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Numerical flow simulation methods and additive manufacturing methods for the development of a flow optimised design of a novel point-of-care diagnostic device

Abstract: For the development of a novel, user-friendly and low cost point-of-care diagnostic device for the detection of disease specific biomarker a flow optimised design of the test system has to be investigated. The resulting test system is characterised by a reduced execution period, a reduction of execution steps and an integrated waste management. Based on previous results, the current study focused on the design implementation of the fluidic requirements, e.g. tightness, inside the test device. With the help of fluid flow simulations (CFD – computational fluid dynamics) the flow behaviour inside the test device was analysed for different designs and arrangements. Prototypes generated from additive manufacturing technologies (PolyJet modeling) are used for validating the simulation results and further experimental tests.

Keywords: point-of-care diagnostic (POC), Line Immunoassay (LIA), computational fluid dynamics (CFD), additive manufacturing

1 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 [1, 2]. For the development of a novel, user-friendly and low cost point-of-care diagnostic device for the detection of disease specific biomarker a flow optimised design of the test system has to be investigated. 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). The ELISA system is state-of-the-art and used for biochemical detecting of several antibodies and antigens. Another specialty of the device is the transfer of the LIA-membrane into a flow optimised test case, which should move the test execution from the lab to the point-of-care (POC). In a previous study the basic design was developed based on the given requirements on the device. Accordingly, 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.

The current study focused on the design implementation of the fluidic requirements inside the test device. The feasibility to switch between large and small fluid volumes during the test execution, the avoidance of mixing waste- and reagents fluid and especially to ensure tightness respectively, are only a few examples. With the help of fluid flow simulations (CFD – computational fluid dynamics) the flow behaviour inside the test device was analysed for different designs and arrangements. Prototypes generated from additive manufacturing technologies (PolyJet modeling) are used for validating the simulation results and further experimental tests.

2 Previous results and requirements

In previous investigations [3] first design studies were developed. The test device consists of a 60x30x30 mm cuboidal casing. An also cuboidal membrane basin and a

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waste reservoir for the reagents waste are located within the casing. 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 liquids via the tipping edge from the membrane basin into the waste reservoir. In this case, no rest fluid should remain in the membrane basin after tipping, 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.

A lot of these requirements were fulfilled with the first prototype designs developed so far. This includes the arrangement of the different components within the case as well as the shape of the membrane basin, which can be seen in Figure 1. But the important point of tightness is not taken into account with this cuboidal shape of the test case. Experimental tests showed leakage losses especially in the edges of the casing during the tipping process. Furthermore the requested handling of the test case does not meet the desired requirements.

3 Methods

The path towards the development of a flow optimised design of the diagnostic product is based on an iterative process. First, the design implementation is done with the CAD tool Creo 2.0 (PTC, Needham USA). Subsequently, the CAD design is exported to the CFD tool ANSYS CFX 16.1 (Canonsburg USA). The basis of most CFD calculations is a spatial discretization [4]. The volume occupied by the fluid is divided into discrete cells. The uniform mesh (approximately 1 million grid points) must have a sufficient resolution to get plausible results. Afterwards, the physical modelling and the boundary conditions are defined, e.g. initial conditions, inlet, outlet, etc. After preprocessing, the simulation is started on a computing cluster and the Navier-Stokes equations, which describe the motion of the viscous two-phase fluid, are solved iteratively in a transient way [5]. Then, a postprocessor is used for the analysis and visualization of the resulting solution. With the help of the visualized results, further modifications are made with respect to the geometry of the diagnostic product. Thus, the iterative process starts again until an analysed partial solution meets the requirements.

With the calculated and optimised design, first prototypes are built with an additive manufacturing process. For this case, a Poly Jet 3D-printing technique is used. (Objet Eden, Stratasys, Eden Praire USA). With this 3D-printing technique it is possible to produce components quickly and cost-efficiently.

4 New results

Current investigations led to the development of round or ellipsoidal housing geometries of the test device. Such edgeless geometric shapes have the advantage that stan-
standardized sealing rings can be attached between the basic housing and the lid on the top. It is thus possible to ensure that no liquid escapes during tipping movement of the test case. Two basic geometries were designed for the basic housing. An ellipsoidal housing (l=60mm, w=25mm, h=12mm) for two devices without a lid can be seen in Figure 2, each with a different arrangement of the likewise ellipsoidal membrane basin.

![Figure 2](image)

Figure 2: top: CAD model of two ellipsoidal housings with different membrane basin arrangement, left: two tipping directions, right: three tipping directions; bottom: 3D printed parts for experimental analysis

For this geometry, however, the size of the waste reservoir is not sufficiently large enough to absorb the amount of liquid of at least 9 ml during the test run. An increase in the overall dimensions of the housing would lead to a limitation of the handling of the device.

To maintain the approximate dimensions of the housing given by the membrane strip size, a circular geometry for the housing was chosen.

![Figure 3](image)

Figure 3: CAD models of circular housings with different shapes and arrangement of the membrane basin

In circular housings the shape of the membrane basin can be made more variable. Figure 3 shows different shape variations of the membrane basin. The diameter of the housing is about 50 mm.

With the help of experimental investigations with 3D printed prototypes and the results of the numerical flow simulations the tipping process was simulated. It could be shown that during the tipping process liquid (here water) spills over the edge of the housing. A reliable seal, as can only be achieved by round, edgeless shapes, is therefore of great importance. Figure 4 shows exemplary the tipping process for geometry e) (see Figure 3) for two tipping directions.

![Figure 4](image)

Figure 4: Tipping process over the longitudinal axis (left) and transverse axis (right). The fluid is blue colored.

The filling process via syringe was also investigated with the help of numerical flow simulations. Parameter studies with regard to the filling location and the filling volume flow were carried out. Figure 5 shows three different filling locations. It can be recognized that a central filling of the membrane basin appears to be most suitable. Especially the decentralised filling over the tipping edge at high volume flows over 2 ml/s can lead to an overflow over the opposite side of the basin, as depicted in Figure 5 c).

![Figure 5](image)

Figure 5: Simulated filling process for different filling locations and filling speeds

Furthermore, with the help of the additively manufactured components, complete test cycles were simulated experimentally. This includes several filling processes, lateral movements and the associated tipping processes. The waste reservoir was equipped with absorbent material, which absorbs the predominant portion of the tipped liquid. Figure 6 shows exemplary the test execution for geometry b) and d) from Figure 3. It turned out that geometry d) shows the most advantages with regard to feasibility and handling. The housing of the test device is closed with an overlying lid with an integrated inlet opening, which is not shown here. The tightness of these parts is guaranteed by a commercially available sealing ring between these parts.
5 Conclusion

Building on the previous results, a new, edgeless test device was successfully engineered. A round housing with the membrane basin and the waste reservoir inside fulfils all criteria including tightness. For the arrangement and the shape of the membrane basin there are several possibilities. With the help of numerical flow simulations and experimental tests with additive manufactured prototypes it was shown that geometry d) in Figure 3 has the best properties in terms of feasibility and handling. As a further step for the future, a production-ready design for injection moulding is envisaged.

Author's Statement

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