Lab on a chip application

- Pharma (R&D in drug development, quality control, screening)
- Environment (water monitoring, pollution)
- Medical (Allergen detection, toxicology, implantable drug delivery system, flow meters in biomedical implants, tailored medication)
- Life Science (Diagnosis of disease, gene identification)
- Industrial Pollution Control (Bioreactors, food composition to check pesticides and antibiotic residue
- Forensic medicine

Other applications

- Microreactor
- Contacting in extraction
- Heat exchanger in electronic circuits
- Microdroplet as templates

Advantages of lab on chip

- Shorter time
- Upfront capital investment – reduced
- Close to real time measurements (Blood, food, effluent samples
- Small requirement of samples – smaller chemical footprint
- Digital output and interfacing with software
- In drug discovery, small volume of expensive reagents, parallel operation, high throughput screening, reduced human error

Advantages .....contd.

- High surface to volume ratio → Increased catalytic activity and better heat dissipation for highly exothermic reaction → reduced coking, thermal run-away, sintering.
- Robustness of the reactor
- Hazardous reaction at the point of use
- Difficult reaction that requires precise control, and otherwise attainable in a randomly packed bed (e.g., propellant from CO_2 in space-ship)
- Others

Components of lab on chip

- Pumping
  - Centrifugal force
  - Surface force
  - Electrokinetic force
  - mechanical
- Valve
  - Hydrogel
  - Hydrophobic layer
  - Mechanical
- Separation
  - Field flow fractionation (electrical, thermal, flow)
  - Electrophoresis, Dielectrophoresis, DEP + FFF
  - Diffusion based separation (H-Filter)

Components of microfluidic device ..contd.

- Mixing
  - Passive using grooves, laminations
  - Active
- Diffusion between layers
  - T-Sensor
- Heating
  - Cyclic heating for PCR reaction – DNA hybridization
- Detection
  - Optical interrogation
  - Amperometric sensing

Flow is laminar and the interaction between layers are utilized in most of these components

Pumping

- Use of moving parts as in a conventional pump with the help of micromachining.
- Centrifugal force to drive fluid through channels in radial direction (lab on CD).
- Use of coating with favorable contact angle, and pillars in the channel to enhance a “capillary rise” type flow.
- Electro-osmosis: Polar liquid in contact with solid wall induces surface charges, which in turn influences migration of charges within the liquid near the wall. Voltage gradient along the length of the channel pulls the charges, and the bulk liquid along with it.
- Electro-wetting: The change in contact angle of a droplet on a surface when an electric field is present at an interface. A droplet is held between two sets of planar electrodes (upper one consists of single continuous ground electrode, and bottom one with an array of independently addressable control electrodes). By spreading the droplet using the electric field such that droplet touches adjacent electrode in the array, and then switching on the adjacent electrode – movement of droplet is accomplished.

T-sensor

- Sample Stream:
  - Sample antigen to be measured (SA)
  - Fluorescently labeled antigen (LA) kept to a concentration 2-3 orders of magnitude less than anticipated SA concentration
- Other Stream:
  - Known concentration of antibody (AB) to the target analyte

AB molecules are larger and slow to diffuse

1. AB binds with all LA if SA is not target analyte → Bound LA cannot diffuse into AB stream → color stays near interface
2. AB binds with SA and some LA if SA is target analyte → Lot of free LA and free SA to diffuse into AB stream → spread of color into AB stream.
3. More than one T-sensors in the chip with different AB to target analyte.
4. Spread of color can be determined digitally.

H-filter

- Two parallel laminar streams will flow. One is the sample stream (e.g., blood containing aggregates of different sizes). The other is acceptor reagent (e.g., saline water).
- Smaller molecules diffuse faster.
- Smaller components of the sample stream will diffuse into the acceptor stream.
- At the end of the channel, two parallel flows are split up into two reservoirs.

Detection

- Laser induced fluorescence system
  - Fluorophores are conjugated with migrating analytes
  - Laser beam excites the fluorophores
  - Resulting fluorescence signal is filtered to block background illumination from the excitation source.
  - Fluorescence signal is recorded using CCD camera, PMT, APD
- Electrochemical
  - Monitor variation of electrochemical potential as analytes migrate past a working electrode, positioned within the separation channel.
  - The conductivity is related to the concentration of species.

Electrophoresis

- Migration behavior of charged species under the influence of an electric field.
- Analytes are suspended in an ionic buffer environment at a specific pH
- Each species migrates with a different mobility, allowing them to be resolved as distinct zones, and separated on the basis of size and charge.
- Biological macromolecules (e.g., proteins) are analytes
- Drag and electrophoretic mobility are the counteracting forces. Gravity is neglected.
- In some cases, polymer gel acts as sieving matrix material in the separation channel. The gel matrix reintroduces a size-dependence to the electrophoretic migration.
- In gel electrophoresis, analytes travel through the porous gel network with smaller fragments experiencing less resistance and eluting faster

Dielectrophoresis

- Particles are separated based on dielectric properties.
- A non-uniform electric field is generated by the use of planar and point electrodes.
- More polarizable particle will be attracted to strong field region.
- DEP can be used as a trap or in FFF mode. In the second case, gravity acts against DEP forces in settling the particles at a particular height in the channel.
- Live cells can be separated from dead cells by this method.

Electrical Field Flow Fractionation

- Top and bottom walls of the channel comprise of electrodes. Voltage is applied lateral to the direction of flow.
- Particles with high electrophoretic mobility will pack more closely to the wall.
- Flow in the channel is laminar, and easily characterized (e.g., parabolic).
- Each layer moves at different velocity, and particles carried by the layer elutes at different times from the outlet.
- Slugs of particles, separated based on their size/charge is detected at the outlet, and identified based on prior calibration.

Other modes of FFF

- Flow FFF
  - Use of transverse flow with membrane attached to wall
  - Concentration polarization directs the particles to settle in a layer depending on the diffusivity (size).
  - Laminar flow carries the particles at each layer to downstream with different residence time
- Thermal FFF
  - Diffusivity is a function of temperature and particle size
  - One of the channel walls is hot, and the other wall is cold – thus creating a thermal gradient across the channel.
  - Higher molecular weight particles compact more tightly against the cold wall than do lower molecular weight particles.
  - Because of laminar velocity profile of the carrier, lower molecular weight samples will have a higher average velocity, and elute before higher molecular weight samples – resulting in a fractogram.

Valve made of hydrogel

- Posts on the channel with hydrogel jacket around it.
- Hydrogel in its expanded state, block the channel.
- Contracted hydrogel allows the flow of fluid down the channel.
- Expansion / contraction by external trigger (pH or thermal)
- Response time is critical. Fractional change in diameter should reach 1.0 within seconds.
- Time response can be tailored by selecting the right number of posts and the thickness of the hydrogel layer.

Valve made of hydrophobic layer

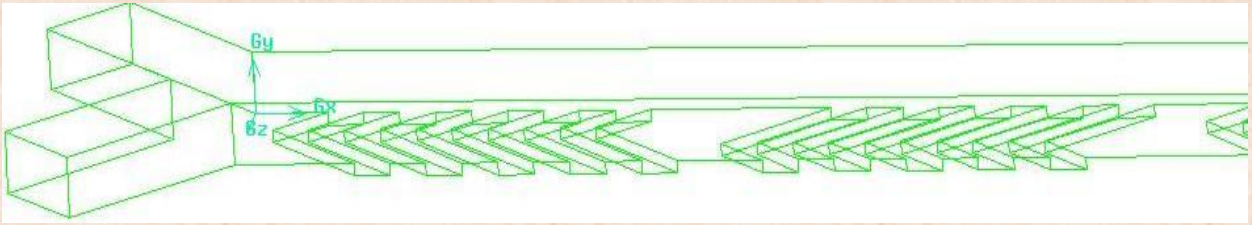
- A liquid being unable to expand freely, forms an interface with second liquid or gas.
- If interface is curved, there is pressure difference across the interface. The pressure is higher on the concave side. The pressure increase is balanced by surface tension forces.
- For flow to take place, the applied pressure gradient has to be greater than the capillary pressure.
- An abrupt change in the width of the channel causes pressure drop at the point of restriction.

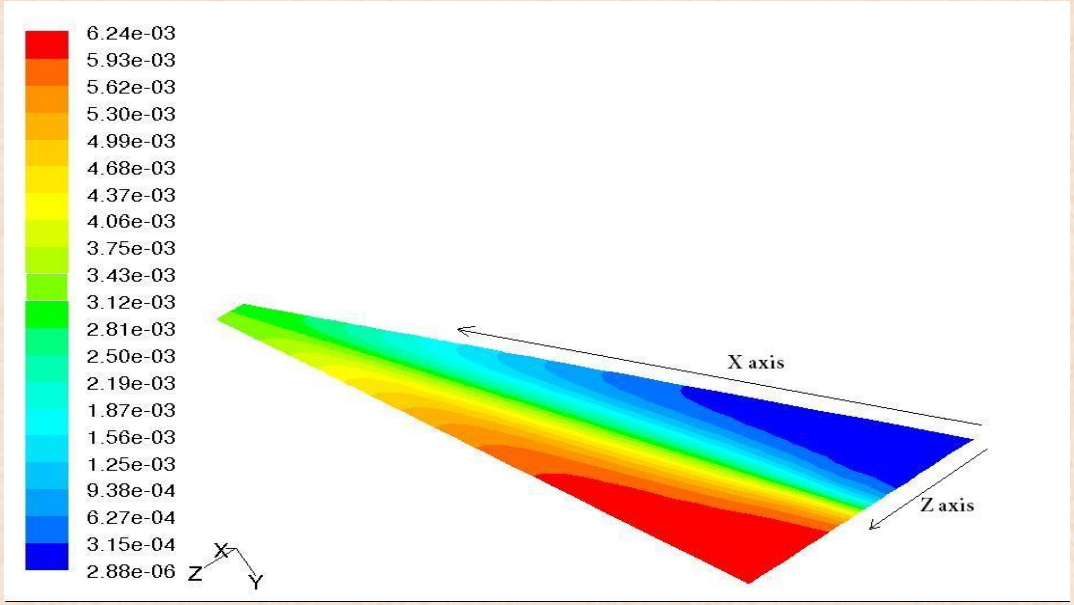
delta P = 2 (sigma_liq) (liq)cos_{cric}[(1/w1 + 1/h1) - (1/w2 + 1/h2)]

- By adjusting the width and height of the channel at the constriction, and with wall coating that provides adverse contact angle, it is ensured that flow can take place only when pressure at upstream side exceeds pre-specified value.
- Similar concept can be used for flow splitting.

Passive mixing

- Diffusion between two parallel streams in laminar flow – enhanced interface between the streams.
- Two streams are allowed to intermingle, brought close to each other, and then depart from each other due to baffles in the channel.
- Cross-flow between two streams is induced by inclined grooves.





Microfabrication

Fabrication accuracy

City (10 km)---House(10 m)----Optical fiber (1 mm)----Bacteria(1µm)----Virus(0.01µm)---1A°

Traditional mechanical machining

- Object of size 1mm to 50 cm
- Precision of the order of 10 µm

Special mechanical machining