Lab-on-a-Chip

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Screening in One Sweep using the Slipchip

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Microfluidic laboratories, which involve chemical systems that are shrunk to fit on a single microstructured chip, are full of promise. Such miniaturized systems, in which chemical processes occur in microcavities or microchannels the size of a human hair, have great potential for high-throughput screening. This potential is due to fascinating features of so-called lab-on-a-chip devices, such as minimal reagent consumption, high process speeds, and ease of multiplexing. However, challenges in microfluidic systems include exact dosing and dispensing of liquids at the nanoliter scale.

In the macroscopic world, liquid handling is realized using valves and pumps, but it is challenging to integrate such mechanical components into microfluidic chips. In the microscopic world, the most robust systems are usually devices which avoid the use of moving mechanical components. In this context, the most straightforward methods to pump and dispense liquids in microfluidic systems are capillary forces or the application of electrical fields using electrophoretic or electroosmotic effects. The latter approach is applied in the successfully commercialized technique of microchip electrophoresis. It is, however, extremely difficult to shrink various more complex chemical processes into the microscopic world without using pumps or valves. To meet these challenges, various remarkable approaches have been reported that apply highly sophisticated microsystem technology to integrate micromechanics and microfluidics into a single device.

A contrast to such a tour de force in microsystem technology is offered by a recently introduced, remarkably simple approach for chip-based high-throughput screening on the nanoliter scale. With the so-called slipchip system, it is possible to mix liquids in micro-wells by simply slipping two microstructured glass plates over each other. This principle of directing liquid flow by moving one structured plate relative to another is well-known, for example in HPLC-valves and everyday products such as single-handle faucets. There have already been some early reports in the literature[1] using this simple but efficient approach for mixing of liquids in miniaturized systems.

With recently published work from the group of Ismagilov,[2] this approach could develop into a new microfluidic platform that opens up new possibilities for the realization of robust chip laboratories. The working principle of the slipchip developed by Ismagilov's team is illustrated in a basic version[2a] of the device in Figure 1.

The system consists of two glass plates with wells and ducts on its surface, which serve as reservoirs and fluidic pathways if sandwiched on top of each other. By moving the plates relative to one another, wells in the two plates move in and out of contact, creating fluidic pathways that can be used for reagent delivery (Figure 1 a–d). By further slipping of the plates, reagent and sample solutions can be brought into contact and accordingly mix in a highly parallelized and simultaneous manner. This approach can be utilized to add a reagent solution to many small-volume samples in parallel. An exciting field of application of such parallelized microbatch experiments is screening of experimental conditions in protein crystallization. Just as in previous work in related droplet-based systems,[3] the researchers were able to prove the functionality of the device in this application area. The slipchip system illustrated in Figure 1 impresses by its simplicity and is, according to the authors, especially attractive in a resource-poor environment. Because of the technically demanding loading procedure, the chips should in this case arrive preloaded with reagents at the user, which presupposes the long-term stability of the reagents. Very recently, the authors reported an advanced version of the device that not only circumvents these limitations by introducing a user-loadable slipchip variant, but it also facilitates the realization of more complex chemical processes by a skilful arrangement of microstructures.[2b] For this purpose, more complex microstructures are utilized, enabling, for example, the definition of various mixing ratios by variation of the cavity size. Such a more complex chip, in which samples can be combined in a parallelized manner with reagents at several mixing ratios, is shown in Figure 2.

The authors succeeded in performing 480 different crystallization experiments, thereby consuming only 12 μL of a protein. By up-scaling of the successful chip experiments in well plates, high-quality protein crystals for X-ray diffraction were obtained.[2c]

The suppression of analyte–wall interactions is a major challenge in all microfluidic devices owing to the high surface-to-volume ratio. The slipchip approach circumvents this cross-contamination-causing problem in a similar manner to droplet-based microfluidics using wetting fluorocarbons. Furthermore, the hyrophobicity of the chip surfaces and the hydrophilicity of the wells could be adopted by surface coating or nanopatterning.

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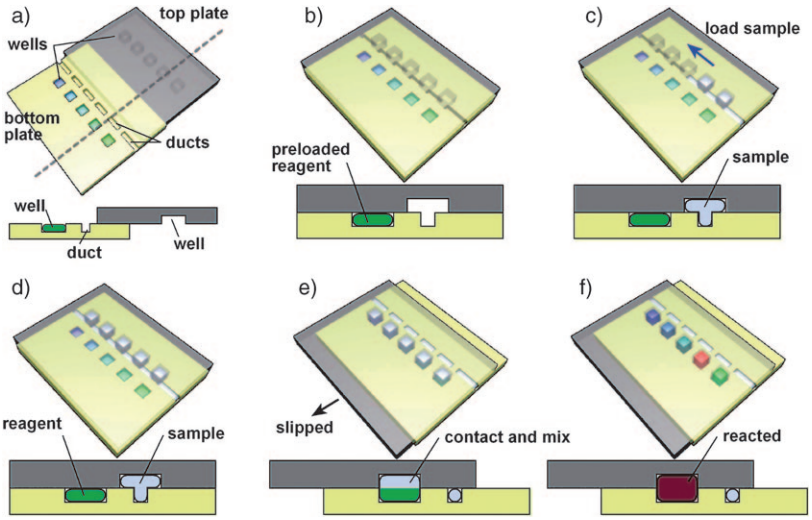

Figure 1. Step-by-step illustration of the slipchip operation according to Du et al.[2a]

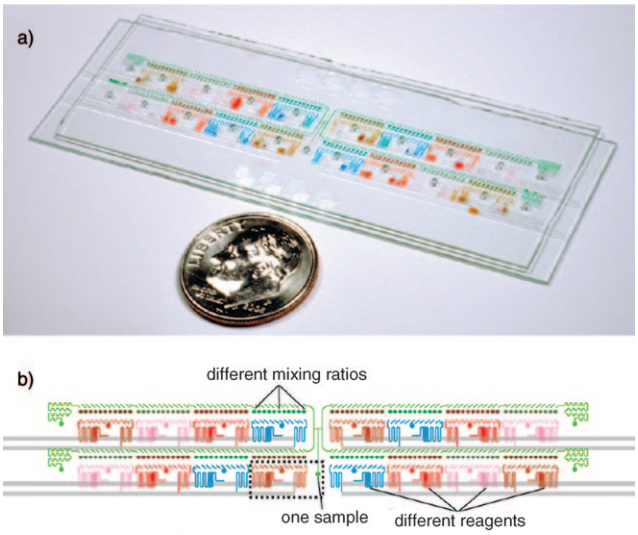

Figure 2. a) Photograph of a so-called user-loaded slipchip filled with food dyes and b) a drawing of the device to screen one sample (green) against 16 different reagents (other colors) at different mixing ratios according to Li et al.[2b]

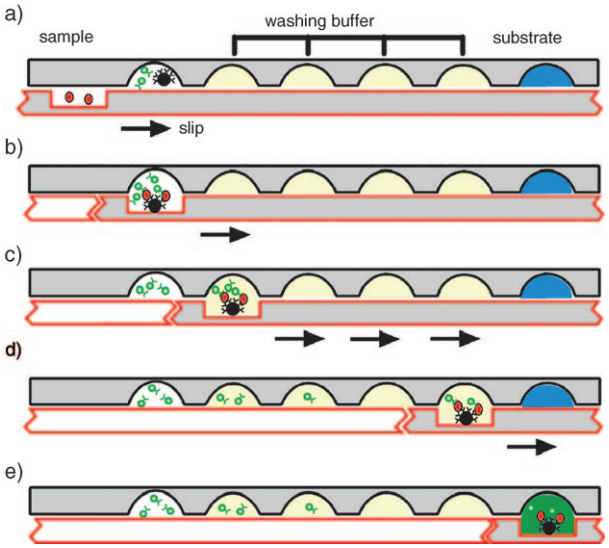

Figure 3. Illustration of the multistep process of an immunoassay, including several washing steps and detection (e) with a slipchip according to Liu et al.[2d]

The slipchip is not only suitable for protein crystallography, but has also been used for immunoassays in nanoliter volumes.[2d] What is most impressing in this latest advancement of the slipchip approach is the ability to perform multistep processes. This was demonstrated by performing a magnetic-bead-based immunoassay in which the processes utilized for forming the sandwich complex (Figure 3a,b) followed by multiple washing steps (Figure 3c,d) and for detection (Figure 3e) proceed by repetitive slipping the two plates relative to one another.

The intended chemical program is actually encoded into the chip as a micropattern, and can be executed by simply moving the plates. This is reminiscent of coding punch cards in the early days of data processing. As the microstructured plates move, wells in the two plates are combined and split up in a defined sequence, creating and breaking up microfluidic pathways.

The working principle of the slipchip is reminiscent of a valve, and therefore it would be interesting to extend this approach for the construction of robust microfluidic systems with more complex functions. It should be feasible to dose fluids in three-dimensionally stacked microfluidic chips between the different functional layers to advance towards the realization of an integrated chemical circuit.[4]

Such systems would be highly attractive to realize multidimensional HPLC in microfluidic chips. A solution to the challenge of combining microfluidics with robust valves could accordingly be the integration of the microfluidic structure into a macroscopic valve rather than shrinking a valve to fit

into a chip, meaning the creation of a "lab-on-a-valve". A major challenge in this context will however be creating a robust and wear-free connection at high pressures, which is already challenging in conventional HPLC valves from a materials point of view.

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