From sample to sensor

DOI:
10.26481/dis.20220126bh

10 Appendices

10.1 Impact Paragraph

The thesis concerns itself with questions around Point-of-Care (PoC) diagnostics, especially PoC for low-income countries (LIC). Point-of-care diagnostics are methods of disease diagnostic that can be performed fast and easy at the patient-side. Here, no sample has to be sent to a laboratory for analysis, as is the case in regular diagnostics, instead, a compact, fast and self-reliant PoC device is used. The results are available within minutes, instead of the hours or days of conventional laboratory diagnostics. Examples of PoC devices that are widely used are pregnancy tests and blood-glucose meters. In high-income countries, PoC devices are researched in order to streamline the diagnostic process and save large amounts of time and money. In low-income countries on the other hand, PoC-devices could even mean the difference between life and death, since LIC often suffer from a large burden of infectious disease accompanied by an often underequipped healthcare infrastructure. Here, PoC devices are a promising tool to 'fill the gaps' in patient care, since they do not have any reliance on existing infrastructure, are cheap to manufacture, and can be distributed easily.

This thesis aims to improve the application of PoC in LIC. To this end it starts with a review article with meta-study elements that focuses on the current usage of PoC devices in LIC. The main question answered was why the many innovations that are created in the laboratory do not result in implementation into healthcare systems. While laboratories develop amazing PoC applications, the majority of devices that are actually used in the market are typically still based on the crude lateral flow principle used in pregnancy tests. By analyzing the problem on a social and economic level, the important factors for success or failure of PoC devices were discovered. This resulted in an open-access publication in the Journal *MDPI Biosensors*, which was featured as a cover-page article and later won the journals Editors-Choice award. The main findings included factors strongly intertwined with social, economic and political considerations. Problems for the application of PoC in LIC start with research, which is often performed from a high-income country perspective and not adapted to the later usage scenario in LIC. Intellectual property hurdles pose another barrier. Problematic stock management as well as low trust in the devices are further problems hindering market penetration. One of the biggest shortcomings however are the absence of valorization pathways that take every stakeholder into account. This results in unused or misused PoC devices when the intended use-case of a device is not the use-case that generates most profit for all stakeholders along the value chain.

With the new insights brought to light by this publication, researchers can make early adjustments in their design and scale-up consideration in order to improve the possibility of actual implementation of their research in LIC healthcare systems. It is crucial to make design considerations with the found themes in mind. The generated knowledge increases the likelihood of new research actually entering the market, which is the place it needs to be to make a difference in the life of patients, therefore this study can have immense impact on societies around the globe. The findings are not only interesting for researcher that develop diagnostic devices in the laboratory. Since the main focus is the use in society, the results are also applicable for social scientists, decision makers and legislators, as several of the problems are of structural nature that can be fought on the legislative level.

Following this, the next chapter of the thesis covers research conducted on the heat-transfer method, which lends itself for use in LIC due to its affordable setup. The work was published open-access in *Physica Status Solidi A*. Here a proof of application for the diagnosis of urinary tract infections was created, using several samples from different adults; *E.coli* were detected in urine in clinical significant ranges. It was shown, that the method is applicable regardless of gender, different levels of hydration and other metabolic factors. Additionally the importance of sample-analysis close to sample taking was demonstrated and shown how sample quality strongly declines over time. This additionally highlights the points made in the previous chapter. With this study, the potential of the heat-transfer method for actual use with different patients was shown, which is a step further towards its market implementation, for which studies of bigger scale will be the next steps.

Another important aspect of PoC devices is sample handling. The sample has to be processed, purified and transported to the sensor, for this microfluidic circuits are commonly employed. However, the creation of microfluidic systems is difficult and expensive, as it usually requires cleanroom facilities costing thousands of Euro per square meter. This creates a barrier for many research groups, especially in LIC where access to such infrastructure is more scarce. A potential solution for this is 3D printing. Therefore, another open-access article was published in *Physica Status Solidi A* where the applicability of 3D printing for the creation of microfluidic channels was benchmarked. Here a Form2 benchtop 3D printer and three different resin types as raw materials where used for the creation of microfluidic channels in different sizes and orientations towards the buildplate. Standard equipment and consumables were used in order to optimize the printing procedure in the most readily available setup, to promote fast adaption in other institutions and therefore create the greatest impact. It was found that size as well as the orientation of the channels have tremendous impact on channel creation. This gave valuable insights on enhancing internal channel manufacturing via resin choice and print orientation optimization. It was furthermore shown that open surface-channels are easier to produce and can be manufactured in smaller channel sizes compared to internal channels inside the print.

Therefore, the production of open channels on the surface of a 3D print is preferred in order to produce smaller and more reliable channel. However, open channels need to be closed, which is difficult if the 3-dimensonal structure is very complex. To solve this problem, topographical vacuum sealing (Tovas), a method to easily close open surface channels on complex 3-dimensional topographies, was developed. In tovas, a 3D printed substrate that features open surface channel is used together with vacuum forming. A thermoplastic sheet is heated and stretched over the 3-dimensional substrate, and vacuum applied. The pressure difference aligns the thermoplastic with the geometry of the substrate and closes the open surface-channels. This new method enables the use of 3D printing for the creation of small surface-channels in 3D geometry. The implementation cost of this new method is very low, entry-level resin 3D printer are available for 300 Euro and a vacuum forming machine for under 100 Euro, which makes this technology especially promising for LIC. Tovas is furthermore interesting for LIC, as the 3-dimensional microfluidic circuits can be easily adapted to other already existing hardware. An example given in the thesis is the manufacturing of a microfluidic cuvette that fits in a standard spectrophotometer. The manuscript for this new technology was published open access at MDPI Biosensors and was furthermore presented at the *European Biosensor Symposium 2021*. A patent of tovas is pending at the European Patent Office.

The work on 3D printed microfluidics presented in the thesis has the potential of an enormous impact, especially in LIC. Its low cost of implementation opens up a branch of science to a large number of research institutes that do not have access to hugely expensive cleanroom facilities. Furthermore the possibility to adapt microfluidic devices to already existing technology, will enable researcher to extend the potential of their old devices, enabling them to improve their research without large additional investments.

The gained knowledge was furthermore used to create a microfluidic measuring setup for the heat-transfer method, which was presented at the *12th International Workshop on Engineering of Functional Interfaces*. The setup was created to replace the old measurement cell, which had to be assembled by four screws and then arrested in a clutch in order to immobilize it for the experiment. To improve this process the new 3D printed system was inspired by LEGO building blocks, and is able to fit together without any screws, using LEGO-like connectors, which makes the assembly process much easier. Several addition modules were created to fit easily onto the flow-cell, like an inclined ramp and a bubble trap to prevent air from disturbing the measurement.

Based on the success of the LEGO-inspired measuring cell, a complete system of 3D printed building blocks that feature microfluidic channels was created. These LEGO-like blocks were used to create a science education kit called Flui.Go. With our kit, students can assemble the building blocks in different ways, creating networks of microfluidic channels, mixers and reaction vessels, and then flush them with different liquids to experience scientific phenomena.

The building blocks are ideal to teach science in a natural and exciting way, as children intuitively use the blocks to recreate the experiments distributed with the kit. The modular aspect enables children to use their creativity to modify the experiments and even create completely new ones, simply by replacing or adding different blocks. Flui.Go won the competition '*Science + Engineering for Society*' at Maastricht University, after securing additional funding the spin-off company *Flui.Go Science* was created. Since then we improved our building blocks and created a complete science kit including several different kinds of blocks and pumps. The results were published in the *Journal of Chemical Education* and we are currently working on another publication about the application of the microfluidic building blocks for education in primary schools. The current aim is to scale-up the production and deliver the first kits which were ordered by primary schools in the Netherlands. Given the reliance on technology in our world, STEM education is essential for a prosperous society. Therefore tools that inspire the next generation to take an interest in the STEM fields have enormous impact for the future. Our kit showed already great success in tests with primary school students and the order of 52 first kits by 26 primary schools already indicate the great impact Flui.Go will have in inspiring the next generation of scientists.