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Seminar

MICROFLUIDICS

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Abstract

In this seminar the basic concepts of microfluidic, including flow dynamics, devices used for manipulating the flow inside the microchannels, and detection methods are introduced. There are also some examples in microfluidic applications.

Contents

1 Introduction

Microfluidics deals with technology and systems that are used for processing or manipulating of small (10^9 to 10^{18} liters) amounts of fluids, using channels with dimensions of a ten to several hundreds micrometers. Microfluidics exploits small size of channels and laminar flow of fluids in microchannels. It offers fundamentally new capabilities in control of concentrations of molecules in space and time[1].
The history of microfluidics dates back to the 1950s, principally in inkjet printer manufacturing. The mechanism behind these printers is based on microfluidics; it involves very small tubes carrying the ink for printing. In 1970s a miniaturized gas chromatograph was realized on a silicon wafer. By the end of the 1980s the first micro-valves and micro-pumps based on silicon micro-machining had also been presented. Within the following years several silicon based analysis systems have been presented. All these examples represent microfluidic systems since they enable the precise control of the decreasing fluid volumes on the one hand and the miniaturization of the size of a fluid handling system on the other hand. Later on researchers spent a lot of time in developing new microfluidic components for fluid transport, fluid metering, fluid mixing, valving, or concentration and separation of molecules within miniaturized quantities of fluids within the last two decades. Today, many different types of micro-pumps, mixers and microvalves are known and used in microfluidic applications[2].
Together with new methods of fabrications, microfluidics attend new insight into certain fundamental differences between the physical properties of fluids moving in a large channels and those traveling through micrometer-scale channels[1].

2 Basic Principles of Microfluidics

2.1 Laminar flow

Motion of viscous fluid is described by Naver-Stokes equation [3]:

$$\rho(\frac{\partial \mathbf{v}}{\partial t} + (\mathbf{v}\nabla)\mathbf{v}) = \mathbf{f_{ext}} - \nabla p + \mu\nabla^2\mathbf{v}, \tag{1}$$

where ρ is fluid density, $\mathbf{v}$ is fluid velocity, $\mathbf{f_{ext}}$ is external force acting on fluid, p is pressure of fluid and μ is the kinematic viscosity of the fluid. From it's dimensionless form follows the Reynolds number, defined as

$$Re \equiv \frac{vL}{\mu}, \tag{2}$$

where v is the characteristic velocity of the flow, L is the characteristic length of the geometry[4]. Reynolds number can be interpreted as the ratio of the inertial force to the viscous force,

$$Re = \frac{F_{inertial}}{F_{viscous}}. \tag{3}$$

Fluid flow in microscale environment, has some advantages in comparison to macroscale environment. Main advantage is a low Reynolds flow, where Reynolds numbers are typically $< 10^2$, since Reynolds number is proportional with dimension of channel, which is small in the case of microfluidics. Low Reynolds flow represent situation in which flow is considered essentially laminar. On the other hand fluid flow in macroscale systems is almost always turbolent, with Reynolds number grater than 10^3. Laminar flow makes transport of fluid in microchannels much more predictive compared to the macroscopic systems[4].

2.2 Peclet number

Peclet number is another dimensionless number, that represent ratio between the system length and the diffusion length, and is usefull parameter when mixing of fluids is wanted. Peclet number is:

$$Pe = \frac{Lv}{D}, \tag{4}$$

where L is characteristic length, v is average fluid velocity and D is diffusion coefficient. If $Pe >> 1$, the diffusion length is much shorter than the system size and gradients can be very high. Large changes in concentration in one region in the reactor will have no effect on other regions if the time involved is short enough that the diffusion length is small. On the other hand if $Pe << 1$, the diffusion length is much longer than the system size, the profiles of concentration must be essentially linear. A change in one part of the reactor is reflected throughout the reactor in a diffusion time ($\frac{L^2}{4D}$). In this case fluid velocity is generally not important: diffusion dominates transport[5].

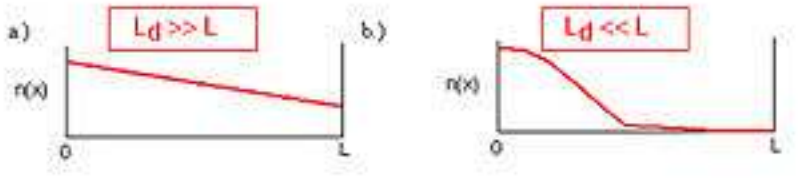

Figure 1: Diffusion length compered with characteristic system length; a.)Pe«1 and b.)Pe»1.[5]

2.3 Pressure driven flow

Pressure driven flow is commonly found in fluid systems, including microfluidic devices. At this kind of flow, fluid is pumped through the device by positive displacement pumps. One of the basic assumptions of fluid dynamics for pressure driven flow is so-called no-slip boundary condition, which means, that velocity at the walls must be zero. In this case velocity has only component in z direction and the Navier-Stokes equation is,

$$0 = -\frac{\partial p}{\partial z} + \mu \nabla_{\perp}^2 v_z. \tag{5}$$

Solution of this equation is a parabolic velocity profile within the channel, with highest velocity along central streamline [4];

$$u_z(r) = -\frac{1}{4\mu}\frac{\partial p}{\partial z}(h^2 - r^2). \tag{6}$$

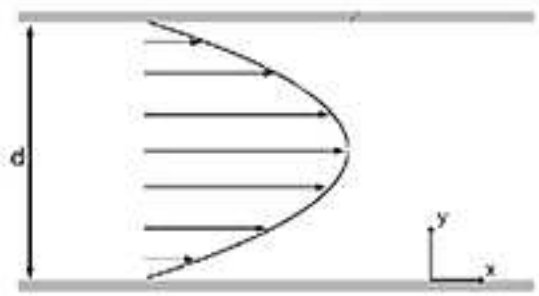

Figure 2: Parabolic velocity profile for pressure driven flow.[4]

2.4 Electro-osmotic flow

Pressure driven flow in microfluidics devices often requires components with moving parts, such as micropumps and microvalves, which can be complicated to design, and they are prone to mechanical failure. Alternative to pressure driven flow is electro-osmosis, where no moving components are required.
Most surfaces in contact with polar solution acquire a finite surface charge density. This highly charged region of ions at the liquid-solid interface is known as electrical double layer. When external electric field is applied across the channel, the ions in the double layer move towards the electrode of opposite polarity. This creates motion of fluid near the walls and transfers via viscous forces into convective motion of the bulk fluid. If the channel is open at the electrode sides, then velocity profile is uniform across the entire width of the channel - plug flow[4].
Electro-osmotic flow is described by additional source term in Navier-Stokes equation. This extra source term is the electromechanical force density that can be derived from the Maxwell electromechanical stress tensor. Navier-Stokes equation can be written as:

$$\rho(\frac{\partial \mathbf{v}}{\partial t} + (\mathbf{v}\nabla)\mathbf{v}) = -\nabla p + \mu\nabla^2\mathbf{v} + \rho_e\mathbf{E}, \tag{7}$$

where ρ_e is local charge density and E is external elactrical field. Equation can be simplified for microfluidic channel. Local charge density is constant everywhere in the liquid and can be written as:

$$\rho_e = -\epsilon\epsilon_0 k^2\zeta, \tag{8}$$

where k is the Debye-Huckel parameter and ζ is electric potential in the electric double layer. Inverse Debye-Huckel parameter defines the characteristical thickness of electric double layer. Navier-Stokes equation can be rewritten as[6]:

$$0 = \mu\nabla^2\mathbf{v} - \epsilon\epsilon_0 k^2\zeta\mathbf{E} \tag{9}$$

Using boundary conditions, that velocity at the walls is zero, solution of this equation is[6]:

$$\mathbf{v}_{average} = \frac{1}{h}\int_{-h/2}^{h/2}(\frac{\epsilon\epsilon_0 k^2\zeta\mathbf{E}}{2\mu}(z^2 - \frac{h^2}{4}))dz = -\frac{\epsilon\epsilon_0 k^2\zeta h^2}{12\mu}\mathbf{E}. \tag{10}$$

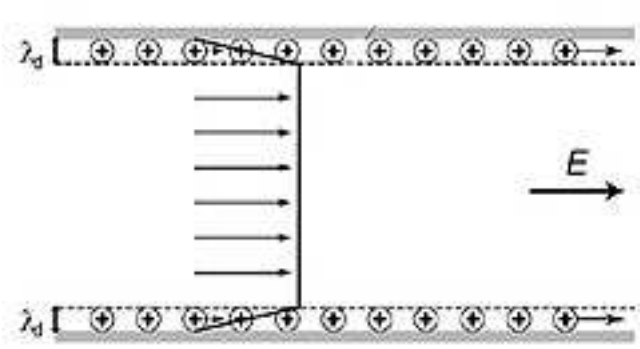

Figure 3: Flat velocity profile for electro-osmotic flow.[4]

3 Micropumps

Micro pumps are components based on a large variety of operating principles. Pumps are divided into two large groups by their working principles, mechanical micropumps and non-mechanical

micropumps. The typical operation range of mechanical micropumps lies between $10\mu l/min$ and several milliliters per minute. For flow rates less than $10\mu l/min$, non-mechanical pumps are needed for an accurate control of that small fluid amounts[7].

3.1 Mechanical micropumps

Mechanical pumps can be further categorized, according to the principles by which mechanical energy is applied to the fluid, into two major categories: displacement pumps and dynamic pumps. In displacement pumps, such as peristaltic and rotary pumps, energy is periodically added by the application of force to a movable boundary. In dynamic pumps, such as ultrasonic pumps and centrifugal pumps, energy is continuously added to increase the fluid velocities within the pump. The higher velocity at the pump outlet increases the pressure[7].

3.1.1 Peristaltic pump

In peristaltic pumps, the pumping concept is based on the peristaltic motion of the pump chambers which squeezes the fluid in the desired direction. Peristaltic pumps need three or more pump chambers with actuating membrane. On figure4 there is a peristaltic micropump using three piezoelectric disks for actuation[7].

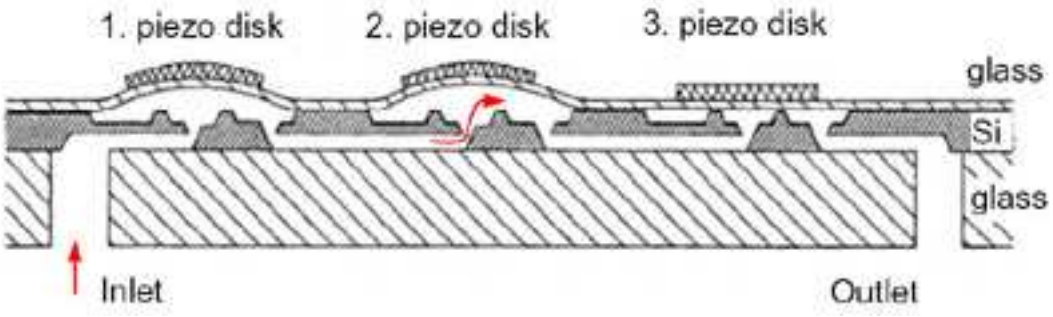

Figure 4: A peristaltic micropump using three piezoelectric disks for actuation.[7]

3.1.2 Centrifugal pump

A centrifugal pump works on the principle of conversion of the kinetic energy of a flowing fluid into static pressure. This action is described by Bernoulli's principle. The rotation of the pump impeller accelerates the fluid as it passes from the impeller eye (center) and outward through the impeller vanes to the periphery. As the fluid exits the impeller, a fluid momentum is then converted to pressure. Typically the volute shape of the pump casing, or the diffuser vanes assist in the energy conversion. The energy conversion results in an increased pressure on the downstream side of the pump, causing flow[7].

3.2 Non-mechanical micropumps

Non-mechanical micropumps add momentum to the fluid by directly converting non-mechanical energy into kinetic energy without mechanical movement of a structure. While mechanical pumping is mostly used in macroscale pumps and micropumps with a relatively large sizes and high flow rates, non-mechanical pumps and their advantages in the microscale. Since the viscose resistance in microchannels increases in the second order with miniaturization, the first category pumps can not deliver enough power to overcome the high fluidic impedance in the microscale. The driving forces can be electric, magnetic, thermal, chemical or surface tension forces. The non-mechanical micropumps can be categorized into capillary pumps, electrohydrodynamic (EHD) pumps, electrokinetic pumps, magnetohydrodynamic (MHD) pumps and phase difference pumps[7].

3.2.1 Electrokinetic pump

Electrokinetic pumps utilize a static electric field for pumping conductive fluid. The electrokinetic phenomenon can be divided into electrophoresis and electro-osmosis. Electrokinetic flow results from the effect of electrical field on charged particles in the fluid and fluid itself, when fluid is placed in a narrow capillary. The force on the particles in the fluid leads to electrophoresis while the force on the fluid in a narrow capillary leads to electro-osmosis. Since electrophoresis and electro-osmosis occur at the same time, electro-osmosis usually determines the overall direction of the fluid flow[7].

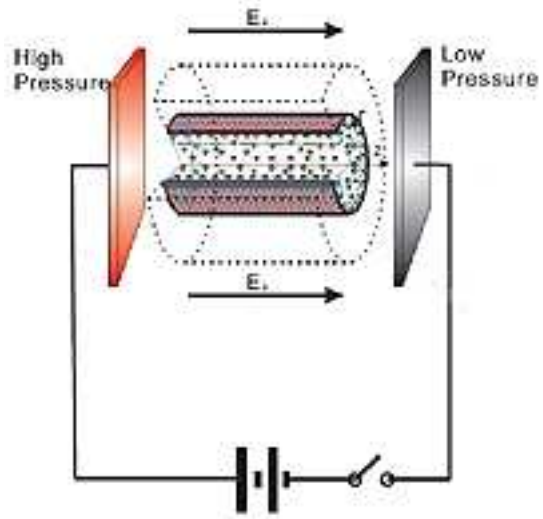

Figure 5: Electrokinetic pump.[9]

3.2.2 Magneto-hydro dynamic (MHD) pump

An application of an electric field across a microfluidic channel containing a conducting solution and a magnetic field in the channel results as Lorentz force. The magnitude of the force depends on the electric current across the channel, the magnetic flux density and the width of the channel. The resulting Lorentz force affects the ions in the solution and thus, propels the fluid. Because Lorentz force acts on the bulk fluid and creates a pressure gradient, MHD pumps generate a parabolic velocity profile similar to pressure driven flow[7].

4 Micromixers

In biomedical and chemical analysis, a sample solution is to be tested with reagent. Mixers are used for mixing two solutions (e.g. a sample and a reagent) to make the reaction possible. In microscale, mixing mostly relies on diffusion due to the laminar behavior of fluid at low Reynolds numbers. The diffusion time (or the mixing time) is proportional to the square of the mixing path. Thus, faster mixing can be achieved with a smaller mixing path and larger contact surface[7].

4.1 Active micromixers

Active micromixers can be classified according to whether or not they have moving parts. In micromixers with moving elements, these elements (microscopic stirrer bars, piezzo electric membranes, gas bubbles) can either rotate or perform oscillatory motions. In active mixers, an actuator is used for the agitation of the fluid[7].

4.1.1 Planar laminar bubble mixer

Planar laminar bubble mixer can be used as a mixer and also as a pump. It is composed of bubble pumps and bubble check valves. Thermo-capillary bubble valves operating is based on creating a vapor bubbles within chamber, that prevent flow through the chamber. Bubble pump (mixer) operates by turning on and off micro-heaters to create or eliminate bubbles within chamber. When bubble is created fluid is pumped into mixing chamber, where mixing occurs, and when bubble is eliminated, the fluid is pumped into bubble mixer. The pumping process creates chaotic advection to mix fluid streams in the planar, laminar chamber[8].

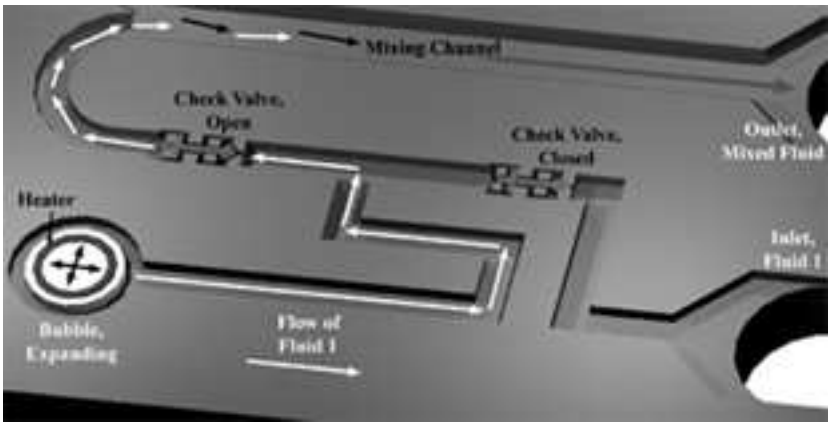

Figure 6: Schematic of bubble micromixer[10]

4.1.2 MHD mixer

MHD could be used not only for the purpose of pumping fluids, but also to control fluid flow in microchannels and to induce secondary flows that maybe beneficial for mixing. By depositing an array of transverse electrodes on the bottom of microfluidic conduit, the electrodes are connected alternately to positive and negative terminals of a DC power supply. As a result, electric currents are induced in opposite directions between adjacent pairs of electrodes. The interaction between these currents and uniform magnetic field perpendicular to the bottom of the channel led to the formation of Lorentz forces in opposing directions between adjacent pairs of electrodes. This, in turn, led to the formation of convection. This convection could be used to fold and stretch material lines and enhance mixing[8].

4.2 Passive micromixers

In passive micromixers, no moving parts are involved and mixing relies entirely on diffusion. Passive mixers can be categorized into lamination mixers, injection mixers and valve mixers. Lamination mixers are the most common type of micromixers. Splitting and laminating fluid layers accelerate the mixing process. Two major concepts are parallel lamination mixers (T- and Y-mixers) and sequential lamination mixers. Injection mixers (or microplume mixers) split one stream into several substreams using nozzles and inject them into the second stream. In valve mixers, a passive valve is used for releasing one of the two fluids into a channel where the other fluid flows[7].

4.2.1 T-type mixers

In many microfluidic devices, to introduce reagents into the device, the T-type shape of channels are often used. The "Y" shape, cross, and other similar shapes follow the same design principles and can be categorized into T-type channels. When the size of microchannel is a few tens of microns, the contacting of two substreams in a T-type channel was sufficient enough to achieve

adequate mixing. Many of electroosmotic driven microfluidic devices use channels that have the sizes less than $100\mu m$, and could contact reagent and sample directly in T-type mixer without any other mixing assistance.
A T-type of micromixer, also termed T-sensor, is one of the micro Total Analysis System (μTAS) components. Two or more fluid layers enter the channel side by side, and mixing takes place between the fluid streams only by diffusion. Assuming a rectangular cross section, the relevant dimensions are the length (L), the diffusion dimension of the channel (d), and the width of the channel (w). The d-dimension is typically from 20 to $5000\mu m$, the w-dimension commonly ranges from 5 to $100\mu m$. For a pressure-driven flow in a microchannel, the flow patterns are parabolic-like profiles in one direction or even both directions that are perpendicular to the flow axis and the flow velocity is zero at the wall and maximum velocity in the center of channel. Due to the parabolic flow profiles, the fluids that are close to the wall move slower, hence, have more residual time for diffusion and are mixed first. To reduce the inconvenience of the Taylor dispersion effect for sensing, the depth to width aspect ratio of T-mixer is usually kept small for the solute to diffuse rapidly across the depth direction to achieve uniformity before the detection zone[8].

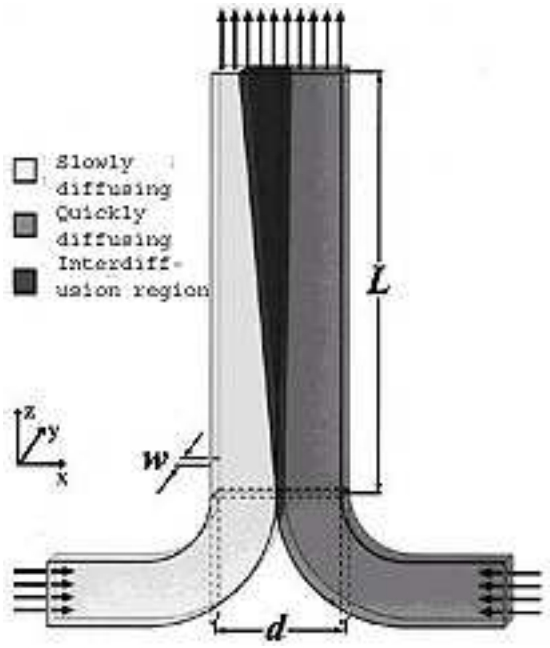

Figure 7: A schematic working principle of T-sensor[8]

5 Soft lithography and PDMS (Polydimethylsiloxane)

Soft lithography refers to a set of methods for fabricating or replicating structures using "elastomeric stamps, molds, and conformable photomasks". It allows rapid fabrication of complex microfluidic structures in flexible polymer substrates. The most commonly used polymer is PDMS or Polydimethylsiloxane, many other materials are suitable, such as photocurable hydrogels, thermoset plastics and elastomers, and others[11].
The basic outline of the process entails that the master initially is produced on a silicon wafer, most commonly by UV-photolithography, which is capable of resolutions of $> 1\mu m$. Here the device layout is printed on a transparency or on chrome mask making some areas transparent and other opaque to UV-light. A Si wafer is than spin-coated with a photo curable resist which is exposed to UV-light through the mask. The wafer is then subjected to an etching solution

that removes the uncured photoresist and the master is complete. The master is used as a mould to cast a negative structure in an elastomer. This elastomer casting is either the end product or it in turn is used as a mould to make another generation of elastomer castings with structures similar to those of the Si-master[12].
One of the greatest advantages of soft lithography is that devices can be produced very quickly, inexpensively and the end product often has a high quality. This makes the technique ideal for fabricating prototypes.
PDMS is a polymer which is often used in microfluidic applications. It has many advantages to other materials used in microfluidic assays such as glass or silicon. PDMS is flexible, optically transparent to wavelengths $> 230nm$, impermeable to water, non-toxic to cells and permeable to gases. It is also inexpensive and an excellent material for soft lithographical techniques.
A problem connected with the elastic properties of PDMS is the risk of elastic deformation. Because of the elastic nature of the material it will most likely deform slightly. A serious risk of structural collapse exists if aspect ratio of a structure in PDMS is too far from unity[12].

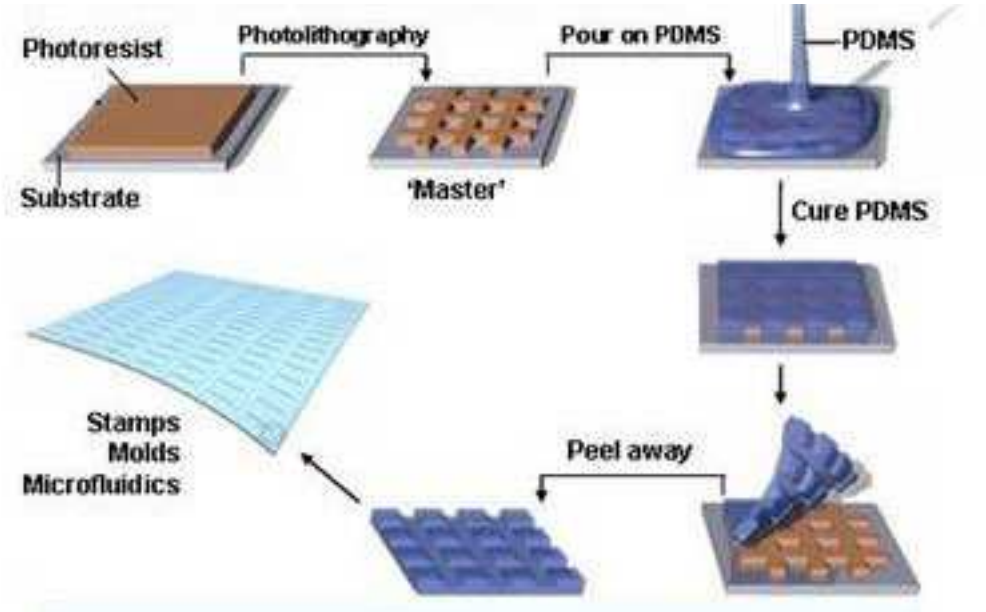

Figure 8: Steps of soft lithography[13]

6 Detection methods

Decreasing the dimensions of reaction systems to small volumes with small amounts of analytes requires adequate, high-sensitivity detection techniques. Beside electrochemical methods and mass spectrometry, optical techniques such as absorption, refractive-index variation, chemiluminescence and fluorescence measurements are usually used, because they are non-invasive and provide high temporal and spatial resolution for a suitable experimental set-up[14].

6.1 Optical methods

Fluorescence analysis is particularly attractive because fluorophores can be excited and detected selectively. Furthermore, the excellent sensitivity of fluorescence spectroscopy is greatly enhanced by reducing the size of the detection volume, because the background signal that is generated by impurities of the sample scales linearly with the size of the detection volume. The fluorescence signal of a single molecule, on the other hand, is independent on the dimensions of the detection volume and remains constant.

Detection methods such as surface plasmon resonance or detections related to evanescence fields do not depend on geometrical scaling but on the wavelength of the light; however, they are subject to the same restrictions with respect to statistical coverage. These methods will only strictly fulfil scaling criteria if the mechanical confinement becomes smaller than the wavelength of light[14].

6.1.1 Fluorescence

Fluorescence is the result of three-stage process that occurs in certain molecules called fluorophores or fluorescent dyes. First a fluorophore absorbs a photon energy and an excited electronic state is created. There are multiple excited states or energy levels that the fluorophore can attain, depending on the wavelength and energy of the excitation photons. Since excited states are not stable they eventually decay to the lowest-energy excited state, which is semistable. Time that the electron is in excited state is called fluorescence lifetime and is between (1-several hundreds nanoseconds). Then the fluorophore goes from semi-stabile excited state back to the ground state, and the excess of the energy is released and emitted as light. Energy of lowest excited state is much smaller than the energy of excitation photons, because of that the energy of emitted photon is lower, and therefore of longer wavelength, then the excitation photon, this is called Stokes shift (Figure 9). The fluorophore can absorb photon energy again and go through the entire process repeatedly[15].

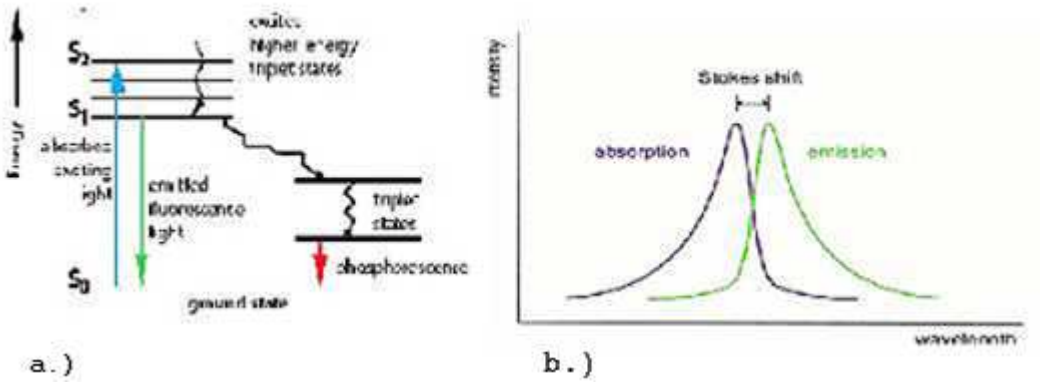

Figure 9: a.)The Jablonski Diagram shows a number of possible routes by which an excited molecule can return to its ground state via unstable triplet states. b.) Stokes shift, the difference between wavelength of absorbed and emitted photons.[16]

6.1.2 Surface plasmon resonance

Surface Plasmon Resonance (SPR) is a physical process that can occur when plane-polarized (p-polarizes) light hits a metal film under total internal reflection (TIR) conditions. TIR is achievable when a light beam propagating in a medium of higher refractive index hits an interface with a medium of lower refractive index at an angel of incidence above critical angle the light is totally reflected at the interface and propagates back into the high refractive index medium. Although the light beam is fully reflected, it leaks electrical field, called an evanescent field, into the low refractive index medium. The amplitude of this evanescent field decreases exponentially with distance from the interference. If the TIR-interface is coated with a thin film of a noble metal such as gold, silver, etc. the p-polarized component of the evanescent field may penetrate the metal layer and excite electromagnetic surface plasmon waves (electron density waves) propagating within the conductor surface that is in contact with the low refractive medium. For a non-magnetic metal this surface plasmon wave will also be p-polarized and will create na enhanced evanescent wave (Figure 10). For plasmon excitation by a photon to take

place the energy and momentum of these "quantum-particles" must both be conserved during the photon "transformation" into plasmon. This requirement is met when the wavevector for the photon and plasmon are equal in magnitude and direction. The direction of the wavevector is the direction of the wave propagation, while magnitude depends on the media. The wavevector and energy match enables a resonant absorption of energy via the lightevanescent wave field, a plasmon excitation (SPR) causing a characteristic drop in the reflected light intensity. For a given wavelength of incident light, SPR is seen as a dip in the intensity of reflected p-polarized light at a specific angle of incidence[18, 17].

The gold layer in the sensor chip creates the physical conditions required for Surface Plasmon

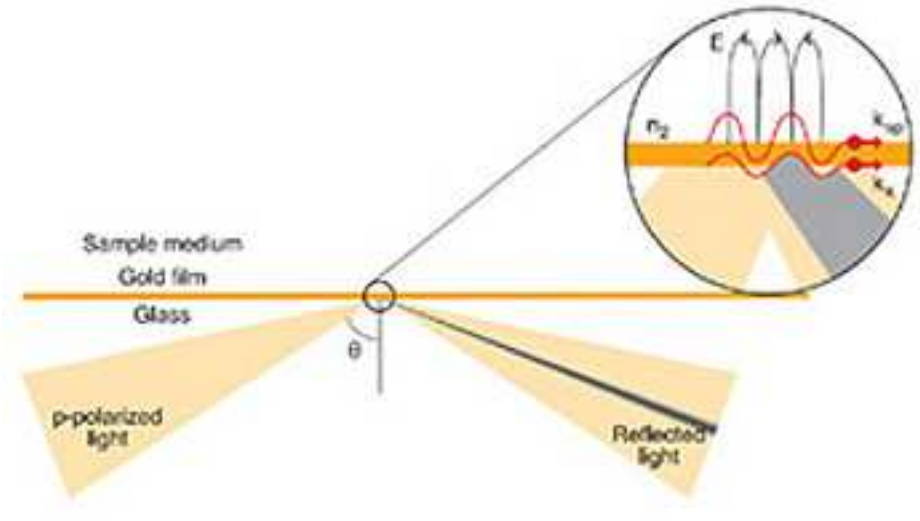

Figure 10: SPR is excited by p-polarized totally internally reflected light at a glass/metal film interface, the surface plasmon enhancing the evanescent field amplitude, E. [18]

Resonance (SPR). SPR detects changes in the aqueous layer close to the sensor chip surface by measuring changes in refractive index (Figure 11). When molecules in the test solution bind to a target molecule the refractive index changes and when they dissociate the refraction index changes again. Based on change of the refraction index it is possible to deduce what kind of molecules are in the test sample. This simple principle forms the basis of the sensorgram (a continuous, real-time monitoring of the association and dissociation of the interacting molecules). The sensorgram provides quantitative information about active concentration of molecule in a sample, kinetics and affinity. This means that the composition of fluid can be detected, based on changes in refractive index. Studies can be carried out in colored or opaque environments, and there is no need to label molecules with fluorescent or radioactive tags - so avoiding the possibility that labels may compromise activity. Molecules can be studied in their native state to provide results that reflect in vivo activity[19].

6.2 Mass spectrometry

A mass spectrometer determines the mass of a molecule by measuring the mass-to-charge ratio (m/z) of its ion. Ions are generated by inducing either the loss or gain of a charge from a neutral species. Once formed, ions are electrostatically directed into a mass analyzer where they are separated according to m/z and finally detected. The result of molecular ionization, ion separation, and ion detection is a spectrum that can provide molecular mass and even structural information. Four basic components are, for the most part, standard in all mass spectrometers: a sample inlet, an ionization source, a mass analyzer and an ion detector (Figure 12). All sample molecules undergo the same processes regardless of instrument configuration. Sample molecules are introduced into the instrument through a sample inlet. Once inside the instrument, the

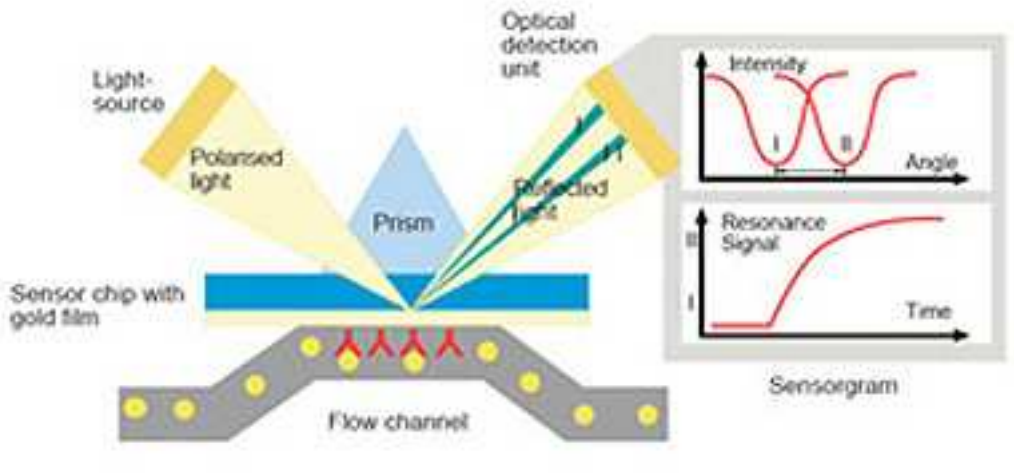

Figure 11: Illustration of detector with sensor chip and Integrated micro Fluidics Cartridges (IFC).[19]

sample molecules are converted to ions in the ionization source. There are diferent ionization methods that work by either ionizing neutral molecule through electron ejection, electron capture, protonation, cationization, or deprotonation, or by transferring a charged molecule from a condensed phase to the gas phase. Ionized molecules are then electrostatically propelled into the mass analyzer. Ions are there separated according to their m/z within the mass analyzer. The detector converts the ion energy into electrical signals, which are afterward transmitted to a computer[20].

Significant progress has been made in the development of miniaturized mass spectrometers.

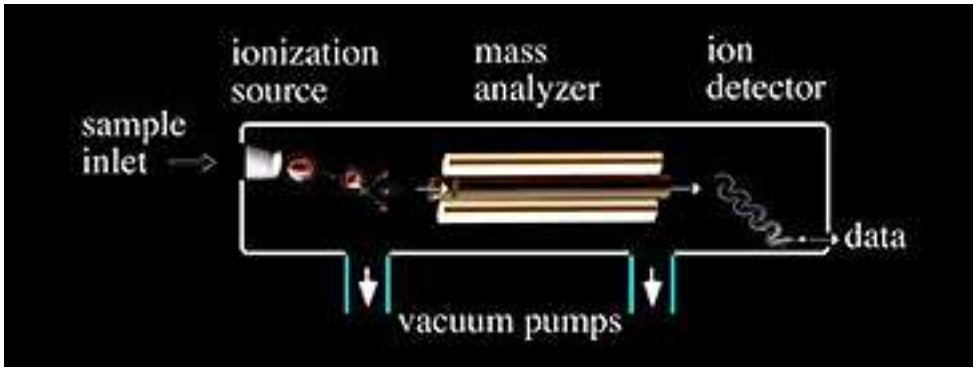

Figure 12: Components of a mass spectrometer[20]

Plasma discharges are used as excitation sources for molecular mass spectrometry components. This approach can identify the smallest dimension for which a plasma discharge can be sustained under atmospheric pressure. Most microplasmas developed for analytical purposes have so far concentrated on gaseous samples, which limits potential applications in the field of ąTAS and lab-on-a-chip. They are not universal devices able to measure any kind of sample. The main reason for this is the difficulty in achieving adequate sample transport from the liquid to the gas phase, and in increasing the coupled electric power into the plasma without destroying the discharge housing over a certain limit. For miniaturized plasmas, the volume and discharge power is such that even small amounts of liquid can easily extinguish the discharge. For the analysis of liquid samples, microplasmas can either be coupled with different sample-injection

12devices or applied as plasmas that use one electrode as a liquid, or they can be ignited directly in the liquid. The miniaturization of almost every type of mass analyzer (quadrupole ion trap, time of flight, magnetic sector and linear quadrupole) is an active area of research. Miniaturized mass analysers reduce vacuum-system demands, because the maintenance of a constant collision frequency allows an increase in pressure as the analyzer size is scaled down. Consequently, power consumption for vacuum and backing pumps may be reduced[14].

7 Applications

Microfluidic systems have diverse and widespread applications. Some examples of devices and systems include inkjet printers, portable blood analysers, DNA and proteomic chips, lab-on-achip systems and micro total analysis systems. Applications can be found not only in diagnostics (point-of-care analysis, total analysis systems), pharmaceutics (drug discovery, drug testing, process quality control), biotechnology (DNA chips, protein chips, cell chips) and environmental technology (soil (also agriculture), water and air quality measurements) but in consumer electronics (ink-jet printers, local cooling of electronics, fluidic power systems, well-being), pulp and paper and chemical (lab-on-a-chip, microreaction), automotive (fuel injection, oil quality monitoring, exhaust gas analysis) and food industries (food diagnostics, packaging (smart sensors)) as well[21].

7.1 Microreaction

Microreactors are microchannel devices in which chemical reactions take place. Two or more fluids are injected separately into the microreactor. The fluids will mix by diffusion, without turbulence. The chemical reaction time of the fluids is determined by the pressure or the channel length. The maximum number of separate fluids for the chemical reactor depends on the size of the chip, but their number can be high.
The microreactor is usually a continuous flow reactor (contrast with/to a batch reactor). Microreactors offer many advantages over conventional scale reactors, including vast improvements in energy efficiency, reaction speed and yield, safety, reliability, scalability, on-site/on-demand production, and a much finer degree of process control[22].

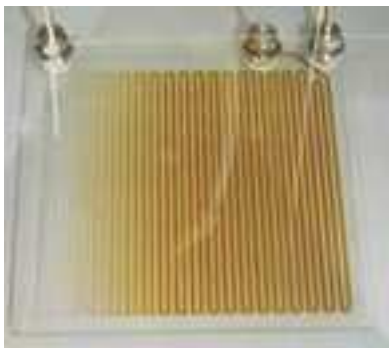

Figure 13: 1: Reaction in a glass microreactor at –100 ^0C[23]

Microreactors have many advantages. Processes within microfluidic systems can be designed in such a way, that all processes within microreactors are highly reproducible. Due to a micro fluidic channels time for reaction is shorter, heat can be introduced and extracted from within few micrometers of where the reaction is happening. Mixing can be effected by a number of mechanisms to give very precise conditions and hence highly homogeneous conditions over time. Microfluidic processes are inherently safer than macrofluidic processes, purely due to the smaller quantities of materials present within the system at any one time. In addition, as small quantities of explosive materials do less damage than larger quantities, toxic materials are less hazardous

in smaller quantities and the energy stored in pressurized systems scales with the size of the pressure vessel meaning failure of a small system results in a minuscule energy release when that vessel is only micrometers in cross section[21].

7.2 Micro fuel cell technology

Micro fuel cells are small-sized power sources that convert chemical energy into electrical energy. Fuel cells operate by oxidising combustible fuel, such as hydrogen or alcohol. These energy sources, on a large scale, have been deployed in motor vehicles. Most of these devices use hydrogen. Recently, downscaled fuel cells have been developed for use with devices such as digital cameras, portable radios and notebook computers. Those devices use fuels other than hydrogen, most notably methanol. Microfluidics plays a major role in such technology[22].

7.3 Lab-on-a-chip

anthrax from 12 days via agar plates to a few hours and less. This is one of the major current interests in microfluidics, enabling DNA and protein analysis, chemical reactions, highthroughput screening, ion/particle characterisation and all manner of mixing/heating/control/separation of liquids[22]. Lab-on-a-chip technology will allow cheap and portable systems to perform analyzes currently available only at large laboratories. Systems can communicate online with the user or directly with the doctor. Wearable or implantable devices make constant health monitoring a reality, giving an early warning to serious diseases like cancer. Such systems will also be extremely important for the military, for monitoring the soldiers' health and stress levels, and greatly improving diagnostics in field hospitals. Similar gains applies to relief work in remote or underdeveloped areas. The latter includes AIDS monitoring in Africa , to which large WHO programmes are devoted. For athletes, implantable systems will make it possible to optimize training programs through monitoring parameters like lactate levels. Implantable MF systems can also be used on animals, for instance on racing horses[24].

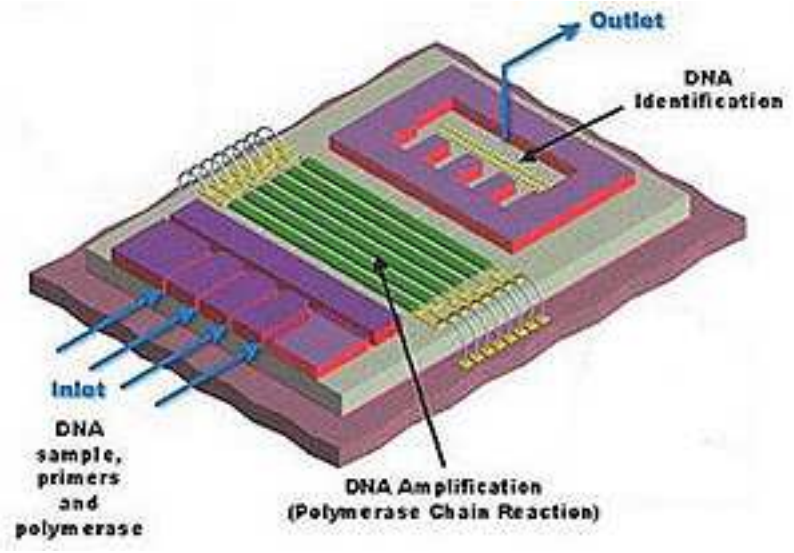

Figure 14: Lab-on-a-chip[26]

7.4 Drug delivery

Microfluidic components play a vital role in a number of drug delivery solutions. The applications range from micronozzles that spray drugs for inhalation to micropumps for accurate dosing of various therapeutic compounds with dedicated delivery profiles. The application can be extraor

intracorporeal. Target therapy markets are diabetes treatment, pain control, chemotherapy, total parenteral nutrition and anaesthetics. An interesting example of a microfluidic system is the integration of a drug container, controlling electronics and a microdelivery system into a dental implant. This is a piezzo driven membrane pump. Its setup is straightforward: a piezoelectric membrane deflects and moves a volume of fluid. Passive check valves ensure the fluid travels in only one direction. The design allows gases and liquids to be pumped: water at a rate of $50nL/min$ to $5mL/min$ and gas at $50\mu L/min$ to $15mL/min$. The micropump fits into mobile systems to provide easy handling for patients and operators. Its biggest advantages are its size and low power consumption. Powered by two $1.5V$ batteries, the pump can run for two to three days independently at maximum power. The cost and structure of this micropump means it can be used in disposable devices, which will thereby decrease the risk of contamination or spread of bacteria. Similar to a syringe pumps, once the pump and its reservoir have been used for a patient they are thrown away, but the external electronics can be reused.To have full flow control, the pump must be combined with a flow sensor. In a hybrid setup, the principal function of the pump in interaction with a flow sensor has been confirmed. To achieve the flow sensing and therefore controllability of the pump across its full dynamic range a specific sensor is now developed. The sensor will be of a size that allows it to be integrated into the pump without changing the overall size of the existing pump. This intelligent system offers operation over a range of conditions such as flow range, chemical resistance and long-term stability for delivery flexibility and versatility in the design of a therapy. Other potential applications are mobile air monitoring systems where the micropump continuously delivers samples to the sensor to detect the properties of ambient air. This system can be used to ensure occupational health safety in dangerous environments[24].

Figure 15: Small, portable disposable micropump with broad flow dynamics[25]

7.5 Bio-sensors

Cell-based biosensors monitor physiological changes in reporter cells exposed to biological or industrial samples containing pathogens, pollutants, biomolecules or drugs. The read out can be optical (for example, fluorescent, luminescent or colorimetric) or electrical (for instance, measuring changes in impedance or electrical potential).
The chemical-dependent electrophysiological activity of certain cell types, such as neurons and cardiac cells, has spurred their use in chip-based biosensors. Changes in electrical activity can be monitored by planar microelectrode arrays, which are easily integrated into microfluidic devices and can be made with large numbers of measurement points per device. A portable, highly integrated cell-based biosensor system for the analysis of biochemical agents has been realized by integrating a complementary metal oxide semiconductor (CMOS) chip as digital interface with recording electrodes as well as with temperature control system that includes heater electrodes to sustain the environmental requirements of the cells in the microfluidic culture chamber. Challenges still remain in using living cells as sensors, because variables such as cell density and cell interaction can significantly affect the sensor properties[27].

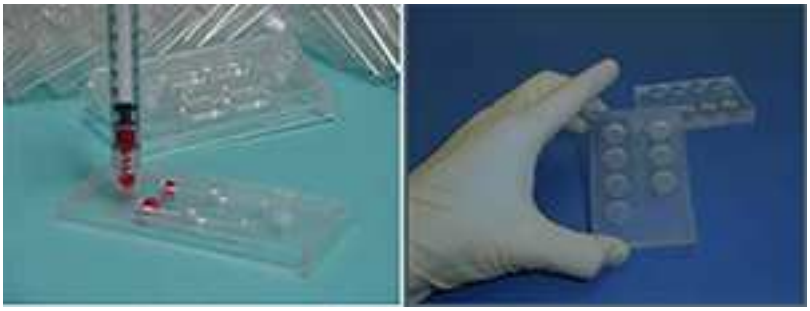

Figure 16: Platform for blood analysis (left) and platform for seven bacterial tests in parallel (right)[28]

7.6 Stem cells

The promise of stem cells for cell-based therapies in human disorders and tissue engineering has resulted in a growing interest in applying microtechnology to stem-cell culture. The controlled microenvironment of microfluidic platforms can be very useful in the study of stem cells. Manipulating the chemical environment of the culture in time and space allows the behavior of stem cells, such as proliferation and differention, to be controlled.
A microfluidic stem-cell culture platform with a concentration gradient has been used to study the effect of growth-factor concentration on human neuronal-stem-cell behavior. The observed proliferation rate in the device was proportional to growth-factor concentration,whereas differentiation (to astrocytes) was inversely proportional. In these studies, flow in the device minimized autocrine and paracrine signalling. However, it is also possible to set up a linear concentration gradient in a static microfluidic system, preserving autocrine and paracrine signals. Recently, a microfluidic device for strem-cell culture with both logarithmic varying perfusion rates and concentration gradients has been developed, making it possible to explore a wide range of biological conditions simultaneously. Future integration of advanced culturing techniques using heterotropic culture and 3D cues is likely to further increaser the value of microdevices for stem-cell research[27].

7.7 Single-cell analysis

In both conventional studies and microsystems, the analysis of single cell has typically been performed using image based techniques and intercellular florescent probes. However, the ability of integrated microfluidics to accurately manipulate, handle and analyze very small volumes has opened up new opportunities for analysis of intracellular constituents. For example a standard microbiology analysis needs purified isolated bacterial colonies, it also requires millions of cells for detecting bacterial response. On the other hand a microfluidic device, with integrated pneumatic valves, is capable of isolating single cells, out of the heterogeneous fluid stream. Then by using a chemical lysis buffer microfluidic devices are able to extract and recover messenger RNA from a single cell. A similar device that also integrates electrophoretic separation can analyze amino acids from the lysed contents so single cell. Single-cell analysis by electrophoretic separation but with electrokinetic flow-driven cell loading, docking and lysis have also been demonstrated[27].

7.8 Ink-jet printers

Ink Jet printers are commonly known. They are renowned because of the fact that while they are much faster and more precise than dot-matrix printers, they are cheaper and more compact than laser printers. The mechanism behind Ink-Jet printers involves very small tubes diameter of $70\mu m$. There are between 300 to 600 of these tubes carrying the ink for printing. A thin-film resistor is placed near to the tube and as the ink in the tube heats up, it evaporates, and a bubble is formed in the ink that causes a rise in pressure and forces the ink towards the opening

at the end of the tube, known as the nozzle. There is a cooling element at the nozzle which cools the hot ink. This cooling process also creates a partial vacuum that pulls more ink into the place of the ejected ink to keep the flow going, these printers are called bubble-jet printers. It can be noted that this heating/cooling process occurs about $12,000$ times per second. Each dot produced by a nozzle is as small as $70\mu m$. These tubes can combine and isolate from each other to change the tone of the colors as they appear on the page. Another type of ink-jet printers instead of heating uses a piezoelectric crystals that are placed on the wall of the ink chamber in the print head. When an electrical pulse is applied to the crystal, the nozzle head deforms to create a pressure wave that causes the ink droplet to be ejected. This process occurs about $20,000$ times per second[29].
Beside the working differences there is another difference between bubble-jet and ink-jet printers. Bubble-jet printers have typically $600dpi$ (dots per inch) - printing with 600 nozzles per inch. While ink-jet printers have $720dpi$, but are printing with 180 nozzles per inch, this means that ink-jet printer requires four passes to complete the same area that bubble-jet printer completes with only one pass[30].

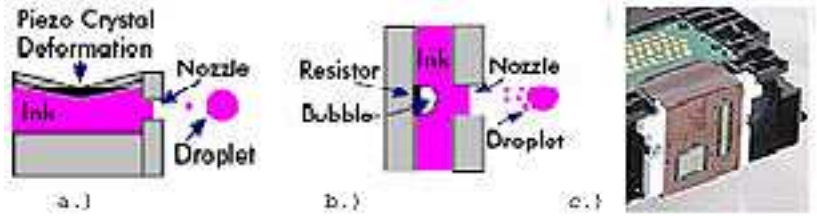

Figure 17: a.)piezzo technique of ink-jet printing b.) heat technique of ink-jet printing c.)printhead[30]

8 Conclusions

Main characteristic of microfluidic systems is laminar flow inside channels, due to the low Reynolds number for viscous fluid in microscale environment. Laminar flow is an advantage in this systems, while mixing and transport of fluid inside channels can be predicted and controlled. In microfluidics various detection methods that allow precise single-cell detection and analyse are needed, because of that there is parallel development on other research areas.
Microfluidic systems are in early phase of development. In the future there are going to be more microfluidic applications, making possible more precise analysis of various molecules, like DNA, proteins, bacteries, and because of better analysis there is going to be faster and better drug development. With development of a lab-on-a-chip and μ TAS the diagnostics will be cheaper and faster, and that is going to be handy in the developing world.

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