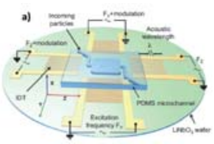
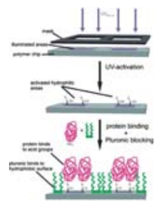
Introduction to BioMEMS & Medical Microdevices

Lab-on-a-Chip Part 1 – Cell & Molecule Manipulation

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



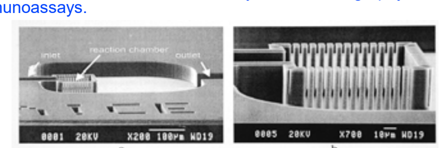


Cell & Molecule Manipulation

- Methods to manipulate micro or nano scale objects:
  - Optical
  - Acoustic
  - Electrical
  - Centrifugal force
  - Hydrodynamic
  - Magnetic
  - Surface modification
- Examples
  - Mechanical – barriers, porous membranes.
  - Impedance
  - Surface Acoustic Waves.
  - Dielectrophoresis.
  - Optical Tweezers and Scissors.
  - Electrowetting & Digital
  - Lab on a Disk – DNA, ELISA.
  - Surface Modification – plasma, CVD, laser, UV radiation, biofunctionalization, selective protein adsorption, and PEG/gold.

Mechanical

- A filter chamber fabricated by DRIE in a silicon substrate - 3 µm wide and 50 µm high pillars, and 2 µm spacing.
- This device was used for a pyrosequencing reaction whereby light emitted from the reaction chamber is collected by a CCD camera.
- Also useful for bead based DNA analysis, chromatography and immunoassays.



a b

van der Wijngaart, W. and et al. Handling of beads in microfluidic devices for biotech applications, *Lab-on-a-chip: Miniaturized Sytems for BioChemical Analysis and Synthesis*, Edited by R.E. Oosterbroek and A. Van den Berg. Elsevier, The Netherlands (2003).

Semipermeable Membranes…

- Permselective membranes for cell immunoisolation:
  - High density uniform pores allow sufficient permeability to nutrients and hormones while preventing the passage of immunoglobulins.
  - For example islet-cell transplantation.
- Uniform pores can be micromachining in silicon.
- Polyethylene terephthalate (PET) membranes may be machined with an excimer laser to produce pores as sieves.

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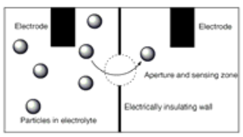
Impedance Cell Sizing (Coulter principle)

- Cells passing through an aperture displace electrolyte and give rise to a change in impedance over the insulating wall.
- By giving the sensors a constant current, changes can be recorded by changes in voltage across the electrodes.
- Each cell crossing gives a pulse shaped response, the magnitude being related to the volume.
- Thousands of cells can be analyzed in a second.



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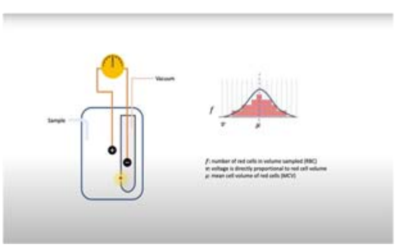
Counting Red Cells…



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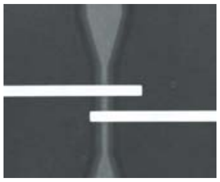
https://youtu.be/SVqk44sZ9n0

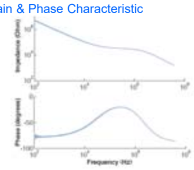
Example: Impedance Detection of C. Albicans

When an appropriate *frequency* is applied to two electrodes present in a microfluidic channel, the *impedance* change in the detection volume can be used to distinguish *between unbound beads and beads bound to pathogens*.



Micrograph of chip in detection region. Channel depth/width of 19x40 micrometer.

Gain & Phase Characteristic



Top: impedance as a function of frequency
Bottom: phase as a function of frequency

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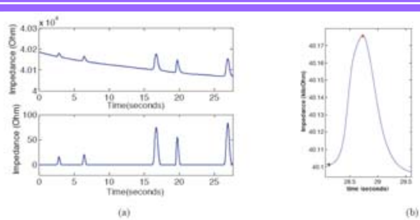
E.J. van der Wouden et al. / Procedia Engineering 25 (2011) 1465 – 1468

Impedance Detection of C. Albicans…



(a) Electrical detection of cells in PBS (phosphate buffered saline) buffer passing the detection volume. Top - raw measurement signal. Bottom - signal corrected for drift.
(b) Magnification of a measured impedance response for a passing yeast cell.

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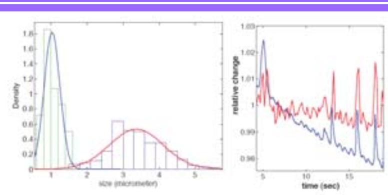
Effective Diameter from Impedance Changes…



Left - Effective *diameter* extracted from measured impedance changes, with a normalized fit for populations smaller and larger than 1.5 μm.
Right - Impedance (blue) and optical signal (red) of beads and pathogens passing the detection volume.

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Acoustic Forces

- Applications
  - Single cell isolation.
  - Cell focusing and sorting.
  - Cell washing and patterning.
  - Cell–cell fusion and communication.
  - Tissue engineering.
- Examples
  - Forces acting on cells and molecules in fluid suspension.
  - Cell manipulation in 2D based on resonance, frequency change and nodes.
  - Acoustic cell separator.

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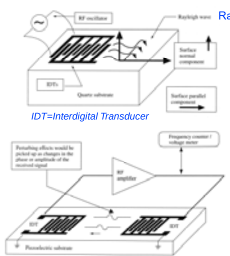
Barani A, Paktinat H, Janmaleki M, et al. Microfluidic integrated acoustic waving for manipulation of cells and molecules. *Biosensors & Bioelectronics.* 2016;85:714-725.

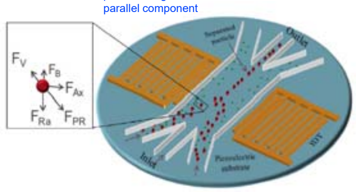
Surface Acoustic Waves – Gardner et. al.…



Rayleigh ("ray-lee") wave

IDT=Interdigital Transducer

Surface particles on the substrate move in elliptical paths having a similar surface-normal and surface-parallel component



Left) Gardner, JW, VK Varadan and OO Awadelkarim, *Microsensors, MEMS and Smart Devices*. John Wiley & Sons, Ltd. W. Sussex (2001).
Right) Barani A, Paktinat H, Janmaleki M, et al. Microfluidic integrated acoustic waving for manipulation of cells and molecules. *Biosensors & Bioelectronics.* 2016;85:714-725.

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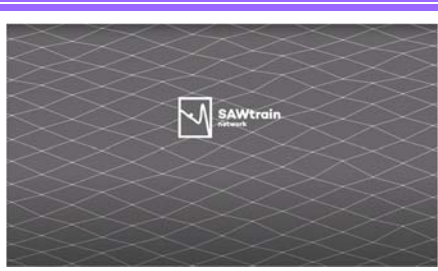
SAW Devices…



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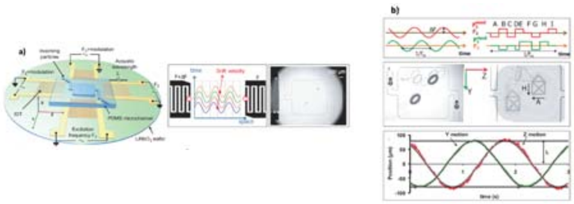
https://youtu.be/H0MJstxNDQM

Cell Manipulation in 2D & Resonance Frequency…



a, b) Moving a cell in 2D by altering the frequency in Hz scale. Since the frequency modulation is small in contrast to the resonance frequency, this moves the node position but keeps the resonance mode.

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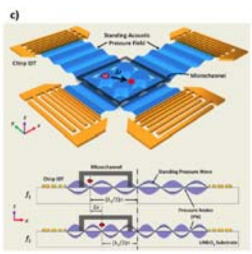
Tran, S.B.Q., Marmottant, P., Thibault, P., 2012. Appl. Phys. Lett., 101.

Effect of Altering Frequency…



c) For moving a trapped cell in a node in 2D pattern, the resonance frequency is shifted to the next resonance frequency which produces different nodal points. The trapped cells move to the adjacent nodes produced by a new frequency. (Note the $LiNbO_2$ substrate.)

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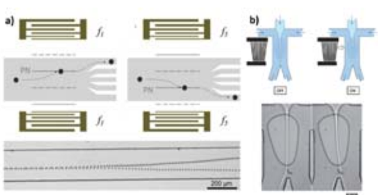
Ding, X., Lin, S.-C.S., Kiraly, B., Yue, H., Li, S., Chiang, I.-K., Shi, J., Benkovic, S.J., Huang, T.J., 2012a. PNAS 109 (28), 11105–11109.

Acoustic Cell Sorting – Ding et. al.…



a) Acoustic based-device for sorting the cells in different lines across the channel. By changing the nodal line, cells are sorted in different positions across the channel.
b) Pushing the fluid, carrying the cells toward the desired outlet by acoustic force.

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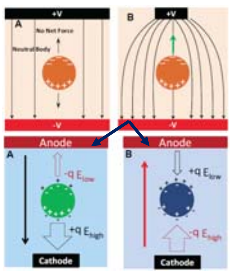
Ding, X., Lin, S.-C.S., Lapsley, M.I., Li, S., Guo, X., Chan, C.Y., Chiang, I.-K., Wang, L., McCoy, J.P., Huang, T.J., 2012b. Lab. Chip 12, 4228–4231.
Franke, T., Braunmuller, S., Schmid, L., Wixforth, A., Weitz, D.A., 2010. Lab. Chip 10, 789–794.

Dielectrophoresis

- Motion of polarized (uncharged) particles in a nonuniform electric field.
- Dielectrophoretic forces depend on:
  - Charge of the particle (may be uncharged).
  - Geometry of the device.
  - Dielectric constant of the medium and particle.
  - Physiology of the particle.
- Uses:
  - Trapping, sorting, focusing, filtration, patterning, and assembly particles from 10nm to 100um.
  - Separating biological entities/particles suspended in a buffer medium.

Steven S. Saliterman Jubery, TZ and P. Dutta. A new design for efficient dielectrophoretic separation of cells in a microdevice . *Electrophoresis* 2013, 34, 643–650

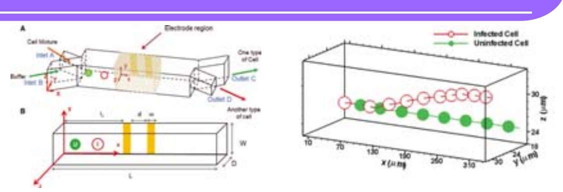
Dielectrophoresis…



A. Uniform electric field
B. Nonuniform electric field.
   A. Particle is more polarizable than the medium and it experiences net force toward the higher electric field (E_{high}) region. This process is known as pDEP.
   B. Particle is less polarizable than the medium, and the net force on the particle acts toward the lower electric field (E_{low}) region. This type of particle motion is known as nDEP.

Steven S. Saliterman Jubery, TZ and P. Dutta. A new design for efficient dielectrophoretic separation of cells in a microdevice . *Electrophoresis* 2013, 34, 643–650

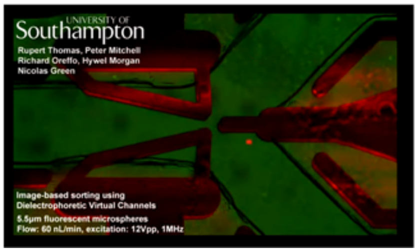
Proposed Device – Jubery et. al.…



A. A mixture of cells is introduced through inlet A and buffer is introduced through inlet B. The bulk fluid flow velocity through these inlets is 200 m/s.
B. Computational domain for simulation-considering particles. This domain is considered from the shaded region in the actual device.
C. Translocation path of cells in actual domain.

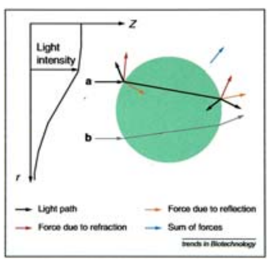
Steven S. Saliterman Jubery, TZ and P. Dutta. A new design for efficient dielectrophoretic separation of cells in a microdevice . *Electrophoresis* 2013, 34, 643–650

Dielectrophoresis Separation…



https://youtu.be/9O4V242rX2I

Optical Forces on a Dielectric Particle…



Laser light of intensity (z) varies across space (r) as shown in the graph, and is reflected and refracted at the interface of the particle.

Photons have momentum and so their redirection by interacting with the particle results in a momentum transfer to the particle.

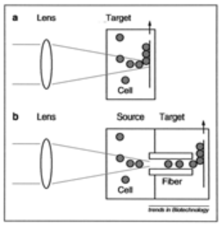
Light is strongest at a (a) resulting in movement towards the beam axis. The net result is shown by the blue arrow.

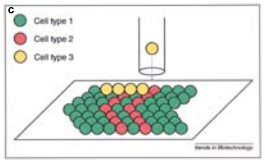
Odde, DJ and MJ Renn. Laser-guided direct writing for applications in biotechnology. *Trends in Biotechnology* 17(1), pp 385-389 (1999)

Optical Tweezers and Scissors

Munce , NJ 2005

Applications…





a) Direct writing system.
b) Coupling with hollow optical fiber to target surface.
c) 3D patterning of multiple cell types.

Odde, DJ and MJ Renn. Laser-guided direct writing for applications in biotechnology. *Trends in Biotechnology* 17(1), pp 385-389 (1999)

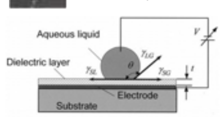
Electrowetting

- *Young's equation* (after Thomas Young who first proposed it in 1805) describes the simple balance of force between the liquid-solid, liquid-vapor, and solid-vapor interfacial surface energies of a droplet on a solid surface:

$$\gamma_{LG}\cos\theta + \gamma_{SL} = \gamma_{SG},$$

where
γ_{LG} (gamma liquid-gas) is the liguid-gas interfacial tension,
γ_{SL} (gamma solid-liquid) is the solid-liquid interfacial tension,
γ_{SG} (gamma solid-gas) is the solid-gas interfacial tension, and
θ (theta) is the contact angle.

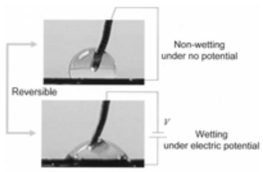
Thomas Young lived from 1773 to 1829 and was an English scientist and researcher. Discovered interference of light.



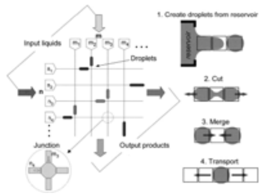
Cho, SK, et al., "Creating, transporting, cutting and merging liquid droplets by electrowetting-based actuation for digital microfluidic circuits." *Journal of Microelectrochemcial Systems* 12(1) pp. 70-80 (2003)

- Surface tension is a property of the liquid and is dependent on temperature and the other fluid it is in contact with.
- At the interface between a liquid and a gas, or between two immiscible liquids, forces develop in the liquid surface that causes the surface to behave as if a "membrane" were stretched over it.
- This phenomenon is due to unbalanced cohesive forces acting on the liquid molecules at the fluid interface.
- Surface tension is the *intensity of molecular attraction per unit length* along any line in the surface.

Digital Manipulation…



Electrowetting and electrocapillary - an externally added electrostatic charge will modify the surface tension or capillary forces at the fluid-surface interface.



Digital microfluidic circuit for manipulating samples and reagents. Division, transport and merging.

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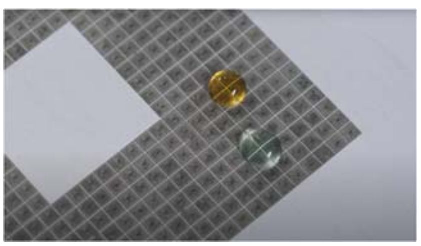
Cho, SK, et al., "Creating, transporting, cutting and merging liquid droplets by electrowetting-based actuation for digital microfluidic circuits." *Journal of Microelectrochemcial Systems* 12(1) pp. 70-80 (2003)

Digital Microfluidics…



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https://youtu.be/z0NBsyhApvU

- The effect of a potential *V* on the contact angle is then determined by the following:

$$\cos\theta(V) - \cos\theta_o = \frac{\varepsilon_r \varepsilon_o}{2\gamma_{LG} t} V^2,$$

where
θ (theta) is the contact angle,
θ_o (theta-nought) is the equilibrium contact angle at $V = 0$,
V is the electric potential across the interface (V),
ε_r (epsilon) the dielectric constant of the dielectric layer,
ε_o (epsilon) is the permittivity of a vacuum (8.85×10^{-12} F/m),
(where F = farad per m) and
t is its thickness (m).

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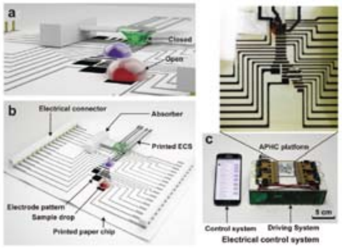
Paper-Based Microfluidic Chip – Ruecha et. al.…

A printed, paper-based active microfluidic chip actuates drops by electrowetting.

a) Partially open (blue and red drops) and closed (green drop) forms.
b) A modularly assembled platform.
c) An integrated portable electrical control system consisting of the chip platform, the driving system, and the mobile-based wireless control system.

This system was able to detect glucose, dopamine and uric acid with its electrochemical sensors.



Ruecha, N., Lee, J., Chae, H., Cheong, H., Soum, V., Preechakasedkit, P., Chailapakul, O., Tanev, G., Madsen, J., Rodthongkum, N., 2017. Adv. Mater. Technol. 2 (3), 1600267.

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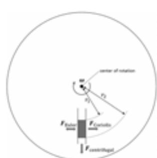
Centrifugal Microfluidics – CD Size Disks

- Applications
  - Clinical chemistry.
  - Immunodiagnostics
  - Protein analysis.
  - Cell handling.
  - Molecular diagnostics.
  - Food, water, and soil analysis.
- Features
  - Pneumatic energy for switching or pumping "inward"
  - Pre-storage and release of reagents
  - No external pumps.
  - Volumes from nL to mL.
  - Channels, chambers and sensor matrices.
  - Bubble removal.
  - Metering and mixing.
  - Parallel operations.



Strohmeier O, Keller M, Schwemmer F, et al. Centrifugal microfluidic platforms: advanced unit operations and applications. *Chemical Society Reviews.* 2015;44(17):6187-6229.

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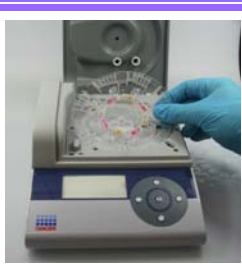
Lab-on-a-Disk: DNA – Mark et. al.…



Example:
Nucleic acid based detection of pathogenic microorganisms and the immunoassay based detection of toxins.

Process:
1. Storage of liquids and lyophilized reagents on the LabDisk and their time-controlled release.
2. Transfer of sample material by the use of antibody-coated microbeads.
3. Aliquoting of sample material for simultaneous analysis on one LabDisk.

Mark, D., et al. 2012. Automated and miniaturized detection of biological threats with a centrifugal microfluidic system. *Smart Biomedical and Physiological Sensor Technology* Ix 8367, 83670E.

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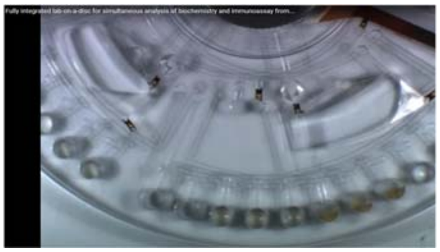
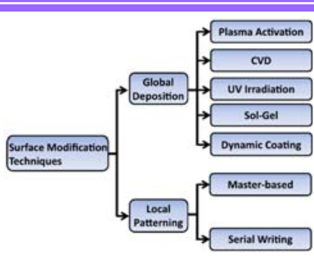


1.09 m, https://youtu.be/iXUtVtpP6Q8

Surface Modification - Polymers



Kitsara, Maria, and Jens Ducree. 2013. Integration of functional materials and surface modification for polymeric microfluidic systems. Journal of Micromechanics and *Microengineering* 23, no. 3:033001.

Functions of Surface Layers…

- Change of contact angle.
- Provision of functional groups for surface.
- Lowering surface energy.
- Immobilization (of molecular capture probes).
- Suppression of non-specific absorption/biofouling.
- Establishment of barrier properties to prevent swelling/dissolution.
- Gas permeability.
- Tuning of optical and thermal properties, dirt protection.
- Scratch resistance.

Kitsara, Maria, and Jens Ducree. 2013. Integration of functional materials and surface modification for polymeric microfluidic systems. Journal of Micromechanics and *Microengineering* 23, no. 3:033001.

Global Deposition…

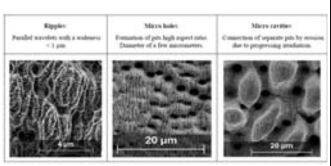
- Plasma Activation. (Ar, Ne, He, H_2, NH_2, CO, CO_2, O_2, H_2O, N_2, NO_2 and F_2)
  - e.g. Oxygen gas induces the formation of *hydrophilic* groups on the surface. (Although transient, as they quickly revert back.)
- Chemical Vapor Deposition.
  - Solvent-free integration of thin films and nanostructures.
- UV Irradiation
  - Short-wavelength radiation in this range can be applied to the surface modification of fluorocarbon polymers.
  - In UV light at low wavelengths (180–190 nm) acidic groups are created on the polymer surfaces that are available for patterned protein binding and cell adhesion.
- Sol-Gel
  - Low reaction temperature
  - May provide improved bonding, barriers, corrosion protection.
- Dynamic Coatings
  - Surfactant solutions are pumped at a certain constant speed through the channel and physisorb to the channel surface. Eventual desorption from the surface.

Kitsara, Maria, and Jens Ducree. 2013. Integration of functional materials and surface modification for polymeric microfluidic systems. Journal of Micromechanics and *Microengineering* 23, no. 3:033001.

Hydrophobic & Hydrophilic Surfaces…

https://youtu.be/FLegmQ8_dHg

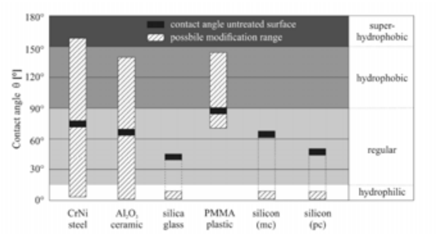
Ultra Short Laser Pulse Modification…



Hildenhagen, J. et al. 2013. Simultaneous Micro Structuring and Functionalization of Surfaces with Picosecond Laser. *International Conference on Optics in Precision Engineering and Nanotechnology* (Icopen2013) 8769, 87691D.
https://youtu.be/ciyxPgiEjlk

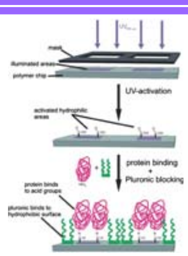
https://youtu.be/ciyxPgiEjlk

Obtained Contact Angle Modification…



Hildenhagen, J. et al. 2013. Simultaneous Micro Structuring and Functionalization of Surfaces with Picosecond Laser. *International Conference on Optics in Precision Engineering and Nanotechnology* (Icopen2013) 8769, 87691D.

Biofunctionalization…

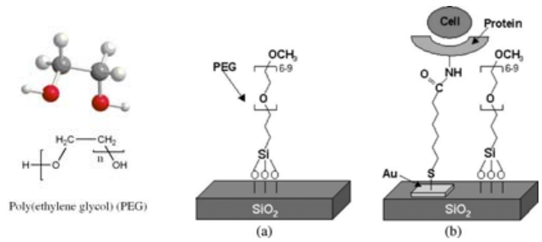


Schutte J, Freudigmann C, Benz K, Bottger J, Gebhardt R and Stelzle M 2010 A method for patterned in situ biofunctionalization in injection-molded microfluidic devices Lab Chip 10 2551–8

Selective Protein Adsorption…

- *Biofouling* occurs as platelets, fibrinogen, IgG and albumin bind to sensors and other surfaces.
- *Foreign body giant cells* (FBGC) may envelope surfaces in response to macrophages being drawn to areas of inflammation.
- *Poly(ethylene glycol)* (PEG):
  - A nontoxic, non-immunogenic and non-antigenic polymer may prevent these phenomena.
  - Stable, non-fouling surfaces may be created by:
    - Chemical coupling reactions,
    - UV-induced graft polymerizations,
    - Self assembled monolayers (SAMs).

PEG and Gold Surface Modification…



Lan, SM et al. "Surface modification of silicon and gold-patterned silicon surfaces for improved biocompatibility and cell patterning selectivity. *Biosensors and Bioelectronics* 20(9), pp. 1697-1708 (2005).

Summary

- Methods to manipulate micro or nano scale objects:
  - Mechanical Barriers - barriers, porous membranes.
  - Impedance
  - Surface Acoustic Waves.
  - Dielectrophoresis.
  - Optical Tweezers and Scissors.
  - Electrowetting & Digital Manipulation
  - Lab-on-a-Disk
  - Surface Modification – Plasma, CVD, Laser, UV radiation, Biofunctionalization, Selective Protein Adsorption, PEG/Gold.
- Appendix – LOC material comparison. Plasma, CVD, UV & sol-gel coating techniques. More Lab-on-Disk.

LOC Materials…

Table 3. Comparison of Typical Materials Used for the Fabrication of LOC Systems

material	characteristics
silicon	rigid, high temperature resistance, ease of surface modifications (silanol), biocompatible, low unspecific binding, not gas-permeable, active fluidic system requires polymer hybrid device
ceramics	rigid, good mechanical, thermal and electrical properties
glass	rigid, transparent, ease of surface modification
poly(methyl methacrylate) (PMMA)	rigid, transparent, low water absorption
cyclic olefin copolymer (COC)	rigid, transparent, low water absorption
polystyrene (PS)	rigid, transparent
polycarbonate (PC)	rigid, transparent, highly heat resistant
polydimethylsiloxane (PDMS)	flexible, transparent, biocompatible, chemically inert, highly gas permeable
Whatman chromatography paper	rigid, pure cellulose, homogenous, reproducible, biocompatible

Wongkaew N, Simsek M, Griesche C, Baeumner AJ. Functional Nanomaterials and Nanostructures Enhancing Electrochemical Biosensors and Lab-on-a-Chip Performances: Recent Progress, Applications, and Future Perspective. *Chemical Reviews.* 2019;119(1):120-194.

Fabrication Costs…

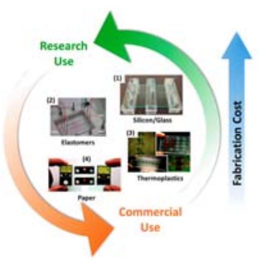


Table 4. Evaluation of Practicability of LOC Materials for Use in Biosensor-Related Applications[71]

applications	silicon/ glass	elastomers	thermoplastics	paper
electrochemical detection	good	limited	moderate	moderate
cost of production	high	medium	low	low
reusability	yes	no	yes	no
disposable device use	expensive	good	good	good
online monitoring	yes	yes	yes	no

Wongkaew N, Simsek M, Griesche C, Baeumner AJ. Functional Nanomaterials and Nanostructures Enhancing Electrochemical Biosensors and Lab-on-a-Chip Performances: Recent Progress, Applications, and Future Perspective. *Chemical Reviews.* 2019;119(1):120-194.

Plasma and CVD Techniques…

Table 1. Characteristics of plasma treatment techniques in polymer microfluidics.

Research group	Polymeric substrate	Type of gas and contact angle	Stability of the coating
Tsougeni *et al* [98]	PMMA, PEEK	O_2, ≤5° C_4F_8, 153°	20 days (PMMA), 60 days (PEEK) Months to years
Tserepi *et al* [99]	PDMS	O_2, ≤5° Teflon-like coating + O_2, ~140°	Not evaluated
Vourdas *et al* [100]	PMMA + Si-containing photoresist	O_2, ≤5°	Not evaluated
He *et al* [101]	PMMA	O_2 + CYTOP, 120° O_2 + CYTOP-polyaniline, 170°	Not evaluated
Subramanian *et al* [102]	PMMA, COC, PC	O_2 + heptadecafluoro-1,1,2,2-tetrahydrodecyl trichlorosilane (HFTTCS), ≥145°	Not evaluated
Maheshwari *et al* [103]	PDMS	O_2, ~8° O_2 + bPEI, 32°	85% recovery after 5 days Stable for ~5 days
Roy and Yue [104]	COC	O_2, 7° Ar, 10° N_2, 3°	Not evaluated
Wang *et al* [105]	PDMS	Air + APTES, 106° Air + APTES + mPEG, 64°	4 weeks

Table 2. Characteristics of CVD techniques in polymer microfluidics.

Research group	Polymeric substrate	Deposited material	Stability of the coating
Chen and Lahann [108]	PDMS	Poly-(4-benzoyl-*p*-xylylene-*co*-*p*-xylylene)	Not evaluated
Riche *et al* [109]	PDMS	Poly(PFDA-*co*-EGDA)	Not evaluated
Dudek *et al* [110]	COP	SiO_2	27 weeks
Gandhiraman *et al* [111, 112]	COP	APTES, APTES + EDA, DEGDME, MPTMS	Not evaluated
Eichler *et al* [113]	PC, COC	HMDSO, TMS, TEOS, SiH_4	20 days
Joshi *et al* [114]	SU-8	Amine groups due to the pyrolytic dissociation of ammonia	Not evaluated

Kitsara, Maria, and Jens Ducree. 2013. Integration of functional materials and surface modification for polymeric microfluidic systems. Journal of Micromechanics and *Microengineering* 23, no. 3:033001.

UV Irradiation and Sol-Gel…

Table 3. Characteristics of UV irradiation techniques in polymer microfluidics.

Research group	Polymeric substrate	Wavelength (nm)	Stability of the coating
Schütte *et al* [119]	COC	185	Acid groups' density decrease to 25% within 19 weeks
Pfleging *et al* [120]	PS	Laser: 193 Mercury lamp: 185	Not evaluated
Nagai *et al* [121]	PDMS	248	Not evaluated
Hozumi *et al* [122, 123]	PMMA, PS	172	PMMA: not evaluated PS: only 100 kPa remains stable after 30 days

Table 4. Characteristics of sol–gel techniques in polymer microfluidics.

Research group	Polymeric substrate	Deposited material	Stability of the coating
Yang *et al* [126]	PDMS	Glass layer from TEOS	No available data
Abate *et al* [125]	PDMS	Glass layer from TEOS and MTES	
Roman and Culbertson [127]	PDMS	Glass layer from isopropoxide, zirconium isopropoxide and vanadium triisobutoxide oxide	

Steven S. Saliterman

Kitsara, Maria, and Jens Ducree. 2013. Integration of functional materials and surface modification for polymeric microfluidic systems. Journal of Micromechanics and *Microengineering* 23, no. 3:033001.

Carrier for Immunoassay…

Disposable test carrier for immunoassay: reagents are stored in aluminium pouches. If centrifugal force is applied, the pouches burst due to the increased hydrostatic pressure of the liquid.

Steven S. Saliterman

Mark, D., et al. 2012. Automated and miniaturized detection of biological threats with a centrifugal microfluidic system. *Smart Biomedical and Physiological Sensor Technology* Ix 8367, 83670E.

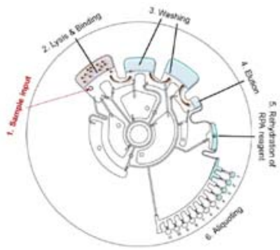
Transfer of Magnetic Beads…

The transfer of magnetic beads is automated by rotating the disk over a magnet.

Steven S. Saliterman

Mark, D., et al. 2012. Automated and miniaturized detection of biological threats with a centrifugal microfluidic system. *Smart Biomedical and Physiological Sensor Technology* Ix 8367, 83670E.

Nucleic Acid Analysis…

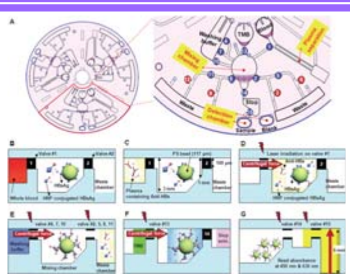


Process for the nucleic acid analysis.

After extraction and amplification the sample is divided into multiple chambers.

Mark, D., et al. 2012. Automated and miniaturized detection of biological threats with a centrifugal microfluidic system. *Smart Biomedical and Physiological Sensor Technology* Ix 8367, 83670E.

Lab-on-a-Disk: ELISA – Lee et al.…



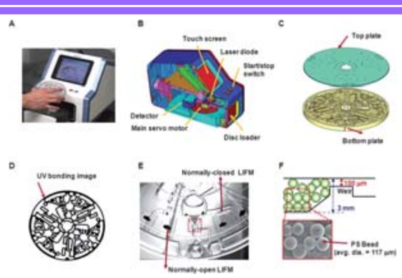
Automated enzyme-linked immuno-sorbent assay (ELISA) system.

Starting with whole blood, this microbead based system can measure the concentrations of the antigen and the antibody of Hepatitis B virus (HBV), HBsAg and Anti-HBs.

Compared to conventional ELISA, time was reduced from 2 hrs. to 30 min.

Lee, B. et al. A fully automated immunoassay from whole blood on a disc. *Lab Chip*, 2009, 9, 1548–1555

ELISA…

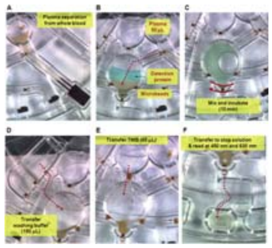


Lee, B. et al. A fully automated immunoassay from whole blood on a disc. *Lab Chip*, 2009, 9, 1548–1555

Spin "Program" and Images

Table 1 Spin program

Spin No.	Speed (rpm)	Time (sec.)	Operation
1	3600	180	Plasma separation
2	2400	20	Transfer plasma into mixing chamber
3	+250~−250	600	Mix beads, plasma & detection probe
4	2400	35	Remove residue to waste chamber
5	—	2	Close 1st waste channel
6	2400	20	Transfer 1st washing buffer (150 μL) to mixing chamber
7	+250~−250	20	Mixing beads and washing buffer
8	2400	35	Remove 1st washed residue
9	—	2	Close 2nd waste channel
10~17		170	Repeat 6~9 twice for 2nd and 3rd washing step (each 100 μL)
18	2400	20	Transfer TMB to mixing chamber
19	+250~−250	600	Mixing beads and TMB
20	2400	20	Transfer to stopping solution chamber
21	+250~−250	20	Mixing with stopping solution
22	2400	20	Transfer to detection chamber
23	—	20	Detection



Lee, B. et al. A fully automated immunoassay from whole blood on a disc. *Lab Chip*, 2009, 9, 1548–1555