Living la vida LOCa

A brief insight into the world of Lab On a Chip and Microfluidics

Throughout history humans have always looked for improvement in the tools they used. Animals were bred to be bigger, means of locomotion were improved and engineered to become larger and carry more. Up until not too long ago, bigger was better, both to maximize utility and for the resulting status implications.

Today it seems the opposite is true, cameras are becoming so small that not only you can fit them in your wallet, but you an also lose them easily, which of course is quite profitable for the company selling them. Every day we experience pressure for buying smaller computers, cell phones, and even smaller cars. In the 70s, any Buick owner would have laughed at a Smart car (of course people do so even now but only when the driver of the Smart still has problems parallel parking). Why has this size reduction been so important? Is it because of gas prices? Are we running out of space?

Science has moved at least at the same speed towards smaller devices. The word "nano" (a billionth of a standard size) is so hot right now that it seems like any respectable scientist should include it at least once in each sentence. One of the latest developments toward the realm of the small is the so-called "lab on a chip" (LOC), or a device about the size of your palm, able to perform the tasks of a standard laboratory. This idea has been around for a while; certainly it is very convenient to fit a lot of equipment on a portable device. The LOC is envisioned to be a simple tool, easy to operate, requiring very small amounts of samples. Even more appealing is its disposability, making it extremely useful for clinical procedures. It is possible to conceive having a device that needs only a small sample of bodily fluid (whether blood, saliva, or urine) to diagnose a patient's illness. All it would require is a system that could multiplex several tests under varied conditions. The glucose tester diabetics use in order to maintain their sugar levels constant is very similar to a simplified version of an LOC. Nevertheless the complexity of the device needs to increase so that a higher number and more complex procedures can be addressed. LOCs are also of great interest to safety and military departments, who would greatly benefit from having portable chemical detection systems.

Although the concept of scaling down a system seems simple, the operation of LOC devices is quite complicated. Different rules apply at small scales: viscous friction (or the resistance to flow) dominates the micro world. The media a molecule such as a protein moves in is in effect incredibly dense because the atomic size of the fluid molecules is comparable in size to the protein itself. Every time a macroscopic object moves it displaces millions of molecules but for a microscopic entity dislodging similar sized molecules can be challenging. If you were swimming in an overcrowded swimming pool every other person around you would be an obstacle even if they were smaller than you. Therefore, gravity and inertial effects no longer matter at this scale, a molecule has to primarily confront viscous forces and random Brownian motion. For these reasons, the design of a device intended to be very small and yet precise is not easy. It is essential to keep in mind how differently the system is going to behave compared to the macro scale.

One of the main players in the lab on a chip industry is the microfluidics platform. Micro stands for a unit of measure that is a millionth of the normal scale, i.e. a micrometer is a millionth of a meter. It is hard to visualize such small scales; micrometer-sized features can be more than 100 times smaller than a human hair. The volumes of fluid transported in microfluidic channels can be as little as few nanoliters (a nanoliter corresponds to a billionth of a liter), and sometimes even smaller. In order

to handle a large number of samples in small fluid volumes, microfluidic chips contain thousands of channels connected to form a micro fluidic circuit. This setup allows not only the use of tiny reagent volumes but also a high task parallelization since several procedures can processed on the same chip.

In microfluidic channels the flow of liquid is completely laminar: all of the fluid moves in the same direction and at the same speed. Unlike turbulent flow this allows the transport of molecules in the fluid to be very predictable.

Applying pressure to the fluid commences motion. Pressure driven flow is characterized by a parabolic velocity profile as the fluid does not move on the channel walls and has maximum velocity in the center.

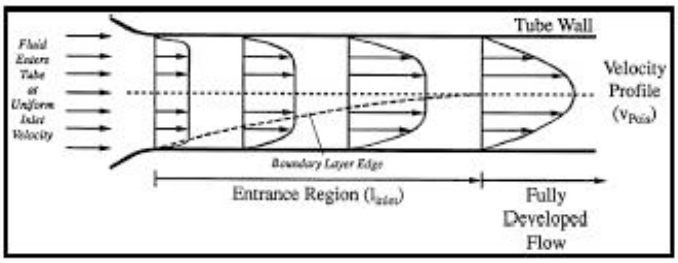

Figure 1. Adapted from ref (3).

Microfluidic devices are generally made in glass or plastics but several laboratories utilize PDMS, a type of silicone. Some advantages of PDMS are that it is very cheap, optically clear and permeable to several substances, including gases. The latter is very convenient, making it possible to inject fluid into a channel that has no outlet, as the air will quickly diffuse out.

Let's say we want to make a very simple branched channel, as outlined below.

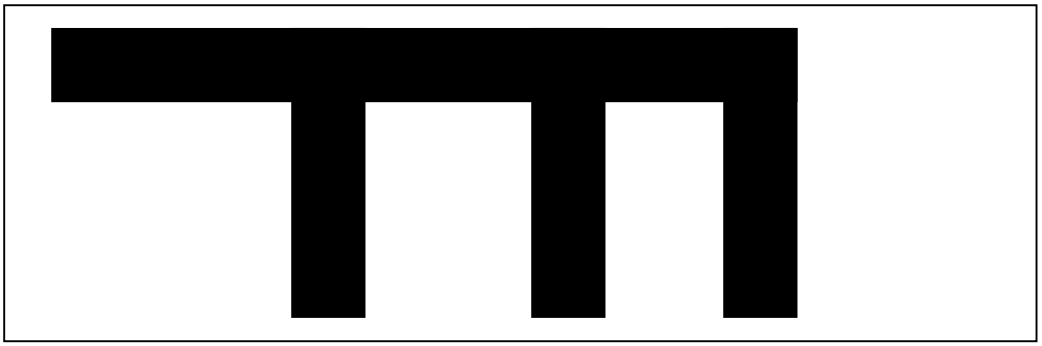

Figure 2. Hypothetical design.

In this top view, the dark lines represent the flow channels. Let's say that each channel is to be 100 micrometer wide. These features are not very easy to physically carve out in order to make a mold. A machine with high precision on such minute details would be very expensive and would require a lot of time to perform its task. We therefore need to rely on another method: soft lithography. This technique allows the production of countless features in the same time needed for one. Unlike machining the time required does not scale with increased number of elements, as we will demonstrate shortly.

For PDMS devices, soft lithography is based the utilization of substances that become soluble to particular solvents when exposed to UV light. These substances are called photoresists and they appear to be very dense transparent liquids. Upon baking their consistency becomes harder.

If we were to print the design from Figure 1 onto a transparency slide we could use it to make our mold as follows. We can place the slide on top of the baked photoresist (made of the thickness required), and then expose the entire setup to UV light. Under the dark drawing lines the photoresist will not be exposed to the light, while in the exposed areas the photoresist will become vulnerable to the solvent. Upon washing it will dissolve and come off. We will then be left with a cast of the initial design where the dark lines have become solid photoresist 3D lines. You can see that the level of complexity of the chip depends only on the design, and the time required to make the features depends only on the UV scan and the wash step.

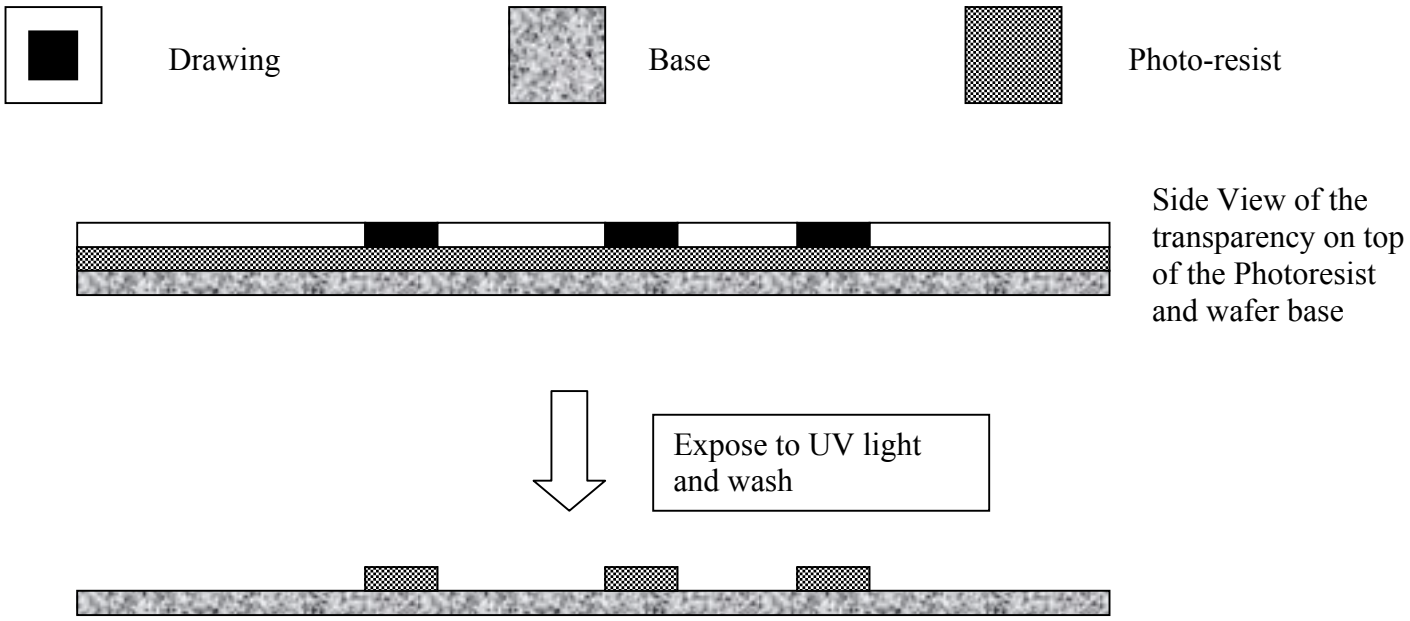

Figure 3. Fabrication of the flow layer of a microfluidic chip.

We have now completed the first step towards the fabrication of our chip. If we wanted to add more features to our chip we could do it by following the same procedure as outlined above. We would need to start over with new photoresist. Several layers with different patterns can be made and stacked on top of the previous ones to form a complete microfluidic chip. Layers can be connected vertically by perforating the membrane separating each layer. Of course it is essential to have accurate alignment of each layer. In order to achieve this, alignment marks are made on each one of the layers so that it is possible to position each part correctly.

We are now ready to coat our mold with PDMS – the remaining photoresist lines will become the hollow channels.

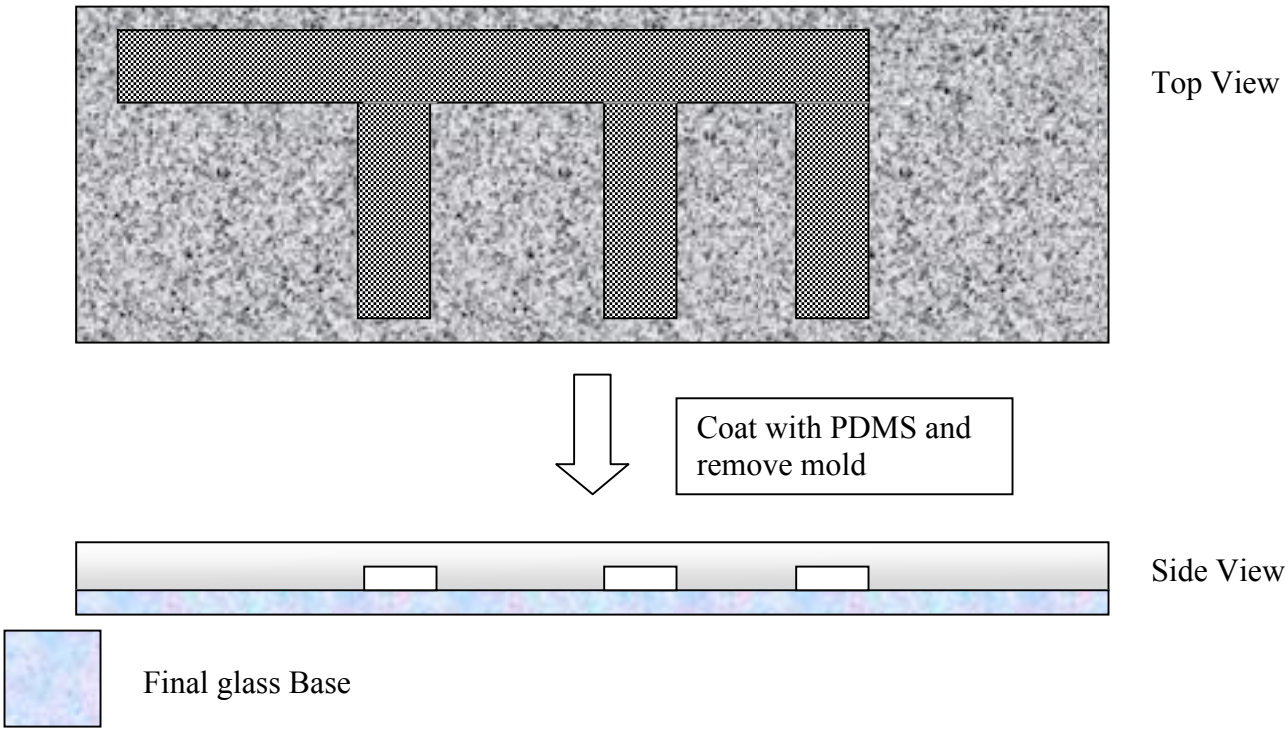

Figure 4. Coating with PDMS to produce the final chip.

The procedure outlined here is a simplification of the protocol used to make microfluidic devices, but it should give you an idea of how the manufacturing works.

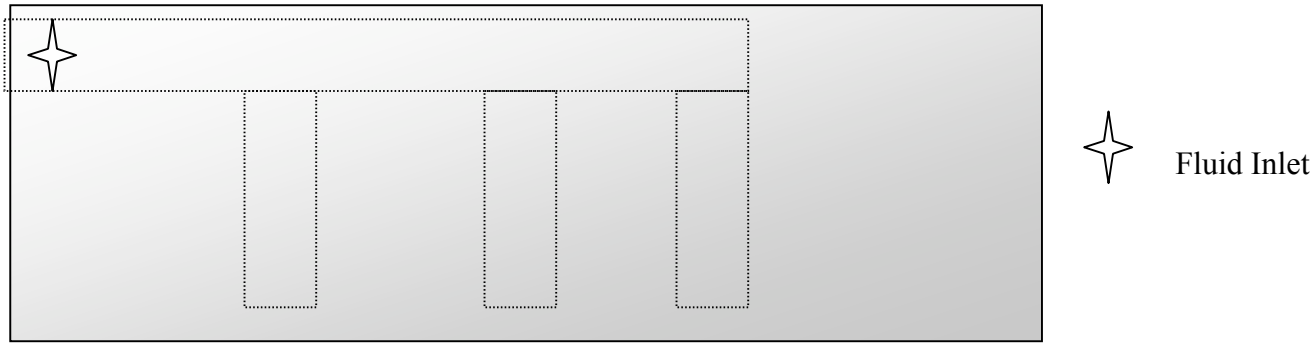

Figure 5. Top view of the PDMS chip with one flow layer.

If we wanted to control the fluid through the different channels by forming a valve, we would need to design an additional layer for our chip. For instance, we might want the fluid to go through the third branch only some of the time.

To do this, we design a control layer and place it in contact with the existing flow layer. If the membrane separating the two layers is thin enough we can easily use the control layer to affect the fluid movement in the flow layer. In fact, if we pressurize a fluid in the control layer the thin PDMS membrane that separates the two layers will deflect and completely block the flow channel.
For the valve to be effective, it is essential that the two layers are separated by a thin membrane: if it was too thick, pressurizing the control channel would not affect the flow layer while if there was no membrane the fluid in the control layer would directly circulate in the flow layer.

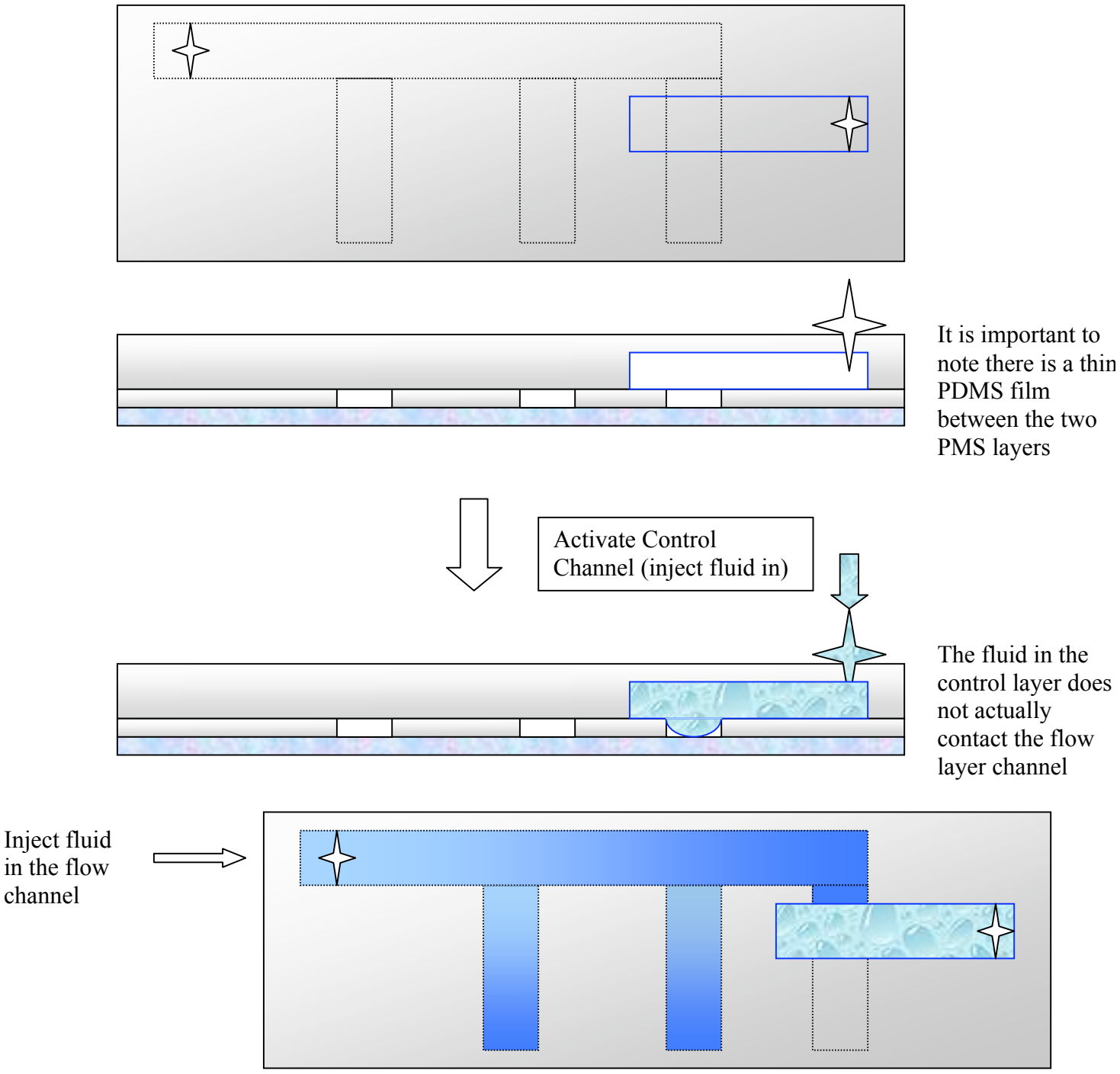

Figure 6. Action of the control layer on a microfluidic chip.

The details of fabrication of the control layer are very similar to the ones outlined for the flow layer. When more complicated chips with several layers are made, different types of photoresist are usually employed to vary the thickness or some other property of the layer: the procedure varies slightly with the different types of materials used.

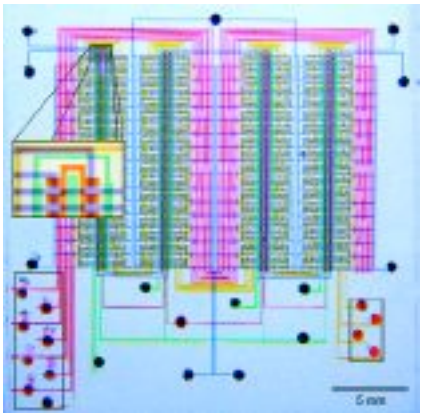

Figure 7. The level of complexity of microfludic chips can become extremely high. Reproduced from ref (1).

By combining valves and channels in different configurations, scientists have been able to develop peristaltic pumps, fluid mixers and filters: they have achieved the miniaturization of numerous tools towards the development of the Lab On a Chip. Microfluidic devices are currently employed in a large variety of fields, from medicine to biology and chemistry. Some of the great advantages of these devices lie in operating at such small scales, where experimental sensitivity and precision are much easier to achieve thanks to laminar flow and the well-defined physics of these systems. But even more advantageous is the parallelization that can occur when operating at such small scales. While the amount of reagents needed for the experiments is greatly decreased, the multiplexing of the experiments allows for much higher throughput. These efforts are ultimately resulting in a product that is in very high demand not only in pharmaceutical and biotech research, but also environmental monitoring and security applications.

Hopefully I have convinced you how convenient and widely applicable microfluidic chips are. LOC microfluidic platforms have been used from miniaturized fuel cell to DNA sequencers and it seems like the range of applications keeps growing. Maybe it won't be too long until we will all be able to have our own lab on a chip at home, feel sick one day and know what is wrong by simply loading a sample of saliva into a microfluidic device… Until then we can just comfort ourselves with some macroscopic amounts of Tylenol.

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