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Seminar

Devices in microfluidics

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Abstract

Miniaturization has been very popular for the last fifty years. Besides electronic devices, which are getting smaller each day, microfluidic devices are being widely developed. These devices operate with very small amounts of liquids, which have a lot of advantages, like low cost of reagents, portability, safety, but they also have some disadvantages that complicate the construction. This seminar will present the issues that are related to scaling, the construction method of microfluidic devices like channels, pumps, mixers, filters, sensors and research done in our Laser tweezers research group.

Contents

1 Introduction

During the last fifty years, development of miniaturized devices has proven to be very successful. This is especially true in microelectronics. Due to miniaturization computers and other high-tech devices have been created, which have completely changed our life.

Another similar miniaturization can be made with the manipulation of fluids. Devices can be made where tiny amounts of fluids can be used for chemical synthesis or analysis [1]. These kinds of devices are called *microfluidic devices* and usually operate with fluid volumes of nano to picoliters.

Small volumes normally reduce time needed to synthesize or analyze the products. The control of molecular concentrations and interactions is greatly improved and the cost of reagents and the amount of chemical waste is vastly reduced [2].

Due to the small size a compact device or a chip can be made. This so called *lab-on-a-chip* can contain all the necessary components for laboratory operations and at the same time it can be easily transported. Samples can be therefore analyzed at the point of need rather than at centralized laboratory and the results can be available in a few minutes instead of few days.

The research of microfluidics was greatly increased at the end of the cold war, when chemical and biological weapons posed major military and terrorist threats. Numerous projects were supported that aimed at developing field-deployable microfluidics systems designed to serve as detectors for chemical and biological threats [1]. Today the microfluidic devices are used in many different areas. Chemists are using them for synthesizing new materials and biologists to study complex cellular processes. These devices also offer interesting diagnostic cabilities that can be easily implemented in medicine. Other uses can also be found in environmental monitoring and industry.

We shall start this seminar by discussing scaling effects, which strongly govern the construction of microfluidic devices. For example, laminar flow dominates in this scale, resulting in slow mixing of fluids that leads to devices like mixers. Next, we shall take a look at the technology used to construct microfluidic devices - a method called soft lithography and the construction of some widely used microfluidic devices.

2 Scaling effects

Chemical engineers first came across scaling problems around fifty years ago, when they tried to scale up chemical production from milliliter scale to cubic-meter scale. The problems encountered were heat and mass transport, which resulted in the increased formation of by-products and lower yields.

Similar scaling effects occur when we scale down to nano-liter scale. Fortunately, the theory of scaling has already been developed in nineteen fifties. It introduces the dimensionless parameters by which the importance of competed physical phenomena occuring in microfluidic devices is weighted. These dimensionless parameters tell us where a system sits in fluidic parameter space.

One of the most important dimensionless parameter is the *Reynolds number*. From the dimensionless Navier-Stokes equation we see that it represents the ratio of inertial forces (ρv) to viscous forces (η/L)

$$Re = \frac{\rho v L}{\eta}, \tag{1}$$

where ρ is the fluid density, v is the average velocity, η is the dynamic viscosity and L the charasteristic lenght, such as the width of the channel. Reynolds number characterizes the fluid flow as being laminar or turbulent. The transition occurs around $Re = 2000$. For $Re > 2000$, the flow is turbulent, and for $Re < 100$ the flow is laminar. From expression 1 we see that Re is proportional to characteristic length L. In microfluidics characteristic length is micrometer and Reynolds number is therefore around 1, indicating that the flow of a liquid in microfluidics is always laminar.

Another interesting dimensionless parameter is the *Peclet number*. It represents the ratio of convection to diffusion and is relevant when mixing together different fluids

$$Pc = \frac{vL}{D}. \tag{2}$$

There v is the average velocity, D is the diffusion coefficient and L the charasteristic lenght. Dimensionless parameters are useful when constructing devices and trying to optimize the yields. When scaling even further down to nanometer scale the theory fail to give accurate results, because the continuous nature of fluids vanished at these scales and descrete nature should be considered.

3 Soft lithography

The main contribution to microfluidics fabrication was from microelectronics. One of the most successful techniques used in silicon microelectronics was photolithography, which was than transferred to microfluidics. Some of the earliest work in microfluidics did, in fact, use silicon, but it has largely been displaced by plastics. Silicon is expensive and opaque to visual and ultraviolet light and therefore not suitable for conventional optical methods of detection.

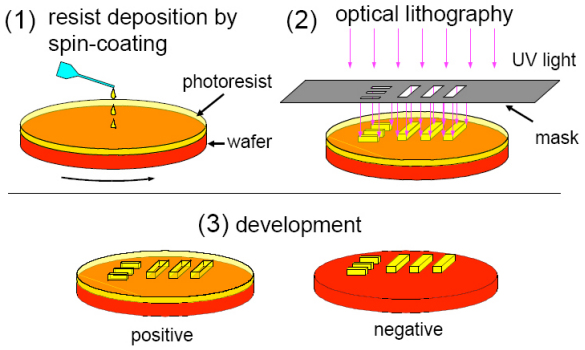


Figure 1: Photolithography procedure [5]. (1), spin-coating the photoresist. (2), exposing with patterened UV light. (3), results after appling developer.

The technique similar to photolithography, but adapted for microfluidics, is called soft lithography. It consists of two stages. In the first stage a light-sensitive material called photoresist is spin-coated on a substrate's surface (see figure 1 (1)). Then the photoresist is exposed to a pattern of ultraviolet light. The exposed pattern of photoresist becomes less chemical robust if photoresist is positive, and more chemical robust if it is negative (see figure 1 (2)). In the final stage the developer is applied, which removes only the less chemical robust photoresist, resulting in creation of the structure (see figure 1 (3)).

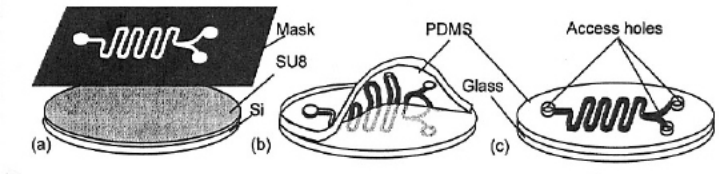


Figure 2: Soft lithography procedure [5]

After photoresist is developed, instead of etchant, PDMS (poly-dimethylsiloxane) is applied to the structured surface. PDMS is then baked, gently removed from photoresist and layed on another substrate. At the end, the access holes should be drilled and the microfluidic device is constructed (see figure 2).

4 Devices

We shall now take a closer look at the construction of some widely used devices in microfluidic applications. The essential part of every microfluidic device is the micro channels. We will discuss some physical phenomena that occure in micro channels like hydraulic resistance, electrophoresis and electroosmosis. To create an internal liquid flow micro pumps are used. The pressure driven flow is crucial for fluid manipulation and can be achieved only with pumps. From scaling laws we already know that fluids flow only in laminar region, which makes it almost impossible to mix together. Therefore, devices like mixers should be constructed to enhance mixing of fluids. At the end, two more interesting devices will be presented, H-filter and T-sensor. They both exploit the laminar nature of flow and therefore have interesting, unintuitive performing abilities.

4.1 Channels

A channel is a long enclosed space with one inlet at the beginning and one outlet at the end. Its function is to lead fluid from one point to another within the microfluidic structure. The flow (Φ) through a long channel is induced when a constant pressure drop (Δp) from one end of a channel to another end of a channel is applied. The flow of the fluid can be obtained by the Navier-Stokes equation and it is called the Poiseuille flow. For a rectangular channel it can be written like

$$\Phi = \frac{wh^3}{12\eta L}\Delta p, \tag{3}$$

for height $h << $ width w, where η is the dynamic viscosity and L the charasteristic lenght. It can be shown that the profile is parabolic in both vertical and horizontal dimensions.

For channels with constant geometry along the channel axis a concept of *hydraulic resistance* can be introduced. In such a channel it is seen that the flow rate depends on a pressure drop and a constant factor, given by the channel dimensions and the fluid used. This is very similar to Ohm's law ($U = RI$), where U is the electrical potential drop, I is the electrical current that flows in the wire and R is electrical resistance of the wire, given by the wire dimension and material of the wire. If we define Hydraulic resistance as a relationship of Φ and Δp, a similar equation to Ohm's law can be written

$$\Delta p = R_{hyd}\Phi. \tag{4}$$

Therefore, similar equations that apply for electric resistance can be also used for hydraulic resistance

$$\frac{1}{R} = \frac{1}{R_1} + \frac{1}{R_2} \qquad R = R_1 + R_2. \tag{5}$$

With these equations flow rate of all channels in fluidic network can be calculated, by knowing only dimensions of channels and pressure drop over a network system, which is useful when constructing complex microfluidic devices.

Besides transporting fluids, micro channels have also other usages. Microscale *electrophoresis* devices, which consist of long micro channels, have proven to be more accurate and faster than conventional macroscopic ones and due to their small size they can monitor molecules even inside of the living creatures [1]. Electrophoresis is a method that uses the difference in mobility coefficients of different molecules to separate them with applied electric field. Charged molecules in a solution

move in one direction, when external electric field is applied. The velocities of different simple molecules in diluted solution are proportional to their electrophoresis mobility coefficient (μ_e), and amplitude of external electric field (E)

$$v = \mu_e E. \tag{6}$$

Electrophoresis method in microscale dimensions is widely used especially for DNA and other biomolecules analysis.

Another phenomenon appears in micro channels if the walls of the channel are charged that can still improve electrophoresis' efficiency. This phenomenon is called *electroosmosis*. If the walls of the channel are charged a layer of counter ions from the solution will form at the walls. When an electric field is applied across the channel, the ions in this layer move towards the electrode of the opposite polarity. The electric force near the walls compensate the viscous force. Therefore, the velocity profile of the fluid changes form parabolic to uniform [6] (see figure 3).

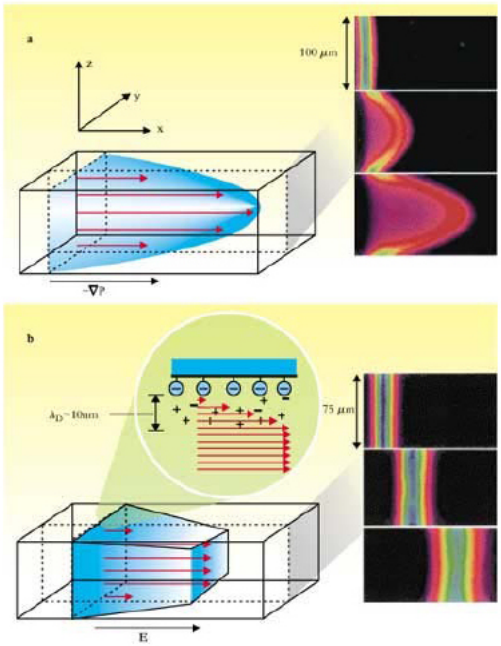


Figure 3: Parabolic profile and uniform profile [6]

The electroosmosis phenomenon can enhance the performance of electrophoresis method. When walls of the channel are not charged, the electroosmosis phenomenon does not occur. The velocity profile is parabolic, which means that velocity of fluid near the walls is much smaller than velocity in the middle of the channel. This difference decreases the efficiency of electrophoresis method; therefore the electroosmosis and a uniform profile is preferred.

4.2 Pumps

Every microfluidics application requires at least one pump for the transportation of fluids. Almost every commercial microfluidic application today requires external macroscopic pumps, which decreases flexibility, the whole application is larger, more complex and more expensive.

The solution to this problem are micro pumps integrated in a microfluidic device. Researchers have already proposed some potentially useful micro pumps, but only as a proof of concept. In one

approach they constructed the pumps with colloidal microspheres, which can be propeled with a laser tweezers.

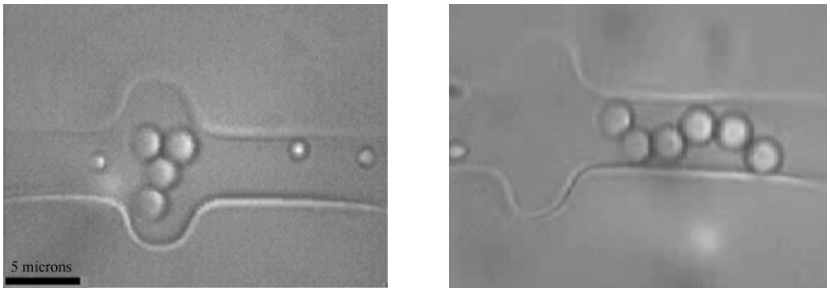


Figure 4: A lobe pump and a peristaltic pump [8]. Typical velocities of tracer particles are $4\mu m/s$ and the pressure drop is $10kPa/m$.

This method allows them to move the colloids in such a way that the flow of the fluid can be generated. Two types of colloidal movement was demonstrated. One is so called lobe movement, where four colloids are used in a micro channel. The top pair rotates clockwise and the bottom pair rotates counterclockwise, which creates flow in one direction around these four colloids. Another type of movement is a peristaltic movement also creating a directed flow [8] (see figure 4).

The problem with this approach is that pumps work only in laboratories, which have laser tweezers. Therefore, clearly not suitable for a lab-on-a-chip device.

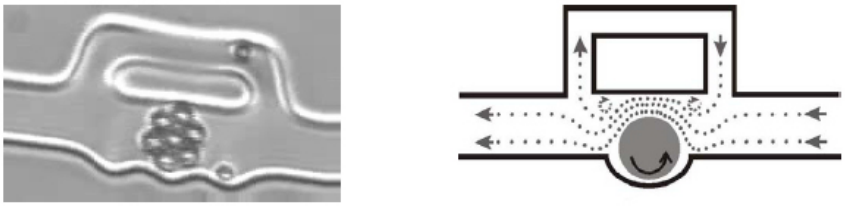


Figure 5: Magnetic colloid pump [9]. These pumps create preassure drop of $2kPa/m$, which means that the velocity of fluid is around $1\mu m/s$.

Another idea for creating micro pumps is to use magnetic colloids. In applied magnetic field a magnetic dipole will appear within these colloids. Two magnetic colloids will therefore attract and align in the direction of external magnetic field. In rotational external field the colloids will try to follow so they will rotate as well. If in a simple micro channel, no effective flow will be generated. To solve this problem the symmetry of a channel must be broken. This is achieved by rerouting the main channel over the colloids on one side only with a smaller channel [9] (see figure 5).

This kind of a pump is suitable for lab-on-a-chip device since it requires only a rotating magnetic field. A large array of pumps ($30000 pumps/cm^2$) can be constructed this way where all colloids can be rotated at the same time by the external magnetic field (see figure 6). The construction of an array is even further simplified because the magnetic colloids have the abillity to self assemble in a rotating magnetic field. The problem of how to control individual pumps, which is very important for microfluidics applications and lab-on-a-chip devices, remains to be solved. I will present one solution in the last section.

4.3 Mixers

Mixing two fluids together is necessary for every chemical reaction. In microfluidics mixing is very slow, due to the laminar flow through the micro channels. Because there is no turbulent flow the

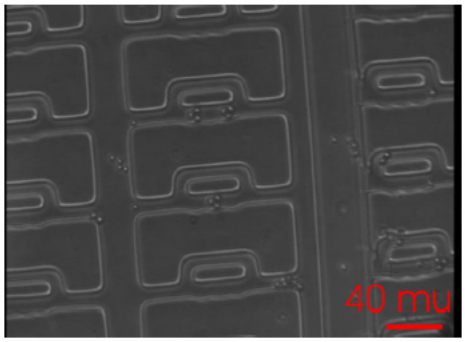


Figure 6: Array of magnetic colloid pimps [9]

only phenomenon that mixes fluids is diffusion. A lot of research has been done over the past few years to improve mixing of fluids in a micro channel. Two different types of mixers have been studied, passive mixers with no moving components and active mixers with moving components, usually magnetic colloids.

4.3.1 Passive mixers

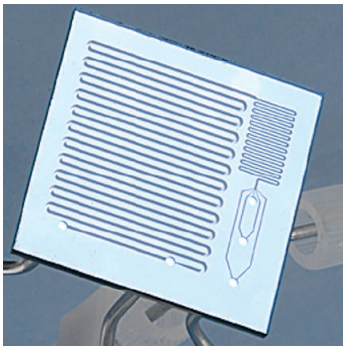


Figure 7: Mixing in a very long channel [10]

One of the first mixers used was simply a very long channel. Due to the laminar flow only diffusion is responsible for mixing fluids and it is known to be very slow. To overcome this problem the time required for diffusion process should be dilated. Normally the fluid flow cannot be easily altered therefore a longer channel is constructed. This way fluids that flow together have enough time to mix. Since in microfluidics a lot of space is available for construction, a long channel is easily implemented. A longer channel also requires higher pressure drop for the same fluid flow, but when external pumps are used this can normally be neglected.

Other passive mixers that base on *chaotic advection effect* have also been studied. Chaotic advection enhances mixing in laminar-flow systems, because it continuously "stretches" and "refolds" concentrated solute volumes. The effect can be achieved if obstacles are introduced within the channel or if channel geometry is modified. In each case, the modications enhance stretching, folding and breaking of the flow. A good example of such mixer is a three-dimensional serpentine channel consisting of repeated segments in orthogonal planes. Another example is channel with grooves (see figure 8). These grooves can be either diagonal or herringbone-shaped, which have proven to be very efficient.

Passive mixers are not ideal mixing devices. The velocity profile in a channel is parabolic,

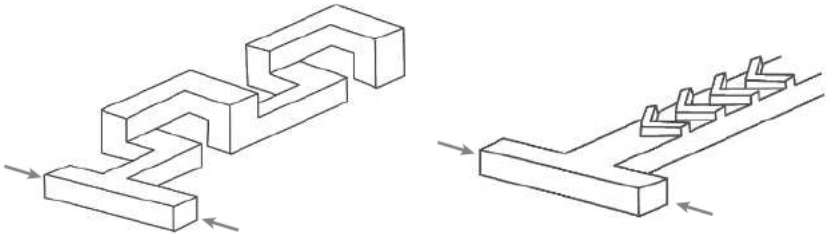


Figure 8: 3D serpentine channel and a chanell with grooves [11]

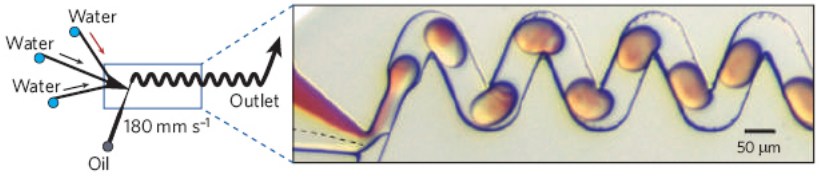


Figure 9: Mixing within droplets [11]

resulting in a time distribution of fluid spent in a channel. This causes a variation in the yield and efficiency of mixing. The problem can be overcome if the fluids, we want to mix, are localized within a discrete droplet [11]. Droplets can be made spontaneously when multiple streams of aqueous fluids are injected into an immiscible carrier fluid. The use of twisting channel geometries is then effective in generating chaotic mixing within the droplet (see figure 9). This type of mixing is rapid and fluid transport occurs with no dispersion.

4.3.2 Active mixers

Active mixers consist of at least one moving part. A good example is few magnetic colloids in a rotational magnetic field. As we already know colloids will group together and rotate in the rotating external magnetic field. The rotation of colloids will mix the fluid, but only in a close proximity. We can obtain better results if colloids are not grouped together in a cluster but rather form a rotating line. This can happen if the frictional force does not exceed the magnetic force between colloids.

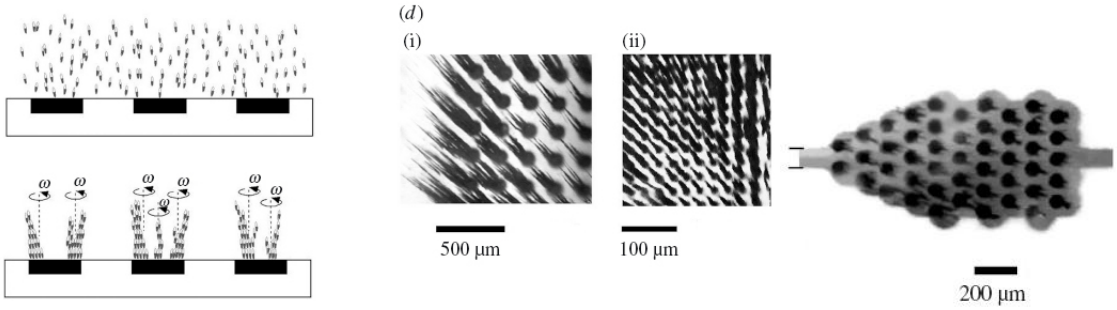


Figure 10: Self assembled active mixers [12] (left and centered pictures). Right picture shows active mixing of two fluids, with frequency $\omega = 10Hz$.

The problem with these kind of mixers is that while rotating, colloids are moving in the channel, and can therefore clog the outlet and stop the flow. To avoid this problem some colloids need

to be attached to the channel bottom. This can be done with an array of ferromagnetic metal islands that can be constructed in similar way to microelectrodes. If magnetic field is applied perpendicular to the channel bottom, ferromagnetic islands will attract magnetic colloids, which will lineup in the direction of magnetic field, in our case upwards. Additional rotationally magnetic field parallel to the bottom will rotate the chain of colloids by an angle which depends on the ratio between perpendicular and the parallel magnetic field. With this procedure anchored rotating bars of colloids can be constructed with the ability to change frequency and the inclination.

Active mixers described above are especially interesting not just for their excellent working characteristics, but also for the unique ability to self assemble (see figure 10).

4.4 H-filter

In devices presented so far the laminar flow was a problem that we wanted to overcome. The H-filter is a kind of a device, however, that exploits the nature of laminar flow. Its function is to continuously extract the molecular analytes from a fluid containing interfering particles. This is done without the need for a membrane filter or similar components that requires cleaning or replacement.

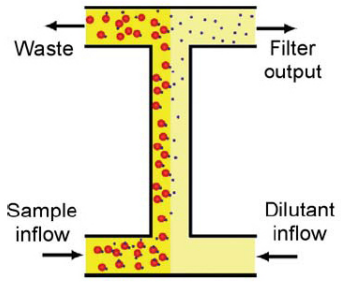


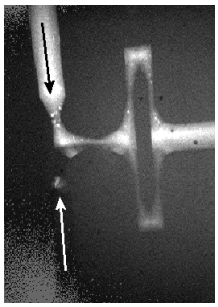
Figure 11: Schematic diagram of H-filter [14]

We already know that in micro channels Reynolds number is generally well below 1, which means that no convective mixing of fluids occurs. The only way by which solvents solutes and dispersed particles move perpendicular to the direction of the flow is by diffusion. The root mean squared distance traveled by molecules is described by the Einstein relation

$$r_{rms} = \sqrt{2Dt}, \tag{7}$$

where D is a molecular diffusion coefficient and t is time. Molecular diffusion coefficient depends on the size of molecules and to some extend on the shape of molecules. Smaller molecules have larger diffusion coefficients and will travel longer average distance per time then bigger molecules, which have small diffusion coefficients. The difference between diffusion coefficients can be used to separate smaller molecules from bigger ones (see figure 11).

H-filter is H shaped system with two input channels, one main channel and two output channels. When fluids from input channel, normaly a sample and a reagent, meet at the beginning of the main channel, they do not mix, due to the laminar flow, but rather flow side by side through main channel. Only diffusion is responsible for transfer of molecules from one side to another, which largely depends on the diffusion coefficient for a given molecule. The time spent in the main channel can be carefully adjusted with its length. The diffusion causes equilibration of small molecules across the channel, whereas larger particles do not equilibrate during the transit time. At the end of the main channel modified streams are separated. One output channel contains reagent with a some concentration of small molecules from the sample and the other channel contains sample with the same concentration of small molecules and reagent (see figure 12).



channel width = $40\mu m$
channel length = $200\mu m$
fluid velocity = $130\mu m/s$
D(small particles) = $340\mu m^2/s$
D(large particles) = $60\mu m^2/s$

t(small p. diffusion) = $0.5s$
t(large p. diffusion) = $7s$
t(through channel) = $1.6s$

Figure 12: A fluorescence image of H-filter in which soluble fluorescent dye is extracted from a mixture of beads and dye [13].

4.5 T-sensor

The basic principles of H-filter can also be used for many different reusable chemical sensors. The controlled continuous diffusion between sample and reagent creates a region from where particular information regarding the sample can be extracted. This region can be probed by optical absorption or fluorescence. The T-sensor can be used to detect various chemicals and since it operates with small amounts of sample, it has very fast response and produces little waste.

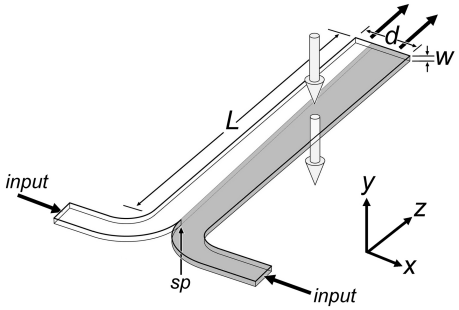


Figure 13: Schematic of T-sensor [15]

A T-sensor looks like H-filter without two output channels (see figure 13). Typically one input stream contains analyte of interest like proteins, drugs or blood and the other input stream contains a receptor molecule like fluorescent indicator, enzyme, antibody, pH indicator or else. When these two streams meet at the stagnation point (SP) they do not mix, due to laminar flow, but continue to flow side by side. The only means by which the molecules in opposite streams can mix is by molecular diffusion across the interface of the two fluid streams. The reaction events that occur along this interface produce measurable signals, like fluorescence, that can be used to calculate a parameter of interest for our sample, like concentration, diffusion coefficient or pH.

As an example let us look at the measurement of the pH of an unknown sample. The sample flows into one of the input channels and a pH sensitive fluorescence dye in another. Due to diffusion these two chemicals slowly mix, resulting in a boundary line between two colors which, appears at the specific pH. In a controlled flow rate and concentration of pH sensitive dye, the angle between these two colors can be used to calculate the pH of the unknown solution.

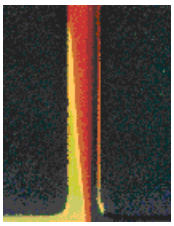


Figure 14: Measuring pH with T-sensor [15]

5 Recent experiments

This experiments have been conducted in the Laser tweezers laboratory at our faculty where we study and develop new kinds of micro pumps and try to improve pumps that have already been demonstrated by other research groups. We have developed a new way of constructing artificial swimmers that we can use as pumps when they are attached to the surface. Magnetic micro pumps that have been presented earlier have a great potential, but are not suitable for lab-on-a-chip application, due to large and heavy devices like laser tweezers, needed for their operation. Therefore, we have developed a controlling system that can regulate the frequency of individual micro pump. Another pumping system that we have also been studying is an array of self assembled magnetic colloids imitating cilia.

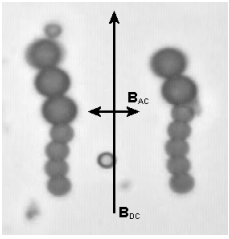


Figure 15: Artificial swimmers

Artificail swimmers consist of different sized magnetic colloids. Bigger ones represent the head and smaller ones represent the tail (see figure 15). In external magnetic field colloids align in the direction of a field. With the laser tweezers and applied static magnetic field the artificial swimmer can be individually constructed by putting desired colloids together. When adding AC magnetic field perpendicular to static magnetic field the constructed swimmers move forward like they were swimming. This will not happen unless a symmetry is broken (see figure 15). The boundary conditions on both sides of a swimmer must be different, which is achieved with a head and a tail part. With oscillating external magnetic field and two different boundary conditions symmetry breaks in time and a sort of wave motion is created [16]. To construct a micro pump, artificial swimmers should be attached to the surface, either by laser tweezers or ferromagnetic island.

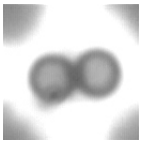


Figure 16: Two colloids in the middle of four electrodes. Particle's size is $4.5\mu m$. For typical frequencies $\nu = 5Hz$ forces are $\sim 10^{-12}N$ and torque $\sim 2 \times 10^{-18}Nm$.

We have developed a system that can control the rotation of individual magnetic colloidal pump

mentioned earlier. To control such pumps quadrupole electrodes are constructed around the pump (see figure 16). When a voltage is applied to electrodes (+ - + -) a quadruple potential appears with minimum at the center. A pair of colloids is not only confined in the minimum of the potential, it also has two preferable angles. When colloids rotate in external rotating magnetic field and voltage is applied to electrodes, electric and magnetic torques compete. Changing of the electric field the magnetic influence can be compensated and thus the rotation of colloids can be regulated. The pump can be switched on and of or a frequency of rotation can be regulated (see figure 17).

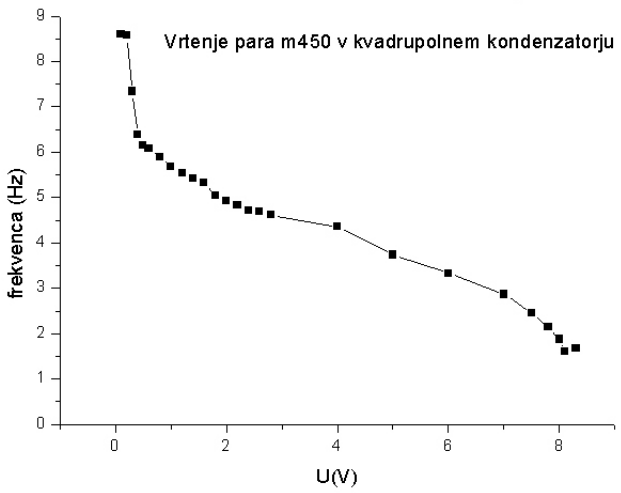


Figure 17: Frequency versus voltage graph

Another type of distributed pumps was inspired by the nature. We have constructed an array of magnetic colloids that mimic cilia. The idea is that by moving cilia a global flow of surrounding fluid will form. This can be then used in microfluidic devices as a pump and mixer at the same time. The construction is similar to that described of active mixers. An array of ferromagnetic islands is constructed on the surface and after applying vertical magnetic field, colloids form vertical line on top of the islands (see figure 18). To create a fluid flow the symmetry must be broken. The theory predicts that the rotation around inclined axes should create such flow. So far we were not able to create uniform cilia of colloids. The flow, however, was generated, but the pumps were not effective enought to create it on a global scale. We have new ideas how to solve this problem. However, the technology still needs to be improved.

6 Conclusion

In this seminar I have presented a general overview of microfluidics and devices in microfluidics. The construction of microfluidic devices is relatively simple due to the soft lithography procedure. The scaling effects are also very important when designing microfluidic devices. They can tell us how the fluids will behave in micro scale systems. For example, the flow of the fluid in a micro channel is always laminar. The laminar flow causes many problems in micro devices like slow mixing of fluids. The mixing is for example essential when doing chemical reactions. But on the other hand, its nature can be also used as an advantage in devices like H-filter and T-sensor. For the operation of microfluidic devices pumps are needed to create fluid flow though the device. Several pumps have been presented including those designed in our research group. We have also developed a controlling system for magnetic pumps, which can bring as a step closer towards the lab-on-a-chip applications.

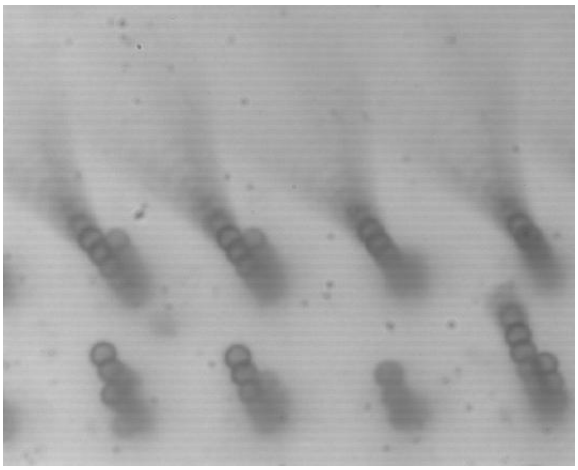


Figure 18: An array of collodal cilia

Due to construction procedure simplicity and increasing interest of industry, researchers all over the world are starting to work in this area and contribute new ideas and propose new uses for microfluidic devices. Many of these devices are only a proof of concept and not yet suitable for lab-on-a-chip applications. This is perhaps one of the reasons why microfluidic applications are not yet widely used in everyday's life, although they offer incredible capabilities and excellent performance. Perhaps in fifty years or so, the technology of microfluidic devices will improve to such extend that microfluidics will be as important as electronics is today.

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