Universität Rostock

Traditio et Innovatio

Flow optimised design of a novel point-of-care diagnostic device for the detection of disease specific biomarkers

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Introduction

Rapid test systems for the diagnosis of current diseases are attracting more and more attention in medical technologies. Particularly in vitro diagnostic devices play an important role in the examination of patient samples (blood, plasma, urine) for different disease specific biomarkers. A novel user-friendly and easy to handle diagnostic product is developed by combining the benefits of existing concepts. The basic element of the device is a Line-Immunoassay (LIA) with a membrane for the solid phase based on the Enzyme-Linked-Immunosorbent-Assay-technology (ELISA). Another speciality of the device is the transfer of the LIA-membrane into a flow optimised test case, which should move the actual execution of the test from the lab to point-of-care (POC). The resulting test system is characterised by a reduced execution period, a reduction of execution steps and an integrated waste management. A wide range of biomarkers (e. g. the cytomegalovirus) can be implemented in the test system. In this study, the development of the flow optimised design of the diagnostic product is presented. CAD (computer-aided design) and CFD (computational fluid dynamics) tools are used. Based on the CFD results, first prototypes are printed using an additive manufacturing process.

Requirements for the device

The diagnostic product should be very user-friendly. This is achieved by using an easy to handle body. A membrane basin and a waste reservoir for the reagents waste is located within the body (see **Figure 1**). A membrane strip with dried up reagents is positioned within the membrane basin. The dimensions of the membrane strip are 25x3 mm.

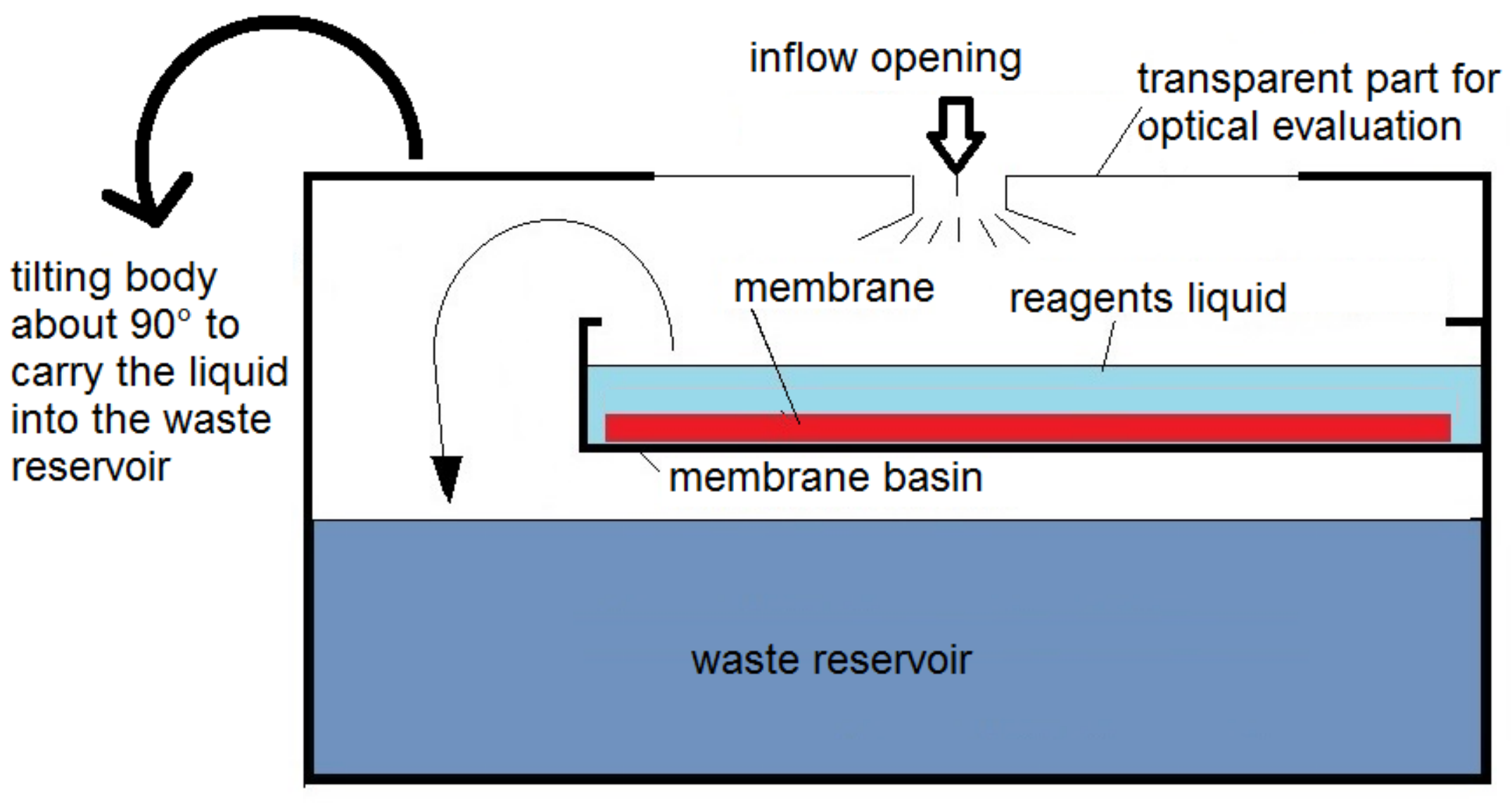

Fig. 1. First draft of the diagnostic product

The test principle involves successive reaction steps, where several solution steps and subsequent wash steps are necessary. After every single step a lateral movement (5°-10°, for mixing) and a subsequent tilting of the body by about 90° follow in order to carry the liquid fluid from the membrane basin into the waste reservoir. In this case, no rest fluid should remain in the membrane basin after tilting, since this would lead to erroneous results if new liquid were added. Another challenge is the ability to switch between large and small volumes during the test execution. The membrane basin must be designed in such a way, that it is big enough for large fluid volumes of about 5 ml (incubation of the patient sample), but also in such a way that small volumes of about 0,5 ml (solution and wash steps) ensure a sufficiently high liquid column over the membrane in order to ensure complete wetting. Furthermore, a mixing of waste and reagents fluid in the membrane basin must be avoided. After finishing the test execution a total of 9 ml of liquid is delivered. So the waste reservoir must be designed for such a liquid volume. The inflow of the liquids takes place through an opening in the cover of the body. The cover is transparent in order to allow for optical evaluation of the membrane strip.

Results

To satisfy the requirements mentioned above, two important geometrical aspects are considered. First, based on the draft in Figure 1 and the dimensions of the membrane strip, the initial shape of the membrane basin is developed. During the iterative development process several shapes of the membrane basin are designed and improved. Some shapes of the membrane basin can be seen in **Figure 2.** Shape 1 and 2 show a membrane basin geometry in an early stage of development. Substantial disadvantages can be seen with the help of CFD simulations. The simulations show that it is not possible to empty the basin at an angle of 90°. A rest fluid remains in the basin and leads to erroneous test results.

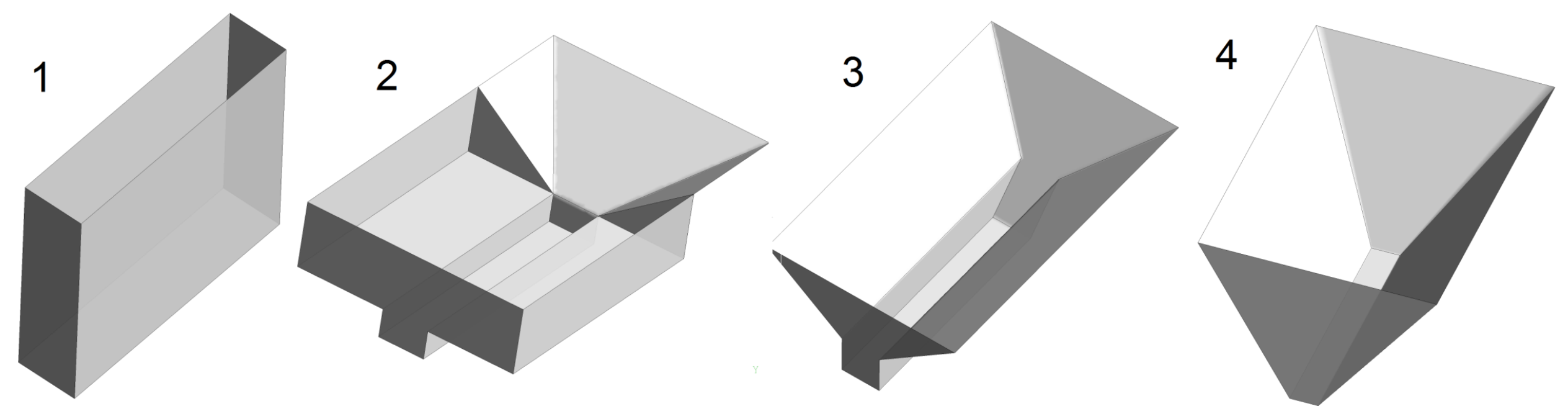

Fig. 2. Different shapes of the membrane basin

The second important fact is the size and the arrangement of the waste reservoir in the body. The reservoir should be designed for a total waste of about 10 ml. In the first stage of development, the reservoir is located under the membrane basin at the bottom of the body. The membrane basin (shape 4 in Figure 2) is centred on the front face. The simulation study in **Figure 3** shows the effect of tilting the basin forwards and then backwards again into the initial position with this arrangement. The membrane basin is filled with 5 ml of water in the initial position (see Figure 3-a). In this study only the gravitation vector is changed. Figure 3-b demonstrates the maximal tilting position of 90°. The fluid flows out of the basin. In Figure 3-c the body is tilted backwards and the fluid flows back into the waste reservoir. Due to the inertia the fluid sloshes against the opposite wall (see Figure 3-d). If the rotating velocity of the tilting is higher than 1.5 m/s, fluid can splash back into the membrane basin. This particular case leads to incorrect results and has to be avoided. In the further course of development, the geometry of the body is changed so that the waste reservoir is located next to the membrane basin, as can be seen in **Figure 4 (left).**

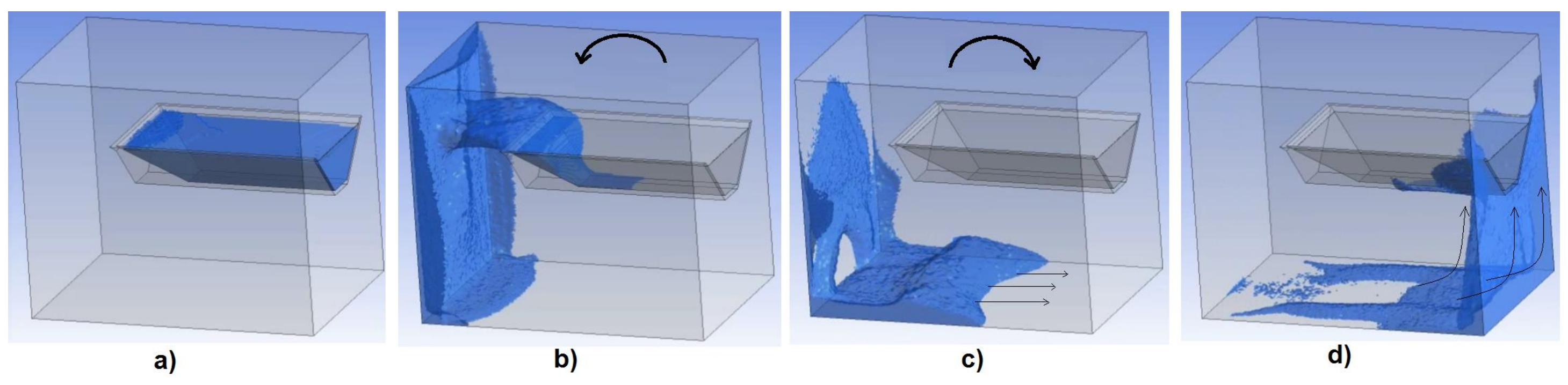

Fig. 3. CFD simulation study: Tilting forwards and backwards; reservoir under the basin

The width of the basin extends up to the side walls of the body. With this modification, the height of the body can be reduced by about 40% up to 25 mm. To ensure that no fluid splashes back into the basin during the tilting phase, the faces of the waste reservoir are equipped with absorbent material. This material absorbs the predominate part of the fluid. **Figure 4 (right)** shows a 3D-printed prototype of the CAD model presented in Figure 6. It was printed using the Poly Jet technique. A membrane strip is located in the membrane basin (shape 3 in Figure 2). The waste reservoir next to the membrane basin is equipped with fleece material.

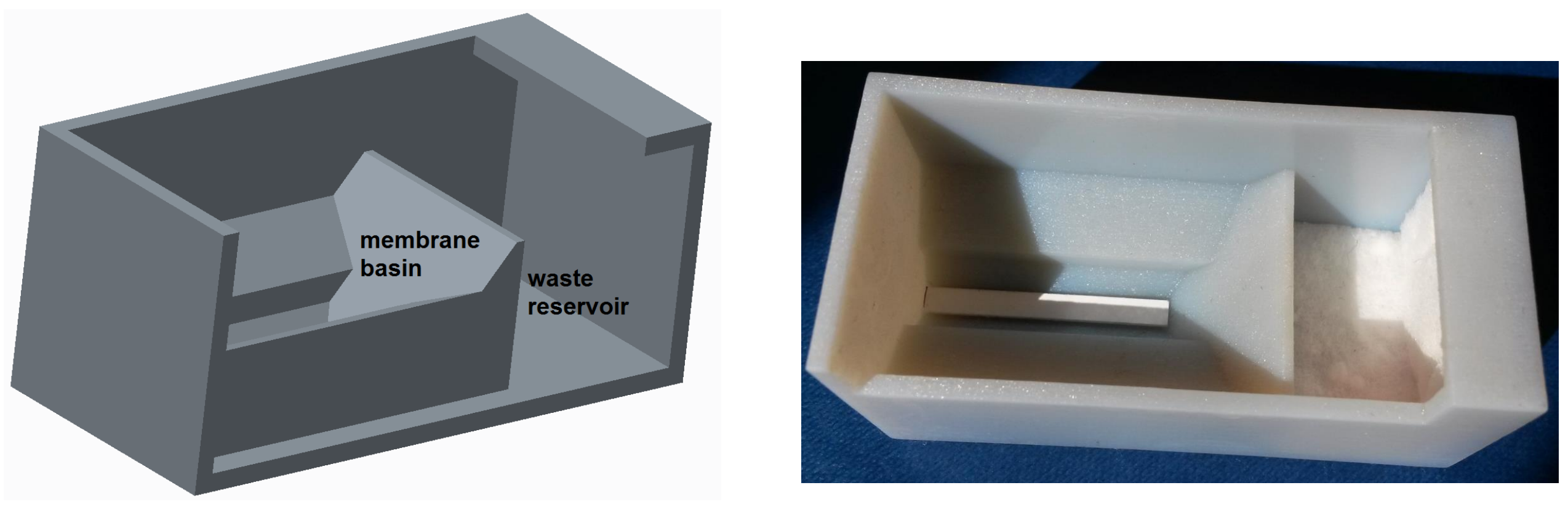

Fig. 4. CAD model: new arrangement of basin and reservoir (left), 3D printed prototype of diagnostic product without cover(right)

Conclusion

For the development of a new diagnostic product, a flow optimised design was successfully engineered. With the help of computational fluid dynamics, a novel, simple and user-friendly test body was designed which satisfies all requirements. It was demonstrated that for an optimised shape of the membrane basin and a suitable arrangement of the basin and waste reservoir a reliable test implementation is guaranteed. The dimensions of the body are 60x26x27 mm and thus make it easy to handle. In a next step, a cover with a click closure should be designed and further experimental investigations will be conducted. Once the biochemistry for relevant biomarkers is developed, the diagnostic product can then be tested for marketability.

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