INTRODUCTION TO WEARABLES AND IMPLANTABLES

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

- 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

Light-Activated Glue for A Broken Heart

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

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

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

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3631569/
Bio-Medical Devices

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

Hyperspectral Imaging

HANDHELD APPLICATIONS TARGETED BY IMEC HSI

Food quality grading (e.g. sugar content in fruits, monitoring calorie intake, etc...)

Cosmetic / Skin tone measurement (e.g. make-up advice, etc...)

Skin-care / personalized medicine (e.g. melanoma, diabetic ulcers, wound care...)

Anti counterfeiting spectral tag readers

+ many new ideas / application to be generated when HSI handled platform ready!

Bio-Diagnostics and Bio-MEMS

miniaturized total chemical analysis systems (µTAS)

Bio-Chip and Micro Device Development

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]

<table>
<thead>
<tr>
<th>Device Categories</th>
<th>Biological Effect</th>
<th>Other$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contact Duration</td>
<td>Initial</td>
</tr>
<tr>
<td></td>
<td>A: Limited</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(≤ 24 hrs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: Prolonged</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(&gt;24 hrs to ≤30 days)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: Permanent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(&gt;30 days)</td>
<td></td>
</tr>
<tr>
<td>Body Contact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Mucoal Membranes</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Breached or</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Compromised</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Surfaces</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>External</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communicating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Devices</td>
<td>Blood Path,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indirect$^1$</td>
<td></td>
</tr>
<tr>
<td>Tissue $^1$</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Bone/Dentin</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Communicating</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Circulating Blood</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Implant Devices</td>
<td>Tissue/Bone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Blood $^3$</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

1. Tissue includes tissue fluids and subcutaneous spaces.  
2. For all devices used in extracorporeal circuits.  
3. Pyrogenicity/Materials Mediated should be considered.  
4. Supplemntal tests for consideration  

![ISO Evaluation Tests for Consideration](image_url)  
6. 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
Homopolymer

Random copolymer

Alternating copolymer

Block copolymer

Graft copolymer
POLYMERS IN MEDICINE

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

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

Figure 8.03

Nitrile

Isoprene

Polyurethane

PTFE

Polyethylene (PE)
Polytetrafluoroethylene (PTFE)
Polypropylene (PP)
Polyvinylchloride (PVC)
Polydimethylsiloxane (PDMS)
Poly(methyl methacrylate) (PMMA)
Polyethyleneterephthalate (PET)
Poly(hydroxyethyl methacrylate) (PHEMA)
Nylon 6,6
Cellulose
<table>
<thead>
<tr>
<th>Polymer</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>UHMWPE</td>
<td>Knee, hip &amp; shoulder joints</td>
</tr>
<tr>
<td>Silicone</td>
<td>Finger Joints</td>
</tr>
<tr>
<td>Polylactic acid, polyglycolic acid, nylon</td>
<td>Sutures</td>
</tr>
<tr>
<td>Polymethyl methacrylate (PMMA)</td>
<td>Bone Cement, Contact Lenses</td>
</tr>
<tr>
<td>Acetal, polyethylene, polyurethane (PTFE), PVC</td>
<td>Pacemakers</td>
</tr>
<tr>
<td>Blood Vessels</td>
<td></td>
</tr>
<tr>
<td>Hydrogels</td>
<td>Ophtalmology, Artificial Organs</td>
</tr>
<tr>
<td>Polydimethyl siloxane, polyurethane</td>
<td>Facial Prostheses</td>
</tr>
</tbody>
</table>
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).
Mechanism I: Cleavage of crosslinks between water soluble polymer chains

Mechanism II: Transformation or cleavage of side chains (X) leading to the formation of polar or charged groups (Y)

Mechanism III: Cleavage of backbone linkages between polymer repeat units
1) **Temporary support device:** Temporary mechanical support until tissue gains its strength
   Sutures [PGA, Dexon]; vascular grafts, bone fixation devices.

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 or more highly electronegative atoms resulting in charge asymmetry and H-bonding.
- Porous and hydrophilic, 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
- Anionic
- Cationic
- Ampholytic
- Amorphous
- Semi-crystalline
- Hydrogen-bonded hydrogels
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
a

Oxidation

Reduction

b

Oxidation +NaClO aq.
+GSH Reduction

Gel

Sol

c

Oxidation +1.0 V versus Ag/AgCl

Δ (50 °C, 1 h) Reduction

Gel

Sol

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

sol

acrylamide-modified chitin

aggregation of the chains

gel

heating

cooling

http://pubs.rsc.org/en/content/articlelanding/2014/tb/c4tb00067f#!divAbstract

SOFT ROBOTICS and IONOPRINTING
BIOFABRICATION

PHOTOLITHOGRAPHY

JOVE

3D-Bioprinting

ORGANONONOVO
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 (5-CFDA) and dying cells red (PI) prior to transplantation (F) and two months posttransplantation (G). Reproduced, with permission, from [91] © 2005 Lippincott Williams and Wilkins.
## MWCO of different Artificial Cell Membranes

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

- Prevalence of Coronary Heart Disease (2010): 11.8% of the American population ([http://www.cdc.gov/nchs/fastats/heart.htm](http://www.cdc.gov/nchs/fastats/heart.htm)).


- 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](http://www.idataresearch.net/idata/report_view.php?ReportID=822)).
SUSTAINABLE WATER-BASED CHEMISTRY
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.
• 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.

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

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% CaCl₂ membrane/core 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.
Spectrophotometry (UV-Vis)

Fluorescence Microscopy

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

Sample diffusion profile for creatinine.

Non-dimensionalized Fick equations

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

\[ a = \left( \frac{3MW}{4\pi \rho N_A} \right)^{1/3} \]
Alginate AFM imaging was done using Alginate 5500 AFM under contact mode. The Z range, and 0.05 Å 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.

<table>
<thead>
<tr>
<th>Alginate Pore Sizes Observed with AFM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alginate Concentration, Cross-linked with 1.5% CaCl₂</td>
</tr>
<tr>
<td>0.50%</td>
</tr>
<tr>
<td>Δx</td>
</tr>
<tr>
<td>Δx and Δy range (nm)</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Average</td>
</tr>
</tbody>
</table>

Area: 0.1 micron square
0.5% Alginate 5-12 nm
HYDROGEL THEORY AND DEMO
Figure 20.01
Q is related to the mechanical properties of the Hydrogel.

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

\[ V_{2,s} \quad \text{polymer volume fraction of gel} \]

\[ Q \quad \text{degree of swelling} \]

<table>
<thead>
<tr>
<th>Hydrogel</th>
<th>D1 (mm)</th>
<th>D2 (mm)</th>
<th>Q</th>
<th>V1 (ml/mol)</th>
<th>v2,s</th>
<th>λ</th>
<th>v (cm³/g)</th>
<th>Mn</th>
<th>PDI</th>
<th>Mw</th>
<th>Mc</th>
<th>ρ</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>4</td>
<td>64</td>
<td>18</td>
<td>0.05825</td>
<td>0.154</td>
<td>0.95</td>
<td>1000000</td>
<td>2</td>
<td>48335</td>
<td>2.18E-05</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>1</td>
<td>1.5</td>
<td>3.375</td>
<td>18</td>
<td>0.28635</td>
<td>0.154</td>
<td>0.87</td>
<td>200000</td>
<td>1.4</td>
<td>257</td>
<td>4.47E-03</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>3</td>
<td>27</td>
<td>18</td>
<td>0.154</td>
<td>0.87</td>
<td>0.87</td>
<td>300000</td>
<td>1</td>
<td>21028</td>
<td>8.81E-05</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>1</td>
<td>2</td>
<td>8</td>
<td>18</td>
<td>0.154</td>
<td>0.54</td>
<td>0.45</td>
<td>40000</td>
<td>1.2</td>
<td>2500</td>
<td>8.89E-04</td>
<td></td>
</tr>
</tbody>
</table>

\[
\text{PDI} = \frac{M_W}{M_n}
\]

\[
V_{2,s} = \frac{1}{Q}
\]

\[
\text{Q is related to the mechanical properties of the Hydrogel}
\]