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SPIE.

Event: SPIE BiOS, 2018, San Francisco, California, United States

Automated assembly of microfluidic “lab-on-a-disc”

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ABSTRACT

Point-of-care (POC) testing attracts more and more attention in the medical health sector because of their specific property to perform the diagnostic close to the patient. The fast diagnosis right at the hospital or the doctor's office improves the medical reaction time and the chances for a successful healing process. One of this POC test systems is a “Lab-on-a-Disc” (LoaD) which looks like a compact disc crisscrossed with microfluidic tubes and cavities. The fluid to be analysed is placed in the LoaD and an external device then rotates the LoaD. The cavities inside the LoaD and the centrifugal force ensure a clearly defined sequence of the analysis. Furthermore, we aim for an inexpensive manufacture of the medical product without neglecting its quality and functionality. Therefore, the Fraunhofer IPT works on an assembly cell to implement dissolvable films concisely into the disc. This dissolvable film demonstrates its successful usage as a gate for the fluid, which opens after a predefined moment in the cycle. Furthermore, we investigate to integrate a laser welding process into our gantry system and demonstrate its efficiency with the welding of polymer discs. This procedure is clinically safe because no further laser absorption material is needed in the sealing process, which might pollute the LoaD. Moreover, this process allows the alignment of several discs before the welding and therefore leads to precisely manufactured LoaDs in large quantities. All these methods together enable a fast, cost-efficient and reliable mass production to bring POC testing among the people.

Keywords: Point-of-Care, Lab-on-a-Disc, microfluidics, passive alignment, wafer handling, bonding

INTRODUCTION

Point-of-care (POC) testing are very coveted in the medical health sector because of the possibility to perform diagnoses close to the patient contemporary. The “Lab-on-a-Disc” (LoaD) with their microfluidic properties fulfil the demand for easy testing and fast results. However, the production of LoaDs requires a precise and reliable process that can be quickly and easily adapted to different physical requirements. The Fraunhofer IPT works on an assembly cell to implement dissolvable films into the discs. Furthermore, we investigate to integrate a bonding system into our gantry. Suitable materials are either PMMA or COC whereas PMMA is much cheaper than COC. The injection molding process is the easiest and fastest way to scale up the wafer production. The individual wafers are then stored in a magazine and form the basis for the following assembly steps.

Description of the application

The discussed assembly task aligns a microfluidic package, composed of two or more polymer wafer and several dissolvable membranes as seen in Figure 1. The microfluidic systems are used in medicine to quickly and easily perform analyses on cells and blood components. Both the microfluidic channels as well as the dissolvable membranes lie within the POC system. After assembling the LoaD, a medical assistant fills the LoaD with necessary fluids through small openings in the top pane. Subsequently, an external device rotates the LoaD. In this case, specifically different rotational frequencies apply in order to control the centrifugal and Coriolis force on the fluid and therefore the movement of the fluid itself. Figure 2 a-e demonstrates a typical application for a microfluidic system with channels, syphons, and dissolvable membranes. In Figure 2 a, despite the rotational frequency of 60 Hz, the liquid from the reservoir cannot exceed the second arc of the siphon because the control film (CF) is occluded and impermeable to air. Therefore, a hydrophilic auxiliary liquid is required, which is introduced into a second chamber as seen in Figure 2 b. The surface tension prevents automatic passage of the channels of the auxiliary liquid up to a certain rotational frequency. With higher rotational frequency, the auxiliary liquid moistens the membrane and dissolves it as seen in Figure 2 c. Next, the

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primary liquid moves along the microfluidic channel until it reaches its equilibrium state. At the same time, the primary liquid activates the second dissolvable film (Figure 2 d). Finally all gates are open for the primary fluid to reach the last chamber as seen in Figure 2 e [1]. This demonstrates a typical situation whereas different liquids are mixed within one system at different times.

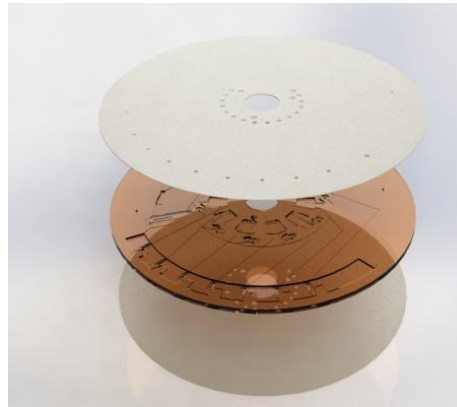


Figure 1: Schematic representation of a LoaD consisting of three discs. The lowest disc, also called “blank disc”, closes the system from below. The following disc contains the microfluidic channels. Not shown, further elements can be placed on or in the disc, such as soluble membranes or other functional components. The closure is the top disc with its openings to fill the LoaD.

Study of uncertainties and challenges

As mentioned in the introduction, one of the goals is to make the LoaDs as modular as possible in order to assemble new layouts in series as quickly as possible. Uncertainties and challenges during assembly arise as follows:

- Transportation of single wafer and complete LoaDs
- Pick and place of different sized membranes
- Passive alignment of wafers relative to each other ($\pm 40 \mu\text{m}$)
- Wafer bonding

Especially the picking up process of different sized objects and later wafer bonding are currently part of the optimization and development process.

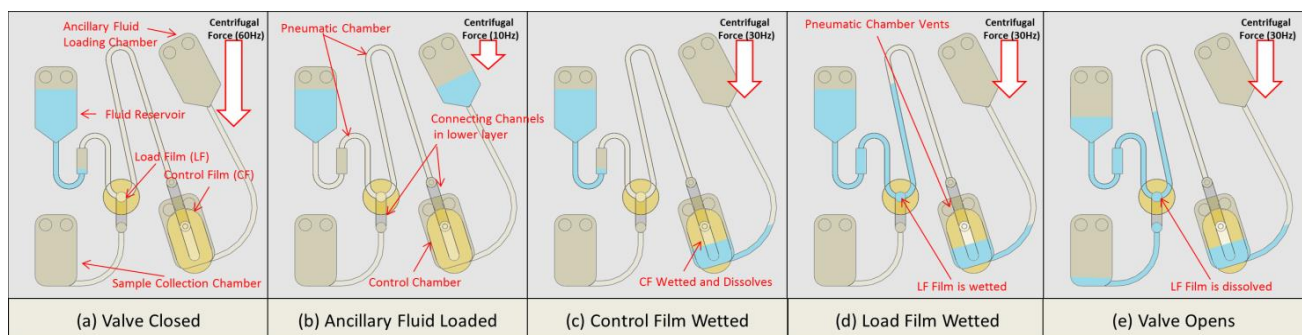


Figure 2: Exemplary construction of a switchable, microfluidic system with the aid of several soluble membranes, small channels, siphons and collecting chambers. In Figure A, the system is blocked despite the rotational frequency of 60 Hz, because the control film (CF) is occluded and impermeable to air. To open the gate, a hydrophilic auxiliary liquid is required, which is introduced into the second reservoir as seen in Figure B. Next, we start with a rotational frequency of 30 Hz, which moves the auxiliary liquid to the control chamber, moistens the first membrane, and opens the gate as seen in Figure C. Next, the primary liquid moves along the microfluidic channel until it reaches its equilibrium state. After a predefined time, the primary liquid dissolves the Load Film (LF) and thus opens this gate in Figure D. After a certain amount of time, the primary liquid is released through the valve (Figure E) [1].

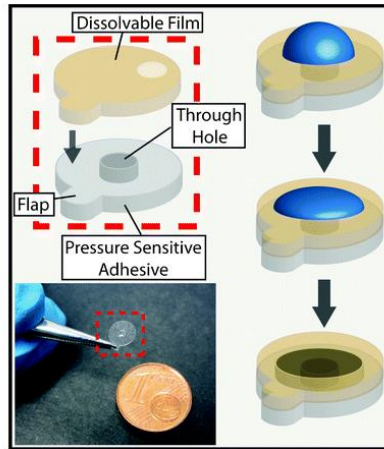


Figure 3: Assembly principle, mode of operation and size comparison of a typical, water-soluble membrane. We center the membrane over the through-hole in the disc and fixate it using pressure-sensitive adhesive. Once the membrane is wetted with a hydrophilic liquid, the central area of the membrane slowly dissolves and becomes permeable to the liquid. The skillful choice of appropriate materials and material thicknesses controls the duration until the dissolution of the membrane. The challenge in assembling the membranes is that they are only a few millimeters in diameter [2].

MATERIALS AND METHODS

The pivotal point for our automation task is an assembly cell design, which includes standardized industrial components and control equipment to provide a robust and targeted solution. A gantry system with linear motors and a spindle axis for horizontal stroke covers the work area. The tool-head is equipped with various tools and on the breadboard, new machines can be quickly installed for the specialized assembly tasks. A soft PLC forms the basis for controlling the machine architecture and processes all tasks in real time. Safety monitoring and air-conditioned working environment with Airflow Box are part of the assembly cell to ensure an optimal and safe working environment with consistent results. In order to be able to guarantee the highest possible degree of flexibility during process development, attention is turned to an adapter for high-level languages. Thus, easy integration of e.g. LabView or Python commands possible, which favors the rapid development of new processes. These programs exceed standard PLC programming whenever incorporating computer vision, machine learning or any other kind of complex algorithms. Figure 4 depicts the basic machine cell design:

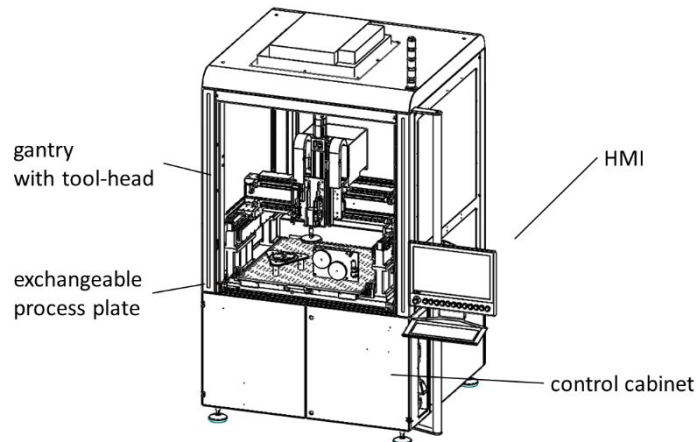


Figure 4: Automated assembly cell for microfluidic LoADs. The control cabinet includes all components for controlling the assembly cell. The HMI visualizes the feedback about the assembly task and its status on the display. On the process plate, we place the membrane dispenser, the assembly stage and the wafer tray. The wafer and membrane gripper are part of the gantry system and they are integrated into the tool-head.

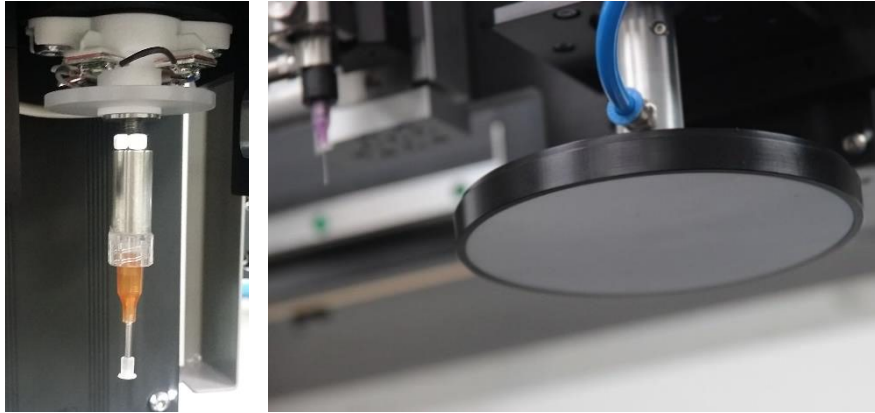


Figure 5: Left: The membrane gripper. The gripper interface allows quick change of the hook tip depending on the task. The tip of the gripper is provided with a soft rubber so as not to damage the gripped components. Right: Vacuum wafer gripper bottom view. The gripper fits the diameter of the standard LoAD system and its surface is filled with a porous ceramic. Through the vacuum connection and the small cavities within the ceramic, we achieve a uniform vacuum level on the entire gripper surface. The gripper axis tolerates rotation to align the individual wafers after gripping and the vacuum level can be controlled.

Description of application specific parts and assembly setup

As mentioned before, the machine cell is equipped with specialized parts, necessary for handling, operating and evaluating the contemplated assembly. The first essential tool is the wafer gripper (cf. Figure 5, right). The gripper diameter is as wide as the wafer, so it can hold the wafer over its entire surface. The gripper is an internal development made of anodized aluminum. The inside is filled with a porous ceramic, so-called “metapor”. This ceramic allows with its tiny cavities for a homogeneous vacuum level over the full gripper area. Some of the discs have large channels and cavities, causing leakage when gripped. However, the gripper surface does not necessarily have to be completely covered in order to function, because this obstacle can be avoided by raising the vacuum threshold.

The membrane gripper is an in-house development and serves to pick up a membrane from the tape and places it on the glass (cf. Figure 5, left). The layout was designed on a simple interface of the gripper to quickly change the claw tip in the state as a prototype. The linear axis on which the gripper is located, just like that of the wafer gripper, is part of the tool-head and allows the gripper to rotate 360°. Due to the radial symmetry of the wafer and the elliptical geometry of some membranes, alignment is necessary. This alignment is not feasible solely by the lateral movement and therefore requires a rotation along the vertical axis.

The assembly stage is an equilateral bracket made of anodized aluminum (cf. Figure 6). In the middle of the stage is a round glass plate, which is interspersed with micro channels. A tripod holds the stage several inches above the breadboard. This gives us the possibility to position multiple cameras and a LED lighting unit below the assembly stage. The cameras are necessary for referencing geometrical marks on the wafer and helps to align them. The LED-lights increase the contrast for geometry recognition within the image processing. The micro channels within the glass plate are custom-made and manufactured by an etching process. The homogeneous distribution of the openings allows a uniform distribution of the vacuum over the wafer surface. This is necessary to smooth the disc and prevent it from slipping during assembly. The vacuum for this tool is controlled independently of the rest of the system.

The membrane dispenser (cf. Figure 7) is equipped with two stepper motors on the rear side, which are limited to 200 steps per full circle. The motors are controlled via a Beckhoff control in the rear part of the assembly cell. On the front of the machine, the two coils are mounted on the motors and on those the tape is wound or unwound. The coils are equipped with a quick release system, which allows them to be changed easily. The tape is held not only by the two spouts, but also by a special guide, which is adapted to the width of the band. One end of this guide is rounded to prevent damage to the tape during movement. The other end was replaced with a 45° bevel. This bevel also reduces the risk of damage to the belt and is at the same time so small that the membranes can later shear off from the tape. In addition, a camera with a telocentric lens with 1x magnification is attached below the guide. The camera is oriented in such a way that the membrane is exactly in focus and a part of the guide can be used as reference mark. A lighting unit also increases the contrast here, similar to the assembly stage.



Figure 6: Assembly stage with vacuum channels. The mounting plane is raised on a three-dip to attach below the glass plane more tools. Several cameras are positioned below, which help to align the wafers. Furthermore, several LED lights provide a reasonably high contrast in the recordings. The connection for the vacuum supply is also located on the underside of the glass plate. A special etching process created the cavities within the glass.

Assembly steps

First, we place the injection-molded discs in their holder on the process plate. Next, the gripper (cf. Figure 5) picks up a wafer and places it over the assembly stage (cf. Figure 6). Before the wafer gripper releases the wafer, the bottom side cameras below the assembly stage reference the wafer by its geometrical marks. As soon as the wafer lies on the assembly stage, we activate the vacuum to prevent the wafer from slipping. Next, the membrane gripper moves over the pick-up point on the dispensing machine. This coordinate, as well as that of the wafer magazine, was once referenced by hand and stored within the software routine. The two stepper motors start to rotate, but the motors being activated with a time delay. This has the consequence that the tape is tensioned and the membranes then shear off during the sharp-edged movement of the tapes on bevel's guide (cf. Figure 7). The bottom camera records the movement of the membrane over the edge and the image processing software uses the data to calculate the optimal time to pick the membrane. The optimal position was found by various experiments. If the membrane sticks out too far, then it starts tilting and the gripper cannot pick up the membrane properly anymore. However, if the membrane is still too sticky to the tape, then the gripper cannot pick it up. The membranes are covered with a pressure sensitive adhesive (PSA) and this is activated when placed by a contact pressure, so that the membranes adhere. The CAD layout and the microfluidic channels and cavities within the disc define the lateral membrane position and its orientation. These coordinates are recorded once by hand relative to the prototypical layout of the wafer and then they are stored within the main program. As soon as all membranes are placed on the disc, the wafer gripper collects the disc and stores it on the wafer tray. The subsequent assembly, alignment, and bonding with another disc is possible in principle, as discussed in the next section.

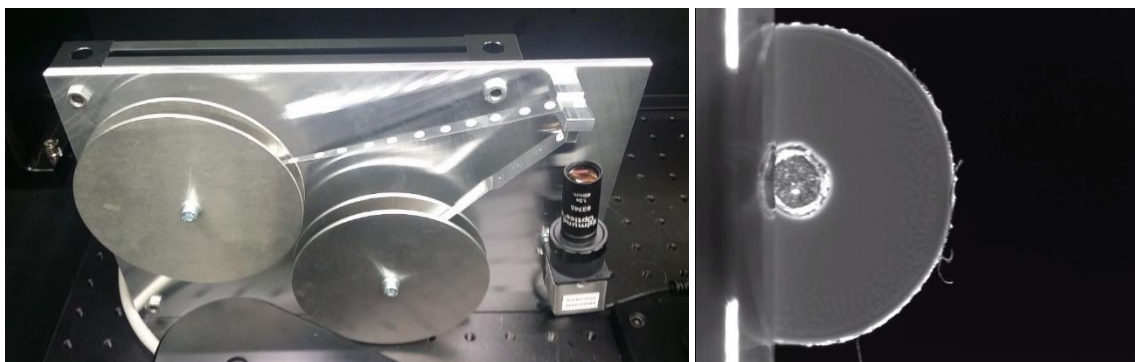


Figure 7, Left: Membrane dispenser with loaded and strained tape. Two electric stepper motors on the backside of the dispenser control the movement of the tape. A bottom side camera observes the process. Right: Successful separation of membrane from tape. Image edge detection based on the intensity distribution of the membrane observes the process. Once the membrane is detected, the internal circuitry causes the motors to stop moving and the pick and place process starts.

CURRENT RESEARCH

One of the key elements of creating a Load system and still part of the current research is the bonding process. Two possible bonding techniques are already identified as most successful, the laser welding and the usage of a photosensitive adhesive. Both techniques have their limitations with respect to speed or processibility. Laser welding bases on an absorber material on or within the polymer disk. While additional absorbent particles are not only a cost factor, they must also meet the requirements for a medical product. This problem can be circumvented by the use of a laser in the micrometer range. In the near-infrared region, however, transmission and absorption change, so that a sufficiently high power density can be achieved within the polymer. The energy supplied by the laser causes the material near the focal plane to melt and thus connects two polymer disks to one another. The disadvantage is a long processing time because the laser has to weld around the microfluidic channels.

In contrast to this is the process with light-curing adhesives. In particular, UV-curing adhesives has the benefit of their long workability before they are cured within a few seconds using suitable UV lamps. The application of the adhesive can be done quickly and inexpensively using suitable transfer methods such as rollers or films. The challenge in working with the adhesives is their low viscosity. The time it takes to apply the adhesive and pick up and align the next disk can cause the adhesive to run into the microfluidic channels and seal them during curing. The consequence would be a non-functioning or only partially functional Load. Another challenge with the use of adhesive arises when aligning the discs to each other. The moment the second disk is lowered and is exposed to the adhesive, we recognized a short-term increase in air pressure in the system, which pushes away the adhesive.

As mentioned in the previous section, the alignment of a single Load is achieved by its geometrical properties like cavities and the microfluidic channels. However, the focal depth of roughly 1mm limits the telecentric cameras. Therefore, an optical pattern on the individual discs is needed, which allows aligning the discs to each other. First experiments with alignment markers (cf. Figure 8) show good results and are taken over into the existing injection molding tool.

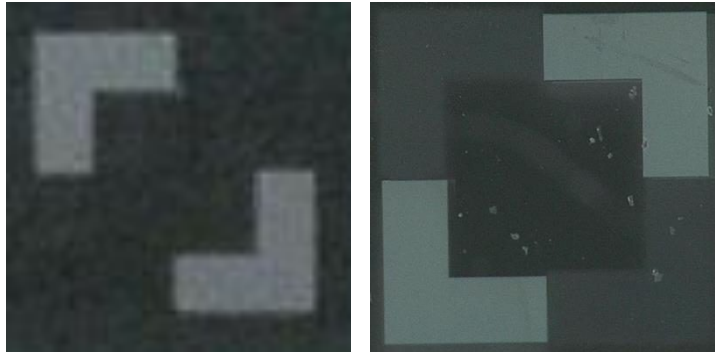


Figure 8: Optical alignment markers in polymer disc. Left side shows a single marker, which in combination with your second disc, adds up to a square. Right: Two discs have been successfully aligned.

DISCUSSION AND OUTLOOK

The Fraunhofer IPT plans to improve to given process by parallelization of membrane dispensing and gantry movement. Furthermore, the membrane dispenser has been tested successfully but the order of the membranes is too inflexible due to the linear band. In order to efficiently accommodate different membranes, the membrane dispenser is reworked so that several bands can be used in parallel. Furthermore, the number of required motors can be reduced to one with the same functionality.

ACKNOWLEDGMENTS

Part of this work was performed within the Fraunhofer Project Center in Dublin, which is a joint venture of the Dublin City University DCU and the Fraunhofer Institute for Production Technology IPT.

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