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Achim Wixforth

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# Flat Fluidics: Programmable On-Chip Networks for Biological and Chemical Applications

Achim Wixforth<sup>\*,\*\*</sup>

<sup>\*</sup>Chair for Experimental Physics I, University of Augsburg, 86159 Augsburg, Germany

<sup>\*\*</sup>Advalytix AG, 85649 Brunnthal, Germany

## ABSTRACT

We present a novel approach towards the needs of a versatile microfluidic chip-based microfluidic system with unique properties and functionality. Like for microarrays and in contrast to many existing microfluidic technologies, the fluid handling is performed on the flat surface of a programmable chip, where fluidic tracks and functional blocks such as valves, dispensers, mixers, and sensing elements are chemically defined using standard lithographic techniques. The actuation of the fluid, the driving and addressing of the functional elements as well as possible sensors are based on electrically excited mechanical acoustic waves, propagating along the surface of a chip. The combination of such fluidic networks and our unique pumping technology results in fully programmable microfluidic processor chips. The whole system has no moving parts, and is easily fabricated employing standard semiconductor technologies. Moreover, due to the planar nature of the chip all functional blocks are readily accessible from the outside, e.g., by pipettes or spotting robots. This unique feature makes our programmable fluidic processors fully compatible to existing laboratory environments and most any chemical and biological processes and assays.

**Keywords:** microfluidics, biochip, surface acoustic waves, acoustic streaming, microarray

## 1 FLAT FLUIDICS

Small is not only beautiful – it is also very different! Tiny amounts of liquid being processed in microfluidic systems do not obey the rules that we are familiar with in our daily life and our macroscopic world. Water doesn't necessarily always flow downhill, it doesn't necessarily trickle out of its container if tipped over, it may seem to be as thick and viscous as honey if pressed through a narrow tube. Although in many cases surprisingly counter-intuitive, these effects have been well known for a long time: physicists parameterize the strange behavior of micro- or even nanofluidic devices like the complete absence of turbulence by a single figure - the Reynold's number. Basically, its value divides the fluidic world into two

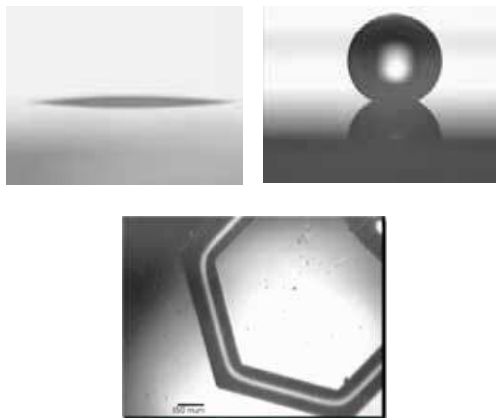
regimes: Large Reynolds numbers mean 'as usual', whereas small values denote the nightmare of microfluidic engineers. Simple things like pumping, mixing or stirring require sophisticated techniques having little or nothing in common with a plumbers task. The reason for this behavior, amongst others is the increased importance of surface effects, as the surface to volume ratio increases dramatically with decreasing system size.

Why is there a growing interest in microfluidic systems? Reducing the dimensions of macroscopic biological or chemical laboratories is advantageous for the following reasons: The small scale allows for the integration of various processes on one chip analogous to integrated microelectronic circuitry. Thus manual handling, e.g. transferring reagents from one process step to the next, can be reduced. Such an integration is the prerequisite for a fully automated data management system covering all steps of a given chemical or biological process. Furthermore, the required reagent volumes are reduced thus saving both material costs and process time as many of the time consuming amplification steps for biological substances can be omitted. Finally, the miniaturization results in enhanced precision by providing more homogenous reaction conditions and in shorter reaction times, as less sample volume is present at higher concentrations.

So far, in most of the microfluidic systems liquids are confined and moved in tubes or capillaries. Usually, the application of such systems is restricted to continuous flow processes. Small amounts of liquid cannot be handled separately in tubes, as these need to be completely filled in order for the pumping mechanism to work properly. Such systems hence mimic laboratories using hoses and tubes rather than beakers and test tubes. Most of the work in macroscopic laboratories, however, is carried out as a batch process. A typical example is the mixing of two reagents or dissolving a substance in a liquid. A lab assistant would measure the required amounts in separate beakers, and then pour the substances in a third beaker while agitating with a magnetic stirrer.

Is there a way to make surface effects friend instead of foe? When carefully looked at a microscale fluid, one realizes that the effects of surface tension, for instance, by far exceed those of gravity. The shape of a droplet on a surface

is given by the properties of the liquid itself, and by the properties of the substrate. It either remains a droplet or it wets the surface, depending on whether the substrate is hydrophobic or hydrophilic.



**Fig.1:** Lateral modulation of the wetting angle on the surface of a chip. Parts of the surface can be functionalized to be hydrophilic (top left) or hydrophobic (top right) to result in complex geometries forming fluidic tracks (bottom).

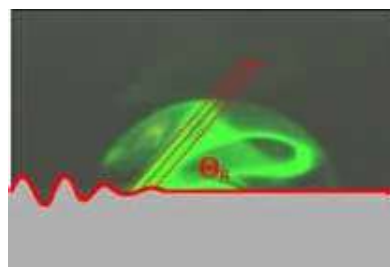
This is the basic idea behind the Advantix technology: Small amounts of liquids do not really need to be confined in tubes and trenches. They form their own test tubes, held together by surface tension effects! A chemical functionalization of the surface or parts thereof can be employed to laterally define a modulation of the wetting properties, thus creating fluidic pathways or tracks forming virtual potential wells for a fluid on the flat surface of a chip. The technology to create such fluidic tracks very much resembles the one used to define conducting paths on a electronic semiconductor device. Photolithography and micro imprinting have been demonstrated. Both can produce a laterally defined, large contrast of the wetting angle on a substrate.

## 2 PLANAR LAB ON A CHIP

A true 'laboratory on a chip', however, requires more than just test tubes. Most importantly, their cargo has to be moved around, mixed, stirred or processed in general. Using the Advantix technology, actuation of single droplets or closed loops of liquid on a fluidic track is achieved by sending a pulse of lattice vibrations of the substrate towards the liquid. Here, we use so called surface acoustic waves (SAW), being widely used in the completely different field of radio frequency signal processing over the last twenty years or so. Each cell phone, for instance, contains two or more devices operating on SAW [1].

A surface acoustic wave (SAW) is the nanometer analogon of an earthquake. Its amplitude and wavelength, however, can be precisely controlled by an electrical signal applied to an appropriate transducer. Such transducers, again, can be produced in a quite simple and well known process known from semiconductor technology. Unlike a quake on the surface of the earth, however, the direction of the SAW, too, can be precisely predetermined. This way, the waves can be sent towards the desired amount of fluid and interact with it. At low amplitudes, e.g. below one nanometer, a striking SAW pulse creates internal streaming within the fluid. Its energy is strongly absorbed and radiated into the fluid under the Rayleigh angle  $\Theta$ .

The upper boundary of the fluid, defined by its surface bends the streaming lines, resulting in a continuous flow within the droplet, as visualized in figure 2, where we depict a time series of snapshots of such streaming in a 50 nl droplet, stained by a fluorescent dye.

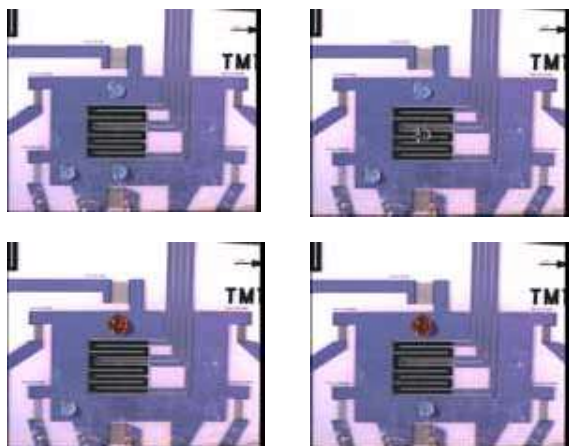


**Fig. 2:** Acoustic streaming induced in a droplet deposited on the surface of a chip. A surface acoustic wave propagating on the chip surface hits the droplet from left to right. Absorption of the wave creates a streaming pattern by coupling to a pressure wave in the liquid, which is excited under the Rayleigh angle  $\Theta$ . The streaming pattern is visualized by a fluorescent dye.

At larger amplitudes, the internal streaming becomes a movement of the whole droplet into the desired direction on the chip with a desired speed. Velocities close to one m/sec can be achieved, this way. In this sense, the transducers generating the surface acoustic waves can be regarded as pumps without moving parts, that can be remotely operated to control the position of one or more single droplets on the planar fluidic network on a chip. Several droplets can be controlled independently, very much like the trains on a model railway. The fact that the surface of our chip is easily accessible from the outside world means that it can be loaded or unloaded by conventional means - either manually or by pipetting robots.

Many functions of a real world laboratory can be implemented on our microfluidic processors this way. Using the same 'hardware', and running different software, many complex chemical and biological processes can be run on the same chip. This is possible due to the two-

dimensional character of the Advalytix chips which does not require to redesign the hardware to implement new functions.



**Fig. 3:** Subsequent snapshots of an Advalytix chip in action. Three different chemicals of about 100 nl volume each are manipulated along the surface of the substrate. Electronically controlled two-dimensional movement of the droplets is used to merge and mix the separate small volumes and to induce a chemical reaction (color change).

Moreover, the flat surfaces of the Advalytix chips are ideally suited to also host additional devices like sensors, heaters or even complex electronics [2]. Especially surface acoustic wave sensors [3] are a natural component of our microfluidic processors [4]. The same structures acting as pumps or mixers can be used as sensing devices for charge, mass loading, viscosity etc.

## 2.1 Quasi chaotic mixing in capillary gaps

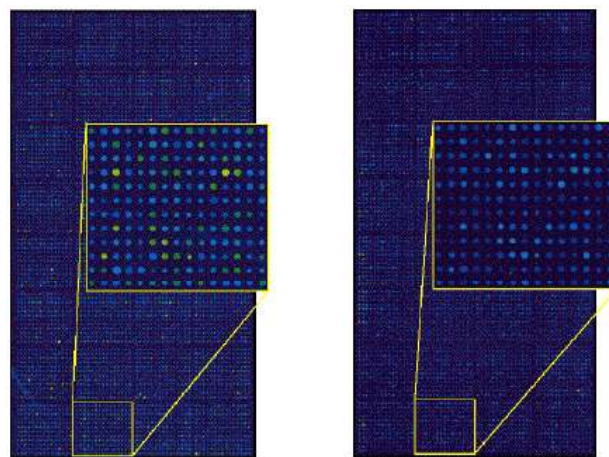
The first product employing the Advalytix technology bases on the attractive possibility to efficiently mix a fluid on a chip [5]. As mentioned above, at very small length scales or volumes, there is no turbulence - all flow is basically laminar. As shown in Fig. 2, however, SAW are able to induce a complex streaming pattern within a liquid. Its wavelength and amplitude define the actual streaming patterns. Within a confined volume of fluid it can be computer controlled to execute a quasi-chaotic mixing.

The Advalytix "ArrayBooster™" (see Fig.4) makes use of this fact for micro array hybridization purposes. One or more remotely controllable SAW chips are the heart of the "AdvaCard™", being used like a conventional cover slide for hybridization of DNA or protein microarrays. The ArrayBooster controls the temperature during the incubation process and an appropriate software protocol (which can be easily edited and adjusted by the user) takes care of the controlled mixing and stirring at zero dead volume [6]. This way, a reduction of the incubation time by

at least a factor of 5 and a simultaneous significant signal increase as compared to a conventional hybridization has been successfully demonstrated (see Fig. 5).



**Fig. 4:** The Advalytix "ArrayBooster™", a hybridization station as described in the text.



**Fig. 5:** Fluorescence images of a typical microarray after hybridization. Left: SAW agitated, right: Diffusion only conventional approach.

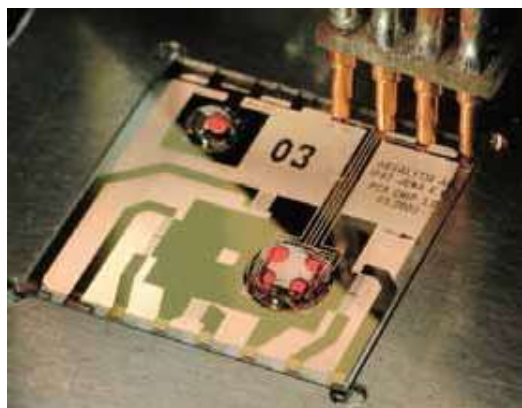
## 2.2 PCR on a chip

Combining the SAW technique with thin film resistance heaters a biological analysis chip with integrated DNA amplification by polymerase chain reaction (PCR) and hybridization was designed. To prevent evaporation of the PCR reagents at high temperatures the sample is enclosed in droplets of mineral oil, thus forming „virtual“ reaction tubes. For this purpose, a special surface chemistry had to be devised, allowing for large contact angles for both aqueous solutions and the cover oil.

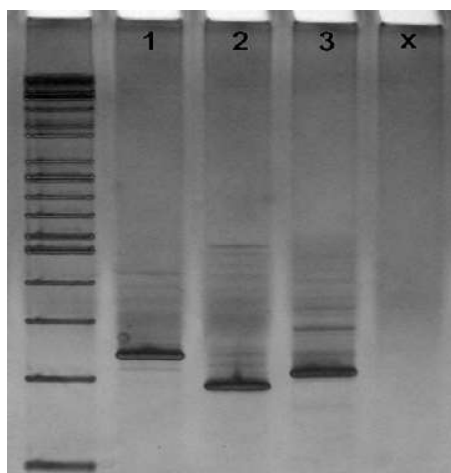
On this PCR - chip (see Fig. 6) the SAW based actuation of small amounts of fluids can be used to simultaneously resolve the necessary primers in dry form, moving the oil covered sample liquid volume between the two heaters and



to mix or stir during hybridization [4]. The chip is able to perform a highly sensitive, fast, and specific PCR in a volume as low as 200 nl. During the temperature cycles online monitoring of the DNA concentration is feasible with an optical unit having a high sensitivity of only 0.1 ng. The successful PCR is either followed by a standard gel electrophoresis (Fig. 7) or a hybridization on an on-chip DNA microarray [5]. With our chip we were able to detect a single nucleotide polymorphism (SNP) responsible for the Leiden Factor V syndrome from human blood.



**Fig. 6.** PCR chip based on acoustically mediated fluid actuation as described in the text.



**Fig. 7.** Gel electrophoresis for a multi spot PCR on the acoustically driven biochip. Lanes 1, 2, and 3 represent the results for different primers, lane x shows a negative control experiment within the same virtual reaction tube.

### 3 SUMMARY

In summary, we have shown that a change of the paradigms of microfluidics can result in a powerful technology to handle smallest amounts of liquid on the planar surface of a chip. Employing planar technology as known from

semiconductor industry, much easier and cheaper manufacturing can be achieved as compared to conventional microfluidic devices.

The actuation and agitation of the liquid on such flatland chips is achieved by employing surface acoustic waves, which can be electrically controlled to either mix and stir the fluid, or even actuate a complete droplet along predetermined trajectories.

The powerful agitation abilities of the Advantix technology have been successfully applied to a first product, the ArrayBooster for hybridization of DNA or protein microarrays.

### 4 ACKNOWLEDGEMENT

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