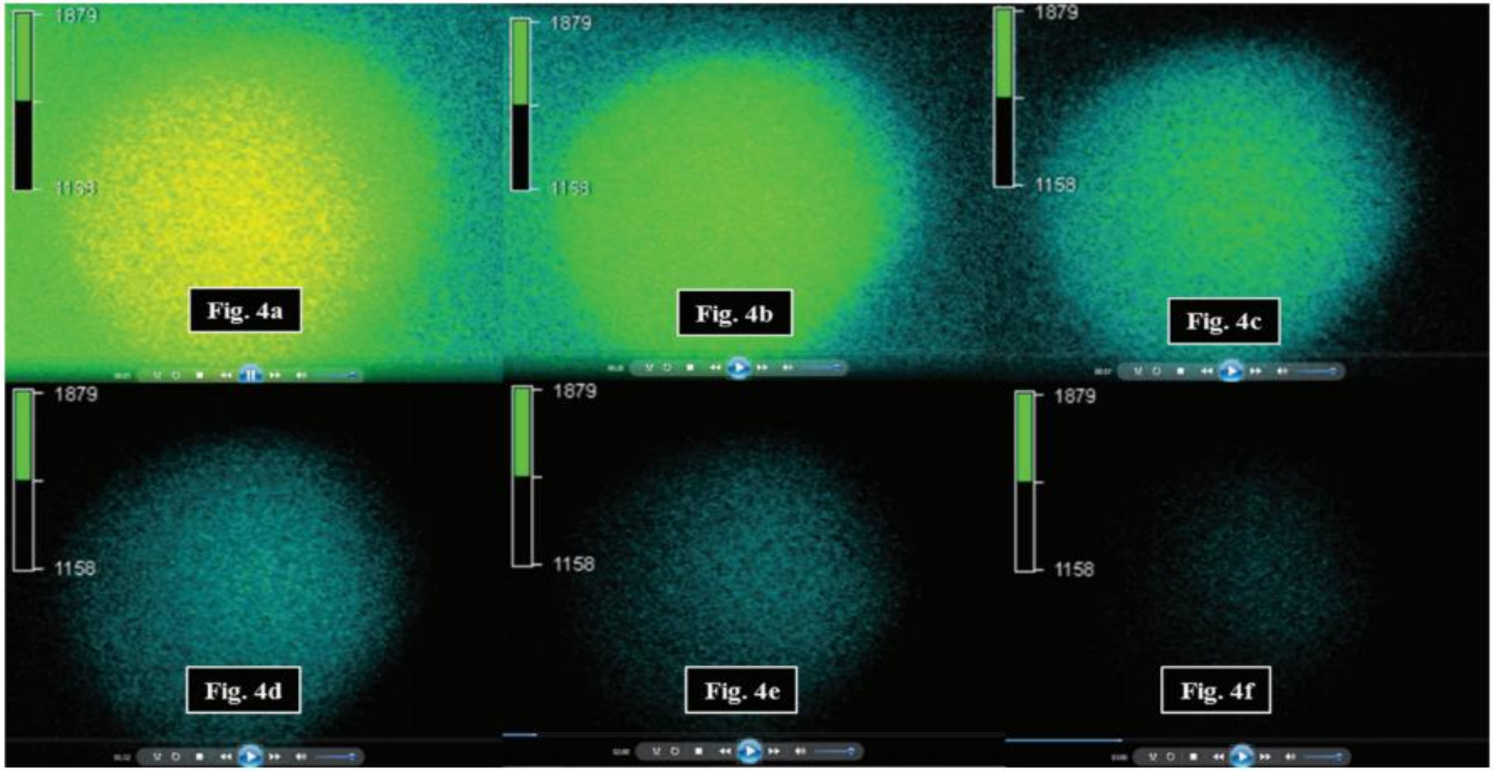


Figure 4. Snapshots of outward diffusion of the FITC 4 kDa marker from microcapsules captured at (a) 5 s, (b) 28 s, (c) 57 s, (d) 92 s, (e) 120 s, and (f) 180 s. Shown on each image is the pseudo-color intensity scale.

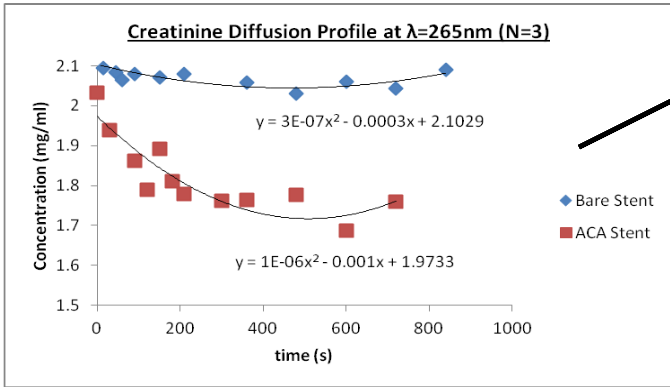
Stent Fabrication

$$\frac{\partial C}{\partial t} = \frac{1}{r}\frac{\partial}{\partial r}\left(rD\frac{\partial C}{\partial r}\right)$$

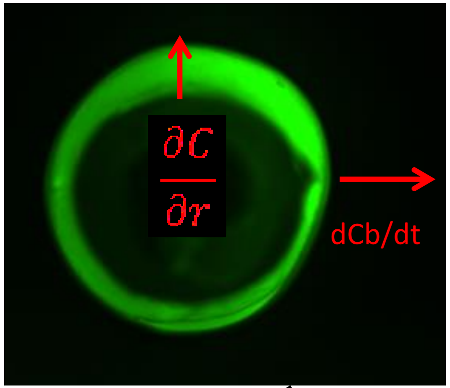
(Fick's 2nd Law in cylindrical coordinates, 1-D)

Spectrophotometry (UV-Vis)

Fluorescence Microscopy



Sample diffusion profile for creatinine.



$$\frac{dC_b}{dt} = D\frac{A}{V}\frac{\partial C}{\partial r}$$

(Fick's 1st Law)

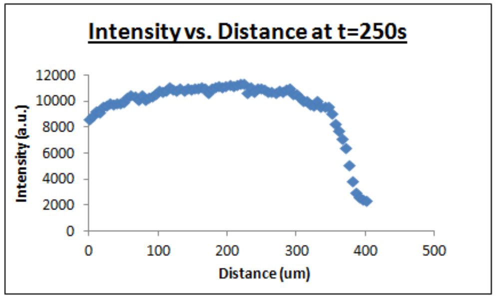
Hollow alginate stents mixed with FITC-dextrans (4K, 70K, and 500K).

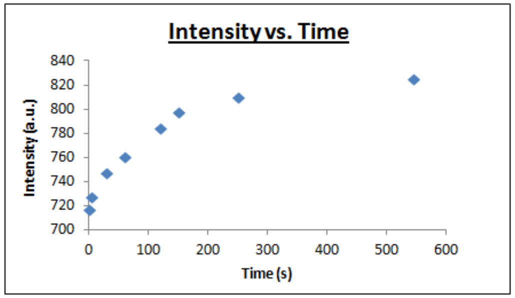
Non-dimensionalized Fick equations

$$\frac{\partial \xi}{\partial \tau} = \frac{1}{\chi}\frac{\partial}{\partial \chi}\left(\chi\frac{\partial \xi}{\partial \chi}\right)$$

I.C.:	$\xi(\chi, 0) = 0$
B.C. 1:	$\frac{d\xi}{d\tau}(\chi, \tau) = 0 \; at \; \chi = \chi 1$
B.C. 2:	$-\frac{d\xi b}{d\tau} = 2\frac{V2}{Vb}\left(1 - \frac{R1}{R2}\right)\frac{\partial \xi}{\partial \chi} \quad at \chi = \chi 2$

Diffusion coefficients across alginate membranes were determined in Matlab for creatinine, PEG and albumin (Stokes' radii ranging from 0.36-3.5 nm).

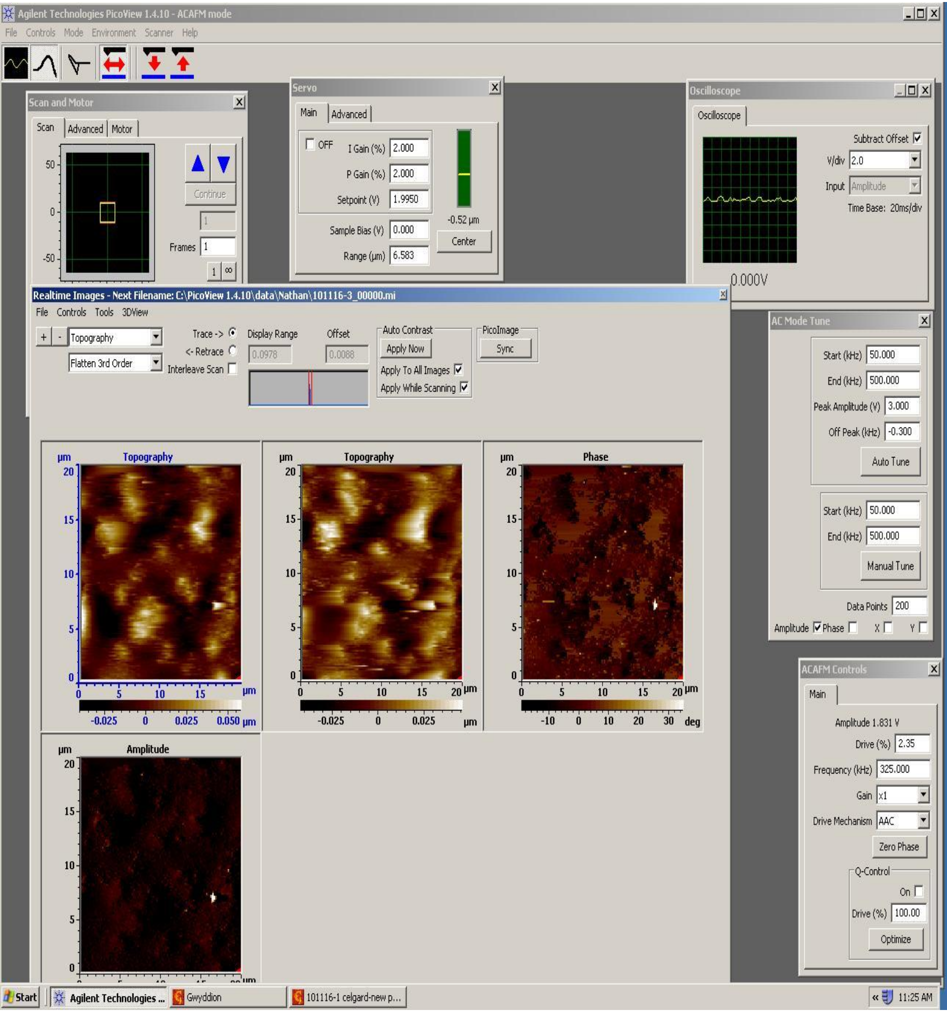




Diffusion Modeling of Bioresorbable Alginate Stents Using Fick's Laws

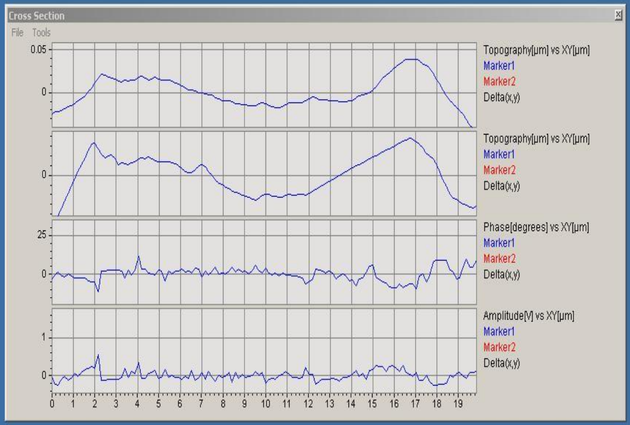
How Do Membrane Pore Size and Porosity Change as a Function Alginate Concentration ?

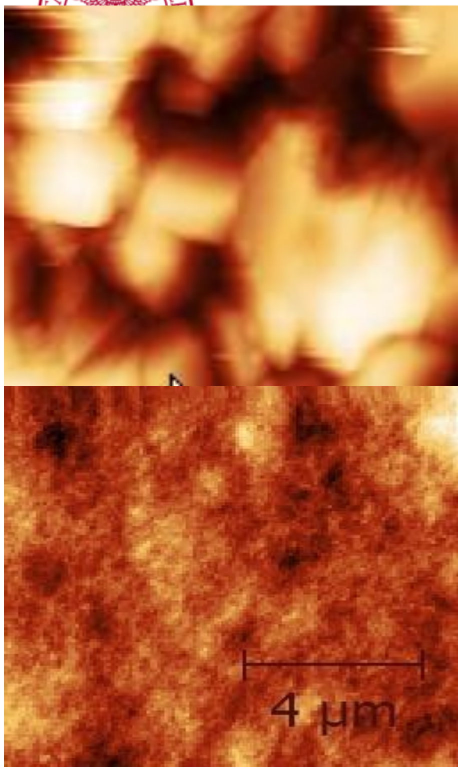
Surface Characterization of Semi-Permeable Alginate Stent

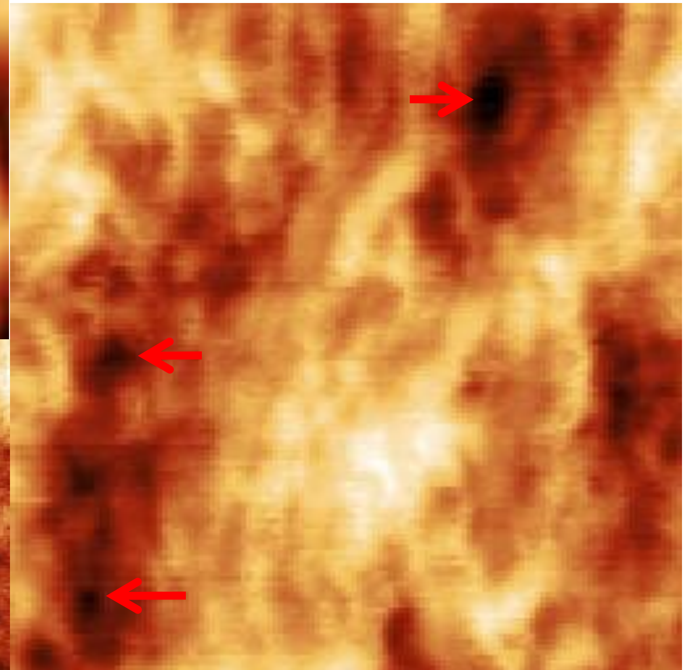


$$\sigma = 1 - \left(1 - \frac{a}{R_p}\right)^2 \left[2 - \left(1 - \frac{a}{R_p}\right)^2\right] \left[1 - \frac{2}{3}\left(\frac{a}{R_p r}\right)^2 - 0.165\left(\frac{a}{R_p}\right)\right]$$

$$a = \left(\frac{3MW}{4\pi \rho N_A}\right)^{1/3}$$







Area: 0.1 micron square
0.5% Alginate 5-12 nm

Alginate AFM imaging was done using Alginate 5500 AFM under contact mode. the Z range, and 0.05 A in Z sensitivity. The X and Y resolution is estimated 20-30 nm. Gwyddion was used to transpose our AFM images to 3D for quantification.

Alginate Pore Sizes Observed with AFM														
	Alginate Concentration, Cross-linked with 1.5% $CaCl_2$													
	0.50%		1.00%		1.50%		2.00%		Uncoated 0.5%LV		Coated 0.5% LV		Dialysis Membrane	
	Δx	Δy	Δx	Δy	Δx	Δy	Δx	Δy	Δx	Δy	Δx	Δy	Δx	Δy
Pore size range (nm)	6.3 - 12.9	4.7 - 12.3	3.7 - 5.6	4 - 6.2	4.8 - 6.4	4.2 - 5	5.5 - 6.0	5.5 - 7.5	6.4 - 7.9	2.9 - 12	5.0 - 14.4	4.6 - 5.6	2.7	7.00
Median Δx and Δy	8.00		4.20		5.00		5.75		7.05		5.70		4.85	
Average Δx and Δy	8.40		4.74		5.19		6.13		7.22		7.00		4.85	

HYDROGEL THEORY AND DEMO

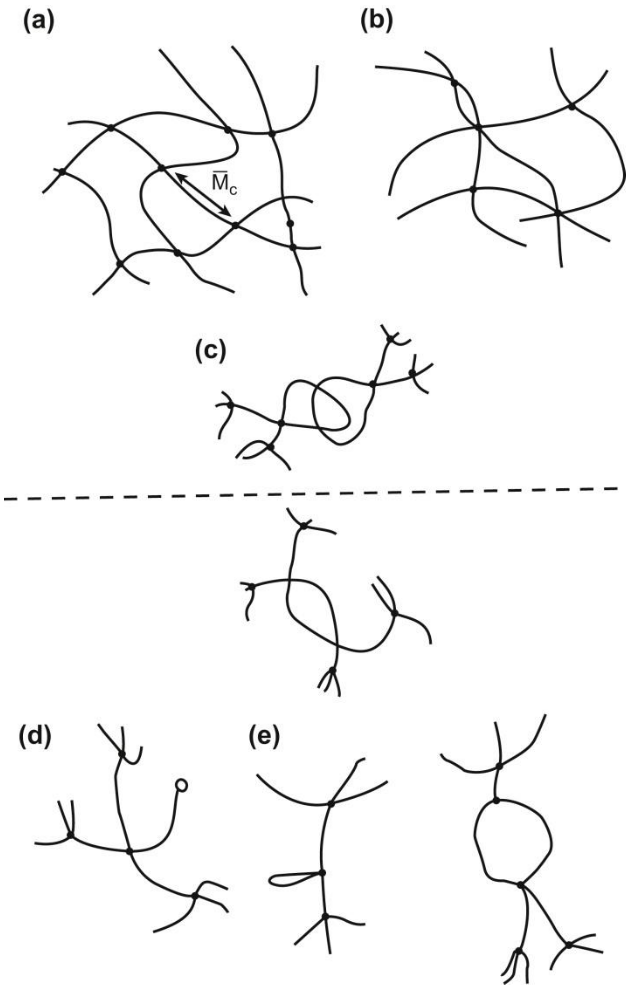


Figure 20.01

THERMODYMICS OF SWELLING

Hydrogel	D_1 (mm)	D_2 (mm)	Q	V1 (ml/mol)	v2,s	χ	ν (cm^3/g)	Mn	PDI	M_w	Mc	ρ
A	1	4	64	18	0.015625	0.154	0.95	1000000	2	2000000	48335	2.18E-05
B	1	1.5	3.375	18	0.296296296	0.154	0.87	200000	1.4	280000	257	4.47E-03
C	1	3	27	18	0.037037037	0.154	0.54	3000000	1	3000000	21028	8.81E-05
D	1	2	8	18	0.125	0.154	0.45	40000	1.2	48000	2500	8.89E-04

PDI=MW/Mn

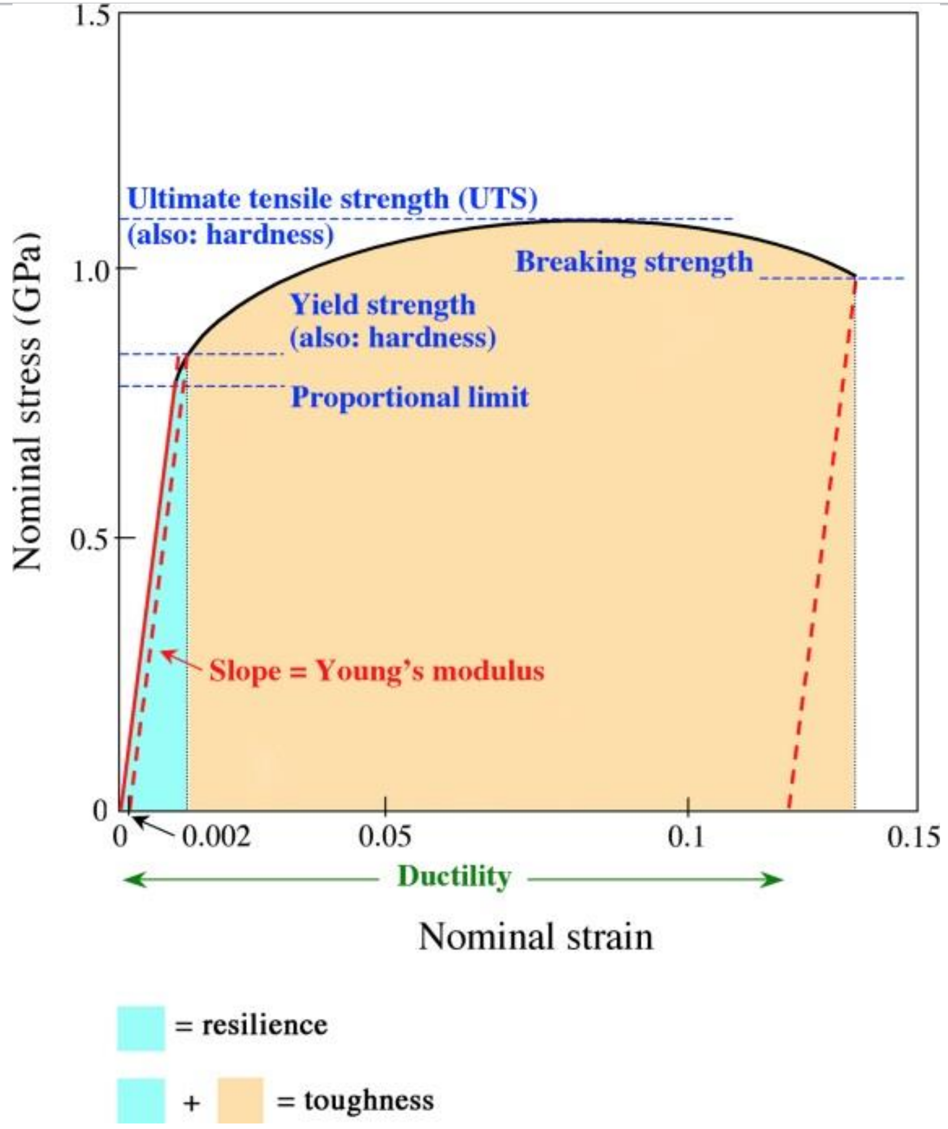
v2,s	volume of unswollen/volume of swollen
Q	1/V2,s
Mc	Interchain MW (use the formula in the book)
ρ	cross-density (use the formula in the book)

$$V_{2,s} = \frac{Volume\ of\ Polymer}{Volume\ of\ gel} = \frac{V_p}{V_{gel}} = 1/Q$$

$V_{2,s}$ polymer volume fraction of gel

Q degree of swelling

Q is related to the mechanical properties of the Hydrogel


1.5
1.0
0.5
0
Nominal stress (GPa)
Ultimate tensile strength (UTS)
(also: hardness)
Breaking strength
Yield strength
(also: hardness)
Proportional limit
Slope = Young's modulus
0
0.002
0.05
0.1
0.15
Ductility
Nominal strain
= resilience
+
= toughness