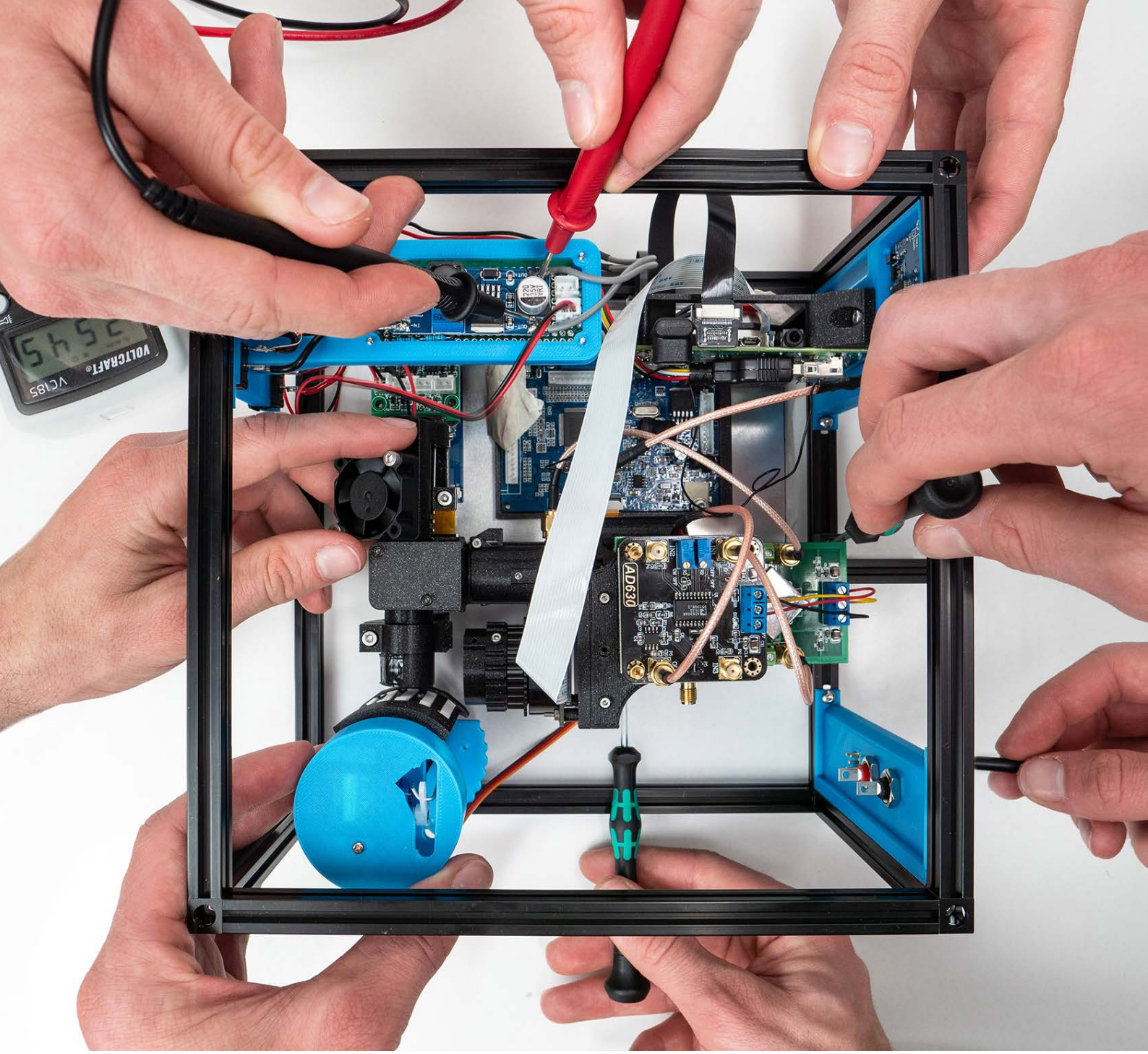

Accelerating the development of UCP-LF CAA strip readers for schistosomiasis diagnosis

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Abstract

This document reports the exploration of the development of a context-specific strip reader for an innovative lateral flow test detecting schistosomiasis.

Schistosomiasis is a common poverty-related parasitic disease in many Sub-Saharan African countries. Transmission happens in infested water, putting especially children at risk. Schistosomiasis can be effectively treated. In order to do that, accurate diagnostics are needed at the point of care to target communities at risk. Leiden University Medical Center is developing a lateral flow test that detects the antigen CAA with high accuracy, using upconverting particles. The test has great potential in terms of accuracy, but a dedicated reader is needed to interpret the test result. A reader typically limits the accessibility of a test in low-resource settings, because of its size, high costs, and limited user-friendliness and robustness. On the other hand, one could benefit from the opportunities that come with such a device, such as reducing human error, quantifying results, and real-time data collection. The starting point was to explore the possibilities of developing a context-specific strip reader dedicated to the new test.

The approach of this project was based on systemic design methodologies. It deals with complexity by creating interventions that move the system to a more desired state in incremental steps. Transitions towards desired states were described on four different levels of abstraction. On a global level, we aim towards leaving no one behind, making healthcare accessible for everyone. Big forces, like climate change and COVID-19, and smaller forces, like stigmas and technological challenges, are risk factors that could steer change away from the desired direction Meanwhile, opportunities arise, such as the rapid digitization of Sub-Saharan Africa. From a systemic viewpoint, it became clear that new frames are needed to create a strong and attractive narrative for the role of strip readers in diagnostics.
Based on the insights, an intervention strategy was proposed to accelerate the development of a context--specific strip reader by early involvement of stakeholders. The strategy consists of two elements.

1) Three new narratives are proposed as an alternative to the current, negative frame of the use of readers in low-resource settings. These narratives were used to formulate multiple development paths of different technical concepts.

2) The Block Reader was developed to support the narrative with evidence and as a means for collaborative prototyping. It enables to gain and share insights, and to communicate with stakeholders. The device is fully modular, allowing the user (developers) to iterate on the technology and user-interaction quickly.

Lastly, an outline of the next steps is discussed.

Introduction	Background information	Systemic approach	Transitions	Interventions	The Block Reader	Conclusion
Introduction of topic and challenges	Essential background information to understand schistosomiasis, the role of diagnostics and the new UCP-LF CAA test.	A proposal for an intervention approach	Important transitions and risk and opportunities, on different levels of abstraction	Interventions: three narratives and development paths	Introducing the Block Reader as part of the intervention	Conclusion, discussion and reflection
	Chapter 1- 4	Chapter 5	Chapter 6	Chapter 7	Chapter 8	Chapter 9

Reading guide

Medical glossary

Name	Description
Analytical sensitivity	Analytical sensitivity and measures the ability of a test to detect very low concentrations of a substance
CAA	Circulating Anodic Antigen
Case management	Diagnosing and treating individuals
CCA	circulating cathodic antigen
Diagnostic accuracy	Percentage of correct diagnostic assessments. It is a combined measurement of the sensitivity and the specificity
Diagnostic precision	The degree to which a repeated measurement gives the same outcome
Diagnostic reliability	The degree to which a repeated measurement gives the same outcome
Diagnostic sensitivity	Diagnostic sensitivity is a measure of how well a test can identify true positives
Diagnostic specificity	Diagnostic specificity is a measure of how well a test can identify true negatives
Disease control	Controlling the morbidity of a disease
Disease elimination	For schistosomiasis: “elimination as a public health problem”. There is no strict definition of when a disease is eliminated as a public health problem. After elimination as public health problem, targets can be set on interruption of transmission (full elimination)
Disease mapping	Mapping the prevalence (and other related factors) of a certain disease on a map
ELISA	Enzyme-linked immunosorbent assay
FC	Flow Control
Integrated control	multiple control strategies are integrated in on program, such as treatment, education and and improved hygiene
LF	Lateral flow
LOD	Limit of Detection, measure of the smallest amount that can be detected
LUMC	Leiden University Medical Center
MDA	Mass Drug Administration
Multiplexing (assay)	Detecting multiple analytes with a single sample.
MαCAA	mouse anti-CAA
NG Biotech	French company of rapid diagnostic assays
NGO	Non-governmental organization (non-profit organization)
PoC	Point-of-Care
QC	Quality Control
REASSURED	REASSURED is a set of criteria that needs to be taken into account when developing a diagnostic tool for point-of-care use. It is an abbreviation that stands for Real-time connectivity Ease of specimen collection, Environmental friendliness, Affordability, Sensitivity, Specificity, User-friendliness, Rapid and robust, Equipment-free, and Deliverable to end-users.
S. Hemeatobium	Schistoma species causing urogenital schistosomiasis
S. Mansoni	Schistoma species causing intestinal schistosomiasis
Schistosomiasis	Disease caused by a Schistosoma infection. Also: bilharzia.
SD	Standard Deviation
TCA	Trichloroacetic acid
UCP-LF CAA test	Up-converting Phosphor Lateral Flow Circulating Anodic Antigen test. A lateral flow test that is sensitive to the antigen CAA, which is excreted by Schistosoma worms. The upconverting phospers functions as a marker that allows the user to detect CAA that is binded to the UCP and the test and/or control line.
WHO	World Health Organization

Technical glossary

Name	Description
3D printing	Rapid added manufacturing method to produce parts and products
AC	Alternating current
Analog to digital converter (ADC)	Converts an analogue signal to a digital (binary) signal
Aperture	A hole through which lights travels. The aperture number often refers to the size of the hole in relation to the focal distance.
Bandpass filter (optical)	A filter that only lets light of a specific band of wavelength through
Chromatic abbreviation	A lens defect causing different wavelengths of lights have different focal points. Color separation can be observed
collimated	The beam is completely parallel (not converging or diverging).
confocal illumination	The sample is illumiated from above, through the same lens as the lens through which the sample is being observed
DC	Direct current
Depth of field	The range in which light can be projected in focus. High depth of field means a large distance between the closest and the furthest point that is in focus
dichroic mirror	A mirror that only reflects a particular band of wavelengths, and let other wavelengths pass through
Focal length	The distance between the lens and the focus point of the lens
Function generator	Generates an analogue signal with a specific shape and frequency, for example, a square wave or a sinus
IR	Infrared
Laser diode	A semiconducter that emits light at a specific wavelength
Lock-in amplifier	An instrument that can remove noise from a extremely noisy signal using a modulated pulse
NIR	Near-infrared
off-axis illumination	Opposed to confocal illumination, the axis of illumination is not the same as the axis through which the sample is observed
Opamp	Operational amplifier, amplifies analogue signal
PCB	Printed Circuit Board
Photo diode	Sensor that converts light to a current
Raspberry Pi	Low costs small sized computer, often used for learning and developing technology
SMA	Coaxial cable connector
Spherical abbreviation	Outer part of the lens have a different focus point than the inner part of the lens, causing an unscharp image
symmetric power supply	Power supply that has a negative voltage, a ground and a positive voltage
synchronous detection	The principle behind a lock-in amplifier. A electrical signal covered in noise is recovered by multiplying the signal with the reference signal, and integrating the signal. Effectively, it functions like an extreme narrow band-pass filter
wavelength	A measure of the length of a light wave. A high wavelength has a less energy than a short wavelength.

Introduction to the topic

Globally, hundreds of millions of people are affected by poverty-related diseases. It is a trap in which poverty is both the indirect cause and consequence of the disease. For example, poor sanitation, inadequate education, or limited access to health care facilities are poverty-related circumstances that increase the risk of poverty-related diseases. The consequential diseases, like HIV, tuberculosis, and malaria, disable people to participate in society, limiting financial and social progress in poor communities[1]

One particular group of poverty-related diseases is called Neglected Tropical Diseases (NTDs). NTDs are infectious diseases, mainly occurring in tropical parts of Sub-Saharan Africa. Those diseases have been overshadowed by the 'big three': HIV, tuberculosis, and malaria. Consequently, research on NTDs is underfunded, and interventions are inadequate[2].

Despite the neglect, progress has been made in the last decades, thanks to collaborative efforts of the World Health Organization (WHO) and other NGOs, (local) governments, private and public funders, researchers, and the pharmaceutical industry. Effective preventative drugs have been developed, targeting a significant part of the NTDs.

Essential in the fight against NTDs is access to rapid diagnostics at the point of care. It allows for test-and-treat approaches, and it enables data generation for mapping, monitoring, and surveillance. Stakeholders can keep track of the prevalence and infection intensity and adjust interventions and supply chains if needed. Next, it provides researchers with data to study medical, demographical, and contextual determinants to further improve intervention strategies and tools.

In 2019, INSPiRED was commenced; an interdisciplinary collaboration between European (LUMC and TU Delft) and African partners that aims for "development and validation of inclusive, smart, easy to use, cost-effective and efficient optical devices for the diagnosis of poverty-related parasitic diseases in Nigeria and Gabon"[3]. One of the targeted diseases is schistosomiasis.

Schistosomiasis is a neglected tropical disease caused by a parasitic worm. Infection and transmission occur via water, putting especially children, women, and fishermen at risk. The disease is common in rural areas in many Sub-Saharan African countries. Infection is often asymptomatic and pathological effects mainly occur in the long term. This makes it challenging to bring the disease under attention. Nevertheless, long-term consequences are severe, including growth defects, organ failure, and risk of deathly co-infections. Traditional diagnostics for schistosomiasis, including the gold standard microscopy, lack the sensitivity, speed, affordability or point-of-care use to bring schistosomiasis closer to elimination.

Leiden University Medical Center (LUMC) is working on a promising new diagnostic test to detect schistosomiasis with high accuracy: the UCP-LF CAA test. It makes use of the well-known lateral-flow (LF) principle, but instead of using visual or usual fluorescence labels, it makes use of upconverting phosphors (UCP). These particles possess unique fluorescence qualities, allowing the test to be very sensitive and specific. The assay detects the Circulating Anodic Antigen (CAA), a preferred analyte thanks to its specificness and relation to the infection intensity. This allows for semi-quantitative measurements, essential for monitoring.

Although the test shows great potential to become the new reference standard for schistosomiasis diagnostics, challenges remain to make the test accessible for those in need.

One of those challenges is that the UCP particles require the test to be read with a dedicated strip reader. Such readers are only produced on demand and are not suitable for low-resource settings, limiting the accessibility of the new test. However, a digital strip reader could also solve other hurdles of today's point-of-care tests: observer-dependent interpretation and real-time data generation and collection. Stakeholders are hesitant to get on board of UCP-LF CAA, partly because of the need for a dedicated reader that does not exist yet.

This project, initiated by INSPiRED, is concerned with the exploration of the development of a context-specific, connected strip reader suitable for the UCP-LF CAA test. It aims to gain insights into the technology and the contextual system and involve stakeholders to bring UCP-LF CAA closer to the field.

What makes this quest challenging is the complexity of the systems in which diagnostics are developed and used. A systemic design approach addresses those unknowns by focusing on interventions rather than solutions. By taking incremental steps that influence the system, the desired change (outcome), the patterns of relationship (how), and the needed elements (what) are co-developed in parallel. The desired outcome, the what, and the how will be explored and co-developed in this project and turned into concrete action.

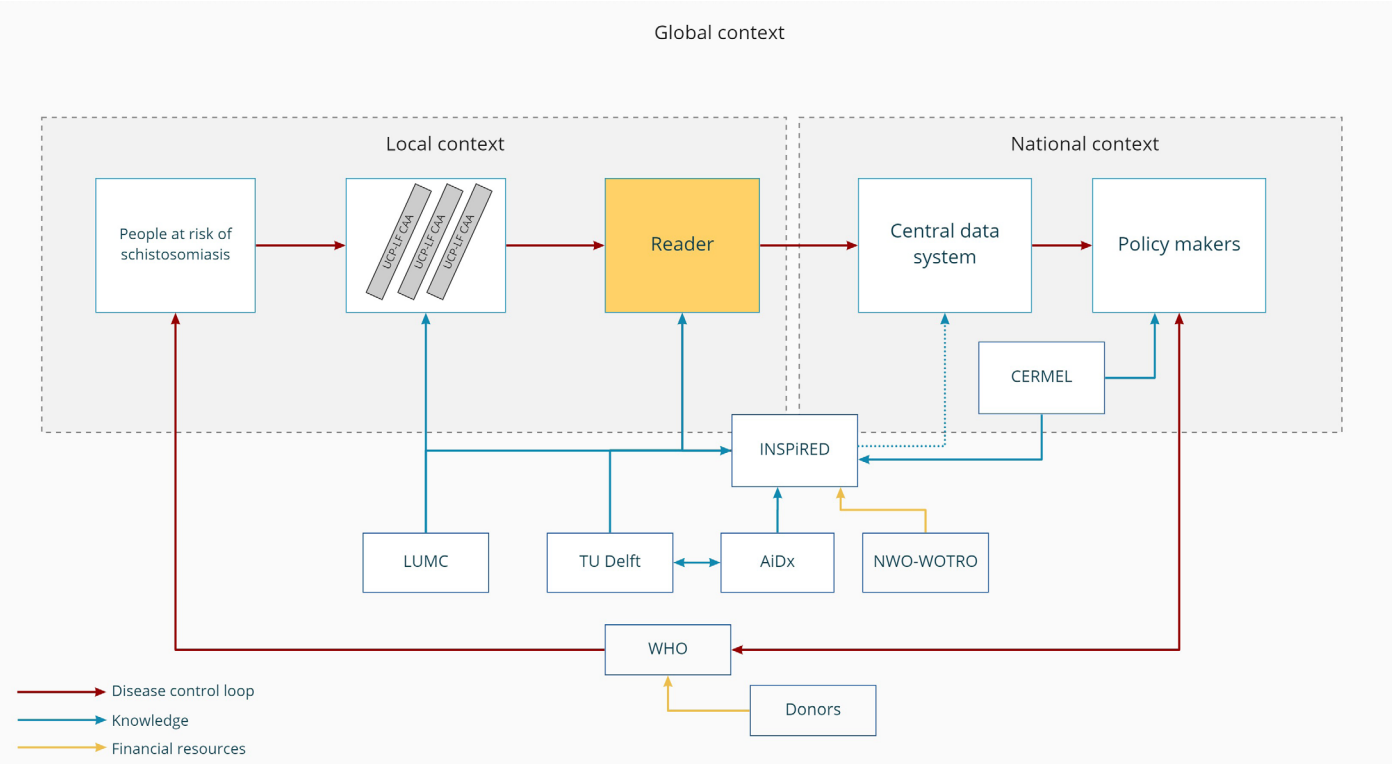


Figure 1: the system in which the reader and this project is situated. Within the local context, the strip reader is used to interpret the result of the UCP-LF CAA test. The generated data is collected (central data system) and allows policy makers to adjust their strategies, in dialogue with the World Health Organization (WHO). The WHO provides Praziquantel to the infected communities. This project is initiated by INSPiRED, which functions on the crossroad of the local, national and global context. INSPiRED is a collaboration of several partners and is concerned with the development of smart diagnostics, like a strip reader. AiDx is a start-up developing smart diagnostics, bridging the gap between academic knowledge and practice.

Part 1

1. Neglected tropical diseases

In this chapter, Neglected Tropical Diseases (NTDs) are further discussed to put schistosomiasis in a perspective of larger structural challenges and the need for structural approaches.

An introduction

In 2020, the WHO published its roadmap to combat Neglected Tropical Diseases (NTDs) in the coming decade[4]. As described in the report, although 600 million fewer people compared to 2007 require interventions against NTDs, still, more than 1 billion people are affected worldwide. The roadmap is ambitious: it strives to a "90% reduction of people requiring interventions against NTDs"[4]. According to the WHO, an cross-cutting approach is needed to take action across multiple sectors and integrate the interventions within the health system.

The NTDs form a group of twenty medically diverse diseases that are poverty-related, commonly occurring in tropical areas, and neglected in different ways[5]. For centuries, large parts of the world have been suffering from these diseases. In many places, they disappeared by improved living conditions and hygiene. However, areas with the lowest socioeconomic status continued suffering from the NTDs. The diseases are neglected in different ways. First, they have been overshadowed by HIV, malaria, and tuberculosis ('the big three'). Second, the population at risk usually is not able to put the issue on the agenda of decision-makers. Third, NTDs are especially affecting disadvantaged populations in low and lower middle income countries. Little research and development on NTDs were done by high-income countries, which are usually not affected at all by NTDs[6].

It is important to understand that most people that are affected are not able to afford interventions unless they are free of charge. Also, those groups are most likely to live in remote places, out of reach of advanced health care. This means that interventions are likely being performed by community health workers with limited training [5]. Often, NTDs are present in hotspots, pockets with a high burden of several NTDs. Not only multiple NTDs are found within those hotspots, individuals are also often affected by multiple NTDs[7]. Those hotspots easily disappear in statistical averages[5].

In 2007, the first NTD global partners meeting was organized by WHO. Partners agreed to take action and the industry committed to donating large quantities of medicines[5]. Since then, big steps have been made in fighting NTDs. In 2012, a meeting was held in London, attended by major pharmaceutical companies, governmental representatives, scientists, the WHO, and Bill Gates. Ambitious goals were set for the year 2020 and agreements were made to ensure massive (financial) support. According to the WHO, medicines with a total worth of 2 billion to 3 billion dollars are donated yearly[5]. Big achievements have been made since then, although not all goals for 2020 have been achieved[4].

Funding

However, when studying the global funding to combat neglected diseases in developing countries, a striking trend can be seen. The 2019 G-FINDER report provides data on the global investments in fighting different diseases, specified per type of investment (product types)[8]. Although the total sum of investments reached a new record in 2018 ($ 4,055 million), the NTDs remain neglected, as shown in the report. Despite the success story of the increased funding by the industry, public and private funding fell, leading to a total decrease in funding in the last years. In 2018, NTDs received around 250 million dollars, as can be seen in figure 2[8]. To put those numbers in perspective, this is 0,14% of the global expenditure on pharmaceutical R&D in 2018[9].

To eliminate NTDs, structural and adequate funding is essential. Without adequate funding of intervention programs, one would be able to impact the prevalence, but it the disease will return as soon as control interventions are retracted. Next to that, more research and development is needed to understand the complex set of social, medical and demographic determinants. Lastly, new diagnostics tools and medicines have to be developed to reach the very perifery of each areas, to permanently eradicate the disease[10].

Fighting NTDs

Control strategy

The NTDs can be divided in two groups based on the control strategy. One group can be fighted with Mass Drugs Administrations (MDA) campaigns because an affordable preventative drug is available that has few side effects. The second group can only be fought with individual diagnosis and tailored interventions.

Currently, the seven most prevailing NTDs (lymphatic filariasis, onchocerciasis, soil-transmitted helminthiasis, schistosomiasis, and trachoma) are addressed by MDA programs[11]. Preventative chemotherapy is applied to targeted populations at risk. Since multiple NTDs often co-exist in at in specific areas, the preventative drugs are

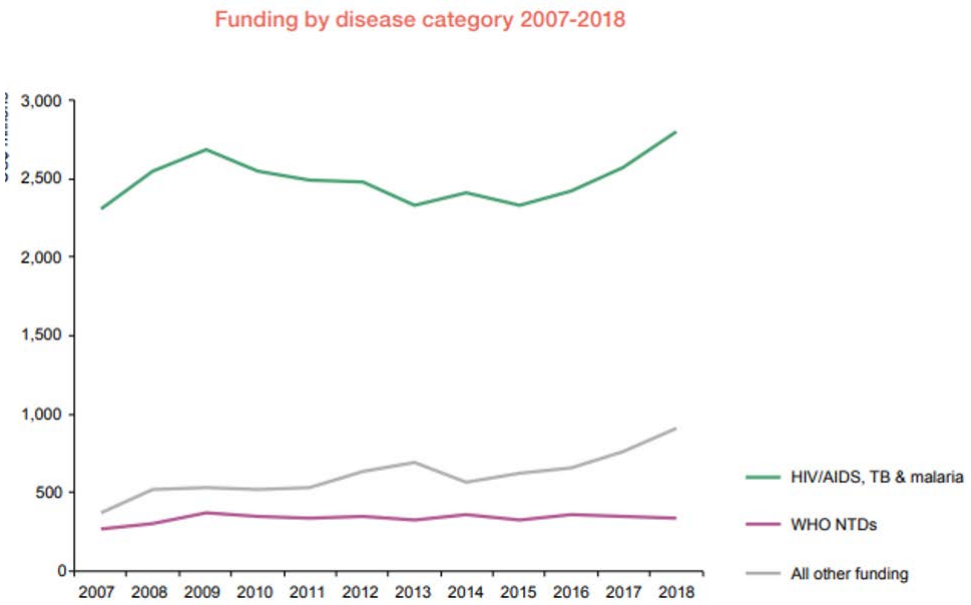


Figure 2. Funding by disease category 2007-2018. Graph by Policy Cures Research[12].

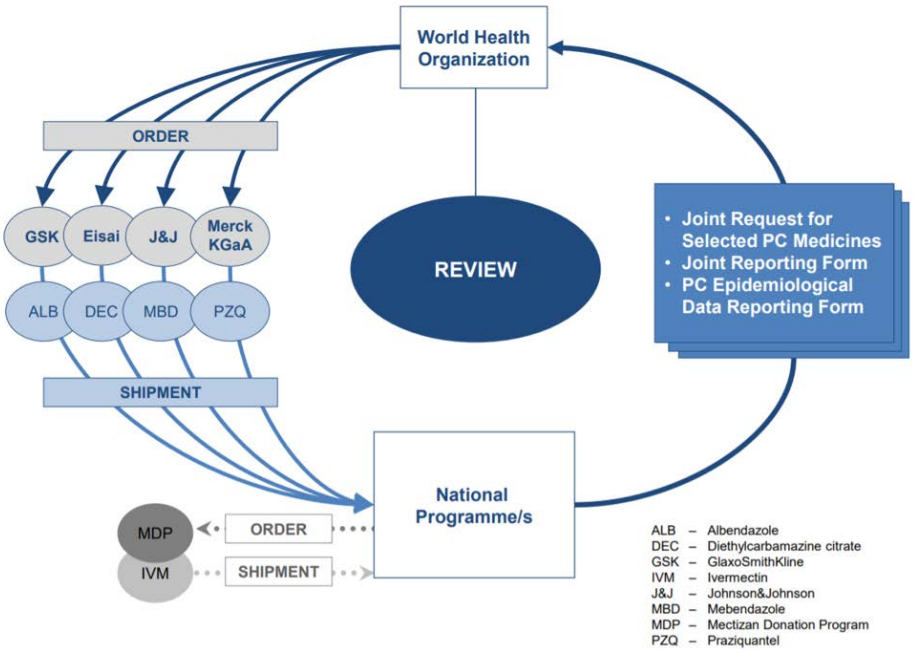


Figure 3: Joint mechanism of the coordination of drugs supply by the WHO[17].

often offered as a package, also described as 'integrated NTD control'[12]. Such MDA control strategies are characterized by several factors[12]:

- The diseases can be controlled with preventative chemotherapy, which is safe, inexpensive, and often donated by the pharmaceutical industry
- The diseases share similar risk groups
- The intervention is undemanding, can be performed by non-medically trained personnel and individual diagnosis is not required
- There is often only a very weak health system to rely upon.
- The World Health Organization plays an important role in the coordination of the MDA programs and the supply of preventive chemotherapy drugs, as can be seen in figure 3. The whole cycle can take six to eight months[13].

For the NTDs that cannot be addressed with preventative chemotherapy, the intervention strategy still relies on individual diagnostics, as described by Taylor[14]. The strategy often includes screening and follow-up testing, which makes mass intervention complicated. For those specific diseases, diagnostics tests have to become more convenient (single test, reliable), or a safer drug should be developed that could allow the use of an MDA strategy[14].

Healthcare system

The health care system in Sub-Saharan African countries can be divided into four levels, as can be seen in figure 4. On those different levels, different resources in terms of skills and equipment can be expected. Typically, the highest burden of Neglected Tropical Disease is occurring in areas in which only primary health care is available. Primary care settings are very limited in terms of equipment and skills to support diagnostic tests. This is also referred to as the healthcare paradox: "the burden of NTDs is highest at the lowest healthcare level"[15]. Rapid Diagnostic Tests (RDTs) are likely to be performed by community health workers, only equipped with limited knowledge and skills regarding dealing with NTDs[16]. The community health workers not only have a critical role in strengthening health systems[17], but also in the implementation and evaluation of point-of-care testing.

Diagnosing NTDs

The significant attention that has been raised in the previous decades for the development of effective, safe, and low-cost drugs addressing NTDs, has only led to minor expenditures in the area of diagnostic tests. Fortunately, as the elimination of some NTDs becomes within reach, a large shift can be seen towards the development of prevention and elimination strategies, including an emphasis on improved point-of-care diagnostics and an important role for (real-time) data[14].

This is demonstrated in the WHO roadmap for NTDs in 2020-2030, in which the need is expressed for strong monitoring and evaluation mechanisms to be able to increase the efficiency and effectiveness of the control programs[4]. An important dimension is the "availability of effective, standardized, affordable diagnostics for timely detection, assessment of end-points, surveillance" and, the "availability of point-of-care diagnostics (where appropriate) usable at community-level and in low-resource settings"[4].

Almost all NTDs can be diagnosed, however, it lacks diagnostics that are accessible and affordable for those in need.

The types of testing appropriate at each tier will be country specific and will depend on factors such as electricity, reagant--grade water, phlebotomy and specialized human resources[5].

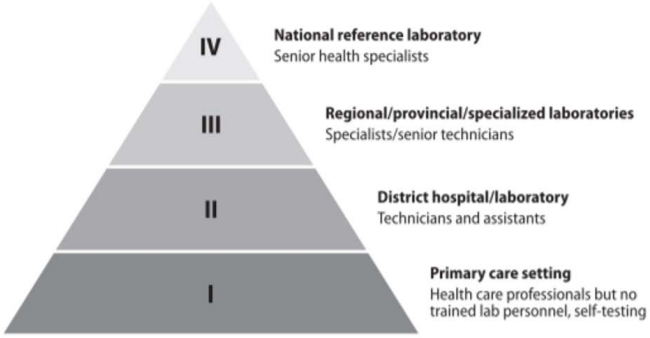


Figure 4: Different levels of health care settings[22]

Challenges of eliminating NTDs

Eliminating NTDs brings specific challenges concerning diagnostics.

With a low prevalence of a disease, it is much harder to identify the cases to completely stop transmission. Two factors contribute to this. A larger group has to be tested to generate significant results with a low prevalence. Secondly, the intensity of the infection is often lower when the prevalence (and thus the transmission rate) is lower. This leads to the need for diagnostics that have high diagnostic sensitivity, high analytical sensitivity and high diagnostic specificity. This latter is relevant to prevent over-treatment of a large group of non-infected people.

Also, quantitative diagnostics are desired to measure the effect of control efforts and to determine the relationship between the burden of the disease and the transmission risk[19]. Equally important, the tests should be at least as sensitive and specific as the tool used for the mapping, to prevent needless extension of the MDA program[19]. The tests should generate the relevant data, preferably real-time, to serve decision-makers in their stopping decision[20].

From a cost perspective, paradoxical patterns can be seen as well when working towards elimination. The lower the prevalence of a disease is, the more people have to be included in mapping strategies to determine the prevalence with statistical significance. At some tipping point, the costs of the diagnostic tests will be higher than the costs of preventative treatment for all[21].

Also from a social perspective, it has been found hard to keep up the motivation of the health staff while working towards the elimination of schistosomiasis. Surveillance capacity has to be maintained for several years while only detecting a few cases, challenging both cost efficiency as motivation[22].

Last, for disease elimination, even the most remote areas have to be reached. Point-of-Care diagnostics are urgently needed to address those communities as well.

Discussion and design implications

- Although medically diverse, NTDs often share a similar story and would benefit from an integral approach. Despite the relatively small amount of funding that is available for R&D, MDA have been proven to be an effective control strategy. However, when moving towards elimination, new challenges require new strategies. The success of those strategies heavily rely on the ability to approach the challenge in an integral and evidence-based way. As the cases become harder to detect, more resources have to be invested to further reduce the prevalence and definitely eliminate the disease. Diagnostic will play an increasingly important role and have to be further developed to satisfy the needs.

- Diagnostic tools have to be further optimized to be used in evidence-based strategies and low-endemic settings.

- Fighting NTDs is largely a political matter. Investing in NTD programs is a sustainable investment but needs the right priorities, the right organizational resources, and an integral and long-term approach.

2. Schistosomiasis

In this chapter, schistosomiasis is further investigated to get an understanding of the specific challenges that fighting schistosomiasis brings. Insights that are relevant to the field of diagnostics are discussed.

As described in the introduction, schistosomiasis is one of the neglected tropical diseases, caused by the parasitic flatworms of the Schistosoma genus[23]. According to the WHO, "at least 290.8 million people required preventive treatment for schistosomiasis in 2018, out of which more than 97.2 million people were reported to have been treated"[24]. When adding the people that are in a post-infection stage but still suffer from schistosomiasis, the number of people with schistosomiasis is estimated to be close to 440 million, which makes schistosomiasis one of the NTDs with the highest burden[23,25]. The number of deaths is hard to estimate because many people remain undiagnosed, but estimations vary from 24.000 to 200.000 deaths per year[24]. Schistosomiasis is a common disease in tropical and subtropical areas, especially in Africa. People living in poor communities with no access to sanitation and safe drinking water are most at risk. Infection occurs when the skin is in contact with infested water. Larvae of the parasite penetrate the skin and manifest themselves in the blood vessels, growing to adult worms. Eggs that are released in the body partially end up in the urine or feces (depending on the species). The urine or feces is excreted in the water; the eggs find their way back to their intermediate host, the freshwater snail, closing the lifecycle of the Schistosoma worm[24]. A visualization of this lifecycle can be found in figure 5.

Because infection occurs in water, people can be infected during all kinds of activities, like agricultural work, fishing, cleaning, and playing. Women risk developing female genital schistosomiasis, a highly underdiagnosed disease due to unawareness and the lack of effective diagnostics[26].

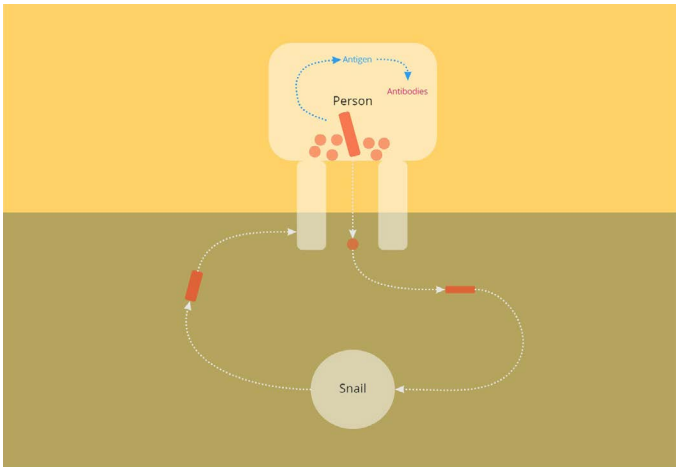


Figure 5, the lifecycle of the Schistosoma genus

Figure 6: 1659 adult Schistosoma mansoni worms obtained by live surgical perfusion of an 18-year-old patient in 1970[30].

Multiple ***Schistosoma*** species can be distinguished, of which ***Schistosoma haematobium*** and ***Schistosoma mansoni*** are the most common ones in Sub-Saharan Africa. The different species may cause different symptoms and pathologies since they are located in different parts of the body. ***S. heamatobium*** causes urogenital schistosomiasis (the eggs can be mostly found in the bladder, and so in the urine). ***S. mansoni*** causes intestinal schistosomiasis, which can be detected by eggs in the intestine and stool. Consequently, diagnostic tools are not always interchangeable for both species.

Pathological effects

The pathological effects of human schistosomiasis range from anaemia (decreased ability of the blood to carry oxygen), impaired growth, impaired cognition, to fibrosis, lymphoma (tumor), and urogenital inflammation[23]. The morbidity is not induced by the worms, but by the eggs, that become trapped in the organs and result in chronic schistosomiasis[23]. When untreated, children that are infected over a longer period of time are likely to develop disabilities that are irreversible[28]. The diversity (non-specific) and the slow development of pathological effects contribute to the fact that schistosomiasis is being neglected. Although the (co)morbidity is severe, cause and effect are not as easily identified as, for example with malaria.

Symptoms

Often, schistosomiasis infections are asymptomatic. Symptoms like fever, diarrhea, or blood in the urine are associated with acute schistosomiasis, but are general symptoms that are hard to differentiate from other diseases. Symptoms of chronic schistosomiasis may only develop after 5-15 years[22].

Groups at risk

As mentioned before, people that have frequent contact with water are among the people at risk. Children and young adults are especially exposed because they have lower hygienic standards and come in contact with fresh water often. As the differences amongst age groups are significant[23]. However, treating infants and preschool children has been previously overlooked and still faces some challenges in terms of a lack of strategy and regulation[29]. At a global level, a high prevalence of schistosomiasis is mainly seen in Sub-Saharan Africa, with the highest endemicity in the regions of Mozambique, Madagascar, Ghana, and Mali[30].

Treatment

Schistosomiasis can be effectively treated with Praziquantel, an effective, inexpensive drug invented in 1979[22]. Praziquantel kills the adult worms, in the body. This makes the timing of the treatment important. Treatment in a too early infection stage may not be effective; a delay of 6-8 weeks after the infection is advised[31]. Treatment is often part of large-scale MDA programs, targeting communities whose (estimated) prevalence exceeds a certain threshold (10%).

Prevention and control

Control of schistosomiasis is not only based on treatment, but also on interrupting the transmission in other ways. Improved sanitation, education, and snail-control are essential strategies to minimize the risk of transmission[24].

Funding for schistosomiasis

Research on schistosomiasis, like all other NTDs, is underfunded relative to its impact. While HIV/AIDS accounts for 36% of the funding for neglected diseases (not to be confused with neglected tropical diseases), schistosomiasis only receives 0,6% of the funding budget[8]. Although HIV/AIDS undisputedly has a higher impact, the number of deaths of schistosomiasis may be up to 40% of the AIDS-related deaths[32]

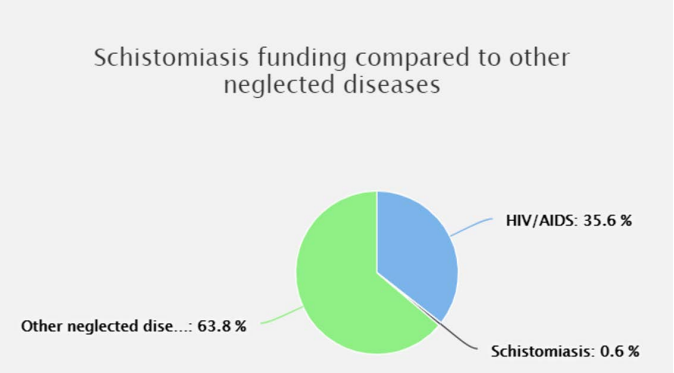


Figure 6. Funding of schistosomiasis research compared to neglected diseases, like HIV/AIDS[12].

Conclusion

- Although easy to treat and reasonably easy to diagnose, schistosomiasis still has a significant burden, especially in African countries.
- Without acute symptoms and with limited knowledge, the disease is easily neglected, even by people that are suffering from the disease themselves. However, the long-term effects are devastating, both for individual health as on a societal and economic level.
- Funds for combatting Neglected Tropical diseases like schistosomiasis are very limited in size.
- This neglect makes it even more important to make diagnosis and intervention as accessible as possible. With only limited symptoms, people might not be willing to participate in a test that is experienced as invasive, like stool microscopy. Fast results and non-invasive sample materials could decrease the threshold and thus the effectiveness of a diagnostic tool.

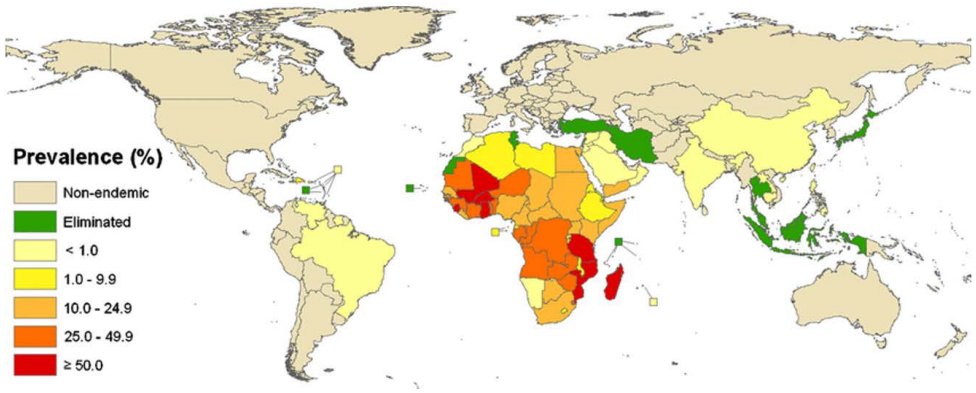


Figure 7: current global distribution of schistosomiasis. Graph by Utzinger et al.[33]

3. Schistosomiasis diagnostics

This chapter describes the detection principles and diagnostic tools for schistosomiasis. Furthermore, the requirements for the ideal test for different applications will be described. This aids the positioning of the UCP-LF CAA test compared to other test methods.

Detection principles

There are several direct and indirect methods to detect the presence of schistosomes in the body. Direct methods are detecting eggs in the urine or stool, mostly done by microscopy. Indirect methods are detecting antibodies, detecting antigens, detecting DNA, or detecting blood in stool or urine. Using blood in the urine or stool as an indicator for schistosomiasis, or counting eggs found in urine or stool, have been the most common principles of detecting schistosomiasis. However, other detection methods are gaining traction, especially in low-endemic areas, in which high sensitivity and low price are becoming more and more important.

Diagnostic applications

In combatting a disease, the diagnostic tools are continuously adapted to the stage of the disease and the constraints given by the context. Different applications of schistosomiasis diagnostics are distinguished, of which the most important ones are summarized in table 1.

Depending on the application, the test result will have a different diagnostic function to the user (see table 2). This distinction is of importance, since it dictates different requirements regarding test performance and quality assurance specifications. As one can imagine, a test that has diagnosis as diagnostic function, has to be very specific, because it will be the sole determinant on which decisions are based. By contrast, a test as 'aid to diagnosis' will only be one of the indicators. The diagnosis will be done based on another test or clinical symptoms and is the responsibility of a health professional.

Target product profile

In 2021, WHO drafted a Target Product Profile (TPP) for schistosomiasis which was published for public consultation[33]. The purpose of the TPP is to provide guidelines to industry and organizations for developing diagnostic tools targeted at impact monitoring and surveillance.
The most interesting parts from the TPP are listed below[33]:

Mapping and monitoring

- This test will be performed by health personnel, community health workers, and community volunteers.
- The test will be performed under "zero-infrastructure" conditions, including but not limited to schools, community health centers, households, and outdoor conditions.
- Tests should have a clear result for the naked eye (minimum) and should be semi-quantitative (ideal)
- The test should not require capital costs
- Highly portable with no specialized transport needs.

Evaluation

- For lab-based tests: tests can be performed in a centralized (e.g., regional or national) diagnostic testing laboratory (minimum)
- For lab-based tests: the test may include instrument-based detection of a signal that provides unambiguous determination of a qualitative or semi-quantitative measure. For point-of-care tests, results shall be a high-contrast and clear result for the naked eye; indoor and outdoor reading of a signal that provides a definitive "yes/no" result. Signal interpretation may be qualitative or semi-quantitative.

Diagnostic function	Application[1]	Definition used by WHO
Diagnosis	• Case management	Diagnostic tests are used to determine, verify or confirm a patient's clinical condition as a sole determinant.
Aid to Diagnosis	• Case management • Test and treat	Aid to Diagnosis tests are used to provide additional information to assist in the determination or verification of a patient's clinical status. The test is not the sole determinant.
Screening	• Screening • Mapping • Stopping decision • Surveillance	Screening tests are used to determine the status of a disease, disorder or other physiological state in an asymptomatic individual.
Monitoring	• Monitoring	Monitoring tests are used for the measurement of analyte levels for the purpose of adjusting treatments/interventions as required.

[1]According to distinction in WHO Model List of Essential In Vitro Diagnostics

Table 2: overview of diagnostic functions used by the WHO and the corresponding applications of the diagnostics[18]

Application	Requirements
Post-elimination surveillance Surveillance on the presence of the disease, after the intervention has stopped	• two-step test strategy • sensitivity 88%, specificity 99.5% (combined) • sample pooling • point-of-Care + lab testing • rapid turn-around time not needed
Stopping decision Determine whether the disease is eliminated, according to the set targets	• two-step test strategy • sensitivity 88%, specificity 99.5% (combined) • sample pooling • point-of-Care + lab testing • rapid turn-around time not needed
Impact monitoring Monitoring the effect of an intervention strategy	• high throughput • point-of-care • sensitivity <60%, specificity <95% • (semi-)quantitative • centralized data sharing • no capital costs • only sensitive to present infections
Mapping Determine the prevalence of disease amongst a certain population to decide on control strategy	• high throughput • point-of-care • sensitivity <60%, specificity <95% • centralized data sharing • no capital costs • only sensitive to present infections
Test and treat Start treatment directly (the same day) as the test is taken	• Immediate results (within a day) • point-of-care
Screening Identify potential presence of a disease in an (asymptomatic) population. For diagnosis, additional tests should be performed.	• sample pooling is a plus • high throughput • point-of-care or lab test • high sensitivity
Case management Determine the presence of a disease in an individual suspected of having the disease	• With case management, multiple tools are likely to be combined. For example: asking for specific symptoms (blood in urine or stool) followed up by microscopy. • local examination • high specificity • point-of-care or lab based

Table 1: overview of different diagnostic application and corresponding requirements

What could be concluded from this TPP draft is that there is an existing frame that excludes the use of non-visual labels, probably because additional instruments are considered never to meet the other criteria.
Furthermore, in the initial draft, the topic of data collection or compliance with data systems is not even mentioned. Although the draft stems from 2021, it seems like the framework is drafted from a relatively traditional perspective. There is much focus on the performance of the RDT itself, without considering the bigger system in which it operates. This also applies to the pricing, which is is based on the current Kato-Katz-level pricing. Although it is only a framework, it implies that pricing is an absolute number, not related to the added value a different approach could bring.

REASSURED – criteria and terminology for (POC) diagnostics

In 2003, the WHO presented a set of criteria for diagnostics tests used in the developing world, especially for sexually transmitted infections and infectious tropical diseases[37]. Those criteria include the most important factors that should be considered when developing and evaluating a PoC-test: Affordability, Sensitivity, Specificity, User-friendliness, Rapid and robust, Equipment-free, and Deliverable to end-users (ASSURED). The criteria could be clustered to Accuracy, Accessibility, and Affordability. A trade-off between those factors is described by Land et al.[24]. Accessibility and affordability are often related and at the cost of decreased accuracy. Considering new developments and insights, Land et al. propose extending ASSURED to REASSURED. The R represents Real-time connectivity and the E means Ease of specimen collection and Environmental friendliness. The client of this project expressed the need for the diagnostic test to meet the ASSURED criteria and preferably the REASSURED criteria as well.

Real-time connectivity

Real-time connectivity is described as: "Tests are connected and/or a reader or mobile phone is used to power the reaction and/or read test results to provide required data to decision-makers."[20]. Real-time connectivity allows decision-makers to adjust during the intervention so that the effectiveness and cost-effectiveness can be optimized. With the data, supply chain management can be enhanced, the effect of the intervention can be measured, and the progress of the program can be tracked[14,35]. Efforts of the WHO to use real-time data for decision-making on NTD strategies have resulted in ESPEN Collect, a mobile application that is designed for field data collection regarding schistosomiasis and three other NTDs that are targeted by preventative chemotherapy[36]. The data is collected with surveys and uploaded to a central server. The data is used, among other things, for the Joint Application Package[37]. This tool is part of a joint mechanism to optimize and coordinate the use and acquisition of preventive chemotherapy for multiple diseases[13].
Another more recent development is the study by Kadam et al., defining a Target Product Profile (TTP) for a mobile app in a consensus process involving 51 relevant stakeholders. The TTP is designated to promote the development of an app that helps to interpret RDT results and ease the process of reporting, to support healthcare programs with data in their decision making[38].
An interesting concern that is described in the study is how to encourage health workers to administer the results, especially negative results. In the case of UCP-LF CAA, as will be described later in this report, the test can only be used with a scanner, which brings as an advantage that every test will be registered (if the reader is operating in a connected system)[38].

Ease of specimen collection and processing

Specimen collection ideally is non-invasive, especially for tests that could be performed by the patient itself[20]. Urine for example, is less invasive than stool or blood. Although processing the sample is routine work in laboratories, the steps required by some tests, like centrifugation, can already lead to challenges when working at the point of care. Few solutions are available for this, so the sample processing should be as simple as possible.

Environmental friendliness

Land et al. promote environmental friendliness as a factor that should be accounted for, especially with the increase of diagnostic tests being performed[20]. An example could be the increased use of paper instead of plastic in lateral flow tests, or to reduce the number of disposables (e.g. filters). However, besides the notice by Land et al., few organizations seem to already implement this factor in their consideration.

Affordability

Given that NTDs are poverty-related diseases, affordability is a key factor in diagnostics. As mentioned before, most of the diagnostics and treatments have to be funded by external parties. With limited resources, more affordable diagnostics means that you can test more people. Affordability is hard to be specified, especially because many context factors are at play, like salaries, quality assurance, and the procedure. In comparison studies, often only the costs of the materials or tests themselves are counted. This makes some laboratory procedures like the Kato-Katz method seemingly affordable. However, when taking all costs into account, RDTs like the PoC-CCA can be more affordable than Kato-Katz[39]. For schistosomiasis, a one-dollar test is considered to meet the affordable criterium. Although affordability should not be confused with cost-effectiveness, certain charac-

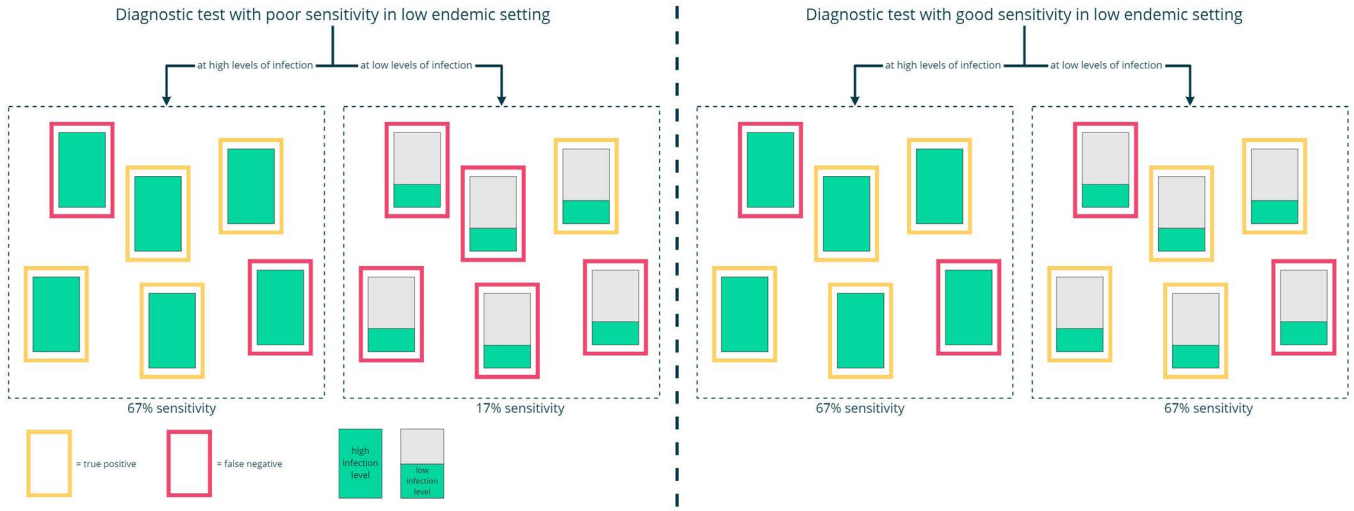


Figure 8: The diagnostic sensitivity of the test can be different at low levels of infection due to poor analytical sensitivity. At the left: a test that is not suitable for low endemic settings due to poor sensitivity at low infection levels. Right: a test that has the same diagnostic sensitivity at different levels of infections, thus more suitable for low endemic settings.

teristics of a diagnostic tool, for example, the ability of sample-pooling, or a rapid turnaround time, could lead to better cost-effectiveness at the expense of affordability of a single test.

Sensitivity

Diagnostic sensitivity is a measure of how well a test can identify true positives[40]. In other words, a high sensitivity minimizes the false negatives. This is especially an important attribute in screening purposes and schistosomiasis detection in low-endemic areas. Special care has to be taken concerning the terminology. Diagnostic sensitivity is a measure of the percentage of positive results of samples that are all infected. It only holds true for a certain infection load. That is why a test could have different sensitivity values for different infection levels (see figure 8). As opposed to the diagnostic sensitivity, analytical sensitivity and Limit of Detection (LOD) measures the ability of a test to detect very low concentrations of a substance[41,42]. In low-endemic settings, often both the infection level is low, and the prevalence is low. A test has to have a high diagnostic sensitivity to gain a reasonable predictive value (to prevent getting more false positives than true positives) and has to have good analytical sensitivity (and low LOD) to detect cases with a low infection load.In this report, the term 'sensitivity' will refer to diagnostic sensitivity. Sensitivity for low concentration or low infection intensity will be referred to as 'sensitivity in low-endemic settings'.

To evaluate a test's sensitivity, it should be compared to a so-called gold or reference standard. However, with schistosomiasis, the gold standard is microscopy, a highly specific but not very sensitive tool with high risks for human errors[43]. In studies in which new diagnostic tests are evaluated, often the new test outperforms microscopy in terms of sensitivity, which results in a skewed conclusion regarding the accuracy of the test. Quantitative CAA detection could become the new gold standard because of its high sensitivity, specificity, and relative ease of use compared to the high-performing PCR test.

Specificity

Diagnostic specificity is a measure of how well a test can identify true negatives[40]. A high specificity minimizes the false positives. This is especially important with case management to prevent misdiagnosis and a potential overlooked real cause that is left untreated. Concerning schistosomiasis, specificity is of less concern (but still important in some programmatic phases) because overtreatment does less harm than missing cases. Again, analytical specificity should not be mistaken as diagnostic specificity.

User-friendliness

User-friendliness refers to the ease of performing the test. The test "should require minimal training with no prior knowledge of diagnostic testing" and "easy to perform in two to three steps"[20]. User-friendliness is more than just a nice attribute. According to a South African study, only 3,4% of the HIV RDTs were performed according to the exact procedure[44]. This could challenge the actual reliability of the test in practice. Thus, user-friendliness is an important contributing factor to how well the test will perform in practice.

Rapid and robust

Ideally, test results should be obtained within an hour after sample collection to enable patients to be treated im-

mediately. This simplifies logistics and improves the efficiency of the program. The robustness of the test should be sufficient to withstand the circumstances of delivering the test to the point of use, including climate factors, a large time span, and mechanical stress[20]

Equipment-free

The test should be performed without any special equipment unless the equipment is portable and battery or solar powered[20].

Deliverable to end-users

The test will only be of value when there is an infrastructure and organizational structure to ensure the test can be delivered to the end-users. This can be especially challenging in rural areas.

Diagnostic tools and their performance

In table 3, an overview of the different diagnostic tools and their relative performance can be found. The different tools can be classified in different ways to determine their relative position in the field of application. One important determinant is accuracy, which is related to the sensitivity and specificity of a test. High accuracy is needed in low-endemic settings because, with low prevalence, the impact of a false-positive or false-negative on the statistical result is larger. High sensitivity is needed to detect the few cases, and high specificity is needed not to overestimate the prevalence. Low accuracy is acceptable in high-endemic areas with high levels of infection. Accuracy is also related to the purpose of the test. For case management, the tool should be sufficiently specific so that false positives do not lead to real causes being left untreated. For the stopping decision, the tool should be at least as accurate as the tool used for mapping.

Another important determinant is the suitability for field use (which is, in the case of schistosomiasis, an important point of need). For test and treat purposes and real-time mapping and monitoring, the test should be compatible to be used in the field, to ensure immediate results and to facilitate direct action. For some other applications like stopping decisions, post-elimination surveillance, or case management, field compatibility is of less importance as long as samples can be collected in the field.

The last crucial determinant is the cost of the test. Again, the target cost depends on the use case. For non-endemic settings, with no need for large-scale mapping campaigns, the cost is of less importance. For high endemic settings, the cost is important, but the return on investment is relatively high since many cases are detected or

Brief overview of important diagnostic tools for schistosomiasis		Accuracy	Accessibility	Affordability	Limitations	Description
Detecting blood in urine or stool	Questionnaires/visual inspection	Sensitivity / Specificity			Dependent on interpretation	Self assessment: ask people to the color of their urine or stool
	Reagent strip	Sensitivity / Specificity			Dependent on interpretation	Self assessment: ask people to the color of their urine or stool
Detecting eggs	Stool microscopy (Kato-Katz)	Sensitivity / Specificity			Needs skilled personnel and laboratory equipment.	Microscopy assessment of stool according to the Kato-Katz procedure. Quantitative method.
	Urine microscopy	Sensitivity / Specificity			Needs skilled personnel and laboratory equipment.	Microscopy assessment of filtered or centrifuged urine. Quantitative method.
	FECT, Mini-FLOTAC IN DEVELOPMENT	Sensitivity / Specificity			Needs skilled personnel and laboratory equipment.	Concentration method for increased sensitivity of stool analysis. Quantitative method (FLOTAC).
Detecting antibodies	ELISA/IHA	Sensitivity / Specificity			Needs skilled personnel and laboratory equipment. Cannot distinguish present from past infections.	Laboratory procedure to detect antibodies in blood.
	Western Blot	Sensitivity / Specificity			Needs skilled personnel and laboratory equipment. Cannot distinguish present from past infections.	Laboratory procedure to detect antibodies in blood.
	PoC SmCTF IN DEVELOPMENT	Sensitivity / Specificity			Not very accurate.	Finger prick RDT antibody test.
Detecting antigen	PoC CCA	Sensitivity / Specificity			Dependent on interpretation (or needs a reader). Only sensitive to S. mansoni.	Urine lateral flow test in RDT format with visual reading. Semi-quantitative.
	CAA/CCA ELISA	Sensitivity / Specificity			Needs skilled personnel and laboratory equipment. Hard to obtain the reagents needed to perform the assay.	Laboratory procedure to detect CAA or CCA antigen in blood. Semi-quantitative.
	UCP-LF CAA IN DEVELOPMENT	Sensitivity / Specificity			Needs a dedicated strip reader to be read out test and control lines. Sample preparation demands lab equipment.	(RDT) lateral Flow strip test to detect CAA in urine. Semi-quantitative.
Detecting DNA	PCR	Sensitivity / Specificity			Needs dedicated equipment and skilled personnel.	Molecular laboratory procedure to detect specific DNA molecules in blood, urine and other body fluids.
	LAMP, PoC RPA IN DEVELOPMENT	Sensitivity / Specificity			Still needs much development. Not suitable for impact monitoring.	Simplified DNA detection method that can be performed in a moderately equipped lab or even at PoC.

Table 3: a brief overview of important diagnostic tools for schistosomiasis

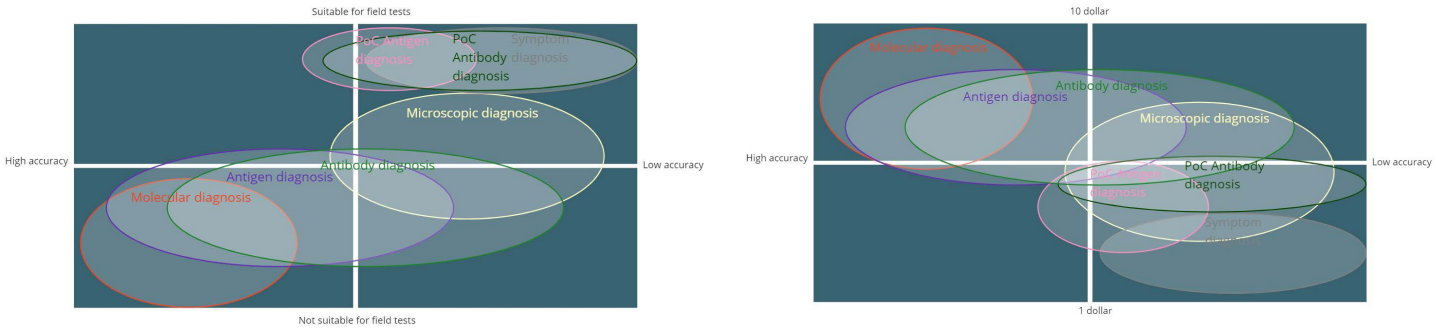


Figure 9: different diagnostic principles plotted on different axis. A gap can be seen at high accuracy, low-cost tests that are suitable for use in remote settings.

prevented. For low-endemic settings, expenditures of the diagnostics will compete with higher prioritized issues, and many tests will only result in few cases. Therefore, the cost-effectiveness of the test for mapping purposes will be of great concern.

In figure 9, different categories of tools are plotted on two different matrices. It becomes immediately clear that there is a large gap of affordable, accurate, and field-applicable diagnostic tools.

In figure 10 the important diagnostic tools are plotted on a scale of usability in endemic or non-endemic settings against the field-suitability of the test. The colors indicate the different species of *Schistosoma*. The usability of the test for endemic or non-endemic settings is not only determined by the accuracy, but also by the throughput and the ability to distinguish present from past infections.

In figure 11, the different diagnostic tools are positioned regarding their suitability for endemic or non-endemic settings at different use-cases. It becomes clear that the further one moves towards elimination, the fewer diagnostic tools are available. In a later stage of impact monitoring (when the prevalence has significantly decreased), the tool should be highly sensitive, high throughput, low cost, (semi-)quantitative, only sensitive to present infections (rendering antibody tests useless) and able to provide relevant and real-time data. Such tools are barely available or still being developed. At the surveillance stage, accuracy and sensitivity have to be so high, that a combined test is proposed by the Target Product Profile. A test with high sensitivity will be followed by a test with a high specificity to reach a combined sufficient accuracy.

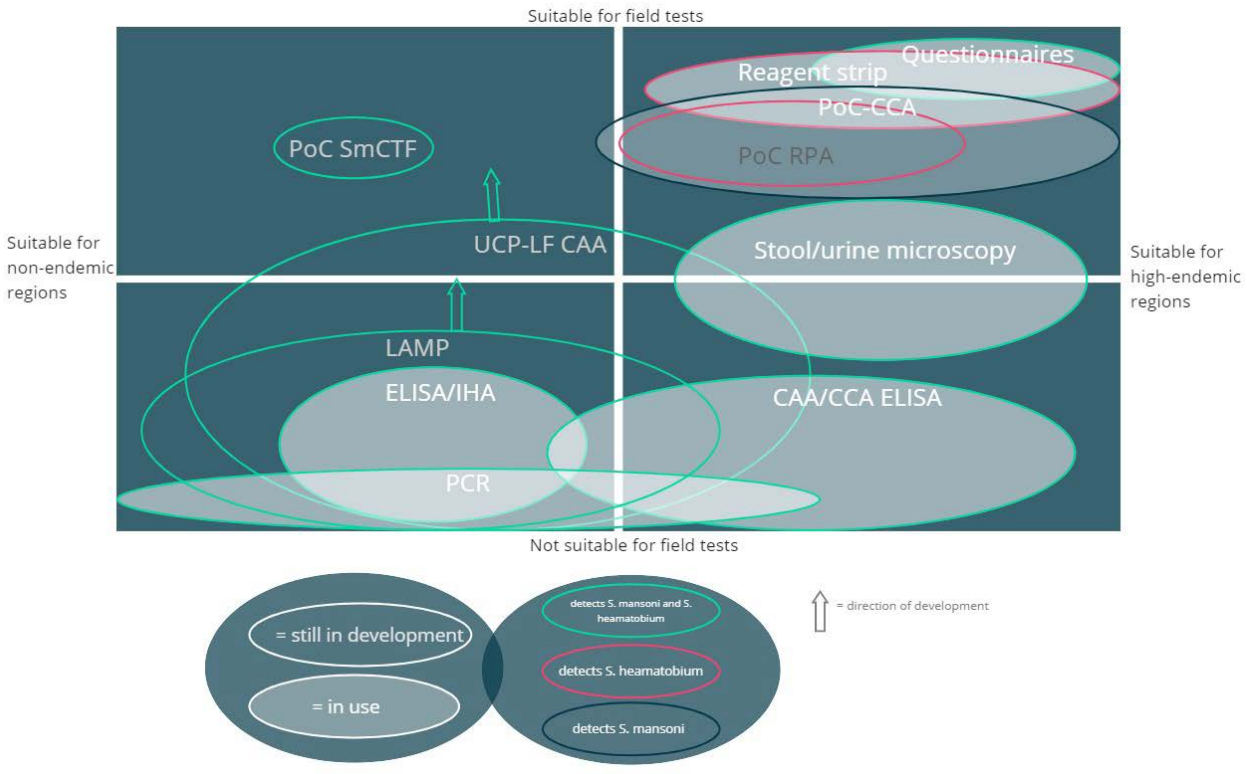


Figure 10: diagnostic tools for different species of Schistoma, including promosing tests in development (without fill).

Relevant developments

Other than the UCP-LF CAA test, which will be discussed in detail in the next chapter, certain developments are worth mentioning.

The FIND consortium, of which the LUMC is also part, is working on a fingerprick blood-based RDT to detect CAA without the use of UCP particles. The test can be read by the naked eye. Although promising (it is sensitive to all *Schistosoma* species, unlike the PoC CCA test), the test will still lack sensitivity in low-endemic settings and will not give quantitative results[45].

Smart diagnostics (see also: chapter 6)

- Algorithms can reduce human error and speed up the diagnostic procedure.
- AiDx works on an affordable smart microscope to detect schistosomiasis
- Phone-based solutions are emerging, for example, in combination with lateral flow tests

Lab on a chip (see also, chapter 6)

- Lab on a chip is a diagnostic tool in which the sample preparation and the test procedure are all being performed on one small 'chip'. For example, a drop of blood is automatically mixed with a buffer and concentrated. Then, a fluorescence label is added before it runs through a lateral flow strip. The chip can then be read out with for example, a fluorescence reader.
- Although academic demonstrations showed promising progress, the development is still in an early stage. It is challenging to keep the costs low.

Multi-disease platforms

Multi-disease platforms can detect multiple diseases with one sample. Advantages are that it facilitates the much desired integrated approaches in which multiple diseases are targeted at once. Also, it could lead to cost-savings in the supply chain and the need for additional equipment. Although promising in theory, there are some challenges to put such platforms into practice.

- It is hard to keep the costs low, and if one of the tests within the test fails, a new test has to be used.
- Testing on multiple diseases also brings a political and organizational challenge: if people test positive, you have to treat them accordingly. However, this could be logistically and financially challenging with regards to the accessibility of drugs (P. Corstjens, personal communication, 2021).
- Often, development is funded with a budget designated for a specific disease. It makes it more challenging to fund developments that serve multiple diseases (L. van Lieshout, personal communication, 2021).

Discussion and design implications

- For schistosomiasis, individual test results are of less importance compared to real-time data generation, since the treatment is classified as preventative. Even with test-and-treat strategies, only groups of people are treated when surpassing a certain threshold of prevalence (often 10%). The diagnostic tools and system have to be optimized for this kind of use.

- There are quite some effective and low-cost tools that can indicate the presence of schistosomiasis and work well in high prevalence settings, like the urine dipstick, questionnaires, or the PoC-CCA test. Also, there are sophisticated methods to detect schistosomiasis with high accuracy in a lab setting. However, tools that can provide real-time quantitative data from the field are lacking.

- Different stages in fighting schistosomiasis can be distinguished. The impact monitoring stage and the stopping decision stage are the most challenging in terms of diagnostics. It requires quantitative real-time data generation, high sensitivity in low-endemic settings, a good interface with information systems, and it needs to be suitable for point-of-care use.

- The cost of the test is a very relative attribute. Large variations can be seen in costs comparisons of different diagnostics. Often the price of the materials directly related to a single test is considered and compared, while working hours, transport, investments in infrastructure, or tooling like microscopes, are only sometimes taken into account. When it comes to the decision-maker, they often are more concerned with the purchase price of the test materials than with man-hours or equipment like microscopes. What is even more striking is that price comparisons are only based on costs, without mentioning the added value or return on investment. **This way of thinking about costs is not very beneficial for innovations aimed at value creation.** This should be considered in the proposition of the reader. For example, a proposal could include a service model that don't require investment costs. Or, it could emphasize added value instead of costs. Or cost-savings at other places of the chain.

- The question of whether the test can be too sensitive is open to debate. Not much is known about the transmission of schistosomiasis in people with low infection intensities. It might be undesirable to detect and/or treat people that are not contributing to the transmission of the disease. The threshold is not only a medical, but also a political choice, since expenses and time can only be spent once.

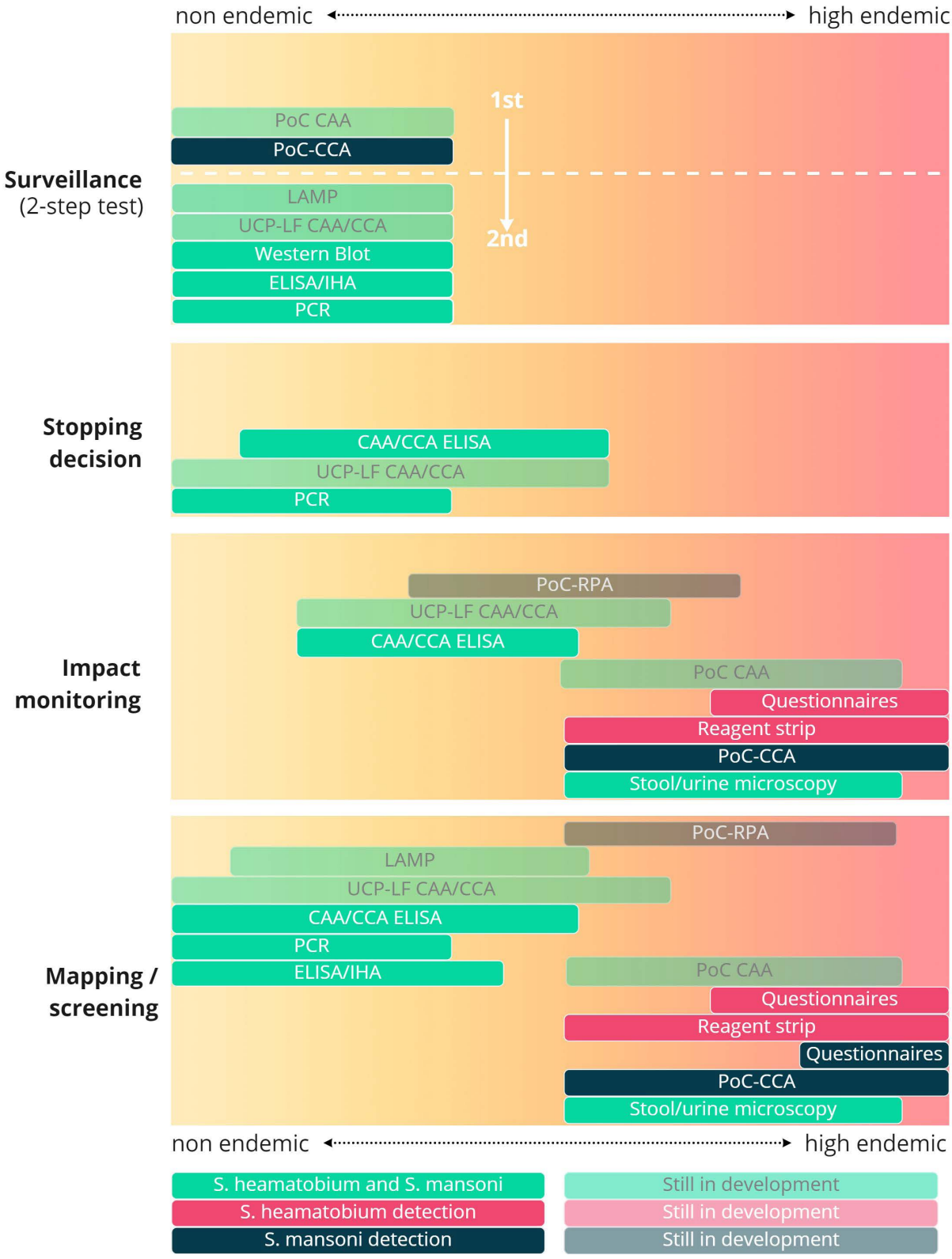


Figure 11: The available diagnostics and diagnostics in development per diagnostic stage and per species of Schistosoma. The selection is based on the requirements described in the right column.

4. UCP-LF CAA

In this chapter, the innovative UCP-LF CAA test that is being developed by the LUMC, is described. Furthermore, the potential use cases and positioning with respect to competing tests is investigated. With the help of a timeline, past and future milestones will be visualized. Understanding the potential of the UCP--LF CAA test is crucial for positioning the reader and drafting a long term strategy for the development of such reader.

The principle

UCP-LF CAA is the abbreviation of a Lateral Flow (LF) test that detects Circulating Anodic Antigen (CAA) using Up-Converting Phosphor particles. Those three components, UCP, LF, and CAA, will be further discussed.

Upconverting Phospor (UCP)

Upconverting Phosphors are particles that have unique qualities with regards to their fluorescence behavior. With many biological substances, fluorescence can be observed. Fluorescence materials emit light after having absorbed light. In nature, the emitted wavelength will be longer (= lower energy) than the excitation wavelength due to energy loss during the process.
This phenomenon is often used in bioscience to visualize the presence of a specific molecule. By using a fluorescence label, a specific substance can be detected, which is useful and commonly used for diagnostics. However, since the effect is natural to many materials, it is hard to distinguish the label from background fluorescence, which limits the analytical sensitivity of the test method.
With upconverting fluorescence, however, the material emits light with a shorter wavelength (=higher energy) than it is excited. This phenomenon is called photon upconversion (see figure 12). Because photon upconversion is not found in nature, background fluorescence can be eliminated. This allows the test to have a high analytical sensitivity.

The underlying principle of photon upconversion is multiphoton excitation. In multiphoton excitation, in contrast to the conventional one-photon excitation, two or three photons excite a molecule from their ground state to a higher state. This allows the single photon that is emitted by the molecule after having absorbed multiple photons to have higher energy, thus a shorter wavelength[46]. Multiphoton excitation only takes place when the photons hit the molecule within a specific timeframe. The chance that this happens increases according to a quadratic (in the case of two-photon excitation) or cubic (in the case of three-photon excitation) law with respect to the excitation intensity. Thus, Especially for three-photon excitation, high excitation intensities are required.

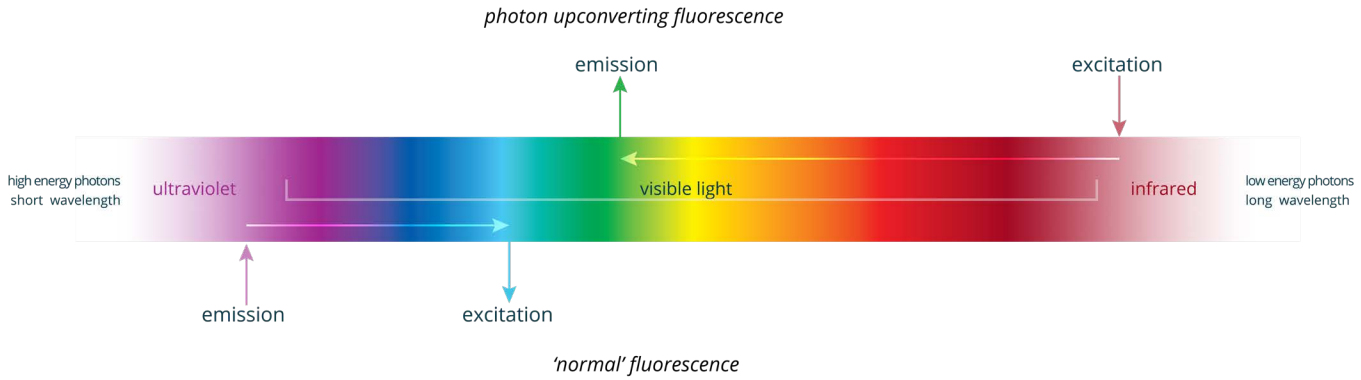


Figure 12: the principle of photon-upconversion. Low energy excitation in the infrared spectrum is converted to the emission of high energy green light. In contrast, normal fluorescence converts high-energy light to low-energy light-

Figure 13: Paul Corstjens demonstrating the principle of photon upconversion. Different UCPs are present in the tubes. The UCPs are excited with a near-infrared laser.

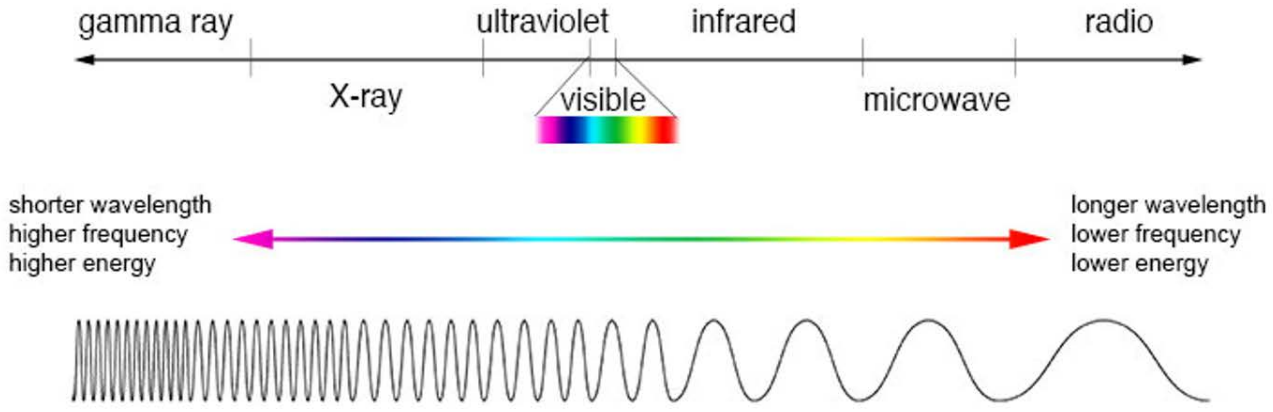


Figure 14: the entire electromagnetic spectrum, of which visible light and infrared light is a part[47].

The patented UCP particles that are used in the UCP-LF CAA test are currently Yb^{3+}-Er^{3+} ions co-doped in yttrium fluoride crystals, indicated with $NaYF_4$:Yb^{3+}, -Er^{3+} of 40 nm diameter[48]. The shape and size can be varied, resulting in slightly different characteristics. However, for this application, it is key to produce homogenous particles that behave consistently.

Lateral flow (LF)

A lateral flow test is a widely used test format that is rapid, easy to use, and low-cost. The principle relies on capillary flow, which moves the analyte across a strip that contains molecules that interact with the analyte. The test result is indicated by a colored line and can be read by eye or with a dedicated reader. Lateral flow tests are especially suitable for point-of-care use in developing countries. They can be used by untrained staff and usually do not require any laboratory equipment. Well-known examples of lateral flow tests are a pregnancy test, a COVID-19 test, and malaria test.

The later flow strip consists of different parts with their own function in the assay (figure 17). First, the sample, for example, blood or urine, is absorbed by the sample

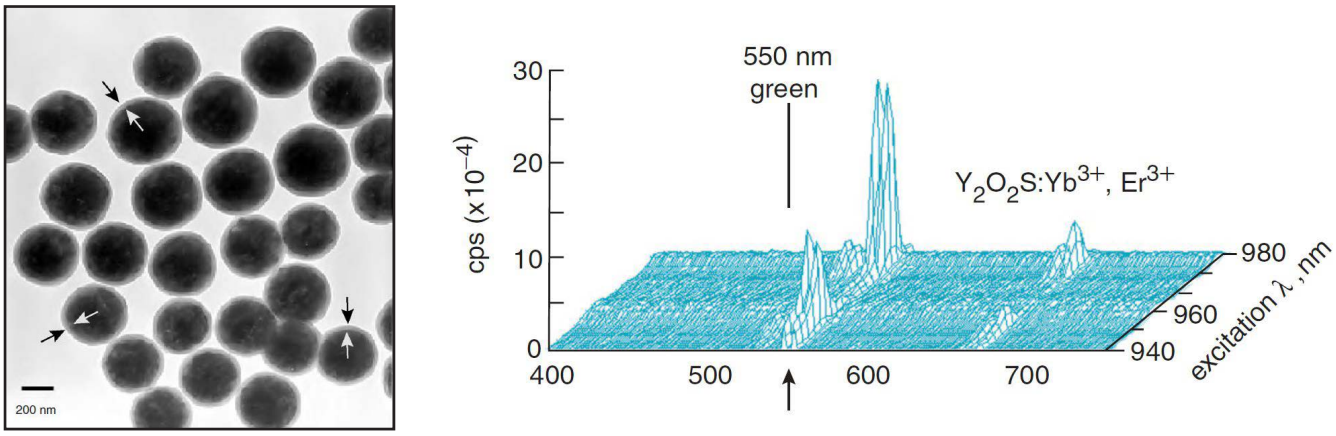


Figure 15: UCP particles (left) and their upconverting characteristics (right)[51]. Although a another crystal matrix is used, the characteristics are similar to the $NaYF_4$:Yb^{3+}, -Er^{3+}.

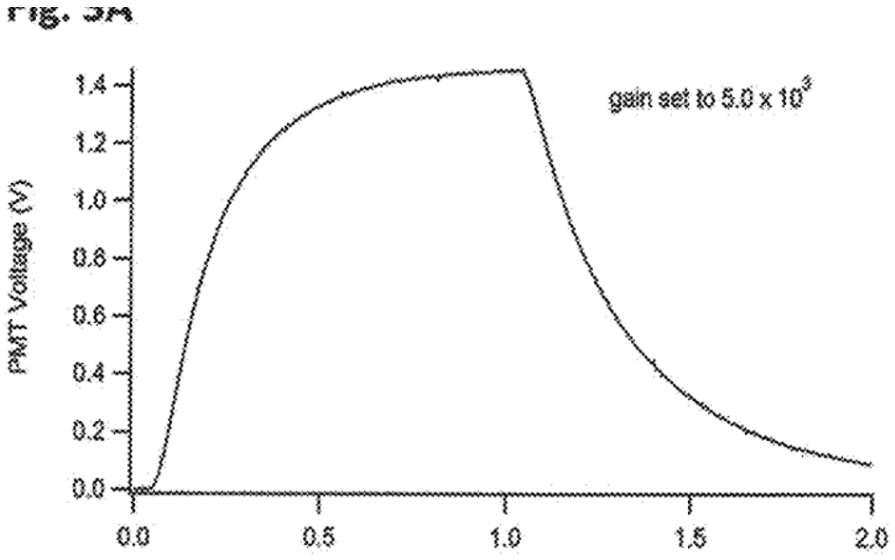


Figure 16: Emission over time of a $NaYF_4$:Yb^{3+}, -Er^{3+} particle[52].

pad. The liquid flows through the conjugate release path. In the conjugate release path, specific antibodies that are conjugated (joined) to colored or fluorescence labels are stored. If the sample liquid flow through the conjugate pad, the antibodies bind to the analyte of interest. The liquid moves further across the strip, driven by the capillary qualities of the membrane. The test line contains antibodies or antigens that react with the analyte of interest that is bounded to the antibodies. The control line binds to the remaining antibodies that are not targeted, verifying a proper flow across the test strip. The absorbent pad absorbs the remaining liquids[51].

Circulating Anodic Antigen (CAA)

The circulating Anodic Antigen (CAA) is a much-preferred analyte to detect all species of ***Schistosoma.*** CAA is an antigen-specific to the ***Schistosoma*** genus. It is excreted by the schistosomes (worms) and can be found in urine, blood, stool, vaginal lavage, and sperm. There is a relation between the amount of CAA and the number of worms, which allows doing semi-quantitative measurements on infection level. Also, CAA can be found very shortly after the first infection, making it a suitable target for early detection. When the amount of worms decreases (for example, by treatment), the level of CAA in the body immediately drops. This makes CAA a suitable analyte for distinguishing current from past infections, in contrast to anti-body detection.

Figure 17: the working principle of a lateral flow strip

Field of application / positioning

In chapter FIXME, the UCP-LF CAA test was already included in the diagnostic overview. It showed that the UCP-LF CAA test has the potential to fill existing gaps, especially when it can differentiate even more from molecular techniques by becoming more user-friendly. Ideally, UCP-LF CAA is used for mapping activities in low-endemic areas and impact monitoring of interventions. It has the desired qualities in terms of performance, but progress has to be made to make the test easier to perform with minimal training and equipment.

The advantages and disadvantages of the UCP-LF CAA test are listed below.

Specific benefits compared to other methods

- Sample can be taken at any time (in contrast to microscopy, egg variation per time of day is variable)
- Non-invasive sample material (urine, fingerprick of blood)
- The sample material (urine) can be used some time after collection
- High analytical sensitivity
- High diagnostic sensitivity in low-endemic settings
- High specificity
- Can detect all species of *Schistosoma*
- After running the test strip, the test remains very stable and can be read out even years after the test is done.
- Robust and stable, no specific circumstances are required to transport or store the test.

Disadvantages

- Cannot distinguish different species
- Cannot distinguish different species
- No other causes of symptoms can be found (unlike microscopy)
- Sample preparation steps complicate the procedure and require equipment that is hardly accessible in the field
- The result cannot be read by the naked eye

The procedure

In figure 18, the procedure of the UCP-LF CAA assay is explained. Although the procedure changed slightly over time due to further advances in the assay, the key steps remain the same. In order for the test to work, the CAA in the urine has to be concentrated. TCA is added, and the sample is centrifuged. The UCP reporters are mixed with the sample and incubation is required in a shaker or overnight. Then, the lateral flow strips are dipped into the sample and dried for 40 minutes. After that, the strips are ready to be scanned. In order to perform a quantitative analysis, reference samples have to be made every batch to compare the result with, which increases the labor intensiveness of the procedure.

A UCP-LF CAA strip reader

The lateral flow part of the strip appears white to the naked eye. When the sample has been run across the strip, no difference can be seen. This is the core functionality of the needed reader: to visualize the phosphor particles that have bound to the test and control line. This is done by exciting the particles with 980 nm light to trigger the two-photon upconversion process. The ratio between the emission intensity of the test and the control line depicts the concentration of CAA in the sample. Ironically, **reading** the emission with the device is of secondary importance since the emission is in the visual spectrum and

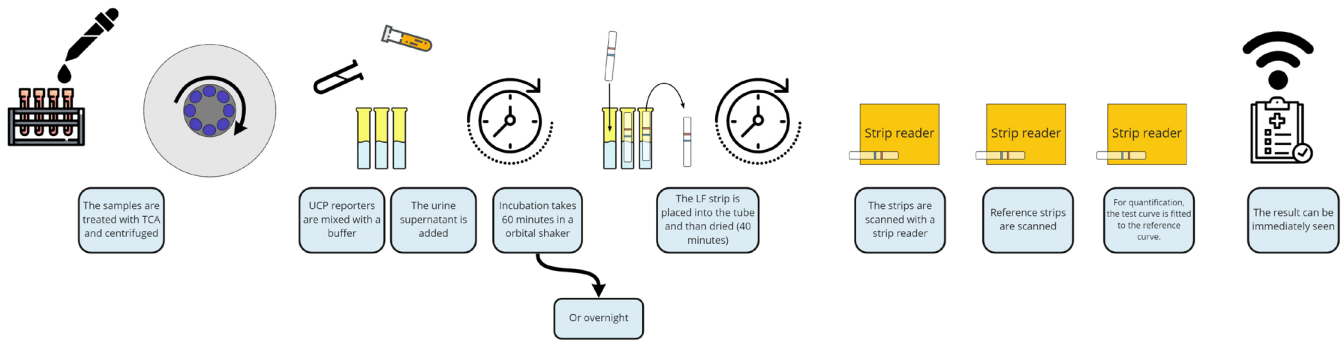


Figure 18: different steps in the UCP-LF CAA assay

could be seen with the naked eye. Although secondary, the reading is still essential. First, the concentrated light source can only excite a small part of the line, making it hard to see. Secondly, the emission intensity is low; daylight would already make the emission invisible to the eye. Third, and most important, reading the line with the reader could exploit many advantages over human inspection. Including consistent reading (no human errors), measuring very low light intensities, quantifying the results and linking the data to a connected system.

The market

Currently, no off-the-shelf readers are available that can excite UCP particles. On request, Dialunox, a German company, can modify the ESEQuant LR3 reader to be used with the UCP-LF CAA test. However, the lead times are long and the reader is considered to be too costly for schistosomiasis applications (€ 5000,- for the reader and € 15.000 for the software). Other than that, the ESEQuant LR3 is not designed to be used by an untrained person in rural settings. The LUMC also makes use of a modified Labrox reader, which is a very manual machine. The UCP-LF CAA test is not yet commercialized and the market may be too small to trigger commercial interest for companies to developed such a dedicated device.

The difference

Still, many readers exist that can scan regular RDT lateral flow tests, like the PoC CCA. Also, readers capable of scanning regular fluorescence test are available. So what makes a UCP-LF CAA reader different? Although the two-photon upconversion of the UCP particles is a form of fluorescence, the excitation and emission wavelengths are very different. Therefore, it requires other optical components (excitation and emission filters, light source). Second, the emission at a similar excitation power is much lower with UCP particles. This means UCP particles need a more powerful and sensitive system to be accurately measured than regular fluorescent particles.

Lateral flow strip readers

Though, it is interesting to take a look at the fluorescence readers. Apart from the optical system, the product architecture could be close to a UCP-LF CAA reader.
An overview of some strip readers and relevant specifications can be found in figure 19. It can be seen that all products are connected, and most of them are portable and can function stand-alone. Also, most of the readers do quantitative read-out, which means they also analyze the line's intensity, not only fail or pass. By analyzing product videos, the user interaction of almost all readers seems to leave much room for improvement. For example, by limiting the number of steps to take, provide better use cues and more visual structure. One thing is striking. Only one of the readers receives much attention from research related to NTD diagnostics: the Deki Reader. It is frequently used to study the effect of using a smart reader at the point of care, with positive results[52–55]. Although the performance was variable across the different studies, the potential of integration with data management and guiding the user in the process steps was highlighted. The Deki reader comes as a product integrated with a network mapping and monitoring tool. One difference between the Deki reader and the others readers stands out: it is produced by a company specialized in data systems and smart algorithms. Most other readers are produced by biotech companies producing lateral flow strips or advanced optical systems, adapting their systems originally developed for the western market[38].

Current developments

At the moment, the UCP-LF CAA assay is evaluated in a trial in Gabon involving pregnant women[56]. The test is used to diagnose ***Schistosoma*** infections and to monitor the effect of the Praziquantel treatment. NG Biotech is working on the commercialization of the test, which would make the test more reliable and up to ten-fold less expensive (aiming at 1 euro). The sample preparation steps remain the pressing challenge and limiting factor to make the test suitable for point-of-care use. The sample preparation requires both equipment and skills that are not likely to be present at the point of care. One solution could be using new technologies like an electrically charged metal mesh to extract the CAA in another way. Still, much research is needed. On the positive side, advances in the UCP particles themselves are likely to make the incubation step redundant.
A promising aspect of the UCP-LF principle is that it can be applied to other diseases in urgent need of diagnostics, such as leishmaniasis. Currently, other applications are being researched as well, increasing the chance that UCP-LF assays would become successful.
In the far future, UCP technology could be incorporated in microfluid chips. This would be particularly interesting because it would solve the challenge of the sample preparation

Dialunox - ESEQuant LR3

- Fluorescence scanning
- Quantitative read-outs
- Scanning with sensor
- Patented optical system can scan two wavelengths simultaneously
- High optical performance
- 1 strip capacity
- Battery powered (stand alone)
- € 5000,-
- LIS/HIS connectivity

NG Biotech - NG Reader

- Colometric scanning
- Quantitative read-outs
- Scanning with camera
- Interface via phone
- Connected to cloud system
- Multiplexed strip scanning
- 1 strip capacity
- Battery powered
- Produced by company that makes lateral flow tests

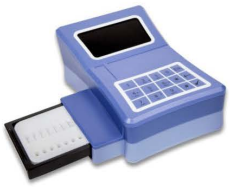
Biosynex - BSX reader

- Colometric scanning
- Scanning with 5 MP camera
- Connected to cloud system
- Produced by company that makes lateral flow tests
- LIS/HIS connectivity

Weldon Biotech - iChroma II

- Colometric scanning
- Quantitative read-outs
- Connected to cloud system
- Produced by company that makes lateral flow tests
- LIS/HIS connectivity
- User interface expansion via Android

Chembio - opTrilyzer



- Colometric scanning
- Quantitative read-outs
- Connected to cloud system
- Multiplexed strip scanning
- Battery powered
- Produced by company that makes lateral flow tests

Chembio - Cube reader

- Colometric or fluorescence scanning
- Quantitative read-outs
- Camera based
- Very small
- Connected to cloud
- Battery powered
- Produced by company that makes lateral flow tests

Deki reader

- Colometric or fluorescence scanning
- Designed for point of care (indoor)
- Camera based
- Connected to integrated data system
- Battery powered
- Produced by company that makes data systems and smart algorithms

Figure 19: overview of lateral flow strip readers

Discussion and design implications

- Lateral flow is a suitable test format for point-of-care settings
- The antigen CAA is a very suitable analyte for mapping and monitoring purposes. It has a direct correlation with the number of worms, making quantification possible. It disappears from the body after worms have died, making it suitable for endemic regions (you can distinguish current from past infections). All ***Schistosoma*** species excrete CAA so that you can detect all species with one test. It is specific for ***Schistosoma*** so that the test can have high specificity. And last, CAA can be extracted in a non-invasive manner via urine or blood.
- UCP particles allow for a very low limit of detection of CAA, because of their unique qualities. This makes the test suitable for low-endemic regions and monitoring purposes. Furthermore, UCP particles and CAA are very stable and can be read out months after the test is completed.
- A high-power concentrated light source is necessary to visualize the presence of UCP. Reading the emission with a reader utilizes the potential benefits of the UCP-CAA combination most, like high sensitivity, automatic interpretation, and real-time data sharing.
- There are no readers on the market that could unlock the potential of UCP-LF CAA. Only modified readers can be requested, which lack the affordability, the integration with a mapping tool, ease of use, and the suitability for remote settings.
- Similar readers for non-UCP lateral flow tests are mostly not equipped for these needs as well. The one that stands out, the Deki reader, is promising because of its integration with data systems and ease of use. It is the only reader that is designed as a product-service system.
- The connectedness of a reader does not create value on its own. It should be connected to and integrated with a relevant system for mapping and monitoring purposes. Most readers are compatible with the laboratory information system or the hospital information system. One could question of those systems are the right way to go for large-scale programs.

Part 2

5. A systemic approach

This chapter outlines the theory of systemic design thinking and connects it to an approach for this particular project.

Approaching complexity

Solving problems does not seem to contribute to a less complex world. In fact, the world, and the problems it is facing, seem to be more complex than ever. New ways have to be found to deal with this complexity. According to the design theorist Kees Dorst, the world is complex, open, dynamic and networked[57]. It means that "a small local action can lead to an incredibly complex chain of effects". There are no clear borders of what belongs to the system, and the system is in constant movement. Problems can not be isolated because they exist in networked structures.

Dorst points out that there is only one form of reasoning that applies to complex problems. He calls it design abduction (see figure 20a)[57]. In design abduction, only a desired outcome might be clear, but the what (elements) and the how (pattern of relationships) are unknown. To approach such a situation, the what, how and outcome have to be co-developed by experimentally frame and reframe the situation. Those frames propose a hypothetical relationship that leads to the outcome, see figure 20b. Once the what, how and outcome are in place, deduction can be used to validate the frame.

Dorst proposes a new paradigm to solve truly complex problems. He argues that we should step away from trying to find a solution, because in complex problems, there is no fixed solution. Instead, we should try to change the system by interventions that bring the system closer to a more desired state[58]. The system is not analyzed by traditional mapping, but by bringing the system in movement ("kick the system"), so that important relationships become apparent. This incremental approach should be performed in continuous reflection to adjust our goals and frames on the way.

Eisenstein, a mathematician and philosopher, argues that we should not change the system but change the narrative, because systems are build upon those narratives[59]. A new narrative is able to show what is wrong with the current narrative, and proposes a better one.

In architecture, similar movements related to systemic thinking emerge. "regenerative practice is not about the performance of the object, but about how the process of designing and delivering that object acts as a catalyst for change and developing potential"[60].

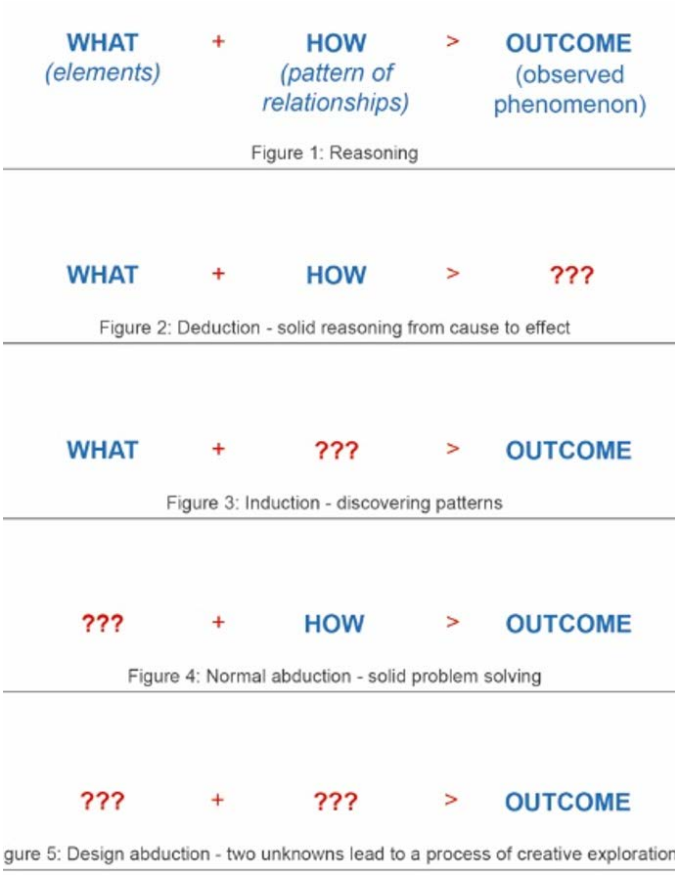


Figure 20a: The logic of creation – Design Abduction, by Kees Dorst[56]

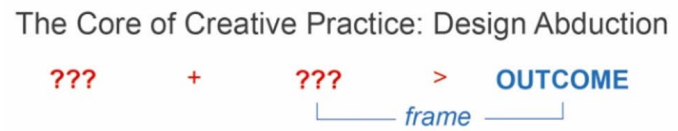


Figure 20b: The logic of creation – Design Abduction, by Kees Dorst[56]

Approaching this project

First of all, it should be determined whether this project is occurring in a complex situation.

The initial project's goal was:
Improving the accessibility of circulating antigen-based diagnosis of schistosomiasis, leading to more precise and efficient mapping of the distribution of Schistosoma infections within endemic regions and better monitoring of intervention and control programs.

With as objective: Exploration and conceptualisation of a UCP-LF CAA strip reader as part of a product-service-system with real time data collection.

The problem was not described as a complex, open, dynamic and networked challenge, in order to narrow the scope down to a manageable project. However, when working on the project, more and more of these elements came into play. For example: the dynamic context in which COVID-19 is rapidly changing existing systems. Or the networked nature of the problem, having many stakeholders on different levels involved. Or the openness of the boundaries of the system, in what way does this project contribute to the higher aim of developing health care?

The systemic design theory is used as a reference for the approach of this project. Thus, the outcome, the what, and the how should co-evolve.

The following questions will be addressed in the coming chapters:

- What is the more desired situation (outcome) that we want to move towards?
- How could we move towards that more desired situation (framing)?
- What is needed for that?

Although this report will describe the process quite orderly, in reality, the what, the how and the outcome evolved throughout the whole project, from the start to the end and probably beyond.

A close example of such a intervention that leads to incremental system change, is the commercially available DEKI reader (figure 21). It is a mobile medical application that reads and interprets RDT tests and uploads the results to the cloud. Multiple studies were done to validate the use in context[52]. In one of those studies, the reader was even customized to provide feedback to the community health worker, permitting the evaluation of the community health worker's skill level and providing a learning experience by giving relevant feedback[61]. Findings show that the DEKI reader could improve the quality of community testing by not only standardizing the read-out of the test, but also by giving real-time feedback to the community health workers. This provides a new frame or narrative on the use of such readers in context. Another innovation that builds further on the DEKI reader is the Connected Dx project. It integrated the DEKI reader in a service system that provided the user with

Figure 21: The Deki reader[61]

6. The system in transition

We now have an overview of the separate components and the challenges that arise in the context of schistosomiasis. This chapter will bring these components together in four levels of abstraction. On every level, different desired directions of change are formulated. The different transitions carry risks and opportunities that could steer away from the system or could bring the system closer to the desired state. This approach will aid the positioning of this project, targeting specific changes with specific interventions.

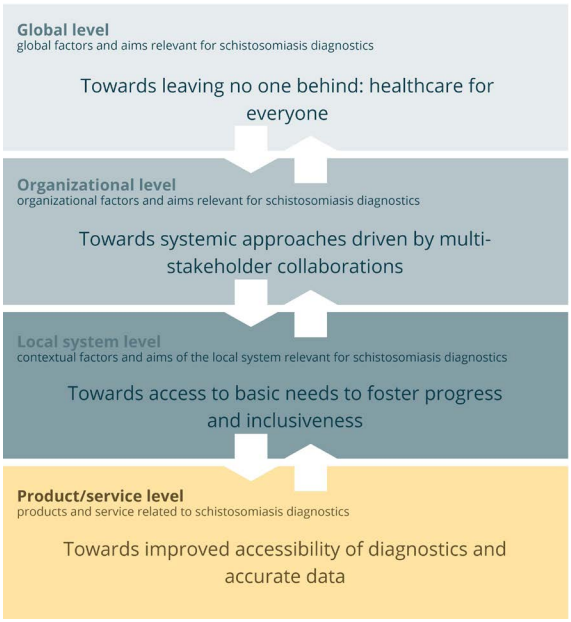
The four levels of abstraction

The overview of the different levels of abstraction and the desired change can be found at the right. The levels ought to cover the system of schistosomiasis diagnostics in a holistic way.

The levels ought to cover the system of schistosomiasis diagnostics in a holistic way.

The relation between these levels can be found with progressive abstraction: transitions below contribute to the transitions above. Moving downwards the levels, you find means, moving upwards, you find the 'why'.

The desired directions of change are abstracted from different factors that are described in more detail in the next paragraph.



Global level

Towards leaving no one behind: healthcare for everyone.

The world is facing two major crises at the moment: climate change and the COVID-19 pandemic. What they have in common is that they both disrupt existing systems and that they impact the poorest communities most[63,64]. Universal Health Coverage (UHC) is an important step in fighting this inequity[65–67]. It means that basic health services are accessible for all, without suffering financial hardship by paying for them. Currently, not even half of the world population is covered by essential health services[65]

"100 million people are pushed into poverty each year through out-of-pocket health spending" [67]

The multi-stakeholder platform UHC2030 uses the following key principles for their action[66]:

- • Leaving no one behind: a commitment to equity, non-discrimination and a rights-based approach
- • Transparency and accountability for results
- • Evidence-based national health strategies and lea-

dership, with government stewardship to ensure availability, accessibility, acceptability and quality of service delivery
- • Making health systems everybody's business – with the engagement of citizens, communities, civil society and private sector
- • International cooperation based on mutual learning across countries regardless of development status and progress in achieving and sustaining UHC, and development effectiveness principles.

Unfortunately, COVID-19 puts the goals for UHC under pressure. Economic fallback is expected, as described in the next paragraph.

The impact of COVID-19

For the first time in modern history, a global pandemic puts the entire world to hold. The COVID-19 pandemic has drastically changed future perspectives of countries, organizations and individuals. Looking at the numbers, in African countries, the infection and mortality rate of COVID-19 remains relatively low, see figure 22. For Africa, the biggest threat does not come from the virus itself, but from the economic and societal consequences in the coming decades. A scenario analysis to 2030 finds that much of the progress made in the last years fighting poverty will be reversed due to the consequences of COVID-19[68] (see figure 24)

Not only an increasing amount of individuals will be challenged by poverty, Sub-Saharan African countries and the private sectors are also facing debt increases[70]. Financial restrictions will further limit expenses to universal access to health care, clean water, and other basic infrastructure. "Fragile and conflict-affected states are expected to be hit particularly hard" based on the World Bank forecast[71].

When moving the scope from the future to the present, one can see severe disruptions due to COVID-19 in health care and national health programs. Various factors contribute to this, including personal financial constraints, disrupted supply chains, and people refraining from health check-ups due to COVID-19[72]. The disruption of health programs, like distributing mosquito nets or AIDS treatment, is expected to have a big impact.

The Global Fund calculated COVID-19 could result in a setback of 10 and respectively 20 years of progress of fighting HIV, tuberculosis, and malaria, causing 1.4 million additional deaths in 2020[8]. Also, health services for NTDs are disrupted on a large scale. "The delays expe-

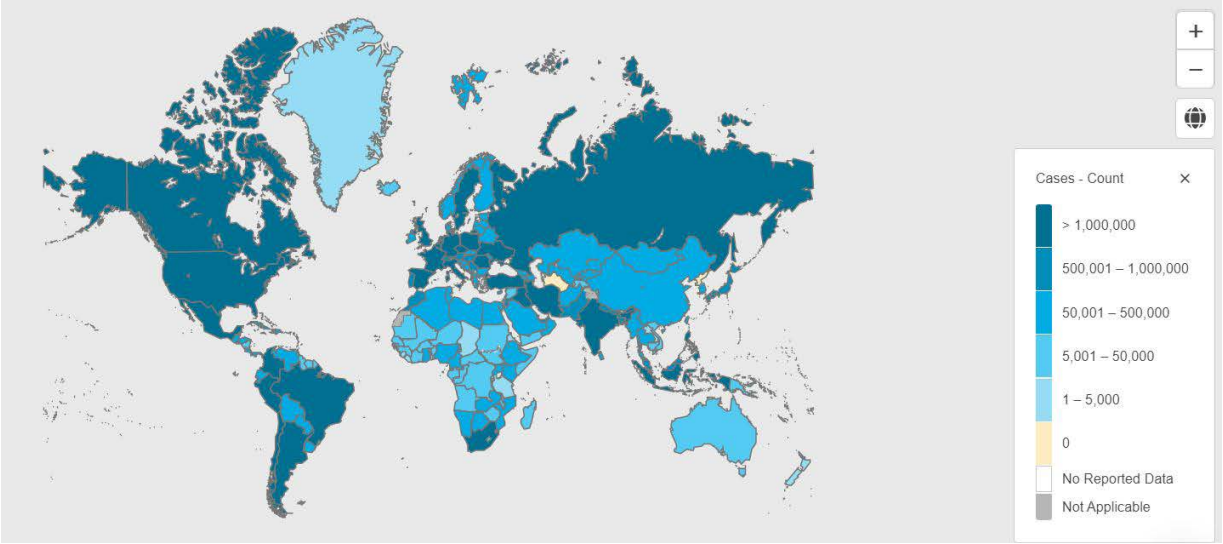


Figure 22: Global COVID-19 case count according to the WHO dashboard on 5-6-2021[69].

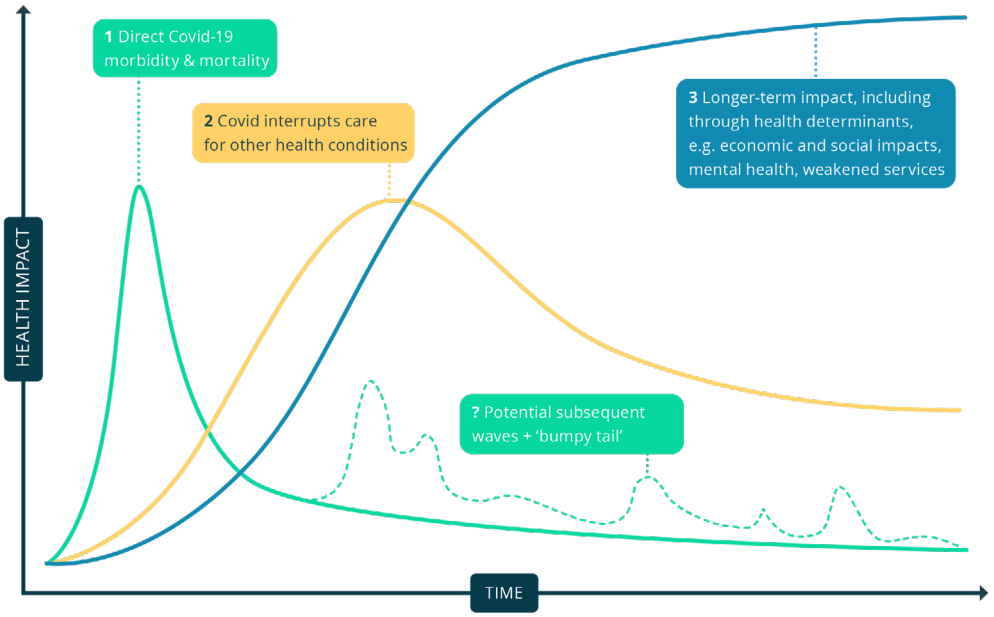


Figure 23 Illustration of impact of COVID-19 on health, adapted from Universal Health Partnership[63]

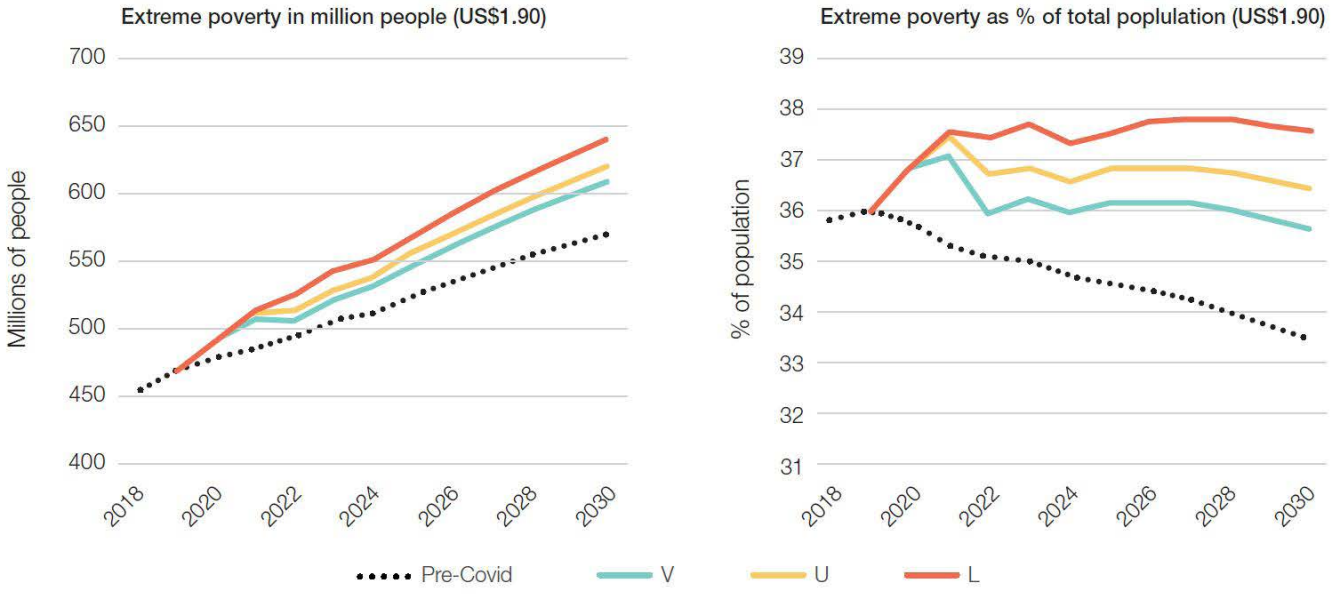


Figure 24: extreme poverty is expected to signifcantly increase due to COVID-19. V, U and L represent different scenarios[68].

rienced in diagnosis, treatment, and care, and also in manufacture, shipment, transport, and delivery of donated medicines, are significant."[73]. The impact of the disruption of an MDA differs per disease. Specifically for schistosomiasis, the impact is relatively high because of the short lifespan of the worm and the high transmission rate (see figure 25)[74].

In a call for action signed by world leaders from Europe and Africa, the message was that the world cannot end the pandemic without winning the COVID-19 battle in Africa[75]. Unfortunately, this call did not lead yet to a succesfull vaccination campaign in Africa. Only 3 out of 100 people have been vaccinated in Africa, compared with 59 out of 100 in Europe[76].

Opportunities of COVID-19

The severe impact of COVID-19 highlights the existing vulnerability of Sub-Saharan African countries, particularly with respect to the strength of the health care system. The call for UHC is stronger than ever (26)[77,78]. This could provide an extra incentive to make changes to a system in crisis. Some of those changes can already be seen. For example, medical drones are emerging, and even The African Drone and Data Academy in Malawi has been recently opened[79]. E-health is expanding, creating opportunities for access to (specific) expertise, improved efficiency, new business models, and more.
Other opportunities arise from the disruption of MDAs.

Figure 26: UHC is pushed by governements forced by the COVID-19 pandemic[78]

By monitoring the effect of the disruption, relevant data can be acquired about the impact of the interventions and the accuracy of the predictive models[74]. Also, the disruption requires organizations to revisit their strategy, which could lead to new opportunities.
Apart from healthcare-specific advances, COVID-19 could accelerate Africa's digitization, "establishing new work practices and cultures in the process"[68]. This digitization is also seen in education, where it could make education possibly more accessible to some.
Last, the global need for rapid diagnostic tests for COVID-19 could lead to new innovations or further development of existing technologies. For example, the suitability of UCP for COVID-19 test is studied, which could boost the adaption of UCP as a suitable reporter label.

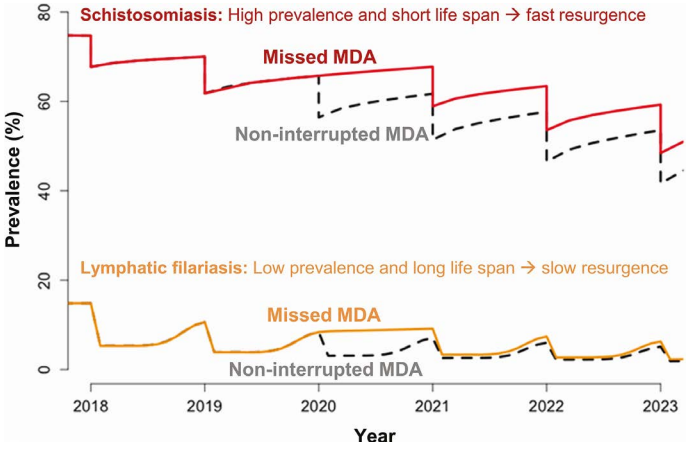


Figure 25: projection of the impact of missing a round of MDA for schistosomiasis compared with lymphatic filariasis. The missed MDA has a larger impact on schistosomiasis prevalence because of the higher tranmission rate and shorter lifespan of the worms[74].

Climate change

As aforementioned, climate change is another crisis that As aforementioned, climate change is another crisis that puts the UHC goal at risk due to economic stagnation and increased poverty[80]. Besides that, climate change is likely to affect the geographic location that diseases thrive. Models predict that schistosomiasis moves to new areas, possibly even leaving areas that are now at risk behind[81]. This creates the need for surveillance and response systems to closely monitor areas at risk of becoming endemic by climate change[81]. This development could trigger further advances to diagnostics capable of surveillance. Furthermore, multiplexed surveillance could address multiple diseases, increasing cost-effectiveness.

Organizational level

Towards systemic approaches driven by multi-stakeholder collaborations.

Organization: Towards systemic approaches driven by multi-stakeholder collaborations	Transition: Current situation	Transition: More desired situation	Relevant factors: Emerging challenges	Relevant factors: Emerging opportunities
	UHC with little political priority	Political commitment and leadership for UHC		The importance of UHC is once again highlighted by the COVID-19 pandemic.
	Single issue approaches	Systemic approaches	Systemic approaches need new ways of working together, communication and leadership.	Multiple issues can be targeted in one approach, resulting in a more effective and efficient execution.
	Poorly informed decision making	Data driven decision making	Privacy concerns arise when personal data is collected. Also, the selection and interpretation of data has to be done carefully and ethically.	
	Reactive interventions on schistosomiasis	Structural surveillance for schistosomiasis	Structural resources and alertness are prone to decline if no or little cases are detected.	
	Schistsomiasis control	Schistosomiasis elimination	When moving towards elimination, the interest and focus on testing/control could decline, both on political as community level. / With lower prevalence, it is more challenging for diagnostics to be cost-efficient	Elimination requires integrated approaches, not only addressing treatment, but also basic needs. Local communities could benefit on multiple levels.

As already mentioned, political priorities have to shift to close the gap towards universal health coverage. But above that, the whole approach should move to a more holistic or systemic approach[65,66,75,77,82]. Vertical interventions can be effective for controlling one disease, but systemic change is needed to end poverty-related diseases and to realize UHC[12].

This systemic change is one of leadership and new partnerships, addressing health as a global issue. Multi-stakeholder collaboration refers to collaboration on every level, from communities to politics to the private sector[5,83]. This would allow business models, technologies, policies and supply chains to co-develop to ensure integrated, cross-cutting approaches.

Data-driven decision making

Many experts agree on the importance of electronic data capturing and analysis in decision making, which is further highlighted in the WHO 2020-2030 roadmap for NTDs[4]. So far, most mapping efforts have been reported on paper, increasing the administrative work, creating delays, risk of errors and loss of data.

Less consensus can be found on which data is exactly needed for decision-making.

From a scientific point of view, more data give more opportunities to investigate contextual determinents, to link data-sets to each other and create predictive models

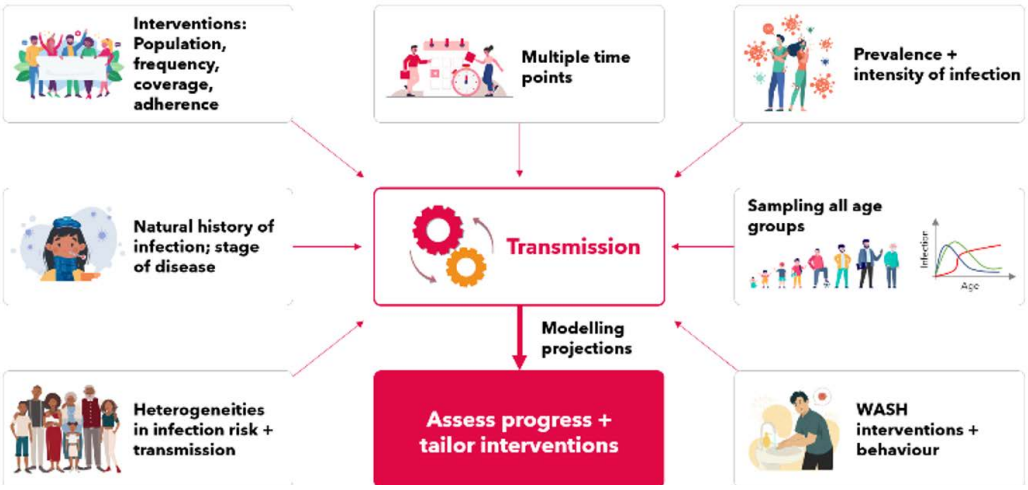


Figure 27: The NTD Modelling Consortium described the key data that are needed for better assessment and tailoring interventions. It is clear that also contextual information is needed[87].

for other disease. For example, data collected for malaria, HIV or TB could be appropriate for estimating the prevalence of certain NTDs[84,85].

From a practical view, the more data has to be submitted, the higher the chance that the data is not submitted by the busy health care workers[38].

From a privacy stance, the less data is collected, the better, especially when the data is not essential for the primary need.

But for ethical reasons, personal data should be collected to better understand inequities that are currently still present in the targeting of people[86].

There is no straightforward answer for which data should be collected in practice, but the advised approach would be: extensive stakeholder engagement, focused on communities' and peoples' needs.

An effort of such a multistakeholder approach was made in 2020. A multidisciplinary group of experts reached a consensus on a target product profile (TPP) for electronic clinical decision support algorithms. It points out the need for human-interpretable and evidence-based algorithms, taking into account contextual information. With regards to data privacy, the implementer should make sure that it complies with local legislations[88]. Although the TPP being general, it is a first step towards global agreements. In a similar collaboration in 2020, experts agreed on a TPP for mobile apps that read rapid diagnostic tests[38].

These events demonstrate the emergence of smart diagnostics and data generation and interpretation as a well-established future perspective.

From control to elimination, from interventions to surveillance

As described in chapter FIXME, goals have been shifted from schistosomiasis control to schistosomiasis elimination. Once areas have fully eliminated schistosomiasis, the focus of the programs will shift to surveillance. Previous experiences have learned that this is a challenging phase from an organizational perspective. Donors, who largely fund such programs, have to be prepared to sustain their contributions after elimination, which has been poorly communicated[86]. Also, political and community priorities are prone to shift away from the surveillance activities once the disease is no acute threat anymore[22].

Local system level

Towards access to basic needs to foster progress and inclusiveness.

Social factors in combating schistosomiasis

In literature, the social factors of schistosomiasis and diagnostics are underreported[22]. Still, it is very important to be aware of the social forces at hand, since they can enable or disable the effectiveness of interventions. More importantly, even when interventions are effective in terms of prevalence of schistosomiasis, the overarching goal to achieve is improving well-being, not just disease eradiation. People suffering from schistosomiasis and poverty, do not only face health and economic deprivation. Poverty is an assault on human rights in multiple aspects, including but not limited to deprivation of civil and political rights and the right to education, and suppression of the autonomy of a person[89,90]. Thus, one should be careful not to fixate too much on fixing one aspect (e.g. stopping transmission), while compromising on another (e.g. decision power, equity).

To bring this back to schistosomiasis diagnostics: it is important to involve the community in such way that the willingness to participate is high and equally distributed. It is advised and ethical to let the community participate in decisions[22].

The willingness to participate can be rather low, especially amongst women. One suggested reason is existing stigmas, but women may also lack the autonomy to travel to health facilities, or may lack time due to household chores[22]. Girls at an Egyptian school were reported to be underrepresented due to a lack of privacy with regards to the specimen collection[22]. An interesting opportunity to involve the community is by sharing test results with the individuals in a well-thought way. This is not always included in test strategies, and could hinder people's willingness to participate in future research, and is a missed opportunity for health education[22].

Another example of ethical/social consideration is the early approach for preventative treatment against onchocerciasis, which was known as community-directed treatment. The community had a high-level decision power and autonomy. However, when emphasis shifted from national control to global elimination, the execution became more centralized. The autonomy and participation of the community were reduced, leading to power imbalances[86].

This project explores a connected strip reader to facilitate data-driven decision-making. Bulk data does not only contain privacy-sensitive data, but is also stripped from subtle context-specific nuances. It is key to ensure the data is valid and correctly interpreted and that data-driven decision-making strengthens, instead of overruling, partnerships with local communities. Secondly, this project focuses on the accessibility of a diagnostic test. However, accessibility is worthless without engagement from the participants, which should be of concern as well.

"The contribution of social sciences will not make schistosomiasis research and control any simpler – but then again, it never was simple. Schistosomiasis is a complex phenomenon that cannot be addressed with technical fixes or magic bullets (Reich, 1988; Cline, 1995), and it appears that interventions need to shift from product-based to knowledge-based approaches"[22]

Digital health (e-health, m-health)

In recent years, digital health innovations have become

an emerging field in Sub-Saharan Africa. The traditional, poor functioning healthcare system leaves a large gap of unfulfilled needs, in which innovative digital solutions can unfold. An important factor is the rapid rise of smartphones. It not only gives users the ability to connect and rapidly share information, but it also gives access to the mobile money market. The mobile money market is dominating in Sub-Saharan Africa and still rapidly expanding, further accelerated by the COVID-19 pandemic[91]. These innovations might be driven by technological advances but also unlock new business and organizational models. The Connected Dx project, as described in chapter 4, is a good example of this.

Although many indications point to the rapid rise of e-health in Sub-Saharan Africa[92–96], a systematic review concluded: "E-Health is evolving in sSA, but with poorly published evidence"[97]. Little overview exists on the current developments, which are mostly evolving from private initiatives. The World Health Organization came up with a global strategy (2020-2025) only this year, illustrative of the slow adoption by prominent institutes.

Different categories of e-health can be distinguished, such as, but not limited to: telemedicine, health IT systems, consumer health IT data, big data systems and mobile health. The common ground is the use of the internet and related (information) technologies to enhance healthcare[98].

Although digital health could potentially make health services more accessible for many people, another substantial part of the population could be excluded from it, enlarging existing divides. A lack of access to the internet or electricity, low (digital) literacy or limited content in the local language could be substantial barriers to digital health care.

Even more worrying, existing gender and urban-rural divides in accessibility could further deprive the ones that are already disadvantaged[95]. In 2017, only 1 in 5 people in Sub-Saharan Africa used internet[99]. Although the share is rapidly increasing, the numbers remain far lower than in the rest of the world. Especially internet access in regions outside the capital city tends to be lagging.

A lack of access to electricity is a key barrier constraining access to the internet among poor Africans[99]. Internet is mostly accessed via mobile phone. However, Sub-Saharan Africa has the world's worst mobile gender gap: "women are 13% less likely to own a mobile phone than men"[100]. Another potential issue for digital health could be the fact that 45% of the people in Sub-Saharan Africa lack a verifiable digital identity, compared with 15% in Middle-East and North-Africa[101].

	2019	2025
Mobile subscribers (percentage of population)	45%	50%
Mobile internet users (percentage of population)	26%	39%
Smartphone connections(percentage of total connections)	44%	65%

Table 4: Predicted mobile phone and internet use in 2025 in Sub-Saharan Africa[101].

Product-service level

Towards improved accessibility of diagnostics and accurate data.

Product/Service: Towards improved accessibility of diagnostics and accurate data	Transition: Current situation	Transition: More desired situation	Relevant factors: Emerging challenges	Relevant factors: Emerging opportunities
	Laboratory diagnostics	Point-of-Care diagnostics	Point-of-Care diagnostics are often used by people with limited training. Misuse or interpretation could give inaccurate or unreliable results.	Point-of-care diagnostics can greatly expand the reach and accessibility of health care and generate relevant data for decision makers and researchers.
	Poor accuracy of PoC diagnostic in low prevalence settings	High accuracy of PoC diagnostics in low prevalence settings	More knowledge has to be gained on the relation between infection intensity and risk of transmission to determine the most efficient strategy.	High accuracy quantitative diagnostics can help to understand factors related to transmission.
	Manual and limited data sharing	Automatic cloud based data sharing	The privacy of people is a big and important risk that has to be taken into account. Also, a lack of internet access could hinder point-of-care use.	Big data could provide many new insights in the social and demographic risk factors of schistosomiasis. Also, it allows for real-time monitoring and decision making.
	Diagnostics prone to human error	Human error in diagnostics is reduced	Human skills like microscopy examination are getting redundant and lost.	Smart devices like a strip reader could decrease the risk of human error, increasing the reliability of the test.
	Diagnostics as a product	Diagnostics as a service	Multiple service systems are used in parallel, increasing workload, errors or costs.	Connected (smart) diagnostics enable new service models, in which for example the data and the diagnostic system are integrated in one service subscription.

Many of the elements on the product-service level have been described in the above paragraphs. Some specific elements will be highlighted below.

Smart diagnostic connected devices

Smart diagnostic devices use artificial intelligence to detect or predict the presence of a disease. This could be by automatic in-vitro analysis, by measuring physical circumstances in the body, or by interpreting the test result of a secondary test, like an RDT. Even body movements and facial expressions can be interpreted by smart devices for diagnostic purposes. The field is rapidly evolving, with for example, wearables as a broadly accepted consumer product.

The most interesting application for schistosomiasis is either performing direct sample analysis or indirect RDT readouts. In the past years AiDx have been working on various smart optical instruments for detecting malaria and schistosomiasis, using image processing. Other instances have been working on similar devices, often based on smartphone cameras. Commercially available devices for the point-of-care capable of direct sample analysis don't exist yet but might be close to reality.

Readers capable of reading RDTs are already common, although often not intended for the remote settings that are relevant for schistosomiasis diagnostics. The readers do not outperform trained humans and the user interface could be hugely improved[52]. However, much potential lies in reducing human errors, automating data generation and sharing, and performing quality control on the RDT and the user.

Developments that are still in an early stage of development concern multi-disease platforms, that optimally support integrated approaches targeting multiple infectious diseases. Such formats could make use of the lab-on-a-chip principle, which is supposed to perform many operations to detect multiple analytes, all integrated on a single chip (figure 29)[19]. The chip is equipped with valves, fluid microchannels, conjugate pads and testing mechanisms which all work in conjunction to perform complicated sample preparation and analysis without human intervention. The chip is expected to be read out with an external device, which could for example, be a fluorescence reader. In the near future, the lab-on-a-chip will be out of reach for point-of-care applications in Sub-Saharan Africa due to the high costs. Nevertheless, such portable integrated platforms, that can serve multiple NTD programs at different stages at the same time, remain a goal to work towards[19].

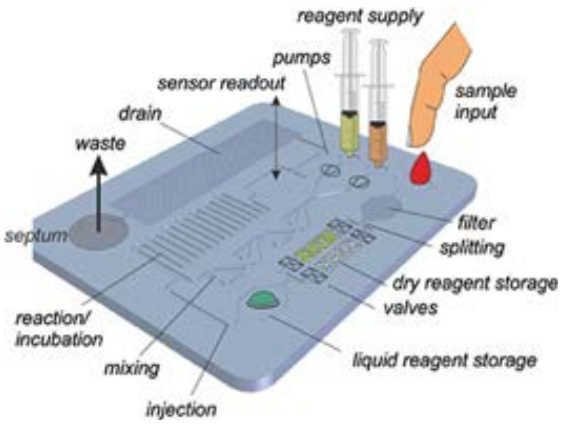


Figure 29: illustration of a lab-on-a-chip[102]

To connect such devices, one could not only rely on a wifi network. Internet of Things (IoT) connections in Sub-Saharan Africa account for only 1% of global cellular (via SIM card) IoT connections[101]. Most of the cellular IoT connections can be found in South Africa, followed by Nigeria. Still, a further increase is expected. In Kenia, a narrow-band IoT network is being installed to serve IoT applications. Now, one of the applications is monitoring water supply to health facilities to ensure adequate supply[101].

Data management platforms:

The data that is generated and shared by smart diagnostics must be brought together for further use. Because policies or frameworks for such platforms do not exist yet, many different platforms are in use. One organization that is much involved with developing such platforms is eHealth Africa. The company has more than 500 full-time employees and executes projects for governments, NGOs and other national and international institutions[94]. They run a free, open-source development platform to enable organizations to build data solutions for e-health[103].

Fionet is a company that offers a testing and tracking platform, specially designed for large-scale RDT programs. It combines the Deki RDT reader with a network platform. The platform is also capable of integrating third party data databases and other mobile devices such as phones and diagnostic devices. At the moment, the company is fully focusing on a platform for pandemic diseases like COVID-19. However, the platform has also been proven to work in a very remote setting testing malaria[62].

Diagnostics as a service

While diagnostics get more and more integrated in data platforms, they cannot be considered as only a product anymore. Instead, it becomes a product-service combination. Services often require a different business approach then products. The user will be far more engaged with the product-service over a longer period of time. It means that selling the product comes with the expectation that the service will support the product over a certain period of time. It could also be offered as a service alone. The user would pay for using the product-service by means of a monthly subscription instead of owning the device and the software, for example. Although this project will not further elaborate on possible business models, it should be part of further explorations.

Stakeholders

INSPiRED

The INSPiRED project is a key player in this project, aiming to "reduce the burden of malaria, schistosomiasis and hookworm"[3]. Furthermore, the project wants to engage stakeholders and to generate knowledge in Africa and Europe in multi-disciplinary collaborations. The INSPiRED project is a consortium of several partners:

LUMC

Leiden University Medical Center has a coordinating role in the INSPiRED project and is involved in the medical aspects of the developments and laboratory and field testing.

TU Delft

Delft University of Technology (TU Delft) contributes to the technical, strategic, and user-centered research and development within the INSPiRED project. Students and professionals with different expertises are involved and connected. They have a coordinating role together with LUMC.

CERMEL

CERMEL is involved in project INSPiRED and project FreeBILy. CERMEL is a medical research center in Gabon, with close links to organizations on national and international level and the Gabonese Government[104]. The FreeBIly consists of two clinical trials that evaluate both the UCP--LF CAA test and the POC-CCA test[105]. The UCP-LF CAA test is used in combination with a modified reader of Labrox. The CERMEL technicians are facing challenges with regard to the user-friendliness of the reader (P. Hoekstra, personal communication, 2021).

University of Lagos

The University of Lagos is not specifically related to this project. However, in future activities like user tests, field tests and connecting to stakeholders, there might be opportunities to involve them as well.

University of Ibadan

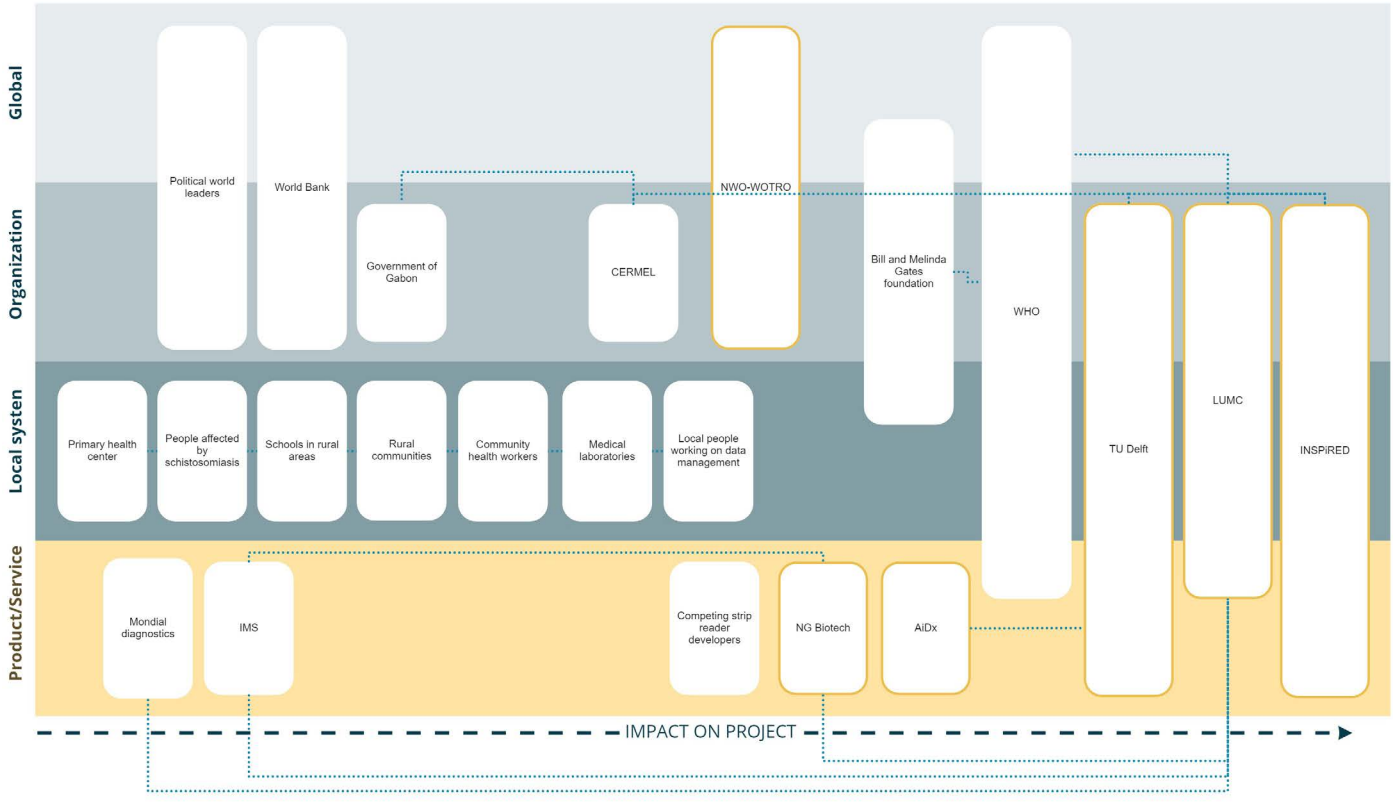
The University of Ibadan is not specifically related to this project. However, in future activities like user tests, field test and connecting to stakeholders, there might be opportunities to involve them as well.

AiDx

The start-up AiDx develops smart optical diagnostic devices that are affordable and field compatible[106]. It makes use of artificial intelligence to increase the capabilities of diagnostic microscopes. AiDx is working together with INSPiRED to bridge the gap between the academic and the commercial world and to bring research into practice. The company is a potential partner to further develop and commercialize a UCP-LF reader.

World Health Organization

The World Health Organization (WHO) is a key player regarding health interventions in this context. They decide, together with (local) governments on mass intervention campaigns, are the link between governments and drug donors and decide on appropriate diagnostics. In a re-



cently published roadmap, they aim to eliminate schistosomiasis in the coming decades[4].

Bill & Melinda Gates Foundation

The Bill & Melinda Gates Foundation is the largest private foundation in the world. It aims at fighting inequity, reducing poverty and enhancing healthcare around the world[107]. The foundation runs a program to fight NTDs, not only by supporting program approaches and drug donation, but also by supporting the development of diagnostics with an emphasis on data[108]. However, the foundation has shown hesitancy regarding diagnostic test needing a dedicated reader (G. van Dam, personal communication, 2020).

Intelligent Material Solutions

See confidential appendix.

NG Biotech

See confidential appendix.

Competing strip reader developers

Developers and manufacturers of fluorescence strip readers, like Upcon system and Dialunox might be aware of the potential of UCP-LF CAA. (see confidential appendix). Although they have shown that they master the technology (with custom modified systems), it could be doubted if they are able and willing to properly adresss the needs for a very affordable, user-friendly, connected and context-specific reader simply because it might be not that interesting from a commercial standpoint.

Potential customers

Potential buyers of the UCP-LF CAA test might be governments, a variety of NGOs, and the WHO. For example, the government of Gabon and the Nigeria Centre for Disease Control has expressed the need for real-time quantitative data for strategic decision making[109,110]. Whether the buyers of the test and the buyers/renters of additional equipment would be the same is not clear and may be depending on the offered construction (service contract, ownership, etc.).

Potential users

Potential users of the UCP-LF CAA test could be local lab technicians, community health workers, medical trained personnel and data technicians. Users of the whole system, including the generated data, could be the targeted population, the decision-makers, community leaders, researchers, government and NGOs.

Conclusions and design implications

This chapter focused on the desired transitions and the obstacles and enablers that one could run into. On the highest level, the aim is to leave no one behind, and make healthcare accessible for everyone. The aims at the organizational, local system and product-service level should contribute to this greater aim. The challenge that emerges is: how can we be sure that any intervention actually contributes to the greater aim? The answer is most likely: we cannot until we start to pull on the strings of the system. From a systemic design point-of-view, such a system cannot be understood by only looking at the current state. Only while interacting with it, desired outcomes, patterns of relationship and desired elements become more clear. The system that is drawn should not be considered as set in stone but as some framework to start moving from (see figure 30).

What the system can show is new narratives or frames of the problem, which is useful for creating and communicating interventions. For example, the existing frame of the reader as an obstacle is outdated, given the fact that RDTs might be very accessible but not sufficient alone in the fight against NTDs. RDTs are often misused, badly interpreted and only give manual results.

Smart devices are not only needed to reduce human error by data interpretation but also to support the community health worker with feedback, and to reduce the administrative workload. A service subscription could ensure that the user is not worried about maintenance or high investment costs, while verified test results could integrate diagnostics with new payment methods like digital health wallets. Also, one smart device could be used for multiple diseases. This would not only spread the costs, but even reduce cost, as integrated approaches could save supply chain and overhead costs.

Different narratives could be created by emphasizing different needs on different levels. From an organizational view, reliable data and low costs is of importance. From a local system view (the direct user of the device), user friendliness and suitability for the settings is of importance. At the same time, for the patient, decision power and involvement is key. In chapter FIXME, the new narratives for different users will be further elaborated.

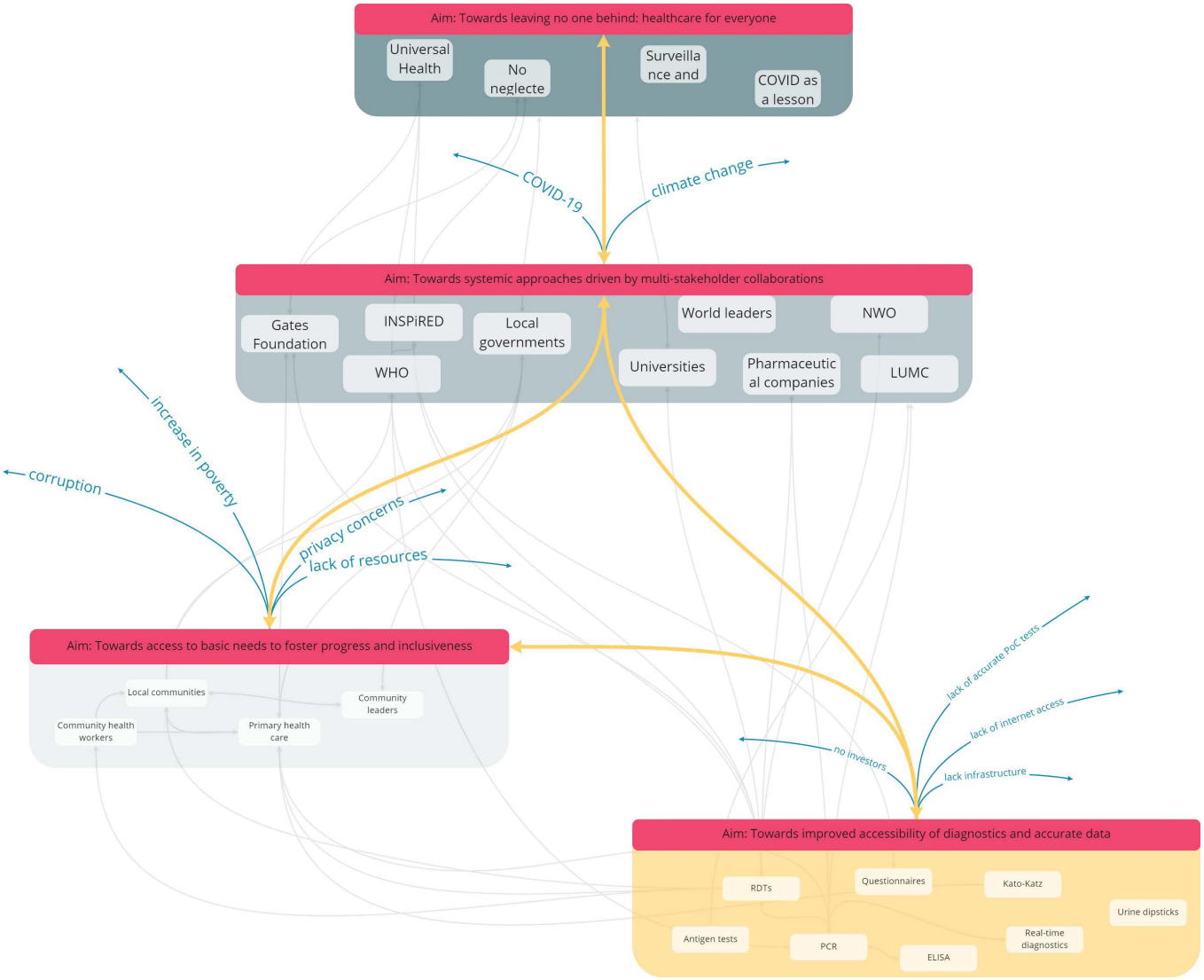


Figure 30: A complex, open, dynamic and networked system. The yellow arrows indicate how one level should contribute to the other. The blue arrows represented forces that might pull the system in an undesired direction.

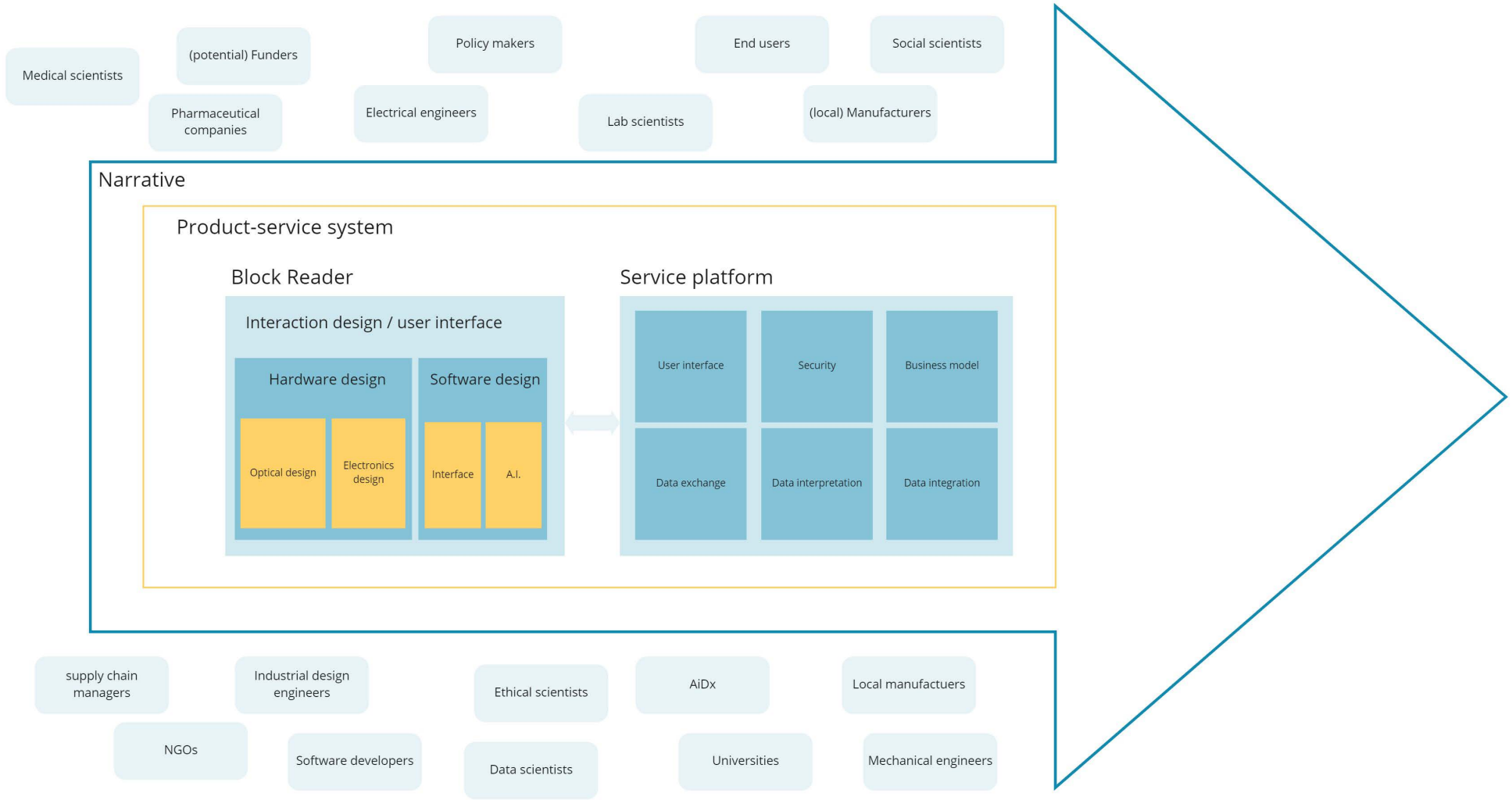


Figure 31: The narrative as an interface between the stakeholders evolves over time.

7. Towards a strip reader: three narratives

On a product-service level, we aim towards improved accessibility of diagnostics and accurate data. UCP--LF CAA is a promising diagnostic test that is still being developed. A reader is needed but also desired for real-time data generation, reducing human errors and supporting the users of the test. Currently, no off--the-shelf readers are available for UCP-LF CAA, being one of the limiting factors in implementing UCP-LF CAA tests. How could an intervention accelerate the development of context-specific UCP-LF CAA readers? What should this intervention be?

How?

The lack of suitable strip readers is not rooted in technological limitations or a lack of companies with the capacity to build such a reader. Rather, it is a lack of organizational power to co-develop such a reader together with the surrounding service system, addressing the needs of the variety of stakeholders across the different parts of the system. The different stakeholders, from policymakers to technical experts to end-users, should be involved from an early stage. This is not only important for their input and approval but also for building innovation capacity within the system in which the reader will be used.

Even within the LUMC, a lack of innovation capacity can be observed. Although UCP-LF CAA has been promising from the start, a clear strategy to implement the technology in practice has been lacking.

This matter could be reframed to: how could the relevant stakeholders be involved in an innovation that is not yet tangible and has no clear outcomes?

What?

Two elements are proposed:
Three strong narratives on the role of smart devices within the context of UCP-LF CAA diagnostics for schistosomiasis.
A proof of principle of the technologies to support these narratives.

Remember what Eisenstein pointed out: do not change the system, but change the narratives on which the system is built. A convincing narrative could contribute to multi-stakeholder collaborations by bringing the opportunities and challenges to life with a clearly conveyed story. The three proposed narratives have a different focus, and require different technical solutions.

To support the narratives with evidence and to have a prototyping tool for further collaborative development, a research instrument is proposed: the Block Reader. The Block Reader is a modular research instrument capable of scanning UCP strips.

The reader allows for quick iterations, technology demonstrations, co-development of different technical aspects and user interactions. It helps with understanding and communicating the stakeholders' needs, opportunities and challenges by making them tangible. This reader will be discussed in detail in chapter 8.

Three directions

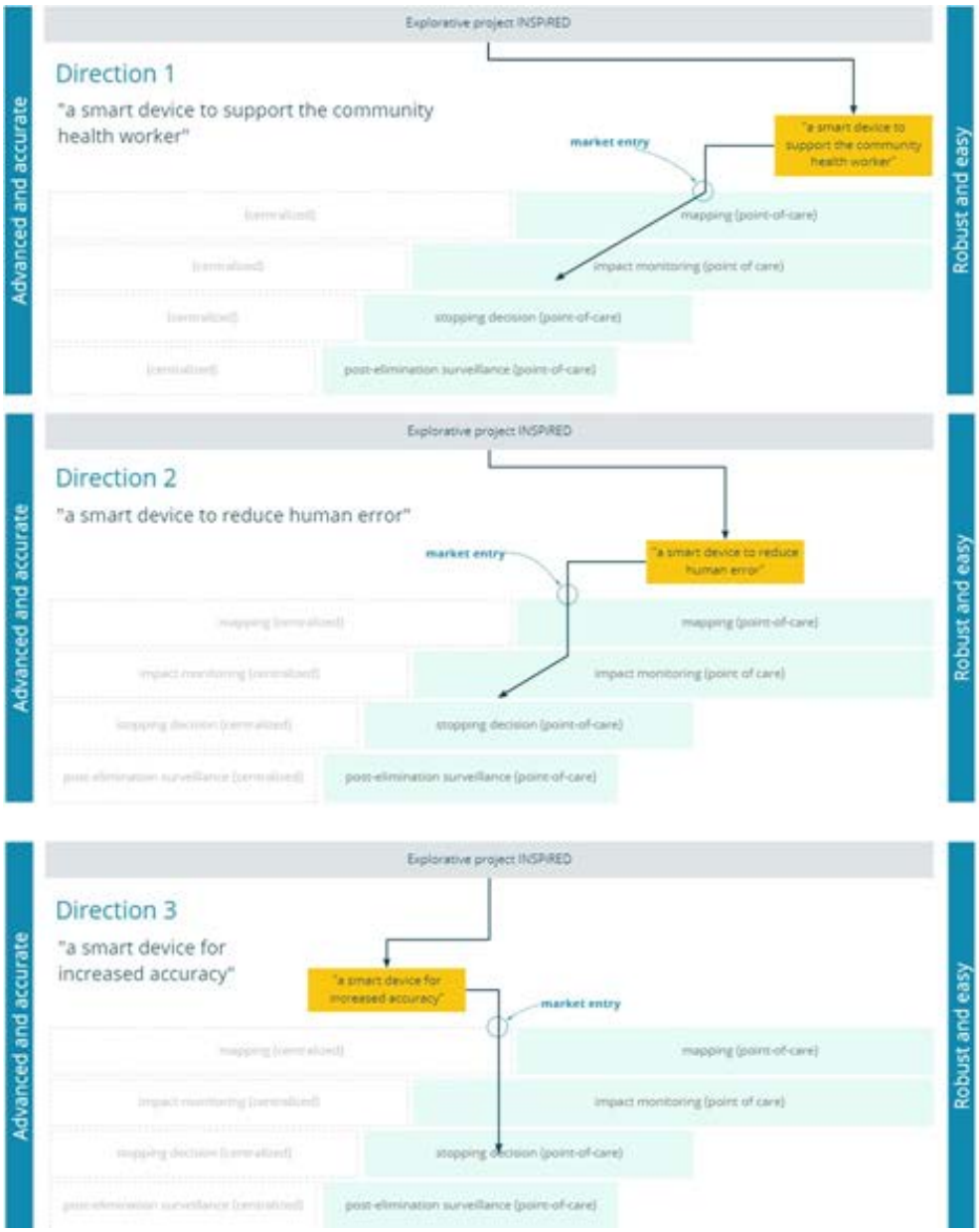
In this paragraph, future steps will be outlined by proposing three possible strategic and technical directions, based on different narratives.

The development path is displayed on a scale from left to right that represents the most important trade-off: an advanced solution with high diagnostic accuracy against a robust and easy device that is very accessible for the user. On this scale, the most important phases of disease control and elimination are plotted. Mapping requires a very accessible tool which may compromise accuracy.

When moving to impact monitoring, the performance has to increase, adding quantitative measurements and higher sensitivity in low-endemic settings. However, the tools have to remain very robust and easy to use.

The stopping decision and post-elimination surveillance require highly sensitive tools in low-endemic settings, which may compromise on the easy of use and/or robustness. All phases can also be performed centralized in a lab-based setting. This demands less robustness and ease-of-use but is undesirable because of high costs, slow turn-around time, and the lack of appropriate infrastructure and capacity.

The three directions have different entry points in the market and tell a different story. Direction 1 is much focused on simplicity, delivering the best experience for the community health worker. Direction 2 has very reliable performance, reducing human error. Direction 3 is the most advanced device, delivering high accuracy to optimally support decision-makers.



Direction 1

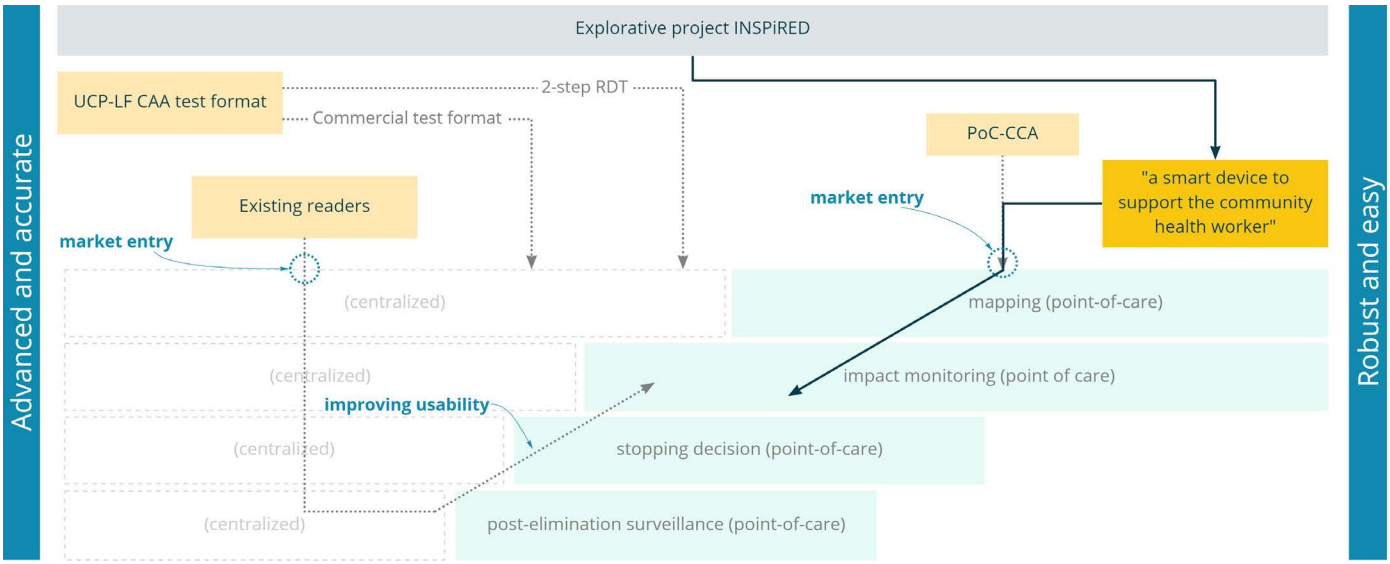
The development path (Direction 1) has to be placed in the context of other developments. The UCP-LF CAA test format is still under development and even not yet commercialized. In the coming time, NG Biotech will work on the commercial format, improving the robustness and ease of use. Still, the test will not be applicable at the point-of-care, because of the sample preparation steps required. Hopefully, at a further point in time, a 2-step RDT will be developed, bringing UCP-LF CAA much closer to the point of care. Existing UCP readers are advanced but have a long way to go to become easy to use and robust enough for point-of-care settings.

Direction 1 proposes a radically different narrative than the existing one, focusing on the experience of the community health worker. Undoubtedly, the CHW has a crucial role in the fight against NTDs and the deployment of universal health coverage. A smart device could support the CHW, reducing administrative work and providing feedback or guidance in the use of the RDTs, ultimately reducing human error.

For the development of such a device, the type of RDT (whether it is UCP or immunochromatography) is of secondary importance. The added benefit to the CHW and the intervention program is of most importance.

Since it might take years before a 2-step UCP-LF CAA RDT is available, this device could be first developed to aid the CHW in the use of the already available PoC-CCA, or in the finger-prick, blood-based CAA RDT, developed in the FIND project. In this case, the device should already be prepared to be adapted to the UCP technology. This would make a strong case, since the ease of use and the added benefits are already proven by then. This would contribute to a new frame in which the reader is not the obstacle but the enabler of diagnostics.

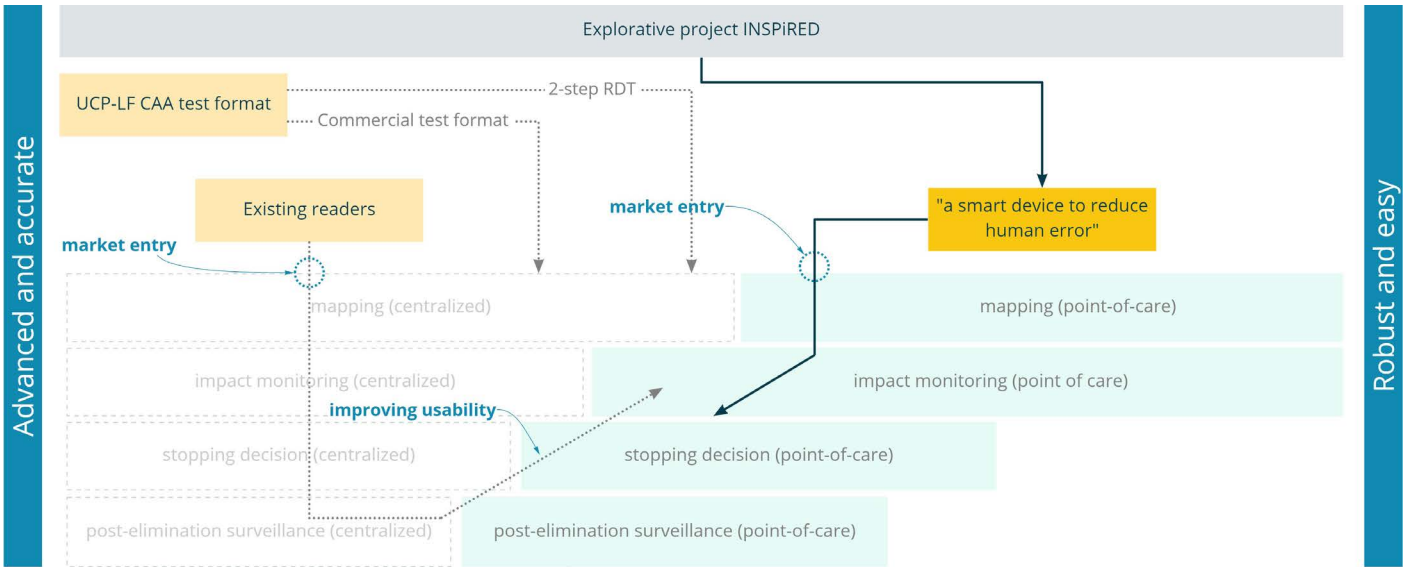
From a technical point of view, the reader would be equipped with a camera that is able to capture both lines in one shot, reducing the need to move the strip. The laser would be placed off-axis, exciting the strip via a mirror. By a small rotation of the mirror, the laser can move across both lines. An additional simple white LED would enable the reader to be used with visual RDTs like the PoC CCA. Further research with the Block Reader should point out whether it is possible to run the system without bandpass filters to reduce costs and remain multifunctional.



Direction 2

The second direction builds on the narrative of a smart device to reduce human error. It is focused on the organizational level, which requires accurate and reliable data. Reducing human errors results in a higher quality of data to rely on. The performance of the device is important, but the ease of use equally, since a device that is hard to use would contribute to the number of human errors. The device should be suitable for mapping and impact monitoring when entering the market and might be improved along the way to increase accuracy for stopping decision stage.

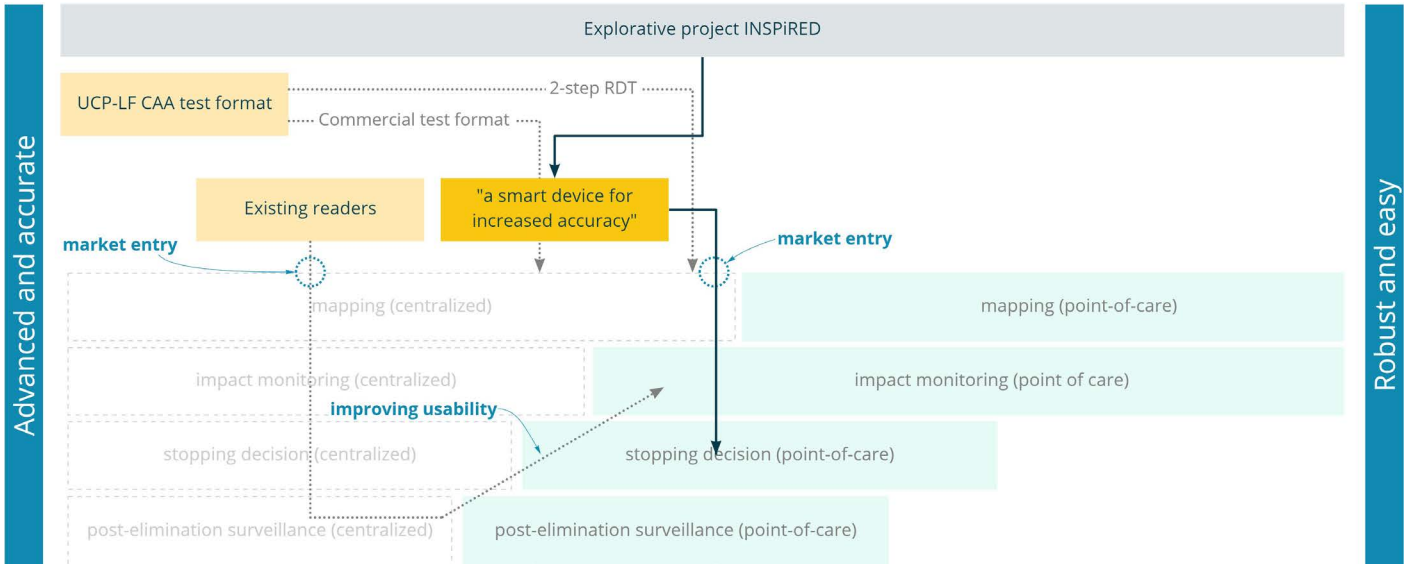
From a technical point of view, the device is equipped with a camera, which provides more information than a single-point photodiode. The algorithms could use this 2-dimensional image to improve the reliability of the data further, being able to distinguish loose particles from the test line. The camera could also provide feedback on the reliability of the performed test, by identifying wrong use like excessive sample volume. The excitation would be confocal, to increase the reliability and accuracy. The strip is scanned by moving the strip in one direction. The Block Reader could be used to investigate the use of smart algorithms for image interpretati
on.



Direction 3

The third direction is focusing on one of the key qualities of UCP-LF CAA: high accuracy in low-endemic settings. It addresses the needs of policy makers to have a highly sensitive and specific tool for disease elimination. The resulting reader would the most advanced of the three directions, to ensure a low limit of detection. As a consequence, the reader would not be directly employable at the point-of-care for mapping purposes, although it could be used in a more hybrid approach, in which tests are done locally and read-out at a central place. Still, the reader would be much more robust and easy to use than the existing readers by focusing on excellent user interaction and reliable components. The reader-test combination would differentiate from other highly accurate tests like molecular techniques by its ability to be performed with only basic equipment and skills.

From a technical point of view, the reader would make use of a confocal setup, a laser for excitation, and a photodiode for a low limit of detection. Optical components like bandpass filters and a dichroic mirror increase the signal-to-noise ratio by separating excitation and emission as well as possible. The Block Reader could be used to further optimize the optics, the electronics and the software.



Discussion and design implications

The project was initiated by the need for a strip reader that better fits the needs, like user-friendliness, affordability and the ability for real-time data collection and was aimed at exploration. By analyzing the system and the context, talking to stakeholders and exploring the technology, I found out that the project is best taken forward with more collaboration and better insights in the needed specifications and technologies. In the context of COVID-19 and the multifaceted challenge, I decided not to find answers to all the questions myself, but to aim for a solution that facilitates finding answers together with the variety of stakeholders and expertises.

8. Towards a strip reader: Block reader

To support the narratives with evidence and to have a prototyping tool for further collaborative development, a research instrument is proposed: the Block Reader. The Block Reader is a modular research instrument capable of scanning UCP strips. The reader allows for quick iterations, technology demonstrations, co-development of different technical aspects, and user interactions. It helps with understanding and communicating the stakeholders' needs, opportunities and challenges by making them tangible. This chapter focuses on the requirements, functions, and design of the Block Reader. Also, design considerations for UCP strip readers are considered.

What

The developed solution is called the Block Reader. It is a device that can scan UCP-LF CAA strips and:

- aims at R&D activities
- is modular so that components can be separately developed and compared
- can be incrementally improved
- can be easily transported
- can function stand-alone
- can compare multiple strips
- can display the result of the scan
- communicates technology, opportunities and challenges

Why

The goals are to:

- Support new narratives about smart, easy to use strip readers with evidence
- To compare different technological solutions (and determine which ones are promising for further development of the reader)
- To have a reference and prototype for parallel development of subsystem components such as smart algorithms, the optic system, and the user interaction
- To sensitize stakeholders

Goal	User Need	Solution
Support new narrative	Have proof of principle or other research-based evidence to demonstrate the feasibility of the narrative.	A device that can actually perform the key tasks that are proposed in the narrative with relatively affordable and off-the-shelf components. One key task is the ability to measure the presence of UCP particles on the test and control line of the strip test.
Compare technologies	Optimize technology for a chosen use case	Modular system which facilitates experimentations with different technologies and components
To have a reference and prototype for parallel development of subsystem components	To be able to quickly iterate on different (sub)-components in collaborative development processes.	Individual subsystems are easily changed and can be individually improved. Connections are standardized, and the design is well documented. Test results can be captured and compared. The device is compact and stand-alone so that it can be easily transported to different test locations and workspaces. The device makes -when possible- use of well-known standard components, like a Raspberry Pi, 5V USB supplies, and a standard aluminum extrusion build system.
To sensitize stakeholders	The involvement of stakeholders such as RDT manufacturers, funders, end-users and NGOs is crucial for the UCP-LF CAA test and a strip reader to be further developed. Clear and attractive communication of the project is needed	A physical object is a strong means of communication. Other than existing readers, the Block Reader is transparent about what's inside. The bottom is see-through. When operated in normal mode, light will not enter the inside (preventing disturbing the measurement). However, the device can be turned upside down to show the technology that is inside.

BLOCK READER

FULLY MODULAR RESEARCH STRIPREADER FOR COLLABORATIVE PROTOTYPING AND STORYTELLING

CONNECTIBLE

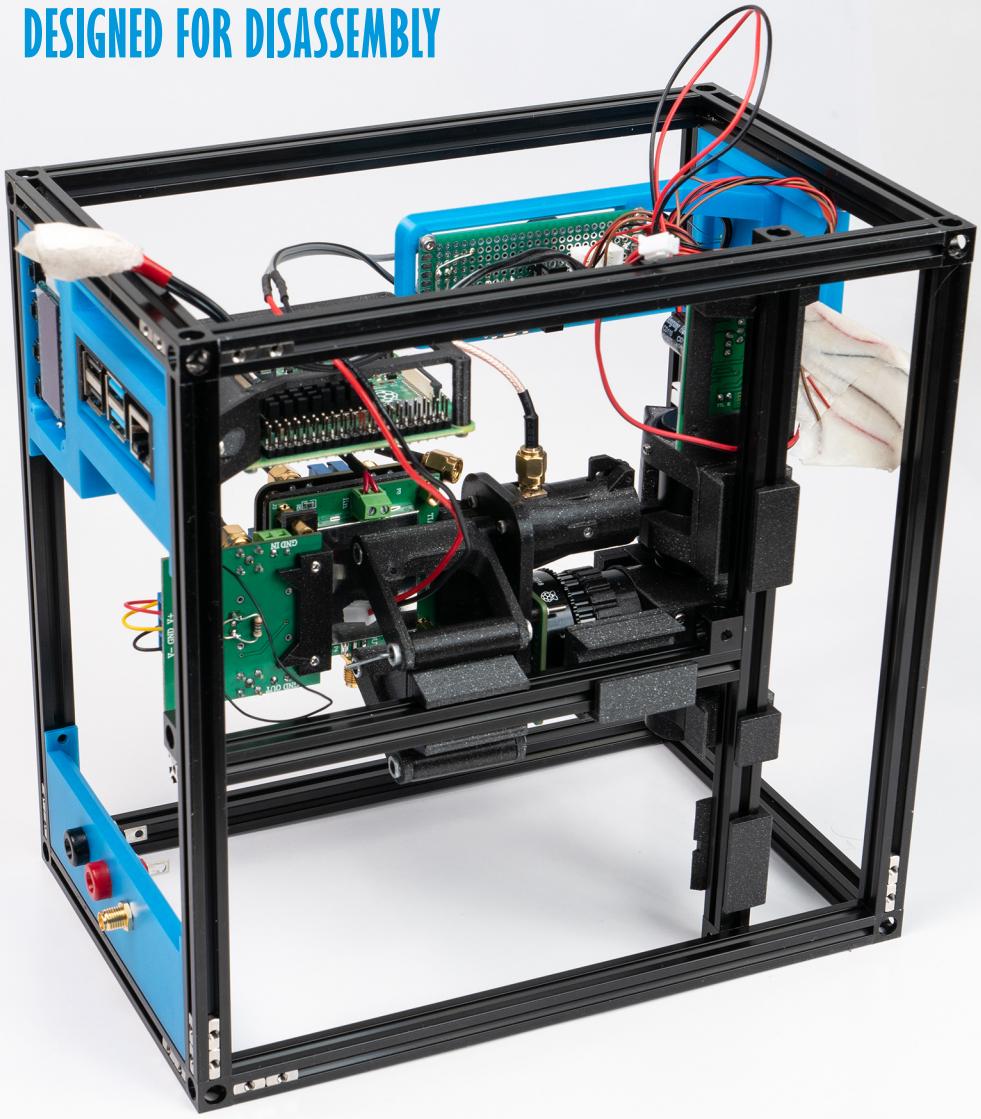
TOUCHSCREEN INTERFACE

5 STRIP CAPACITY

HIGH ACCURACY MEASUREMENTS

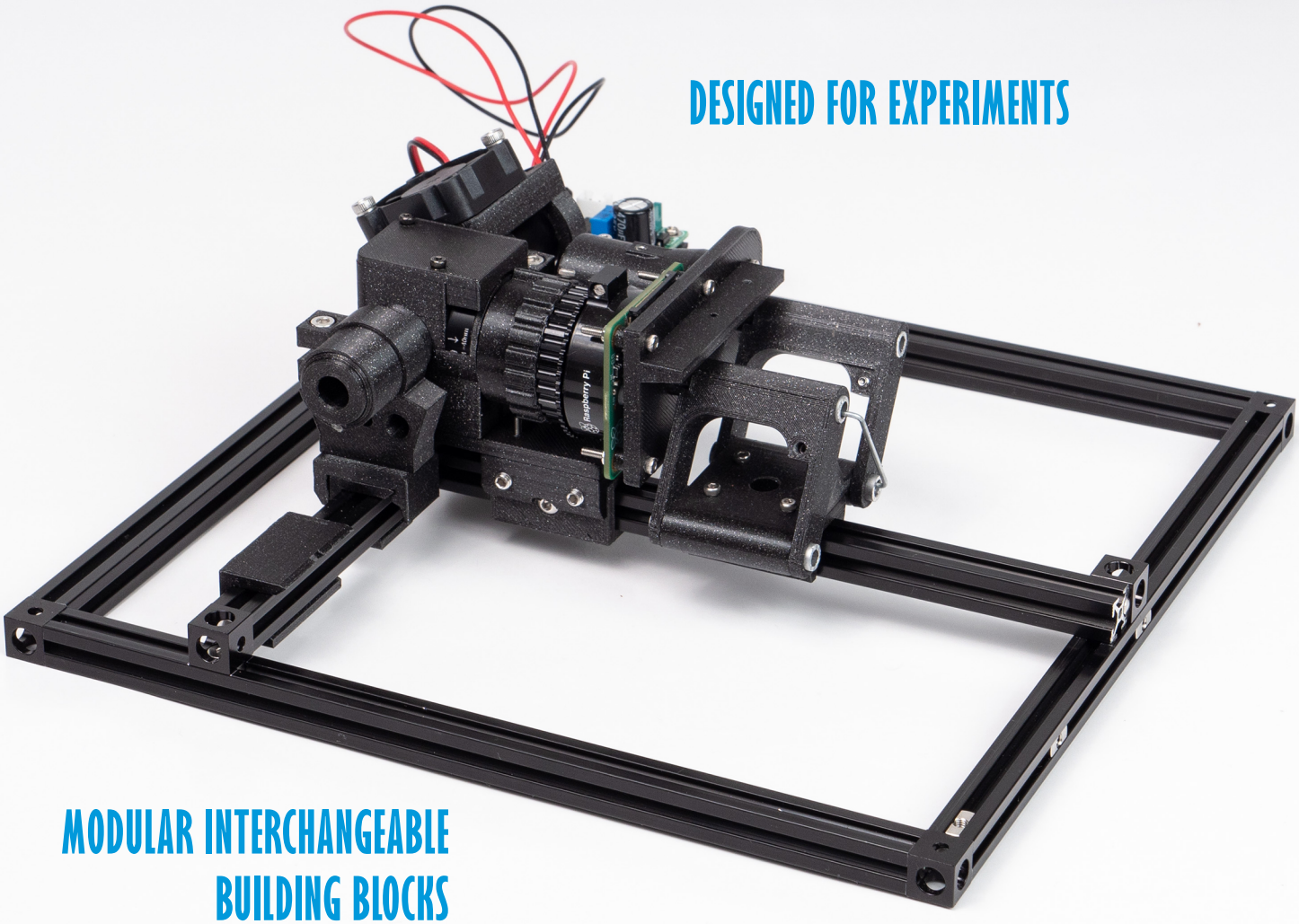
INTERACT WITH THE DEVICE WITH EASE

DESIGNED FOR DISASSEMBLY



TURN IT AROUND FOR THE TECHNICAL STUFF

DESIGNED FOR EXPERIMENTS



MODULAR INTERCHANGEABLE
BUILDING BLOCKS

For who (user)

The users of this solution are the project's stakeholders, like engineers, funders, and commercial partners. During the project, it became clear that the most crucial factor for success in this project is effective collaboration and stakeholder management. It is vital that (potential) manufacturers and/or funders believe in the potential of both a frugal strip reader as UCP-LF CAA becoming a viable business. At the same time, strategic decisions have to be made regarding the positioning of this device on the market and the feasibility to deliver matching specifications with certain technologies. For this, the technologies have to be validated.

Where

The intended use places of the Block Reader are research labs, medical laboratories, workshops, boardrooms, presentations, institutes in the local system like hospitals, universities and offices. The Block Reader is not intended to be used in the context of real diagnostics activities, for example, in laboratories at the point of care. This would require different specifications with regards to safety, reliability, user-friendliness, and robustness that would compromise the core-functionalities as described above.

When

The Block Reader is already being used and has served some of the goals already. Throughout the project, the modular functionality was extensively used for gaining insights in working principles, troubleshooting and experimentation. Also, findings from early tests were used to further elaborate on the narratives. In the near future, the Block Reader will be continued to be used since the project is further extended for at least one year.

Desired specifications

Based on the evolving understanding of the technological challenges and the described user needs, a list of the most important specifications is drafted. It serves as a (dynamic) reference for the design of the Block Reader.

Performance

- It can excite the UCP particles on the test and control line with the specific desired wavelength (980 +-10 nm)
- It can measure the emission of the UCP particles bound to the test and control line with the same limit of detection as the ESEQuant LFR reader (to be determined empirically)
- It can determine whether the UCP-LF CAA test result is positive or negative with the same accuracy as the ESEQuant LFR reader
- It can measure the intensity of the emission of the UCP particles
- It can examine the total length and width (4 mm) of the lateral flow strip (20 mm
- It can read multiple (up to 5) strips in a row
- It allows comparing different excitation sources (LED, Laser) and different measurement principles (photodiode, camera sensor)
- It is able to function stand-alone, with only a power supply

Handling/ergonomics

- The product allows experts to work on sub-components without demanding to understand other sub-components that are beyond their discipline
- The working mechanism is transparent to user and stakeholders to ease communication
- The product should facilitate easy alignment and focusing of the optical system
- The product can be transported in a bag, thus not exceeding 300 x 300 x 300 mm, and 10 kg
- The product makes use of standardized components that are common in the particular field of expertise (e.g. Python as programming language)

Modularity

- Sub-components are interchangeable by means of a standardized interface
- The sub-components can be removed without losing the alignment.
- The product can be fully disassembled
- Sub-components can be individually removed.
- Connection interfaces (screws etc.) remain accessible for tools
- The product makes use of off-the-shelf components or components that can be manufactured using widely accessible FDM printing or laser cutting.

Input / output

- The device is powered by a conventional power standard (5V)
- The device can be controlled with conventional computer controls (mouse & keyboard)
- High-quality lab instruments can be connected to the device via a standardized connection (banana plugs, SMA coax cable) to measure signal intensity directly
- The output should be in such format that it can be analyzed afterward (.csv, JPEG, MP4)

Environment

- The performance of the device is not affected by the quality or intensity of environmental light
- The effect of other environmental influences like temperature and humidity can be measured with the device itselfPerformance
- programming language)

Main design

The main design is divided into several systems with different functions (figure 32)

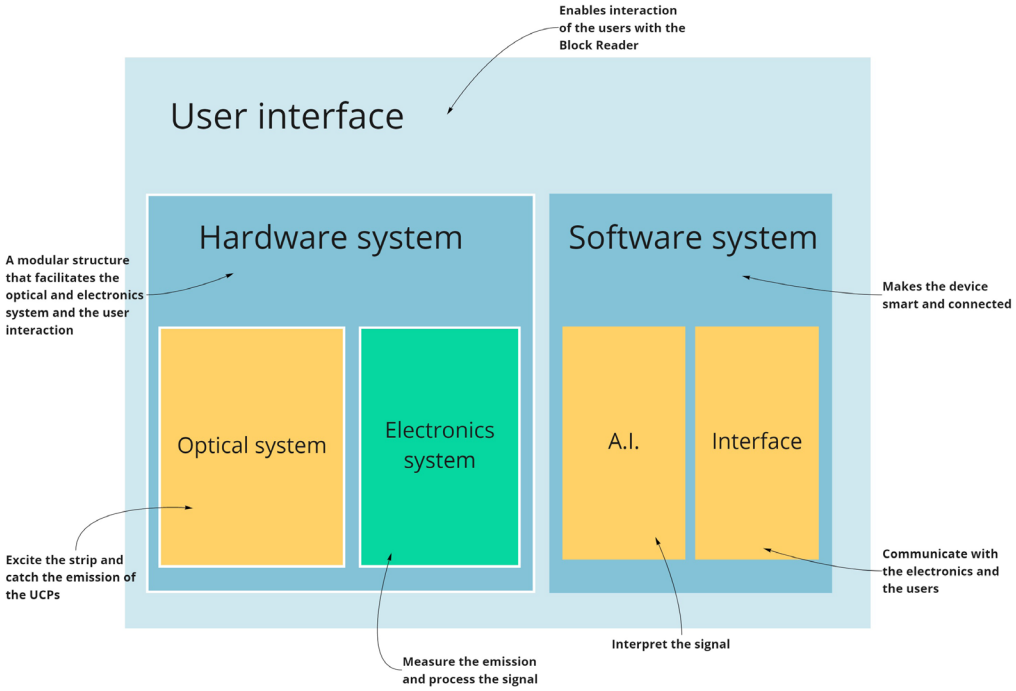


Figure 32: the system of the Block Reader (above) and the products components

The main function is to excite the UCP particles on the test and control line of the UCP-LF CAA strips with a particular wavelength (980 nm) to trigger the two-photon upconversion.

Typically, the more UCP particles have bound to the line, the higher the emission intensity. The emission is captured with a sensor. This core functionality is mostly performed by the optical system, which (currently) consists of a light source, interchangeable lenses, a dichroic mirror (only reflecting a particular wavelength of light), bandpass filters (only letting through a certain range of wavelengths), and two different sensors. See figure 33, 34.

The sensor signal is processed and interpreted by the electronics and the software. The interpretation is communicated with the user via the interface. The interface also allows the user to select which strip to scan (the Block Reader can hold multiple strips) and to alter the settings such as laser power and modulation frequency.

In the current state, the hardware system with its optics and electronics is the furthest developed. The Block Reader does contain the infrastructure to develop the software system by means of a Raspberry Pi.

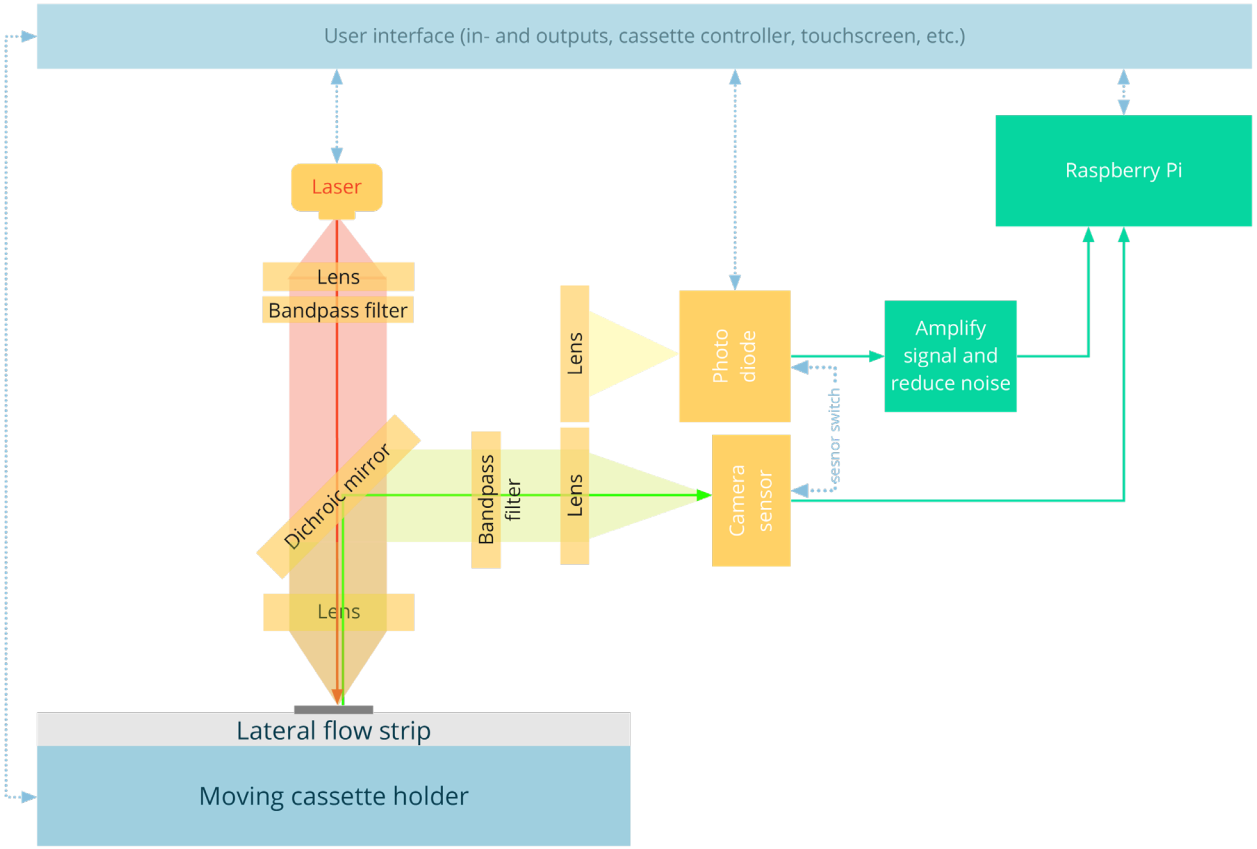


Figure 33: the basic architecture of the Block Reader

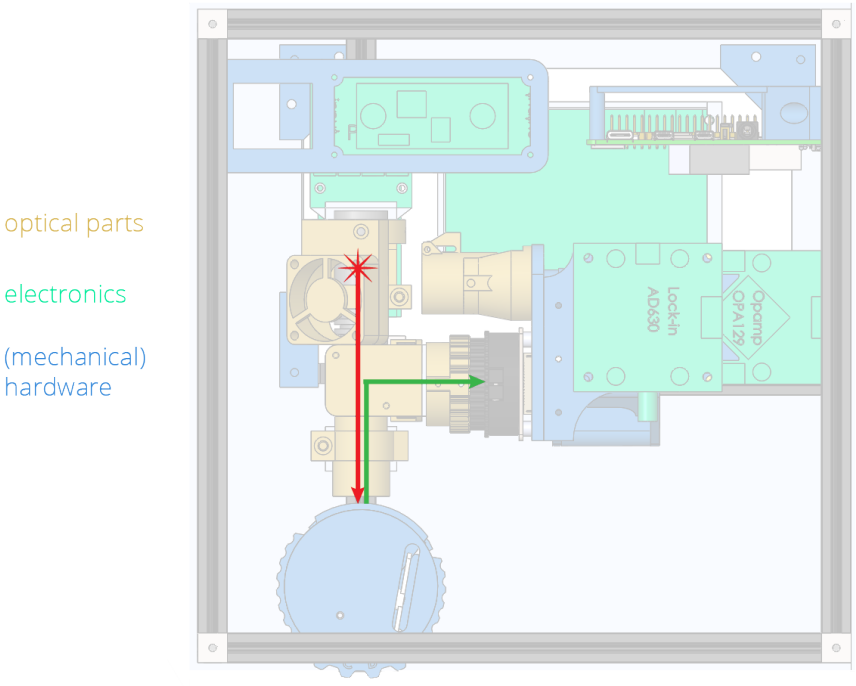


Figure 34: the optical path in the block reader (top view)

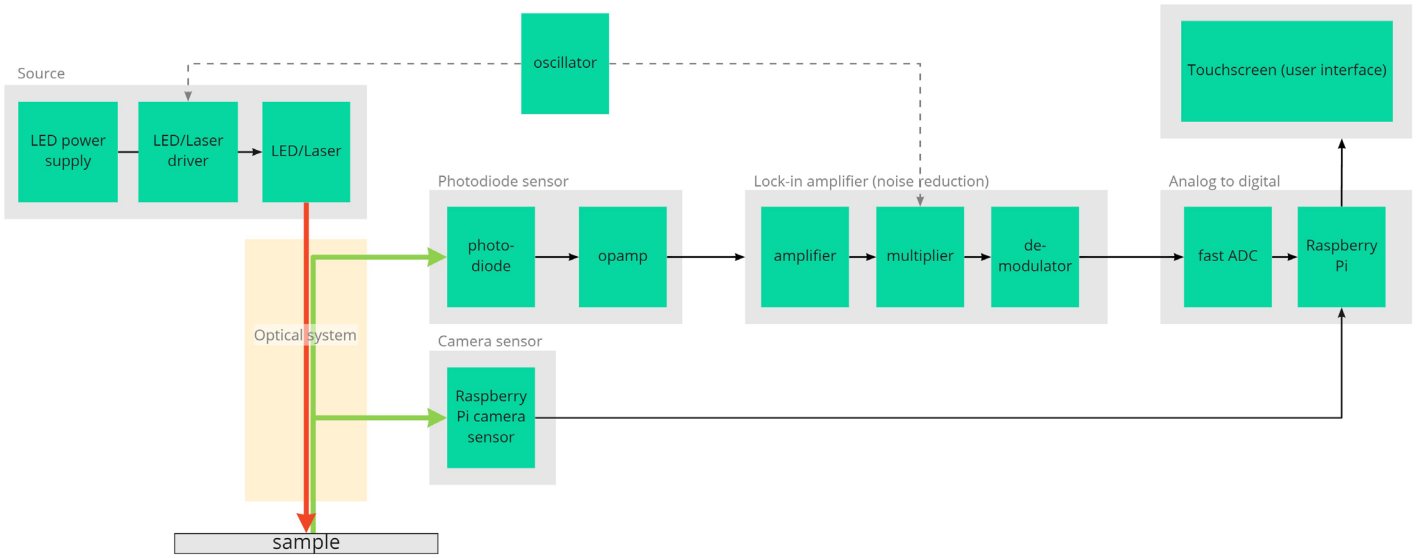


Figure 34b: Electronics system of the Block Reader

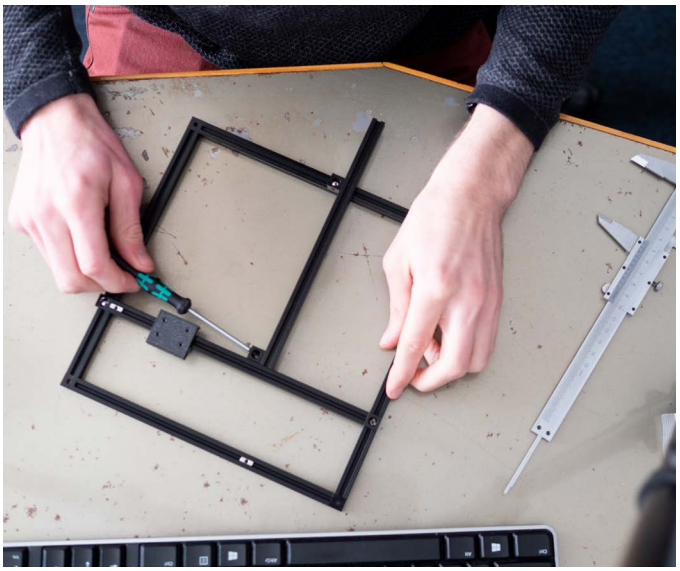
The hardware system

The aluminum frame

The frame is the basis of the Block Reader and is based on the Makerbeam system. Makerbeam is a company selling standardized prototyping hardware, such as extrusion profiles compatible connection equipment such as nuts and bolts.

Makerbeam was chosen as basis because it is widely available, can be easily adjusted and is very versatile.

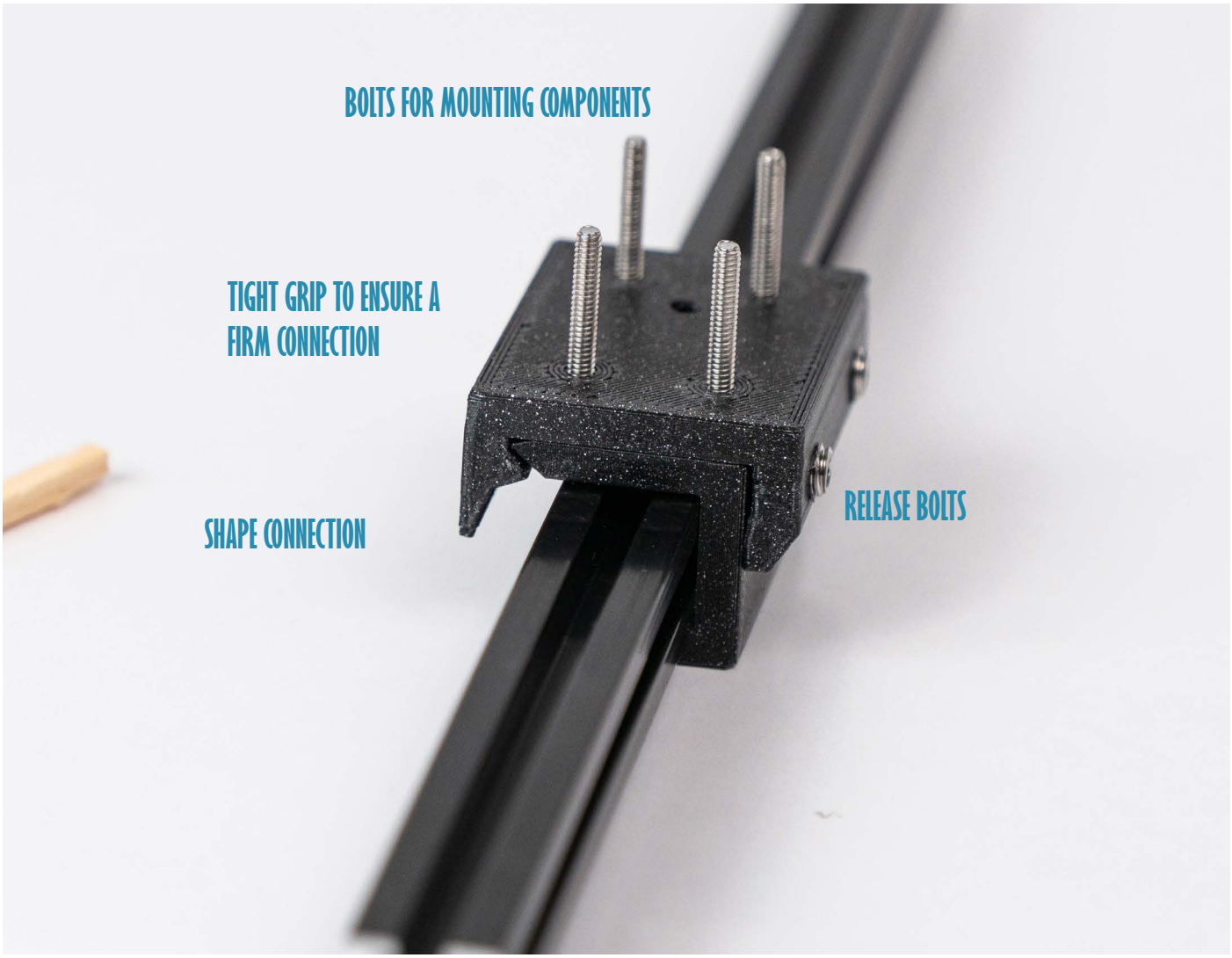
The frame is 22 x 22 x 14 cm but is adjustable to the needs of the user.

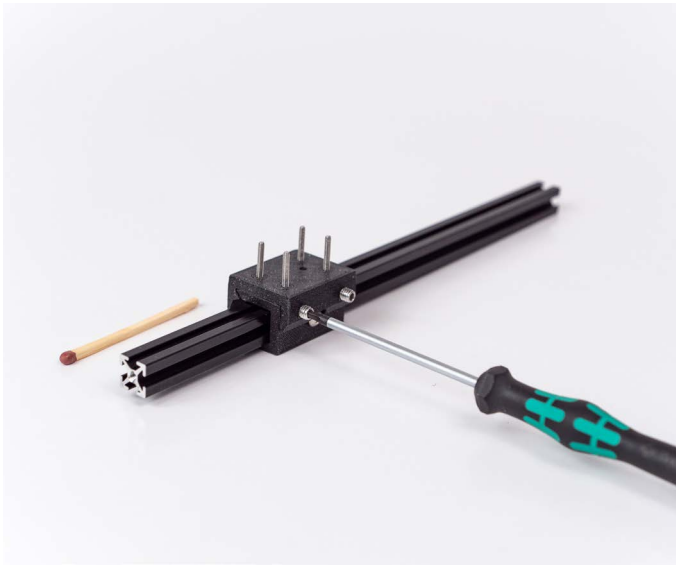


The hardware system

The modular clamps

The modular clamps are 3D printed clamps specially designed for the Block Reader. They have two functions. First, they are the interface between the frame and the components. This connection should be firm but also very easy to release. Second, they should fix the alignment of the components along the axis of the beam they are mounted on. And they should be able to easily slide over the frame when needed.. They are designed in such a way that the adjustment bolts are accessible from one side, so they remain accessible, even when components are installed on top.

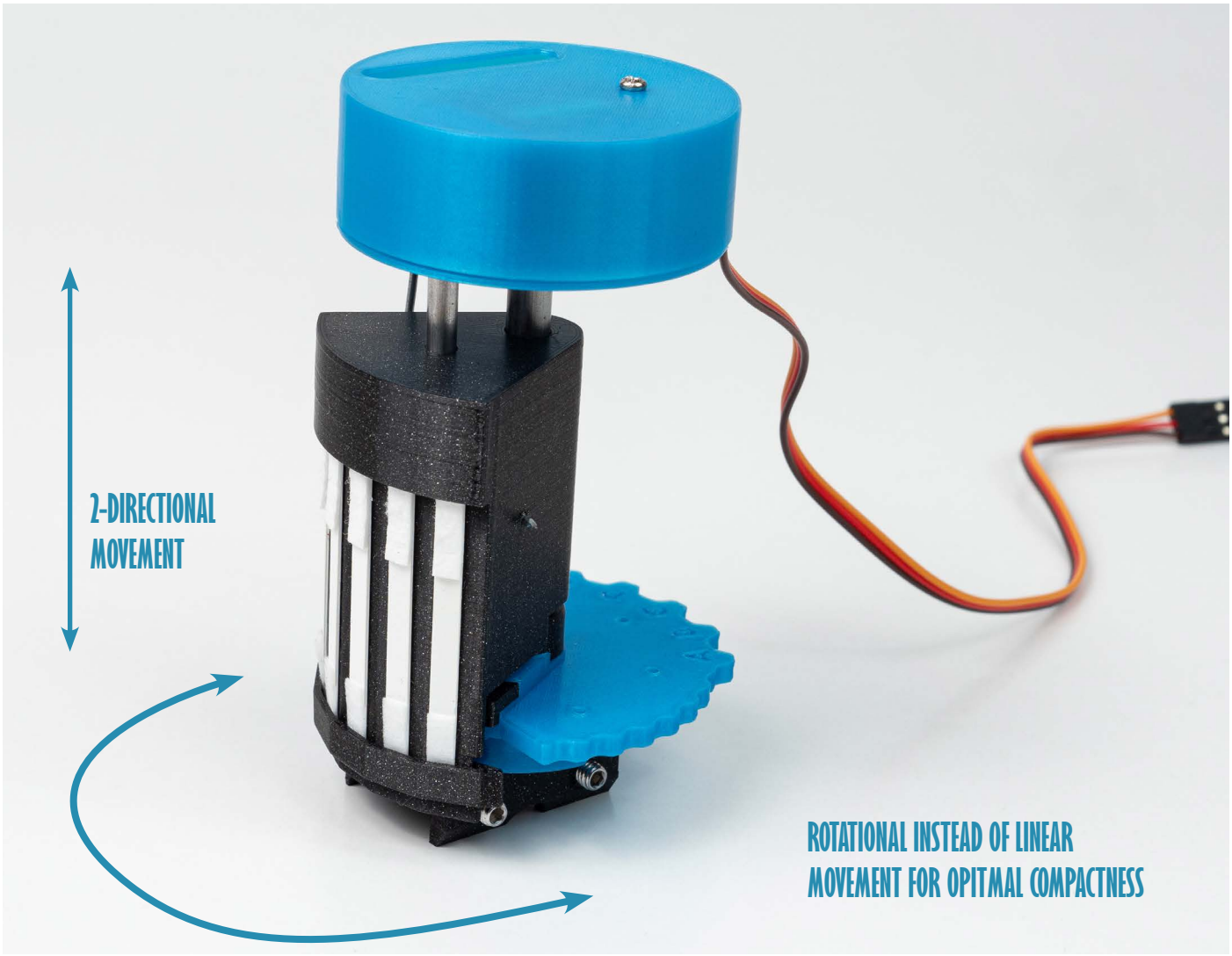


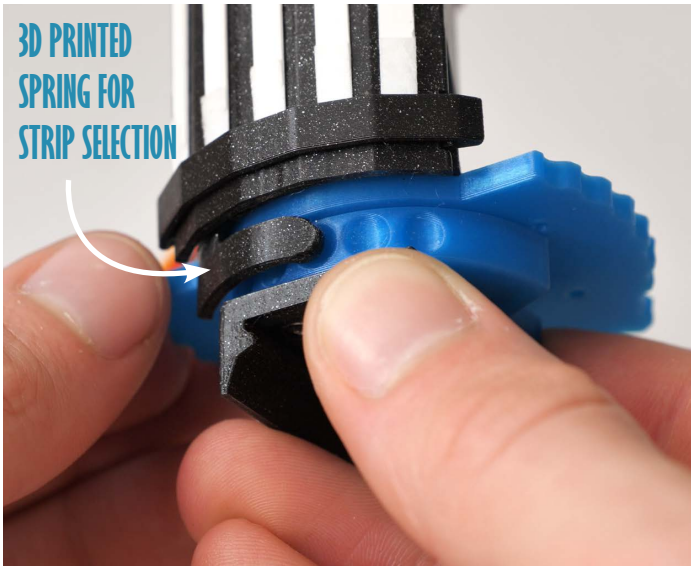


The hardware system

The strip cassette

The lateral flow strip cassette is designed to hold five lateral flow strips. The main function is to move the strips with respect to the light focus point to scan the strip at various points. Also, the cassette should enable to inspect the strip on multiple points across its width and to switch from one strip to another. The strip cassette is 3D printed and a 6 and 4 mm aluminium extrusion profile functions as linear bearing. The strip cassette is mounted on the sliding modular clamp to make focusing easy.

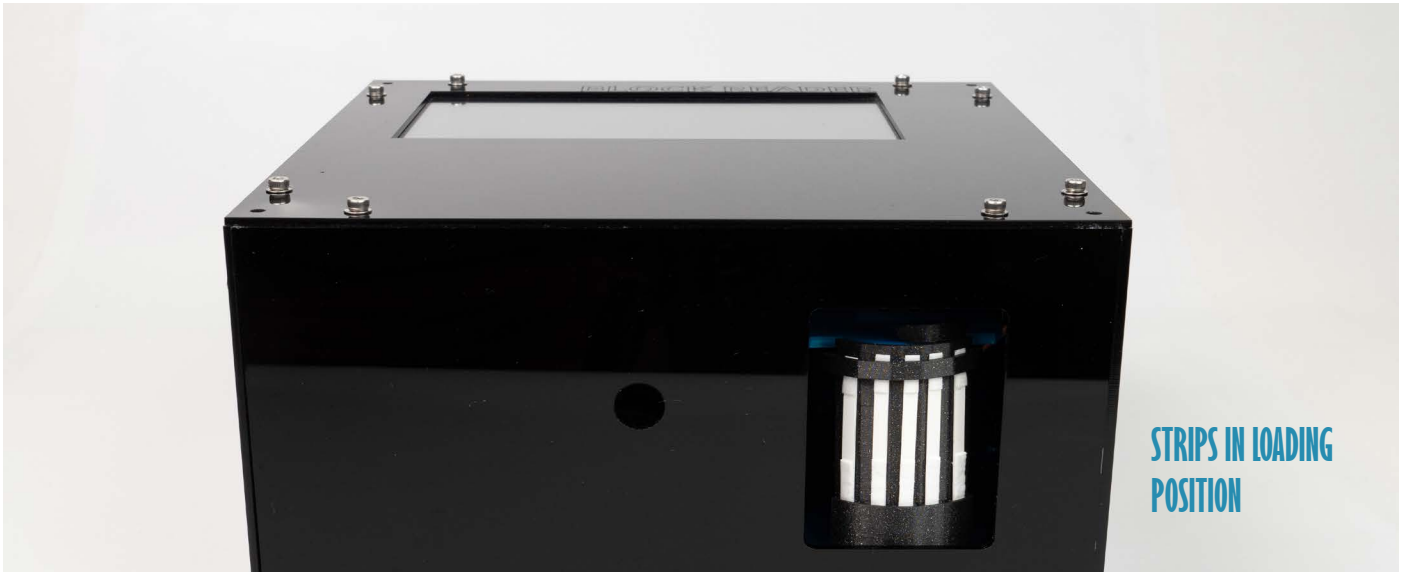


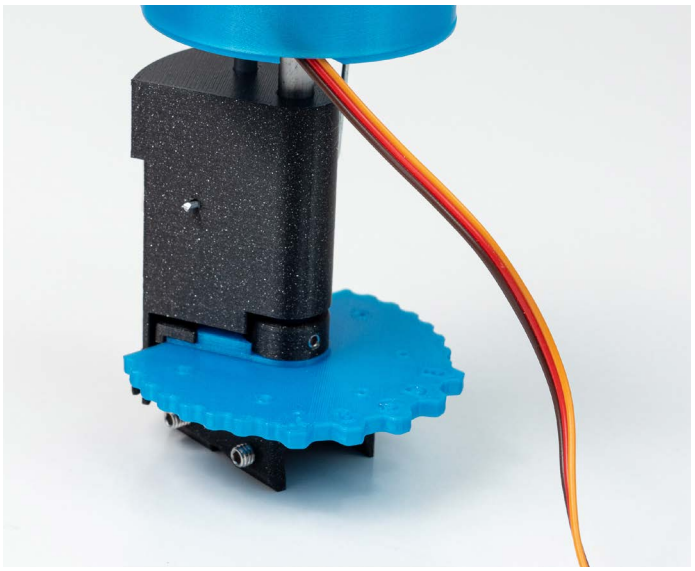


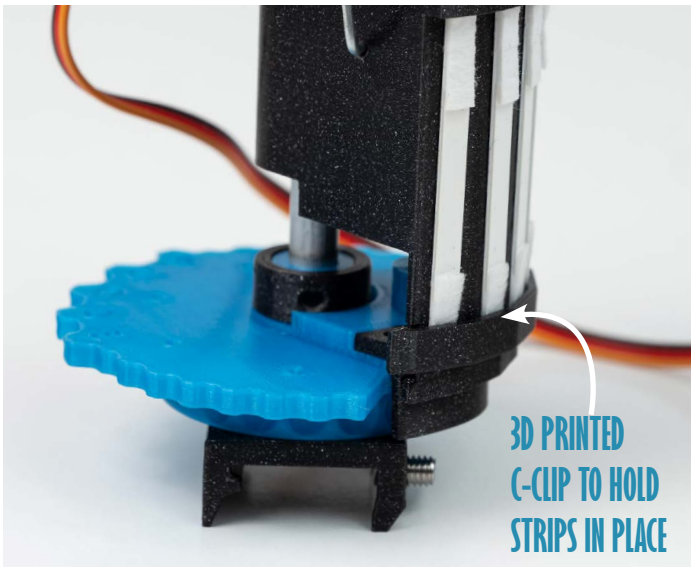
The hardware system

The strip cassette

The lateral flow strip cassette is designed to hold five lateral flow strips. The main function is to move the strips with respect to the light focus point to scan the strip at various points. Also, the cassette should enable to inspect the strip on multiple points across its width and to switch from one strip to another. Because the switching mechanism of the camera and photodiode is very close to the strips, the cassette turns in a rotational movement instead of a linear movement (like most readers) to switch to the next strip. This compact setup might be used as well for later generations of strip readers. The cassette is designed so that it is stiff and has no play, yet can move smoothly. To select one or another strip, a 3D printed ball spring was designed to lock the strips in place. The strip selection is done by hand, and the linear movement is done by a servo-controlled with the Raspberry Pi. To enable the loading of strips without removing the casing of the Block Reader, the cassette can turn 180 degrees so that the strips are facing outwards (see product photos). To scan, turn the cassette 180 degrees again.



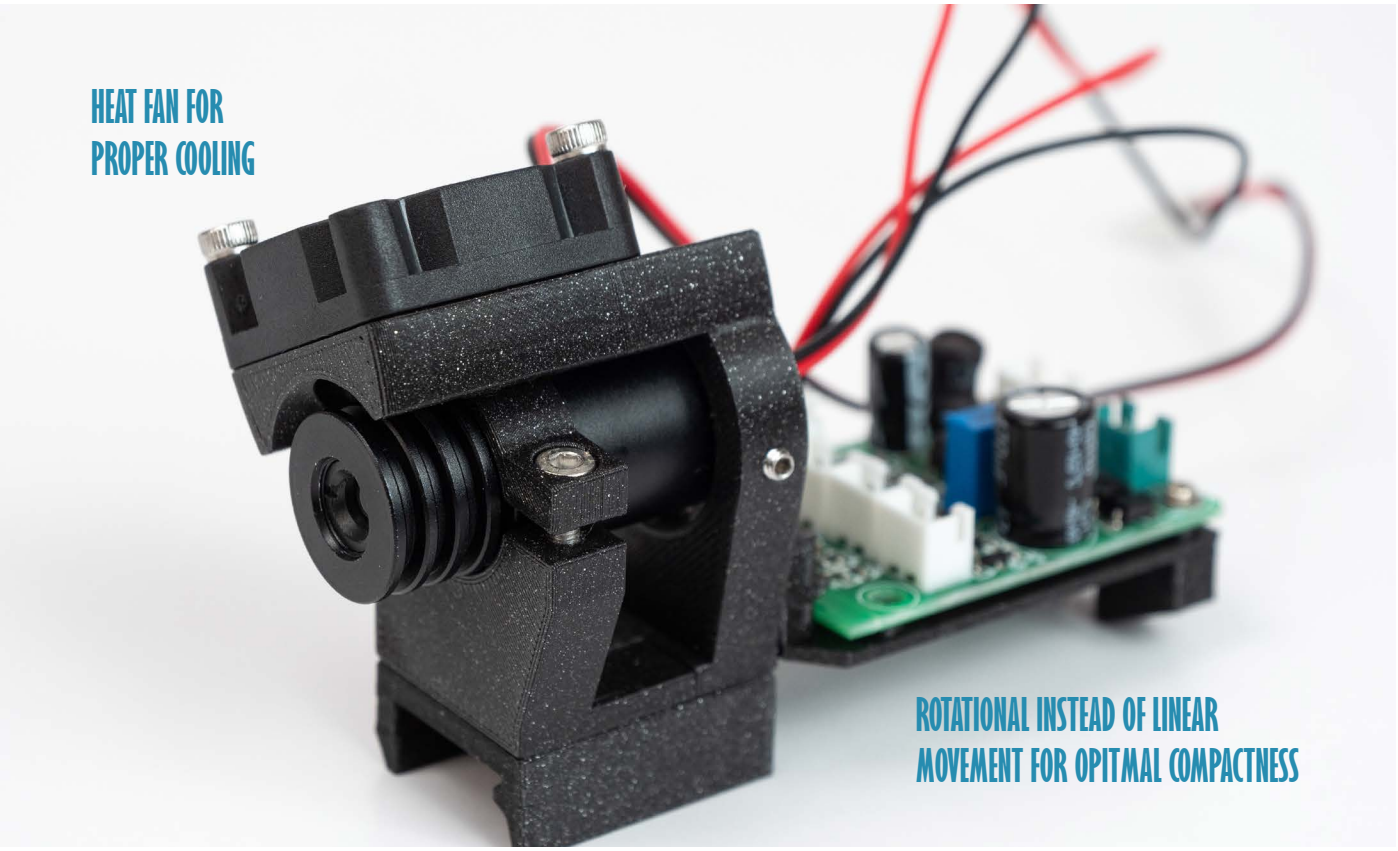


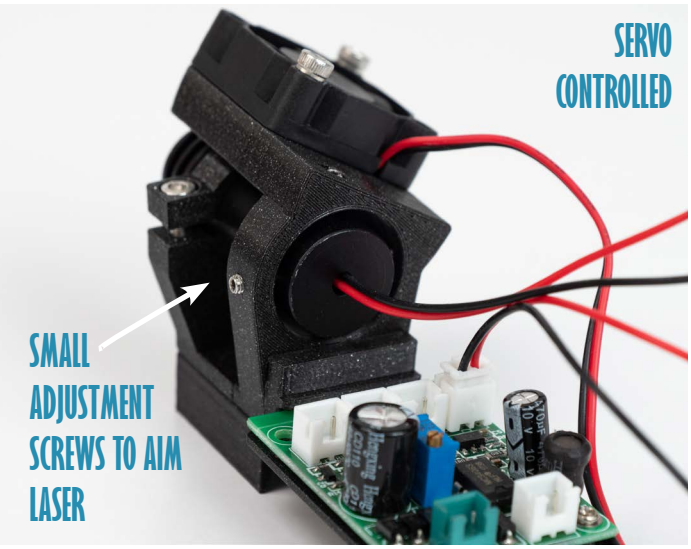


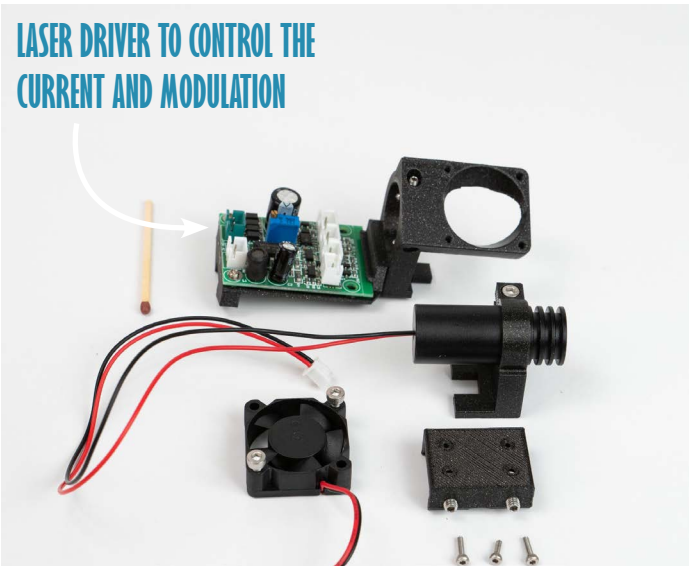
The Optical system

The laser module

The laser module holds a 30 mW 980 nm laser that has an integrated focusing lens. The mounted cooling fan ensures a cool working temperature. The adjustment screws at the back of the assembly allow the user to make small adjustments to the direction in which the laser aims to compensate for deficiencies. The module is equipped with a laser driver to control the power to the LED and to modulate the signal.



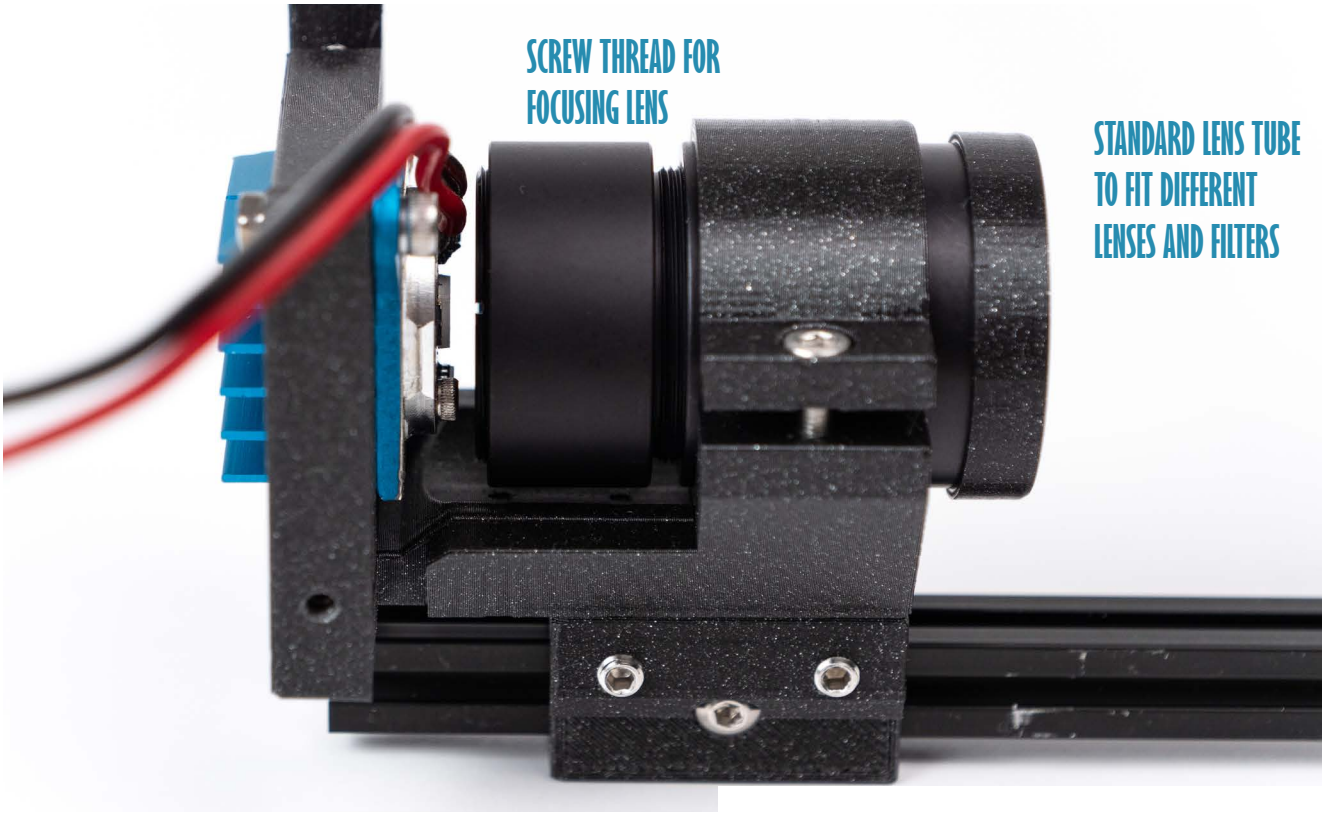


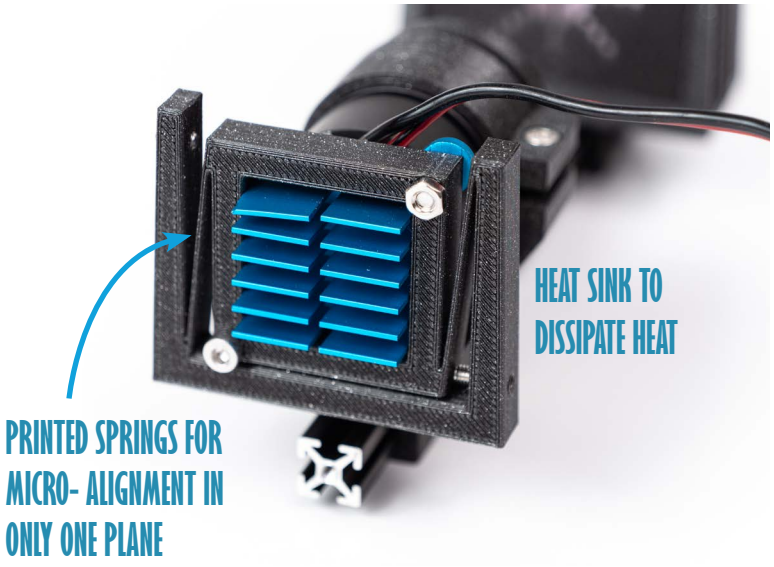


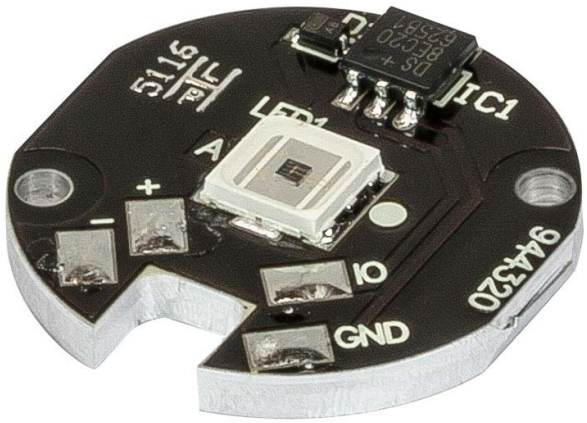
The Optical system

The LED module

The LED module holds the high-power LED module and a lens tube. The lens tube contains optics to collimate the divergent beam and filter the light. The bandpass filter will only let 980 nm light through. The lens tube has a threat for precision focusing. The LED is mounted in a quadrant with 3D printed springs to allow for micro-adjustments to center the LED precisely in the middle of the lens. The LED and the lens are integrated into one subassembly so that the LED module can be dismounted without losing the lens's calibration. The module is equipped with a LED driver to control the power to the LED.





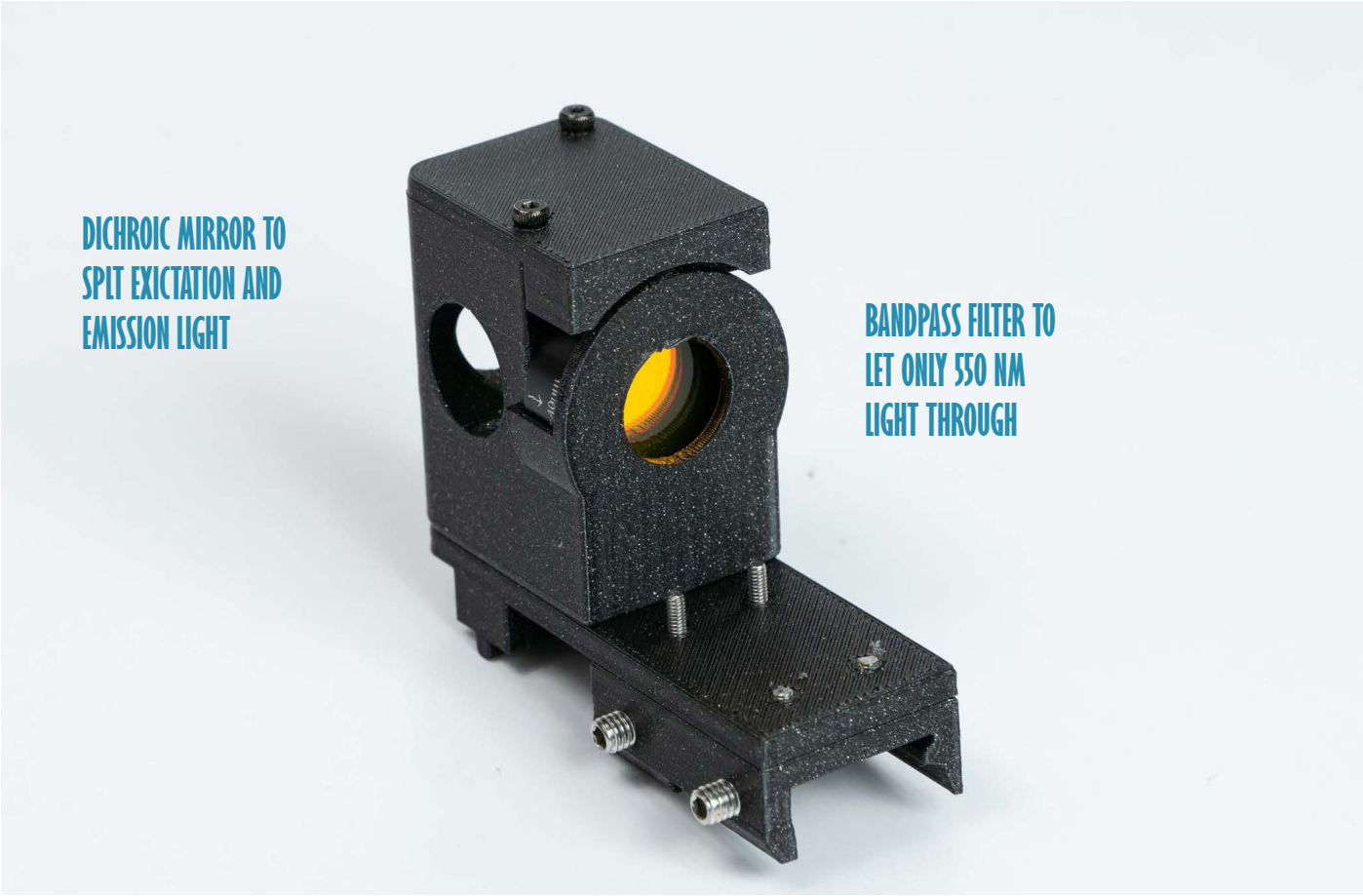


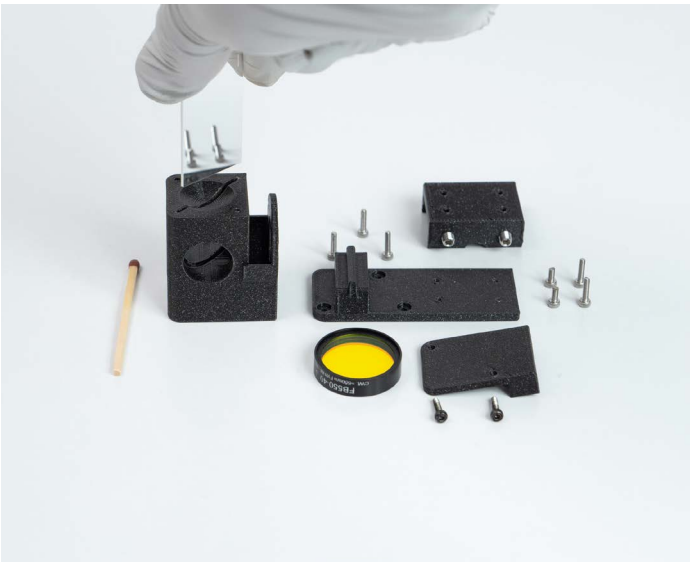
The Optical system

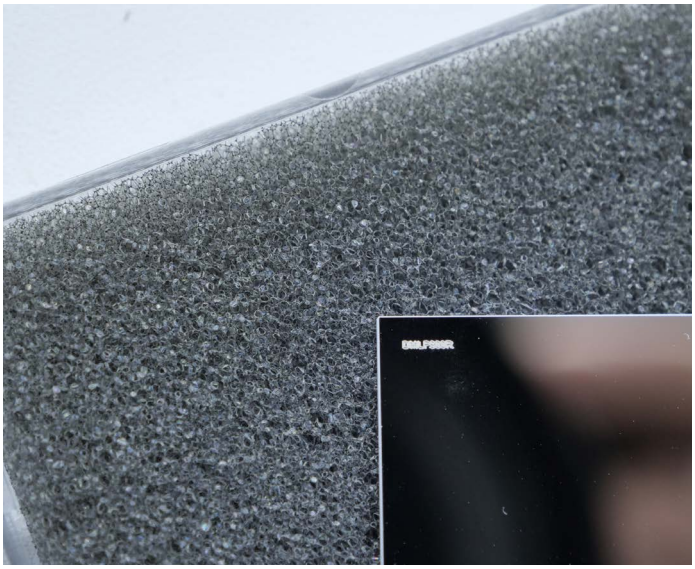
The dichroic mirror

The dichroic mirror is one of the most costly optical parts of the system. It only reflects light of a specific band of wavelengths. The mirror has to be placed at an exact 45-degree angle compared to the optical path to ensure the light focuses on the sensor.

To protect the mirror from incoming stray light, only the exact light paths are cut away from the body. Also, the vulnerable mirror is protected from mechanical stress in this way. The mirror holder allows the installation of a bandpass filter for filtering the emitted light.







The Optical system

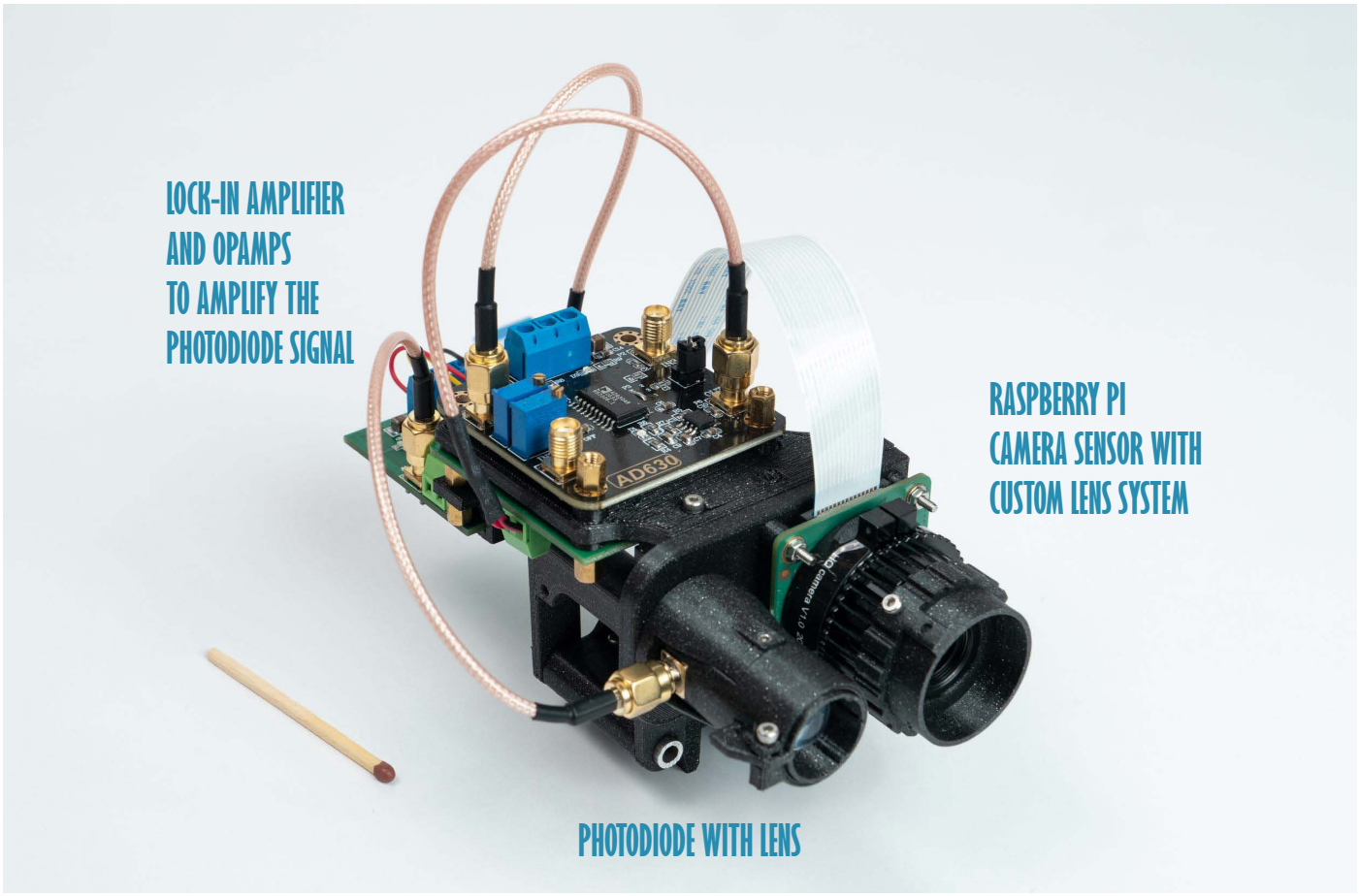
The focusing lens

The focusing lens is an achromat lens with a short focus distance and a high numerical aperture. In this way, as much emitted light can be captured as possible. Because of the small because distance, focusing is very critical. The mount is equipped with additional holes to mount it on a linear slider rail, to enable motorized focusing if needed.

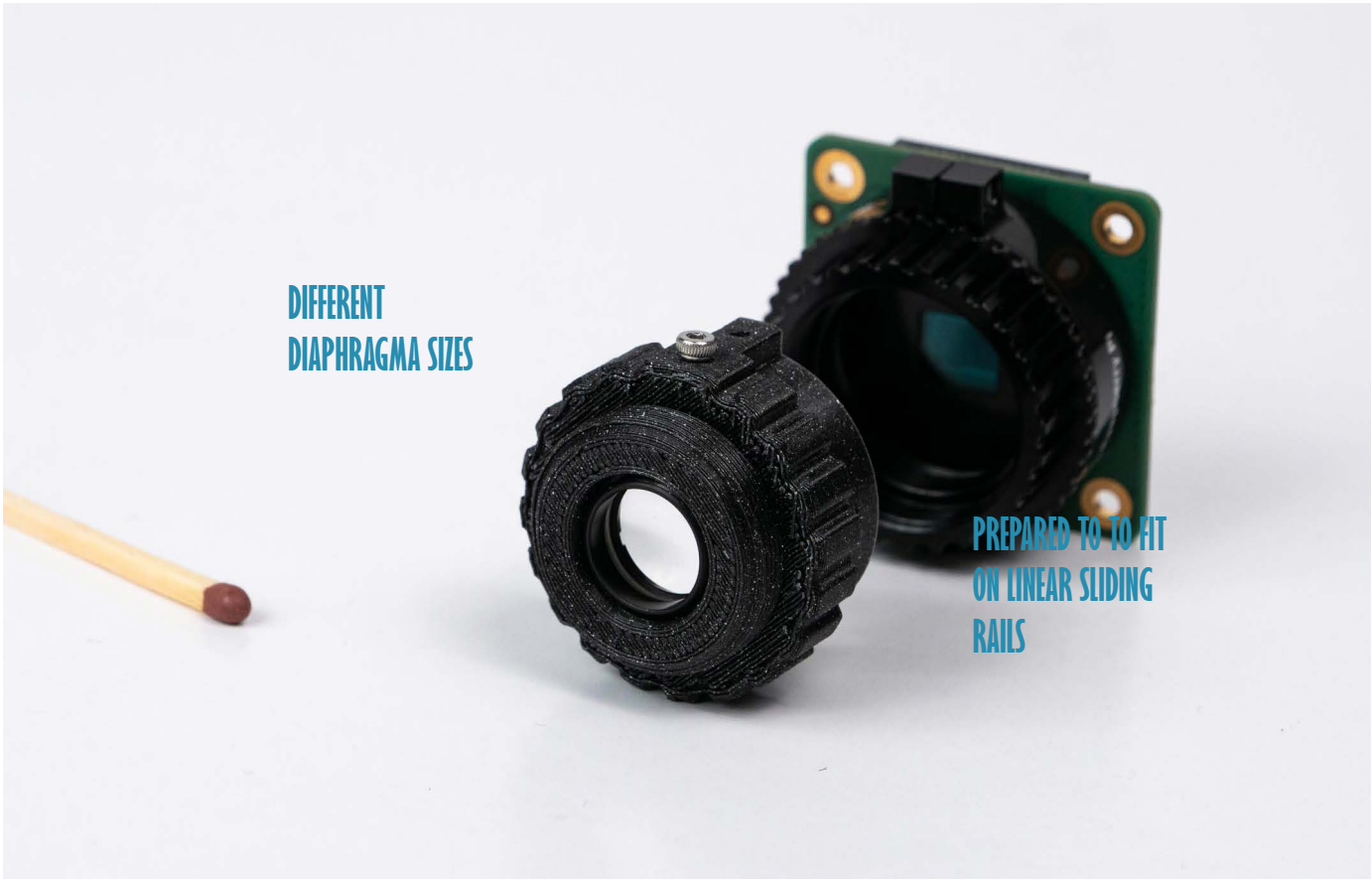
The Optical system

The switching sensor unit

Using a camera sensor or a photodiode is a crucial design choice in a strip reader. It changes the way you could interpret the signal. A camera sensor might be less sensitive, but it does give contextual information. This gives the potential benefit of assessing the quality of the lateral flow strip or the way it is used. The Block Reader enables easy comparison between the camera sensor and the photodiode by the switching mechanism. It lets you decide which sensor you want to use for the measurement. The photodiode signal must be processed with dedicated and carefully selected electronics since it is susceptible to noise. Therefore, two operational amplifiers (opamps) and a lock-in amplifier are installed. Each one has it owns characteristics and is optimized for different use cases. More research has to be done

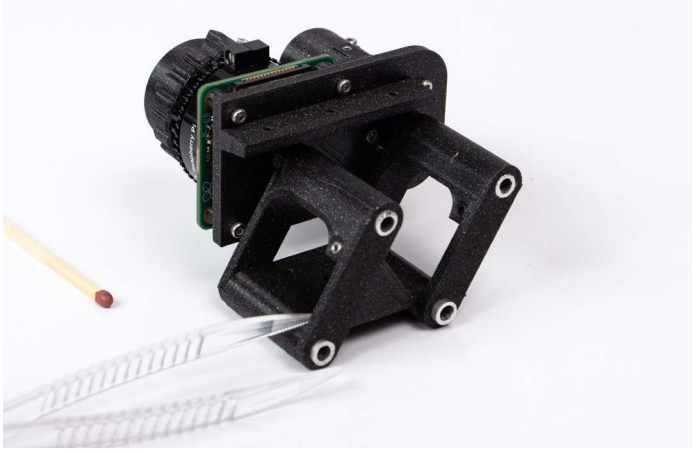


to further optimize this signal path. The camera sensor is directly connected with the Raspberry Pi. This makes the camera sensor easy to use. lets you decide which sensor you want to use for the measurement. The photodiode signal must be processed with dedicated and carefully selected electronics since it is susceptible to noise. Therefore, two operational amplifiers (opamps) and a lock-in amplifier are installed. Each one has it owns characteristics and is optimized for different use cases. More research has to be done to further optimize this signal path. The camera sensor is directly connected with the Raspberry Pi. This makes the camera sensor easy to use.



SWITCH MECHANISM TO SWITCH BETWEEN BETWEEN CAMERA SENSOR AND PHOTODIODE

SWITCH MECHANISM TO SWITCH BETWEEN BETWEEN CAMERA SENSOR AND PHOTODIODE



Further elaboration on the technical aspects of the Block Reader can be found in Appendix A, B and C.

9. Discussion

The project started with a quest to explore at topic, and it ends with a device to explore even more. But many insights have been gained. These insights help understanding what questions should be asked, who should be involved and where to look for. Asides the exploration of the development of a strip reader for the UCP-LF CAA test, it also became an exploration of what design could bring in this field.

Next steps

With the systemic design approach in mind, it does feel redundant to present a detailed roadmap of all the steps that should be taken towards the realization of a UCP-LF CAA strip reader. Instead, it is more valuable to continuously reflect on the project and adapt to the dynamics of the system. Many aspects of the project and the surrounding system remain open, like the future of the UCP-LF CAA assay. This does not mean that there is no reason to think ahead. In figure 35, some steps that could take the project further are outlined on the different levels of abstraction. In the first place, findings and their relevance are to be discussed from multiple perspectives. Not only the content should be discussed, but also the organizational nature. Who should bring this further? And how and with what? The three idea directions should be further elaborated to concepts, including scenarios. Ideally, those scenarios are co-developed with local stakeholders. Relevant partners should get involved to make the next moves together. Different perspectives will inevitably lead to scope changes, and the project should remain a quick learner to ensure that value creation is what we are after at, not the deployment of technology.

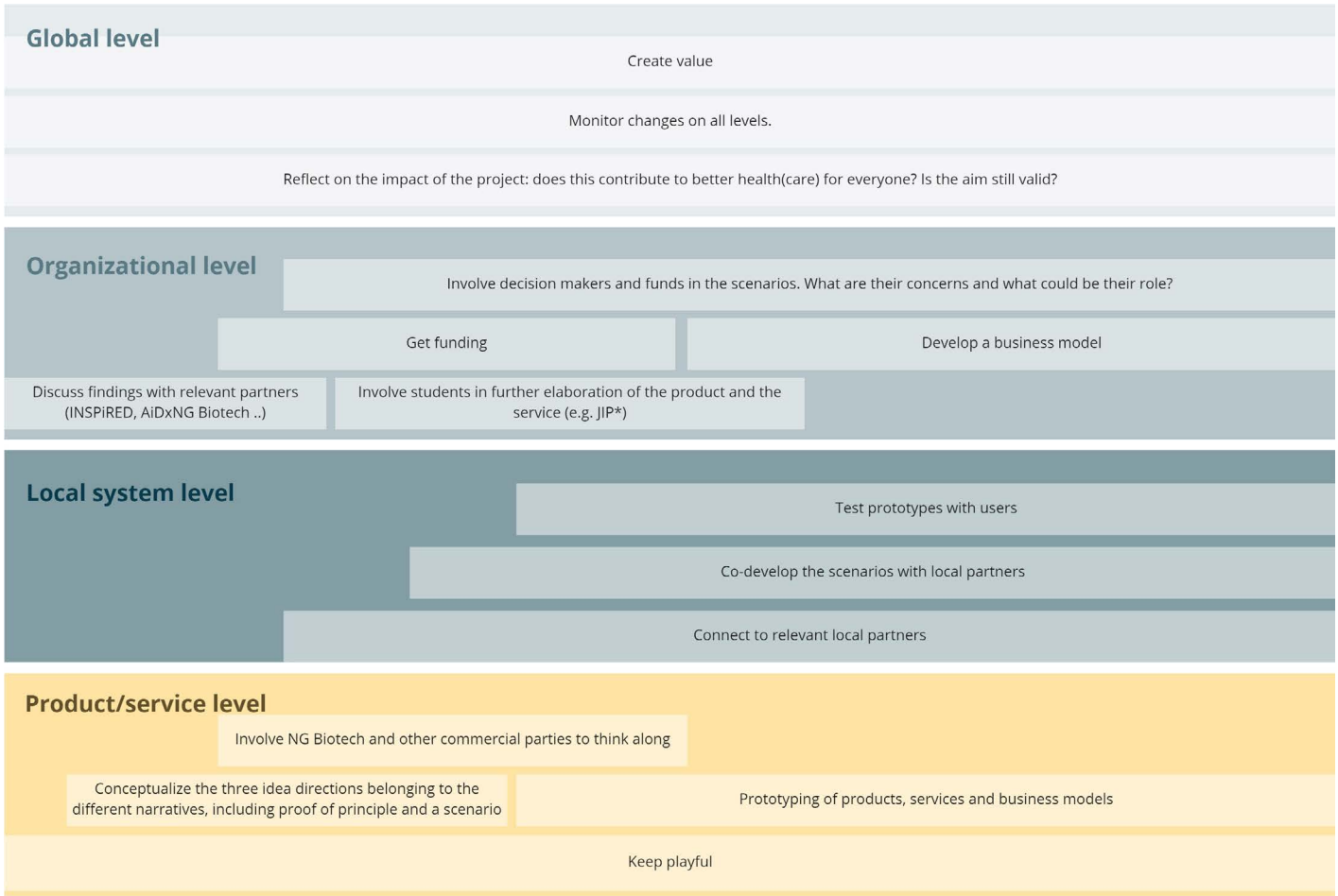
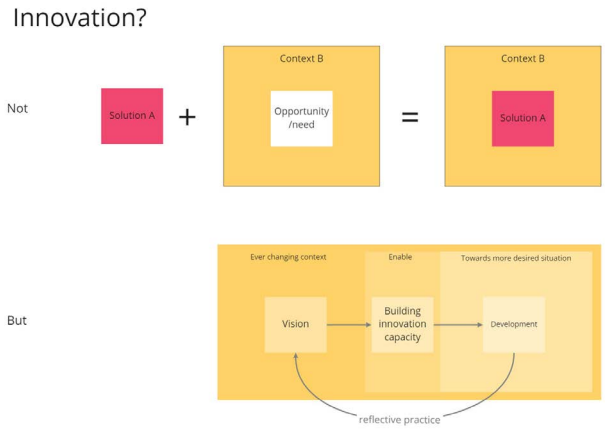


Figure 35: suggested next steps and activities

Most important insights

Designing for change

It is not about implementing a solution in a specific context. It is about infrastructuring systemic change towards a goal within the context.



- The project started as a project to explore the developmen of a UCP-LF CAA strip reader.
- I found out that such additional equipment is seen as undesired for point-of-care applications. However, this is mostly based on existing equipment, which is indeed far from user-friendly and not suitable for the context of rural areas.
- The need for data-driven decision making is broadly shared, but it lacks concrete solutions to facilitate it.
- A new narrative is needed as an alternative to the existing narrative, The new narrative frames the reader as an essential part of an integrated data-driven system, building a future proof platform adressing multiple diseases. In the new frame, the technical principle of the reader is not of importance. It could be e.,g. phone-based or open-source, as long as it fits the requirements of the context and user. But whatever technical principle is chosen, the feasiblity of it should be back-up, to create a convincing narrative. The Block Reader could contribute to the validation of these new frames.
- Many parallel projects focusing on mobile medical applications will contribute to this new narrative, as well as this project. It might be a good approach to find out how the Fionet system of the Deki reader performs and if collaboration could be interesting.
- What + How leads to Outcome. In this case a device to explore and validate technological principles **(what)** + to propose a new frame to enable partnerships and have a prototyping tool for further development **(how)** leads to the acceleration of the development of UCP readers **(outcome)**. The what and how where co-developed with the desired outcome and should be continuously evaluated.
- Closely monitore contextual changes to identify and make use of opportunities for progress. At any time, the dynamics of the system have to be closely watched. For example: if UCP plays a role in a COVID-19 surveillance system: what role could a reader play in there? What kind of developments are happening with respect to data and connected devices? Could parts of the proposal be validated in different settings? Are there other ways to contribute to the higher level goals? With a broad understanding of the technology and system, and strong innovation capacity within the project, the project remains flexible. As Kees Dorst says: "In a complex world, the future belongs to the quickest learner"[57].

Global level

Towards leaving no one behind: healthcare for everyone

- COVID-19 could change the way we think about Universal Health Coverage
- COVID-19 could unlock opportunities for innovation in (surveillance) diagnostics. UCP could play a role in this

Organizational level

Towards systemic approaches driven by multi-stakeholder collaborations

- Global collaboration is needed but many hurdles to overcome (COVAX)
- It is of general interest to co-develop readers alongside the UCP strips, with schistosomiasis only as case study. Linear development of a strip reader after introducing UCP-LF tests would be a missed opportunity because 1) valuable time is wasted 2) there might be a chance to optimize the strip for the reader's performance instead of vice versa 3) better strip readers are needed anyways, even without UCP-LF CAA
- Organizations consider data-driven decision making as an important strategy, but know how and infrastructure is lacking.

Local system level

- Towards access to basic needs to foster progress and inclusiveness
- New business models and E-healh are quickly emerging in Africa
- Surveillance will play an increasingly important role in diagnostics. Climate change and global pandemics could further accelarate this need.
- Social factors should be carefully considered in designing diagnostics, especially when moving towards data driven decision making.
- Accessible diagnostics are worthless if not accepted.
- Data-driven decision making needs an ethical framework. Not only to cope with data privacy, but as well to manage responsibility, accountability and ethical and careful data interpretation. The autonomy of individuals and communities should not be compromised.

Product/service

Towards improved accessibility of diagnostics and accurate data

- UCP-LF CAA is promising in performance, but challenging in practice. We have to remain critical: for which exact application is it most promising, and what is needed to unlock this potential? If the sample preparation cannot made easier, it might be valuable to focus on surveillance systems, in which sample pooling could play an interesting role. Otherwise, it might be interesting to focus on case-management of even more neglected forms of schistosomiasis like genital schistosomiasis.
- Readers and every other 'extra' tooling for diagnostics at the point of care are seen as a big hurdle. However, data-driven decision-making needs digital tools. Framing tools differently could help to make use of emerging opportunities.
- There is much to explore to optimize a reader's performance with creative smart solutions.
- The software is as important as the hardware.
- Contextual information captured with a camera sensor instead of a photodiode can aid (algorithmic) interpretation.
- Dynamic range is of concern when capturing a broad range of infection intensities.
- Doubling the intensity of the light is more effective than doubling the amount of UPC, in terms of emission intensity.
- The most critical part of the product is the excitation and separating excitation from emission.
- To increase accuracy, movement patterns of the strip or the light and combined imaging could be studied.
- The UCP particles on the strips tend to clump together, resulting in unexpected emissions.

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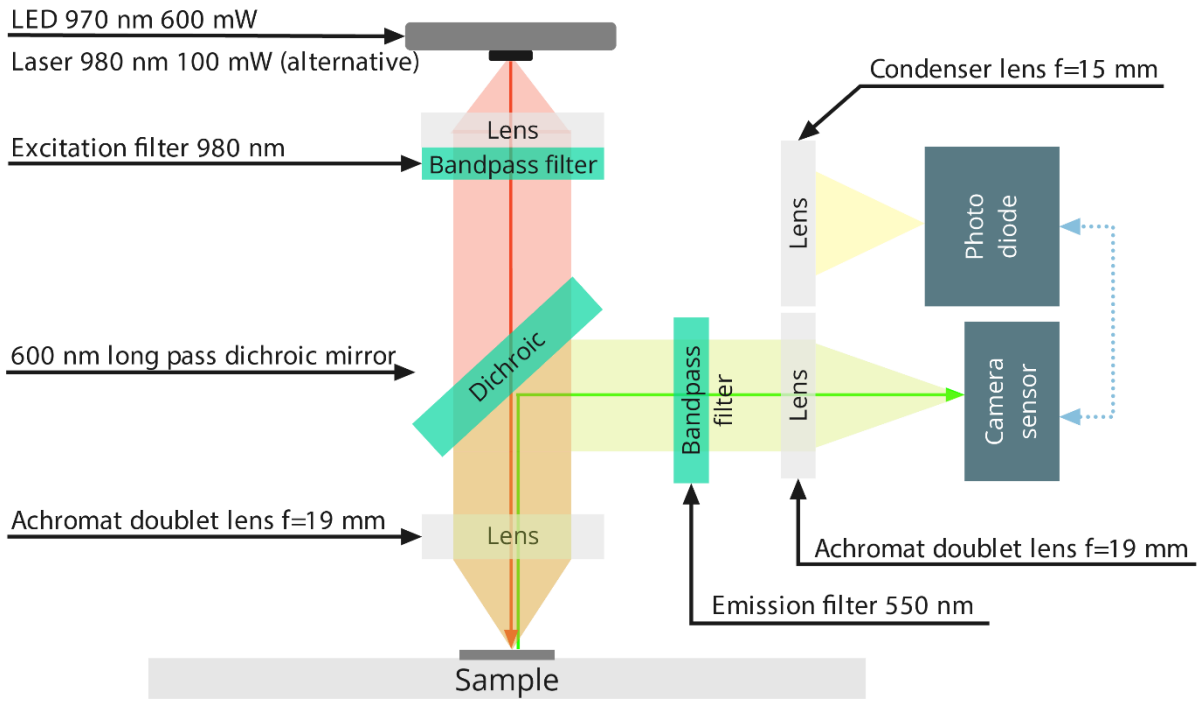
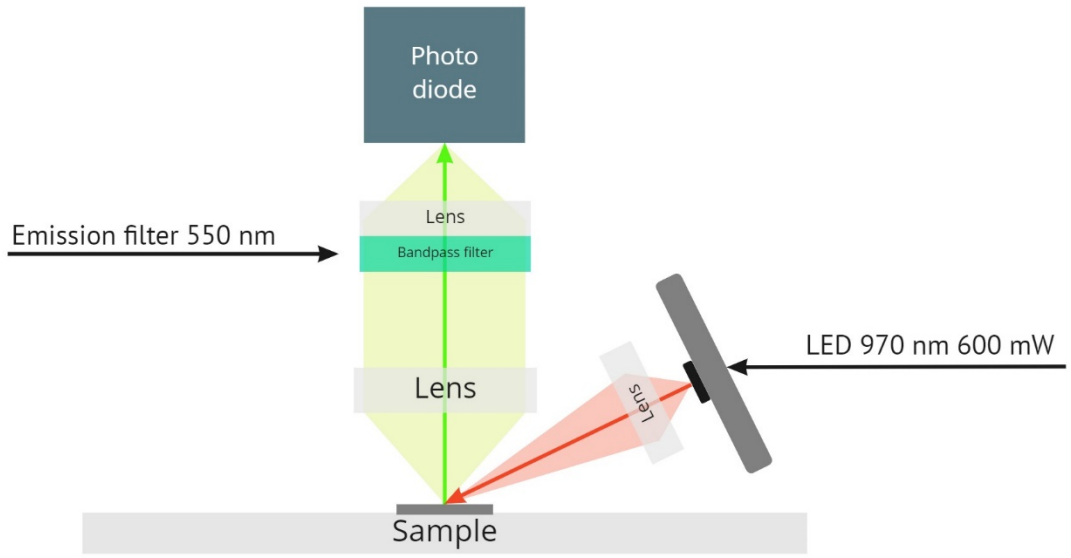
Appendix A – optical design considerations of the Block Reader



Confocal vs off-axis

An important design choice that is made when designing a strip reader is using a confocal or off-axis optical path. This means that the same lens is used to converge the source light on the sample as to converge the light coming from the sample, like in figure FIXME. In an off-axis configuration, those optical paths are separated. The light comes in from an angle or from beneath; see figure below. The most important advantages and disadvantages are summarized in the table below.

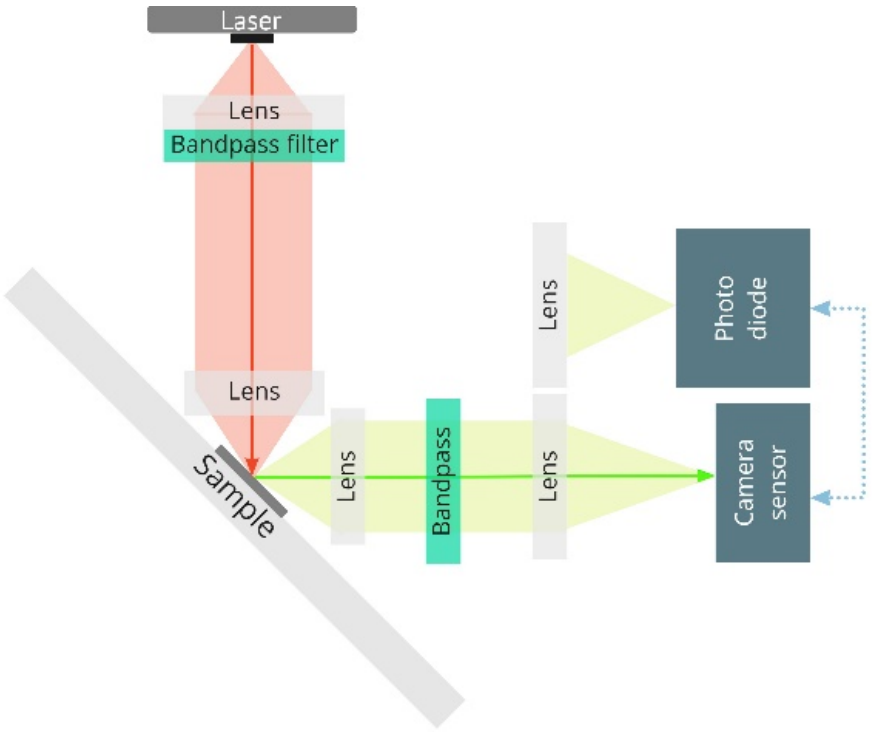


	Confocal	Off-axis
Alignment	+	--
Positioning tolerance	+	--
Optical complexity	--	+
Optical performance	+	+-

Plusses and minuses of a confocal and off-axis configuration

An important consideration to choose a confocal setup is for the performance. The sample is illuminated straight from the top, allowing for a smaller spot size. One other major is the much higher flexibility regarding the detector and sample positioning. When using the off-axis principle, accurate positioning of the sample is highly critical in order to get comparable results. In contrast, when using the confocal principle, the positioning of the sample is less critical. Dialunox chooses the confocal configuration for the last mentioned reason, as described in their patent[111].

However, the complexity and especially the cost is of the optical system is compromised with the confocal principle. One needs a dichroic mirror to split the incoming and outcoming light by their wavelength. Not only does this significantly add to the price of the device (the dichroic mirror used in the Block reader costs € 360), it also limits the flexibility of the system. If a different wavelength is required that is not within reach of the dichroic mirror, it has to be changed.
The Block readers design takes into account off-axis configurations as well. For this, an extra mirror could be used, the laser could be positioned at another Makerbeam, or the sample could be placed under an angle, as illustrated in figure below.

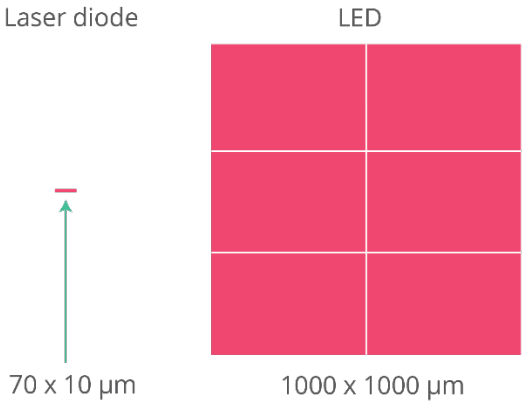


Excitation spot size

The excitation spot size is the size of the projection of the source (the laser or LED) on the strip. In the design and the performance of the reader, the spot size is a crucial factor. The spot size is related to different parameters of the design. Those relations and the trade-offs will be discussed next.

In the ideal optical system, all the emitted energy of the source is guided to the area of interest, which is the strip in this case. To come close to this ideal situation, a lens is used to collect the diverging light of the source, and a second lens is used to converge this light to the desired area. If the projection plane (the strip) is exactly in focus, the spot will be an image of the source. This means that one constraint of the minimum spot size is depicted by the surface area of the emitter times the magnification factor of the two lenses.

In the case of a laser, the emitter area is rectangular and has a very small size of 70 x 10 µm or even smaller[112]. The M970D3 high power LED, in comparison, has an emitter size of 1 x 1 mm, containing 6 active regions, see figure below. As a result, with 1:1 magnification, the minimal spot size of the LED is limited to 1 x 1 mm.

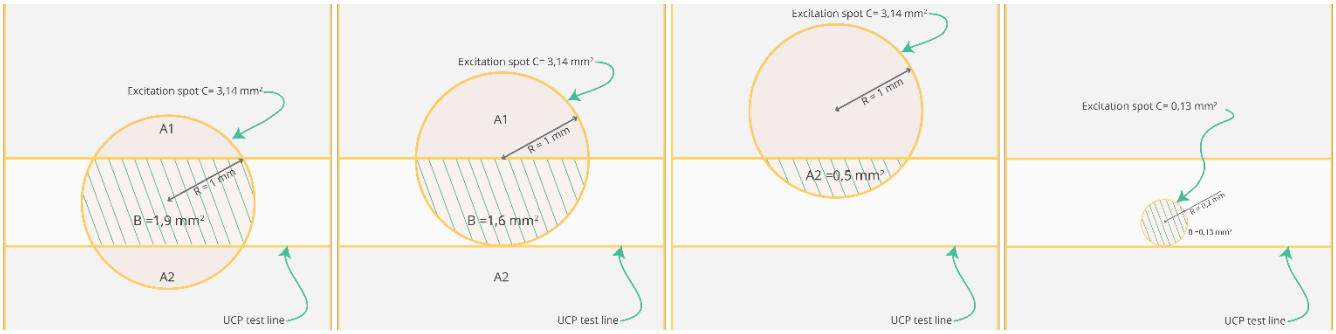


Size comparison of emitter area of LED and laser

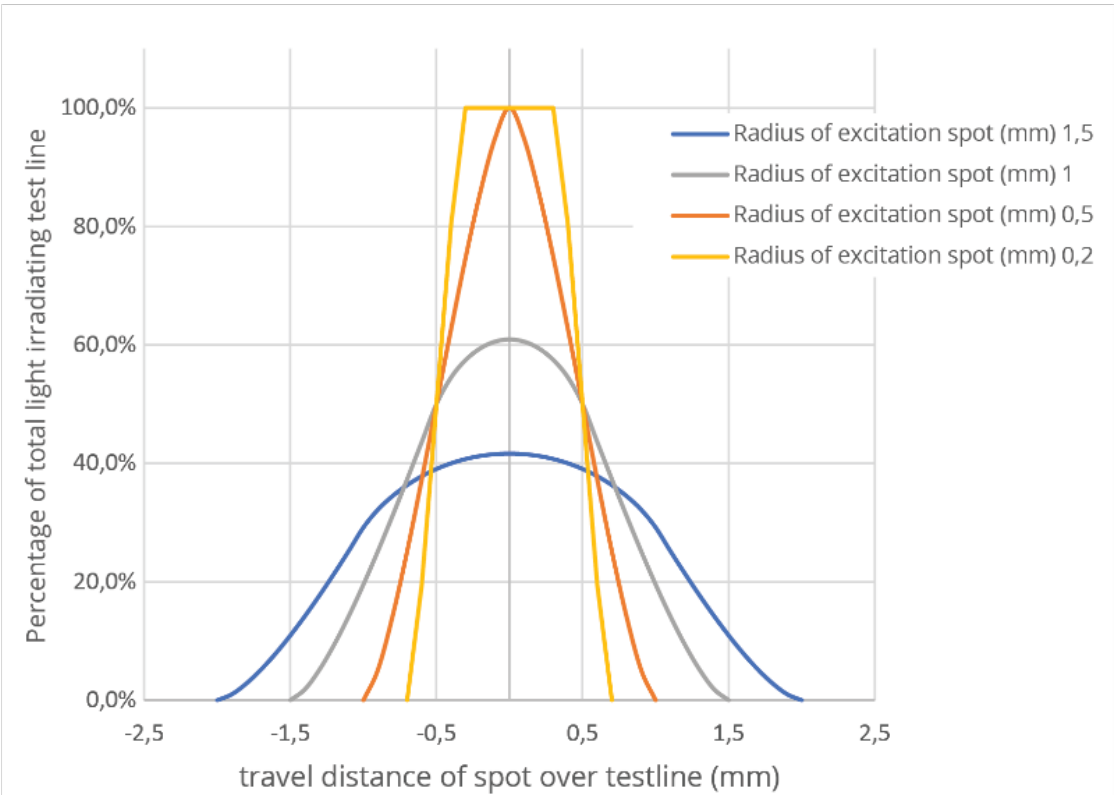
The impact of the spot size on the performance of the system is related to four factors:

- The surface area that is excited
- The intensity of the light
- The uniformity of the UCP particles
- The tolerance of the system
- The complexity of the system

Because the test line on which the UCPs are located is a rectangular area (of 4 x 1 mm) with a different size than the spot (which is assumed to be circular), the excited area is defined by the overlap between the spot and the test line. If the maximum width of the spot is wider than the test line, the total amount of energy that is exciting the UCP particles is limited to the total amount of energy minus the energy that is not overlapping with the test line, see figure below.

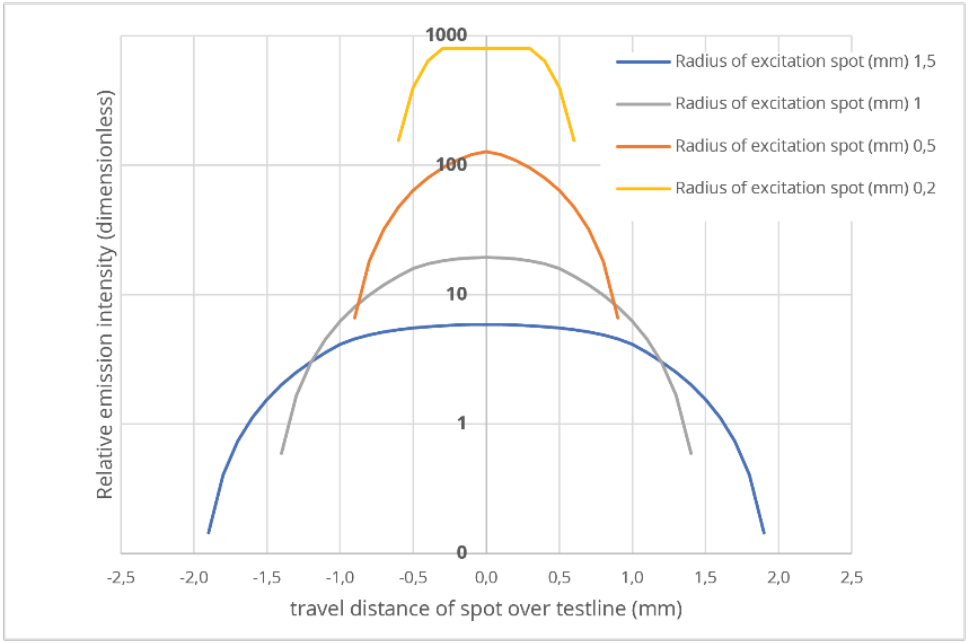


Calculated overlap area (B) for different positions of a spot



The percentage of the total amount of energy that is irradiating the test line, for different radii of the spot. A smaller radius has higher efficiency and a steeper transition when moving across the test line.

The next factor is the intensity (density) of the light. Because of the nature of photon upconverting, there is a quadratic relation between the excitation intensity and the emission intensity. This has an interesting consequence for the effect of the spot size. When the surface area of the spot is decreased by a factor of two, the intensity of the light is doubled. Due to the quadratic law, the emission intensity has increased by a factor of 4 while only halving the area of emission. Thus, to maximize the emission energy, focusing the excitation energy on a small area has a significant impact, as shown in the graph below (mind the logarithmic scale). This finding is also supported by findings from literature[113].



The relative emission intensity in relation to different spot sizes. A small radius (0,2 mm) mathematically results in total emission energy that is 223 times higher than when using a spot radius of 1,5 mm.

Does this mean that the excitation spot should focus on an area as small as possible? From a mathematical perspective, yes. However, other factors play a role as well. As observed with experiments, the UCP particles tend to form clumps instead of homogeneously spreading across the test line. With that in mind, using a bigger focus area averages possible variations across the area, increasing the device's reliability. With that in mind, an area covering at least one quarter (1 mm) of the length of the test line (4 mm), would be the advised minimum.

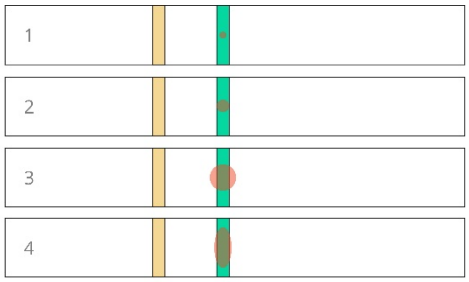
Next to that, a small spot size is more sensitive to small variations in the focus distance. Position variances of only tenths of millimeters, or inconsistency of the thickness of the strip could cause considerable signal variations.

A last important consideration is the complexity of the system. Converging a light source to a very small area, without losing energy, is an optical an mechanical challenge. As described, the light-emitting area should be very small to start with, eliminating using a LED as an option. A laser diode has an elliptical beam shape which requires a special asymmetric lens to converge it to a point. Next to that, a laser diode beam is astigmatic. This means that the diverging light in the y-direction has a different focal point than the diverging light in the x-direction. Consequently, the spot can not be exactly focused in one point. Compensating for this effect requires precisely tuned cylindrical lenses[114].

Conclusion excitation spot size:

- An excitation spot wider than the test line causes light losses.
- However, the impact of the intensity of the light on the emission is far more significant (quadratic relation). Concentrating the excitation energy in a small area gives large gains in emission energy.
- Practical and optical limitations limit the minimum spot size to at least 1 mm.

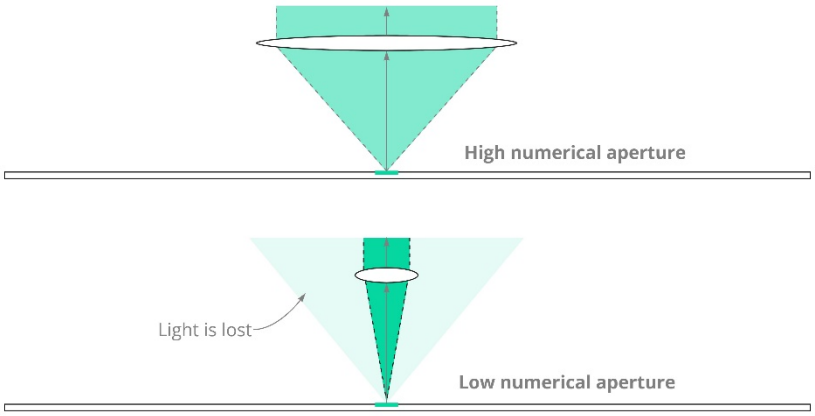
A last remark on the beam shape: as mentioned before, the beam shape of a laser diode is elliptical (without compensation), a LED diverges in all directions with the same angle, giving a round beam shape and a square projection (of the square emitter). It would be interesting to study how those natural shapes can be used to the advantage of the application. For example, by aligning the long side of the ellipse with the test line, covering as much of the test line as possible (see below FIXME number 4).



Different spot (red) sizes and shapes

Numerical aperture and focal length sample lens

The numerical aperture is a measure of the maximal angle light can enter the lens. A high numerical aperture allows a lens to gather much light at a short distance from the sample. To optain a low limit of detection, it is important to catch as much light coming from the sample as possible (see figure below).



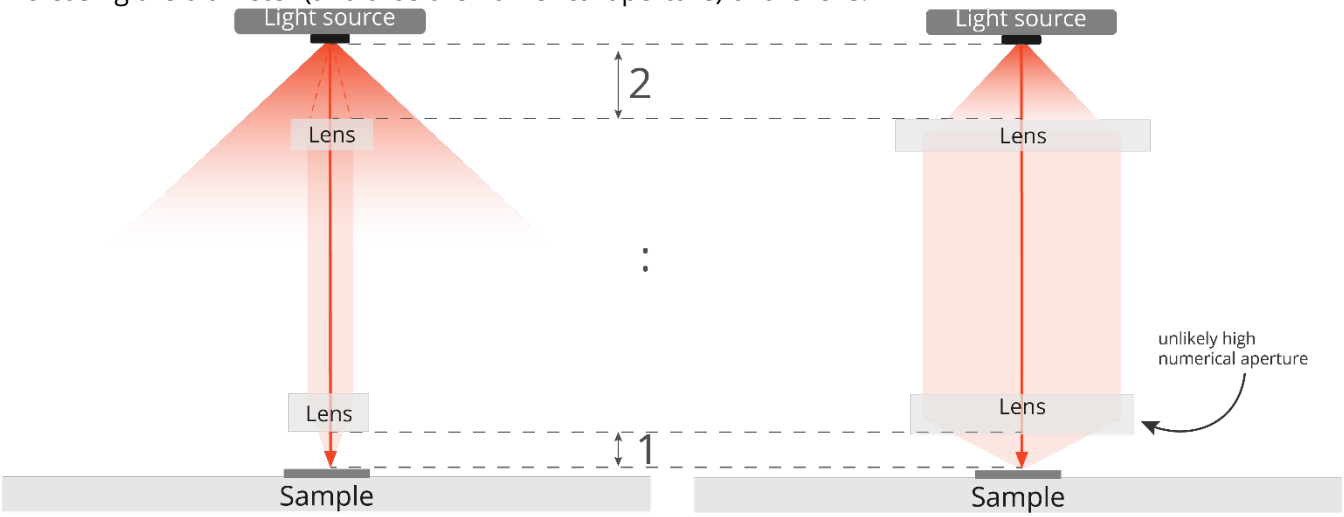
A high numerical aperture has two downsides for the Block reader.

1) The depth of field decreases with a higher numerical aperture. This means that the positioning in the Z-direction becomes more critical.
2) The beam width increases (if the focal length stays the same), or the focal length decreases (if the beam width stays the same). A wider beam needs bigger filters, lenses, and mirrors. This not only increases the size of the device, but as well the costs. Especially the filters and mirrors are priced per surface area. A smaller focal length again decreases the depth of field, thus the positioning becomes more critical. Another downside of a small focal length is the working distance. With a very small working distance (e.g., 4 mm), the lens is so close to the sample that it could physically obstruct the placement. Especially in the future, when the lateral flow strips are embedded in a casing, this could become problematic.

As a rough indication, it is advised to maintain a minimum working distance of 10 mm and a maximum beam width of 10 mm. The resulting NA (dimensionless) would be 0,45.

Numerical aperture and focal distance light source lens

The aperture of the lens collimating the diverging LED or laser emission is also of relevance, especially for the LED. As described before, the emitter surface area of the LED is a limiting factor in spot size. The ratio between the focal length of the LED lens and the sample lens determines the magnification of the projected image, in this case, the projection of the emitter on the test line. By using a long focal length of the LED lens and a short focal length of the sample lens, the emitter image is demagnified. Thus, the spot size decreases. The challenge is that by increasing the distance between the LED and the lens, light of the highly divergent LED is wasted, when not increasing the diameter (and thus the numerical aperture) of the lens.



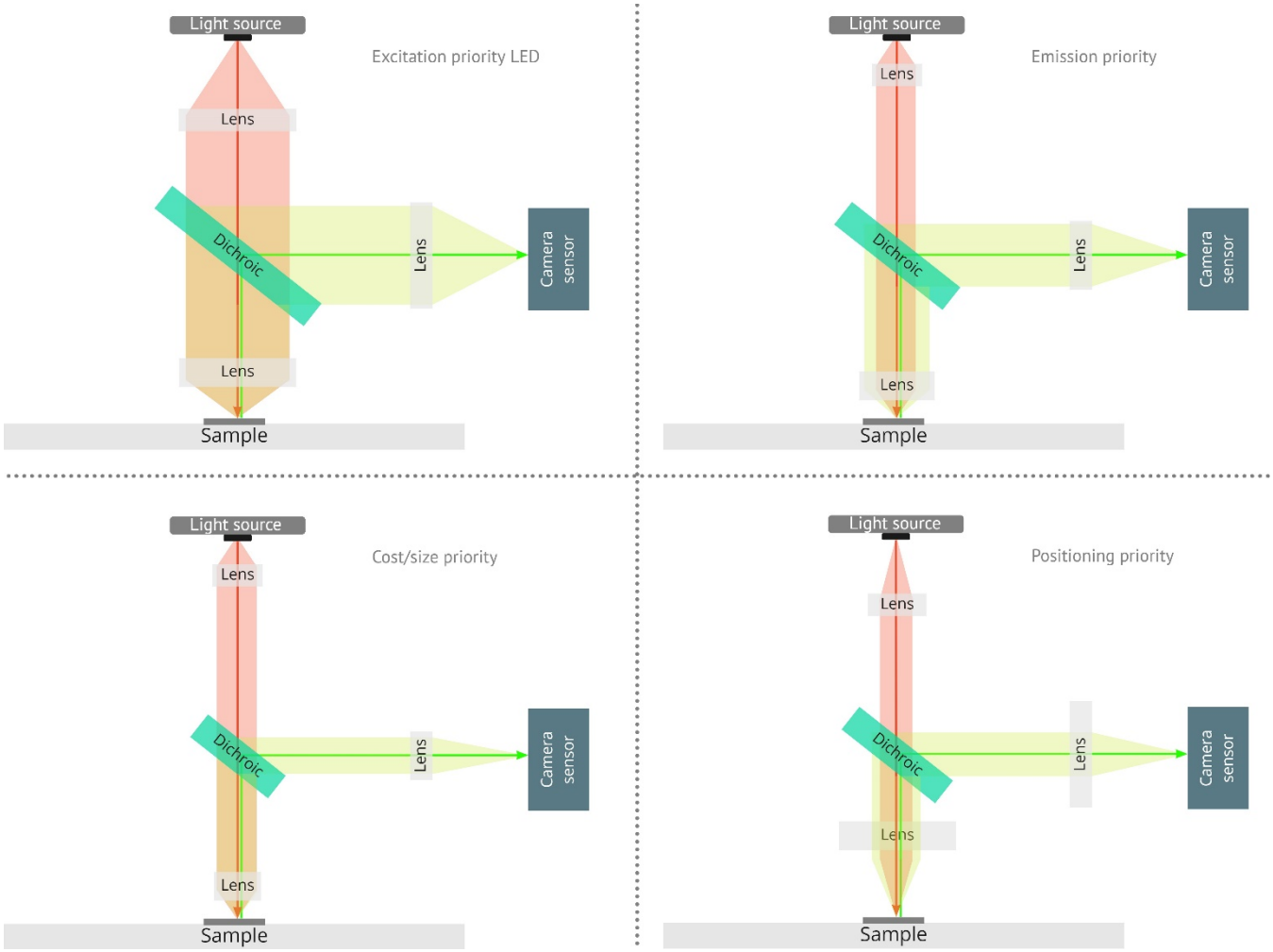
With a demagnifying ratio, one has to compromise the efficiency: light is lost. At the right, optical limits are reached with respect to the maximal numerical aperture

Optical design considerations

In this optical system, many variables are closely related to others. Depending on the design priorities, different choices can be made. Four different design priorities can be distinguished and are summarized in the table and figure below. In the case of using a laser, the two upper rows can be neglected since a laser lens has a high aperture and short focal distance by default. The Block reader is designed to modify those parameters relatively easily.

LED	**Excitation priority** -small focus of spot -demagnification of LED beam		**Emission priority** -catching maximum emission		**Cost/size priority** -keeping beam widths small		**Positioning priority** -keeping focal lengths long and beam width small	
NA LED lens	high	wide beam	high	small beam	high	small beam	small	small beam
FL LED lens	long		short		short		medium	
NA sample lens	high	wide beam	high	medium beam	medium	small beam	medium	medium beam
FL sample lens	short		short		short		long	

Different design parameters for four design priorities. NA = Numerical Aperture. FL = Focal Length. In pink, the limiting parameters are indicated. Note, this table assumes a LED being used as source.

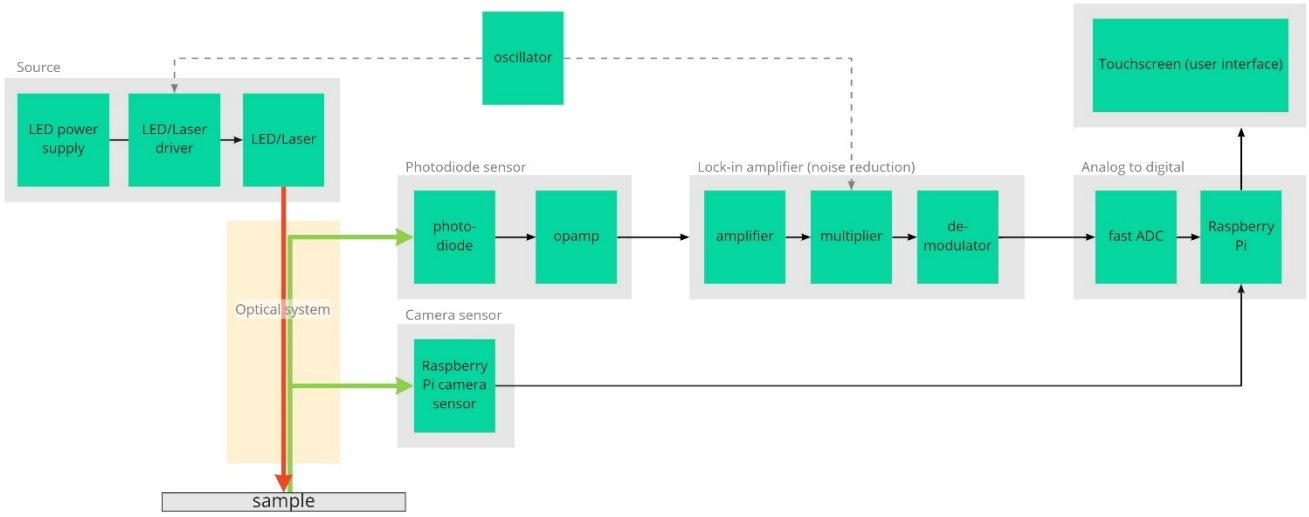


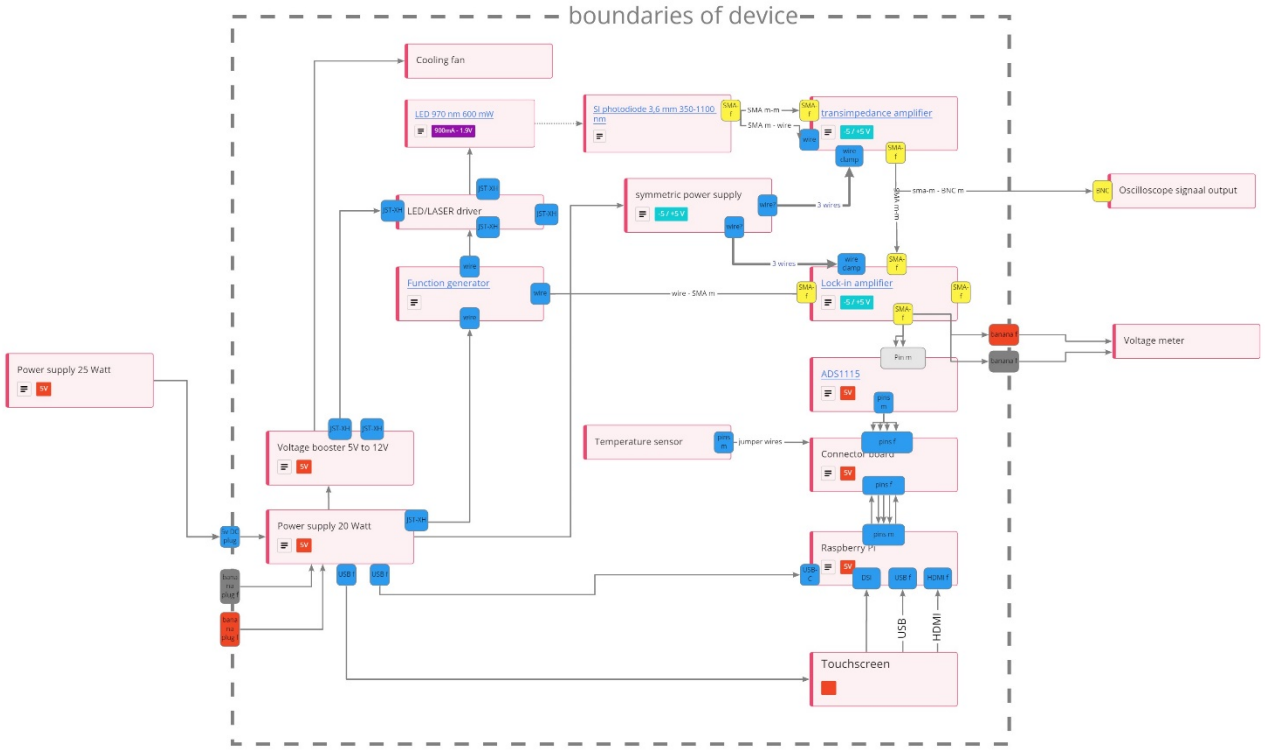
A visual representation of the different design prioritie.

Appendix A – Electronics design considerations of the Block Reader

Electronical system design

Function and system





Wiring and connector design

Photodiode noise

Photodiode noise is generated by two noise sources: shot noise and thermal noise. In photovoltaic use, which will be considered for this application, thermal noise is the dominant noise source. It is caused by the thermal generation within the photodiode due to the shunt resistance. One of the factors determining the thermal noise is the temperature. The noise

increases with a higher temperature. In some applications, detectors are being cooled down to low temperatures for low noise performance[115].

Noise reduction – lock-in amplification

The low-pass filter in the lock-in amplifier rejects all frequencies above a certain threshold, which means that only the DC component of the signal remains. A high frequency low-pass filter has a fast reaction time, which enables the device to scan the strip faster. A low frequency low-pass filter has better noise reduction capabilities at the cost of the scanning speed. In the first instance, the filter has to filter out the modulation frequency that is applied to the source. This means that the filter cut-off frequency has to be significantly lower than the modulation frequency.

Modulation frequency

Thus, there is a dependency between the modulation speed and the scanning speed, which is determined by the filter. In the current design, the filter has a cut-off frequency of around 30 kHz. The modulation frequency has to exceed this frequency. However, this imposes some challenges.

An unexpected effect that seems to be occurring is related to the decay time of the phosphor upconversion. This lifetime signature is unique for different compositions and shapes of the phosphor particles[116].

Because of this, the signature can be used to distinguish different phosphor particles, which bring new opportunities in terms of multiplexed assays, as patented in 2018[50]. The signature of the $NaYF_4$:Yb^{3+}, -Er^{3+} particle can be seen in the figure below. The pink rectangles indicate a single pulse length corresponding with different modulation frequencies as a comparison.

This visualization explains why problems occur at high modulation frequencies (far above 1000 Hz). At 30.000 Hz, the pulse length is very short in comparison with the lifetime signature. As a result, the emission will not have diminished before the next excitation occur. From this perspective, it is advised to not exceed 1000 Hz as modulation frequency.

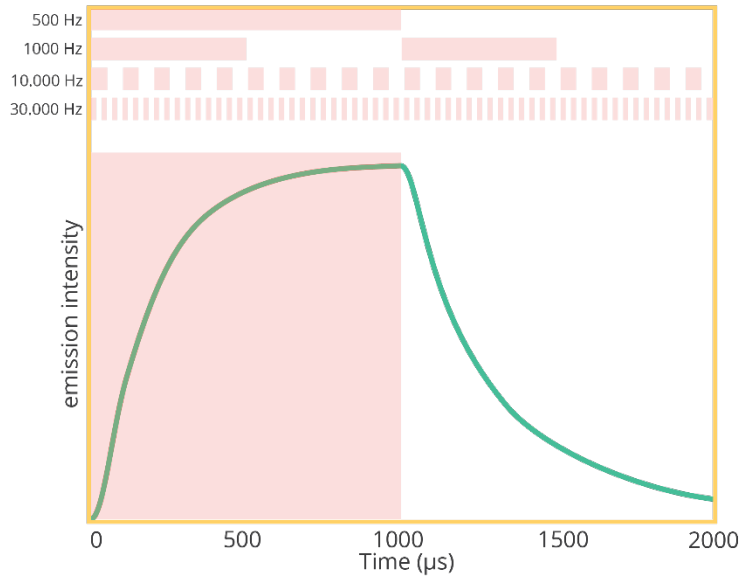


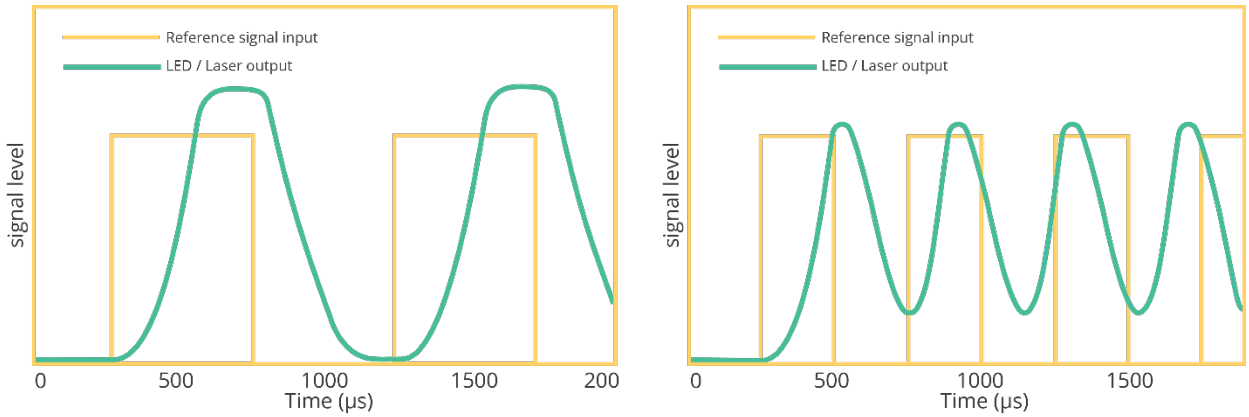
Figure X: Emission over time of a $NaYF_4$:Yb^{3+}, -Er^{3+} particle[50] excited by a single pulse (pink). The pink rectangles indicate the pulse length corresponding with different modulation frequencies as a comparison.

Frequenty (Hz)	100	1000	10.000	30.000	100.000
Pulse width	50%	50%	50%	50%	50%
Duration of pulse (µs)	5000	500	50	17	5

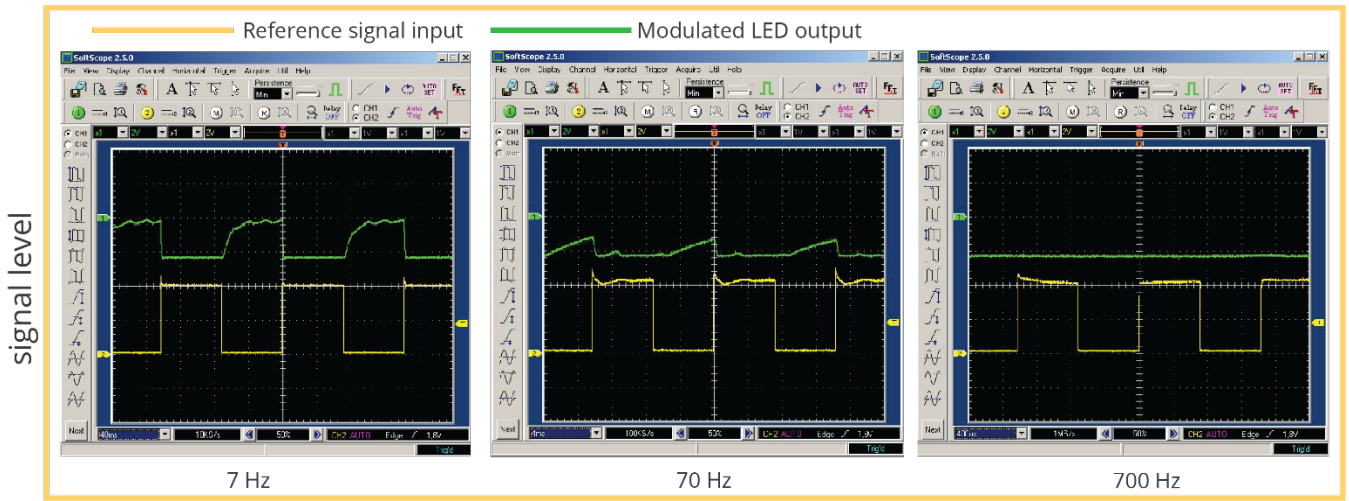
Modulation frequency (Hz) vs duration of pulse (µs)

Another challenge with regards to the modulation frequency is controlling the LED or laser. For optimal performance of the lock-in amplifier, the source has to follow the reference signal (pulse) as close as possible. Both LEDs and lasers are capable of very fast switching frequencies well above 10 MHz. However, switching a high current device with high precision and high frequencies demands a high-quality driver.

With the low-cost LED drivers that were used in this project, the switching is performed with delay and low accuracy, causing the output of the LED or laser not to match the reference signal (see below). In the next figure, actual measurements of the LED driver combination can be found.



Example of source modulation at (left) 1000 Hz and (right) 2000 Hz. The LED / Laser output does not follow the square wave accordingly. At 2000 Hz, is does not fully turn off anymore.



Oscilloscope measurement of modulated LED output (green) measured with the photodiode and OP129 opamp compared with the modulation signal (yellow). Note: the LED output is measured in

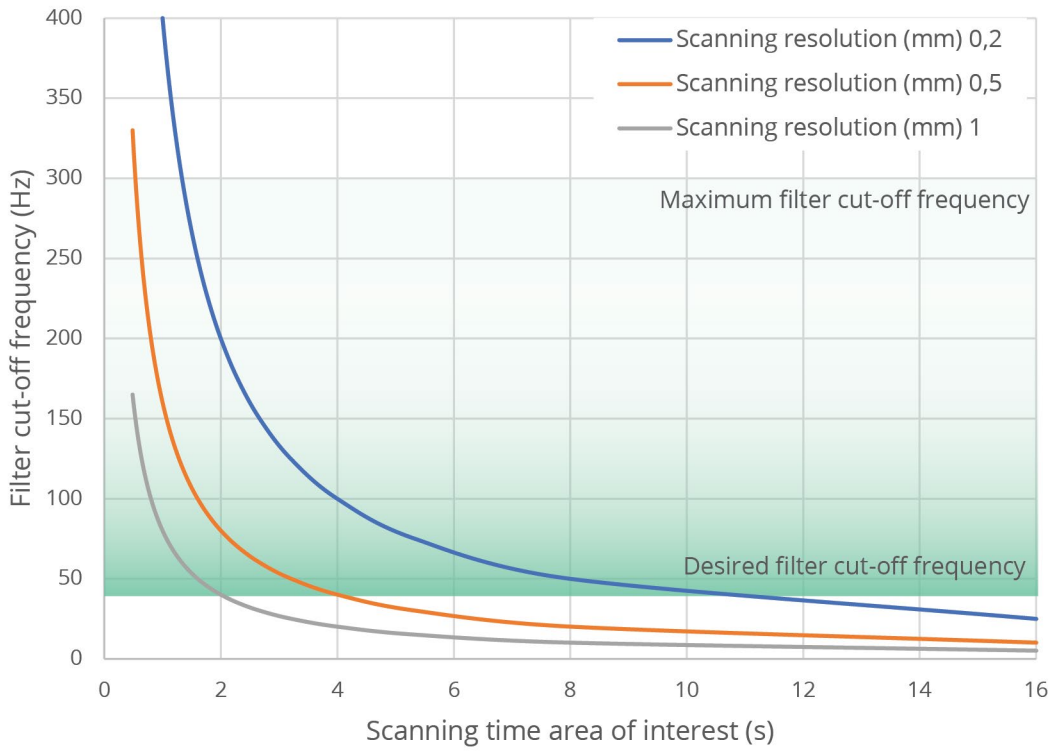
reversed polarity. At 700 Hz, the LED has a continuous output, regardless of the switching reference signal, demonstrating the driver failing to modulate at such frequencies.

To effectively use the lock-in amplifier, the modulation has to be further improved. Suggestions are to

- design a custom PCB equipped with fast switching MOSFETs
- try better quality TTL drivers
- improve current driver

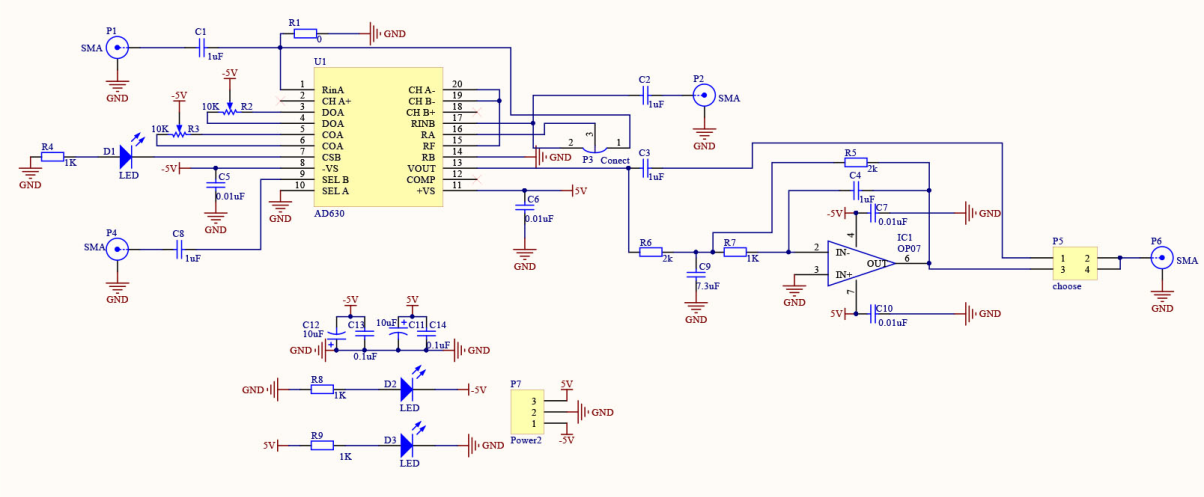
Signal low-pass filter

In this graph, the calculated relations between scanning resolution, cut-off frequency and scanning time are displayed.

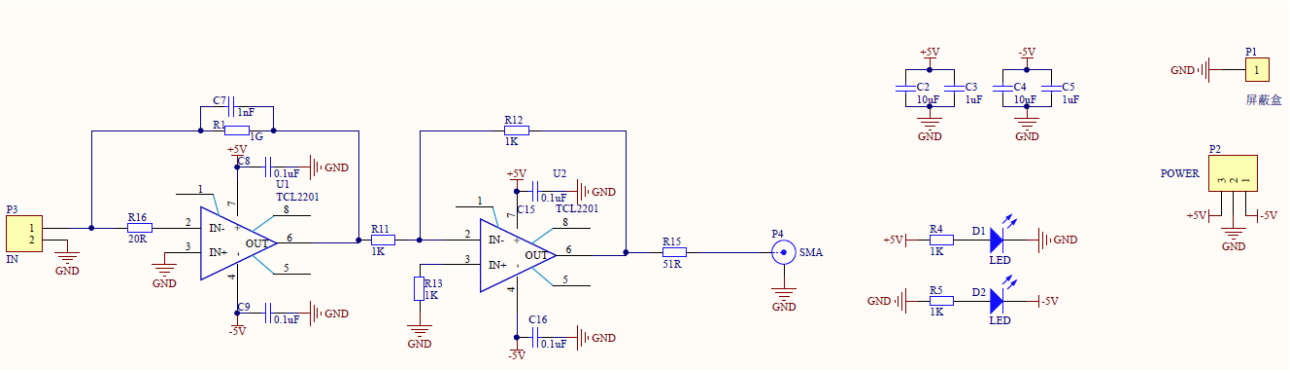


Schematics

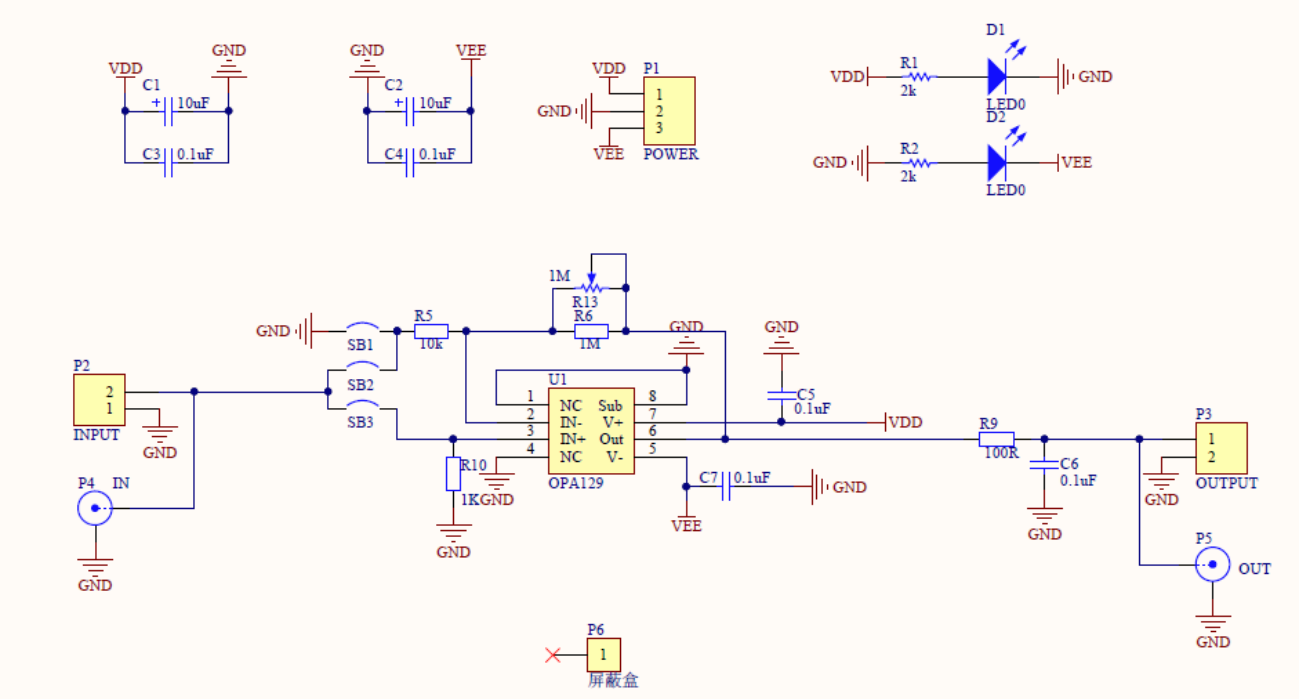
Lock-in AD630 schematic



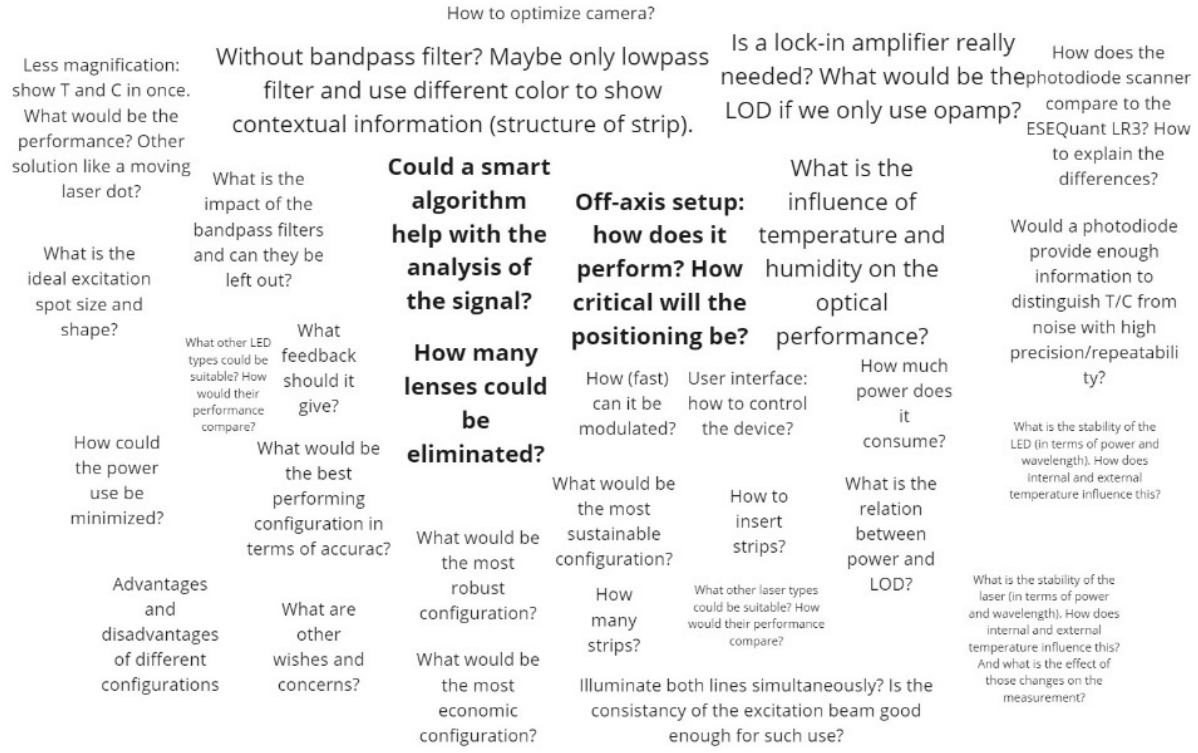
TLC2201 schematic



OPA129 schematic



Appendix C – research questions for further experiments with the Block Reader



Appendix D – project brief

Concept design of UCP-LF CAA strip reader for schistosomiasis diagnosis — project title

Please state the title of your graduation project (above) and the start date and end date (below). Keep the title compact and simple. Do not use abbreviations. The remainder of this document allows you to define and clarify your graduation project.

start date 11 - 12 - 2020 — 11 - 06 - 2021 end date

INTRODUCTION **

Please describe, the context of your project, and address the main stakeholders (interests) within this context in a concise yet complete manner. Who are involved, what do they value and how do they currently operate within the given context? What are the main opportunities and limitations you are currently aware of (cultural- and social norms, resources (time, money,...), technology, ...).

Schistosomiasis is an important neglected tropical disease. The disease is caused by a parasitic worm that causes damage to the organs on the long term. The infection is caused by Schistosoma larvae penetrating the skin when the body is in contact with infected water. Current control programs are effective to some extent. Fully eliminating the disease by using precise mapping in combination with (preventative) treatment is not happening yet. This is partly due to a lack of highly available, sensitive and context specific diagnostic tools and the challenges of data collection. UCP-LF CAA is a technology under development, with the potential to improve schistosomiasis diagnosis dramatically. The technology requires a strip reader to read out the result, bringing the opportunity to design a context specific strip reader that is not only able to indicate the result, but also to share the data in a way that helps organizations to control the disease.

The project is commissioned by LUMC, as an exploration project to bring the technology closer to practice. LUMC (more specifically the Clinical Parasitology Group) is leading in researching and developing the UCP-LF CAA technology for Schistosoma detection, being involved in the topic for multiple decades.

Several parties are already producing devices that are capable of reading the UCP-LF CAA strips. However, those readers are not quite as accessible (not all off the shelve and also not very affordable) and not designed for use in rural contexts. In addition, the reader should facilitate not only the diagnostic process, but also the data processing and sharing in a larger (diagnostic) system.

The sample preparation and diagnosis of schistosomiasis can be done with a variety of methods, all requiring basic laboratory equipment and skills. To make the diagnosis available to rural setting, the required procedure and equipment should be as easy, fast and low-cost to use as possible. The strip reader is one chain in this procedure.

The team consists of:

Student: Ludo de Goeje
Master: Integrated Product Design, Industrial Design Engineering, TU Delft
Client: Lisette van Lieshout / Michel Bengtson (LUMC)
Graduation chair: JC Diehl
Mentor: Armagan Albayrak
Technical expert: Tope Agbana

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introduction (continued): space for images

Project canvas (summarized project brief)

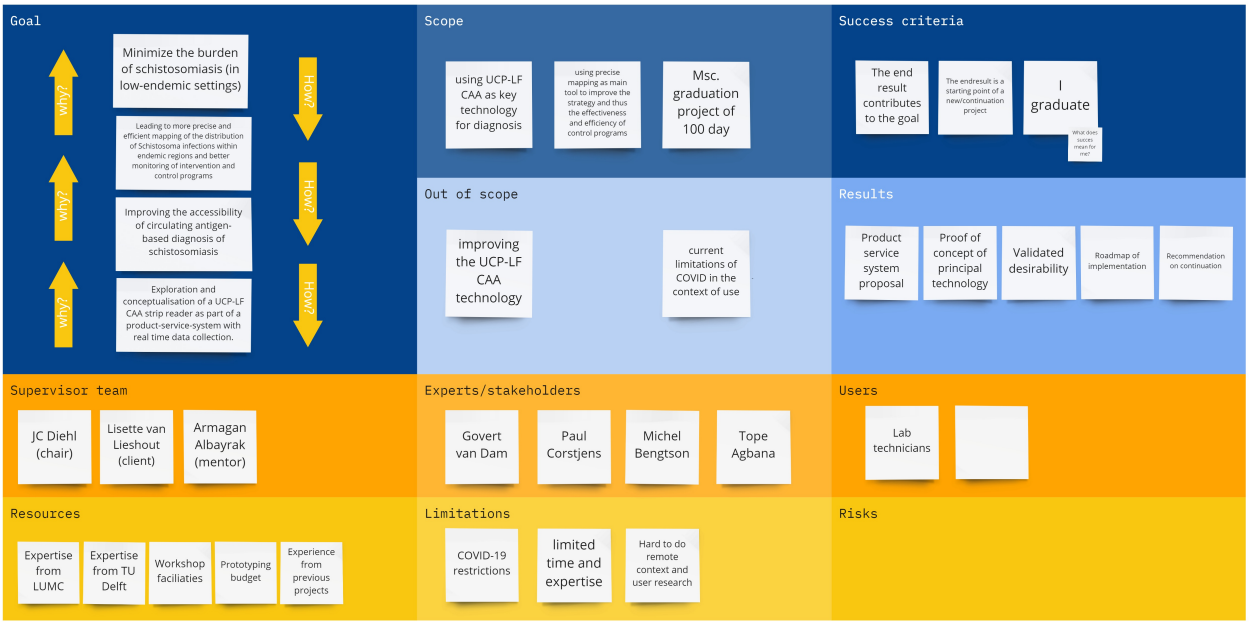
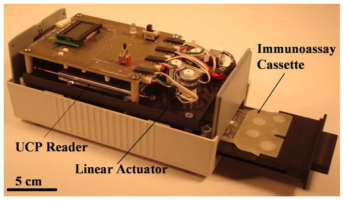


image / figure 1: Project canvas: summary of project brief

UPlink

Packard FluoroCount

ESEQuant LFS reader



University project

UCP module

ESEQuant Go

image / figure 2: Examples of strip readers capable of reading fluorescence strips

Initials & Name _____ Student number _____

Title of Project _____

PROBLEM DEFINITION **

Limit and define the scope and solution space of your project to one that is manageable within one Master Graduation Project of 30 EC (= 20 full time weeks or 100 working days) and clearly indicate what issue(s) should be addressed in this project.

Improving the accessibility of circulating antigen-based diagnosis of schistosomiasis, leading to more precise and efficient mapping of the distribution of Schistosoma infections within endemic regions and better monitoring of intervention and control programs.

The scope of the project includes:
-using UCP-LF CAA as key technology for diagnosis
-using precise mapping as main tool to improve the strategy and thus the effectiveness and efficiency of control programs
-Msc. graduation project (IPD) of 30 ECTS, equivalent to 100 days (20 weeks)
-current limitations of COVID-19 in project execution
-Test and treat at local communities as starting point
-Nigeria as intended market

The scope of the project excludes:
-improving the UCP-LF CAA technology itself
-improving the sample collection process
-current/direct limitations of COVID-19 in the context of use

ASSIGNMENT **

State in 2 or 3 sentences what you are going to research, design, create and / or generate, that will solve (part of) the issue(s) pointed out in "problem definition". Then illustrate this assignment by indicating what kind of solution you expect and / or aim to deliver, for instance: a product, a product-service combination, a strategy illustrated through product or product-service combination ideas, ... In case of a Specialisation and/or Annotation, make sure the assignment reflects this/these.

Assignment:
To design a product-service system concept that fulfills the need for an easy to use, affordable and portable UCP-LF CAA strip reader that is suited for the context and purpose of use. The solution contributes to the accessibility of UCP-LF CAA based diagnosis of schistomiasis in community settings in Nigeria.

Expected results
-Product service system proposal (concept design) of of a UCP-LF CAA strip reader
-Proof of concept of principal technology
-Validated desirability
-Roadmap of implementation
-Recommendation on continuation

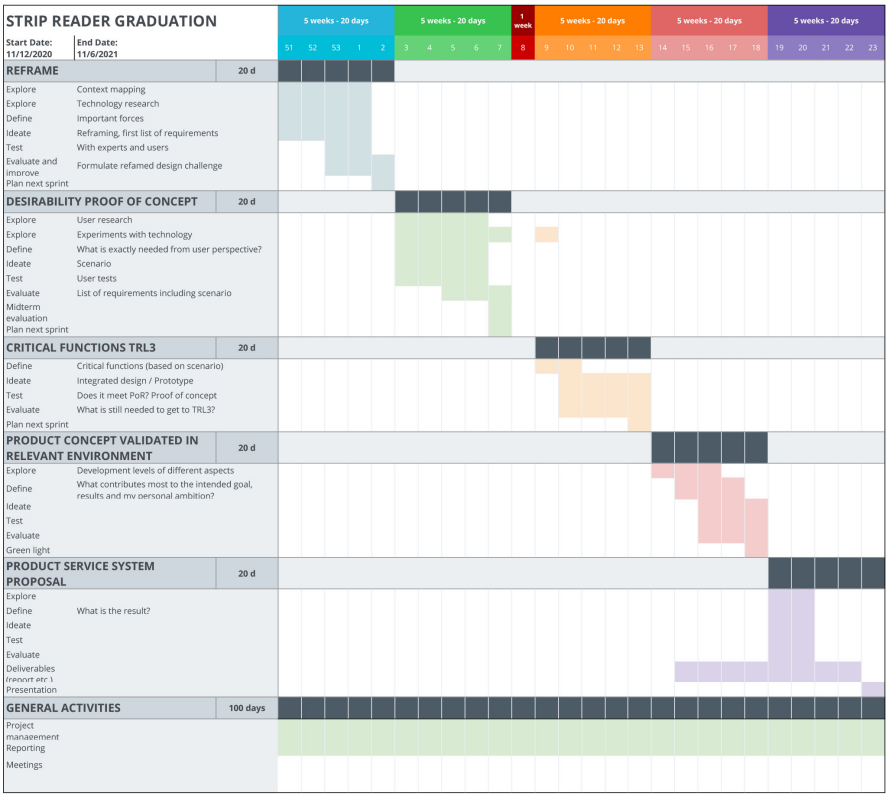
Initials & Name _____ Student number _____

Title of Project _____

PLANNING AND APPROACH **

Include a Gantt Chart (replace the example below - more examples can be found in Manual 2) that shows the different phases of your project, deliverables you have in mind, meetings, and how you plan to spend your time. Please note that all activities should fit within the given net time of 30 EC = 20 full time weeks or 100 working days, and your planning should include a kick-off meeting, mid-term meeting, green light meeting and graduation ceremony. Illustrate your Gantt Chart by, for instance, explaining your approach, and please indicate periods of part-time activities and/or periods of not spending time on your graduation project, if any, for instance because of holidays or parallel activities.

start date 11 - 12 - 2020 11 - 6 - 2021 end date



I plan to work in 5 sprints, in which the (intermediate) solution is improved and evaluated every cycle. Within the sprints, a familiar design cycle or multiple cycles will take place.

Due to having my own business next to graduation, I will graduate for 4 days a week. In week 8 of 2021 I will take one week off.

Initials & Name _____ Student number _____

Title of Project _____

MOTIVATION AND PERSONAL AMBITIONS

Explain why you set up this project, what competences you want to prove and learn. For example: acquired competences from your MSc programme, the elective semester, extra-curricular activities (etc.) and point out the competences you have yet developed. Optionally, describe which personal learning ambitions you explicitly want to address in this project, on top of the learning objectives of the Graduation Project, such as: in depth knowledge a on specific subject, broadening your competences or experimenting with a specific tool and/or methodology, ... Stick to no more than five ambitions.

Throughout my study career I was steering towards sustainable, non-profit and societal projects often. In the bachelor, I choose Towards Circular Product Design as elective. In my masters, I focused on a frugal urine centrifuge design for schistosomiasis diagnosis, (AED), a concept design for composting human bodies as alternative for burials/cremations (ACD), Medisign elective (Capita Selecta) and the elective Design for Emerging Markets. In IDE projects, I like to experiment with technologies and to prototype a lot. However, besides my studies, I developed more strategic and process minded competences. For me, this project has it all. A very thorough understanding of the system as a whole is needed, as well as the ability to integrate all the relevant factors in a integrated (technical) design. The biggest challenge and learning in this project for me will be the user research and user experience design.

In terms of personal leadership, balancing my work, my graduation project and my private life will require a considerable effort. From my experience, I will work hard and with a high quality standard. However, I often struggle with meeting the mandatory deliverables (for example writing the report). This project will be the challenge to prove that I can manage myself well enough.

FINAL COMMENTS

In case your project brief needs final comments, please add any information you think is relevant.

Initials & Name _____ Student number _____

Title of Project _____