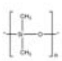
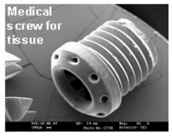
Introduction to BioMEMS & Medical Microdevices

Polymer Microfabrication

Prof. Steven S. Saliterman, http://saliterman.umn.edu/



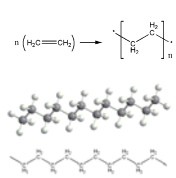


Advantages of Polymers

- Biocompatibility.
- Degradation.
- Enclosure of high-aspect-ratio microstructures.
- Machinability.
- Mechanical properties – e.g., elasticity and swelling (hydrogels)
- Moldable.
- Optical transparency.
- Permeability.
- Photopolymerizable.
- Porosity.
- “Smart” polymers that swell in response to environmental stimuli.
- Surface modification and functionalization.
- Thermal and electrical properties.

Polymerization…

- Addition polymerization:
  - Requires a reactive double or triple bond.
  - Initiation requires a free radical to open the double bond.
  - Propagation occurs by adding monomers.
  - Termination occurs by chain-terminating reactions.
- Step-growth polymerization:
  - Condensation polymers
- Photopolymerization
  - Photoinitiators.

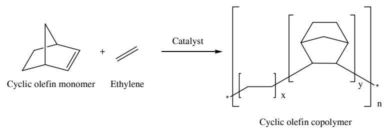


Monomer

Chain Molecule

Copolymers…

- **Homopolymers** contain the same repeating unit.
- **Copolymers** contain more than one type of repeating unit.
  - *Example: Cyclic Olefin Copolymers* (Topas®) for example, are amorphous highly transparent thermoplastics.



Classification based on Mechanical Properties…

- Thermoplastics
  - Consist of linear or branched molecules.
  - Soften and melt when heated and may be used for molding.
  - The molten state consists of a tangle mass of molecules. Upon cooling they may form a glass below the glass transition temperature (Tg), or may crystallize.
  - Liquid crystal polymers found in liquid crystal displays (LCD) are a subset of thermoplastics.
- Rubbers or Elastomers
  - Network polymers that are lightly crosslinked and may be reversibly stretched.
  - Crosslinks prevent the molecules from coming apart during stretching and prevent flow when the material is heated.
- Thermosets
  - Network polymers that are heavily crosslinked and rigid.
  - Flow initially, but once cooled, cure and retain their shape.
  - These include epoxy resins and the phenol- or urea-formaldehyde resins.

Polymers for Medical and Tissue Engineering…

- Naturally Occurring:
  - Hyaluronic acid
  - Collagen
  - Chitin/Chitosan
  - Alginate
  - Fibrin
  - Albumin
  - Chondroitin sulphate
  - Naturally occurring poly(amino acids)
- Synthetic polymers
  - Polyetheretherketone (PEEK)
  - Poly(hydroxyalkanoates)
  - Poly(α-hydroxyacids) (Poly(glycolic acid), Poly(lactic acid) and their co-polymers)
  - Poly(ϵ-caprolactone)
  - Poly(urethanes)
  - Poly(propylene fumarate)
  - Synthetic poly(amino acids)
  - Poly(ortho esters)
  - Poly(anhydrides)
  - Poly(glycerol sebacate)
  - Poly(phosphazenes)
  - Poly(dioxanone)
  - Poly(ethylene glycol) – Poly(ethylene oxide)
  - Hydrogels (synthetic vs natural)

Ozdil D, Aydin HM. Polymers for medical and tissue engineering applications.(Report). 2014;89(12):1793.

Microfabrication Techniques

- Thick resist lithography - ie. SU-8.
- Laser ablation with excimer or Nd:YAG lasers.
- 3D Photopolymerization (Also useful in bioprinting.)
- Thermoplastic injection molding & 3D FDM layer by layer printing.
  - Thermoplastic polymers are heated above their glass transition temperature Tg.
- Soft Lithography.
  - Microcontact printing (μCP)
  - PDMS (polydimethylsiloxane) replica molding (REM).
    - Dow Corning Sylgard 184 PDMS (reagent and hardener)
  - Also, microtransfer molding, micromolding in capillaries & solvent-assisted micromolding.
- Hydrogels

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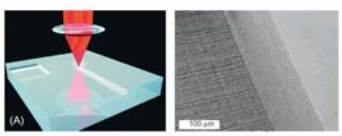
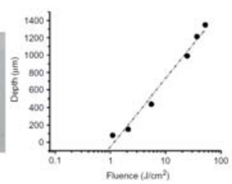
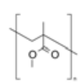
Luttge R. *Nano- and Microfabrication for Industrial and Biomedical Applications, 2nd Edition.* 2016.

Femtosecond Laser Machining…



Scanning electron microscope (SEM) image of ablated microchannel produced in poly(methyl methacrylate) (PMMA).





Ablated depth versus incident laser fluence.
(Optical energy delivered per unit area in joules per square centimeter.)

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Marco, CD. et al. Surface properties of femtosecond laser ablated PMMA, AC Appl. Mater. Interfaces 2(8) (2010) 2377-2384

3-D Photopolymerization…

- 3D photopolymerization is based on layer-by-layer assembly and is used for rapid production of devices including modeling and prototyping.
  - Techniques:
    - 3D Polyjet printers
    - Stereolithography (SL)
    - Microstereolithography (MSL)
    - Dynamic Projection MSL
  - Bioprinting – photocurable hydrogels.

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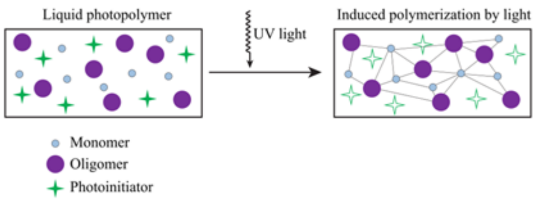

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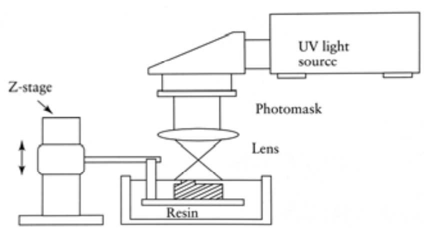
Microstereolithography (MSL)



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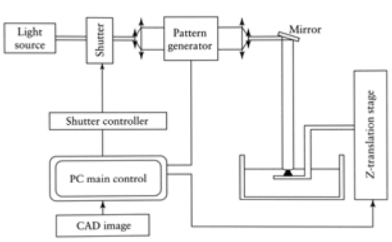
Suzumori, K. and et al., Microfabrication of integrated FMAs using stereolithography. Proceedings of IEEE MEMS, pp. 136-141 (1994)

Dynamic Mask Projection MSL



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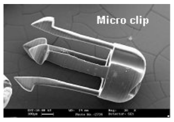
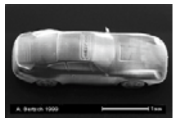
Bertsch, A. et al., Microsterolithography using a liquid crystal display as dynamic generator. *Microsystem Technology* 3(2), pp. 42-47 (1997).

MSL Fabricated Parts

Clips

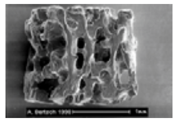


Car



Gear

Bone



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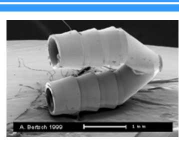
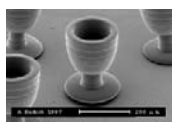
Bertsch A., Personal Correspondence.

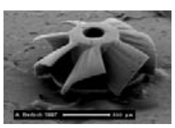
Pipe



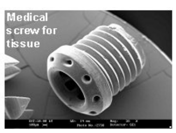
Cup



Gear



Screw



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Images courtesy of Bertsch A.

Injection Molding (Variotherm Process)…

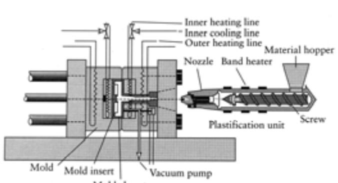
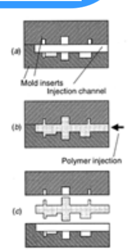


Image courtesy of Thermotech



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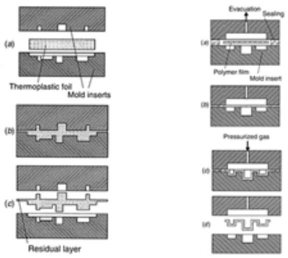
Heckele, M. and W.K. Schomburg, Review on micro molding of thermoplastic polymers. Journal of Micromechanics and Microengineering 14(3), pp. 1-14 (2004).

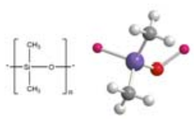
Hot Embossing &Thermoforming…



Heckele, M. and W.K. Schomburg, Review on micro molding of thermoplastic polymers. Journal of Micromechanics and Microengineering 14(3), pp. 1-14 (2004).

PDMS (polydimethylsiloxane) Stamp…

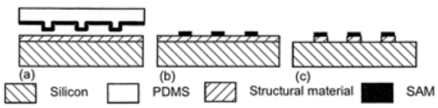
PDMS Stamp (PDMS is a member of the silicone family)



PDMS Monomer

Nguyen, N.T. and S.T. Wereley, Fundamentals and Applications of Microfluidics, Artech House, Boston, MA (2002).

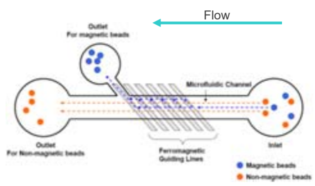
Microcontact Printing (μCP)…

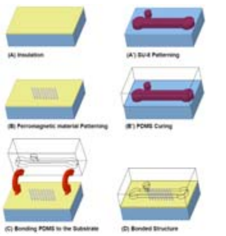


Nguyen, N.T. and S.T. Wereley, Fundamentals and Applications of Microfluidics, Artech House, Boston, MA (2002).

PDMS Replica Molding…

Making a Magnetic Bead Separator





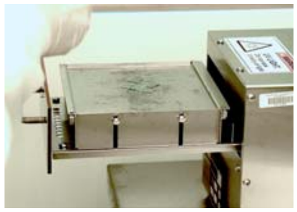
Images courtesy of Jaehoon Chung & Euisik Yoon

Passive Ferromagnetic Bead Separator…

1. A microfluidic system with integrated magnetic structures allowing separation of magnetic and non-magnetic beads contained in a solution passing through it. This could be useful if an analyte of interest is bound to one bead type or the other.
2. Ferromagnetic lines are microfabricated on a silicon substrate using lithography and thin metal film deposition techniques.
3. A master defining the microfluidic channels for PDMS casting is microfabricated on another silicon wafer with SU-8.
4. PDMS is then cast on the master and removed for use.
5. The PDMS is then bonded to the silicon wafer containing the ferromagnetic lines using plasma oxidation.

Preparing and Casting PDMS…

Surface Treatment with Oxygen Plasma…



Alignment on Substrate…

Video Inspection…

Test Apparatus in Lab…

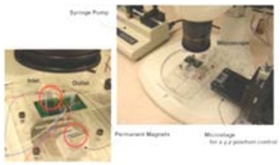
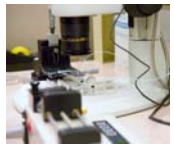


Image courtesy of Jaehoon Chung & Euisik Yoon



Click Picture for Video

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Making a PDMS Microfluidic Device Video…

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Queen Mary University of London (15 minutes) https://youtu.be/lH-FCSxRvrU

Stimuli Responsive Polymers

- "Smart" polymeric materials exhibit significant changes in their characteristics with small changes in their environment.
  - These external stimuli include pH, calcium, magnesium, organic solvents, temperature, magnetic field, electrical potential, and IR and UV radiation.
  - Some materials respond to dual stimuli such as calcium and PEG, calcium and temperature, calcium and acetonitrile, pH and temperature, and light and temperature.
  - Electroactive polymers (EAPs) respond to electrical stimulation.

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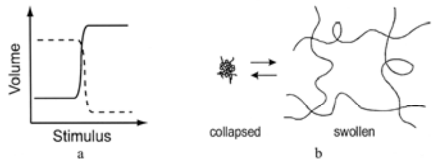
What is Stimulus Response?



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Oosterbroek, R.E. and A. van den Berg, *Lab-on-a-Chip: Miniaturized Systems for (Bio)Chemical Analysis and Synthesis*, 1st ed. Amsterdam, Elsevier (2003).

Parylene Coatings

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Parylene Coating Commercial Application…

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Curtiss- Wright Parylene Coatings https://www.youtube.com/watch?v=Bn-XOsa-xlw

Summary

- Advantages of Polymers
- Microfabrication Techniques
  - Thick resist lithography - ie. SU-8.
  - Laser ablation with excimer or Nd:YAG lasers.
  - 3D Photopolymerization (Also useful in bioprinting.)
  - Thermoplastic injection molding & 3D FDM layer by layer printing.
    - Thermoplastic polymers are heated above their glass transition temperature Tg.
  - Soft Lithography.
    - Microcontact printing (μCP)
    - PDMS (polydimethylsiloxane) replica molding (REM).
      - Dow Corning Sylgard 184 PDMS (reagent and hardener)
- Stimuli Responsive Polymers – Hydrogels
- Parylene coatings.
- Appendix
  - Importance of the substrate surface for promoting cell-substrate interactions.
  - Important Hydrogels

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Controlled Cell-Substrate Interaction

Studying the relationship between the substrate surface and the cell response it evokes:

Bioactive Materials 3 (2018) 355–369

Contents lists available at ScienceDirect

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Bioactive Materials

journal homepage: http://www.keaipublishing.com/en/journals/bioactive-materials/

Micro and Nanofabrication methods to control cell-substrate interactions and cell behavior: A review from the tissue engineering perspective

Menekse Ermis [a,b,1], Ezgi Antmen [a,c,1], Vasif Hasirci [a,b,c,d,*]

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ECM…

- ECM
  - Support material
  - Provides physical & chemical cues
    - These guide cell adhesion, proliferation, morphology and spreading.
  - Synthetic nano- to submicron topologies have similar topologies to *ECM proteins* such as *fibronectin*, *collagen* and *laminin*.
  - These in turn affect *cell-cell interactions* and *cell-cell signaling.*

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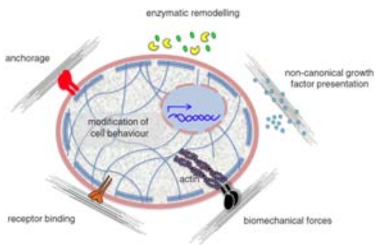
Ermis M, Antmen E, Hasirci V. Micro and Nanofabrication methods to control cell-substrate interactions and cell behavior: A review from the tissue engineering perspective. *Bioactive Materials*. Sep 2018;3(3):355-369. doi:10.1016/j.bioactmat.2018.05.005

Regulating Cell Behavior…

ECM can directly bind different types of cell surface receptors or co-receptors mediating *cell anchorage* and regulating pathways for *intracellular signaling* and *mechanotransduction*. (red, orange & black)

ECM can act by *growth factor* (cyan) presentation, and be remodeled by the action of *enzymes* (yellow pie), which can release *functional fragments* (green)



Gattazzo F, Urciuolo A, Bonaldo P. Extracellular matrix: a dynamic microenvironment for stem cell niche. Research Support, Non-U.S. Gov't Review. *Biochim Biophys Acta*. Aug 2014;1840(8):2506-19. doi:https://dx.doi.org/10.1016/j.bbagen.2014.01.010

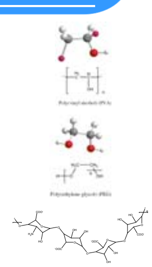
Promoting Cell-Substrate Interactions…

- *Surface engineering* techniques for nano- and micro level *substrate features include*:
  - Photolithography
  - Electron beam lithography
  - Microcontact printing
  - Microfluidics
- *Engineering the chemistry of substrate surfaces* to affect:
  - Cell adhesion
  - Cell spreading or migration
  - Differentiation
  - Shape of the cells
- *Properties* that control these processes:
  - Topography – mimicking the extracellular matrix (ECM)
  - Stiffness
  - Bioactive cell adhesive cues such as peptides and proteins

Ermis M, Antmen E, Hasirci V. Micro and Nanofabrication methods to control cell-substrate interactions and cell behavior: A review from the tissue engineering perspective. *Bioactive Materials*. Sep 2018;3(3):355-369. doi:10.1016/j.bioactmat.2018.05.005

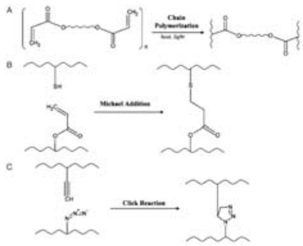
Types of Hydrogels

- Poly(2-hydroxethyl methacrylate)
- PVA - Poly(vinyl alcohol)
- PEG - Poly(ethylene glycol)
- HA - Hyaluronic Acid and Natural Materials
- Fibrin Hydrogels
- Alginate in Hydrogels
- Collagen
- Self-Assembled Peptides



Slaughter BV, Khurshid SS, Fisher OZ, Khademhosseini A, Peppas NA. Hydrogels in Regenerative Medicine. *Advanced Materials*. 2009;21(32-33):3307-3329.

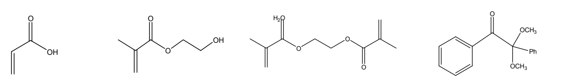
Common Methods for Hydrogel Synthesis…



Slaughter BV, Khurshid SS, Fisher OZ, Khademhosseini A, Peppas NA. Hydrogels in Regenerative Medicine. *Advanced Materials.* 2009;21(32-33):3307-3329.

Example…

- An example of a pH sensitive hydrogel mixture is acrylic acid (AA) and 2-hydroxyethyl methacrylate (HEMA) (in a 1:4 molar ratio), ethylene glycol dimethacrylate (EGDMA) (1 wt %) and a photoinitiator DMPA (3 wt %, Irgacure r 651).
- This mixture, after polymerization produces a hydrogel that swells in basic solution and contracts in acidic solution



Acrylic Acid (AA) | 2-hydroxyethyl methacrylate (HEMA) | Ethyleneglyco dimethacrylate (EGDMA) | 2,2'-dimethoxy-2-phenyl acetophenone (DMPA)

Hydrogel Design…

- Design considerations
  - Hydrogels may be selectively polymerized by using UV (365 nm) light, a collimating microscope and photolithography masks. An energy level of 40 mW/cm_2 can induce polymerization.
  - Biocompatibility
  - Vascularization
  - Degradation
- Network structure and properties
  - Physical structure
  - Equilibrium swelling
  - Rubber elasticity

Hydrogels in Tissue Engineering…

- Applications in tissue engineering
  - Scaffold materials
  - Barriers
  - Controlling the macroenvironment, such as mechanical and physiochemical properties for ECM engineering. For example, stiffness may be tuned to replication cirrhosis and hepatocellular cancer growth.
  - Controlling the cellular microenvironement - cues for cellular growth and proliferation.
  - Drug delivery
  - In-situ valves in microfluidic devices

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Slaughter BV, Khurshid SS, Fisher OZ, Khademhosseini A, Peppas NA. Hydrogels in Regenerative Medicine. *Advanced Materials.* 2009;21(32-33):3307-3329.