Microfluidics in Medical Applications

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The challenge of microfluidics is to control liquids or gases on the micro scale. The developing use of microfluidics in diagnostics, drug delivery and implants is discussed. These technology advances include electrowetting and a piezo-driven membrane micropump.

The potential

The advantages of microstructures are not merely the savings in space and material. They also include the altered physical properties found in microdimensions such as the surface to volume ratio, wetting properties and interfacial tension, and the ability to achieve quick temperature changes because of the small sample volume. These features lead to increased sample processing speed and enable reaction technology on the small scale, which is required for portable diagnostics.

Diagnostics

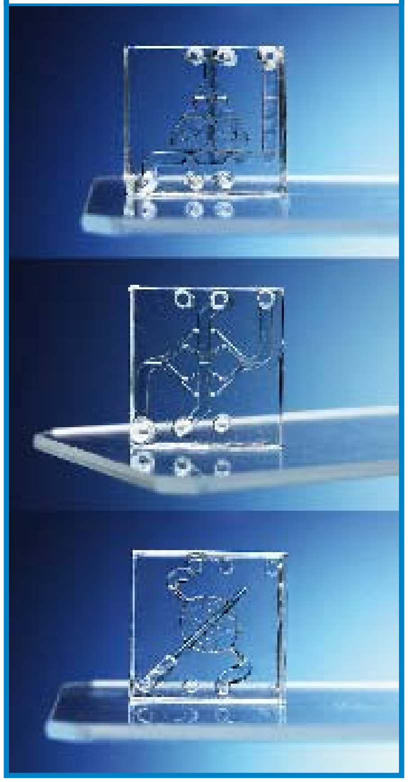
The biggest application of microfluidics has always been in the development of lab-on-a-chip systems. Tests that involve complex mixing and washing or heating steps such as antigen–antibody reactions, clinical chemistry and gene analysis are predisposed to minaturisation. The advantages are less probe and reagents use, portability and more analysis on a smaller space. As one example of many functional elements used in lab-on-a-chip systems, Figure 1 shows different designs of micromixers. In the microdimension, the mixing process is determined by diffusion. Therefore, large surfaces areas are created between the two compounds to be mixed and the mixing result can be achieved by a variety of fluidic geometries. Point-of-care products show the greatest potential for this technology.

The largest group of products on the market are glucose monitoring systems. Glucose test strips for use with glucose meters take up blood by capillary forces and thereby apply microfluidic mechanisms.[1] This technology is also used for other clinical chemistry parameters such as lactate monitoring for fitness control.[2] These systems are purely passive. The liquids are transported by capillary action without any external active transportation support. More complex systems for clinical chemistry are on the market. For example, a clinical analyser that uses centrifugal forces as well as capillary action to mix and direct liquids in small channels and reaction and detection chambers.[3]

Test strips and cassettes also use capillary action in membranes to move liquid; applications include pregnancy-testing kits. These systems are limited to qualitative data (they only provide information on whether or not the agent is above or below a certain point) gained from clear test media such as saliva and urine; blood would interfere with the optical readout.

For other parameters such as cardiac markers, quantitative concentrations in the blood are needed for diagnosis and these tests are usually still confined to the laboratory. Here, separation and filtering of the blood cells must be undertaken before parameter detection. This can be achieved by

Figure 1: Various designs of micromixer.



the integration of membrane filters into the fluidic device or by integration of adequate microstructures. Figure 2 shows a lab-on-a-chip system with a modular set-up of passive fluidic building blocks for immunologic assays or clinical chemistry.[4] Transport of sample, blood and buffer solution is performed by an external pump from the reservoir through a spiral mixer. The blood particles are removed by a separator. After this, the sample volume is divided into five reaction paths in which the immunologic reaction is conducted on fluorescently labelled magnetic beads followed by spectroscopic detection.

Another current development is a lab-on-a-chip device for molecular imaging in cancer therapy aimed at replacing existing bigger radiochemistry synthesis platforms.[5] Because the substances used for these diagnostics are expensive and toxic (radioactive), the enrichment, purification and reformulation of the imaging agents on a microfluidic chip are highly advantageous. With miniaturisation, the volume of the disposable cartridge elements is expected to decrease by more than a factor of 50 and the overall reaction time is expected to be reduced by at least a third. The main requirements for the device are high chemical resistance and medical compatibility of the applicable materials for the device.

As well as capillary or centrifugal forces, electrokinetic phenomena are used for actuation in lab-on-a-chip devices. An alternative approach evaluated for clinical diagnostics is electrowetting. The principle of electrowetting uses electric fields to control the surface tension of conductive or polarised liquids. This allows direct manipulation of microdroplets (Figure 3) for controlled dispensing, transport, mixing and splitting across electrode arrays.[6] This technology can also be used on human physiological fluids; a glucose assay on serum, plasma, urine and saliva could be performed. The clinical applicability on the statistical performance parameters still has to be confirmed.

Drug delivery

For diagnostic applications when one-time filling of a structure is sufficient, capillary forces are the method of choice for moving liquids. When higher pressures or more complex flow protocols are needed, active pumping by centrifugal forces or external pumps must be used. Active flow control by pumping is essential in therapeutics.

Microfluidic components play a vital role in a number of drug delivery solutions. The applications range from micronozzles that spray drugs for inhalation[7] to micropumps for accurate dosing of various therapeutic compounds with dedicated delivery profiles. The application can be extra- or 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 work is being undertaken in an international project of 15 companies, including HSG-IMIT, under the European Sixth Framework Programme.[8]

Other projects focused on developing intra- and extracorporeal medical devices employ micropump mp5 technology (Figure 4). This is a piezo driven membrane pump. As shown in Figure 5, 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 50 nL/min to 5 mL/min and gas at 50 μL/min to 15 mL/min. The micropump, which is 14 × 14 × 3.5 mm^3 in size and weighs 0.8 g, 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 1.5 V 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

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Figure 2: Microfluidic chip for mobile diagnostics.[4]

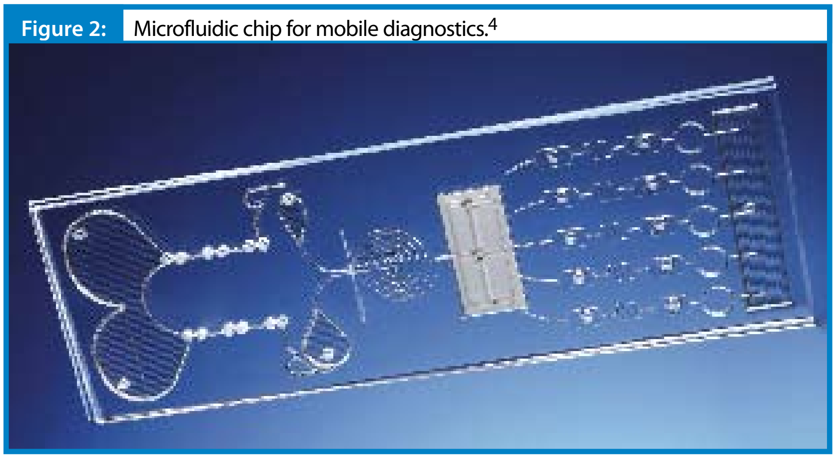
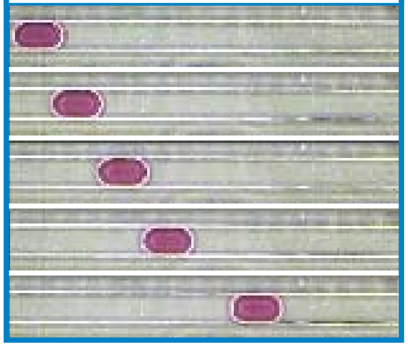


Figure 3: Sequence of liquid movement with electrowetting.



➔ 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. As well as drug delivery, 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

Actuated implants

Pumps can also be used as actuator systems in implants. If liquids are pumped out of a reservoir into a flexible container, the container will swell. Cuffs or balloons that are inflated are appropriate containers. These swelling devices are used as artificial sphincters to treat incontinence or muscular dysfunction of the anal sphincter. In most systems on the market, a balloon regulates the pressure of the cuff and a bulb controls inflation and deflation of the cuff. In newer developments, bidirectional micropumps are applied to inflate and deflate the cuff. Prototypes of this new generation of prosthetics, which consist of the compression-cuff, fluidic reservoir and bidirectional micropump integrated into one compact unit, are now being tested.[9]

Microfluidics have evolved and are now providing valuable solutions for manufacturers and patients. Innovative products are constantly under development that will give patients improved treatment and more flexibility in daily life.

Figure 4: Small, portable disposable micropump with broad flow dynamics.

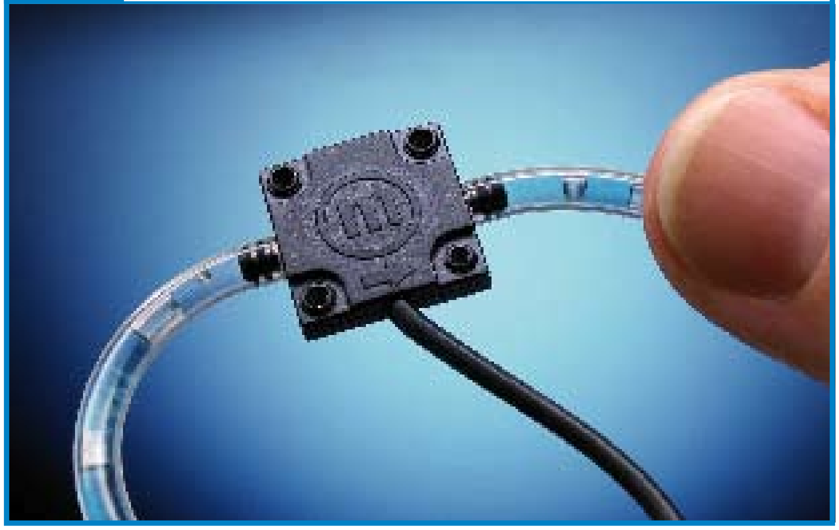
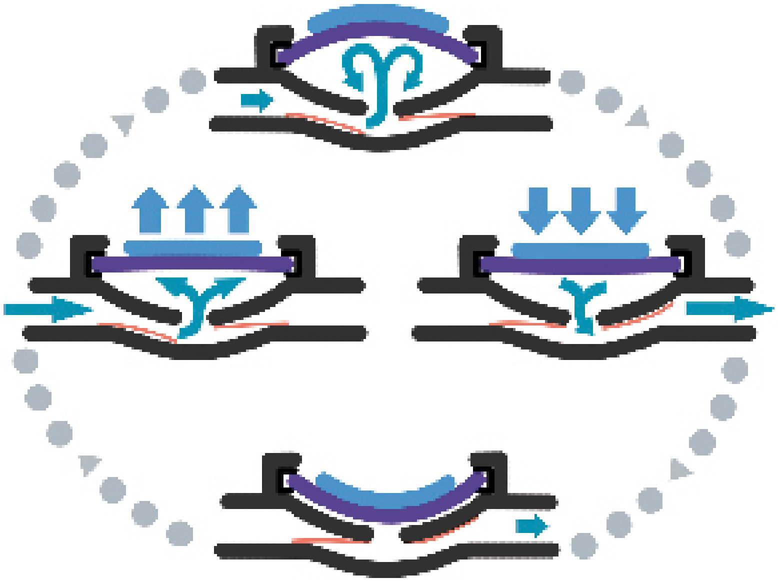


Figure 5: Functional principle of piezo membrane pump.



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