MSc. Integrated Product Design Thesis
Faculty of Industrial Design Engineering
Delft University of Technology

Design and integration of a microfluidic system into LiGalli's MedRing platform

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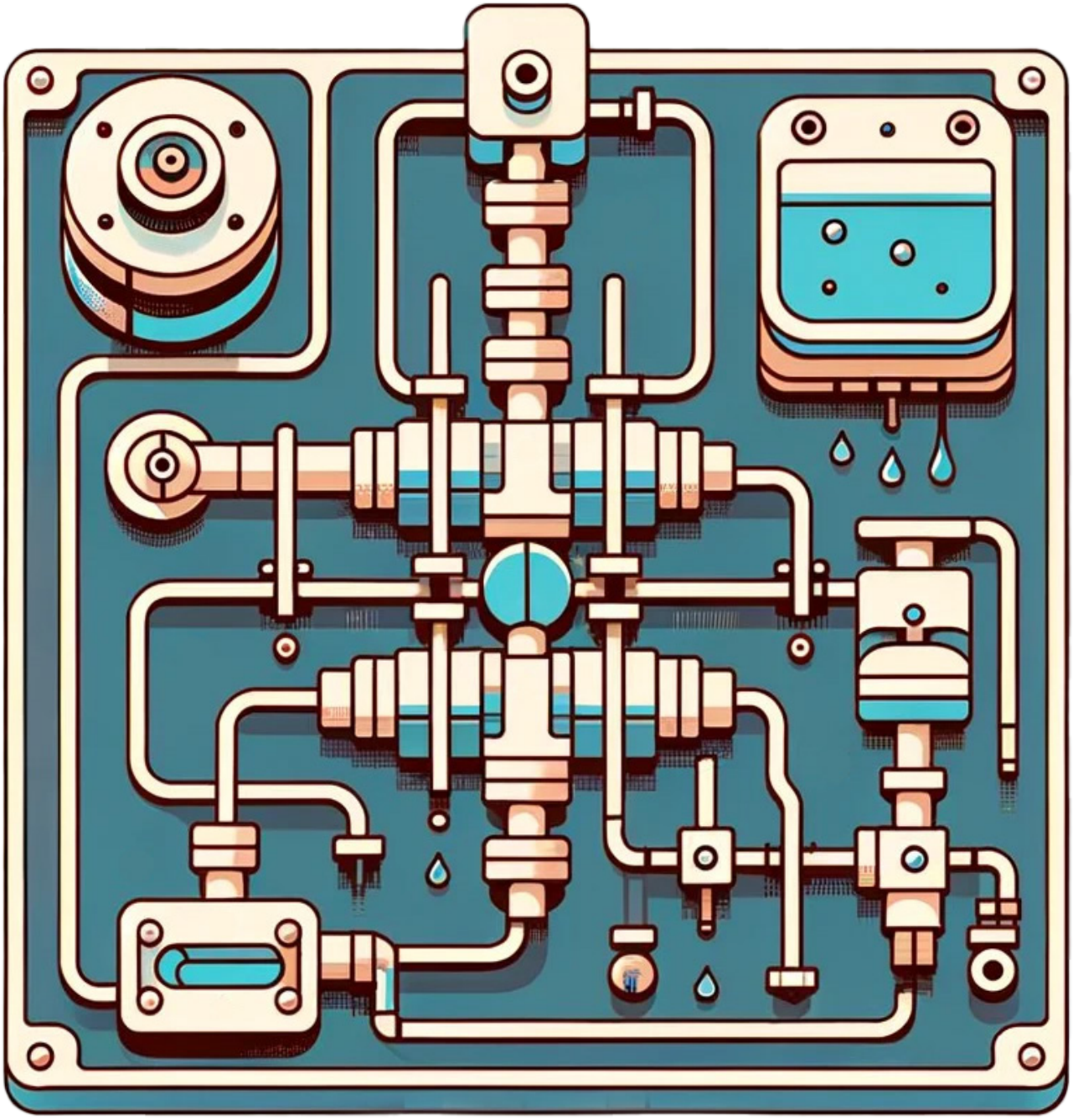

LiGalli TUDelft

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Abstract

This project explores the integration of a microfluidic system within the MedRing device, aimed at enhancing women's health monitoring by non-invasively tracking fertility-related biomarkers. The primary goal is to leverage the MedRing's capabilities to provide real-time, accurate health insights, thereby contributing to the advancement of personalized healthcare technologies.

The advent of wearable technologies has opened new avenues for personal health monitoring. This project focuses on the MedRing, a device designed for continuous health data collection, specifically targeting women's reproductive health. By incorporating a microfluidic system, the project aims to extend the device's functionality to include precise fertility monitoring, addressing the growing demand for non-invasive health management solutions.

The development process involved performing desktop research, interviews with experts and analysing the current market. Then it moves on to designing and simulating the microfluidic system using Computational Fluid Dynamics. Simulations were conducted to evaluate fluid flow, ensuring the system's compatibility with the compact form factor of the MedRing.

A microfluidic system that can be assembled into the MedRing was designed. CFD simulations confirmed that the system achieves the objectives set in terms of laminar flow and fluid path, crucial for the system correct operation. Design adjustments were made to optimize fluid path efficiency and ensure comprehensive sampling within the system's reading chamber. The simulations demonstrated the system's potential to accurately monitor store, transport and gather molecular samples within the constraints of the MedRing's design.

While the project successfully demonstrated the theoretical feasibility of integrating a microfluidic system into the MedRing, the transition from simulation to real-world application necessitates further development. Future work should focus on prototyping and extensive testing to validate the system's functionality in practical settings. Collaboration with biomedical experts will be essential to refine the system's design, ensuring it meets both technical specifications and user needs. This project lays the groundwork for future innovations in wearable health technologies, emphasizing the importance of integrating advanced diagnostic capabilities into everyday devices.

Contents

Motivation

I completed this project as the final assignment for my Master of Science in Integrated Product Design programme. The project was developed in close collaboration with LiGalli, who supplied the framework and resources. The initiative aims to establish a women's health monitoring platform that can offer precise and dependable data while minimising the user's influence on it. The project will initially concentrate on monitoring fertility but aims to produce results suitable for a broader range of biomarkers.

The journey encountered many obstacles. My design process was initially challenging due to my lack of prior knowledge on the subject and the diverse range of stakeholders involved in the project. Developing a medical device for the first time has made me recognise the intricate and demanding nature of this field, particularly when working independently.

Sonja Paus-Buzink, Oda Heerema, and Wolf Song mentored me during the project, offering essential assistance in reaching the final outcome. When I faced challenges or confusion, they consistently helped me get back on course and came up with resources that would prove to be very helpful. I am very grateful for their patience and support.

After experiencing various challenges and successes, this project has concluded, and I have significantly enhanced my understanding of developing medical devices, microfluidics, and women's fertility. As I seek a future as a Medical Industrial Designer, these are subjects that personally interest me and will undoubtedly benefit my future professional endeavours.

I also want to express my gratitude to my friends for their support during this project and over the past two years. They have become an integral part of my family and have consistently been present during both positive and negative moments.

I hope you find my project enjoyable and appreciate the final results of my five-month effort.

I. Introduction

This chapter will present a comprehensive analysis of LiGalli's LIAS project. Additionally, it will explore the cooperation between the stakeholders and the strategic approach for the graduation project, aiming to develop a cohesive and efficient microfluidic system within the MedRing.

LiGalli is a technology company that centres its work on the advancement of cutting-edge solutions pertaining to women's health. An Intra-vaginal Aptamer-based Sensor System (LIAS) is one ongoing project the company is working on with the goal of evaluating women's health by examining biomarkers found in vaginal secretions. The work of my graduation project is based on the future development of this product, projected to form part of LiGalli's portfolio.

The LIAS project was established with the objective of exploring the viability of using vaginal secretions as a possible source of biomarkers for the purpose of monitoring women's health. This study area holds significant importance because of its potential to bring forth revolutionary advancements in the realms of women's health monitoring and diagnosis. By looking at important biomarkers in vaginal fluid samples, the LIAS device might be able to give important health information about a woman and help find different medical problems early on.

1. Context

The issue of fertility has garnered attention from the World Health Organisation, with about 20% of couples worldwide experiencing difficulties in conceiving. This statistic equates to a staggering 50 million people who are confronted with difficulty achieving pregnancy (Njagi et al., 2023). This matter presents significant financial and emotional challenges. In contrast to men, whose fertility can be readily assessed through semen analysis and is consistent throughout their adult years, women undergo cyclical fertility patterns that finally cease. The reproductive endocrine system regulates the amounts of hormones that influence sexual function, development, and reproduction. Disruptions within this physiological system can give rise to a range of symptoms and illnesses, including but not limited to infertility, uterine fibrosis, specific types of malignancies, and virilization, among other manifestations.

At the moment, fertility tests available in the market, like Clearblue and Mira, use a method called lateral flow bioassay. These tests utilise a disposable dual test stick to identify the presence of luteinizing hormones (LH) and/or metabolites of oestrogen (Khelifa et al., 2022). Nevertheless, a thorough examination of fertility should encompass the assessment of follicle-stimulating hormone (FSH), estradiol (E2), and progesterone (P4) levels. According to Khanwalker et al. (2019), the precise tracking of these four essential hormones can provide an accurate timeline of the menstrual cycle, which can be helpful in determining the optimal timeframe for conception.

It is worth noting that the pursuit of efficient hormone monitoring is in accordance with the third Sustainable Development Goal (SDG3) of the United Nations. Specifically, this goal encompasses goals 3.4 and 3.7, which are designed to improve overall well-being and increase the availability of sexual and reproductive healthcare services by the year 2030 (Nakamura, 2018).

2. Meet LiGalli

Founded in 2014, LiGalli is a technology business that focuses on the development of innovative solutions related to women's health. Their initial undertaking involved the creation of a wearable device with the ability to administer drugs intelligently via the vaginal canal called LiGalli MedRing. The ring contains miniaturised elements like a drug container, a pump, a battery, a motor, an antenna, electronics, and sensors.

The LiGalli MedRing platform comprises a vaginal ring, a smartphone application, and a data platform. Women who use the MedRing device are administered a precise dosage of a medication according to their individual prescription.

3. The LIAS project

The company established the LIAS project with the goal of precisely providing early diagnostics for varied health conditions in women. It aims to be integrated as a feature in the MedRing. With the same ring-shaped design, this product consists of an intra-vaginal ring that performs a periodical analisys of the vaginal secretions. By targeting specific biomarkers in vaginal fluid samples, LIAS will be able to provide information about a woman's health and help identify different medical problems early on.

3.1 The appropriate instrument for the task at hand

To assess the viability of using vaginal fluids as a source of significant biomarkers, LiGalli hired a private study with the Clinical Chemistry Laboratory at Maxima Medical Centre in Veldhoven. The results revealed that the technology had the biggest potential in the domains of fertility, cancer, and diabetes monitoring. Biomarkers found in the analysed samples are:

- Glucose
- Luteinizing Hormone (LH)
- Oestradiol (E2).
- CA125 (biomarker commonly used in the field of oncology).
- Carcinoembryonic Antigen (CEA).
- CA15.3 (biomarker commonly used in the field of oncology)
- Alpha-fetoprotein (AFP) commonly used in the field of oncology.

After successfully screening the relevant biomarkers in vaginal fluids, a decision was made to focus on fertility in order to prove the technology can be implemented in the way they envision. The reason for this decision was that there are aptamers to identify LH already available on the market. This way, they can test the concept before they start developing aptamers for the other biomarkers.

3.2 The MedRing

The decision to maintain the same ring platform as the MedRing device for this project (see Figure 1) was based on an internal decision of the company in order to save in development costs. On the other hand, a study conducted by Novák et al. (2003) found that 96% of women from North America and Europe are willing to long-term use a

Figure 1. LiGalli's MedRing, designed for microdosing of medicaments intra-vaginally. This will be the platform for this graduation project

ring-shaped device intra-vaginally. The main reasons for this acceptance were:

- It is easy to use.
- You do not have to remember anything.
- It does not hinder sexual comfort.
- Its effectiveness

Also, LiGalli performed an interim clinical test for the MedRing's design along with Isala (Zwolle), MMC (Eindhoven) and Bergman Clinic (Hilversun) (Appendix A). The study consisted of 21 women wearing a "dumb" version of the device for the duration of a full menstrual cycle. The objectives of the study were to measure the acceptance rate, ease of use (insertion and removal), and comfort of wearing the device. Users had to rate each characteristic from 1 to 10, with one being negative and ten being positive.

Before utilising the MedRing, participants provided good initial evaluations, with an average rating of 7.9 for the design and 7.7 for the material. The expectations for the capacity to self-insert the MedRing were significantly high, with an average rating of 9.0 for premenopausal individuals and 8.5 for postmenopausal respondents. All 21 participants enthusiastically embraced the MedRing, giving it an outstanding average score of 9.3 on the same scale.

Regarding usability, the act of inserting oneself was rated highly with a mean score of 9.4, whereas the act of removing oneself obtained a somewhat lower score of 8.1. The MedRing was found to be exceedingly comfortable, with average daily scores above 9.0 during the second

and third weeks of usage. Only a few adverse effects were reported: one participant had minor discomfort at the introitus, and another suffered modest bleeding. However, no instances of vaginal irritation or lesions were identified during the examination conducted following the final day of using MedRing. Regarding sexual activity, 50% of the participants who had sexual intercourse reported no impact from the ring, while the remaining 50% observed an effect as their partners could feel the presence of the ring. During the follow-up, all participants indicated the absence of any vaginal or other issues associated with the use of MedRing.

Considering the positive results of this study, LiGalli decided that the shape of the MedRing should be maintained throughout the LIAS project as a way to spend resources on the development of the technology in order to assess its feasibility.

3.3 A collective endeavour

Considering the complexity of the project, LiGalli decided to divide it into different work packages, which will be developed by external partners (see Figure 2) and ultimately be integrated into one product. This approach will enable the developers to focus on their respective responsibilities and accomplish their objectives with effectiveness and efficiency. The work packages are the following:

Sensor Fabrication and Development: This package involves the development of aptamers, which are synthetic DNA or RNA molecules that can bind to specific biomarkers. The goal is to create aptamers that can accurately detect biomarkers in vaginal fluids.

Sampling and Fluidic Handling: This package focuses on the process of collecting and processing vaginal fluid samples for analysis. It includes developing methods to sample the fluid without contamination and designing fluidic systems for efficient handling.

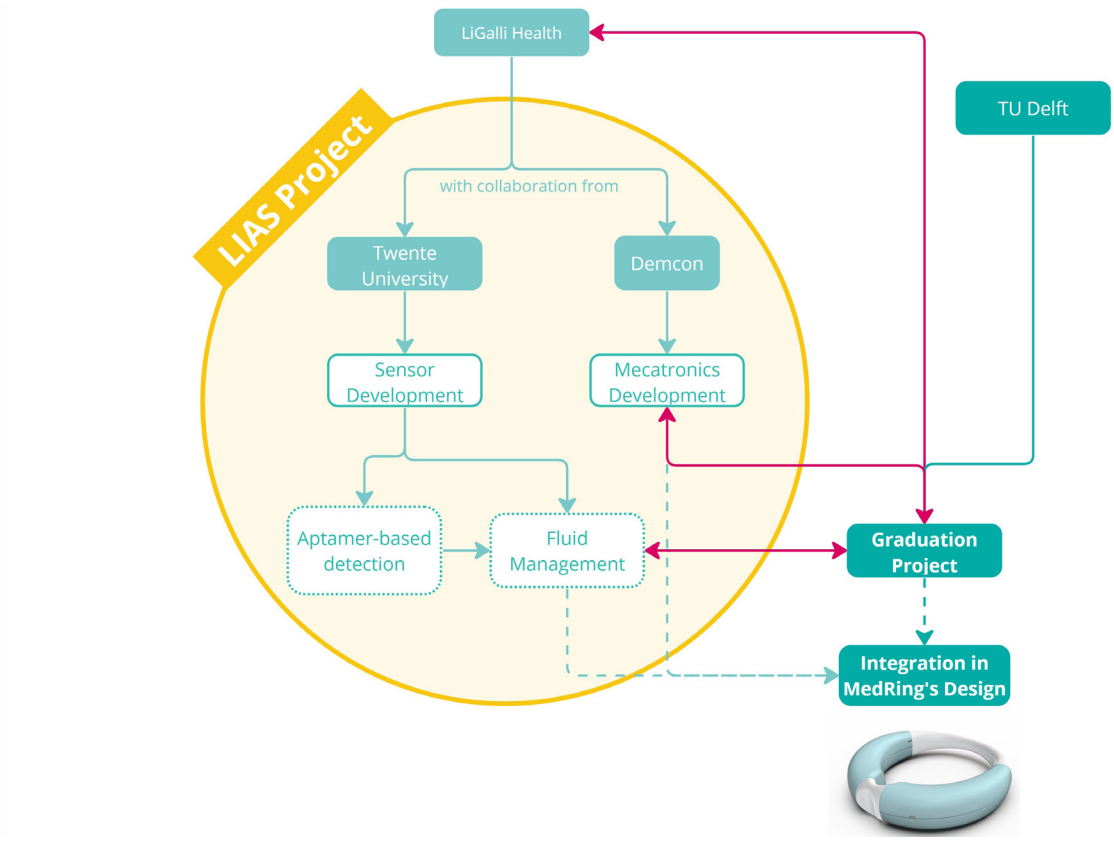


Figure 2. Map of the LIAS project stakeholders and their relation to the graduation project. Red arrows represent the contact points between the stakeholder and the graduation project: LiGalli, Demcon, and the Post-doctorate team from Twente

Instrumental Development: This package involves the development of any necessary hardware for the LIAS device, such as PCBs, liquid containers, and pumps. The goal is to create a robust and reliable platform that can accurately deal with analysing vaginal fluids.

System Integration: This package aims to integrate all the components developed in the previous packages into the existing design of the MedRing device. The objective is to develop a tool that is practical for industrial production and simple to use by its users.

My graduation project falls in the last package, where the integration of the developed technologies into the MedRing needs to be done. As the first integration, the focus is to assess that the components fit in the available space of the ring, so industrial production will not be strongly addressed but will be kept in mind.

The most relevant partners for the scope of my graduation project are: MESA+ NanoLab at the University of Twente and Demcon. Which will be presented in the coming paragraphs.

Demcon

Demcon is the main engineering partner of LiGalli, and they engaged in the challenge of building the ring with the correct layout, dimensions, functioning, and miniaturisation. Communication between me and them is crucial in order to make sure the design can be miniaturised and manufacturable at a microscale.

MESA+ Nanolab U. Twente

The MESA+ NanoLab, located at the University of Twente, is a research facility that focuses on the field of nanotechnology (Figure 3). The LIAS project has two post-doctoral researchers focusing on the development of lab-on-a-chip technology. Their research aims to determine the chemical parameters for the technology and, at a later stage, develop the receptors for the molecules of interest. They become an extremely important stakeholder for my project as they provide the components necessary for the system to accomplish its purpose at a biochemical level, several meetings with this team will go down throughout my project.

Collaboration and communication amongst these different entities is crucial for the project's success. The involvement of multiple stakeholders brings together expertise from different fields; however, it also requires a high degree of coordination and communication between the teams to avoid gaps in the development process. This can hinder progress towards creating a feasible and integrated solution for industrial production. By facilitating alignment and information sharing, my role as a designer aims to foster collaboration and ensure a successful outcome for the microfluidic system for the LIAS project.

4. Assignment and Approach

4.1 Assignment

Problem definition:

LiGalli aims to expedite the process of knowledge integration between the research team in Twente and the engineering team in Demcon. Currently, both partners are failing to promptly exchange information, resulting in new advancements quickly becoming outdated as a result of changes or neglect of requirements. My graduation project seeks to synthesise the existing knowledge of these stakeholders and apply it to the design of a microfluidic system that can be integrated into MedRing's architecture as a technological proof of concept.Key tension areas:

- Balancing the feasibility and viability of the system.
- Determining the relevance of new information.
- Balancing system functionalities with space limitations.

Scope

The result of this thesis consists of a feasibility assessment for the integration of a microfluidic system. This assessment will include an evaluation of the system's technical capabilities, potential impact on MedRing's architecture, and compatibility with existing infrastructure. The objective is to offer a thorough analysis that can direct choices about whether to continue or end this project. The deliverables considered for the end of this project are the following:

- The system designed for this project only considers the requirements to work with fertility hormones.
- Oncomarker molecules are out of scope as they have different requirements.

- The project will only focus on the technical development of the fluid system inside the ring; product usability, electronic components, and communication with the app are not part of the scope.
- The shape of the ring cannot be altered.

4.2 Approach

The design approach for this project will be double diamond, which can be divided into four primary stages: discovery, definition, development, and delivery . Throughout each phase, different design methodologies were implemented taking into consideration the project's nature, as depicted in Figure 4 (next page). The approach mostly relied on the double-diamond concept. During the Discover phase, we performed extensive desktop research and conducted interviews with internal stakeholders to gain a comprehensive understanding of the project's background. The main tasks performed during this phase included conducting market analysis, on-boarding at LiGalli, and collecting literature studies on the female endocrine system, Lab-on-a-Chip technology, and microfluidic systems. The define phase encompassed engaging in discussions with stakeholders regarding the present state of the technologies to be implemented, their capabilities, and their requirements. It also involved establishing a viable system architecture using morphological charts and establishing the vision, requirements, and evaluation criteria. The development phase encompassed the activities of ideation, prototyping (where feasible and relevant), and testing. These activities were carried out in three distinct packages, each corresponding to a certain component of the system, when faced to different technical solutions for the same problem A/B tests were performed in order to assess them and choose one. The design decisions were informed through extensive consultations with stakeholders and specialists. The Deliver phase primarily aimed to incorporate the concepts inside the ring, conduct comprehensive system testing, and formulate roadmaps and future suggestions.

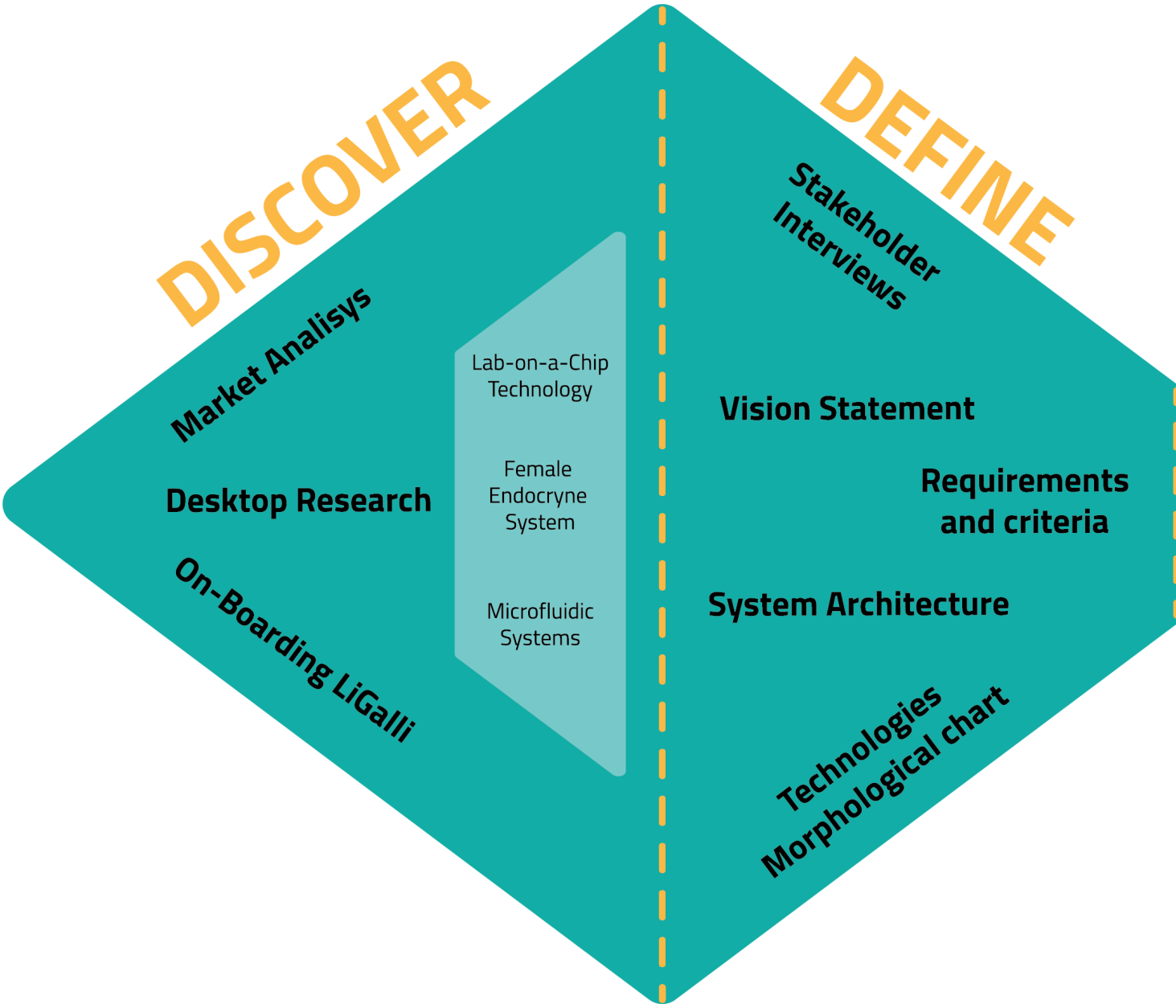
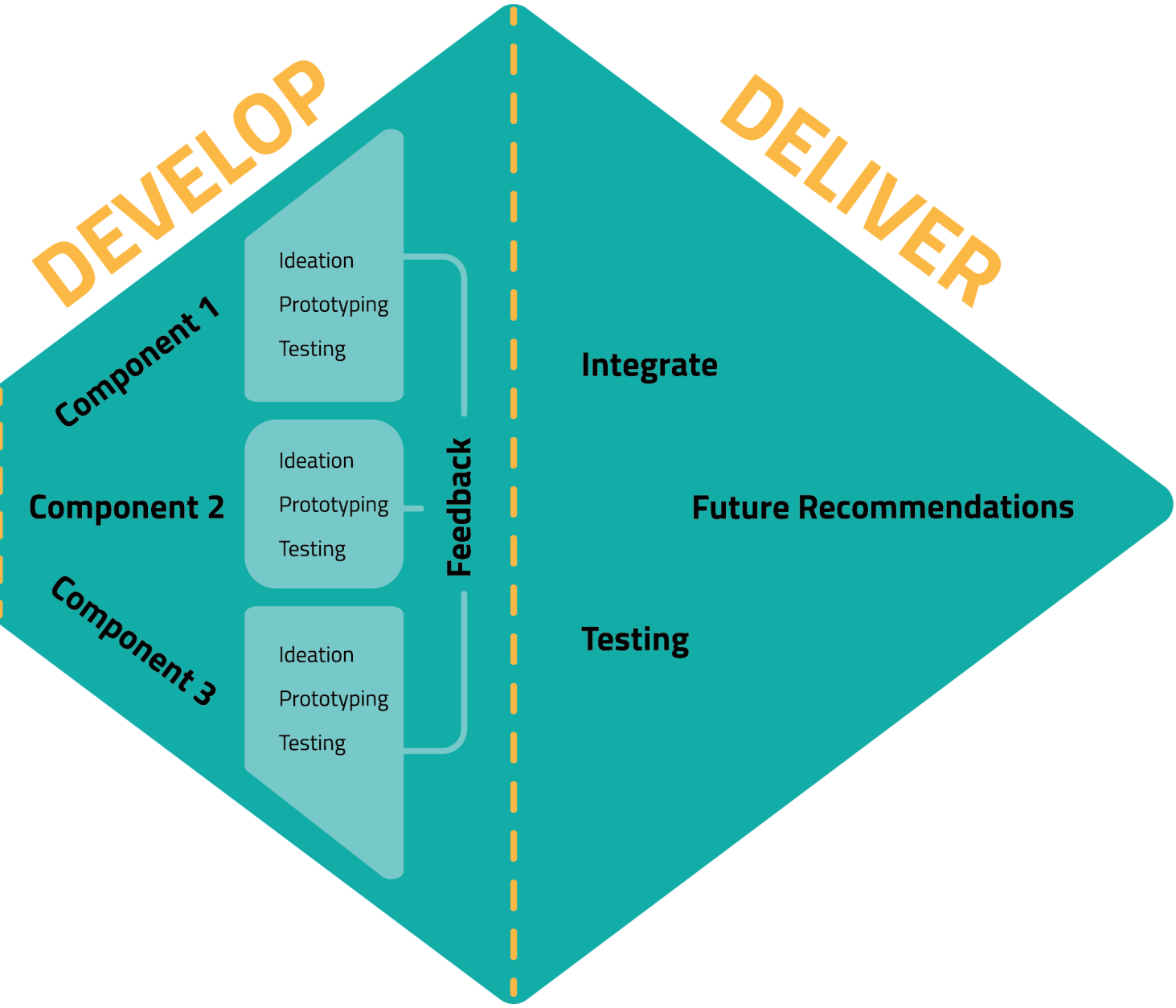


Figure 4. Double diamond diagram showcasing the main planning for thie development of the project.


DEVELOP
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Feedback
Integrate
Future Recommendations
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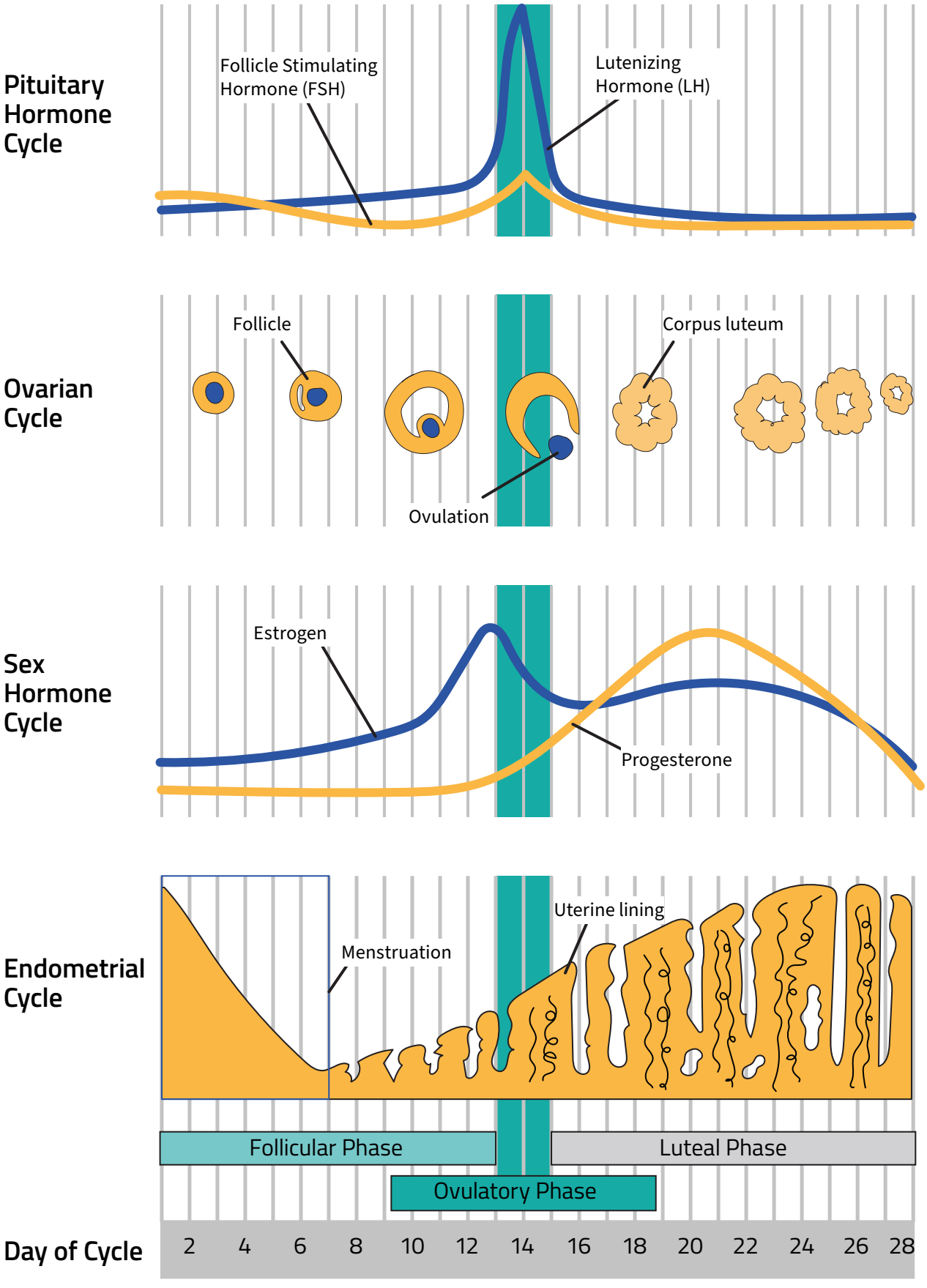


Figure 5. Behaviour of the different hormones and tissue throughout a full menstrual cycle.

II. Exploring the world of fertility

This chapter discusses the endocrine system's function in human reproduction, focusing on menstrual cycle hormonal dynamics for fertility tracking and contraception. It evaluates contraceptive treatments and fertility monitoring tools, notably bodily fluid analysis. Additionally, it summarises fertility tracking history and prospects.

1. The endocrine system and reproduction

This project works around an essential component of human reproduction: the fertile cycle. The fertility cycle in women is a complex interplay of endocrine-regulated physiological processes. It generally extends for around 28 days, and depends on a delicate equilibrium of hormone levels in order to achieve it (Knobil & Neill, 2006). Comprehending this cycle is not solely imperative for understanding reproductive health monitoring but also exerts a substantial influence on the system architecture and requirements as different molecules require different time frames, volumes, and fluids in order to be analysed. During this chapter, information was gathered mostly through desktop research and an interview with the gynecologist Maarten Wiegerinck (Appendix B).

The following topics are covered in this section:

- The endocrine system's relation to the menstrual cycle.
- Fertility monitoring techniques.
- Popular contraceptive techniques.

1.1 The menstrual cycle: a hormonal orchestra

The reproductive endocrine system strictly controls the female reproductive cycle, which is an intricately coordinated series of events that eventually culminates either in menstruation or pregnancy. This system comprises a collection of hormones and organs that are integral to both the menstrual cycle and fertility. The menstrual cycle, which has an average duration of 28 days but can differ among individuals, is composed of multiple phases, each characterised by unique hormonal fluctuations.

During this cycle, there are four main hormones that regulate the whole process, although there are more hormones that influence fertility but are not directly related to the menstrual cycle. The key hormones during the menstrual cycle are:

- Follicle Stimulating Hormone (FSH)
- Oestradiol (E2)
- Luteinizing Hormone (LH)
- Progesterone (P4)

The menstrual cycle (Days 1-6) commences with menstrual flow, which is the physical manifestation of the uterine lining shedding (Cánovas et al., 2023). Concurrently, the follicular phase (Days 1–13) commences when the anterior pituitary gland secretes FSH, which promotes the development of follicles containing an egg in the ovaries. E2, an oestrogen derivative, becomes more abundant as the follicles progress in maturity. Then, on day 14, there is an increase in LH, as shown in Figure 5. This is an indication of ovulation, the process by which a fully developed egg is released from the dominant follicle into the fallopian tube (Serafín et al., 2019). The luteal phase (Days 15–28) commences after ovulation and is characterised by the transformation of the residual follicle of the dominant follicle into a corpus luteum, an ephemeral endocrine structure that facilitates P4 production. Progesterone facilitates the uterine lining's readiness for the possible implantation of a fertilised egg, thereby increasing the likelihood of conception (Khanwalker et al., 2019).

Conversely, in the absence of fertilisation, the corpus luteum undergoes degeneration, leading to a reduction in progesterone levels and, consequently, the removal of the uterine lining, which signifies the commencement of a fresh menstrual cycle. Problems with this balance of hormones can lead to a number of reproductive disorders, including Polycystic Ovary Syndrome (PCOS) and amenorrhoea, both of which can make it harder to get pregnant (Alawan et al., 2020). Hence, hormonal assays, which can be performed through the utilisation of home testing kits, blood tests, or urine tests, are exceedingly

esteemed instruments for determining fertility status and reproductive health (Khanwalker et al., 2019).

Whether the objective is to conceive or abstain from pregnancy the reproductive endocrine system is key to allow women understanding and predicting their fertility. With this information at their disposal, individuals are enabled to make well-informed choices concerning family planning, regardless of. Furthermore, this comprehension enables the timely identification and treatment of reproductive disorders, thereby substantially improving the standard of reproductive healthcare (Cánovas et al., 2023).

1.2 Fertility monitoring techniques

We already discussed how the symbiotic relationship among hormones is fundamental to fertility; therefore, those wishing to conceive or prevent pregnancy must possess a degree of understanding of their behaviour. woman might consider using a fertility monitor in several situations, including but not limited to:

- Trying to Conceive: identify the most fertile days in a woman's cycle, thereby increasing the chances of conception.
- Understanding Menstrual Cycle: learning about their menstrual cycle patterns, can provide insights into cycle length, ovulation timing, and fertile windows.
- Natural Family Planning: to avoid pregnancy naturally, without the use of hormonal contraceptives, can use fertility monitors as part of a fertility awareness-based method to identify safe days.
- Irregular Cycles: Women with irregular menstrual cycles who find it challenging to predict ovulation can identify ovulation with more accuracy.
- Planning for Pregnancy: those planning to conceive in the future but not immediately may use fertility monitors to gather data on their fertility and menstrual health over time.
- Assisted Reproductive Technology (ART) Preparation: Women preparing for ART procedures like in vitro fertilization (IVF) can track their cycle and ovulation to time treatments accurately.
- Fertility Awareness: Individuals interested in a deeper understanding of their reproductive health, regardless of their immediate plans for pregnancy.

In this section, we will focus particularly on the fertility tracking techniques that include sampling of body fluids, as they have a direct influence on the development of this project.

Numerous fertility monitoring techniques and devices depend on the identification of hormonal levels in order to assist users in pinpointing their most fertile days. Common fertility tests quantify concentrations of FSH, LH, oestradiol, or progesterone. For example, the increase in LH, referred to as the LH surge, serves as a reliable predictor of impending ovulation and, consequently, represents an optimal period for conception (Wegrzynowicz et al., 2022). Conversely, this understanding also functions as the cornerstone for specific contraceptive approaches. A multitude of techniques are utilised to monitor fecundity, each possessing distinct merits and demerits in terms of practicality, expense, and precision.

As stated above, the most relevant fertility techniques for this project are those that, in one way or another, gather a fluid sample from the user in order to analyse its chemical composition. From the fertility trackers found during desktop research, the most relevant findings are listed below. For a more thorough review of these methods, visit Appendix C.

Predictor Kits for Ovulation (OPKs):

Figure 6. There is a wide array of OPK formats, but they all require a urine sample to detect LH levels

Widespread use of OPKs to determine the ovulation time of a woman's menstrual cycle. These devices work by detecting the surge in luteinizing hormone (LH) in urine that occurs 24 to 48 hours prior to ovulation (Bauman, 2003). OPKs are popular due to their user-friendliness. Their operation is comparable to that of a home pregnancy test (see Figure 6); a woman must urinate on a stick or

submerge it in urine to obtain the results, which are typically available within minutes.

The affordability of OPKs, notwithstanding their straightforwardness, renders them a viable option for numerous women seeking to track their fertility. However, although OPKs demonstrate efficacy in identifying the surge of LH, they fail to provide a holistic comprehension of the menstrual cycle of a woman. OPK accuracy may be compromised, especially in individuals with irregular periods or conditions such as polycystic ovary syndrome (PCOS). Additionally, looking at fertility through the lens of just one hormone is not possible; other hormones, such as estradiol (E2), progesterone (P4), and follicle-stimulating hormone (FSH), all play important roles in female fertility (Bauman, 2003).

Hormone Monitoring Systems (HMSs)

Figure 7. Despite looking similar to OPK's, all the HMS displayed here incorporate biosensors to yield results.

HMSs are sophisticated instruments that have garnered considerable interest in the domain of fertility monitoring. These gadgets' main job is to measure and keep track of important reproductive hormones like luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), and progesterone (P4) that are found in bodily fluids like blood, urine, and saliva (Khelifa et al., 2022). These hormones have a significant impact on the regulation of ovulation and the menstrual cycle, so women who want to get pregnant or avoid getting pregnant must closely monitor their levels. In contrast to conventional approaches, HMS provides a more accurate and instantaneous assessment of hormonal fluctuations that occur during the menstrual cycle.

There are many technologies that make up HMS (Figure 7), such as radioimmunoassays (RIA), enzyme-linked immunosorbent assays (ELISA), and more recently, electrochemical biosensors, which are also known as Lab-on-a-Chip (LoC). One such platform that is showing promise is the LoC, which is distinguished by its high sensitivity, low cost, and potential for miniaturisation (Bahadır & Sezgintürk, 2015). Nevertheless, the extensive implementation of HMS is impeded by obstacles including the exorbitant expense of hormone assays, the indispensability of specialised apparatus, and the need for proficient personnel to analyse the data (Wegrzynowicz et al., 2022). In addition, individual variations in hormone levels and other physiological factors might influence the precision of these systems. Notwithstanding these obstacles, HMS represents a noteworthy progression in the direction of individualised fertility monitoring, facilitating a route to improved comprehension and administration of reproductive health.

Wearable Fertility Trackers (WFTs):

WFTs have surfaced as a contemporary intervention designed to aid women in the surveillance of their fertility condition. These devices, which are worn internally or externally, present many different formats (Figure 8). WTFs predominantly monitor physiological parameters for the purpose of identifying fertile windows and predicting ovulation, including basal body temperature (BBT), heart rate, and occasionally hormonal levels (Duane et al., 2016). By combining sensors and data analytics, they enable users to receive real-time feedback, which is crucial for empowering them to make well-informed decisions concerning family planning, be it to conceive or prevent pregnancy. One of their main advantages is the non-intrusive and practical surveillance they offer. In contrast to techniques like urinary ovulation predictor kits, these devices enable uninterrupted monitoring without requiring daily active user participation (O'Connor et al., 2006). Furthermore, the applications that come with these devices frequently offer an intuitive interface for displaying and comprehending the data.

However, WFTs are not without their drawbacks. Different brands and models may not be as accurate at predicting ovulation, and they may not be as good as

more established, invasive methods like transvaginal ultrasound (Uchida & Izumizaki, 2022; Moglia et al., 2019). Moreover, WFTs may incur substantial expenses that are not necessarily protected by insurance. Additionally, the potential for misinformation and the privacy and security of sensitive health data gathered by these monitors are causes for concern if the devices are not utilised or interpreted properly. Notwithstanding these obstacles, WFTs constitute a substantial stride in the direction of utilising technology to promote personal reproductive health management. It is anticipated that as technology progresses, WFTs will become more precise, affordable, and secure, thereby increasing the accessibility of fertility awareness for all.

Figure 8. Besides their placement, they can also be cathegorized according to use time: short or continuous. (1) Ring, (2) Skin patch and (6) Arm bracelet are short use. (3) Vaginal thermometer, (4) Vaginal ring and (5) Vaginal Egg are for continuous use.

1.3 Popular contraception techniques

This project also intends to tackle the world of contraception as a secondary goal by providing a non-hormonal yet reliable alternative to traditional contraception techniques.

The use of contraception serves as a preventive measure against health risks associated with pregnancy, particularly for adolescent females. There has been a significant increase in the number of women expressing a desire to utilise family planning services over the course of the last twenty years. Specifically, the figure has risen from 900 million in the year 2000 to approximately 1.1 billion as of 2021 (United Nations, 2022). This practice has a variety of possible non-health advantages, including increased access to education and empowerment for women, as well as sustainable population growth and economic development for nations.

From the year 2000 to 2020, there was a notable increase in the utilisation of modern contraceptive methods among women, with the number rising from 663 million to 851 million. It is expected that an estimated 70 million women will be added to the population by the year 2030. From the year 2000 to 2020, there was an observed increase in the contraceptive prevalence rate, which refers to the proportion of women aged 15–49 who utilise any form of contraceptive technique. Specifically, this rate rose from 47.7% to 49.0% (United Nations, 2022). According to SDG indicator 3.7.1, 77.5% of women between the ages of 15 and 49 will have their family planning needs met globally in 2022. This represents a 10% rise from the 1990 figure of 67% (United Nations, 2022).

Numerous factors, including, but not limited to, its effectiveness, potential side effects, ease of use, and personal preferences, affect the choice of a contraceptive method. The domain of medical research has experienced notable advancements, resulting in the emergence of a diverse array of contraceptive modalities. The mechanisms of action of these approaches differ, leading to specific concerns for women's health (Teal & Edelman, 2021). This section examines the most popular contraceptive methods available to women, analysing their individual advantages, disadvantages, and overall effectiveness. More information is also available at the end of the report in Appendix C.

Oral Contraceptive Pills (OCPs)

OCPs (shown in Figure 9) continue to be widely used due to their reversible characteristics and the several health advantages they offer (United Nations, 2022), including the improvement of conditions such as acne, endometriosis, and premenstrual dysphoric disorder. Nevertheless, it is important to acknowledge the drawbacks associated with venous thrombosis risk and the reliance on user adherence, as these factors significantly impact the efficacy of the intervention. The average efficacy is characterised by a pregnancy rate ranging from 4% to 7% annually (Teal & Edelman, 2021).

Figure 9. The most common contraceptive method, comes in the format of a pill and the tablet is organized according to a regular period.

Progestin-Only Contraception

Pills and injectables like DMPA that only contain progestin are highly regarded because they are easy to use, quickly restore fertility, and have less of an effect on hemostatic variables. Notwithstanding these benefits, they demonstrate diminished reliability in suppressing ovulation and may result in occurrences of breakthrough bleeding. DMPA, specifically, has the potential to induce a postponement in the restoration of fertility. The average efficacy rate is 4–7 pregnancies per 100 women annually (Festin, 2020).

Long-Acting Reversible Contraceptives (LARCs)

LLARCs, such as intrauterine devices (IUDs) and implants (Figure 10), exhibit a remarkable level of efficacy, boasting a failure rate of less than 1% (Teal & Edelman, 2021). Moreover, these contraceptive methods require minimal upkeep and maintenance. Nevertheless, these contraceptive methods require regular clinician visits for both insertion and removal and may result in unpredictable bleeding patterns, particularly in the case of implants. The efficacy of these approaches is similar to that of permanent procedures such as tubal ligation (Teal & Edelman, 2021).

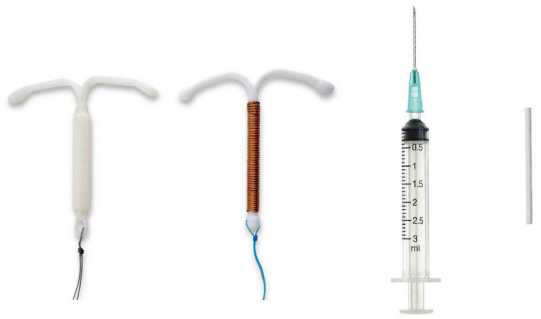


Figure 10. From left to right, Hormonal IUD, copper IUD, contraceptive injection and contraceptive implant (Nexplanon).

2. The Evolution of Fertility Tracking: Past, Present, and Future.

To properly understand the context of this product and its significance, it is necessary to get acquainted with how fertility awareness has been addressed throughout the history of humanity, understand what the situation is nowadays, and what the trend is for the future. This section is divided into three different sections:

- Past: From Ancient Methods to Clinical Observations
- Present: The Digital Revolution in Fertility Tracking
- Future: Towards Personalised and Predictive Healthcare

2.1 Past: From Ancient Methods to Clinical Observations

The precise origin of the discovery regarding women's predicted phases of fertility and infertility remains unknown. The Talmud tractate Niddah explicitly states that a woman can only conceive at specified phases of her monthly cycle, which aligns with the process of ovulation. In the year 388, St. Augustine discussed the practice of periodic abstinence as a means to prevent pregnancy (Schaff, 1887). However, the Roman Catholic Church played a major role in popularising fertility awareness-based practices during the twentieth century.

The scientific approach to fertility tracking began to take shape in the 19th and early 20th centuries. In 1905, Theodoor Hendrik van de Velde, a Dutch gynaecologist, demonstrated that women experience ovulation only once throughout each menstrual cycle (Friend, 2023). During the 1920s, Kyusaku Ogino, a Japanese gynaecologist, and Hermann Knaus, an Austrian researcher, separately determined that ovulation typically takes place approximately fourteen days before the subsequent menstrual cycle (Singer, 2004). Ogino utilised his research to formulate a method for assisting women who are unable to conceive in determining the optimal timing for sexual intercourse in order to achieve conception. In 1930, John Smulders, a Dutch physician who practiced Roman

Catholicism, utilised this revelation to devise a technique for preventing conception. Smulders disseminated his research through the Dutch Roman Catholic Medical Association, establishing the inaugural structured approach to periodic abstinence known as the rhythm method (Singer, 2004).

Women had to monitor their body temperatures every day to find the slight rise that happens after ovulation using the basal body temperature (BBT) method, which Reverend Wilhelm Hillebrand, a Catholic priest in Germany, developed in the 1930s (Hays, 2012). In the 1950s, the Billings Ovulation Method introduced the concept of monitoring cervical mucus to predict fertility. These methods marked a significant shift towards more personal and detailed tracking of fertility signs (Woomb, 2022).

2.2 Present: The Digital Revolution in Fertility Tracking

In recent years, women have been presented with a wide array of methods to monitor their fertile cycle (as described in the previous chapter), each with a different working principle and product. One breakthrough that has been revolutionising fertility tracking nowadays is the incorporation of digital technologies. Smartphones and wearable devices have made it easier and more efficient to track fertility signs.

Current fertility apps such as Natural Cycles or Flo allow women to input data about their menstrual cycle, BBT, cervical mucus, and other physiological changes. These apps then use the data gathered to predict ovulation and the fertile window of their users with increasing accuracy. However, the effectiveness of these apps, especially when used for conception or pregnancy prevention, has been a subject of debate. A study by Setton et al. (2016) found that out of 53 fertility tracking platforms (including websites and apps), only four accurately predicted a woman's fertility window. This inconsistency in prediction is partly because these apps use a woman's natural history to predict her fertile window, which can vary.

Lately, though, the integration of artificial intelligence and machine learning algorithms has significantly improved the precision of predictions and shortened the necessary time to get them. For instance, studies have shown that certain apps can be as effective as some traditional forms of contraception in preventing pregnancy (Jennings et al., 2019). The current market also offers wearable technology and fertility tracking bracelets like the Ava Bracelet, which continuously monitor factors like skin temperature, heart rate, and sleep patterns to predict fertility windows.

2.3 Future: Towards Personalised and Predictive Healthcare

Further technological advancements and a better understanding of reproductive health are likely to shape the future of fertility tracking. We might see the integration of genomics and personalised medicine, where fertility advice and predictions are tailored to an individual's genetic makeup. For example, vaginal fluid sample analysis could reveal specific fertility-related issues, allowing for more targeted interventions.

Another exciting development is the potential use of nanotechnology in fertility tracking. Researchers are exploring the possibilities of nanosensors that could be implanted under the skin to provide real-time data on hormone levels and other fertility indicators (Haleem et al., 2021).

Additionally, as telemedicine continues to grow, virtual consultations with fertility specialists could become the norm, making fertility advice more accessible. This could be particularly transformative for people in remote or underserved areas.

3. Take Aways

By understanding the endocrine system related to human reproduction, and focusing particularly on the hormonal interactions, take aways of this chapter are:

- LH and FSH peak right before ovulation, they are the most important to predict the fertile window.
- By monitoring progesterone, a new opportunity of arises: pregnancy confirmation.
- Most contraception techniques provide a hormoneal or invasive treament for contraception.
- Fertility monitors, require a daily routine adjustment.
- Data like BBT or user input could also be gathered and cross-referenced in order to increase the accuracy of the MedRing.
- Considering the novel technology used in this device, special focus on safety and usability must be applied in its development so as to increase its acceptability among its users.

III. Lab-on-a-Chip: the portable laboratory

This chapter explores the Lab-on-a-Chip (LOC) technology, which plays a crucial role in the MedRing's ability to detect and measure hormones. This text explores the fundamental principles of lab-on-a-chip (LOC) and microfluidics, as well as their integration. Additionally, it discusses the benefits and constraints associated with this technology.

In this section, we will analyse the characteristics of the primary technology that provides the LIAS ring with its unique capabilities. In order to gain an understanding of how the ring will be able to detect and quantify hormones, it is essential to conduct a review of this technology.

In this chapter, we will review the following topics:

- What is a Lab on a Chip?
- Microfluidics and LOC
- Advantages and limitations

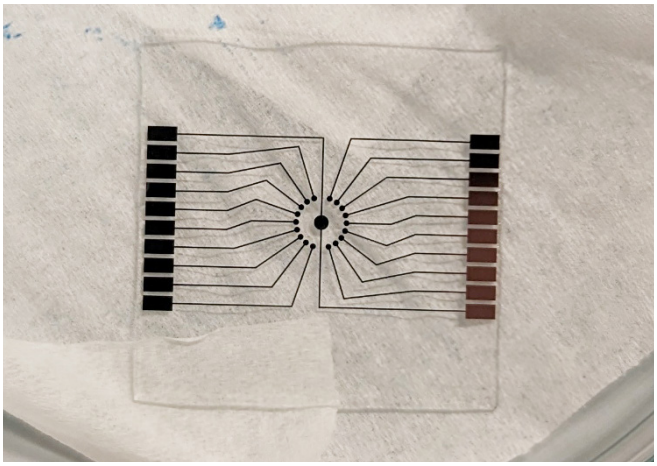


Figure 11. Transducer with 12 in/out used for testing the aptasensors in the LIAS project.

1. What is a Lab on a Chip?

A lab-on-a-chip (LOC) is a compact device that combines multiple laboratory tasks onto a single integrated circuit, typically measuring only a few square centimetres. This integration allows for automation and efficient screening of a large number of samples (Volpatti & Yetisen, 2014). LOC devices have the capability to manipulate fluid quantities as small as picoliters.

These devices are categorised as microelectromechanical systems (MEMS), often known as "micro total analysis systems" (μTAS), and employ microfluidics, which is the scientific field that deals with the physics, manipulation, and analysis of small volumes of fluids. However, the term "lab-on-a-chip" typically refers to the reduction of individual or multiple laboratory procedures to a chip format, while "μTAS" specifically focuses on integrating the entire sequence of laboratory processes to perform chemical analysis (Rushworth et al., 2013).

The research on lab-on-a-chip mostly revolves around various applications such as human diagnostics, DNA analysis, and, to a lesser degree, chemical synthesis. Lab-on-a-chip technology is becoming a viable diagnostic tool because of its ability to miniaturise biochemical operations, which leads to cost reduction, parallelization of operations, and improved diagnostic speed, sensitivity, and accuracy (Team, 2023). Figure 11 shows an prototype of a LOC transducer that converts the reading from a sample into electric pulses that a computer can understand.

History of LOC

During the 1950s, researchers modified the photolithography technique by utilising light to create more intricate and smaller transistors in silicon. In 1964, researchers showcased the inaugural integrated circuit by fabricating resistors, capacitors, and transistors on a single semiconductor substrate. Subsequently, a diverse array of sensors and transducers utilising photolithography processes in silicon were created (Convery & Gadegaard, 2019).

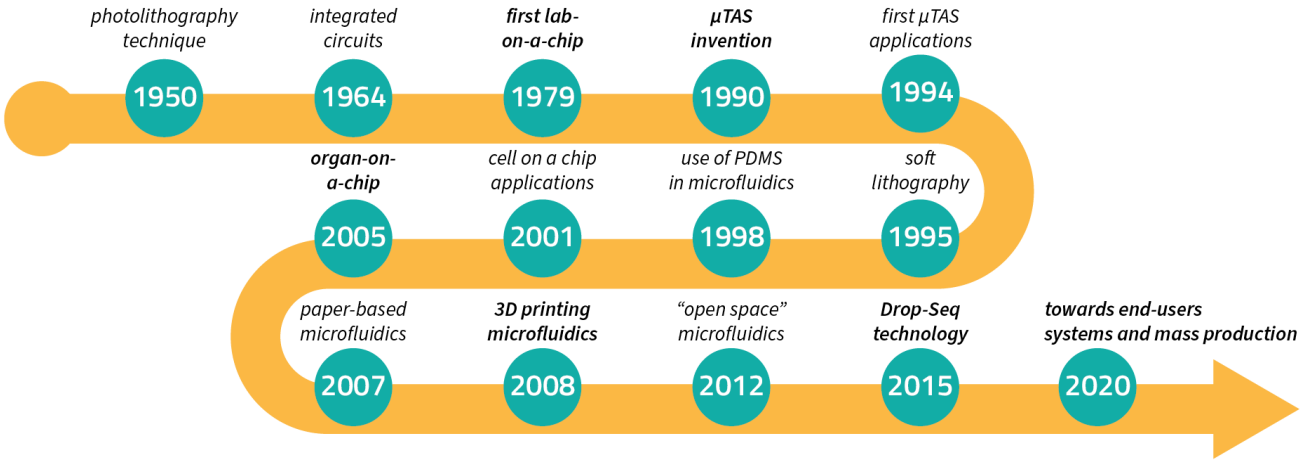


Figure 12. Timeline of the lab-on-a-chip technology development with the most important milestones throughout the years.

In 1979, Stanford University successfully developed the first functional lab-on-a-chip using these manufacturing processes, specifically for gas chromatography. However, the exploration of lab-on-a-chip technology commenced in the late 1980s, when microfluidics was introduced and microfabrication techniques were modified to create polymer chips, also referred to as soft lithography.

In the 1990s, researchers initiated a deeper investigation into microfluidics and endeavoured to downsize biochemical operations. Initial investigations into lab-on-a-chip technology also concentrated on the field of cell biology. It is unsurprising because microchannels are of the same scale as cells, enabling scientists to conduct operations at the individual cell level for the first time. In the end, researchers were able to put all the necessary steps, from collecting samples to doing the final analysis, on a single chip called the micro total analysis system (µTAS). This showed what lab-on-a-chip technology could really do.

Currently, it is feasible to produce completely personalised lab-on-a-chip devices in any laboratory without the need for a controlled environment, thanks to the existence of independent lab-on-a-chip fabrication stations.

2. Microfluidics and LOC

Science and technology that study and use very small amounts of fluids, usually in the picoliter range, are called microfluidics (Whitesides, 2006). Additionally, it encompasses the manufacturing of extremely small-scale electronics. This field functions as the core technology that supports lab-on-a-chip technologies. The technology possesses the capacity to integrate several microchannels, each with dimensions in the micrometre range, into a small chip that can be easily handled in one's hand (Nguyen et al., 2019). This process enables the efficient handling of small volumes of fluids, such as reagents used in biological procedures.

Microfluidic systems commonly encompass the movement, blending, isolation, and manipulation of fluids. Microfluidic devices commonly incorporate elements such as microchannels, microvalves, and micropumps, which facilitate the manipulation of fluid flow (Nguyen et al., 2019). These developments have had a big effect on molecular biology by making it easier to study different kinds of molecules and carry out chemical reactions like polymerase chain reaction (PCR), high-throughput sequencing, proteomics, and chemical synthesis. Another reason why these systems are highly beneficial in molecular biology is that they possess the capability to detect and analyse even minute quantities of liquids. Additionally, they provide an automated analysis from sample to answer with little human interaction (Erickson & Li, 2004).

A lab-on-a-chip is a small-scale device that integrates various laboratory techniques, such as biochemical analysis, chemical synthesis, or DNA sequencing, onto a single microfluidic platform. Lab-on-a-chip devices encompass more than just microchannels; comprehensive lab-on-a-chip diagnostic systems must incorporate integrated electronics, electrical fields, pumps, electrodes, and valves. LOC devices, supported by microfluidics, are frequently compact and suitable for point-of-care applications or deployment in distant areas (Abgrall & Gué,

2007). Presently, there is a diverse selection of flow control devices accessible for the creation of a comprehensive lab-on-a-chip system.

Thanks to microfluidics, the lab-on-a-chip technology demonstrates both the capacity to combine and run operations simultaneously as well as superior performance in comparison to conventional technologies.

3. Advantages and Limitations

Despite being a breakthrough in the field of medical diagnostics, LOCs are no different than any other technology regarding the inherent presence of advantages and limitations (Team, 2023). In Table 1, we present the most relevant advantages and limitations of the technology and how they benefit or challenge the final outcome of the project.

4. Take Aways

The capabilities to carry out scientific operations on a single chip, such as biochemical analysis, chemical synthesis, and DNA sequencing must be incorporated into the ring; enabling discreet and continuous health monitoring.

The system needs to be designed in a way that if an aptamers gets detached from the LoC, it remains inside the system in order to avoid any health-related problem to the MedRing user.

Advantages of LoC	Challenges of LoC
Multiple analyses and diagnosis: Allows numerous tests run on one chip. This allows the LIAS device to measure numerous molecules at once, expanding its usage beyond fertility monitoring.	**Need of an External System:** Requires control systems, which may restrict space, posing challenges in integrating fluid handling within the ring due to limited available space.
Portability: A palm-sized chip can do lab-quality analyses. This is important for this project since it permits to be implemented in the ring-shaped architecture.	**Ethics and Human Behaviour:** The ability to sequence DNA with a small sample and the lack of regulations, may raise concerns about the use of LOC as a diagnostic tool by untrained individuals in home environments. LiGalli must secure and anonymize the device's data.
Low-volume samples: Can operate effectively with low-volume samples. Since LIAS rings use vaginal secretions, they reduce incorrect results owing to insufficient sample fluid.	
Enhanced Sensitivity: Fast microscale reactivity allows real-time chemical reaction environment management, resulting in controlled results. This project, will use aptamers, that bind to analytes allowing for detection of different molecules with the same chip.	**Industrialization:** The majority of lab-on-a-chip technologies are not now suitable for large-scale production, and the established methods for manufacturing highly versatile diagnostic tools are still debatable.
Cost-effective: Multiple tests on one chip reduce study costs. Using LOC technology reduces the need for professional medical staff and infrastructure costs. This allows for multiple tests throughout the day, enhancing its accuracy.	

Table 1. Benefits and challenges of lab-on-a-chip technology and how do they relate to the project.

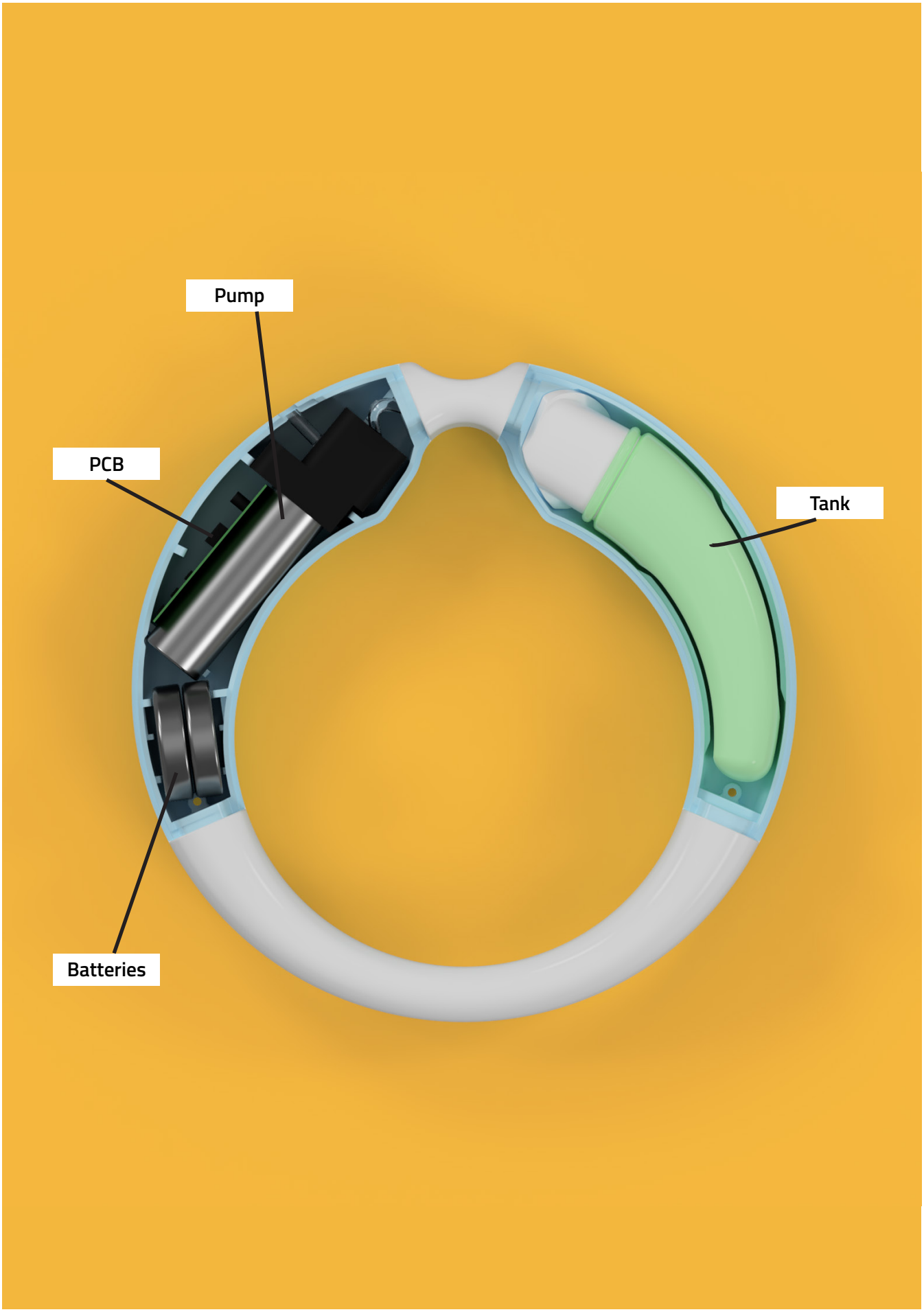


Figure 13. MedRing device with the components for its drug delivery feature. The product also comprises a mobile app to control the dosis and schedule the dosification time.

IV. MedRing as a platform

This chapter outlines the integration of a microfluidic system within the MedRing, focusing on overcoming design constraints and component integration. There is a special emphasis in efficient design choices aimed at optimizing the device's functionality while maintaining biocompatibility and regulatory compliance.

A comprehensive assessment of the MedRing's design will be conducted to get a better understanding of its origins, spatial constraints, integrated components, and the various factors that need to be considered for successful integration of the microfluidic system.

1. MedRing: a drug delivery system

The MedRing project was first envisioned as a vaginal ring that can monitor and apply treatment to women's health issues in an automatic manner. The first use case was a syndrome called Overactive Bladder (OAB), which affects about 17% of the female population in Europe (Temml et al., 2005). Based on this use case, LiGalli decided to develop the first prototype with only drug delivery capabilities.

The design of the ring was commissioned to VanBerlo, who designed the look and feel of it, and then Demcon integrated its components (see Figure 13) for the drug delivery feature and communication with a mobile app. The components fitted inside this ring are listed below:

- A flexible tank with 2 mL of capacity.
- A custom-made peristaltic pump.
- Communication electronics (BLE).
- Main control board (PCB).
- Two 1.55-volt batteries, model 399, connected in parallel.

The ring dimensions were based on the Nuva ring's design as a starting point; this way, LiGalli would be confident about the users being able to introduce it, take it out, and keep the ring in its position. Its thickness is a result of the size of the component housed inside (see figure 14).

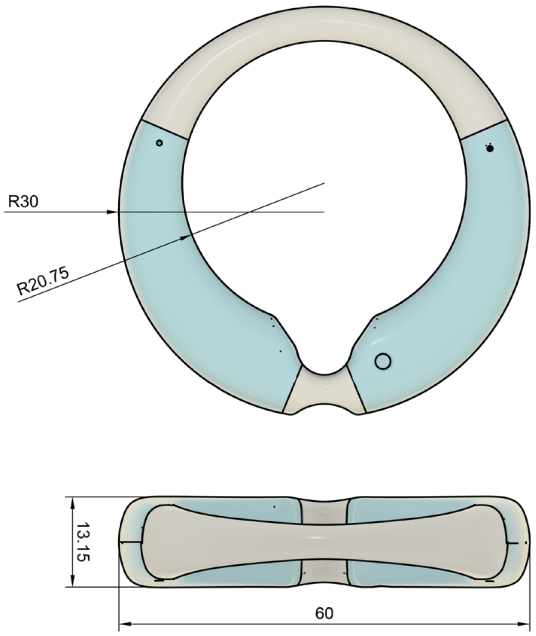
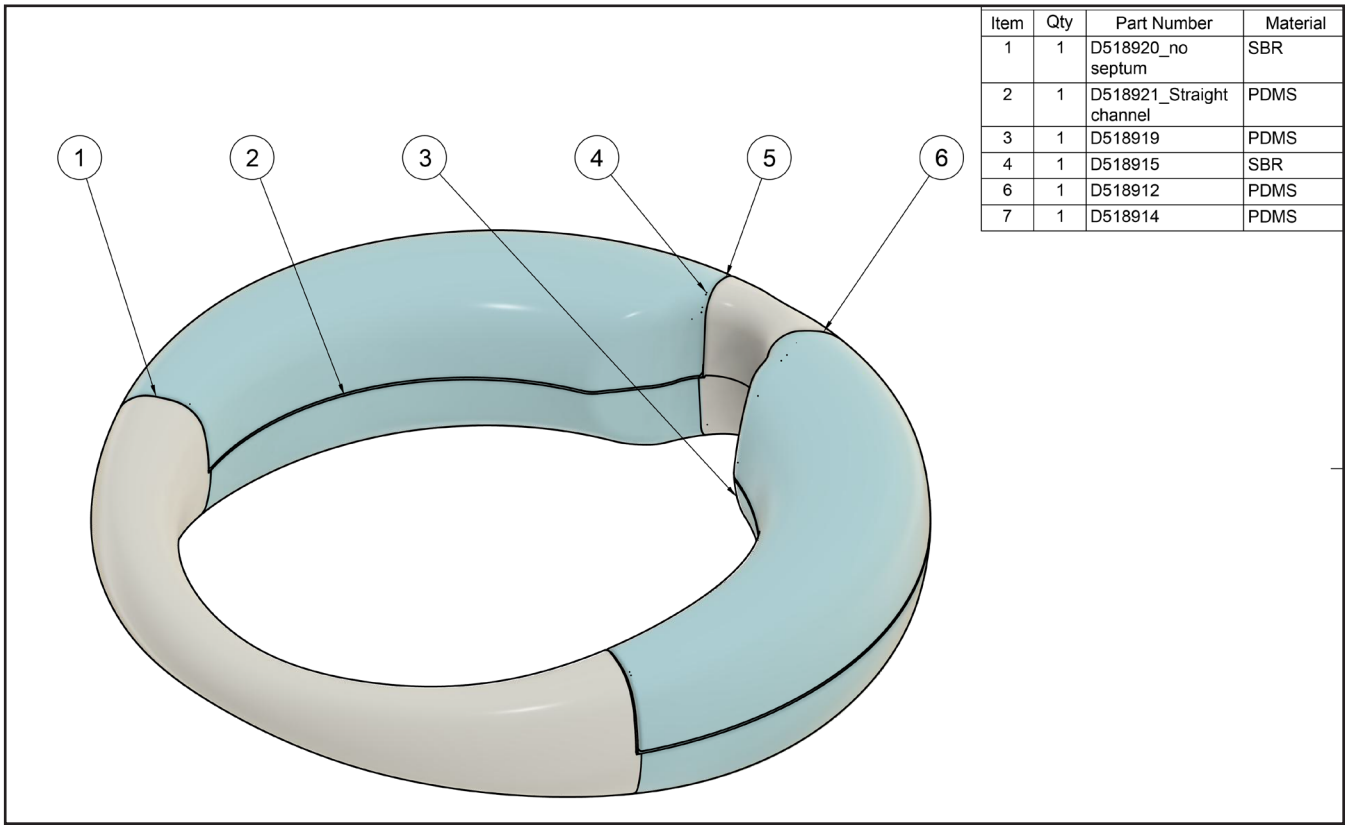


Figure 14. General dimensions of the MedRing

This device housing comprises six parts (Figure 15), all made with biocompatible materials in order to comply with the regulations for a medical implantable device. The materials chosen were:

- Polydimethylsiloxane (PDMS): Widely known as silicone rubber, this material is commonly used due to its excellent biocompatibility, stability, and flexibility. It's commonly used in implants, tubing, seals, and gaskets in medical devices
- Styrene-Butadiene Rubber (SBR): Known for its good abrasion resistance and is often used in non-implant medical devices where durability is required.



Item	Qty	Part Number	Material
1	1	D518920_no septum	SBR
2	1	D518921_Straight channel	PDMS
3	1	D518919	PDMS
4	1	D518915	SBR
6	1	D518912	PDMS
7	1	D518914	PDMS

Figure 15. Components and materials for the housing of the MedRing. All materials comply with the Annex I of the Medical Devices Regulation (EU) 2017/745.

2. Key details and components

Available space

The ring houses a volume of 3.85 mL, or 3.85 cubic centimetres, on each side. Combining the volumes on either side of the ring yields 7.7 mL as the total capacity available for fitting all the components. The working volume will be defined as 3.85 mL, taking into account that the electronics, pump, and batteries are already located on one side. Conversely, according to the research team, the LIAS system currently requires a minimum of 0.98 mL of fluid for its functioning, with 0.49 mL of each fluid being required. This requirement assumes that the system is capable of utilising the entire volume of liquid present in the tanks. The LIAS system must be designed to occupy a volume of 2.9 mL, taking into account the following components:

- Two tanks of at least 0.5 mL each
- Microfluidic channels.
- Lab on a chip.
- Two chambers of at least 2.5 µL each.

The pump

The pump is the most crucial element for the development of this graduation project due to its pivotal role in fluid transportation within a system, its significant energy consumption, and its substantial physical size.

The current pump has an energy consumption of around 1.3 millijoules per revolution and operates at a frequency of 0.5 hertz. Hence, the power usage amounts to around 0.65 milliwatts. When taking into account the power provided by the batteries (1.55 volts and 52 mAh), the current system possesses sufficient power to work constantly for over 10 days. It is crucial to note that the load in question is variable. The load profile exhibits periodic current spikes, which are inherent to the design of a peristaltic pump. The presence of these transient current surges, along with the inclusion of the electrical system, leads to a more rapid consumption of the battery compared to a steady load of 0.65 mW. However, the power supplied is still sufficient.

At present, the MedRing requires the delivery of around 60 microliters of drug on a daily basis, which is distributed across 3 to 6 separate doses. Also, the maximum volume that the current pump can deliver in one go (considering power

consumption and pump capacity) is known to be 20. If additional room is required, the possibility of substituting the motor with a less powerful alternative seems viable and can address the issue through two distinct approaches:

- A motor with lower power output is smaller in size.
- A motor with lower power output requires less energy.

Both of these advantages can be translated into increased space allocation for the microfluidic system.

Rubber links

Both compartments of the ring are joined together via two rubber "links" as depicted in Figure 16. This links are made of a flexible material allowing the ring to be folded at the moment of insertion and extraction.

One of te links is currently used to connect the pump with the tank through an extrusion that serves the purpose of a tube saving space (see Figure 17). If needed, the longer link can also accomodate tiny components such as cables or an extrusion in order to pass fluid from one side to the other.

Figure 16. The links (in black) fulfil both a structural and a functional purpose for the MedRing and are considered "available space"for the integration of the miTAS.

Throughout the project, LiGalli emphasised the possibility of replacing or removing any component to accommodate the microfluidic system, as long as it does not require significant alterations to the ring's design. Additionally, it is crucial to take into account that the majority of the components integrated into the MedRing were custom-made for this purpose. Therefore, it is unlikely that readily available off-the-shelf components that meet the necessary specifications will be accessible or in existence.

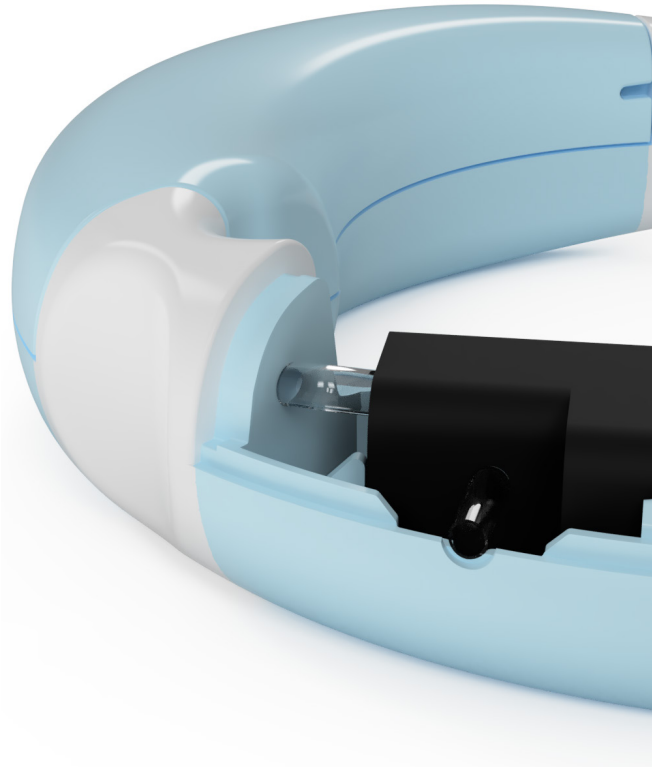


Figure 17. Connection between the pump and the tank across the short link of the MedRing

3. Using a MedRing

Within this section, we will provide an explanation regarding the process of inserting and removing the ring from the vaginal canal. It is important to note that this device is designed to be fully operated by its user for extended periods of time (at least one full menstrual cycle). Because of that, when determining how the device will be inserted, used, and removed, usability and comfort were prioritised as the most important factors.

Inserting the ring

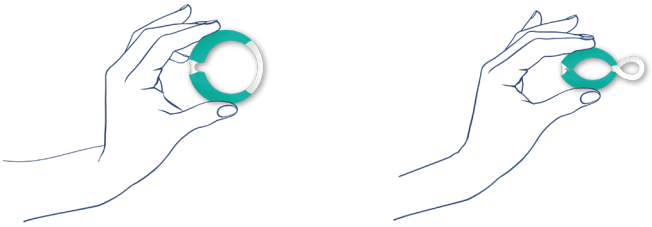
When inserting the ring, the user needs to follow four steps in order to do it correctly. Also, there are some hygiene-related steps that need to be considered before the insertion of the ring takes place.

Hygiene:

- *Wash your hands thoroughly with water and soap.*
- *Wash the device with a soft cleaning agent and water.*

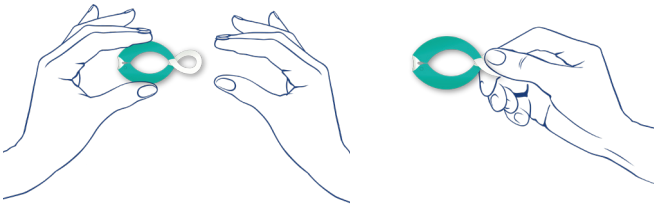
1. Hold the ring with one hand and push the light green areas together (A) until the ring is squeezed (B).

A) B)

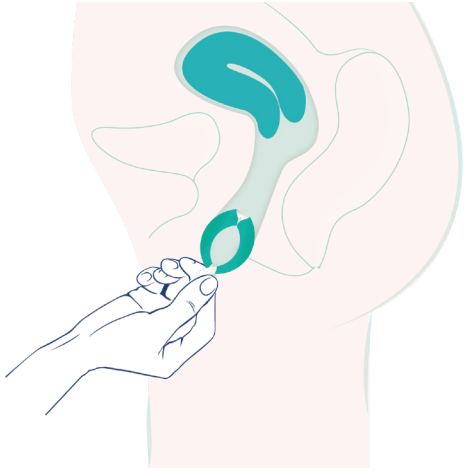


2. With the other hand, grab the ring from the twisted link (A) and hold it preventing it from untwisting (B).

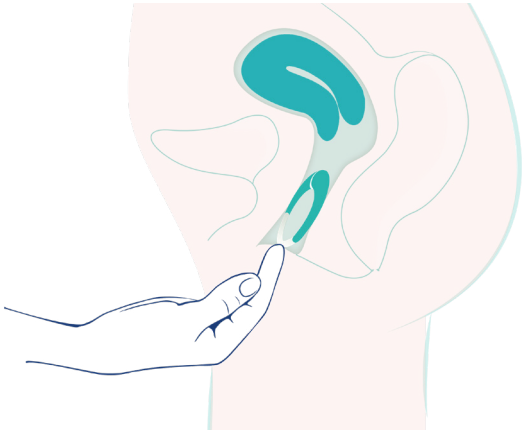
A) B)



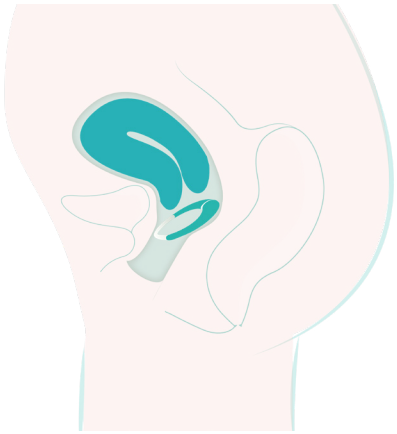
3. While holding the ring in position 2B, carefully insert it into the vagina, once inside release it so it can go back to its original shape.



4. With your finger, push the ring all the way up.



5. Be sure the ring hits the cervix at the top of the vaginal canal.



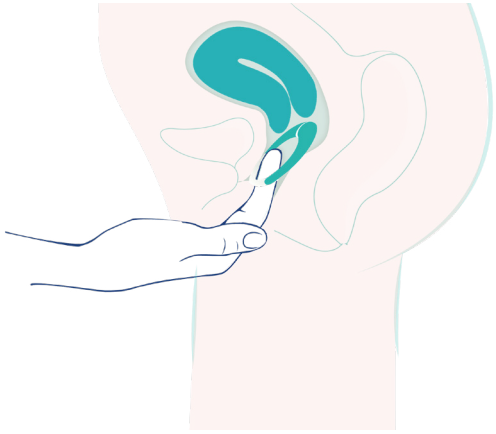
Removal of the ring

Before removing the ring, the user is expected to follow the same hygiene process that when inserting the ring.

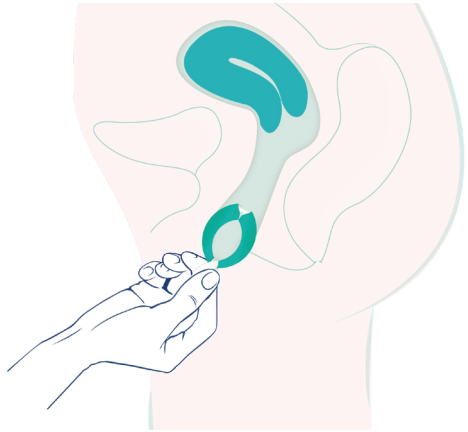
After they have ensured that they have maintained the appropriate level of hygiene, they are required to insert their fingers into the vagina and then use those fingers to pull the ring out of the long white bridge (A). It is possible

for the user to twist the white bridge in order to make the ring more slim and, as a result, easier to remove (B). This can be done before the ring is completely removed.

A)



B)



Mobile App

LiGalli's companion app is a mobile application designed to work with the MedRing. The app serves as a digital interface, allowing users to interact with the data collected by the MedRing in real-time.

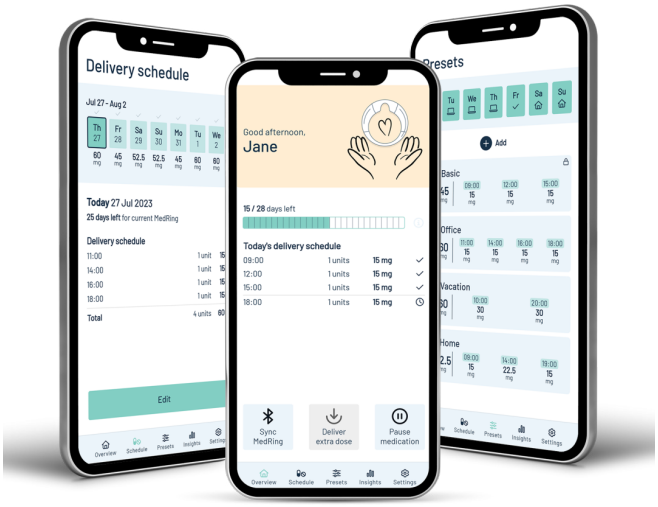
Features of LiGalli's Companion App:

- Real-Time Data Access: Users can view their health data as it's collected by the MedRing, offering insights into fertility windows, menstrual cycle tracking, and overall reproductive health.
- Customizable Alerts and Reminders: The app allows users to set personalized reminders for medication.
- Health Insights and Analysis: It employs algorithms to analyze the collected data, providing users with actionable insights into their health, identifying trends, and potentially alerting them to health issues that may require attention.

How It Works:

The companion app communicates with the MedRing via Bluetooth Low Energy (BLE), ensuring a low-power, continuous connection. Once data is transferred to the app, it's processed and presented to the user. The app's interface is designed for intuitive navigation, allowing users to access different features, view their health data in detail, and make informed decisions about their health.

By integrating closely with the MedRing, LiGalli's companion app also plays a crucial role in enabling users with knowledge about their health, making it a key component of the overall MedRing ecosystem.



4. Take aways

- The pump and battery capacity currently used by the MedRing should be capable of operating the microfluidic system.
- The space available in one of the compartments should be sufficient to integrate the microfluidic system.
- The rubber links can be used as extra space for electric cables (for the lab on a chip) or tubes.

V. Design goal & Requirements

This section examines the design objectives and prerequisites for the microfluidic system of the LIAS project, with a particular emphasis on effective fluid manipulation, reliable instrumentation, and smooth incorporation into the MedRing architecture.

The preceding chapters focused on comprehending the context of the LIAS project and identifying the stakeholders involved. Additionally, they have explored the reproductive cycle of women, the various methods available for contraception, the operational principles of LoC technology, and the integration of this technology into the MedRing platform. This chapter will extrapolate these findings into crucial domains for intervention, a design vision, and the technical prerequisites for implementing this vision.

1. Problem definition

LiGalli is now engaged in the development of the intra-vaginal MedRing system, specifically designed to deliver medications and perform diagnostic procedures. In terms of diagnostics, their main emphasis is on quantifying hormones and other biomolecules present in the vaginal cavity. They achieve this by using specific aptamers as detection instruments and vaginal fluids as the sample. The main objective of this project's development is to carry out the installation of fertility monitoring. The rationale for this decision is grounded in three fundamental factors:

- Today, 20% of women can't get pregnant with natural techniques.
- The concentration of LH analytes in vaginal fluids is sufficient to conduct in-vivo testing with LoC technology.
- An aptamer that can bind with LH is commercially available for conducting tests on the system.

Several companies have previously addressed this issue by offering diverse solutions designed to both encourage and prevent pregnancy. After examining the several techniques in Chapter 2, a clear pattern emerged:

- All the solutions require the user to alter their behaviour in order to gather reliable data.

One approach, for example, entails monitoring your basal body temperature (BBT) each morning immediately upon awakening or, for OPKs, utilising a probe to collect the initial pee of the day. Conversely, the use of contraceptives allows a more flexible methodology, as certain options, such as implants, can be surgically placed into the body, still requiring the user to undergo a medical intervention.

In Chapter 3, we look at how an aptamer-based lab-on-a-chip (LOC) technology might be able to expand the monitoring capabilities by detecting more biomarkers in the vaginal mucosa. These biomarkers may consist of cancer-related biomarkers or glucose levels, for example.

- Aptasensing's exceptional accuracy and specificity make it ideal for such applications.

When defining the system, it is imperative to consider this element and ensure that it is not limited exclusively to LH.

In Chapter 4, we examined the MedRing as a platform and assessed the limitations imposed by its design in terms of form factor and volume. Through this analysis, we determined the available volume for integrating the microfluidic system, evaluated the capabilities of the current electronic components with the system, and explored potential methods for increasing available space, such as utilising rubber links or reducing the size of the motor. These considerations directly translate into requirements that will shape the microfluidic system.

From these takeaways we narrowed down the initial problem statement in order to focus resources more effectively.

The problem this project will address is:

The integration of the monitoring features within the current MedRing platform.

From the problem definition, we can also make our vision statement, which for this project is:

"To create a reliable and automated fertility monitoring system with the least user effort"

2. Design goals

The design goals outlined in this section represent a way to support the vision statement and steer the project towards a successful outcome. The goals defined in this section were presented and deliberated among the stakeholders of the LIAS project in order to make sure they aligned with their expectations. The design goals are:

- ***To deliver a concept that serves as an alpha prototype:*** The outcome of this project should serve at least as the baseline for LiGalli to address the feasibility of a full integration of the MedRing's features.
- ***To integrate aptasensing in a device:*** aptasensing is a technology that has very limited health-related in-vivo applications. With this project, we intend to unveil new opportunities for the application of this kind of technology.

By establishing these objectives, it becomes feasible to tackle the project's difficulty with more clarity. This method ensures that the most crucial aspects are prioritised, ultimately enabling the LIAS project to have a substantial influence in the realm of women's health technology.

3. Requirements

The requirements were derived from the knowledge gathered through the previous chapters of this report, stakeholder interviews, and literature. The list is divided into three main categories in which the requirements are allocated. The following are the categories for the technical requirements for the microfluidic system:

- Usability.
- Safety.
- Operability

Also, some requirements are tagged as WISH, which means that the requirement is not crucial for the system design, but if covered, the design would become more robust by either expanding its capabilities or complying with tighter requests.

In the tables on the right, you can see the categorised requirements and wishes. It is crucial to keep in mind that the requirements are likely to change during the project as additional knowledge continues to emerge.

Usability Requirements	
Full Cycle operation	The system can be kept inside the vagina for a full menstrual cycle (5 weeks) without health complications to its users.
No calibration needed	The sensor requires no calibration during its operational time.
Reusable	**(WISH)** The system can be refilled by the user in order to extend its use. (Affects Usability Req. #1)

Safety Requirements	
Regulatory Compliance	Comply with Medical Device Regulations (Directive EU) 2017/745 Class III.
Fluid Containment	In case of leakage, any fluid from the system must be completely contained inside
Reusable	**(WISH)** The system can be refilled by the user in order to extend its use. (Affects Usability Req. #1)

Operability Requirements	
Analyte detection	Set a platform that can analyze LH molecule.
	(WISH) Set a scalable platform that can also analyze other molecules
Fluid Storage	Must have the capacity to store enough fluid to work throughout the menstrual cycle (Minimum: 1 mL, 0.5 of AB and 0.5 of DB)
Size and Integration	Must fit inside the internal space available in the MedRing.
Free-Flow Protection	Dripping must be prevented in any opening the system may have.
Sampling Gathering	Integrate a way to gather LH hormone.
	(WISH) Enable a way to gather other biomarkers
Efficient Fluid Usage	Minimise fluid waste, enhancing efficiency and sustainability
Power Capacity	Have enough power to operate for 5 weeks, covering at least a full menstrual cycle.


NEW
OLD
PUMP
Flexible material
Steel - ball
Pump Mix LoC
NO PUMP
FLUID
Electric charge pushes water / fluid
Independent pumping
Rotor design
Assembly
Air intakes
Vaginal wall
Membrane
Flush
Air
Association Buffer
Association Buffer & Analytes
Dissociation Buffer
One-way Valve
Lab on a Chip
Pump

VI. Idea generation & Concept

This section explores project ideation and concept generation. The text describes a morphological chart, talks within the research team, and the evaluation of system setup and components. The chapter covers open and closed system approaches, valve design, and tank and pump design. It finishes by comparing two concepts to determine the best design for development.

Morphological Chart

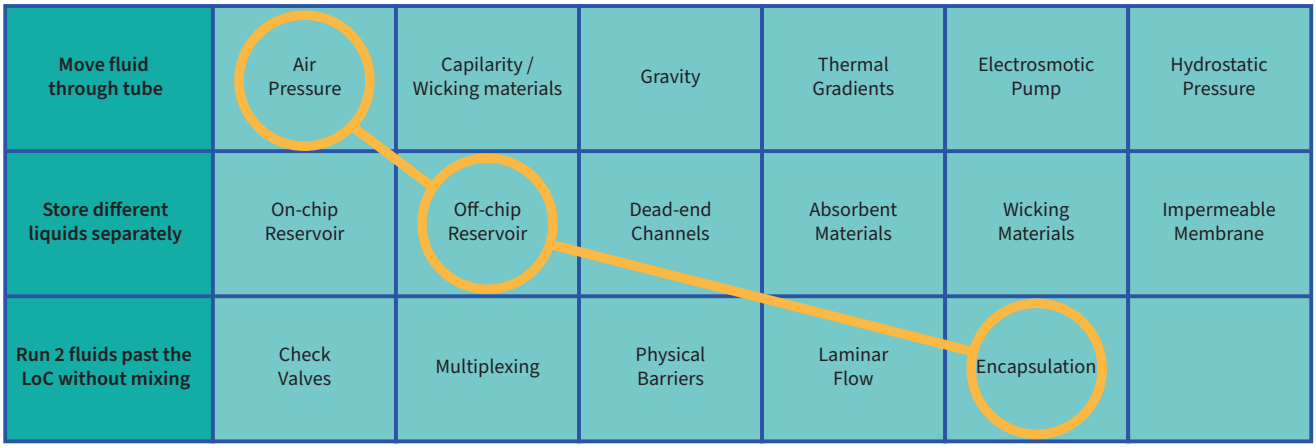


Figure 13. This chart shows some of the technical solutions to the three different problems stated in the first column. Ideas are found by combining one (or more) solutions from each row and analyzing the combination against the requirements as shown in the example in yellow.

1. Idea Generation

The design objectives outlined in this section were presented and deliberated among the stakeholders of the LIAS project. In addition to addressing the objectives of feasibility, viability, and desirability, this thesis will also prioritise the examination of compatibility, performance, reliability, and suitability for the intended purpose.

To begin the ideation process, we decided to do a quick morphological chart (Figure 13) in order to lay down some of the most important features of the system and how to tackle them. This chart served as a guide for discussing and assessing different options for the parts involved in the system. Also, during the ideation phase, several meetings with the research team at the University of Twente and LiGalli took place separately. During those meetings, we reviewed the requirements and assessed them, considering any new findings that could have an impact on them.

Four variables were considered to be open for modifications based on the original MedRing device. The variables are as follows:

- System configuration.
- Valve mechanism.
- Tank Design.
- Pumping mechanism.

1.1 System Configuration

The system configuration was developed in collaboration with experts from Twente University (see Appendix D). The purpose of these discussions was to deliberate on each proposal and ascertain the fundamental elements necessary for the proper functioning of the system. The components are:

- Association Buffer (AB).
- Dissociation Buffer (DB).
- Mixing/sampling chamber.
- LOC chamber.

More information about the functionality of each of these components can be found in Appendix E.

After establishing the basic components, two distinct approaches were adopted for configuring the system. The first approach (Figure 18) involved flushing the used liquids out inside the vaginal canal. The second approach (Figure 19) involved a closed system where all the fluids were contained internally. Subsequently, different options for the variables were investigated.

Open System (Flush)

The primary rationale for this arrangement is based on the system's need for reduced space within the ring, a critical constraint. Additionally, it requires simpler components, which can be viewed as a reduction in potential points of failure. Due to the infusion of fluids into the user's body, the device would be classified at least as Class IIB according to the European Regulations for Medical Devices (European Union, 2017) if this arrangement is used. This implies that a significant allocation of resources would be required to test and verify that the content being flushed is entirely harmless to the user.

The MDR consists of four main categories based on the level of risk they pose: Class I, Class IIa, Class IIb, and Class III, with Class I being the lowest risk and Class III being the highest. The intended use of the device, the length of contact with the body, the device's invasiveness, and whether the device is active or not all play a role in this.

Figure 18's step-by-step explanation:

1. The pump turns counter-clockwise, drawing air through the right air intake.
2. Air is pumped into the left tank, inflating the bladder. The bladder pushes the AB into the system, filling the mixing chamber.
3. Analytes from vaginal mucose permeate through a membrane. After concentration equilibrium is reached between the mucosa and AB, the fluid is pumped to the LoC and flushed after reading the results.
4. Then, the pump rotates clockwise and DB is pumped to "clean" the whole system for the next sample.
5. After reaching the LoC, the DB is also flushed out of the system into the vagina.

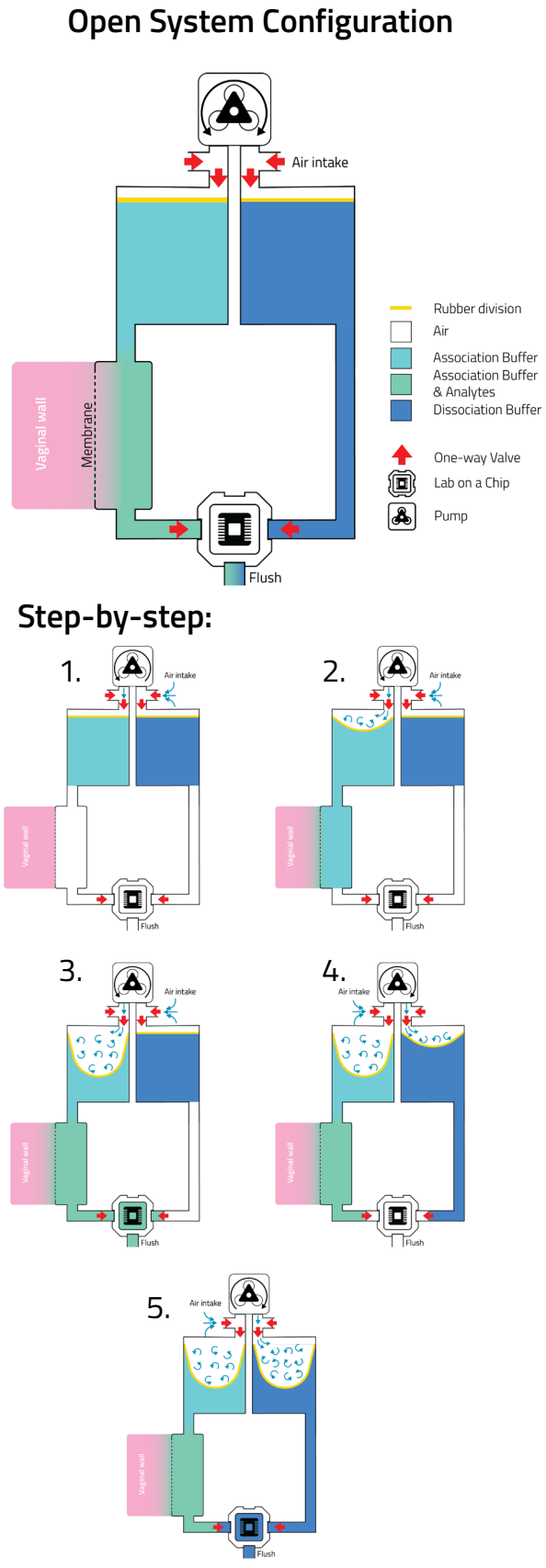
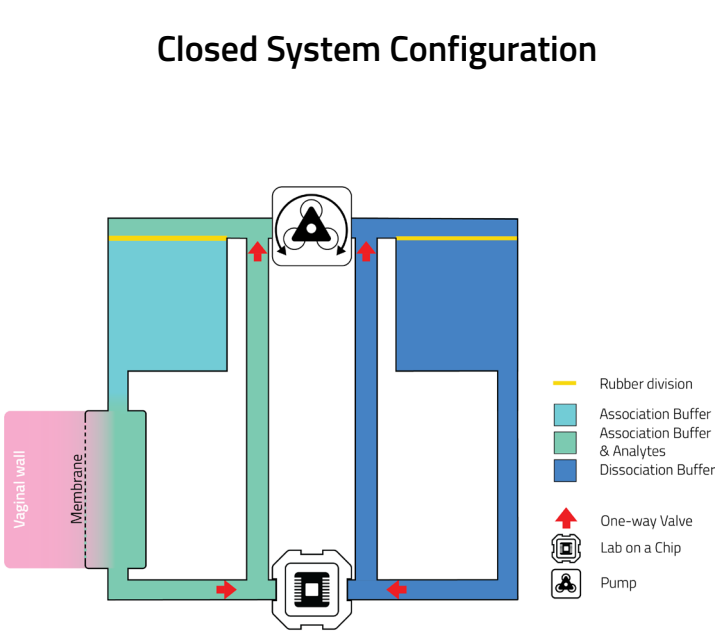


Figure 18. Top: open configuration of the microfluidic system. Bottom: schematic of one full sensing cycle.



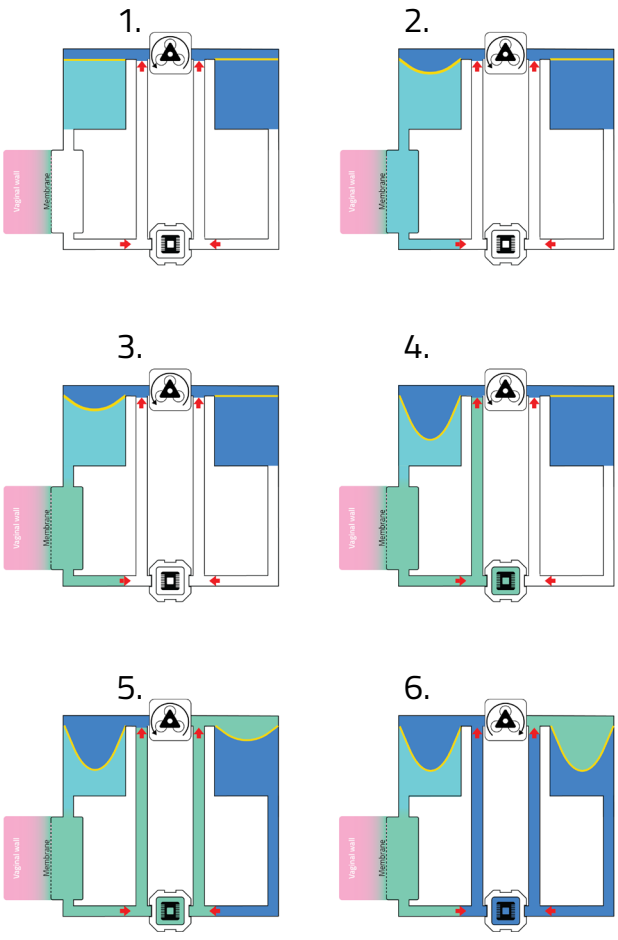


Figure 19. Top: closed microfluidic system; in this configuration the fluid returns to the tanks. Bottom: step-by-step of one sensing cycle.

Closed System

J.J.A. Lozeman, a post-doctoral fellow from Twente University, proposed the closed system configuration for the MedRing (Lozeman, 2023), and it served as the model for the concepts developed under this configuration. Given that this design ensures containment of all fluids, both new and used, the entire apparatus must comply with the standards for a Class IIA device. Essentially, this implies that, as long as you can demonstrate that the device is properly sealed and does not exhibit any leakage, it can be considered safe for use (European Union, 2017). This technique requires fewer resources and less time allocated to certification compared to the open system. On the other side, the complete system gets more complex, with fewer off-the-shelf parts and more resources for manufacturing specific components.

Figure 19's step-by-step explanation:

1. The system is pre-filled completely with liquid. Consider that all the "empty" (white) channels are filled.
2. The pump turns anticlockwise filling the left tank and causing the bladder to expand.
3. Thanks to the bladder, AB fluid is pumped through the system towards the mixing chamber. There, concentration equilibrium is achieved.
4. After that, the fluid is pumped to the LoC. And results are measured.
5. The used fluid is stored in the tanks and used to displace the bladder in order to pump new fluid.
6. For DB fluid, the pump inverts its rotation, and the same process as with AB is followed.

1.2 Valve Design

During the ideation phase, we did literature research on various types of valves that might potentially be incorporated into any of the system topologies. The inclusion of valves in the system is necessary for two primary reasons:

- To incorporate free flow protection into the system.
- To avoid contamination between the association buffer and the dissociation buffer.

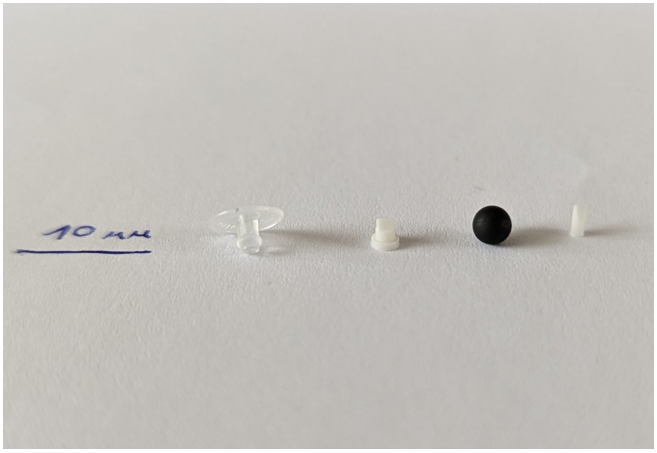


Figure 20. Valves tested for the microfluidic system, on the left, a measured centimeter for size reference.

The valve requirements included:

- Work passively (saving space).
- Allow fluid to pass in only one direction.
- Withstand a forward pressure of 10 mPa.
- Withstand a backward pressure of 100 mPa.

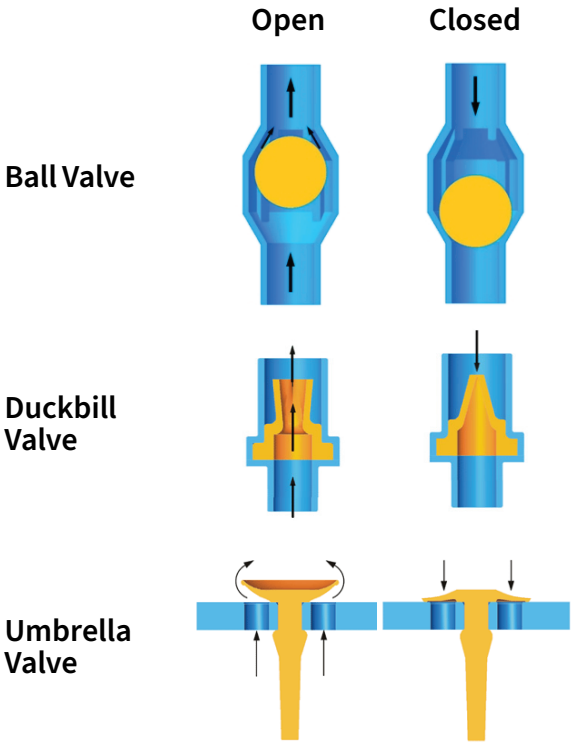


Figure 21. Working principle of the tested valves. Source: Minivalve.

Check valves are mechanisms that regulate the movement of fluids in a single direction, inhibiting the occurrence of backflow. It is essential to prioritise the prevention of cross-contamination in tasks like sample handling. Passive check valves are a type of check valve that functions without requiring external activation. Over the past few decades, a diverse array of passive microfluidic check valves have been developed; some of them are shown in Figures 20 and 21. To analyze the different posible valves, we reached out to a supplier who sent us different check vavlve variations they manufacture.

Assessing the operational pressure range for each type of valve served as a guide for the best valve search. The pump utilised in the MedRing possesses a breakdown pressure of 1 bar, equivalent to 100 kPa. Given that all the specified valve choices function at pressures below this threshold (Table 2), we redirected our attention to the operational flow range, which denotes the required velocity at which the fluid must move for the valve to function. Given that the original pump has a flow rate of 20 µL/min, the only viable option for this purpose is the umbrella valve. However, the design of these valves requires a considerable amount of space, which can provide difficulties due to the device's

Valve Type	Forward flow				Backward flow			
	Flow range (µL/min)		Pressure range (kPa)		Flow range (µL/min)		Pressure range (kPa)	
Cantilever Valve	28	800	0.7	30.9	4	39	0.3	1
Two fixed ends valve	118	1660	22.5	85	-	1	-	8
Wheeled check valve	200	1080000	2.5	345	0.001	1200	3	600
Umbrella valve	3.12	1845	3.65	40.5	-	-	-	-
Ball valve	-	20000	-	10	-	1000	-	40
Duckbill valve	-	192	-	30	-	42	-	30
Bi valvular	-	1600	-	4	-	50	-	4
In plane check valve	90	1400	50	130	-	0	-	60

Table 2. Overview of many types of passive check valves and their respective properties. Derived from a comprehensive analysis of existing material. Some values are incomplete owing to insufficient information.

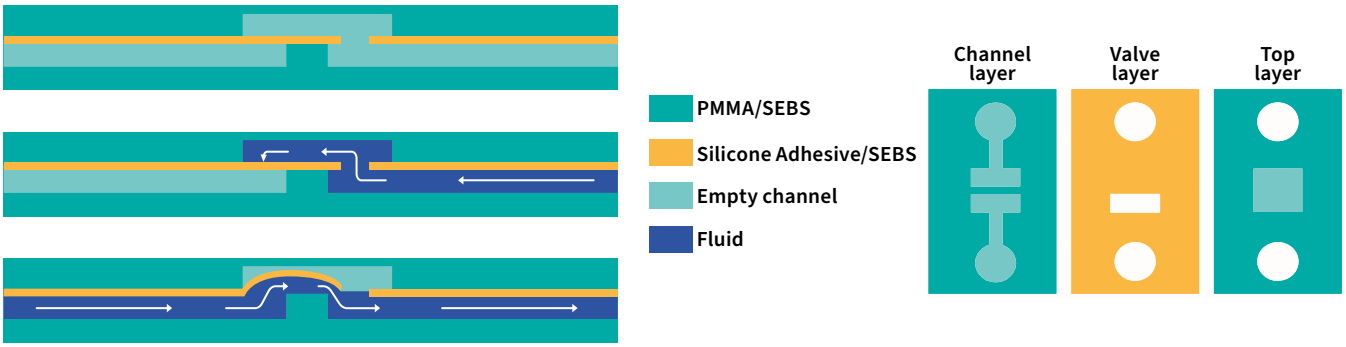


Figure 22. Left: side view of the microfluidic check valve design by J.A. Kaptein from Twente University. Right: schematic of the valve layers. Diagrams are not to scale.

size limitations. Following this impasse, the Twente team informed me that they successfully verified a custom valve design for the system that meets the necessary performance and size criteria.

The newly developed valve by J.A. Kaptein (Figure 22) combines a cantilever and a membrane valve (Kaptein, 2023). The valve features a bifurcated conduit with a stopper, upon which a membrane is situated. The membrane can be bent upward to allow the fluid to flow in a forward direction. When undergoing reverse motion, the membrane will be compressed downward, maintaining its closed state.

1.3 Tank and Pump Design

The ideation process for these two components was conducted in close collaboration with Demcon, with the objective of devising a solution that enables the storage and autonomous manipulation of both fluids. Given the circumstance that we were examining two distinct setups for the system, we endeavoured to devise resolutions for the closed system, as it poses a greater difficulty. Ultimately, we reached a consensus that it would be easier to reduce the number of features in a solution rather than begin including them.

The process began with a brainstorming session to explore various pumping methods, with a particular emphasis on viable concepts. The initial design already incorporated a functional pumping mechanism. However, the goal was to question this approach and explore other pumping mechanisms that would better meet the project's requirements and optimise space utilisation within the ring.

Various alternatives were examined during this stage, each with varying levels of progress (Figure 23). Some remained

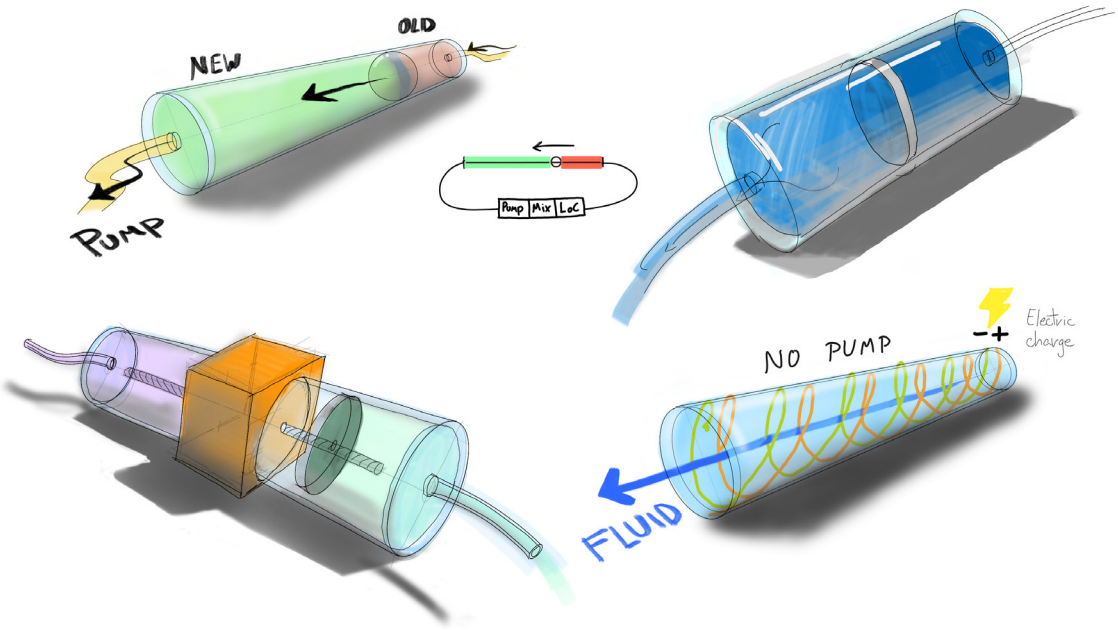


Figure 23. Some of the sketches for exploring pumping and tank possibilities.

theoretical, while others advanced to a prototyping phase to evaluate their practicality and operational principles. Out of the various concepts, two were chosen for further investigation and evaluation to determine their suitability as potential solutions for this project:

- Bladder Tank.
- Pulsative Pump.

The selection of these ideas for prototyping was based on their potential for integration into either of the two system topologies, if proven effective.

Bladder Tank

The concept entails a tank with an inlet, an outlet, and a pliable membrane that serves as a barrier layer, dividing the inside into two halves. The target fluid must be introduced into the compartment that is linked to the tank's outflow. When the pump forces fluid into the tank through the inlet, the membrane will begin to move towards the outlet, thereby forcing the target fluid into the system, as shown in Figure 24.

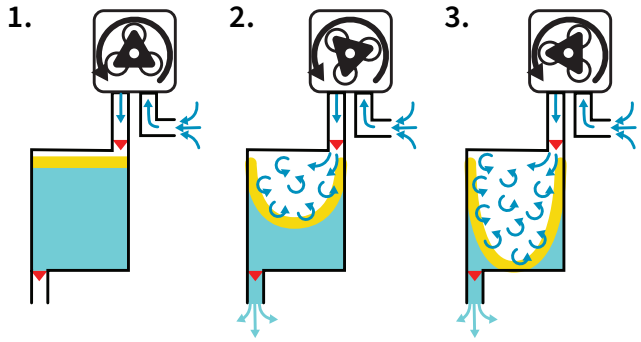


Figure 24. Working principle for the pump and bladder tank system.

The primary parts of this prototype consist of two identical tanks, a bladder, and a peristaltic pump. A 20-millilitre capacity tank was created using Fusion 360 software and fabricated using an FDM Ultimaker 2+ 3D printer. In order to construct the design, it is necessary to fasten or bond two sections together. The receptacle is equipped with a flexible silicone "bladder" that is fastened to the centre boundaries of the tank, separating the inlet from the outlet. There are two MiniValve duckbill valves on the intake side of the tank. These valves serve the purpose of inhibiting the formation of a vacuum and minimising pressure loss while simultaneously enabling the pump to introduce air into the containers. The bladder is designed to match the interior structure of the tanks and has a

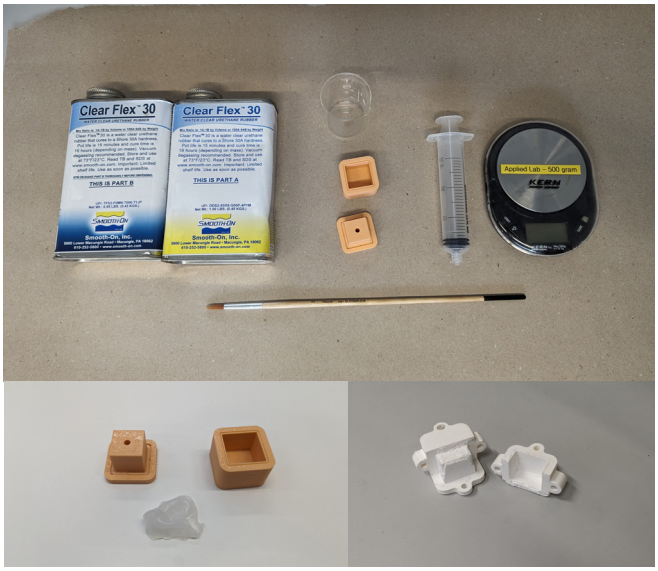


Figure 25. Top: tools and materials used for casting the membrane. Bottom left: first attempt. Bottom right: last attempt

T-shaped edge that improves sealing and retention against the tanks. In order to manufacture the bladder, a custom mould was designed for the purpose of producing it using silicone material (Figure 25). However, due to multiple unsuccessful attempts, we ultimately opted to use a vinyl glove as the membrane instead.

Following the initial prototyping endeavour, it became evident that the positioning of the valves would provide a significant obstacle, primarily due to the extremely restricted accessibility and the manufacturing precision of FDM 3D printing. To overcome this challenge, various designs and printing configurations were investigated.

In order to conduct the experiment, the system was assembled (Figure 26), and the fully assembled tank was filled with a precise volume of 15 mL of water. The pump was linked to the tank's inlet through the tube, with its other end connected to the second tank, only equipped with the duckbill valves. At the exit of each tank, an additional tube was attached and directed towards a syringe body to quantify the volume of fluid expelled. Subsequently, the pump was activated unidirectionally until the fluid ceased to flow. Ultimately, the quantity of liquid was quantified for every repetition. The exercise was performed five times. After all the repetitions were done, the average amount of fluid expelled by the system was 13 mL, with an efficiency of 87%.

The test results confirmed the functionality and efficacy of the mechanism and design. Despite the tanks' parallelepiped design hindering complete drainage, this

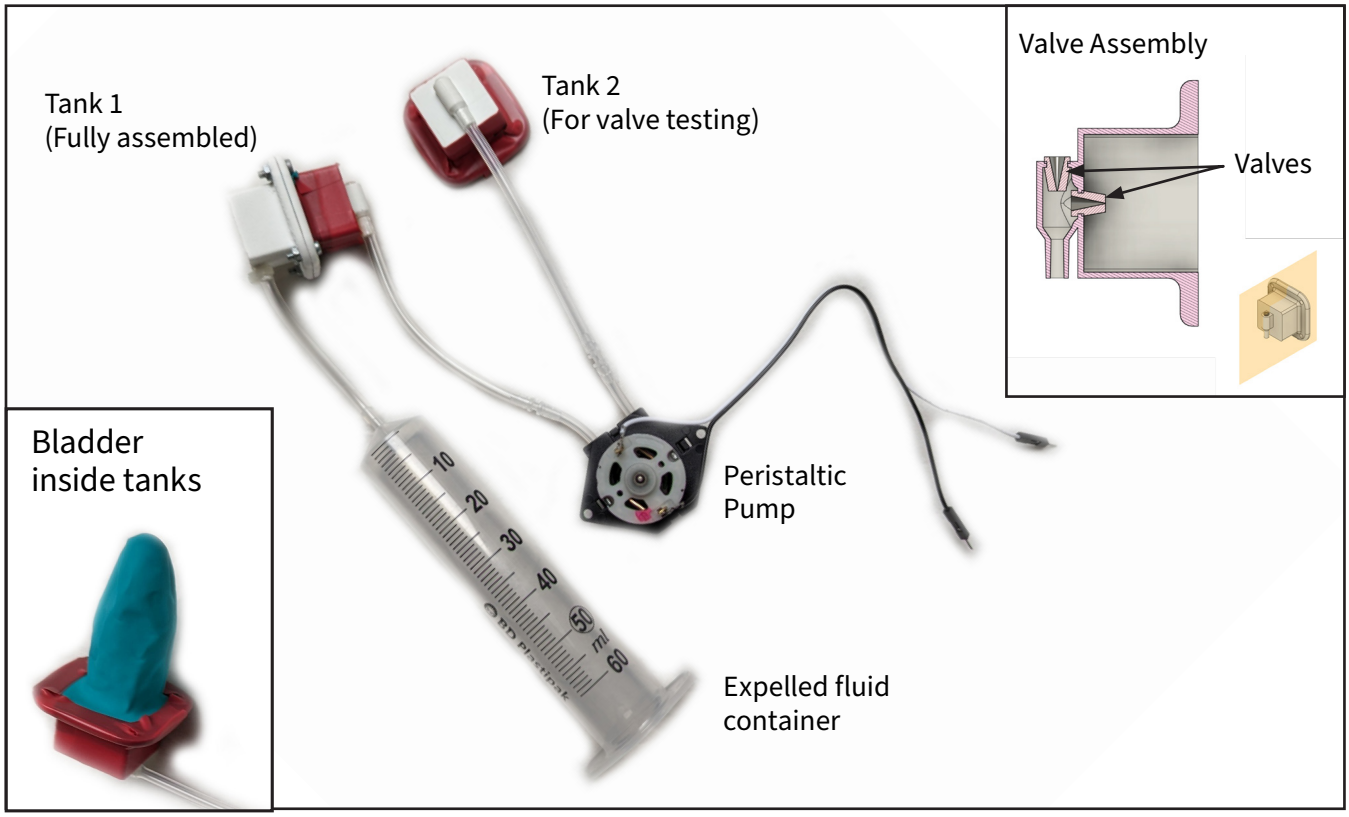


Figure 26. Assembly of the prototype for the bladder tanks idea, two duckbill valves were placed at the inlet of the tanks in order to: A) Retain the air inside the tank; and B) Allow air to ingress the system connected to the peristaltic pump.

issue can be resolved by modifying the tank's shape to enhance its drainage capabilities. Furthermore, it was determined that the valve design has the potential to function within the system. However, due to the absence of the actual pump and the appropriate volume of fluid, the results obtained are still subject to a test in realistic conditions.

Pulsatile pump

The proposal suggests incorporating a custom rotor design into the peristaltic pump to enable the simultaneous transportation of two distinct fluids using a single pump. In this design, the rotor is divided into two levels, each for a different fluid. Instead of having contact points evenly spaced along the tube, one side of the rotor is open while the other side is blocked, as shown in Figure 27.

The prototype comprised a modified peristaltic pump linked to the discharge of conventional tanks on one end, while the other end of the tubes was directed towards a vessel to contain each liquid (see Figure 28). The construction of this prototype involved the use of an Arduino UNO microcontroller, which operates a CX28BYJ48 stepper motor (together with its corresponding driver).

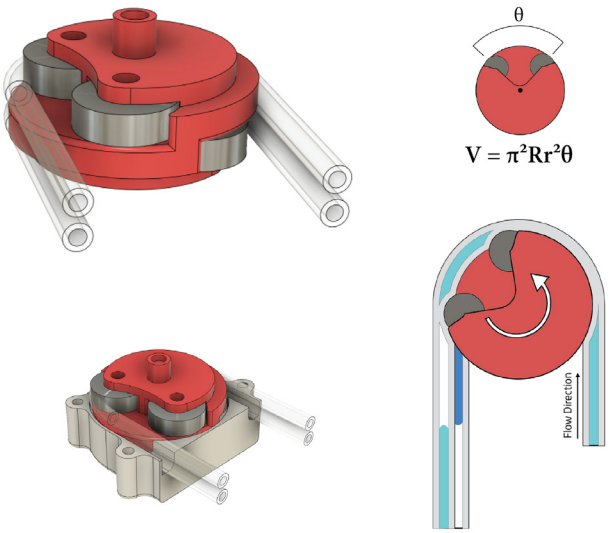


Figure 27. CAD model of the pulsatile pump idea. The formula shown was used to calculate the volume of each pulse.

Additionally, a specially designed rotor assembly was created utilising 3D printing.

While conducting tests, we realised that the pressure required to compress the tube and stop the flow of fluid

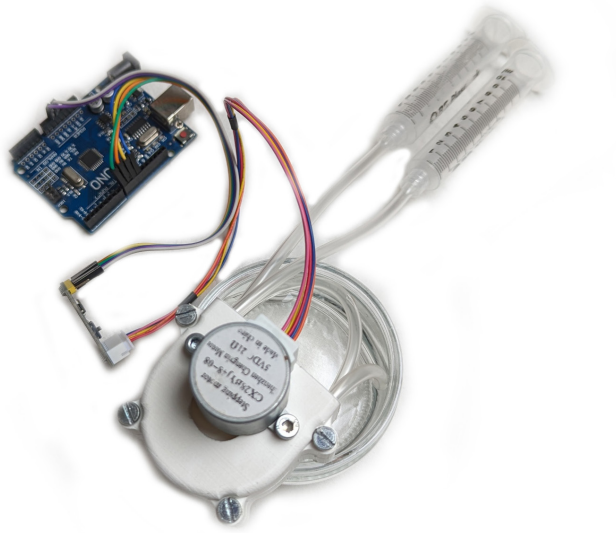


Figure 28. Assembly of the prototype for the pulsatile pump, the engine is mounted on top of a vase with water and the syringes are connected to the outlet to measure volume.

was so high that it produced an excessive level of friction, hindering the rotor's ability to continue functioning. Some solutions were explored to address this issue, such as incorporating rollers along the block side of the rotor (Figure 29). However, when attempting to downsize these solutions, they were challenging to manufacture due to the exceedingly tight tolerances and spatial constraints.

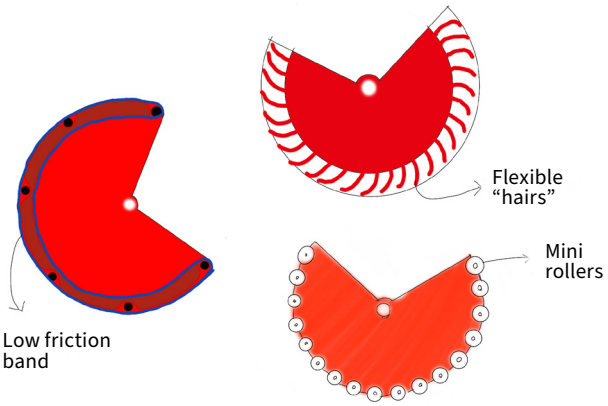


Figure 29. Sketches from the brainstorming to reduce friction between the rotor design and the tubes.

Following these exercises, we held a meeting with Demcon to analyse the outcomes and strategize for further actions (meeting minutes in Appendix F). We analysed the components currently used in the MedRing and contrasted our requirements with the pump's performance. Considering the present situation:

- MedRing delivers 60 microliters of drug on a daily basis, which is distributed across 3 to 6 separate doses.
- This use pattern exceeds the required fluid volume for the LIAS project by four times. And the pump actuation is 1.5 times more than what the new system requires.
- The maximum volume of the current pump is 20 microliters.
- The new system needs to pump at least 3.5 microliters.

The new system to be integrated should run without problems with the existing pump. Collectively, we concluded that retaining the current pump utilised in the ring will streamline numerous unaddressed factors, making it the optimal choice. After the decision was made, we proceeded to incorporate all the ideas within the framework and layout a concept for the system.

2. Concept Development

Following the ideation phase, we transitioned to the process of concept generation. The procedure commenced by selecting the ideas deemed worthy of exploration and determining how to include them in the MedRing. The initial decision to be made pertained to the system's configuration. To accomplish this, we arranged a meeting with Victor Nickolson, who serves as LiGalli's pre-clinical and pharmaceutical advisor (meeting minutes and process in Appendix C).

After deliberating and considering the advantages and disadvantages of the various configurations, we have chosen to implement a closed system due to the following reasons:

- Classified as a class IIA medical device instead of an IIB.
- If all the fluids are kept inside, any leakage or failure in the mTAS won't cause any harm to the user.
- It avoids accidental contamination of the sample mucosa.
- The complexity of the system is not much greater than when flushing.

At this level, we produced one design that incorporates a complete integration of the closed configuration system within the MedRing on a general level. The concept behind it is to have one system-component that can be assembled as one piece in the MedRing, rather than a set of components that have to be assembled directly in the space of the device.

The concept generated was iterated twice in order to optimise its performance and solve integration issues. Both iterations of the concept exhibit similar reasoning and configuration for most of their components. However, the microfluidic system is implemented in different ways. The first approach prioritises feasibility and simplicity of production, but it has the drawback of requiring a larger volume of fluids to function. The second option reduces the necessary operational volume but increases complexity and requires specialised manufacturing methods.

2.1 Concept V1

This was the initial endeavour to incorporate all the elements of the micro-total analysis system (mTAS) into the design of MedRing.

This concept bears a resemblance to a “sandwich” assembly, which consists of two bladder-equipped tanks, each with a volume of 0.7 mL. One tank is positioned on top, while the other is positioned at the bottom. The system also presents two 0.8-mm PMMA layers (Figure 30) sandwiched between the two tanks. These layers contain the microfluidic channels and valves. The two layers of PMMA will effectively seal off the channels and valves of each other, functioning as a unified entity in order to establish the microfluidic system. This idea arose after brainstorming ways in which the device could be easily prototyped in order to be tested. By laying the system flat on the PMMA layers, it can be prototyped with micro-milling technology available at the MESA+ Institute.

The chosen valve design for this concept is the one created by J.A. Kaptein from the University of Twente (Kaptein, 2023). Figure 31 displays the system assembly with some not yet developed parts, such as the mixing chamber.

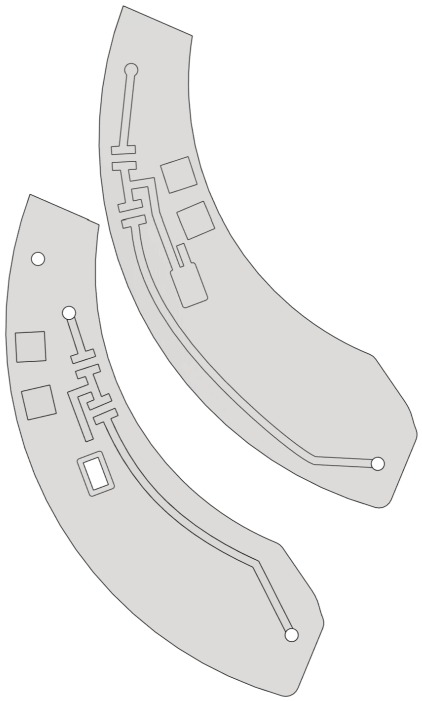


Figure 30. The two PMMA layers separated, the both act as the “negative” of each other, in order to make the system as slim as possible.

The mixing chamber was positioned on the outer side of the ring to optimise the likelihood of the membrane coming into contact with the vaginal walls. Preferably, the chamber should be situated in the broader section of the ring. However, this would result in a notable decrease in the capacity of the association buffer tank, leading to a shortened lifespan of the product. Consequently, it would

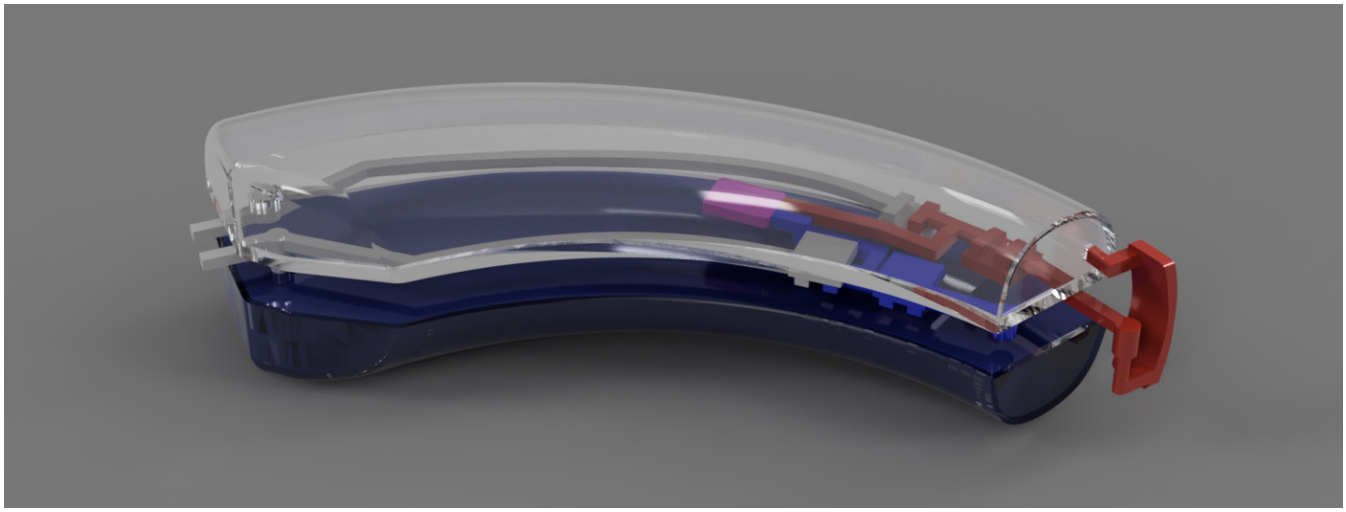


Figure 31. Design of the concept one, with two (empty) tanks arround the microfluidic system. Clear tank for the association buffer, blue tank for the dissociation buffer. In pink: LoC placement; in red mixing chamber minimum required volume.

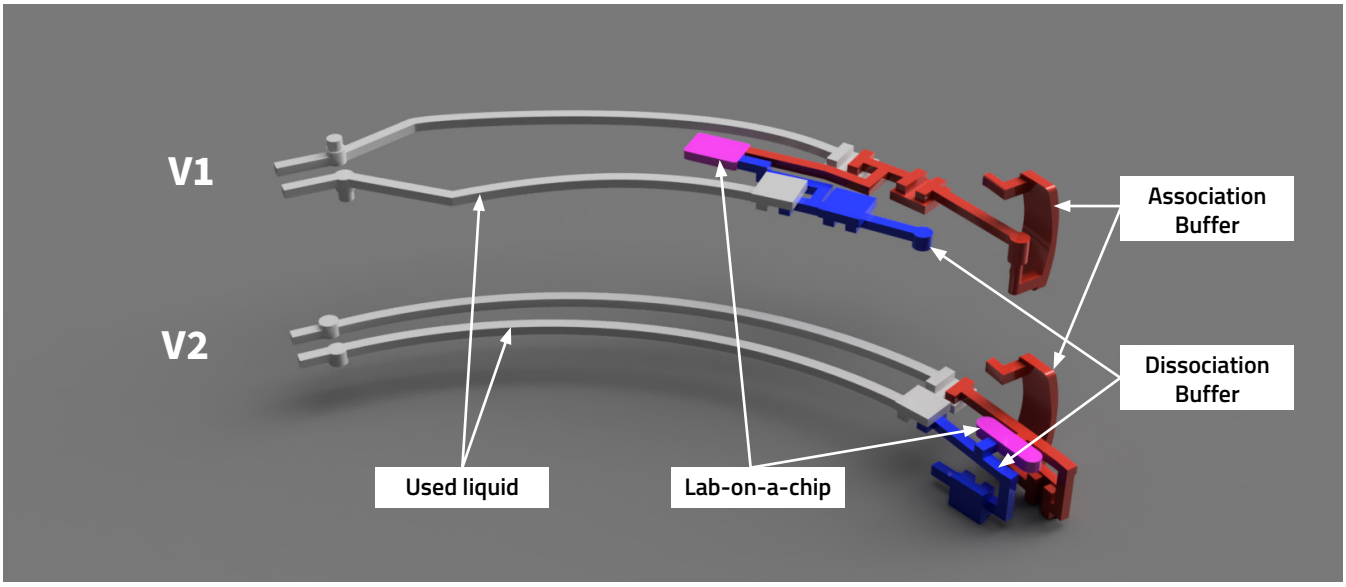


Figure 32-A. Illustration of the paths for the microfluidic systems. Red illustrates the association buffer; blue dissociation buffer; gray is the used fluid after its gone past the LoC; and pink represents the LoC chamber. On top is concept one and bottom is concept two.

not be possible to complete a full menstrual cycle. The membrane should be positioned to retain the buffer within the ring while maximising exposure to the vaginal mucosa for contact.

The LOC component can be positioned either behind the mixing chamber or within the PMMA sandwich, guaranteeing a moisture-free setting for the electronics and sufficient room to accommodate its final dimensions.

2.2 Concept V2

After discussions on the concept V1's fluid use, we determined that prioritising an efficient fluid system outweighed the need for simplified manufacturing procedures. Given the intricate nature of the system and its projected production volume, industrial digital manufacturing methods are a feasible alternative as well.

Considering the aforementioned discussion, the initial implementation of concept V1 needed to be optimized. In this iteration, the entire system is placed in the rear section behind the tanks, along with the mixing chamber, in order to minimise the distance that the buffer fluids need to travel. Figure 32 illustrates a comparison between concept one and concept two. The concept entails a block-shaped component featuring a three-dimensional arrangement for the channels, LOC, and valves, as shown in Figure 33A. In

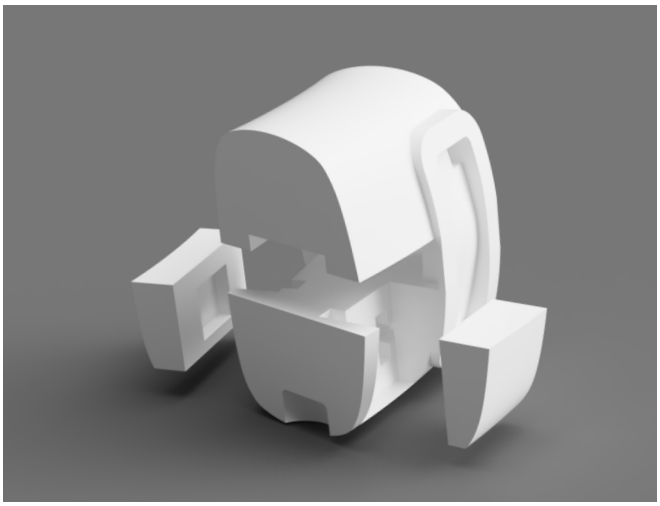


Figure 33A. Isometric view of the "Block" component that integrates two valves, the mixing chamber and the LoC chamber

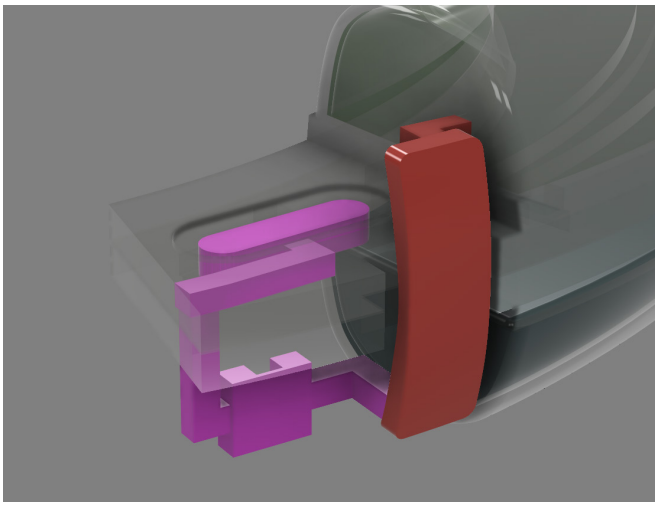


Figure 33B. Capacity of the reading chamber and channels (pink), and the mixing chamber (red) is the same with a volume of 4.5 µL.

order to achieve the assembly of the valves, it is necessary to enter a block into a designated slot, “completing the puzzle” and effectively sealing the system. The identical procedure must be adhered to for the LOC.

Another measure taken into consideration to optimise the system was to design the mixing chamber to be equivalent to the total volume of the volumes from the reading chamber and the channel leading to it (Figure 33B). Consequently, this guarantees that every time the device takes a reading:

1. The mixing chamber is completely empty of equalised association buffer.
2. The reading chamber is filled completely with equalised association buffer.
3. The mixing chamber is fully refilled with “clean” association buffer.

Also, on this occasion, we devoted greater consideration to the system layout, recognising that after the fluid passes through the final two valves, all the fluids combine, resulting in the creation of what we have referred to as the wasted fluids (Figure 34). Taking this into account, we concluded that anything beyond that point is inconsequential. Additionally, if the system is extensive in that area, it is irrelevant, as the membrane tank design requires a prefilling of the system.

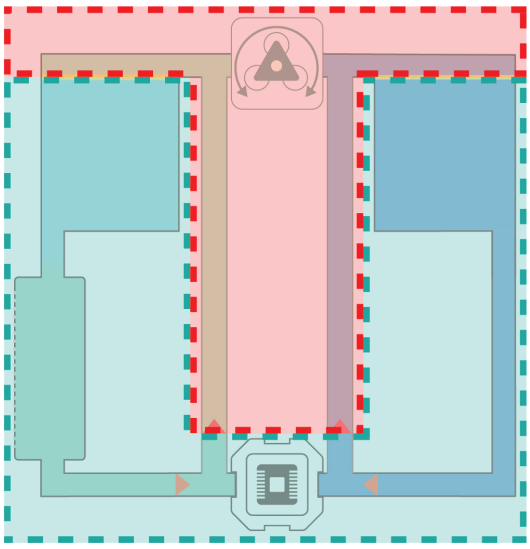


Figure 34. Division of the microfluidic system. In blue, the “useful” fluid’s path and in red the “waste” fluid’s path.

3. Concept consolidation

To begin the consolidation process, it was necessary to compare and analyse the strengths and weaknesses of the previous concepts. Considering that Concept 2 was created as a result of an iteration of Concept 1, it already covers most of Concept 1 weaknesses.

Both methods work the same way when it comes to managing fluids (like independent pumping, the minimum required volume of the tank, and the volume of the mixing chamber). This is because they use the same pumping principle and parts, like tanks, mixing chambers, and pumps.

The tanks were designed with a capacity exceeding the minimum requirement for the ring’s 5-week operation, which involves four daily readings. The least necessary volume of fluid is 500 microliters, so we decided to design the tanks with a capacity of 700 microliters to make sure that the volume used by the rubber bladder and the uncertainty about the system’s efficiency won’t become a problem in the future. With both things in mind, the actual volume of the tanks allows for a safety margin.

The mixing chamber is the same in both configurations due to three factors:

- The level of development of the component at this stage is quite low.
- The ideal placement of the membrane doesn’t allow for much variety in the design of the component.
- This component is assembled on the tank for the association buffer, so it can be considered a subcomponent.

Both concepts were designed with integration into the ring in mind. As a result, the whole design process took place within the bounds of the MedRing. It is worth noting that after reviewing the concept in accordance with Directive EU2017/745, we realised that the device should be classified as class III due to its potential usage as a contraceptive device and its nature as a long-term invasive device.

Rule 15:

All devices used for contraception or prevention of the transmission of sexually transmitted diseases are classified as class IIb, unless they are implantable or long term invasive devices, in which case they are classified as class III.

Concept 1 has an advantage in fluid containment due to having a reduced number of connections compared to Concept 2. Every connection is considered a potential source of leakage, which can result in device malfunction.

Fluid management efficiency is another aspect in which the two concepts diverge. Ensuring a “short” system before the last two valves, as after them the fluid is regarded as waste, increases the lifespan of the product. Concept two requires 25% fewer fluids for conducting tests compared to Concept one, even if Concept one was optimised upon recognising the system’s segregation of clean and unclean fluids.

Considering this contrast, we made the decision to inform LiGalli’s individuals about the outcomes and my selection in order to collectively reach a decision. Following a thorough examination of the manufacturing benefits of Concept One, it was concluded that Concept Two should be selected for further development, while Concept One should be kept as a backup option, referred to as Plan B. After careful deliberation, we arrived at this judgement by taking into account the significance of the characteristics utilised in the comparison.

VII. Delivering a system

The contents of this section offer a comprehensive account of the development of components for the microfluidic system in the LIAS project. The primary challenges involve affixing the membrane to the mixing chamber, establishing the connection between the pump and mTAS, and constructing the bladder tanks. It also evaluates the suggested solutions in terms of their efficiency and reliability.

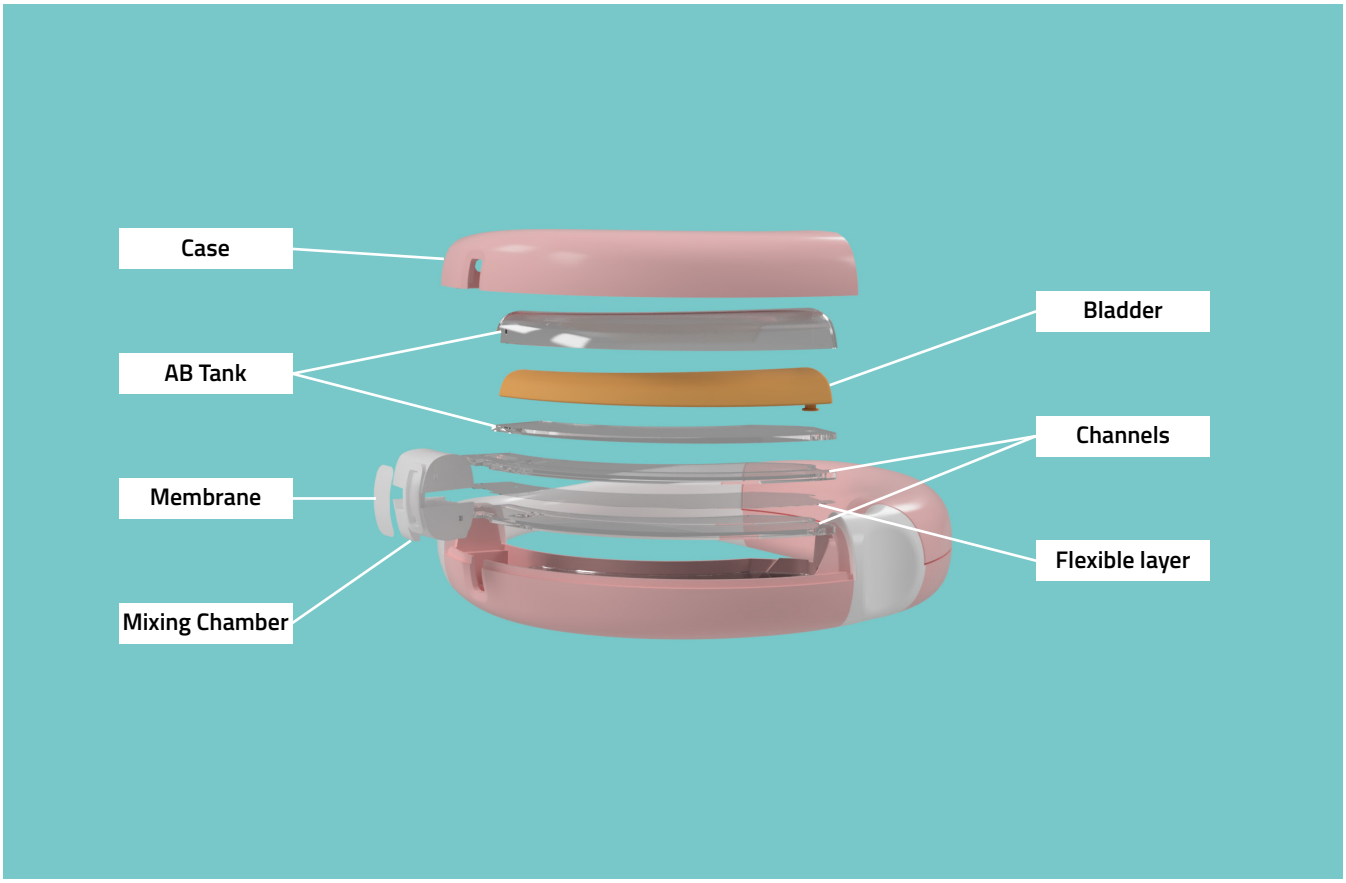
Within the scope of this chapter, we will discuss the process of developing the specifics of the microfluidic system. There are still significant aspects that do not have a thorough answer, despite the fact that several important tasks have already been handled during the idea generation process. All of these aspects are:

- Attaching and securing the membrane to the mixing chamber.
- The pump and mTAS connection.
- The tanks and bladder assembly

In the following sections of this chapter, we will examine the proposed solutions for the issues that were discussed above, as well as evaluate their performance, with the goal of providing an explanation of how these solutions function and how they are integrated into the system.

1. Nothing works without details

In order to address the previously mentioned issues, we found it imperative to redirect my focus towards the more intricate components of the system. Thus far, my primary focus has been on ensuring the appropriate functioning of the system within its broader scope. After finishing the



Exploded view of the new MedRing with the microfluidic system and its components.

design and integration of the system, it is now necessary to tackle the previously neglected difficulties in order to create a comprehensive system that operates efficiently at every level. During the procedure, we held two meetings with Demcon to examine the technical feasibility of alternative solutions and brainstorm ideas (Appendix G). We have collectively agreed that the methods shown here may need further refinement before they can be used in an industrial environment. Nevertheless, they represent a viable initial approach that may be employed to prototype and establish the feasibility of the device.

1.1 Membrane mount

For designing the membrane mount, the first step was to lay down the requirements specific to this component. A set of requirements was laid down in order to guide the solution; these are:

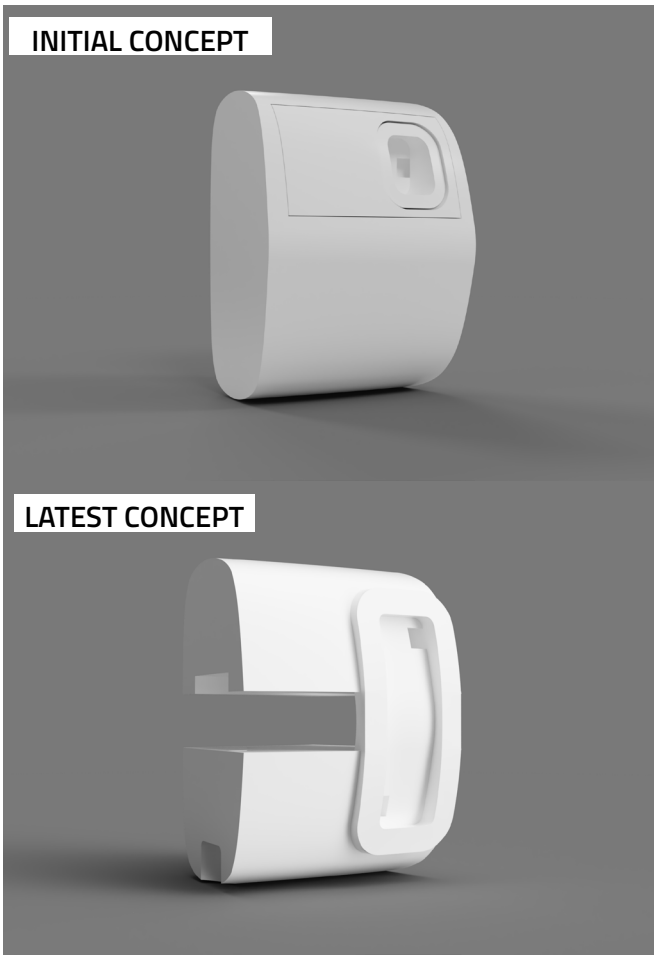


Figure 35. Comparisson between both mixing chambers, on top the initial design with it's deep chamber; bottom, the last design with a shallow chamber

- The membrane has to sit on top of the mixing chamber edges.
- The membrane needs to be secured in its place.
- The joint has to be watertight between the mixing chamber and the MedRing case.

In order to ensure that the membrane's surface is in ideal contact with the vaginal mucosa, the first adjustment that was made to the sampling chamber was to position it in such a way that it is perfectly aligned with the outer shell of the MedRing. The initial chamber design was thought to be extremely deep by the Twente team, which resulted in the construction of a shallower alternative that included an extended surface. The purpose of this updated design is to increase the amount of fluid that is directly exposed to the membrane. When compared to a design that is deeper and has a smaller surface area, this will make the process of reaching a condition of concentration equilibrium in the fluid much more convenient (see Figure 35).

After the new design was finished, my focus switched to the procedure of mounting the membrane onto the mixing chamber. When trying to create a waterproof attachment for a thin layer in a small-scale mixing chamber, particularly for a portable medical device, it is necessary to pay special attention to the materials, manufacturing procedures, and the conditions under which the device is meant to be used. With these considerations in mind, a number of possible solutions were apparent:

O-Ring Seal: A groove around the membrane perimeter is designed for an O-ring. When the membrane touches this O-ring, it seals tightly. O-rings are available in numerous sizes and materials, allowing for personalisation.

Clamp: Physically press the membrane into position for a tight closure. Maintaining pressure around the membrane without destroying it is crucial. Size and space constraints would limit this possibility. They would make it difficult to include an extra element to hold the membrane against the mixing chamber.

Heat sealing or thermal bonding: When the materials allow (as they do in this circumstance), these may work. This approach bonds interface materials using controlled heat and pressure. Its durability and robustness make it popular in medical device manufacturing.

Ultrasonic welding uses high-frequency ultrasonic acoustic waves to combine materials. Because it forms strong, trustworthy bindings without chemicals, it is commonly used in medical device manufacture to link dissimilar materials.

Laser welding: Laser welding makes clean, precise connections for small, complicated items. It's great for hard-to-bond materials. This approach is used on various MedRing assembly pieces.

With these options in hand, we called for a meeting with the team from Demcon, from whom we concluded that, until after proving the technology and having an alpha prototype, the best option would be to glue the membrane between the lip of the mixing chamber and the hole in the MedRing's case, as shown in Figure 36. After an alpha prototype is developed, the solution would be to iterate the design and, with the same layout, apply laser welding instead of using glue.

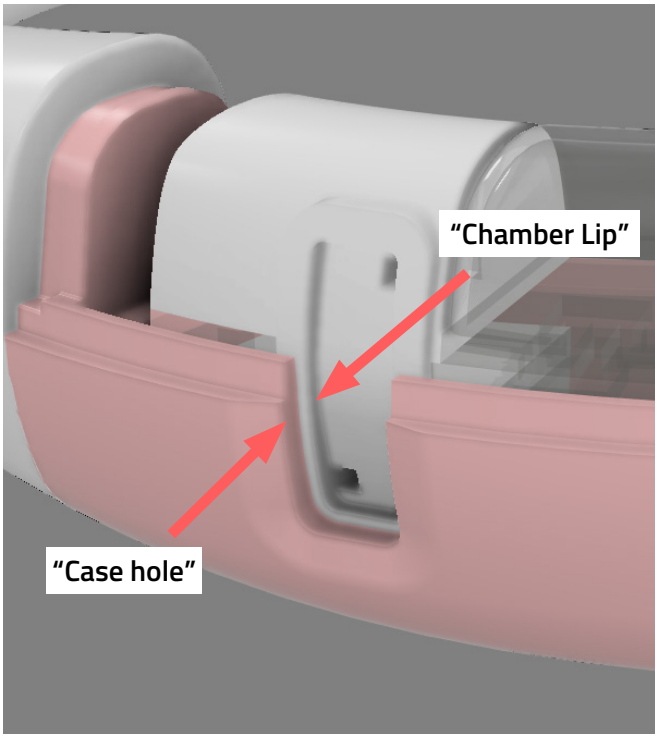


Figure 36. During the early prototype stages, the membrane will be mounted in-between these two components, fixed in its place by glue. Then it would be replaced by laser welding

1.2 Connection between the pump and mTAS

A comparable procedure to that used for the membrane was employed to establish the connection between the pump and the mTAS. The following is a list of requirements for this solution:

- Waterproof connection.
- Enables two-way movement.
- Capable of enduring regular usage without fracturing (the system may experience slight movement within the ring).

Several alternatives were contemplated to address this obstacle:

- Bonding the mTAS to the plastic cover.
- Utilising tubes and a hollow link to establish a connection between the two.
- Linking tubes from the system all the way to the pump.

Following another assessment with Demcon, we have decided to create a block with flexible materials that will be included in the final part of the mTAS and securely attached to the PMMA layers (see Figure 37).

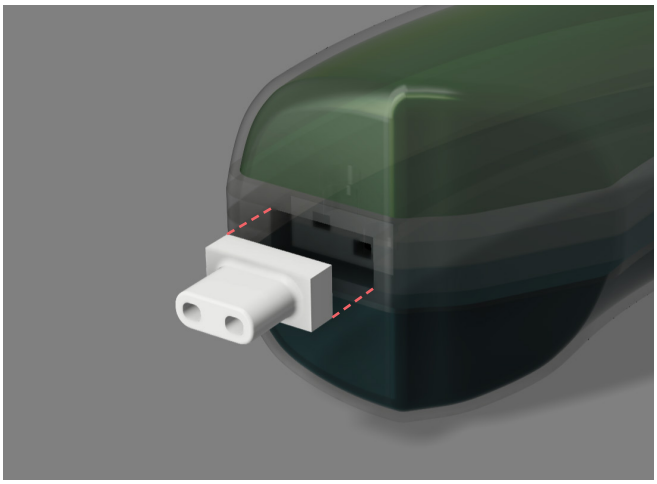


Figure 37. Flexible block and its slot inside the PMMA layers of the microfluidic system

This solution provides an increased contact area with the system, enhancing the ability to create a seal while also allowing for adjustability to simplify the assembly process. Another advantageous feature of this system is its minimal requirement for modifications on the pump side, thereby preserving the majority of the present solution.

1.3 Assembly of the tanks

The objective in this specific scenario is to devise a method for integrating the bladder tank into the bean-shaped tanks of the MedRing. The bladder tanks underwent testing during the ideation process. However, although the proof of concept was successfully demonstrated, minimal effort was taken to develop a formal proposal for integrating this mechanism into the physical design of the tanks until now. Given the tank's asymmetrical shape, the difficulties associated with bladder integration were:

- How to securely join the components in a way that prevents water from entering
- How can one position the bladder in a manner that efficiently separates the tank into two distinct compartments?
- How to design the bladder to enhance the efficiency of the system

In order to address these problems, my initial approach involved analysing the tanks and their connections to the system. This analysis provided valuable insights into the potential methods and locations for attaching the bladder. Given the tank's asymmetrical shape and the location of the inlet, we opted to create a "cap" by detaching the flat face from the rest of the tank. This would provide sufficient room for assembly and could be easily sealed using the bonding techniques already examined, such as laser welding. Alternative methods of accessing the interior of the tanks were explored; however, these methods did not offer sufficient possibilities for securely attaching the bladder and effectively resealing the tanks. Figure 38 shows the selected approach and the different options.

Concurrently, we also investigated two potential approaches for shaping the bladder: one involved creating a partition that would be fixed to the walls, while the other entailed constructing a balloon-like structure. Having a solution that can completely cover the entire volume of the tank without stretching itself (think of inflating a balloon) is of utmost importance. This requirement is crucial because the pumping mechanism lacks the strength to stretch the material. On the other hand, if the bladder is smaller than the volume, two problems may arise:

- The buffer fluids will not be entirely evacuated from their respective tanks.
- The system lacks the capacity to contain all the used fluids within.

Considering these specifications and restrictions, we decided that the optimal approach would involve utilising a balloon-shaped bladder that encompasses the whole capacity of the tank. This bladder would be directly fixed to the outlet, establishing a direct connection between the inlet and the bladder (see Figure 39)**.**

This method will utilise a greater amount of volume within the tank compared to the screen-like option, as it

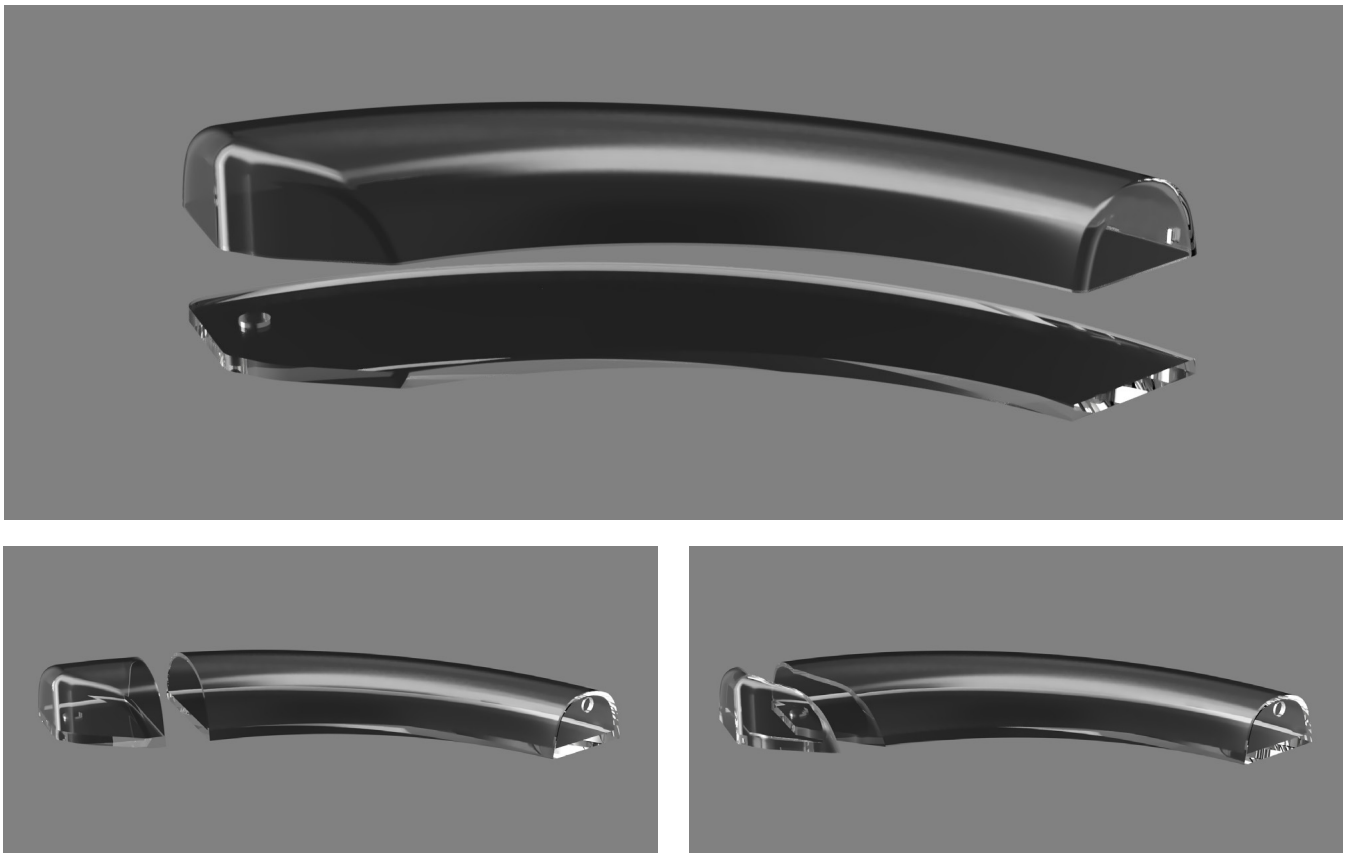


Figure 38. Top: selected partition for assembling the bladder into the tank. Bottom: two different options considered but discarded.

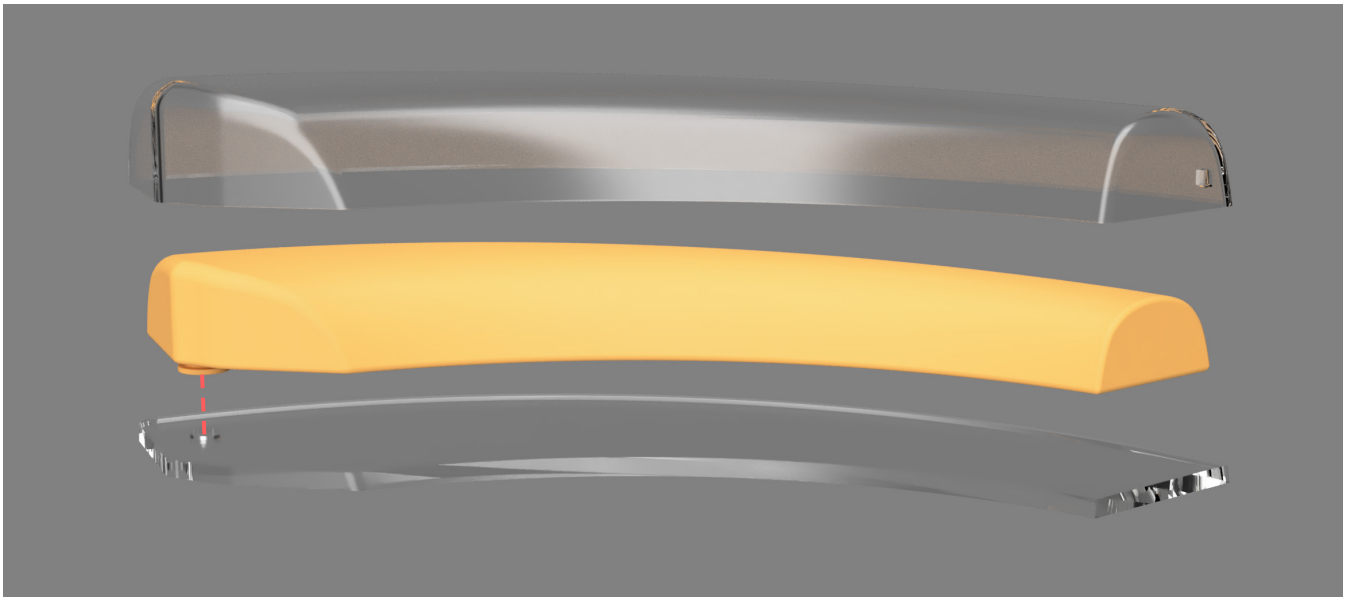


Figure 39. Assembly of the bladder in the tank, its worth mentioning that during the filling process of the tanks (through the outlet) the bladder will be compressed in order to make space to the buffer fluids.

requires the fitting of a larger component inside the tank. However, given that the tanks have an additional 40% volume capacity, this will not pose any operational issues. Additionally, unless there is a material failure, it is possible to ignore any risk of contamination between the clean and used buffer fluids by immediately connecting the balloon-shaped solution to the tank's inlet.

During the assembly process, the bladder would be fitted by folding it into the tank, utilising the additional capacity of the tanks. Additionally, the terminal part of the bladder would function as a sealant for the junction between the micro-Total Analysis System (mTAS) channels and the tanks. To secure the bladder in position, thermal bonding is the preferred assembly method, as it fuses both components together, creating an airtight joint and producing a flat contact with the PMMA layers. Figure 40 shows the bladder inlet assembled through the tank's inlet hole.

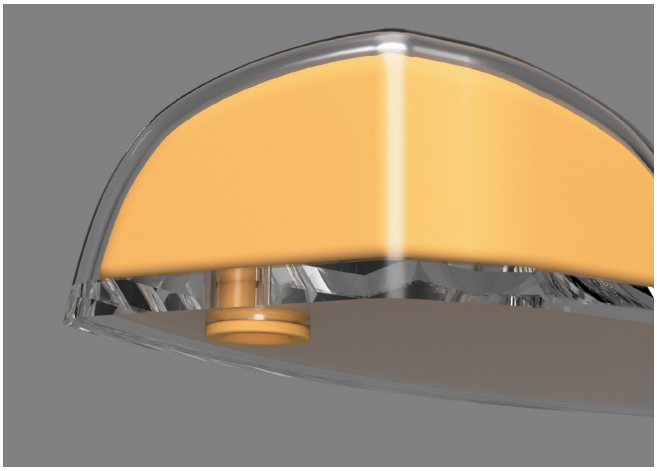


Figure 40. The bladder inlet is inserted through the inlet hole in the tank and its fixed in place with thermal bonding

2. System performance

In order to address the viability of the prototype, the design will be subjected to a fluid dynamics simulation using computer-aided engineering (CAE) tools using SolidWorks software and its Fluid Simulation plug-in. Also, a risk analysis of the product will be performed, paying special attention to the hazards that can be generated by the microfluidic system. Mitigations will only be proposed for hazards that present a medium or high risk.

Risk Analysis

Performing a risk analysis for the microfluidic system is crucial to guaranteeing its safety, dependability, and effectiveness, particularly considering its use as a medical device. This exercise is crucial for identifying, assessing, and mitigating possible dangers that may jeopardise the system's functionality or endanger its users. Through a systematic review of the microfluidic system, our objective is to identify any weaknesses in its design or operational aspects at an early stage of development, thus improving

No	Sequence of events	Hazardous situation	Harm	Severity	Probability	RPN	Mitigation 1	Mitigation 2	Mitigation 3	Mitigation 4	Mitigation 5
1.00	***H01) Mechanical hazards***										
1.04	Glue Failure, parts coming off / mechanical integrity compromised, mucus ingress	S07) MedRing contaminated	R06) Infection	3	2	M	M06	M07	M18		
1.07	Glue Failure, parts coming off / mechanical integrity compromised	S10) Sharp edges	R05) Cuts	2	4	M	M06	M07	M18		
3.00	***H03) Energy Hazards***										
3.05	Device not immune to external radiating devices	S24) MedRing heats up	R08) Burns	3	3	M	M02	M08	M09	M11	
4.00	***H04) Biological Hazards***										
4.04	Bacteria or dirt on MedRing during production	S07) MedRing contaminated	R06) Infection	3	3	M	M10				
8.00	***H08) Packaging/transport/disposal/cleaning***										
8.05	User cleans MedRing before use with unknown/harmful cleaning agent, MedRing degraded by cleaning agent.	S08) Body in contact with non-biocomp component	R02) Adverse body reaction	2	4	M	M04	M13	M20		
8.07	Disposal in normal waste bin	S21) Device (fluids, battery) in environment	R10) Environmental harm	3	3	M	M13				
10.00	***H10) Dropping Hazards***										
10.04	Dropped package - torn package	S07) MedRing contaminated	R06) Infection	3	3	M	M12				
10.05	User drops ring and did not clean it	S07) MedRing contaminated	R06) Infection	3	3	M	M13	M20			
10.07	User drops ring, falls on the ground	S07) MedRing contaminated	R06) Infection	3	3	M	M13				
10.08	User drops magnet, magnet contaminated and touches the ring	S07) MedRing contaminated	R06) Infection	3	3	M	M13				
	Usability										
12.00	***H12) Pull Ring Out***										
12.04	User wants to take out ring, but can not find it or grab it or is too nervous. When ring cannot be removed, a new ring cannot be placed in time	S27) Ring cannot be removed	R09) Emotional d	2	3	M	M16	M17	M18	M19	M20
12.07	User tries to remove ring but pulls it out the wrong way (unfolded)	S33) Pressure against vaginal wall	R01) Bruises	2	3	M	M16	M19	M20		
13.00	***H13) Turn Ring On***										
13.01	Does not know where to shine the light or how long to shine, or how close to hold light source to MedRing	S31) Not able to switch on device	R09) Emotional d	2	5	M	M21	M20			
13.06	User holds magnet in the wrong location	S31) Not able to switch on device	R07) Failed fertility monitoring	1	5	M	M20	M21			
14.00	***H14) Hygiene***										
14.01	User inserts MedRing without clean hands, bacteria on device	S07) MedRing contaminated	R06) Infection	3	2	M	M13	M15	M20		
14.02	User does not clean MedRing before insertion	S07) MedRing contaminated	R06) Infection	3	2	M	M13	M15	M20		
14.03	User stores Medring at a dirty place	S07) MedRing contaminated	R06) Infection	3	2	M	M13	M15			

Figure 41. List of identified hazards that present a medium risk to the user. No hazards were categorized as High risk according to the risk criteria.

the safety of the product. The knowledge acquired from this study will be used to enhance the design, facilitate adherence to regulations, and ultimately aid in the creation of a microfluidic system that is both safer and more efficient. In this report, we will cover only the medium- or high-risk hazards and their mitigations. A more thorough review of the analysis and the criteria for the risk assessment can be found in Appendix H.

Identified Risks (Medium/High)

The identified risks, as shown in Figure 41, were classified accordingly to the type of hazard and also in relation to how or why the hazard is generated (as shown in the sequence of events). Also, mitigations were considered for each of these risks in order to reduce their RPN classification. The RPN classification is a score that comes from the combination of the severity and probability with the harm associated to each risk.

The mitigations (shown in Figure 42) will be presented as future design recommendations for LiGalli, as some of the aspects covered are out of the scope of this project and are not directly related to the microfluidic system.

Computational Fluid Dynamics

A computational fluid dynamics (CFD) study will be conducted. This technology enables us to enhance the design and optimise its performance by offering comprehensive insights into the interactions of fluids with surfaces.

The purpose of this study is to examine and forecast the fluid flow within the microfluidic system.

Study Setup

The first step was to prepare two different models for the study. The reason for doing this is that the software cannot simulate the valve mechanisms, so one CAD model was prepared for each fluid. The different studies were called:

- AB Flow
- DB Flow

For each model, the valves were “manually” closed by disconnecting the path in the places where valves remain closed when pumping each fluid. Also, every component that conforms to the microfluidic system was combined into one body.

Mitigations Risk mitigating actions	
Mxx	Mitigation
M01	Ring design and testing according to 60601-1
M02	Ring testing according to 60601-2 (EMC)
M03	Ring design and testing according to 60601-2-24 (infusion pump)
M04	Ring design and testing according to 10993 (biocomp)
M05	Ring design and testing according to 60601-1-11 (med-wearable)
M06	Implement stronger adhesives or alternative bonding methods like ultrasonic welding to enhance mechanical integrity.
M07	Conduct extensive durability testing under various environmental conditions to ensure reliability.
M08	Shielding critical components within the MedRing to protect against external electromagnetic interference.
M09	Incorporate design features or materials that reduce susceptibility to external radiations.
M10	Establish strict sterilization and cleanliness protocols during the manufacturing process.
M11	Integrate thermal management solutions to dissipate heat effectively and prevent overheating
M12	Use robust, tamper-evident packaging to protect against contamination.
M13	Provide clear user instructions for cleaning with recommended agents only and proper disposal guidelines to minimize environmental impact.
M14	Design the MedRing with shock-absorbing materials or structures to withstand accidental drops.
M15	Include user guidelines on what to do if the device is dropped to prevent contamination or damage.
M16	Provide comprehensive instructions with illustrations or animations demonstrating the proper method to insert and remove the ring. This could be included in the product packaging or as an online tutorial.
M17	Enhance the ring's grip or texture to aid in retrieval. Incorporate a more robust design to prevent breakage if the ring is pulled out incorrectly.
M18	Establish clear guidelines on what to do if the ring breaks or cannot be found, including when to seek medical advice.
M19	Design the ring with a feedback mechanism that reassures the user of correct placement and removal.
M20	Offer a helpline or support system for users to consult if they encounter difficulties or have concerns about the correct use of the ring.
M21	Design the ring with a feedback mechanism that reassures the user of ON/OFF status of the ring

Figure 42. List of proposed mitigations, each mitigation is assigned to at least one hazard, but each hazard may present more than one mitigation, as shown in Figure 41.

The simulation parameters for the simulation are as follows:

Mesh settings (global)	
Automatic initial mesh	On
Result resolution level	3
Narrow channel refinement	On
Physical Features	
Fluid Flow	On
Flow type	Laminar and turbulent
Roughness	0 micrometer
Wall conditions	Adiabatic wall
Initial Conditions	
Thermodynamic parameters	Static Pressure: 101325.00 Pa
	Temperature: 310.00 K
Inlet volume flow	Flow rate: 2.33e-10 m^3/s
	Inlet profile: Uniform
Turbulence parameters	Intensity: 2.00%
	Lenght: 1.076e-04 m

For the fluid in the study, we decided to use water. We know that both fluids are phosphate-buffered saline (PBS) solutions, designed to mimic the isotonic and isoionic conditions of the human body. This means their physical properties are very close to water:

- Density: The density of PBS closely approximates that of water, which is about 1 g/cm^3 (or 1000 kg/m^3) at room temperature. Variations in density between PBS and water are typically minor and depend on the specific concentration of the salts in the PBS solution.
- Viscosity: Similarly, the viscosity of PBS is comparable to that of water. The viscosity of water at 20°C is about 1.002 mPa·s. The addition of salts to create PBS may slightly alter its viscosity, but for practical laboratory applications, this difference is negligible.

Limitations

- Static Mesh: SolidWorks uses a static mesh, making it difficult to simulate dynamic movements of parts like valves or the tank bladder.
- Simplified Physics: It simulates flow assuming fixed geometry, not dynamically moving parts like valves opening or closing, or the unfolding of the tank bladder.

- Single Fluid Domain Assumption: The software assumes one continuous fluid, complicating simulations where a new fluid is introduced.
- Lack of Multiphase Flow Support: SolidWorks has limited support for accurately simulating two different fluids interacting within the same domain.
- Transient Analysis Complexity: Simulating a second fluid introduced into an existing fluid is complex due to limitations in changing fluid properties mid-simulation.

Study Results

A total of four studies were performed during the analysis, two for the flow of the association buffer and two for the dissociation buffer. Special attention will be given to the studies made with the association buffer setup as it presents greater complexity than the path of the dissociation buffer.

The results for both the AB and DB (Figure 43) show that the general flow is correct and the fluid follows the path as intended in the design. It comes out of the tanks, then follows the path through the valves until it returns to its original tank. It's important to consider that the tanks will be equipped with the "bladder" in charge of separating the used fluids from the "fresh" ones.

Taking a closer look, we can also see that the mixing chamber gets completely filled by the AB before continuing to the reading chamber, as shown in Figure 44.

Also, it's possible to notice that, depending on the fluid being pumped, some channels are not filled. This is

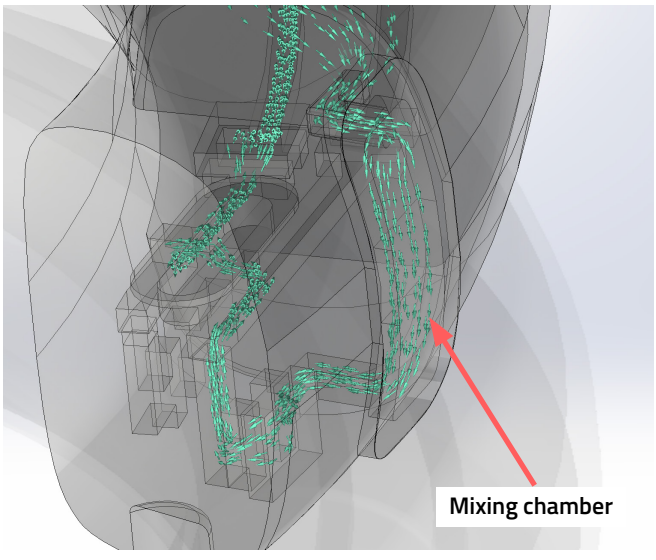


Figure 44. The liquid enters the chamber from the top filling it. The "drain" is located at the bottom.

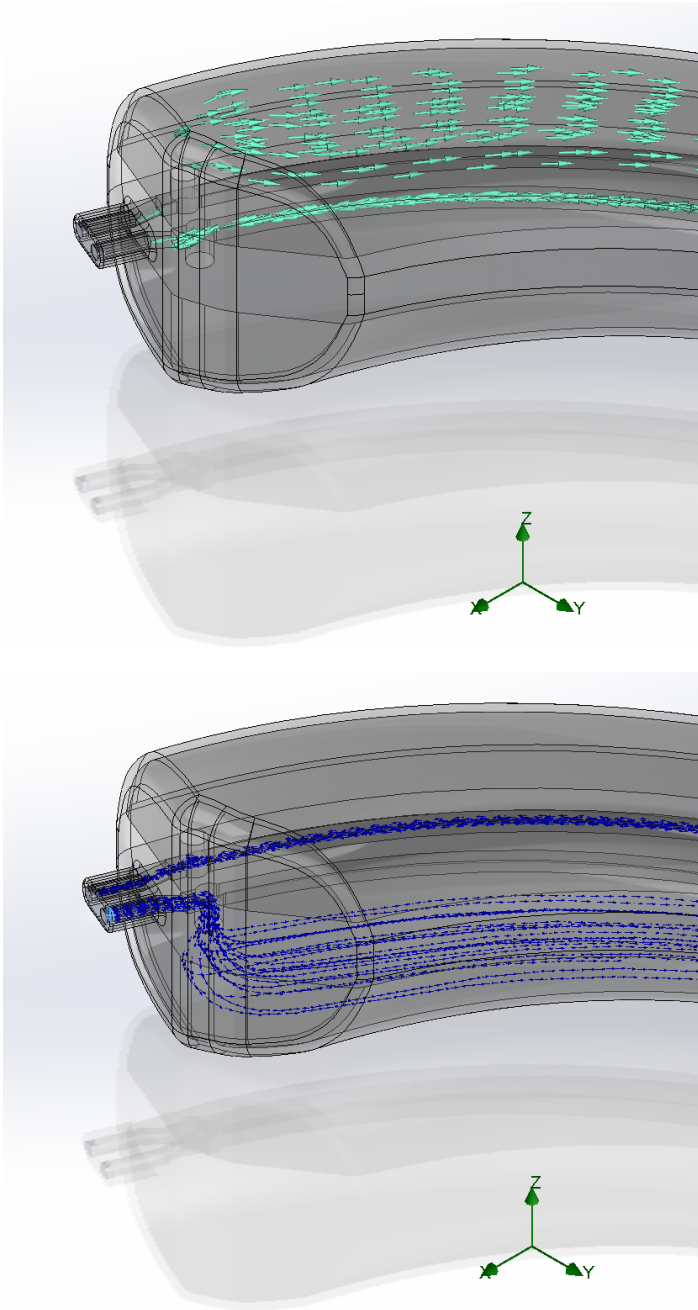


Figure 43a. (Top) Overview of the flow path for the Association Buffer.

considered something positive, as those channels would only be a waste in the operation of the system as they would have to be rinsed when pumping the next fluid. Figure 45 shows the unfilled channels when pumping AB.

After taking a closer look into the reading chamber (where the LoC will analyse the samples), it is possible to notice that it doesn't fill up as expected; instead, the liquids flow directly to the other side, reducing considerably the effective sampling volume. Figure 46 shows a close-up of the situation.

One reason that could explain this behaviour is that, due to the size of the channels, the flow has a laminar nature. This

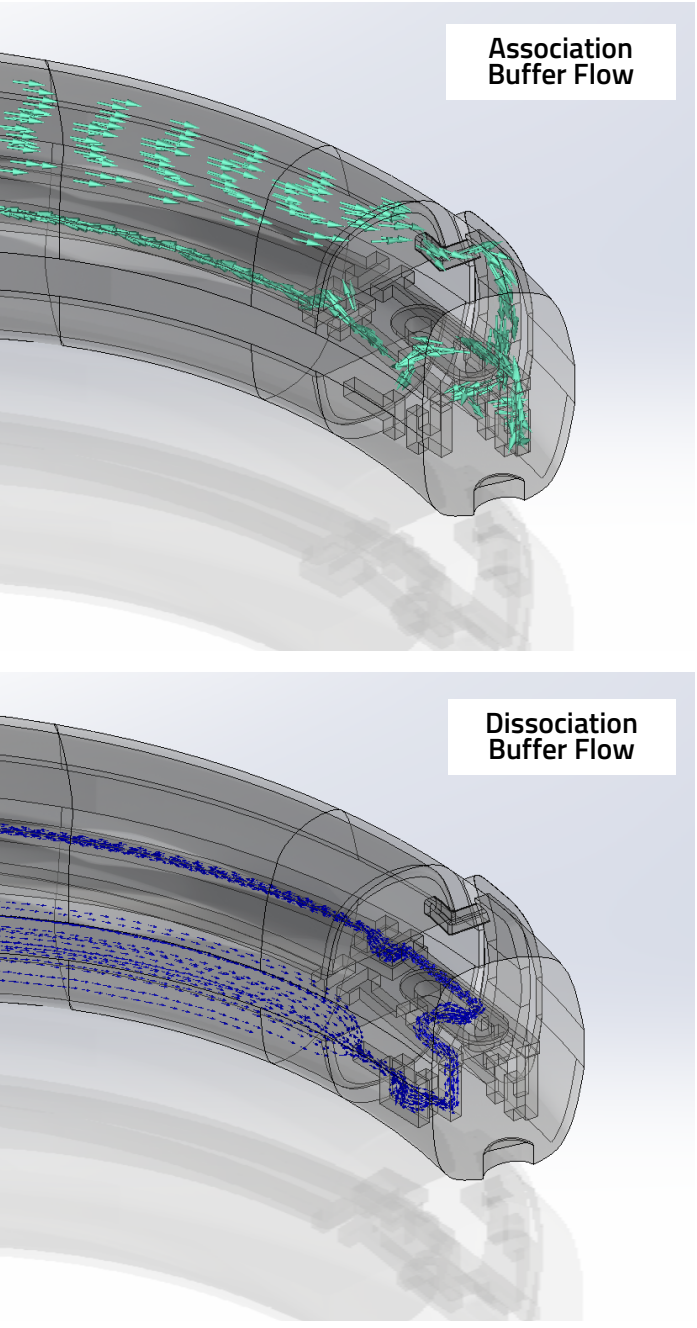


Figure 43b. (Bottom) Overview of the flow path for the Dissociation Buffer.

refers to a fluid motion in which all the particles of the fluid move along well-defined, smooth paths or streamlines. Considering how close the inlet and outlet are in this specific situation, the motion doesn't break, leaving those fluid pockets in which the liquid won't be replaced.

To confirm this hypothesis, the Reynolds (Re) number for the system was calculated using the formula:

$$Re = \frac{\rho \cdot V \cdot L}{\mu}$$

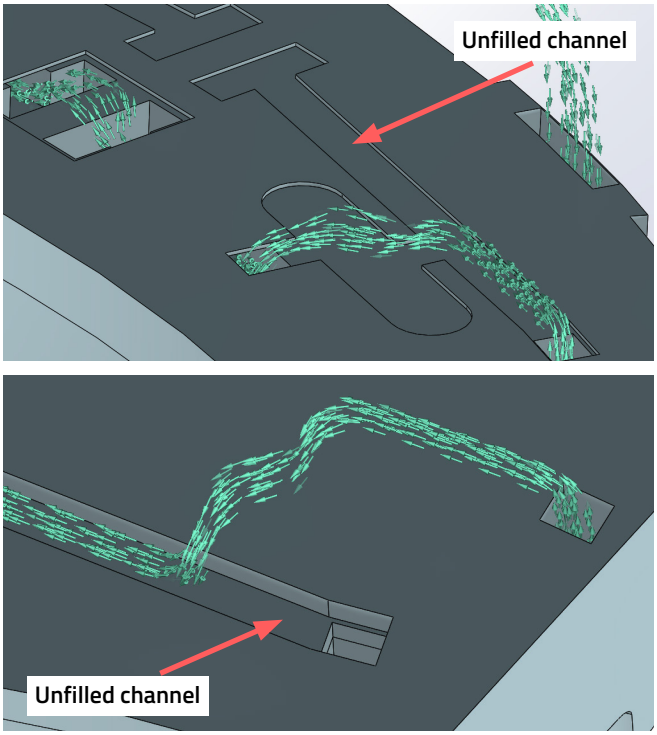


Figure 45. The "unfilled" channels have been previously filled by the dissociation buffer. When association buffer is pumped they wont mix, maintaining its LH concentration.

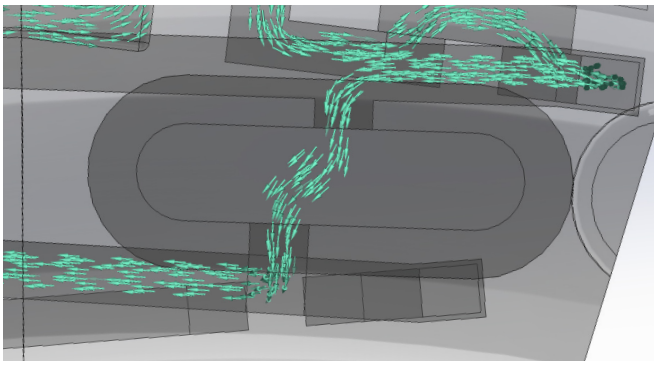


Figure 46. Path followed by the association buffer when reaching the reading chamber

When calculating the Reynolds number, flow is typically considered laminar if

$$Re < 2300,$$

turbulent if

$$Re > 4000,$$

and transitional when the value is in between. In this particular case, the Reynolds number is 0.494, which confirms that the system presents laminar flow.

In order to allow the exchange of fluids in the reading chamber, the CAD model was modified, imitating the inlet/outlet arrangement present in the mixing chamber. The channels leading to the reading chamber were displaced towards each side of the chamber, forcing the flow to go through it whenever a liquid is pumped within the system.

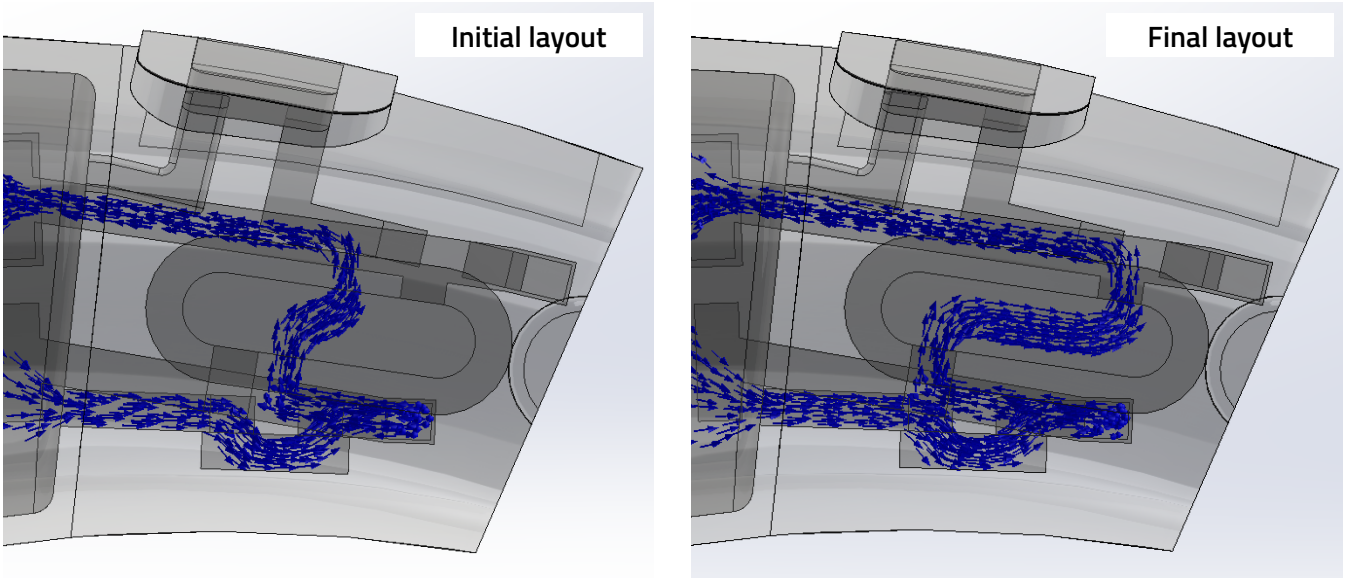


Figure 47. Comparisson between the flow through the reading chamber of dissociation buffer in the initial layout and after the rearrangement of the inlet/outlet positions.

After these changes, a second study for each fluid was performed to determine if the issue was fixed. A comparison of the initial and final layout of the inlets can be seen in Figure 47.

As shown in the pictures, after the modification, the flow covers almost the whole surface of the reading chamber, considerably reducing the problem encountered during the first study. Also, this adjustment did not affect the rest of the flow. On the other hand, another positive side effect of this change is that now the association buffer flow requires less volume to get from the mixing chamber to the reading chamber. This happened because the distance between the mixing chamber outlet and the reading chamber inlet was reduced.

Take aways

Keeping in mind the limitations this study presents, the takeaways and conclusions we could draw from this study are:

- The CFD analysis provided critical insights into fluid interactions within the microfluidic system, enabling precise design optimizations. By simulating the flow of association and dissociation buffers separately, we could identify and address the flow path for each fluid.
- The calculated Reynolds number of 0.494 confirms that the system operates under laminar flow conditions. This is crucial for this system, where controlled and predictable fluid flow is essential for accurate analysis and operation.
- The simulation results led to design adjustments, particularly in the reading chamber. By mimicking the inlet/outlet arrangement of the mixing chamber and adjusting the CAD model, we improved fluid exchange in the reading chamber. This adjustment ensured that the chamber was completely filled.
- The study highlighted the system's efficiency in fluid usage. By ensuring some channels remain "unfilled" during specific fluid pumping phases, we confirm that unnecessary fluid waste is being avoided, contributing to the system's overall efficiency.
- Adjusting the inlet/outlet configuration to ensure thorough fluid coverage within the reading chamber enhanced the efficiency of the system with the current sampling volume.

Key Design Conclusions:

The study underscores the importance of CFD analysis in the iterative design process of microfluidic systems. By integrating simulation insights, we were able to enhance system performance, reduce operational inefficiencies, and ensure precise control over fluid movement.

This analytical approach demonstrates that even in systems constrained by laminar flow and static mesh limitations, strategic design modifications can significantly improve functionality and efficiency.

VIII. Conclusion and Future Recommendations

In this chapter we will discuss the conclusions of the project, what are its contributions and limitations. Also, it provides recommendations and possible directions for further development of the system with an aim to bring this feature to market in the MedRing device. Ultimately, a reflection on the work done is provided as a way to identify the learnings gathered through this process.

1. Conclusions.

This thesis concentrated exclusively on the design, integration, and testing of a microfluidic system designed specifically for MedRing's health monitoring feature.

The main outcome of this work is a detailed design of the system and subsequent analysis that validated the system's functionality under simulated conditions using computational fluid dynamics (CFD). The validation of this system was limited to computer-aided engineering (CAE) studies, highlighting a critical stage of proof-of-concept that still requires real-world prototyping and testing.

The design's compatibility with the MedRing's compact form factor, combined with its potential for non-invasive monitoring of fertility-related biomarkers, represents a step forward towards feasibility evaluation and practical applications.The project met its design objectives by using simulation to demonstrate the system's ability to handle fluids in a way that allows for accurate biomarker gathering and detection. However, the lack of physical prototyping highlights a gap between theoretical validation and practical application, requiring additional efforts to bridge this gap.

2. Future Recommendation and Directions

As we look forward, several paths emerge for the advancement and application of the technologies discussed.

Technological advancements could focus on improving the sensitivity and range of detectable biomarkers by creating more advanced aptamers and refining microfluidic system designs. Furthermore, expanding the MedRing platform's application to monitor a broader range of health indicators could have a significant impact on both personal and preventative healthcare. These collaborative efforts, by pushing the boundaries of current technology, have the potential to further integrate sophisticated diagnostic capabilities into everyday wearable devices.

To move from simulation to application, the immediate recommendation is to begin a comprehensive prototyping phase. This includes prototyping the designed microfluidic system and conducting extensive testing under lab-controlled conditions to evaluate its performance, before moving on to real-world conditions to also address durability and user comfort. Collaboration with biomedical engineers and clinicians could make these efforts easier, ensuring that the system meets both technical and user-centric requirements.

Further recommendations include investigating advanced manufacturing techniques such as 3D printing for microfluidics in order to improve design flexibility and reduce production costs. Furthermore, expanding the system's ability to interface with various sensors may broaden the range of health indicators monitored by the MedRing device, increasing its value to patients.

3. Personal reflection.

Reflecting on this journey, the challenges faced and knowledge gained have been considerable. This project not only improved my technical and research skills, but it also deepened my understanding of wearable technologies' potential to transform healthcare and reignited my appreciation for interdisciplinary collaboration in bringing innovative healthcare solutions to life.

The opportunity to contribute to the advancement of women's health monitoring has been especially rewarding, highlighting the complexities of translating theoretical models into practical solutions, particularly in the field of wearable health technologies. Also, the restriction on CAE studies, while a prudent step in early-stage development, instilled a strong sense of the importance of real-world testing.

In the future, wearable health technologies are expected to be seamlessly integrated into daily life, providing actionable insights into our health rather than just data. The work presented in this thesis represents a step towards that future. I'm excited to see the tangible impact of this work on improving health monitoring capabilities and how future innovations will contribute to this field.

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XI. Appendices

Project Brief

Appendix A:
Interim Analysis: Acceptance and ease of use of the vaginal Dummy MedRing by female volunteers.

Appendix B:
Interview with Dr. Maarten Wiegerinck.

Appendix C:
Overview and market review of fertility tracking and contraception methods.

Appendix D:
Process for definition of microfluidic system architecture.

Appendix E:
Microfluidic system components explained

Appendix F:
Prototype assessment meeting w/Demcon

Appendix G:
Final concept concept assessment w/Demcon

Appendix H:
Risk analysis

Project Brief

IDE Master Graduation Project

Project team, procedural checks and Personal Project Brief

In this document the agreements made between student and supervisory team about the student's IDE Master Graduation Project are set out. This document may also include involvement of an external client, however does not cover any legal matters student and client (might) agree upon. Next to that, this document facilitates the required procedural checks:

- Student defines the team, what the student is going to do/deliver and how that will come about
- Chair of the supervisory team signs, to formally approve the project's setup / Project brief
- SSC E&SA (Shared Service Centre, Education & Student Affairs) report on the student's registration and study progress
- IDE's Board of Examiners confirms the proposed supervisory team on their eligibility, and whether the student is allowed to start the Graduation Project

STUDENT DATA & MASTER PROGRAMME

Complete all fields and indicate which master(s) you are in

Family name	Spoerer	6836	
Initials	SS		
Given name	Sebastian		
Student number	5439973		

IDE master(s)	IPD ✓	Dfl	SPD	
2nd non-IDE master				
Individual programme *(date of approval)*				
Medisign	✓			
HPM				

SUPERVISORY TEAM

Fill in he required information of supervisory team members. If applicable, company mentor is added as 2nd mentor

Chair	Wolf Song	dept./section	SDE/MD
mentor	Sonja Paus-Buzink	dept./section	HCD/AED
2nd mentor	Oda Heerema		
client:	LiGalli		
city:	Leiden	country:	The Netherlands
optional comments			

! Ensure a heterogeneous team. In case you wish to include team members from the same section, explain why.

! Chair should request the IDE Board of Examiners for approval when a non-IDE mentor is proposed. Include CV and motivation letter.

! 2nd mentor only applies when a client is involved.

APPROVAL OF CHAIR on PROJECT PROPOSAL / PROJECT BRIEF -> to be filled in **by the Chair** of the supervisory team

Sign for approval (Chair)

Y. Song Digitally signed by Y. Song Date: 2023.10.03 11:49:48 +02'00'

Name Wolf Song Date 28 Sep 2023 Signature

CHECK ON STUDY PROGRESS

To be filled in **by SSC E&SA** (Shared Service Centre, Education & Student Affairs), after approval of the project brief by the chair. The study progress will be checked for a 2nd time just before the green light meeting.

Master electives no. of EC accumulated in total	32	EC
Of which, taking conditional requirements into account, can be part of the exam programme	32	EC

★	**YES**	all 1st year master courses passed
	NO	missing 1st year courses

Comments:

homologatievakken behaald

Sign for approval (SSC E&SA)

Name K. Veldman Date 5 Oct 2023 Signature K. Veldman

click to add date

APPROVAL OF BOARD OF EXAMINERS IDE on SUPERVISORY TEAM -> to be checked and filled in by IDE's Board of Examiners

Does the composition of the Supervisory Team comply with regulations?

YES	★	Supervisory Team approved
NO		Supervisory Team not approved

Comments:

Based on study progress, students is ...

★	**ALLOWED** to start the graduation project
	NOT allowed to start the graduation project

Comments:

Sign for approval (BoEx)

Monique von Morgen Digitally signed by Monique von Morgen Date: 2023.10.10 09:43:16 +02'00'

Name Monique von Morgen Date 10 Oct 2023 Signature

Personal Project Brief – IDE Master Graduation Project

Name student Sebastian Spoerer **Student number** 5,439,973

PROJECT TITLE, INTRODUCTION, PROBLEM DEFINITION and ASSIGNMENT

Complete all fields, keep information clear, specific and concise

Project title Exploring LiGalli Medring's potential as an intra-vaginal healh-monitoring device

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

Introduction

Describe the context of your project here; What is the domain in which your project takes place? Who are the main stakeholders and what interests are at stake? Describe the opportunities (and limitations) in this domain to better serve the stakeholder interests. (max 250 words)

The project aims to enhance women's healthcare by developing an intra-vaginal health monitoring device equipped with aptamer-based sensors, also known as a lab-on-a-chip. This project will build upon LiGalli's MedRing platform, which currently allows microdosing of medication, with the goal of integrating both microdosing and diagnostic features into one device. By measuring pH values, temperature, and/or hormone levels intravaginally, it is possible to diagnose and monitor ovulation and bacterial vaginosis, for example in (Pal et al., 2020). Figure 1 outlines the features and technologies involved in the integrated ring.

The stakeholders include researchers from UTwente, focusing on the development and clinical validation of these sensors. Demcon, a development partner, ensures the device's design is scalable for mass production. Medical professionals and clinicians are interested in the device's potential for reliable, non-invasive monitoring that can provide early indicators of various health conditions. Patients and consumers seek a healthcare experience that offers less invasiveness, along with convenience and reliability in monitoring their health. Regulatory authorities and ethical committees are involved to ensure the device meets safety standards and ethical research protocols.

While the product brings opportunities for better women's health management and the potential to revolutionize ovulation and fertility tracking, the concept also faces challenges, such as fluid sample management within the compact design of the MedRing as shown in Figure 2. Ethical and regulatory considerations also pose constraints, particularly in ensuring patient safety and data privacy. Additionally, the project has a limited scope for real-world testing due to these technical and regulatory challenges.

(1) Pal, A., Nadiger, V. G., Goswami, D., & Martinez, R. V. (2020). Conformal, waterproof electronic decals for wireless monitoring of sweat and vaginal ph at the point-of-care. Biosensors and Bioelectronics, 160, 112206. https://doi.org/10.1016/j.bios.2020.112206

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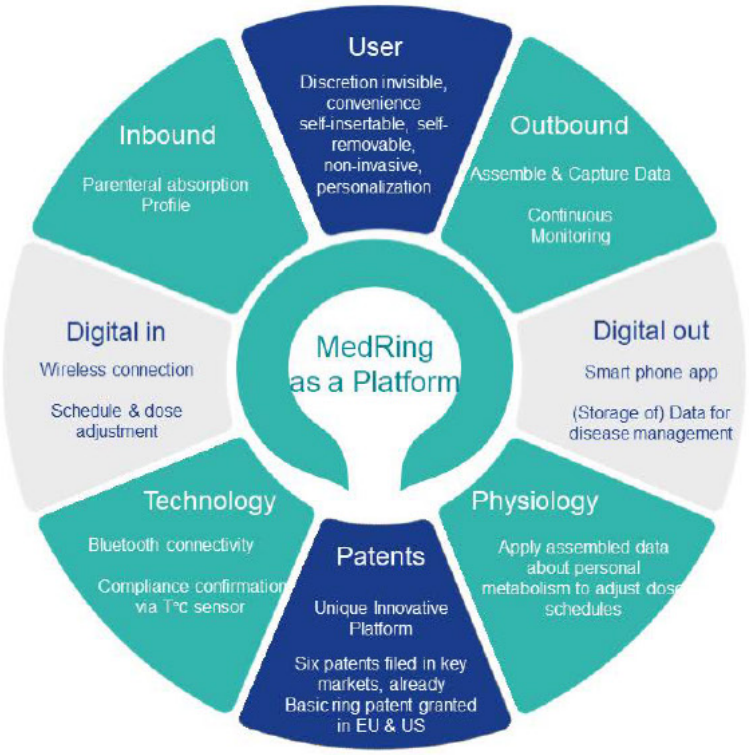

image / figure 1 Projection of features and technologies involved in the integrated ring. Source: linkmagazine.nl

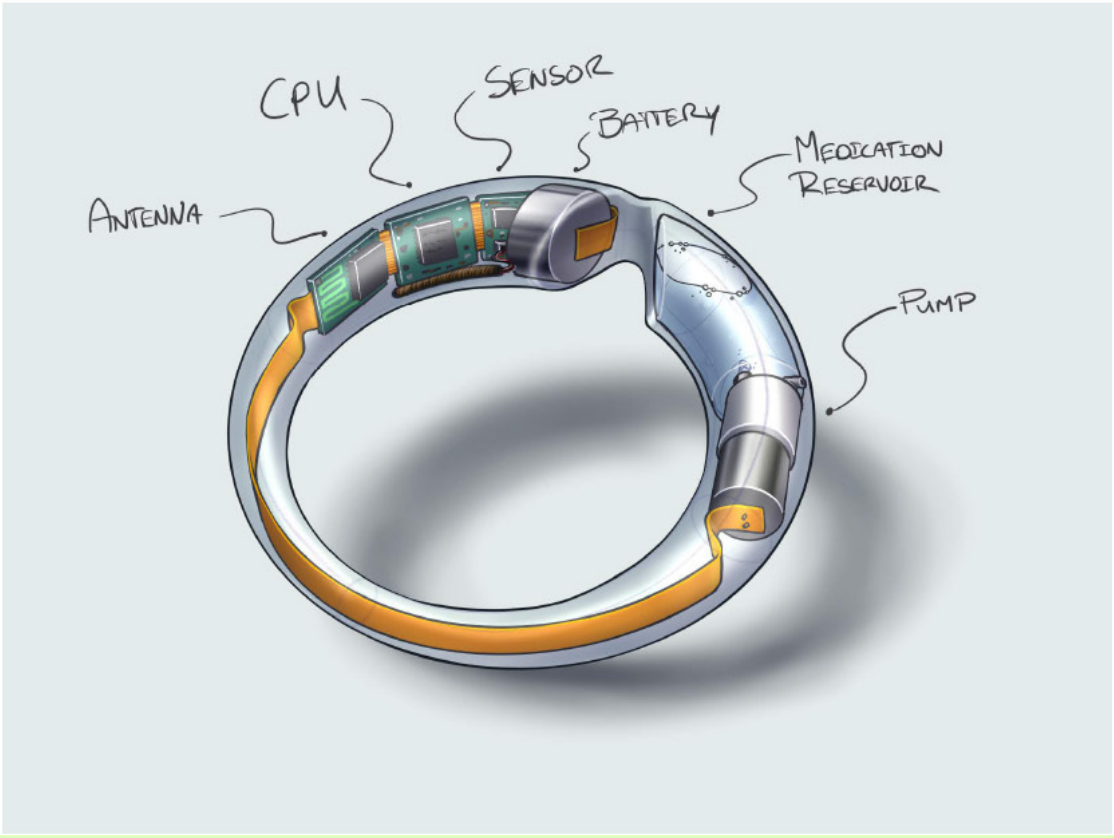

image / figure 2 Sketch of the inside component arrangement of the actual ring. Source: linkmagazine.nl

Problem Definition

What problem do you want to solve in the context described in the introduction, and within the available time frame of 100 working days? (= Master Graduation Project of 30 EC). What opportunities do you see to create added value for the described stakeholders? Substantiate your choice.
(max 200 words)

The primary problem to address during this project is the integration of the "Lab-on-a-chip" technology inside the MedRing patform. Solving the challenges of capturing, storing, releasing, and cleaning vaginal fluid samples within a limited space will require a compact, efficient, and user-friendly fluid management system.

Primary Conflicting Requirements and Knowledge Gap:
Considering the implementation of fluid analysis in within the "sensing " capabilities of the ring, the conflicting requirements stem from the need to maintain the form factor while ensuring precise and reliable fluid sample handling. The knowledge gap lies in designing a system that can efficiently and hygienically manage multiple samples without compromising the device's usability, especially comfort, for the user.

Potential Opportunities:
Opportunities present in this project are in a first level the ability to track and monitor women's reproductive cycle in a non invasive way, presenting lower costs than in the clinics and with accurate data. This way they can either promote or avoid having children without the use of medication.

Assignment

This is the most important part of the project brief because it will give a clear direction of what you are heading for. Formulate an assignment to yourself regarding what you expect to deliver as result at the end of your project. (1 sentence) As you graduate as an industrial design engineer, your assignment will start with a verb (Design/Investigate/Validate/Create), and you may use the green text format:

Design a trustable vaginal fluid sampling system to monitor women's reproductive cycle using LiGalli's Medring platform.

Then explain your project approach to carrying out your graduation project and what research and design methods you plan to use to generate your design solution (max 150 words)

Conducting literature research on topics such as intra-vaginal monitoring, aptamer-based sensors, and medical device development regulations will be crucial. This involves analyzing existing monitoring solutions, understanding their functionalities, and aligning the information with stakeholder's findings. Also, experts and users will be interviewed and observed in order to better understand their needs. Tools like MATLAB and Fusion 360 will aid in data analysis and concept embodiment.

During the same time frame, the ideation phase will take place, guided by a customized Double Diamond Model. This model considers parallel work between prototyping and literature research from early stages of divergence, allowing for a comprehensive exploration of ideas through sketches, low-fidelity prototypes, and 3D renders. Periodic reviews with mentors and user and field tests will refine the design. The project culminates in a combination of functional prototypes, serving as a proof of concept and tangible representation of the work, aligned with the goal of advancing on the integration of this technology for intra-vaginal health monitoring.

Project planning and key moments

*To make visible how you plan to spend your time, you must make a planning for the full project. You are advised to use a Gantt chart format to show the different phases of your project, deliverables you have in mind, meetings and in-between deadlines. Keep in mind that all activities should fit within the given run time of 100 working days. Your planning should include a **kick-off meeting**, **mid-term evaluation meeting**, **green light meeting** and **graduation ceremony**. 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 course activities).*

Make sure to attach the full plan to this project brief.
The four key moment dates must be filled in below

Kick off meeting	28 Sep 2023
Mid-term evaluation	28 Nov 2023
Green light meeting	2 Feb 2024
Graduation ceremony	29 Feb 2024

In exceptional cases (part of) the Graduation Project may need to be scheduled part-time. Indicate here if such applies to your project

Part of project scheduled part-time	
For how many project weeks	
Number of project days per week	

Comments:

Motivation and personal ambitions

Explain why you wish to start this project, what competencies you want to prove or develop (e.g. competencies acquired in your MSc programme, electives, extra-curricular activities or other).

Optionally, describe whether you have some personal learning ambitions which you explicitly want to address in this project, on top of the learning objectives of the Graduation Project itself. You might think of e.g. acquiring in depth knowledge on a specific subject, broadening your competencies or experimenting with a specific tool or methodology. Personal learning ambitions are limited to a maximum number of five.
(200 words max)

My primary objective is to become a proficient medical designer, a field that continually fascinates me. This specific project offers two invaluable opportunities: working with cutting-edge technology and developing a consumer medical product. Throughout my academic journey, I've gained skills in technical feasibility, concept generation, and user-centered design. My internship further enriched my understanding of the medical product design workflow.

My ambitions for this project are:
1. Strengthen my engineering skills, particularly in electronics, to broaden and address gaps present in my portfolio.
2. Transition from medical simulation to medical device design, leveraging this project as a proving ground for my capabilities.
3. Demonstrate my value as an Industrial Design Engineer by contributing meaningful work and insights that aid in the company's product development.

This project will be a significant challenge but also a crucial step toward achieving my career goals in medical product design.

Appendix B

Meeting Summary

Meeting Title:Discussion on MedRing Biomarkers and Technology

Date & Time: Not Specified

Location: Virtual Meeting Platform

Attendees: Sebastián Spoerer Ruiz-Tagle, Maarten Wiegerinck

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1. Meeting Objectives:

- To discuss the selection of biomarkers for fertility monitoring in the MedRing project.

- To understand the technological aspects of MedRing, including aptamer usage and monitoring capabilities.

2. Key Discussion Points:

- Biomarker Selection for Fertility: Discussion on focusing initially on LH hormone due to existing aptamers, with potential inclusion of estrogen and progesterone in the future.

- Technology and Monitoring: Insights into aptamer technology for detecting various biomarkers and the possibility of multiplex detection for monitoring multiple hormones simultaneously.

- Applications Beyond Fertility: Exploration of MedRing's potential in detecting oncology markers, particularly in breast cancer, and its capability in monitoring other health aspects like bacterial vaginosis and acute infections.

3. Decisions Made:

- Decision to start with LH hormone for initial MedRing tests.

- Agreed to explore incorporating other biomarkers like estrogen and progesterone based on technological advancements.

4. Action Items:

- Sebastián to further explore and refine the biomarker selection for MedRing.

- Maarten to provide ongoing support and advice on technological aspects and biomarker selection.

5. Questions Raised and Addressed:

- Discussed the feasibility and effectiveness of different biomarkers for fertility and health monitoring.

- Addressed questions about the technology used in MedRing, particularly aptamer technology.

6. Pending Items:

- Further exploration of additional biomarkers and their integration into the MedRing system.

- Detailed analysis of MedRing's potential applications in various health monitoring scenarios.

7. Next Meeting Plan:

- Not specified in the provided transcript.

8. Additional Notes:

- The conversation also touched upon the comparative effectiveness of various bodily fluids (like saliva, urine, and vaginal mucosa) for health monitoring.

Appendix C

Women's fertility monitoring and contraception techniques.

An essential component of human reproduction, the fertile cycle in females is a complex interplay of endocrine-regulated physiological processes. The aforementioned cycle, which generally extends for around 28 days, serves as evidence of the body's extraordinary ability to produce offspring and the delicate equilibrium of hormones (Knobil & Neill, 2006). Comprehending this cycle is not solely imperative for reproductive health but also exerts a substantial influence on modern methodologies pertaining to contraception and fertility monitoring.

Endocrine reproductive system

The reproductive endocrine system strictly controls the female reproductive cycle, which is an intricately coordinated series of events. This system comprises a collection of hormones and organs that are integral to both the menstrual cycle and fertility. The menstrual cycle, which has an average duration of 28 days but can differ among individuals, is composed of multiple phases, each characterised by unique hormonal fluctuations.

The menstrual cycle (Days 1-4) commences with menstrual flow, which is the physical manifestation of the uterine lining shedding (Cánovas et al., 2023). Concurrently, the follicular phase (Days 1–13) commences when the anterior pituitary gland secretes Follicle Stimulating Hormone (FSH), which promotes the development of follicles containing an egg in the ovaries. Estradiol (E2), an oestrogen derivative, becomes more abundant as the follicles progress in maturity. Eventually, on day 14, an upsurge in luteinizing hormone (LH) occurs, as displayed in Figure ##, signifying ovulation—the process by which a fully developed egg is discharged from the dominant follicle into the fallopian tube (Serafín et al., 2019). The luteal phase (Days 15–28) commences after ovulation and is characterised by the transformation of the residual follicle of the dominant follicle into a corpus luteum, an ephemeral endocrine structure that facilitates progesterone (P4) production. Progesterone facilitates the uterine lining's readiness for the possible implantation of a fertilised egg, thereby increasing the likelihood of conception (Khanwalker et al., 2019). Conversely, in the absence of fertilisation, the corpus luteum undergoes degeneration, leading to a reduction in progesterone levels and, consequently, the removal of the uterine lining, which signifies the commencement of a fresh menstrual cycle.

Besides that, issues with the delicate balance of hormones in the reproductive endocrine system can lead to a number of reproductive disorders, including amenorrhoea and Polycystic Ovary Syndrome (PCOS), both of which can make it harder to get pregnant (Alawan et al., 2020). Hence, hormonal assays, which can be performed through the utilisation of home testing kits, blood tests, or urine tests, are exceedingly esteemed instruments for determining fertility status and reproductive health. (Khanwalker et al., 2019) These tests commonly

quantify concentrations of FSH, LH, estradiol, or progesterone, thereby offering valuable information regarding the operation of the reproductive endocrine system and, consequently, the fertility cycle of a woman. Because the reproductive endocrine system is so important for fertility and the menstrual cycle, it is very important for people to fully understand how it works. With this information at their disposal, individuals are enabled to make well-informed choices concerning family planning, regardless of whether the objective is to conceive or abstain from pregnancy. Furthermore, this comprehension enables the timely identification and treatment of reproductive disorders, thereby substantially improving the standard of reproductive healthcare (Cánovas et al., 2023).

Present fertility monitoring techniques

The symbiotic relationship among hormones is fundamental to fertility; therefore, those wishing to conceive or prevent pregnancy must possess a comprehensive comprehension of their behaviour. For example, the increase in LH, referred to as the LH surge, serves as a dependable predictor of impending ovulation and, consequently, represents an optimal period for conception (Wegrzynowicz et al., 2022). Numerous fertility monitoring techniques and devices depend on the identification of this surge in order to assist users in pinpointing their most fertile days. Conversely, this understanding also functions as the cornerstone for specific contraceptive approaches. A multitude of techniques are utilised to monitor fecundity, each possessing distinct merits and demerits in terms of practicality, expense, and precision.

Predictor Kits for Ovulation (OPKs):

Widespread use of OPKs to determine the ovulation time of a woman's menstrual cycle. These devices work by detecting the surge in luteinizing hormone (LH) in urine that occurs 24 to 48 hours prior to ovulation (Bauman, 2003). OPKs are popular due to their user-friendliness. Their operation is comparable to that of a home pregnancy test; a woman must urinate on a stick or submerge it in urine to obtain the results, which are typically available within minutes (see figure ##).

The affordability of OPKs, notwithstanding their straightforwardness, renders them a viable option for numerous women seeking to track their fertility. However, although OPKs demonstrate efficacy in identifying the surge of LH, they fail to provide a holistic comprehension of the menstrual cycle of a woman. OPK accuracy may be compromised, especially in individuals with irregular periods or conditions such as polycystic ovary syndrome (PCOS). Additionally, looking at fertility through the lens of just one hormone is not possible; other hormones, such as estradiol (E2), progesterone (P4), and follicle-stimulating hormone (FSH), all play important roles in female fertility (Bauman, 2003).

Monitoring of Basal Body Temperature (BBT):

Numerous women use BBT monitoring as a technique to precisely locate ovulation during their menstrual cycle. This method is predicated on the 0.3°C increase in body temperature

that is noted following ovulation as a result of the progesterone hormone surge (Briden & Prior, 2018). Through daily temperature monitoring and recording, women are able to identify the pattern of temperature increase that signifies the occurrence of ovulation, a critical factor in fertility planning. The BBT technique is non-invasive and economical, requiring only a basal thermometer; as a result, it appeals to a large number of users with numerous devices on the market.

However, a number of lifestyle factors, such as illness, sleep deprivation, alcohol consumption, and others, can impair the accuracy of BBT monitoring and result in inaccurate measurements (Fehring, Schneider, & Raviele, 2006). Additionally, it should be noted that BBT solely provides post-ovulation detection, which may limit its utility for women actively seeking to conceive or prevent conception. Furthermore, the technique necessitates a consistent morning temperature reading at a specific time prior to engaging in any activity, which may prove onerous for certain individuals (Barron & Fehring, 2005).

Cervical mucus monitoring

Mapping cervical secretions is an organic approach to determining the phase of the fertile cycle. The foundation of this approach lies in the observation that variations in oestrogen levels, specifically, cause cervical mucus to endure discernible transformations in both quantity and quality during the menstrual cycle (Bigelow et al., 2004). During the fertile window, cervical mucus exhibits increased abundance, clarity, and stretchiness, approximating raw egg whites, for a duration of several days preceding and including the day of ovulation. This characteristic signifies an environment that is favourable for the survival and transportation of sperm (Attar et al., 2002).

Cervical discharge monitoring is an attractive option for numerous women due to its cost-effectiveness and non-invasive nature. However, certain individuals may find it challenging to accurately interpret mucus changes due to the need for specialised knowledge and experience (Guida et al., 1999). Furthermore, the approach is inherently subjective and susceptible to variation based on variables such as vaginal product usage or the presence of vaginal infections. Furthermore, daily examination and a satisfactory level of body literacy are necessary, aspects that may be inconveniencesome or unsettling for certain individuals. As a result, cervical mucous monitoring is a natural and inexpensive method, but it only works if it is interpreted correctly, which could mean that medical professionals or educators on fertility awareness are needed.

Hormone Monitoring Systems (HMSs)

HMSs are sophisticated instruments that have garnered considerable interest in the domain of fertility monitoring. These gadgets' main job is to measure and keep track of important reproductive hormones like luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), and progesterone (P4) that are found in bodily fluids like blood, urine, and saliva (Khelifa et al., 2022). These hormones have a significant impact on the regulation of ovulation and the menstrual cycle, so women who want to get pregnant or avoid getting

pregnant must closely monitor their levels. In contrast to conventional approaches, HMS provides a more accurate and instantaneous assessment of hormonal fluctuations that occur during the menstrual cycle.

HMS is founded upon a multitude of technologies, including radioimmunoassays (RIA), enzyme-linked immunosorbent assays (ELISA), and, more recently, electrochemical biosensors, which are also called Lab-on-a-Chip (LoC). One such platform that is showing promise is the LoC, which is distinguished by its high sensitivity, low cost, and potential for miniaturisation (Bahadır & Sezgintürk, 2015). Nevertheless, the extensive implementation of HMS is impeded by obstacles including the exorbitant expense of hormone assays, the indispensability of specialised apparatus, and the need for proficient personnel to analyse the data (Wegrzynowicz et al., 2022). In addition, individual variations in hormone levels and other physiological factors might influence the precision of these systems. Notwithstanding these obstacles, HMS represents a noteworthy progression in the direction of individualised fertility monitoring, facilitating a route to improved comprehension and administration of reproductive health.

Wearable Fertility Trackers (WFTs):

Wearable Fertility Trackers (WFTs) have surfaced as a contemporary intervention designed to aid women in the surveillance of their fertility condition. These devices, which are worn internally or externally, predominantly monitor physiological parameters for the purpose of identifying fertile windows and predicting ovulation, including basal body temperature (BBT), heart rate, and occasionally hormonal levels (Duane et al., 2016). By combining sensors and data analytics, they enable users to receive real-time feedback, which is crucial for empowering them to make well-informed decisions concerning family planning, be it to conceive or prevent pregnancy. One of their main advantages is the non-intrusive and practical surveillance they offer. In contrast to techniques like urinary ovulation predictor kits, these devices enable uninterrupted monitoring without requiring daily active user participation (O'Connor et al., 2006). Furthermore, the applications that come with these devices frequently offer an intuitive interface for displaying and comprehending the data.

However, WFTs are not without their drawbacks. Different brands and models may not be as accurate at predicting ovulation, and they may not be as good as more established, invasive methods like transvaginal ultrasound (Uchida & Izumizaki, 2022; Moglia et al., 2019). Moreover, WFTs may incur substantial expenses that are not necessarily protected by insurance. Additionally, the potential for misinformation and the privacy and security of sensitive health data gathered by these monitors are causes for concern if the devices are not utilised or interpreted properly. Notwithstanding these obstacles, WFTs constitute a substantial stride in the direction of utilising technology to promote personal reproductive health management. It is anticipated that as technology progresses, WFTs will become more precise, affordable, and secure, thereby increasing the accessibility of fertility awareness for all.

Ultrasonography scans:

Ultrasound scans play a pivotal role in the surveillance of fertility by offering invaluable information regarding the structure and function of the female reproductive system. By providing visualisation of the ovaries, fallopian tubes, and uterus, these scans facilitate the evaluation of their functionality and overall health (Ecochard et al., 2001). With tools like transvaginal ultrasound (TVUS) (Ecochard et al., 2001), doctors can see how the follicles grow, how the endometrial lining gets thicker, and exactly when ovulation takes place. An essential benefit of ultrasound examinations is their capacity to deliver visual, instantaneous, and accurate data regarding the anatomy and physiology of the reproductive system. In addition to being non-invasive and generally secure, they do not involve ionising radiation exposure. Particularly in assisted reproductive treatments such as in vitro fertilisation (IVF), this characteristic renders them the preferred option for fertility surveillance (Youssef et al., 2014).

Nevertheless, ultrasound examinations do have some disadvantages. The utilisation of these scans necessitates the employment of specialised personnel and the provision of specialised apparatus, rendering them more expensive and less accessible in comparison to alternative methods of fertility monitoring such as basal body temperature tracking or ovulation predictor kits. A time-consuming and potentially inconvenient option for many individuals is the requirement to schedule and attend appointments for examinations.

Although ultrasound scans provide information that is unparalleled in accuracy and specificity, their financial and time-consuming nature can pose substantial obstacles to their routine application in fertility monitoring. Although there are certain obstacles to overcome, ultrasound scans remain an essential component of fertility treatment and surveillance, providing a dependable approach to evaluating and comprehending the fertility condition of an individual.

Calendar-oriented approaches

The foundation of calendar-based fertility monitoring methods is the menstrual cycle's predictability. Through the systematic documentation of menstrual bleeding initiation and cessation dates spanning multiple months, females are able to approximate the moment of ovulation, which generally transpires at or near the midpoint of the periodic cycle. The Rhythm Method and the Standard Days Method (SDM) are calendar-based approaches that enable users to approximate their fertile and infertile days by examining their cycle history (Arevalo et al., 2002; Fehring, 2005).

The simplicity and cost-effectiveness of calendar-based methods are two of their primary advantages. Because they do not necessitate any specialised apparatus, tests, or medical appointments, they are universally accessible. Additionally, they foster self-awareness and comprehension regarding the human body and menstrual cycle.

Nevertheless, the dependability of calendar-based methods on the consistency of a woman's menstrual cycle is substantial. Women who experience irregular menstrual cycles may find these methods unsuitable due to the potential for inaccurate estimation of the reproductive window caused by the variability in cycle length (Fehring, 2005). Furthermore, the absence of immediate biological feedback can lead to lost chances of conceiving or unintended pregnancies, particularly among those whose menstrual cycles are irregular or unpredictable. Further, a proficient comprehension of the menstrual cycle and a methodical approach to daily monitoring are prerequisites for calendar-based methods, both of which may present difficulties for certain individuals.

The woman's personal preferences, financial limitations, and specific fertility goals are the main factors influencing her choice of a fertility monitoring method. For women experiencing irregular menstrual cycles or fertility difficulties, seeking guidance from healthcare professionals or utilising more sophisticated hormone monitoring systems may be the most effective means of attaining precise fertility information. At-home hormone monitoring systems are a prime example of the rapid advancement in fertility technology, which bodes well for future developments in fertility tracking that are more accurate, user-friendly, and comprehensive. This would enable a wider range of women to attain accurate and accessible fertility information.

Present contraception techniques

The use of contraception serves as a preventive measure against health risks associated with pregnancy, particularly for adolescent females. Additionally, when considering the time between births, infants born within a span of 2 years after their older sibling face a 60% higher likelihood of experiencing infant mortality. Similarly, those born within a 2–3-year interval have a 10% increased risk compared to those born after a gap of 3 years or more (Cleland et al., 2012). The intervention has a variety of possible non-health advantages, including increased access to education and empowerment for women, as well as sustainable population growth and economic development for nations.

There has been a significant increase in the number of women expressing a desire to utilise family planning services over the course of the last twenty years. Specifically, the figure has risen from 900 million in the year 2000 to approximately 1.1 billion as of 2021 (United Nations, 2022).

From the year 2000 to 2020, there was a notable increase in the utilisation of modern contraceptive methods among women, with the number rising from 663 million to 851 million. It is expected that an estimated 70 million women will be added to the population by the year 2030. From the year 2000 to 2020, there was an observed increase in the contraceptive prevalence rate, which refers to the proportion of women aged 15–49 who utilise any form of contraceptive technique. Specifically, this rate rose from 47.7% to 49.0% (United Nations, 2022).

According to SDG indicator 3.7.1, 77.5% of women between the ages of 15 and 49 will have their family planning needs met globally in 2022. This represents a 10% rise from the 1990 figure of 67% (United Nations, 2022).

Numerous factors, including but not limited to its effectiveness, potential side effects, ease of use, and personal preferences, affect the choice of a contraceptive method. The domain of medical research has experienced notable advancements, resulting in the emergence of a diverse array of contraceptive modalities. The mechanisms of action of these approaches differ, leading to specific concerns for women's health (Teal & Edelman, 2021).

This section examines the many contraceptive methods available to women, analysing their individual advantages, disadvantages, and overall effectiveness.

Oral Contraceptive Pills (OCPs)

OCPs continue to be widely used due to their reversible characteristics and the several health advantages they offer (United Nations, 2022), including the improvement of conditions such as acne, endometriosis, and premenstrual dysphoric disorder. Nevertheless, it is important to acknowledge the drawbacks associated with venous thrombosis risk and the reliance on user adherence, as these factors significantly impact the efficacy of the intervention. The average efficacy is characterised by a pregnancy rate ranging from 4% to 7% annually (Teal & Edelman, 2021).

Progestin-Only Contraception

Pills and injectables like DMPA that only contain progestin are highly regarded because they are easy to use, quickly restore fertility, and have less of an effect on hemostatic variables. Notwithstanding these benefits, they demonstrate diminished reliability in suppressing ovulation and may result in occurrences of breakthrough bleeding. DMPA, specifically, has the potential to induce a postponement in the restoration of fertility. The average efficacy rate is 4–7 pregnancies per 100 women annually (Festin, 2020).

Long-Acting Reversible Contraceptives (LARCs)

LARCs, such as intrauterine devices (IUDs) and implants, exhibit a remarkable level of efficacy, boasting a failure rate of less than 1% (Teal & Edelman, 2021). Moreover, these contraceptive methods necessitate minimal upkeep and maintenance. Nevertheless, these contraceptive methods require regular clinician visits for both insertion and removal and may result in unpredictable bleeding patterns, particularly in the case of implants. The efficacy of these approaches is similar to that of permanent procedures such as tubal ligation (Teal & Edelman, 2021).

Combined Hormonal Contraception:

Combined hormonal contraception refers to the use of contraceptive methods that involve the combination of oestrogen and progesterone hormones. These methods are effective in regulating menstrual bleeding and ensuring the occurrence of frequent withdrawal bleeds (Festin, 2020). The efficacy of complete adherence to the method is considerable, yet when considering ordinary usage, a pregnancy rate of 4–7% per year is observed (Teal & Edelman, 2021). The degree of adherence has a significant impact on the effectiveness of interventions.

Behavioural Methods:

Behavioural contraceptive strategies, such as withdrawal and fertility awareness, provide a non-pharmaceutical, natural approach to contraception. The failure rates of 22 pregnancies per 100 women show that the effectiveness of these methods heavily depends on the users' level of dedication and education (Teal & Edelman, 2021).

Barrier Methods:

Barrier methods, such as condoms and diaphragms, are nonhormonal contraceptive choices that also provide protection against sexually transmitted infections (STIs). One of the primary limitations associated with non-hormonal contraceptive techniques is their relatively reduced efficacy when compared to hormonal approaches (Festin, 2020). In terms of usual usage, these methods exhibit a pregnancy rate of 13 per 100 women over the course of one year.

Emergency Contraception (EC):

ECs are a critical intervention that can prevent over 95% of pregnancies if administered within five days after unprotected intercourse (United Nations, 2022). It is particularly useful in situations such as unprotected intercourse, contraceptive failure, incorrect use of contraceptives, or sexual assault without contraception. The copper-bearing intrauterine device (IUD) is the most effective EC method (Teal & Edelman, 2021). Additionally, the World Health Organisation recommends several emergency contraceptive pill (ECP) regimens, including ulipristal acetate, levonorgestrel, or a combination of ethinyl estradiol and levonorgestrel, as effective alternatives for timely emergency contraception. Its main disadvantage is the limited timeframe for optimal effectiveness.

Fertility Monitoring Competitors

NAME	SAMPLE GATHERED	TECHNIQUE	INDICATORS (RESULTS)	DEVICE FORMAT	CONSUMABLES	PRICE	WEBSITE
Ava	N/A	Physio parameters	Skin temp, resting HR, HR variability, Perfusion and Breathing rate	Wrist Band	NO	€ 250.00	Ava Fertility
ClearBlue	Urine	Pee test	Hormones	N/A	NO	€ 150.00	Clearblue
Clue	N/A	Symptoms log		N/A	NO		Clue Period & Ovulation Tracker
Daisy	N/A	BBT	Body temperature	Thermometer	NO	€ 269.00	Daysy
Everlywell	Urine	Pee test	Hormones	N/A	NO		Everlywell
Femometer	N/A	BBT	Body temperature	Finger Ring	NO	€ 150.00	Femometer Smart Ring
Femsense	N/A	BBT	Body temperature	Skin Patch	YES	€ 20.00 per cycle	Femsense
Glow	N/A	Symptoms log		N/A	NO		Glow
Inito	Urine	Pee test	Hormones	Test reader	NO	€ 150.00	Inito Fertility Monitor
Kegg	Cervical Mucus	Impedance Sensing	Electrolites	Vaginal Egg	NO	€ 250.00	kegg® Fertility Tracker
KnowWhen	Saliva	Optical	Saliva Christalization	Test reader	YES	€ 50.00	KNOWHEN
Mira	Urine	Pee test	Hormones	Test reader	YES	€ 229.00	Mira
Nature-Cycles	N/A	BBT	Body temperature	Thermometer	NO		Natural Cycles
Ovularing	N/A	Symptothermal method	Body temperature	Vaginal Ring	NO	€ 384.00 (6-months)	OvulaRing
Ovusense	N/A	BBT	Body temperature	Vaginal Egg	YES	€ 400.00 (or subscription)	OvuSense
Primatemp	N/A	Physio parameters	Continuous core body temperature	Vaginal Ring	NO		Prima-Temp
RO	Urine	Pee test	Hormones	N/A	YES	€ 180.00	Modern Fertility
Tempdrop	N/A	BBT	Body temperature	Arm Bracelet	YES		Tempdrop

Appendix E

Overview of LIAS Project

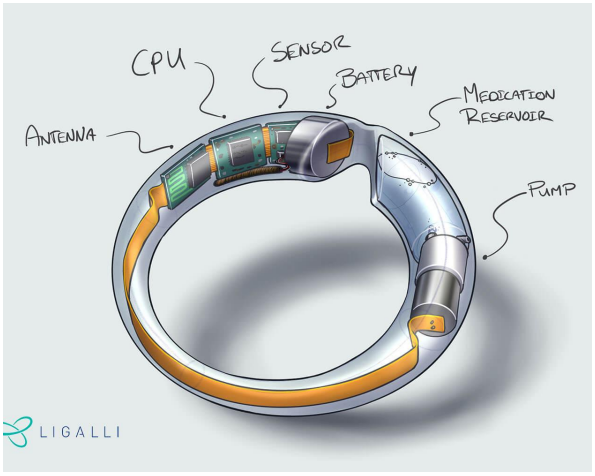
Integration of Microfluidics Management and LH Detection

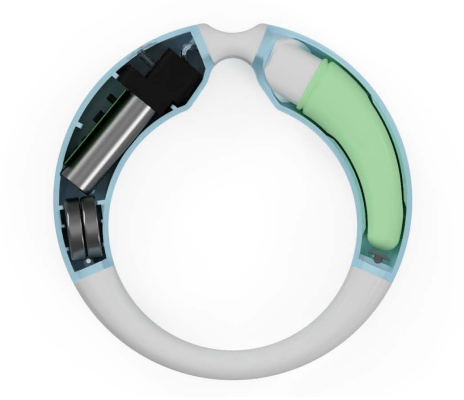
Introduction

The LIAS project by LiGalli aims to integrate the MedRing device's platform with aptasensing technology to effectively monitor and quantify several biomarkers found in vaginal secretions. The initial method involves the identification and quantification of luteinizing hormone (LH) to monitor and forecast fertility. This appendix provides a comprehensive summary of the project's novel methodology, system structure, and the interaction between its essential elements.

System Architecture

Overview





Left: first layout for the components inside the Medring. Right: current layout of components

The Medring platform comprises a ring with dual chambers designed to accommodate its components. The image above depicts an initial draft of its design and the current state of things. The present design incorporates the electronics, battery, and pump on one side, while the tank is positioned on the right side to safeguard the electronics from any liquid exposure. The LIAS MedRing underwent a modification where the tank was substituted with two smaller tanks and a microfluidic system. The components on the left side of the ring remained the same.

Integration of sensors

The system must possess the subsequent components for sensor integration:

- Association Buffer
- Dissociation Buffer
- Mixing chamber
- Lab-on-a-Chip (LoC)

Association Buffer refers to a solution that helps maintain the stability of a chemical reaction by preventing the formation of unwanted byproducts or the loss of desired components. Dissociation, on the other hand, refers to the separation of a compound into Buffer refers to a solution used to maintain the pH and ionic strength of a system throughout an experiment or analysis. A mixing chamber is a space or device where different substances are combined or blended together. Lab-on-a-Chip (LoC) is a miniaturised device that integrates many laboratory functions onto a single

These components are essential for the collection and analysis of the desired biomarkers.

Association Buffer:

The association buffer is the essential fluid required for reading. Its purpose is to act as a conduit for the biomarker molecules to reach the LoC and facilitate the reading process. This fluid possesses the unique characteristic of exerting an attractive force on the desired analytes (molecules) and assimilating them. Subsequently, when the fluid circulates throughout the system, these molecules will ultimately reach the LoC (Lab-on-a-Chip).

Dissociation Buffer:

This solution is essential for purging or flushing the system between samples. During the analysis of analytes, certain substances may fail to separate from the aptamers, resulting in the accumulation of contaminants on the sensor's output. To ensure the system is free from contamination and prepared to receive the fresh sample of association buffer fluid, we circulate this fluid between samples.

Mixing chamber:

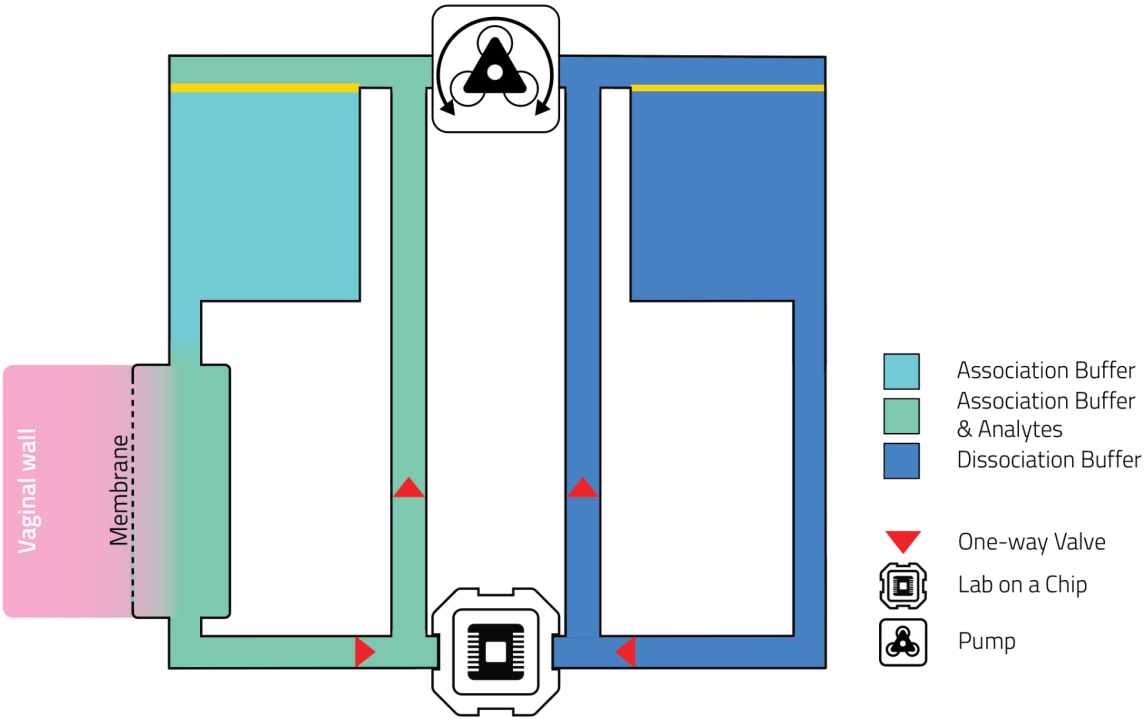
The mixing chamber is the component of the microfluidic system where the association buffer receives the analytes from the vaginal mucosa. It is important to note that no fluids from the vagina enter the microfluidic device; the entire process occurs at a molecular level. The mixing chamber contains a PES membrane that allows only molecules to pass through at a molecular level. When the association buffer reaches this stage, it remains there for a minimum of 6 hours to establish a concentration equilibrium with the vaginal mucosa on the other side of the membrane.

Lab-on-a-Chip (LoC)

The LoC is responsible for analysing the sample and transmitting the signals containing the measured results to the user. To clarify, this is the sensor. This chip is equipped with aptamers.

Microfluidic System Design

The aforementioned components must be placed in a precise manner to get an accurate measurement of the desired analytes. Furthermore, there are certain limitations in place that prohibit them from being mixed together, at least until they reach the LoC. To fulfil this need, valves were incorporated into the system to prevent the mixing of association and dissociation buffers. Displayed below are the arrangements and interactions of these components for the purpose of monitoring women's hormone levels.



It is important to note that the placement of the mixing chamber should be chosen to promote contact between the vaginal mucosa and the membrane. This contact is necessary for the proper transfer of analytes to the association buffer. To accomplish this, the membrane was positioned on the outside circumference of the ring, precisely along its edges to optimise the contact area with the vaginal walls.

Appendix F

Meeting Summary

Meeting Title: Discussion on the pumping concepts and feasibility

Date & Time: 9:30, 14/11/2023

Location: Demcon Delft

Attendees: Sebastián Spoere, Thijs Van Oorschot, John Landers & Jonathan Meijer

---

1. Meeting Objectives:

- To discuss the feasibility of the microfluidic concepts

- To understand the power consumption and mechanisms of the actual ring

2. Key Discussion Points:

- Specifications of inside components: tube diameter, pump power consumption.

    - The tube has an ID of 0.5mm and an OD of 1.3mm, it is also a lot softer than the sample tubes I brought.
    - The pump currently takes ~1.3 mJ/rev and turns at 0.5hz, so the power is approximately 0.65mW. It's good to note here that this is not a constant load, there are current spikes along the profile that are inherent to a peristaltic pump design, and these current spikes drain the battery faster than a constant 0.65mW load would.
    - The motor specifications can be found in the datasheet (attached to email 14/11 John Landers) we have from our supplier, but it isn't very accurate to how the motors perform in practice. The supplier is very cautious and will only put down very loose specifications that they know they can always meet. These supplier specifications are highlighted in yellow (in the datasheet). For our use case we require tighter specifications (see the column to the right 'Demcon required specifications'), and so far, the delivered motors either meet our tighter specifications or can be easily filtered so that motors that don't meet them are rejected before production.

- Design requirements for making changes in the pump

    - The more friction in the system the more power consumption
    - Consider tolerance/movement become more important when you scale down the model. Acknowledge this situation.

- How to address free flow protection (flowing without actuation of the pump)

3. Decisions Made:

- Scaling down the system will be dealt with by Demcon.
- Explore the integration of springs either at the wheels or at the pump's axis.
- Consider a model with just one wheel and a valve.

4. Action Items:

- Sebastián to prototype the concepts and bring them for the next meeting.
- Demcon: provide me with a CAD with the volume used by the inner components of the ring.

5. Questions Raised and Addressed:

- How to work with the tolerance of the components, springs for compliance
- How to incorporate Free Flow Protection
- Duckbill valves require quite some pressure to close, do we have that amount of pressure in the system?
- Do we need discreet or continuous pumping?

6. Pending Items:

- Further exploration of pumping systems and requirements.
- Determine if the duckbill valve is viable.

7. Next Meeting Plan:

- Bring the prototypes, show them working and analyze possible problems.

8. Additional Notes:

-

Appendix G

Meeting Summary

Meeting Title: Assessment of concept details and assembly

Date & Time: 13:00, 15/01/2024 & 13:00, 17/01/2024

Location: Via Teams (Online)

Attendees: Sebastián Spoerer, John Landers & Jonathan Meijer

---

1. Meeting Objectives:

- Technical assessment for solutions on problems encountered with concept.

2. Key Discussion Points:

- How to mount the membrane against the mixing chamber in a safe and secure way:
  - Solution A: wrap the membrane around the chamber edge and install O ring between case and mixing chamber.
  - Solution B: glue membrane to chamber and use foam between mixing chamber and ring case.
  - Solution C: design a “link piece” to hold the membrane and generate a watertight connection between two parts.
- How to connect the PMMA channels to the short link and the pump:
  - Solution A: use tubes, glue them between mTAS and Link.
  - Solution B: glue the mTAS directly to the plastic wall of the case.
  - Solution C: install tubes in mTAS and link, use a hollow link for connection.
  - Solution D: pass a glued tube from the mTAS directly to the pump and back.

3. Decisions Made:

- Membrane mount:
  - For the stage of this project, the membrane will be glued, just to test function, not mass manufacturability.
  - Attach the white lip directly to the hole instead of trying to use the membrane as a middle piece between them, then you can laser weld the lip onto the outer enclosure.
  - Not try to design for welding at this stage.
- mTAS to Pump connection:
  - We came up with new solution, develop a flexible piece that will be glued to the mTAS and inserted into the short link of the ring, keeping the same interface as used on the actual MedRing.

4. Action Items:

- Sebastián will adjust the lip of the membrane, so it matches the depth of the hole.
- Sebastian will develop the piece for the pump and send it to John so he can make a review of it.

5. Questions Raised and Addressed:

- How can we fix and seal the membrane with the mixing chamber and the outer part of the ring’s case?

- How can we make the connections watertight without using glue, is there another way that you've had experience with?
- Are there any strategies to avoid accumulation of residues on the edges of the connections? (Think of dry vaginal mucosa on the sides of the hole)

6. Pending Items:

- Review of solutions.

7. Next Meeting Plan:

- No meeting was scheduled

8. Additional Notes:

-

Appendix H

Risk Analysis

Document Identification and Filing			
Product	LIAS Medring	**Date**	
Project	LIAS	**Classification**	Medical Device Cat. III

Author(s)			
Function	**Name / Organization**	**Date** (YYYY-MM-DD)	**Signature**
Intern	Sebastian / TU Delft-LiGalli	2024/01/15	

Description			

The LIAS Medring is a device used to monitor womens fertility. It consists of an intra-vaginal ring equiped with lab-on-a-chip technology, allowing for periodical analisys of vaginal mucoses of its user. The device is intended to be used at least through a whole menstrual cycle

2. Use and Assumptions

Use

The ring is classified as a Class III medical device intended for continuous use inside the vaginal canal. Its user consists of healthy fertile women who want to concieve a child or avoid pregnancy without the use of hormones. Its operating principle consists of lateral flow two-site noncompetitive immunoassay test with the use of aptasensors.

Reasonably foreseeable misuse

This device is not intended to be used in other human orifices
This device is not intended to be used for sampling other fluids than vaginal mucosa
This device should be only rinsed with water and a soft cleaning agent, do not use a brush or anything that can damage its surface.
This device should not be opened in any circumstances.
This device is not intended to be used as a pregnancy test.

	Assumptions/Scope
1	The MedRing is not used during MRI (magnetic resonance imaging) diagnostics
2	Risks related to production, assembly and the app are out of scope for this project. Only risks related to the microfluidic system and its components are considered.
3	The MedRing is not used during activities involving extreme environmental conditions (diving, acrobatic planes, car racing)

3. Hazards and Harms

Hazard Potential source of Harm	
Hxx	Hazard
H01	Mechanical hazards
H02	Electrical hazards
H03	Energy hazards
H04	Biological hazards
H05	Bolus/occlusion
H06	Filling Hazards
H07	Leakage
H08	Packaging/transport/disposal/cleaning
H09	Lifetime/shelf life
H10	Dropping hazards
H11	Insert ring
H12	Pull ring out
H14	Turn on ring
H15	Hygiene

Hazardous situation Circumstance in which people are exposed to one or more hazard(s)	
Sxx	Hazardous situation
S01	Dosing error changes over time
S02	MedRing non-functional
S03	Ring can't be inserted
S04	MedRing does not pump enough fluid
S05	Battery or electronics
S06	User tries a new ring
S07	MedRing contaminated
S08	Body in contact with non-biocomp component
S09	DC motor overheats
S10	Sharp edges
S11	Loss of free flow protection
S12	Battery or electronics exploding / leaking
S13	Foreign particles enter patients body
S14	Skin in contact with fluid
S15	Body in contact with allergen/irritant
S16	User feels or hears vibrations
S17	Pressure against cavity wall
S18	Sample contamination
S19	Disturbance of other devices
S20	Too high EM-output
S21	Device (fluids, battery) in environment
S22	MedRing external leakage
S23	Toxic liquid released in patient
S24	MedRing heats up
S25	Fluid dumping
S26	No connection with MedRing
S27	Ring cannot be removed
S28	User has to reinsert ring
S29	Monitoring in wrong location
S30	MedRing not used
S31	Not able to switch on device
S32	User has to try multiple times
S33	Pressure against vaginal wall
S34	Loose component in vaginal

Harm Physical injury or damage to the health of people		
Rxx	Harm	Severity
R01	Bruises	
R02	Adverse body reaction	
R03	No fertility data	
R04	User annoyance	
R05	Cuts	
R06	Infection	
R07	Failed fertility monitoring	
R08	Burns	
R09	Emotional distress	
R10	Environmental harm	
R11	No harm	
R12	Electromagnetic radiation effects	
R13	Unwanted pregnancy	

Mitigations

Risk mitigating actions

Mxx	Mitigation
M01	Ring design and testing according to 60601-1
M02	Ring testing according to 60601-2 (EMC)
M03	Ring design and testing according to 60601-2-24 (infusion pump)
M04	Ring design and testing according to 10993 (biocomp)
M05	Ring design and testing according to 60601-1-11 (med-wearable)
M06	Implement stronger adhesives or alternative bonding methods like ultrasonic welding to enhance mechanical integrity.
M07	Conduct extensive durability testing under various environmental conditions to ensure reliability.
M08	Shielding critical components within the MedRing to protect against external electromagnetic interference.
M09	Incorporate design features or materials that reduce susceptibility to external radiations.
M10	Establish strict sterilization and cleanliness protocols during the manufacturing process.
M11	Integrate thermal management solutions to dissipate heat effectively and prevent overheating
M12	Use robust, tamper-evident packaging to protect against contamination.
M13	Provide clear user instructions for cleaning with recommended agents only and proper disposal guidelines to minimize environmental impact.
M14	Design the MedRing with shock-absorbing materials or structures to withstand accidental drops.
M15	Include user guidelines on what to do if the device is dropped to prevent contamination or damage.
M16	Provide comprehensive instructions with illustrations or animations demonstrating the proper method to insert and remove the ring. This could be included in the product packaging or as an online tutorial.
M17	Enhance the ring's grip or texture to aid in retrieval. Incorporate a more robust design to prevent breakage if the ring is pulled out incorrectly.
M18	Establish clear guidelines on what to do if the ring breaks or cannot be found, including when to seek medical advice.
M19	Design the ring with a feedback mechanism that reassures the user of correct placement and removal.
M20	Offer a helpline or support system for users to consult if they encounter difficulties or have concerns about the correct use of the ring.
M21	Design the ring with a feedback mechanism that reassures the user of ON/OFF status of the ring

IEC 60601-1-11 Medical electrical equipment - Part 1-11: General requirements for basic safety and essential performance - Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment

IEC 60601-2-49 Medical electrical equipment - Part 2-49: Particular requirements for the basic safety and essential performance of multifunction patient monitoring equipment

5a. Risk Criteria

Probability, severity and risk acceptance criteria
The used probability and severity scales and the resulting risk classification criteria are described in the chapter “Risk Criteria”. At the start of a development project it is evaluated if these risk criteria are considered sufficient for the project under review. This is determined with the risk management team during the feasibility phase. Per identified risk it is indicated in the risk analysis matrix whether the resulting risk is acceptable or not (chapter "Risk Analysis" in the RMF). For medium, the motivation for accepting the risk is documented in the tab "Conclusions". *Overall residual risk acceptability* *- The residual risk is not acceptable when any items have a "high risk" rating* *Acceptability when the probability of the occurence of harm cannot be estimated* *- Find supporting evidence* *- Assume high probability* *- If the total percentage of medium risks is over xx % of the total, the overall risk is not acceptable.*

Risk Classification criteria (ISO 14971:2012 3.4d)		Remarks on acceptability
L	Low Risks	Acceptable: Risk so low that risk reduction is not mandatory, however when possible risk is reduced.
M	Medium Risks	ALRA*: If, after applying all practicable measures to reduce the risk, the residual risk is still unacceptable, a risk/benefit analysis is needed to establish whether the medical benefits of the intended use outweigh the residual risk. This will be evaluated during the risk-benefit analysis in the RMF.
H	High Risks	Unacceptable: the risk involved does not outweigh the medical benefit

* As Low as Reasonably Achievable

In the table below, several severity scales are shown: severity for patient/operator safety risks, DFMEA severity, and severity for privacy risks. For privacy risks, three columns are given which show examples for privacy risk for 3 categories. It must be noticed that physical privacy risks could be caused by material risks or moral risks.

Severity designation		Severity description patient/operator safety risks	Severity description DFMEA	Severity Description privacy risks
Negligible	**1**	Inconvenience or temporary discomfort	No effect on system's functions	no impact on data subjects rights and freedoms
Minor	**2**	Results in temporary injury or impairment not requiring professional medical intervention	Potentially degrade the system's functions but will cause no damage to the system and does not constitute a threat to life or injury (maintenance might be needed).	Data subjects either will not be affected or may encounter a few inconveniences, which they will overcome without any problem.
Serious	**3**	Results in injury or impairment requiring professional medical intervention	Potentially degrade system performance function(s) without appreciable damage to system or threat to life or injury.	Data subjects may encounter significant inconveniences, which they will be able to overcome despite a few difficulties
Critical	**4**	Results in permanent impairment or life-threatening injury	Potentially result in the failure of the system's primary functions and therefore causes considerable damage to the system and its environment, but which does not constitute a serious threat to life or injury.	Data subjects may encounter significant consequences, which they should be able to overcome albeit with real and serious difficulties
Catastrophical	**5**	Results in death	Potentially result in the failure of the system's primary functions and therefore causes serious damage to the system (e.g. physical loss, fire) and its environment and/or personal injury.	Data subjects may encounter irreversible consequences, which they may not overcome

The probability is defined as: the annual probability that the sequence of events leads to the harm for a single product during the lifetime of the device.

Please note that this is a combination of 1) the probability that the sequence of events leads to the defined hazardous situation

2) the probability that the hazardous situation leads to the defined harm

The following numbers can be used to assess the probability

Total number/time of usage during lifetime:

Probability designation		Occurance	Description
Improbable	**1**	$< 10^{-6}$	Extremely unlikely to occur
Remote	**2**	$< 10^{-5}$ and $\geq 10^{-6}$	Unlikely, to occur
Occasional	**3**	$< 10^{-4}$ and $\geq 10^{-5}$	Likely to occur
Probable	**4**	$< 10^{-3}$ and $\geq 10^{-4}$	Very likely to occur
Frequent	**5**	$\geq 10^{-3}$	Extremely likely to occur

		Probability				
		Improbable	Remote	Occasional	Probable	Frequent
Severity		**1**	**2**	**3**	**4**	**5**
Negligible	**1**	L	L	L	L	M
Minor	**2**	L	L	M	M	M
Serious	**3**	L	M	M	H	H
Critical	**4**	M	M	H	H	H
Catastrophical	**5**	M	H	H	H	H

5. Risk Analysis

No	Sequence of events	Hazardous situation	Harm	Severity	Probability	RPN	Mitigation 1	Mitigation 2	Mitigation 3	Mitigation 4	Mitigation 5	Mitigation 6	Mitigation 7	Mitigation 8	Risk mitigation action	Probability	RPN	New risk introduced?	Effect on previous defined risks?	Remarks
1.00	***H01) Mechanical hazards***																			
1.01	Pump or motor causes vibrations / sound, User feels or hears vibrations	S16) User feels or hears vibrations	R04) User annoyance	1	1	L	M01													
1.02	Mechanical failure of compressing MedRing	S03) Ring can't be inserted	R07) Failed fertility monitoring	1	2	L	M01													
1.03	Mechanical failure of compressing MedRing	S10) Sharp edges	R05) Cuts	2	2	L	M01													
1.04	Glue Failure, parts coming off / mechanical integrity compromised, mucus ingress	S07) MedRing contaminated	R06) Infection	3	2	M	M01	M06	M07	M18										
1.05	Glue Failure, parts coming off / Mechanical integrity compromised	S08) Body in contact with non biocomp component	R02) Adverse body reaction	2	2	L	M01													
1.06	Glue Failure, parts coming off / mechanical integrity compromised	S34) Loose component in vaginal cavity	R02) Adverse body reaction	2	2	L														
1.07	Glue Failure, parts coming off / mechanical integrity compromised	S10) Sharp edges	R05) Cuts	2	4	M	M01	M06	M07	M18										
1.08	Sharp edges on parts due to design	S10) Sharp edges	R05) Cuts	2	2	L														
1.09	Mechanical failure of pump	S11) Loss of free flow protection	R07) Failed fertility monitoring	1	3	L														
1.10	Mechanical failure of pump, for example locking of moving parts	S02) MedRing non-functional	R07) Failed fertility monitoring	1	3	L														
1.11	Pump failure, resulting in reverse flow.	S02) MedRing non-functional	R07) Failed fertility monitoring	1	3	L														
2.00	***H02) Electrical hazards***																			
2.01	Internal liquid into enclosure due to moisture/tube evaporation, Short circuit and corrosion	S05) Battery or electronics overheating	R08) Burns	3	1	L	M01													
2.02	Internal liquid into enclosure due to moisture/tube evaporation, Short circuit and corrosion	S12) Battery or electronics exploding / leaking	R02) Adverse body reaction	2	1	L	M01													
2.03	Internal liquid into enclosure due to moisture/tube evaporation Short circuit and corrosion	S02) MedRing non-functional	R07) Failed fertility monitoring	1	4	L	M01													
2.04	External liquid into enclosure, short-circuit and corrosion	S05) Battery or electronics overheating	R08) Burns	3	1	L														
2.05	External liquid into enclosure, short-circuit and corrosion	S02) MedRing non-functional	R07) Failed fertility monitoring	1	1	L														
2.06	External liquid into enclosure, short-circuit and corrosion	S12) Battery or electronics exploding / leaking	R02) Adverse body reaction	2	1	L														
2.07	Pump gets blocked	S09) DC motor overheats	R08) Burns	3	1	L														
2.08	DC Motor stops working, patient unaware of failure	S02) MedRing non-functional	R07) Failed fertility monitoring	1	4	L														
2.09	LED light breaks, the user does not know if the device is turned on	S31) Not able to switch on device	R07) Failed fertility monitoring	1	2	L														
2.10	Hardware error, pump keeps pumping.	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	1	L														
3.00	***H03) Energy Hazards***																			
3.01	Device above EMC emission limits	S19) Disturbance of other devices	R04) User annoyance	1	1	L	M02													
3.02	Wrong hardware/software settings	S20) Too high EM-output	R12) Electromagnetic radiation effects	1	1	L														
3.03	Wrong hardware/software settings. Communication disturbed or unsuccesfull	S26) No connection with MedRing	R03) No fertility data	1	2	L	M02													
3.04	Device not immune to external radiating devices	S02) MedRing non-functional	R07) Failed fertility monitoring	1	3	L	M02													
3.05	Device not immune to external radiating devices	S24) MedRing heats up	R08) Burns	3	3	M	M02	M08	M09	M11	M18									
4.00	***H04) Biological Hazards***																			
4.01	Pieces of MedRing come loose/breaks off	S13) Foreign particles enter patients body	R02) Adverse body reaction	2	2	L	M04													
4.02	Pieces of MedRing come loose/breaks off	S13) Foreign particles enter patients body	R05) Cuts	2	2	L														
4.03	Patient is allergic to materials	S15) Body in contact with allergen/irritant	R02) Adverse body reaction	2	2	L	M04													
4.04	Bacteria or dirt on MedRing during production	S07) MedRing contaminated	R06) Infection	3	3	M	M10													

4.05	Fluids affect integrity device	S08) Body in contact with non-biocomp component	R02) Adverse body reaction	2	2	L	M04													
4.06	Fluid affect integrity device (container)	S22) MedRing external leakage	R11) No Harm	1	2	L														
4.07	Device affects integrity of fluids	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	2	L														
4.08	Aptamers get loose from the LoC	S02) MedRing non-functional	R03) No fertility data	1	2	L														
5.00	***H05) Occlusion***																			
5.01	Fluidic path blocked, high pressure is built up in system, causing leakage of liquid inside MedRing.	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	2	L	M03													
5.02	Fluidic path blocked	S02) MedRing non-functional	R07) Failed fertility monitoring	1	2	L	M03													
6.00	***H06) Filling Hazards***																			
6.01	Container leaking after puncturing	S22) MedRing external leakage	R11) No Harm	1	2	L														
6.02	Filling not performed correctly	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	3	L														
6.03	Container damaged during filling, membrane punctured	S22) MedRing external leakage	R07) Failed fertility monitoring	1	2	L														
6.04	Container damaged during filling, internal medication leakage	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	2	L														
6.05	Too high pressure needed to fill the MedRing	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	2	L														
6.06	Filling not performed correctly, air present in container, air is pumped	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	3	L														
7.00	***H07) Leakage***																			
7.01	High pressure changes (external)	S22) MedRing external leakage	R11) No Harm	1	1	L	M01													
7.02	Failure of mechanical integrity in fluidic path	S22) MedRing external leakage	R07) Failed fertility monitoring	1	1	L	M01													
7.03	Failure of mechanical integrity in fluidic path, internal leakage.	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	1	L	M01													
7.04	Container leakage	S22) MedRing external leakage	R11) No Harm	1	2	L														
7.05	Container leakage, internal leakage.	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	3	L														
7.06	Container material leaks/diffuses body fluid or water into the container, buffers are diluted	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	1	L														
7.07	Leakage in electronics compartment, electronics in contact with liquid, potential toxic material dissolves in liquid	S23) Toxic liquid released in patient	R02) Adverse body reaction	2	1	L														
7.08	Fluids leakage, present on the outside of the ring	S14) Skin in contact with fluid	R11) No Harm	1	2	L														
8.00	***H08) Packaging/transport/disposal/cleaning***																			
8.01	Dirt and/or bacteria accumulate on MedRing because of inadequate packaging	S07) MedRing contaminated	R06) Infection	3	1	L														
8.02	Transport affects device	S02) MedRing non-functional	R07) Failed fertility monitoring	1	2	L														
8.03	Transport affects device	S22) MedRing external leakage	R11) No Harm	1	2	L														
8.04	Rings getting over/under heated in storage - not detectable. Battery damaged / lifetime not met	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	2	L														
8.05	User cleans MedRing before use with unknown/harmful cleaning agent, MedRing degraded by cleaning agent.	S08) Body in contact with non-biocomp component	R02) Adverse body reaction	2	4	M	M04	M13	M20											
8.06	MedRing in changing humidity (ambient) conditions unknown rate of solvent loss. During shelf life. Not enough volume to dose for 28 days	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	2	L														
8.07	Disposal in normal waste bin	S21) Device (fluids, battery) in environment	R10) Environmental harm	3	3	M	M13													
9.00	***H09) Lifetime/Shelf Life***																			
9.01	Bad battery batch mounted. Battery damaged / lifetime not met	S04) MedRing does not pump enough medication	R07) Failed fertility monitoring	1	2	L														
9.02	Energy consumption is more than expected. (Bad batch of components). Battery damaged / lifetime not met	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	2	L														
9.03	Fatigue of mechanical components resulting in broken parts	S22) MedRing external leakage	R07) Failed fertility monitoring	1	2	L														
9.04	Fatigue of mechanical components resulting in broken parts	S02) MedRing non-functional	R07) Failed fertility monitoring	1	2	L														
9.05	Shelf life material properties (unnoticed degradation)	S22) MedRing external leakage	R11) No Harm	1	2	L														
9.06	Higher than expected material degradation	S22) MedRing external leakage	R11) No Harm	1	2	L														

9.07	Higher than expected material degradation	S02) MedRing non-functional	R07) Failed fertility monitoring	1	2	L														
9.08	Too much fluid evaporates/leaks from container during shelf life, not enough volume for 28 days	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	3	L														
9.09	Too much fluid evaporates/leaks from container during shelf life, fluid concentration increases	S01) Dosing error changes over time	R07) Failed fertility monitoring	1	3	L														
9.10	Fluidic path degradation (e.g. Parylene coating or compression of rotor) which results in smaller diameters of tube due to sticking 'edges' of tube.	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	4	L														
9.11	Too much fluid leaks from pump outlet in shelf life, not enough volume for 28 days	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	4	L														
10.00	***H10) Dropping Hazards***																			
10.01	Internal mechanical failure due to user dropping ring	S11) Loss of free flow protection	R07) Failed fertility monitoring	1	2	L	M01													
10.02	Mechanical failure due to user dropping ring	S10) Sharp edges	R05) Cuts	2	2	L	M01													
10.03	Internal mechanical failure due to user dropping ring	S02) MedRing non-functional	R07) Failed fertility monitoring	1	2	L	M01													
10.04	Dropped package - torn package	S07) MedRing contaminated	R06) Infection	3	3	M	M12													
10.05	User drops ring and did not clean it	S07) MedRing contaminated	R06) Infection	3	3	M	M13	M20												
10.06	User drops ring, ring breaks, no longer watertight	S02) MedRing non-functional	R07) Failed fertility monitoring	1	2	L	M14													
10.07	User drops ring, falls on the ground	S07) MedRing contaminated	R06) Infection	3	3	M	M13													
10.08	User drops magnet, magnet contaminated and touches the ring	S07) MedRing contaminated	R06) Infection	3	3	M	M13													
10.09	MedRing used during extreme sports, ring breaks after impact, internal leakage	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	1	L														
10.10	MedRing used during extreme sports, ring breaks after impact	S22) MedRing external leakage	R07) Failed fertility monitoring	1	1	L														
	Usability																			
11.10	***H11) Insert Ring***																			
11.11	Hand too weak to press ring together, thinks ring is not right	S06) User tries a new ring	R07) Failed fertility monitoring	1	2	L														
11.12	Hand too weak to press Medring together. User tries to force in unfolded ring	S33) Pressure against vaginal wall	R01) Bruises	2	1	L														
11.03	Hand too weak to press ring together, user cannot insert ring	S30) MedRing not used	R07) Failed fertility monitoring	1	2	L														
11.04	Hand too weak to press ring together, user cannot insert ring	S32) User has to try multiple times	R04) User annoyance	1	2	L														
11.05	User presses ring with too much force, mechanical failure of the ring enclosure	S10) Sharp edges	R05) Cuts	2	2	L														
11.06	User does not understand the folding step. User tries to force in unfolded ring	S33) Pressure against vaginal wall	R01) Bruises	2	2	L														
11.07	User is wearing a tampon and brings in the ring. Tampon presses against vaginal wall	S33) Pressure against vaginal wall	R01) Bruises	2	2	L														
11.08	User is wearing the ring and inserts a tampon. Cannot get out tampon without taking along the MedRing. Medring removed the wrong way (unfolded)	S33) Pressure against vaginal wall	R01) Bruises	2	2	L														
11.09	User is wearing the Medring and inserts a tampon. Cannot get out tampon without taking along the MedRing. Medring has to be inserted again.	S28) User has to reinsert ring	R04) User annoyance	1	2	L														
11.10	User too large belly to insert Medring	S33) Pressure against vaginal wall	R01) Bruises	2	1	L														
11.11	Patient is too tensed to insert MedRing	S30) MedRing not used	R07) Failed fertility monitoring	1	1	L														
11.12	MedRing not inserted deep enough in body, user loses ring	S29) User has to reinsert ring	R04) User annoyance	1	3	L														
11.13	MedRing not inserted deep enough in body, user loses ring in the toilet doesn't realize	S30) MedRing not used	R07) Failed fertility monitoring	1	2	L														
11.14	MedRing inserted in wrong cavity	S02) MedRing non-functional	R07) Failed fertility monitoring	1	1	L														
11.15	MedRing inserted in wrong cavity, which is more difficult to reach	S17) Pressure against cavity wall	R01) Bruises	2	2	L														
11.16	Inserting MedRing in the wrong direction, reduced antenna connection	S26) No connection with MedRing	R03) No fertility data	1	4	L														
11.17	User brings in wrong ring (from another	S26) No connection with	R03) No fertility data	1	2	L														

12.01	MedRing doesn't feel comfortable and user takes it out and places it again	S29) User has to reinsert ring	R04) User annoyance	1	4	L															
12.03	User does not pause ring when removing it, ring keeps on dispensing, not enough medication left for 28 days	S04) MedRing does not pump enough medication	R07) Failed fertility monitoring	1	3	L															
12.04	User wants to take out ring, but can not find it or grab it or is too nervous. When ring cannot be removed, a new ring cannot be placed in time	S27) Ring cannot be removed	R09) Emotional distress	2	3	M	M16	M17	M18	M19	M20										
12.05	User tries to remove ring but pulls it out the wrong way; ring breaks, user inserts ring again	S22) MedRing external leakage	R11) No Harm	1	2	L															
12.06	User tries to remove ring but pulls it out the wrong way; ring breaks and starts leaking inside the ring	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	2	L															
12.07	User tries to remove ring but pulls it out the wrong way (unfolded)	S33) Pressure against vaginal wall	R01) Bruises	2	3	M	M16	M19	M20												
13.00	***H13) Turn Ring On***																				
13.01	Does not know where to shine the light or how long to shine, or how close to hold light source to MedRing	S31) Not able to switch on device	R09) Emotional distress	2	5	M	M21	M20													
13.02	User does not have a phone with a (working) light or uses other (weak) light source	S31) Not able to switch on device	R07) Failed fertility monitoring	1	2	L															
13.03	User doesn't know how to activate phone light	S31) Not able to switch on device	R07) Failed fertility monitoring	1	2	L															
13.04	External light source on MedRing, LED light not visible to user, user not aware whether MedRing is switch ON	S31) Not able to switch on device	R07) Failed fertility monitoring	1	2	L															
13.05	User is distracted and waits too long before checking, LED no longer blinking	S31) Not able to switch on device	R07) Failed fertility monitoring	1	3	L															
13.06	User holds magnet in the wrong location	S31) Not able to switch on device	R07) Failed fertility monitoring	1	5	M	M20	M21													
13.07	User tries to switch on the previous ring (empty or almost empty) that should have been disposed of	S04) MedRing does not pump enough fluid	R07) Failed fertility monitoring	1	2	L															
14.00	***H14) Hygiene***																				
14.01	User inserts MedRing without clean hands, bacteria on device	S07) MedRing contaminated	R06) Infection	3	2	M	M13	M15	M20												
14.02	User does not clean MedRing before insertion	S07) MedRing contaminated	R06) Infection	3	2	M	M13	M15	M20												
14.03	User stores Medring at a dirty place	S07) MedRing contaminated	R06) Infection	3	2	M	M13	M15													
14.04	User is using detergent that affects the ring materials	S08) Body in contact with non-biocomp component	R02) Adverse body reaction	2	2	L															
14.05	User uses detergent that affects the glue connections	S22) MedRing external leakage	R11) No Harm	1	1	L															
14.07	User brings in wrong ring (from another user)	S07) MedRing contaminated	R06) Infection	3	1	L															
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