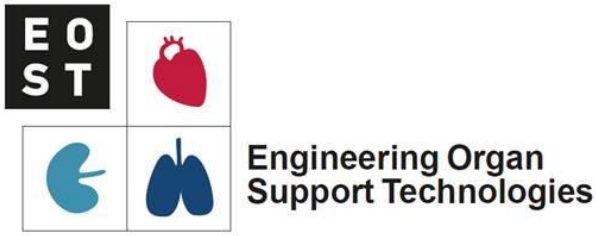
UNIVERSITY OF TWENTE.



Chair of Engineering Organ Support Technology

Univ.-Prof. Dr.-Ing. Jutta Arens

Method for manufacturing a hemofiltration fibre mat for use in a combined lung-kidney assist device

Submitted as	Master Assignment (BE-852)
Name, student no.:	WYTZE DUINMEIJER, 2422867
Date:	04.04.2022
Supervisor	Prof. Dr.-Ing. Jutta Arens
Daily Supervisor	Ana Martins Costa, M.Sc
External committee member	Ir. Edsko Hekman
Internal committee member	Dr. Frank R. Halfwerk

Acknowledgement

Here it is, the end of my master study Industrial Design Engineering. I have started this study to find my way into a more (bio)medical product oriented side of engineering. During courses within my studies I have encountered most of the committee members who, probably unknowingly, have ignited my interest in the medical field even further. The opportunity to finalize my study within the research group Engineering Organ Support Technologies of the department of Biomechanical Engineering at the University of Twente, under supervision of Prof Dr.-Ing. Jutta Arens, was not only a mouthful but also exactly what I was looking for! Therefore, I would like to thank Jutta for not only this opportunity but also for her support, guidance, and feedback the last couple of months. I would also like to thank Frank and Edsko for their critical eye and feedback throughout the project. Furthermore, a word of gratitude to all experts (to be) I have been able to approach for advice.

In addition, I would particularly like to thank Ana, my (sometimes literally) daily supervisor, who provided me much support and with whom I had many MOTIVATIONAL discussions. Beside all the stress from our project related deadlines I feel like we managed to have some fun along the way. I know you will do well with the rest of your PhD and I hope we will be able to release some more krakens together!

Last but not least, I want to thank my family and friends who supported me unconditionally. I believe I have finally found what I was looking for when I started my study career. I'm excited for the next step and look forward to the challenges ahead.

But for now, I simply hope everyone will enjoy reading my thesis!

~ Wytze Duinmeijer

Enschede, April 4th 2020

Problem Definition

Based on preliminary research it will be my task to collaborate in the development of a production method that ensures the position of hemodiafiltration membrane fibres in a predefined distance within one layer. Hemodiafiltration systems are traditionally composed of multiple single fibres arranged in a fibre bundle. Therefore, these fibres are generally commercialized as single fibres and not as fibre mats. In contrast, oxygenator fibres are commercially available as fibre mats, in which a predefined distance between fibres is ensured by knitting threads.

In the project, we will use current available hemodiafiltration fibres (e.g. 3M™ Membrana™ Purema™ Capillary Membranes). These fibres will be utilized outside-in, in opposition to their traditional use. This means that blood will be passing outside of the fibres, as it does in membrane oxygenators, while hemofiltrate or dialysate will be passing inside. The production method that will be developed in this project must ensure that single hemodialfiltration fibres are placed at a predefined distance within one layer and that such fibre-layers can be stacked alternatingly with oxygenator fibre mats. In a later stage it will be important to be able to vary the distance between hemodiafiltration fibres locally. One initial idea is to create a production method to assemble hemodiafiltration fibre mats comparable to oxygenator fiber mats. Eventually, the production methods must be developed in such a way so that the created fibre mats can be manufactured in a reproducible way. This will allow future tests with the fibre mats to be reliable. The overall production method needs to take into account multiple aspects, namely:

- Preserving the equal spacing of the hemodiafiltration fibres within one layer
- Fragility of the fibres
- Fixation of the fibres
- Stacking of oxygenator fibre mats and hemodiafiltration fibres
- Membrane placement (in the housing of the oxygenator)

The process will mainly be an iterative process of research (including literature, standards, and patents), design, prototyping, and analysis. Throughout this iterative process a set of requirements will be created based on the gathered information. The development of the device combining pulmonary and renal support needs to comply with the ISO standards related to this subject. Alongside developing a production method, a risk analysis will be carried out to control the overall risk of the designed production method. Furthermore, to be able to keep track of the requirements, a design requirements and specification plan will be made and finally, a start on the design verification and validation plan will be made to verify the designed production method later on in the project,.

The graduation assignment will start at the beginning of the academic year – 06/09/2021 and will end on 14/04/2022.

Abstract

Acute kidney injury (AKI) is a common complication in patients undergoing extracorporeal membrane oxygenation (ECMO). This mainly occurs due to the lung-kidney crosstalk, which means that loss of one of the two organ functions can lead to dysregulation of the other. Preliminary research led us to the hypothesis that a certain number of oxygenator membrane fibre mats could be replaced by hemodiafiltration membrane fibre mats to accommodate this problem. As no hemodiafiltration fibre mats are currently commercially produced, a mould-based manufacturing method was developed to cater for this need. Fibres are aligned with a predefined interspacing of 0.3 mm in a curved mould and fixated at the ends by using double-sided tape. Thereafter, to combine these mats with oxygenator fibre mats, the fibres are stretched into one horizontal layer and stacked alternately on a potting cap (with oxygenation fibre mats). This stacked membrane bundle can then be potted using the squared potting technique developed by A.F Martins Costa, 2022.

Keywords

Extracorporeal membrane oxygenation (ECMO); Acute kidney injury (AKI); Artificial kidney; Hemodiafiltration; membrane fibre mats; Fabrication; Manufacturing method.

Content

1 Introduction

We need to be able to breathe air to live. This important function is performed by the respiratory system where the lungs have the main task of supplying the body with oxygen (O_2) and to dispose of carbon dioxide (CO_2) [1, 2]. When the respiratory pathway is even slightly obstructed, e.g. by a disease, the gas exchange will decrease as there is no other organ that can accommodate or take over the function of the lungs.

Nowadays, billions of people suffer from some kind of respiratory diseases such as chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), emphysema, or chronic bronchitis [3]. Any advanced variant could damage the alveoli of the lungs or block the path towards these alveoli. This reduces the lung's total surface area for gas exchange, and consecutively the total amount of oxygen that reaches the blood stream [4]. If this condition remains untreated or inadequately treated, the lung does not have the capacity to recover by itself and the complications will inevitably result in death [5]. Therefore, when conventional therapy fails, such as medication or mechanical ventilation, additional lung support equipment is required to be able to provide time for both lungs and body to recover or to provide a bridge to transplant. An extracorporeal membrane oxygenator (ECMO) could provide appropriate assistance for both these matters. As this device is not connected directly to the lungs but to the bloodstream it has several advantages, such as: reduced stress on the lungs, allowing for faster recovery, and the option to make the patient awake and mobile, resulting in a less weakened patient after treatment [6].

1.1 Extracorporeal Membrane Oxygenator (ECMO)

Access to the patient's bloodstream must be obtained to apply ECMO, see Figure 1-1. This is done by the means of cannulas where one cannula is placed to draw blood and another cannula is placed to administer the oxygenated blood. The two most commonly used types of ECMO are veno-venous (VV), and veno-arterial (VA), where VV has become the standard when respiratory failure is the primary indication. After the blood is drawn, tubing is used to guide the blood between all the different components of the ECMO device. A blood pump is used to push the blood through the integrated heat exchanger, the oxygenator, and back into to patient. A gas supply is connected to the oxygenator providing an adaptable mixture of oxygen and air so the oxygen transfer and carbon dioxide elimination can take place.

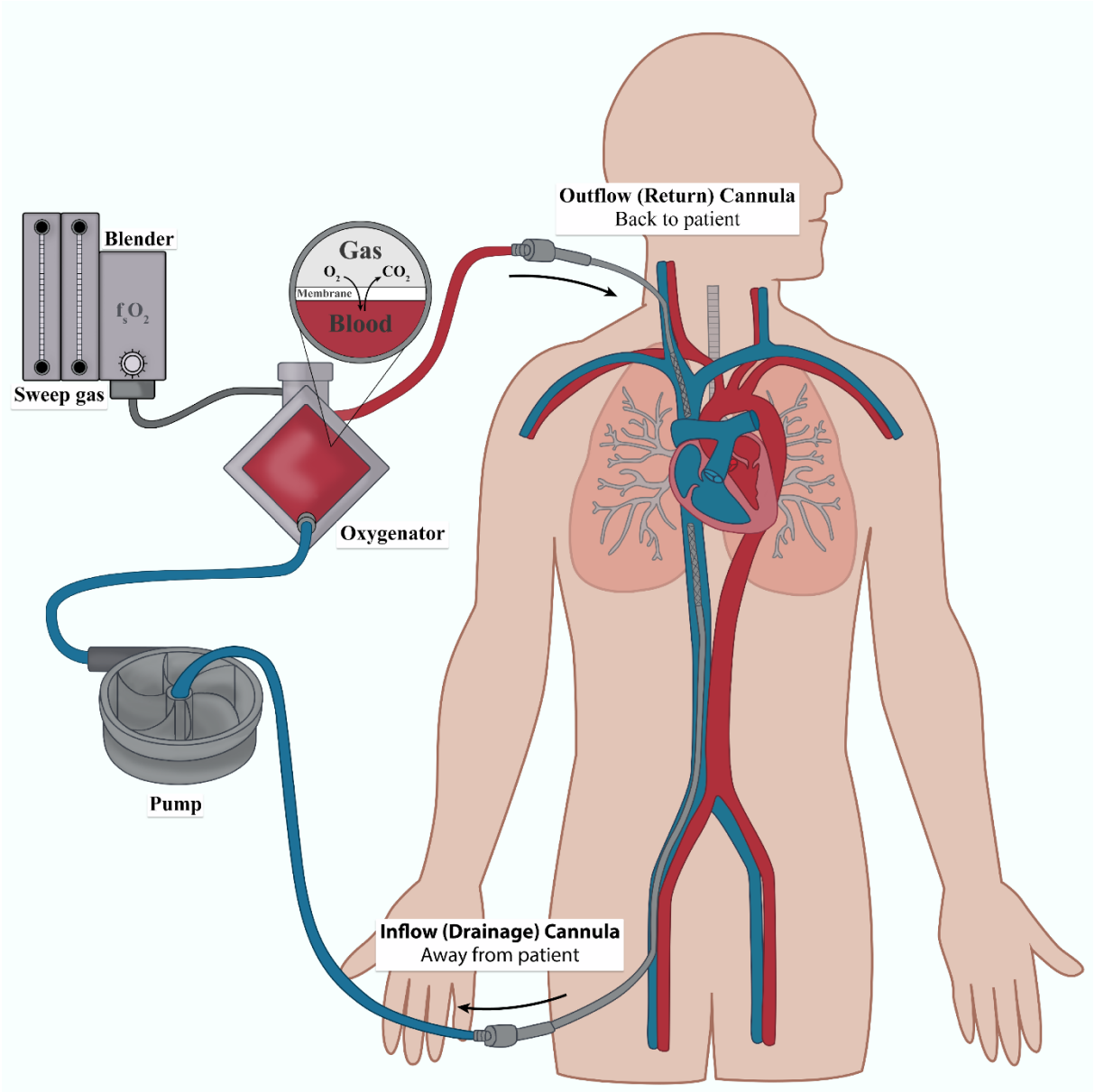


Figure 1-1: Schematic overview of a VV-ECMO set-up. A cannula drains venous blood from the patient. The pump pushes the blood through the ECMO device. The oxygenator is supplied with oxygen enriched air as sweep gas. The membrane fibres within the oxygenator allow for gas exchange after which the oxygenated blood is returned back into a vein of the patient using a return cannula.

The oxygenator housing contains a membrane fibre bundle, allowing the blood to flow around the membrane fibres whereas oxygenated gas flows continuously through the fibres. The material of the fibres has a microporous inner layer which allows for easy diffusion across the membrane wall, and a dense hydrophobic outer layer that prevents liquids from flowing into the fibres. Therefore, gas within the fibres is capable of penetrating the inner layer up to the solid outer layer which acts as a boundary between blood and gas, here the gas exchange takes place. The amount of gas exchange is determined by the gas exchange surface area and the amount of disruption of laminar flow. This disruption is generated by the small secondary flows as blood passes through the irregular grid of stacked microporous fibres. This causes the oxygenated blood cells to mix with the deoxygenated blood cells and plasma. Partial pressure difference on each side of the wall causes oxygen and CO_2 to diffuse. After diffusion, oxygenated blood is redirected back into the body, thus supplying the body with oxygen like the lungs would have otherwise done. [5]

The respiratory system does not just have the singular function of gas exchange but also aids the renal system, together forming the physiological buffering system required to regulate the amount of acid or base in the body to control the pH levels [2]. This means that loss of either one of the functions can lead to direct and indirect dysregulations of the other. Therefore, acute kidney injury (AKI), with the possibility of acute kidney failure, is not uncommon in patients undergoing ECMO [7-10]. More than 70 % of the patients, who before undergoing ECMO therapy had no medical history of kidney related issues, develop AKI due to the ECMO therapy [11-14].

1.2 Renal Replacement Therapy

As the main function of the kidneys is to purify the blood by removing waste and excess fluid from the body to maintain the water, electrolyte, waste, and acid-base balance, this could cause (deathly) complications to the patient. Often, when the kidneys fail, renal replacement therapy (RRT) can be applied to perform the function of the kidneys. There are different types of RRT, among which the most common types are hemodialysis and hemofiltration. Hemodialysis is driven by diffusion while hemofiltration requires a pressure gradient and is often used for patients receiving VV-ECMO [15]. These treatments use an artificial kidney, called hemo(dia)filter, to remove chemicals from blood. A cannula is placed into an arterial vessel and a return line into a venous vessel to access the blood. The blood pump creates negative pressure on the patients' side to draw blood from the patient and a positive pressure on the machine side to drive the blood through the hemodialyzer and return it to the patient. The hemodialyzer consists of a cylindrical membrane bundle created out of hollow fibres through which the blood flows with a straight, laminar flow. This laminar flow causes the cells and particles within the blood to concentrate in the centre of the flow leaving cell-free plasma on the sides of the cylindrical tubes. This is beneficial as the plasma contains those soluble substances which need to be filtered through the membrane to the dialysate. The dialysate flows top-to-bottom, perpendicular to the blood flow, around the membranes, thus creating the highest contact area for solute exchange along the fibres.

A solution to solve the issue of AKI in patients receiving ECMO would be to simultaneously perform RRT. However, this method currently requires the use of separate ECMO and RRT circuits, cannulas, pumps, and tubing which increase the error possibilities and prompts the coagulation cascade as the blood is exposed to a large foreign surface area, which can cause clotting. Platelets can start to adhere and stack onto the fibre's surface, disrupting and redirecting bloodstreams causing an unphysiological blood flow, which is also a known trigger for clotting. These clots can reduce its efficiency, or worse harm the patient when a thrombus is redirected back into the body. For these reasons, the patient is given high doses of anticoagulants to avoid thrombus formation but these drugs are also associated with severe, partly lethal side-effects (e.g. internal bleeding) [16]. Even if the patient does survive the bridge to transplant, the lung-kidney cross talk is still relevant because lung transplant patients require crucial, but nephrotoxic immunosuppressive medication to avoid organ rejection. This medication is known to cause chronic renal failure, associated with mortality [17-19]. Developing a single device for combined pulmonary and renal support could be a solution to the problem. This could significantly reduce the foreign surface area and the issue of the lung-kidney crosstalk before and after lung transplantation.

1.3 Solution Pathway

Unpublished research results suggest that a certain number of fibres/fibre layers in an oxygenator predominantly contribute to the gas exchange by deflecting the blood flow. By deflecting blood flow, these fibres induce mixing of the blood cells and thus, convective gas exchange in the blood phase. This

hypothesis is based on a test with a miniaturized membrane oxygenator with a stacked fibre bundle design (one of the two designs currently used clinically). Here, every second fibre layer was closed by silicone and thus, did not contribute to the gas exchange. Based on the alterations it was expected to have a 50 % decrease in oxygen mass transfer but measurements showed that it only dropped by ca. 20 % instead. Therefore, the research group Engineering Organ Support Technologies (EOST) of the department of Biomechanical engineering at the University of Twente hypothesized that a number of oxygenator fibres mainly contribute to gas exchange by mixing the blood (convection) and can be replaced by e.g. hemodiafiltration fibres (used outside-in in contrast to their intended use) without relevant loss of gas exchange capacity. This would solve the aforementioned issue of an enlarged foreign surface area when ECMO and RRT would be performed simultaneously. It could also address the problem of the lung-kidney crosstalk as replacing the non-contributing fibres with hemodiafiltration fibres could address the AKI in ECMO patients. Because the focus remains on the pulmonary support, which must be performed 24 hours a day and 7 days a week (= 168 h), the needed efficiency of the integrated hemodiafiltration is much lower than classical dialysis which is typically performed only three times a week for 3 – 5 hours per session (= 9 – 15 h). Therefore, it is hypothesized that by applying hemofiltration at lower efficiency (due to the outside-in use), but at 24 h/7 days a week like the pulmonary support, the overall performance could be similar to regular hemofiltration. Therefore, developing an oxygenation and hemofiltration fibre mat combination could be of great asset to the existing problem. Unfortunately, there is currently no method or supplier that provides a fibre mat created out of hemofiltration fibres. This makes testing the theory of a combined oxygenation and hemofiltration fibre mat impossible for now. [20-22]

Aiming to fill this research gap EOST started the RenOx project. This project aims at combining the functions of gas exchange and hemo(dia)filtration in a single device. The first goal of this project is to develop a general production method for combining oxygenation fibre mats and hemofiltration fibre mats. In order to achieve this first goal, a way must first be devised to fabricate hemo(dia)filtration fibre mats out of commercially available hemo(dia)filtration fibres. All this led to the creation of this subproject, the aim of which will be further described in the Objectives.

2 Objectives

The goal of this study is to develop a combined oxygenation and hemofiltration fibre mat combination which can ultimately be used for simultaneous ECMO and hemo(dia)filtration therapy within a singular device.

Hemodiafiltration fibre mats have to be created out of singular fibres using an existing product (e.g. 3M™ Membrana™ Purema™ Capillary Membranes) to achieve this goal. For reliable testing in the future, the production method for this matter must be developed in such a way that the fibre mat combination can be manufactured in a reproducible way. The production method should be able to

- Place single hemodiafiltration fibres at a predefined distance,
- Vary the distance between hemodiafiltration fibres locally in the horizontal layer,
- Stack the created hemodiafiltration mats alternately with oxygenation fibre mats, and
- Pot the created oxygenation and hemofiltration fibre mat combination within a predefined housing.

Parallel to this project, the RenOx project will further focus on the development of a newly square-shaped potting device for the currently existing potting technique [23] to pot the created membrane. Therefore, the oxygenation and hemofiltration fibre mat combination needs to be able to adhere to current and future requirements of this particular potting technique.

During the development of the hemofiltration fibre mats, the fibres should not be damaged as this decreases the efficiency of the fibres and might influence the outcome in future testing. It is estimated that the creation of the hemofiltration fibre mats will mainly be an iterative process of research (including literature and patents), design, prototyping, and analysis. One possibility would be to create an inlay mould where the fibres can be placed manually at a predefined distance. A different interspacing could be achieved through different moulds to be able to vary the distance between the fibres locally. The created hemofiltration mat should be fixated, so it can be stacked alternately with oxygenation fibre mats. Alongside the development of the production method, a risk analysis will be carried out which will most likely result in additional design requirement specifications. These specifications can later on be used to verify the design, with e.g. a design verification and validation plan to test whether the final result adheres to the set requirements and preferences. Eventually, there must be a working solution before the 24th of March 2022 due to project-related milestones.

In this report, the general development process of the project will be described. Starting off with a literature review in which the basic principles of current techniques and developments will be discussed. Next, the design process is elaborated upon up until the final design. Subsequently, the results of the final design will be presented and discussed. To conclude the report, a brief summary of the project will be given with the prospects for the future.

3 Fundamentals and state of the art

To date, there has been no research done that has specifically focussed on the creation of a fibre mat out of hemodiafiltration fibres. In fact there are only few studies [24, 25] or patents [26-30] which focus on the (manual) production process for the fabrication of fibre mats with a predefined interspacing. A predefined interspacing is important as it determines the mass transfer which takes place at the fibre's surface. The studies and patents that did take into account the predefined interspacing were often non-related to the topic of hemodiafiltration but to blood oxygenation. However, the insights gained from these studies could still be beneficial to this project.

3.1 Off-topic related research

Non oxygenator or dialysis related inventions utilizing fibres often do not need a defined interspacing between the fibres but merely need to align them. This is also the case in the field of precision filtration applications e.g. preparation of sterile, drinking or high-purity water and the purification of air.

In 1998 Yamamori et al. applied for a patent regarding their hollow fibre membrane module for precision filtration [31]. The design consists of a structural component to support the entire hollow fibre membrane module, see Figure 3-1a. The structural component includes a fastening component, formed by curing resins such as epoxy, which is filled and secured together with U-shaped hollow fibres, see Figure 3-1b. The rectangle shaped fastening component has a preferred short dimension of ≤ 15 mm as making is too large causes difficulties in fabrication of the hollow fibre mat. To insert the hollow fibres into the structural component, the hollow fibres are knitted into a weft using ordinary yarn (or woven fabric) as the warp, see Figure 3-1c. This allows the hollow fibres to spread into a flat sheet which prevents the bundle from cohering, thus preventing decrease in effectiveness of the hollow fibres.

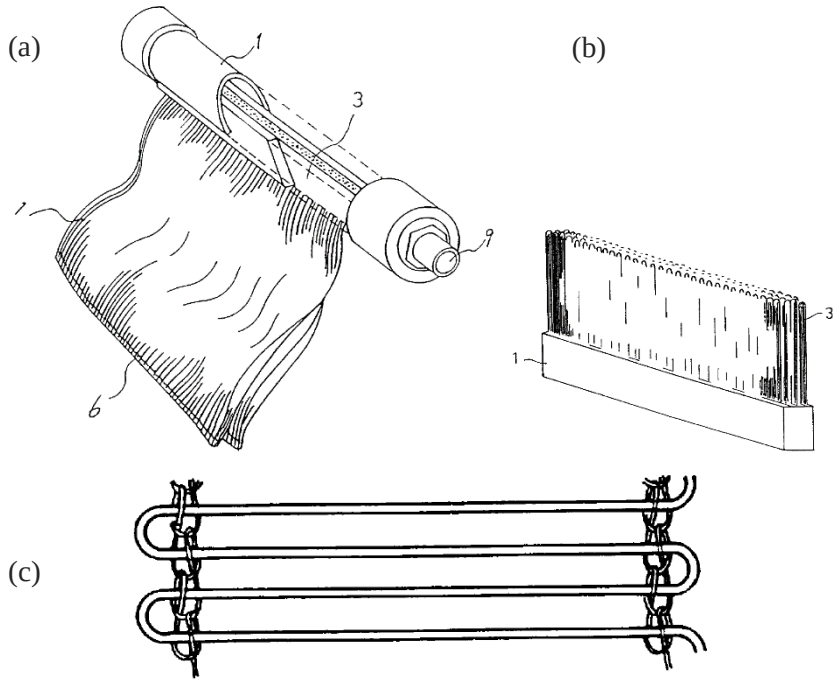


Figure 3-1: Schematics of the process for the hollow fibre membrane module by Yamamori et al. (a) Structural component supplying supporting the hollow fibre membranes. (b) Fastening component (b1) fixates fibres (b3) using a cured resin. (c) Warp technique using yarn to create a flat sheet out of fibres. [31]

A study on the manual creation of carbon fibre on polyimide ultra-microelectrodes by Gillis et al. [24] used adhesive materials to handle carbon fibres with a diameter of 4.5 µm. The fibres were placed in parallel on a custom-made harp. On both prongs of the harp a double sided tape was placed to string 5 to 10 fibres with an approximated 5 mm interspacing, see Figure 3-2a. After the electrodeposition of indium onto the fibres, the strung fibres are fixated by positioning them in a microgroove alignment clip, see Figure 3-2b.

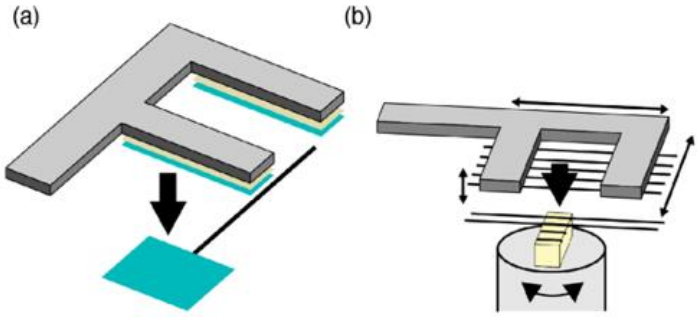


Figure 3-2: Schematic illustration of the creation of carbon mats. (a) The harp like structure with double sided tape. (b) Strung fibres positioned into the microgroove alignment clip. [24]

3.2 On-topic related research

Designs for blood oxygenation membranes seem more applicable to the topic of this study due to the similarities in requirements, e.g. interspacing.

In 1991 U. Baurmeister patented the woven hollow fibre double weft tape with knitted selvedge [26]. This technique uses weft threads perpendicular to the hollow fibres. Two reeds with thread heddles with alternating depts, approximately twice as deep as the heddle, are mounted with staggered opposite thread heddles (Figure 3-3a). As the reeds move alternately up and down from each other the weft insertion

device (Figure 3-3b) moves back and forth to place the weft thread. This way the weft threads go over and under the hollow fibres alternately. A deflecting rod perpendicular to the plane (and hollow fibres) passes through the area of the loom. The tongue needle is then used to stitch the weft thread on the right side, resulting in a knitted edge with lateral loops knitted together (Figure 3-3c). These lateral loops can be tightened further if desired. On the left side of the fibre mat the weft threads form a selvedge due to the back and forth motion of the weft insertion device. These mats are then embedded in head plates or embedded by spinning them into a curable potting compound.

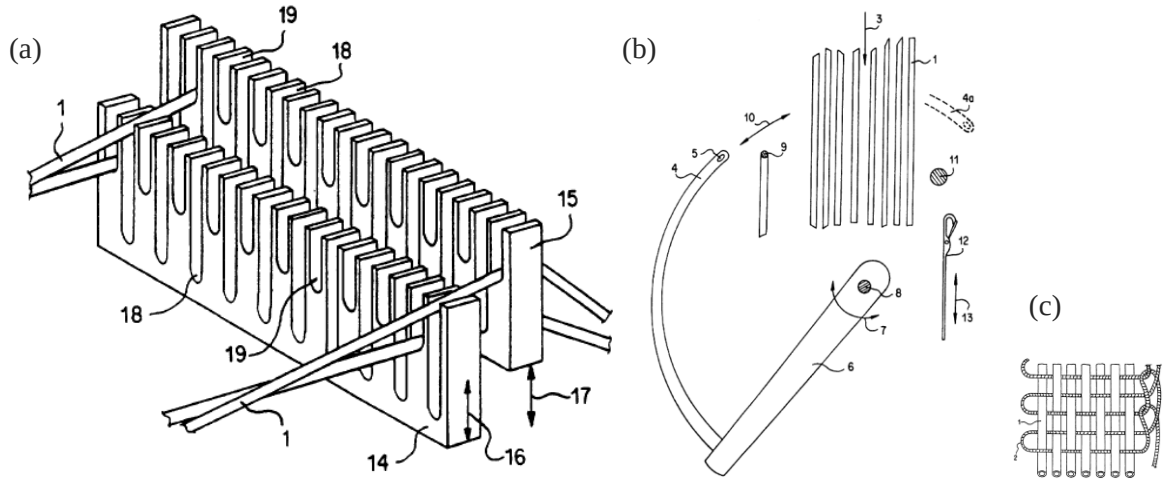


Figure 3-3: Process of the woven hollow fibre double weft tape with knitted selvedge technique [26]. (a) Two reeds with alternating depts. (b) Weft insertion device. (c) Woven fibre mat.

In 1990 J. Tretzel applied for a patent regarding a hollow fibre module for separating gas [27]. Here the fibres are parallel to each other and interconnected by warp threads. The warp threads, either monofilament, multifilament or yarn, are bound using the fringe binding, see Figure 3-4. This binding only has a slight constriction at the binding points, to reduce the risk of damaging the fibres, and can be easily removed (per fibre) if desired. It does not only connect the fibres but also provides interspacing between the connected fibres and supplies stability to the created fibre mat. After the mats are created, the most efficient way to combine them into a membrane bundle is to stack the mats and cut them into rounded segments simultaneously. These segments, about 18 to 50, are then embedded at the end regions using a curable casting compound by e.g. centrifuging.

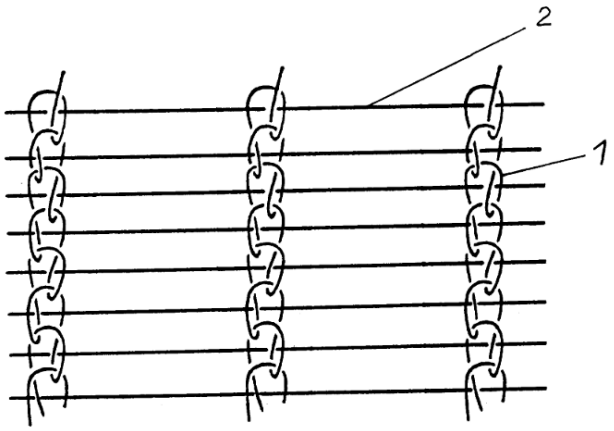


Figure 3-4: Schematic representation of the fringe binding by J. Tretzel (1) connecting the hollow fibres (2) [27].

The aforementioned process can also be applied to hollow fibres that already contain an inner filling, e.g. a fluid, as cutting out the segments can be carried out in such a way that the hollow fibres are closed (welded shut) simultaneously.

P. Riesop & A. Wodetzki developed a technique that is able to generate mats without the need to cut them first [28]. This specific method is applicable for fibres with an outer diameter of 150 to 700 µm and with fibres for gas separation it is down to 30 µm. With the method of Riesop and Wodetzki an endless hollow fibre is laid down, looped 180 degrees at the end, and then returned parallel to the previous fibre and laid down in a loop again until an area of maximum 10 × 10 cm is covered (Figure 3-5a). This way the capillary ends stay intact which prevents the inner filling from falling out. Mat segments can then be turned into a membrane bundle using a meander- or zigzag method, see Figure 3-5b, and can also have different thread counts with alternation as shown in Figure 3-5c. Due to the automated manufacturing method the fibres can have a predefined length and interspacing and with the creation of the mat gap, see Figure 3-5c, it is also possible to separate mat segments without damaging the membrane surface. This method can also be applied to hollow fibres without an inner filling and can even be turned into a continuous process when these fibres are freshly spun.

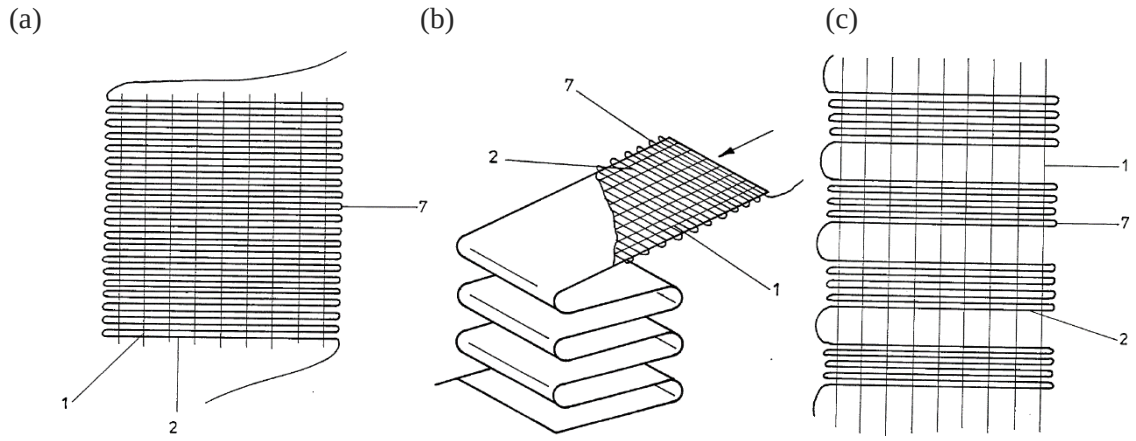


Figure 3-5: A simplified schematic representation of the manufacturing method with a continuous hollow fibre with looped ends. (a) Surface covered fibres (2) with end loops (7) fixated with a warp thread (1). (b) Zigzag stacking method. (c) Mat with different thread counts. [28]

Suzuki et al. describes an industrial knitting machine designed to manufacture hollow fibre mats by looping a freshly spun hollow fibre back and forth in a predetermined area while using a weft yarn to constrain the ends of the hollow fibre [29, 30]. Simultaneously, a warp yarn is used to fix the fibres in parallel to each other, increasing the mechanical strength for manufacturing [25, 29]. Designing a knitting device specifically for the aim of creating a hemodiafiltration mat with the provided fibres could be among one of the objectives solutions.

3.3 Conclusion

In conclusion, most state-of-the-art techniques for the creation of fibre mats and membrane bundles cannot be used directly for the design of the oxygenation and hemofiltration fibre mat combination. In most designs the fibres are a continuous filament cut off after fixation. However, the hemodiafiltration fibres that will be used for the fabrication of the fibre mats in this project are already cut at a predefined length as commercially available hemofiltration fibres are not available on the market in continuous filament. Their current length prevents the possibility to cover the desired surface area of the mat with the U-shape looping technique. It might be possible to use this manufacturing technique industrially when the fibres are still continuous. However, this would mean absolute dependency on a manufacturer and alterations to the fibre mat will not be possible on demand. The design of Yamamori et al. also has multiple layers of fibres in one fibre mat which is not suitable for the oxygenation and hemofiltration

fibre mat combination because a mat should consist of a single fibre layer. In addition, due to the fixation method of the fastening component there is no predefined interspacing between the fibres which is another requirement for the final design of the oxygenation and hemofiltration fibre mat combination. All the other studies mentioned above did take the predefined interspacing into consideration but not all were sufficient due to the lack of precision, e.g. the design of Gillis, et al. [24] .

Furthermore, the most common technique for blood oxygenation membranes seems to be a knitting technique where each single fibre is interconnected to its neighbouring fibres. The interspacing of the hollow fibres is determined by the thickness of the tread, the type of stitch and the tightness of the used stitches, meaning that varying in fibre density locally would require an adjustment of one or more of these variables. The most contemporary stich seems to be the fringe binding which only has a slight constriction of the fibres at its binding point, thus decreasing the risk of any damage to the lumen of the hollow fibres in the process. This type of stitch also allows for the removal of a singular fibre in case this is required. After a fibre mat has been created they are often stacked using the meander method, zigzag method, or by simply placing the cut mats on top of each other. These mats are often embedded in head plates or embedded by spinning them into a curable potting compound either after or before stacking. Eventually, the potting of the stacked fibre mats allows the membrane bundle to be used in the designated device. The basic principles of the applicable aforementioned techniques are still used in contemporary oxygenators. E.g. the basics of the fringe binding in Figure 3-4 (a.k.a. the chain stitch) is currently still used by the only company manufacturing oxygenation fibre mats: 3M™ Membrana™. Therefore, I performed a thorough analysis of the available mats provided by 3M™ Membrana™ as described in the following sub-chapter.

3.4 Detailed analysis of oxygenator fibre mats

The supplied oxygenator fibre mats were 3M™ Membrana™ OXYPLUS™ Capillary Membranes. These mats were investigated further and important observations were taken into account in the design process. The Sensofar S Neox confocal microscope, with a magnification of 10X, was used to take a better look up close. The same magnification was used for all other observations made with the Sensofar S Neox throughout the whole project. These specific measurements were performed to get a better understanding of the oxygenator fibre mat's design including its fixation method (Figure 3-8). For this analysis, the parts of the oxygenator fibre mat were measured from both sides that contained the connecting threads and knots and thus, provided areas with defined interspacing of the fibers.

The knot that is being used seems to be the chain stitch which is similar to the fringe binding as discussed in the Fundamentals and state of the art section (see Figure 3-4). Figure 3-6 demonstrates how the thread passes around the fibre two times at the bottom (a) and one time at the top (b). Removing a single fibre can be done by simply pulling the end of the string, which will unravel its knot and release the fibre.

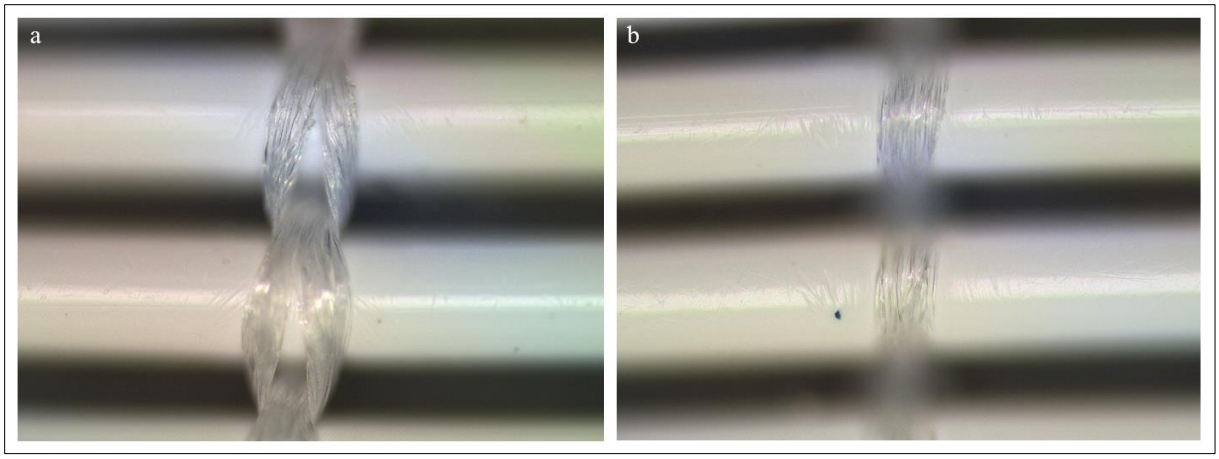


Figure 3-6: A close-up of the applied fixation method of the 3M™ Membrana™ OXYPLUS™ Capillary Membranes: a) bottom view, b) top view.

When comparing the thread to the fibre (Figure 3-7) it becomes clear that the thread consists of multiple smaller filaments and is slightly elastic. When no forces are applied to the thread it is approximately 320 µm thick (Figure 3-7a) and when stretched to its maximum (Figure 3-7b) the approximated thickness is around 81 µm. The elasticity is partly responsible for the indentation of the fibres at the fixation points as can be seen in Figure 3-8a and b. Figure 3-8b shows the difference in fibre thickness to be about 58 µm around the area of the fixation. The interspacing between the fibres (Figure 3-8c) seems to be quite consistent at 128.3 µm with a standard deviation of about 6.1 µm. From knot to knot there seems to be an equal consistence in distance of about 488.69 µm with a standard deviation of approximately 7.2 µm. These observations show that the current fixation method used by 3M™ Membrana™ are accordant and effective.

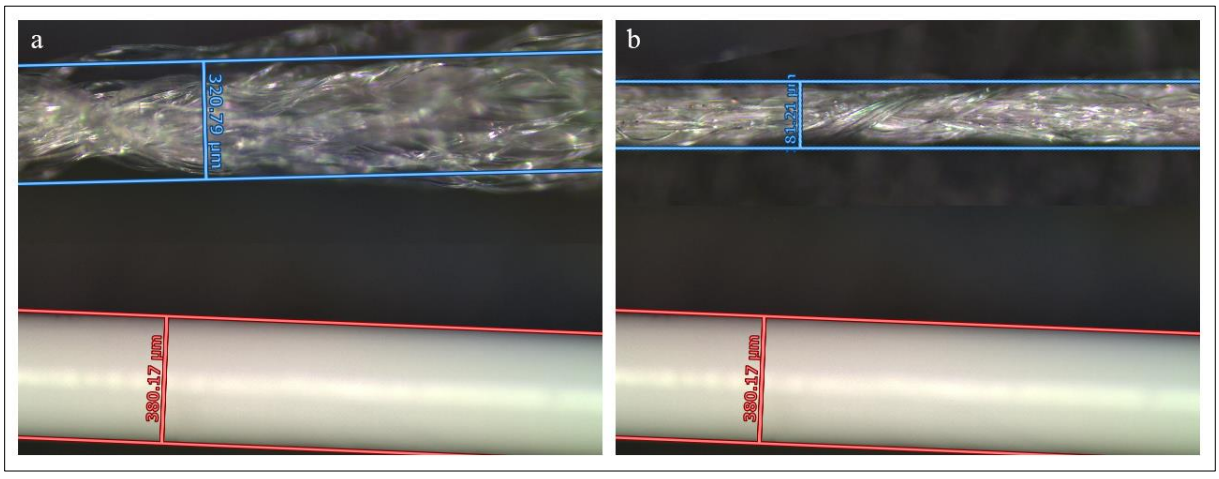


Figure 3-7: Comparing the 3M™ Membrana™ OXYPLUS™ Capillary Membrane (red) and the utilized thread (blue). Where both the thread is compared in a) unstretched and b) stretched position.

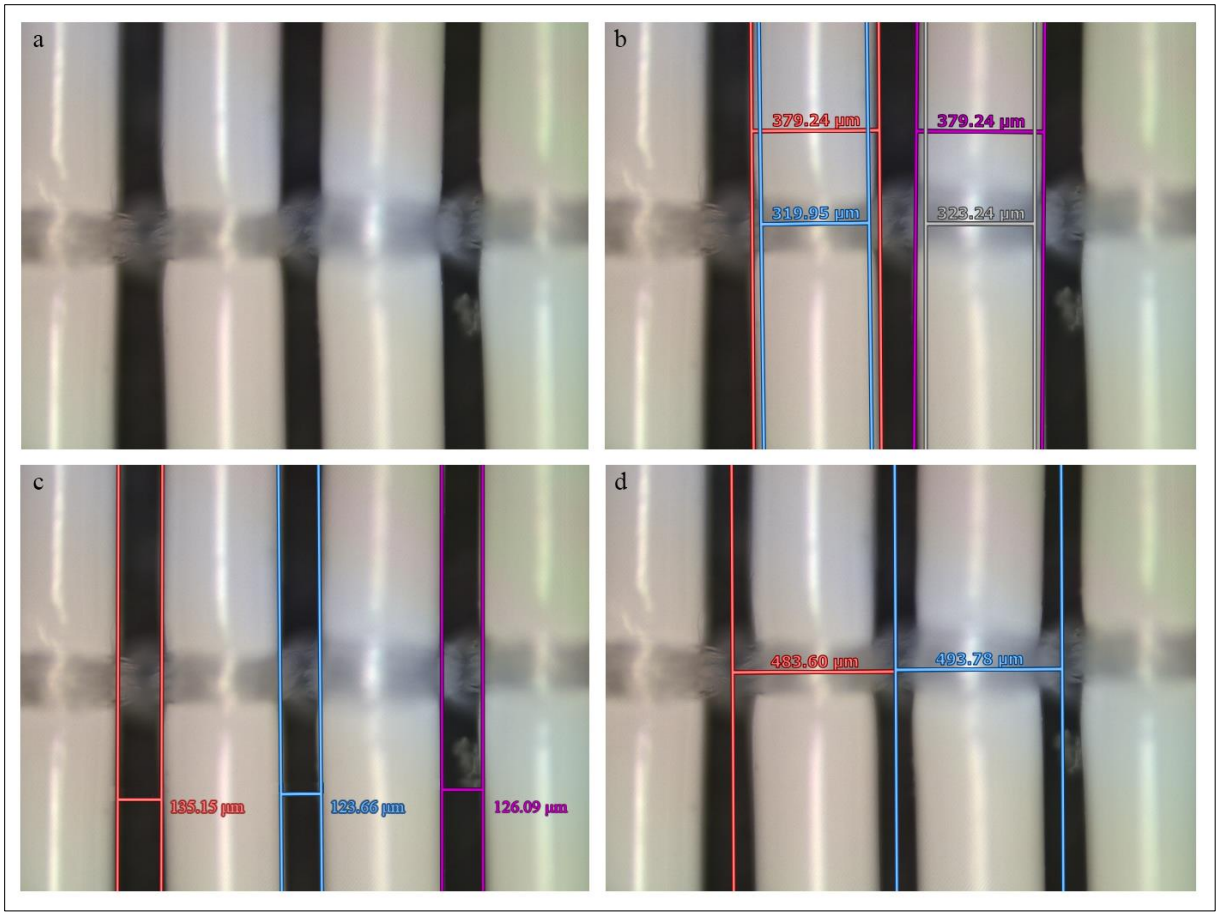


Figure 3-8: A close-up and measurements of the 3M™ Membrana™ OXYPLUS™ Capillary Membranes. Measuring: b) fibre thickness, c) interspacing, and d) knot-centre distance.

The next step was the determination of the required actions to fixate the (oxygenator) fibres together using the chain stitch. The chain stitch is a type of crochet knot, thus the method and the required actions for the fibre fixation could partly be derived from this technique.

To be able to start a chain stitch a slip knot needs to be made. From that point on the movements from Figure 3-9 can be followed to fixate the fibres. By pulling the thread guide backwards, the knot can be tightened after which a fibre can be placed on top of the loop (Figure 3-9a). The needle can then move upwards and the thread guide will then have to move forwards (Figure 3-9b). For the needle to be able to grab the thread, the thread guide will need to move to the side to get the thread in front of the needle (Figure 3-9c). The thread guide then moves to the back, so the thread is pulled against the needle which can now grab the thread as it moves down (Figure 3-9d). This way the needle can pull the thread through the loop (Figure 3-9e) to fixate the fibre using the chain stitch (Figure 3-9f). Now the thread guide can move back to its original position to tighten the knot. This technique will be further researched in the following paragraphs.

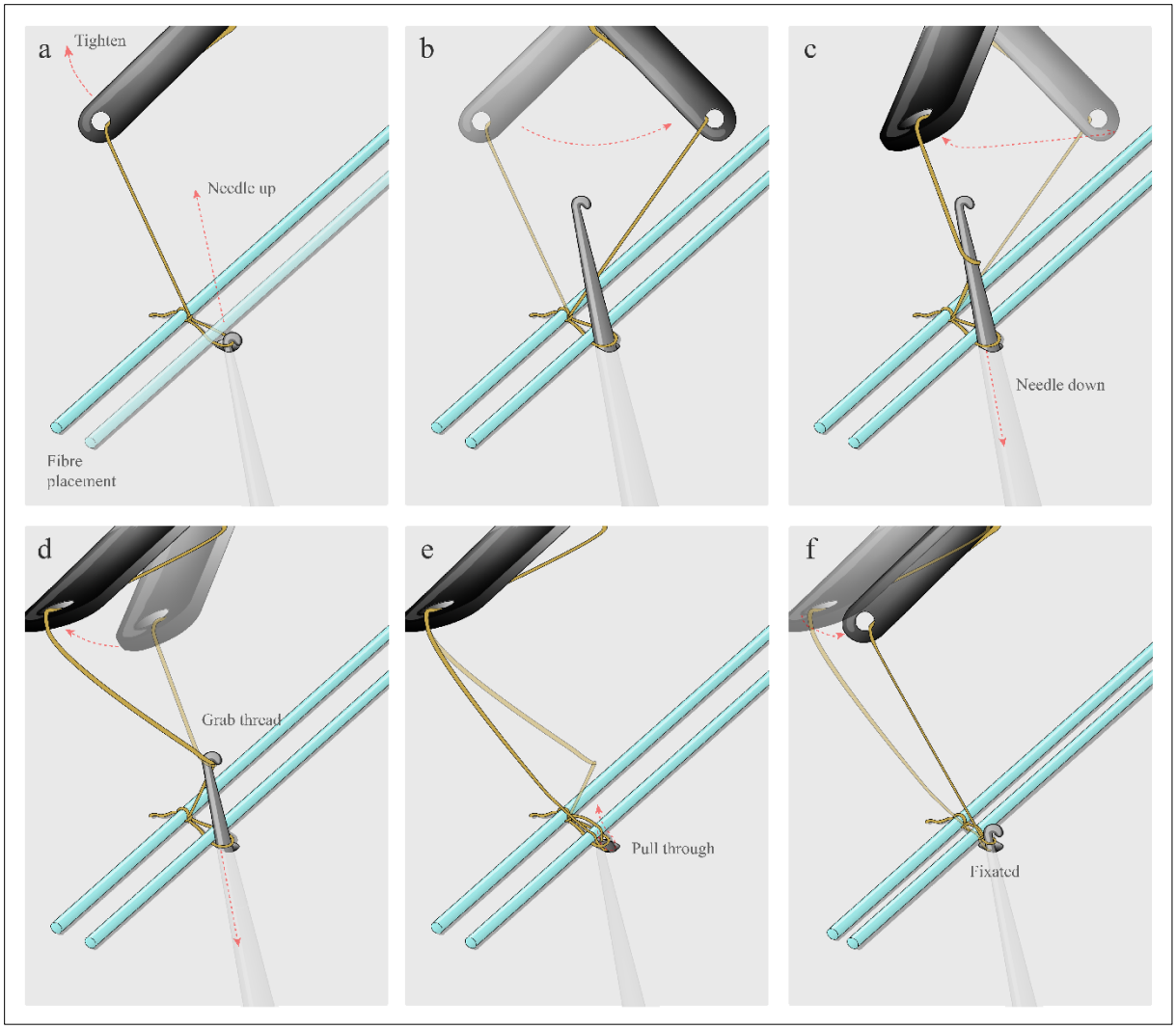


Figure 3-9: Applied chain stitch technique to fixate the fibres: a) tighten loop by pulling the thread guide backwards. b) move thread guide forward and needle up. c) move thread guide in front of needle. d) move thread guide backwards and needle downwards to grab the thread. e) Move needle downwards and pull thread through the loop. f) fixate fibre by moving thread guide to first position and tightening the knot.

4 Design Process

In this section, the design strategy is briefly explained after which the development process is further illustrated up until the final design.

4.1 Design Strategy

As there is still little to no knowledge about how to deal with ready-made hemodiafiltration fibres and manual fibre mat fabrication with a predefined interspacing, it is of importance to quickly gather accurate information for both purposes. Therefore, a majority of the project will be carried out by applying the Design Sprint, see Figure 4-1. This strategy is known to rapidly obtain many different insights in a short period of time.

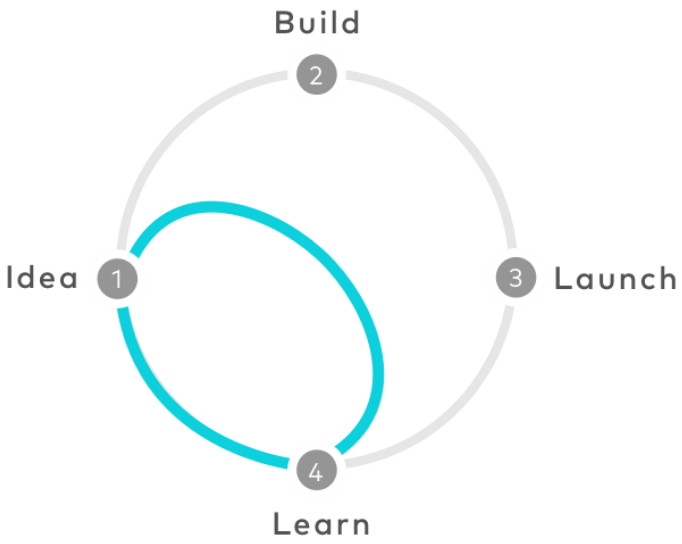


Figure 4-1: The four stages of a typical design project are: idea (1), build (2), launch (3), and learn (4). The design sprint takes a short cut by generating ideas, quick prototyping, and learning directly from these results [32]

The Design Sprint strategy is used to find answers to critical questions through design, prototyping, and testing ideas. These insights can then be considered for any subsequent ideas or conclusions to quickly gain an advanced understanding of the topic. For this study, this method was specifically applied to research the behaviour of the singular ready-made hemodiafiltration fibres in relation to the manual fabrication of a hemodiafiltration fibre mat, as described in the section 4.2 Trial and Error.

Alongside this process (as seen in Figure 4-2), a morphological chart was created to generate different solutions to the functions that must be included in the final product. After the solution ideas were conducted, four different directions were drawn up and for each direction two concepts were created. Each of these four directions has its individual value, and those are: realistic, odd (but realistic), advanced

(semi-realistic), and idealistic. Afterwards, a Harris Profile was applied to aid in the decision making process for selecting the best concept. All outcomes from the different design strategies and tasks were taken into consideration to select a final concept. Subsequently, two or three new designs were made based on the chosen concept. An iterative design process followed leading to the final design. This final design was then further detailed and eventually used to create the final combined oxygenation and hemofiltration fibre mat.

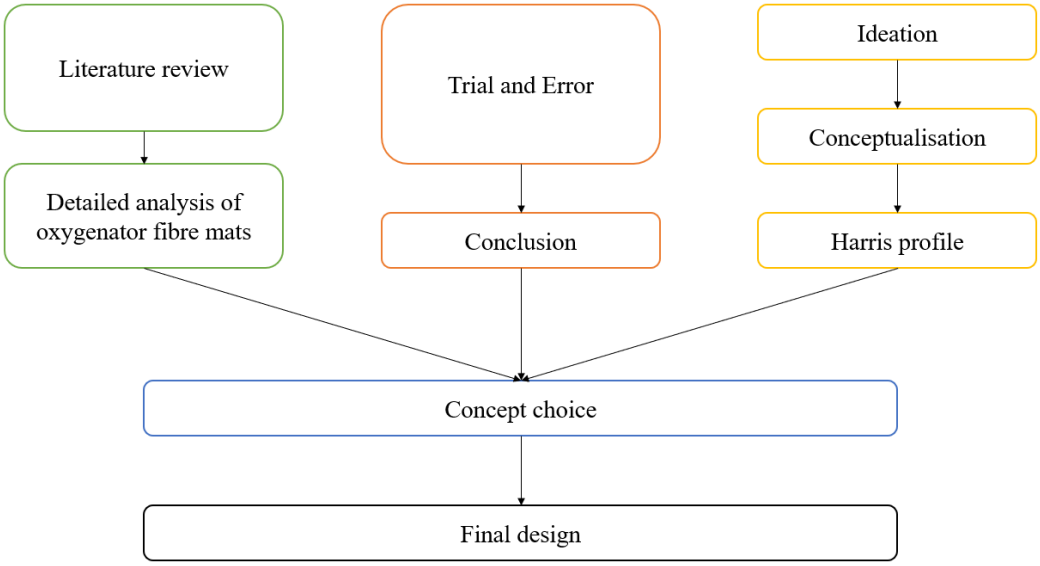


Figure 4-2: An overview of the several design strategies applied to the project. A literature review has been carried out about fundamentals and state of the art after which a detailed analysis of the contemporary oxygenator fibre mats was carried out (green). Alongside these tasks, a trial and error process was conducted (red) while a standard design process of ideation, conceptualisation, and a Harris profile was performed (yellow). All outcomes were taken into account for the concept choice (blue). After which an iterative design process resulted in the final design (black).

To optimize the safety of the design, the V-model (Figure 4-3) was (partly) applied. This project management model is based on the level of detail which increases over time. The user requirement specifications (URS) describe the application and intended use of the product. The design requirement specifications (DRS) are a translation of the URS into technical requirements for the product. Furthermore, a risk analysis (RIA) is performed with the basic requirements to identify risks which need to be addressed by e.g. the design, thus resulting in new requirements for the DRS. At a predetermined stage in the process (March 24, 2022), a design freeze occurred after which the design verification and validation process will be performed. The design verification and validation plan (DVVP) defines test scenarios for verification and validation of the product against the DRS, URS, and any related regulations to see if it is up to standard. All parts of the development process provided feedback and feedforward to one another throughout the entire process. For this project a RIA (see Annex E: Risk Analysis) and DRS (see Annex F: Design Requirement Specifications) were performed without the use of a formal URS document. However, the basic user requirements, as mentioned in section 2 Objectives, are used for the generatoin of the design requirements. The DRS iteratively adapted throughout the project and can be found in Annex F: Design Requirement Specifications together with RIA in Annex E: Risk Analysis. Each risk and design requirement were assigned an unique ID for referencing. The IDs of the risk analysis were constructed as follows RIA-y-xxx. Here, the y represents the risk sector and x represents the risk number count (001 – 999) within this section. The different risk sectors (y) are devided into: application (A), missuse (M), and production (P). Application meaning the application of the final design and its manufacturing process. Missuese indicating the misuse of the design itself, and production refering to the production techniques required to fabricate the final design. The IDs for the DRS contain

a reference to the ID of its origin (z), section in the URS and/or DRS document (y), and requirement count (x). The count jumps by 10 in case of a new requirement per section, and jumps by 1 in case a related requirement to an existing requirement is added. Thus a DRS-ID with a requirement originatig from e.g. RIA-M-001 would look like RIA-M-001-010 and a (e.g.) a DRS-ID with a requirement originating from the URS/DRS would look like 6.1-000.010. Here, 000 indicates that the URS is non-formal.

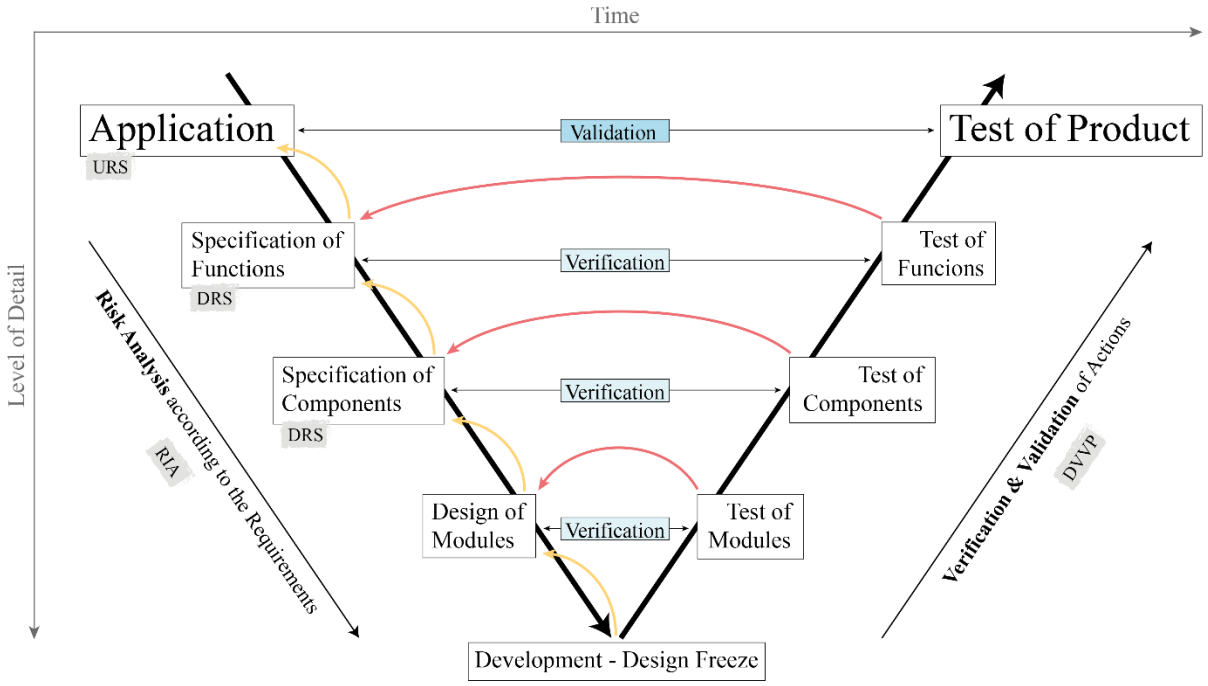


Figure 4-3: A schematic overview of the V-Model.

4.2 Trial and Error

For the trial and error phase, a series of tests was carried out at the start of the project to determine how the fibres would react to different handling methods. These test could help to discover what possibilities would be best to create an oxygenation and hemofiltration fibre mat combination. To keep track of the experimental developments, lab notes were kept and divided in three separate key categories of the design: alignment, fixation, and stacking. Each category represents the purpose of the experiment that was conducted. For alignment, the goal was to align the hemodiafiltration fibres with a predefined interspacing between the fibres in a single plane with the possibility to adjust the interspacing. Fixation was related to the goal of fixing the aligned fibres (mats) to maintain the interspacing throughout the rest of the process. Stacking experiments refer to the stacking methods used to stack the aligned and fixated hemodiafiltration fibre mat alternately with the oxygen fibre mats. All the lab notes include the date of conduction, a test ID, the applied method, pros, cons, future ideas, and additional notes. The fixation and stacking categories also contain a reference to the previous method on which the current experiment was performed.

4.2.1 Alignment

Individual fibres derived from the 3M™ Membrana™ PUREMA™ Capillary Membranes bundle had to be aligned with a predefined interspacing. To test any finalized stacked membrane configuration, it needs to be potted. Potting is a technique to seal the end of the fibres using different materials (e.g.

silicone). This material is applied by centrifugal forces to cover the outer sides of the fibre membrane bundle. Instead of commonly used circular mats with a diameter of 60 mm, squared shaped mats needed to be created due to the adjusted (squared) potting device designed by Martins Costa [23]. This caused the shape of the mat and different requirements to change slightly during the project as this was an ongoing development. The final design required a minimum mat size of 60 × 40 mm. For optimal mass transport efficiency, the final fixation method is supposed to cover as little area as possible of the required potting surface. As a result, different margins were used during the trial and error phase, creating different fibre mat surface sizes. The interspacing was also varying and went from 1 mm to 0.3 mm. As soon as the interspacing became < 1 mm many production methods, such as milling, sewing, and knitting were dismissed. This was mainly due to the fact that the available machinery for these processes at the University of Twente were unable to achieve an interspacing < 1 mm. Other methods such as 3D printing and laser cutting were able to achieve an interspacing < 1 mm and could be used to create the initial idea of a mould to satisfy all the requirements. It was supposed that the mould could be adapted and recreated to vary the density of the fibres locally in the horizontal direction. Different moulds were created utilizing a laser cutting machine and a stereolithography (SLA) printer.

The Trotec Speedy 300 laser cutting machine has a focal point of 500 microns which indicates that it would not be able to achieve an interspacing < 0.5 mm. However, the efficiency of the focal point is highest at the centre of the spot and gradually decreases as the distance from the centre increases. Therefore, it might still be able to create structures with an interspacing < 0.5 mm, but it will most likely alter these structures in the process. When engraving once, the laser cutter is able to engrave polymethylmethacrylate (PMMA) to a maximum depth of 1 mm with the following settings: power (P) = 100 Watt and speed (V) = 10 m/s. Test a1 (Table 4-1) and a9 (Table 4-2) in demonstrated that it is indeed possible to achieve an interspacing < 0.5 mm (0.3 mm) but, as expected, the surrounding structures were altered. These alterations cause changes to the shape, surface, and depth of the structures making the mould less efficient when used for alignment. This is most likely due to deformations to the structure and the maximum depth reduction of 0.25 mm (max. depth = 0.75 mm). Due to these changes it became difficult to align the fibres while using the mould.

The Form 2 SLA printer, with a laser point resolution of 30 – 140 microns in the XY-direction, was able to print moulds with a minimum interspacing of 0.3 mm using a Black V4 resin. This minimum interspacing was not determined by the resolution but by the applicable 3D print design restriction. To prevent deformation of the printed object it should adhere to multiple design guide recommendations [33]. Important guidelines are the minimum unsupported wall thickness (= 0.6 mm) and the minimum vertical-wire diameter (= 0.3 mm), which indicate that an interspacing < 0.3 mm is not possible for any future designs. This might be problematic as the interspacing of oxygenator fibres, obtained with the chain stitch as shown in Figure 3-8c, is around 0.13 mm. Which could indicate that an interspacing < 0.3 mm might be required to e.g. optimize mass transport.

Therefore, the applicability of the contemporary method of the 3M™ Membrana™ OXYPLUS™ Capillary Membranes was further researched. Unfortunately, this method could not be applied manually to the hemofiltration fibres due to combination of the scale of the fibres and the limitations of human motor skills. For that reason, the chain stitch was applied to rigid pens with a diameter of 75 mm, as shown in test a5 (Table 4-1) and test a6 (Table 4-2). The interspacing is determined by the thickness of the thread and the tightness of the stitch, allowing for locally varying densities. Since this method is used by 3M™ Membrana™ it can be assumed that it will work and allow for interspacing around 0.13 mm. However, to fixate the hemofiltration fibres in this way, it probably requires customized equipment.

In addition to achieving the required dimensions of the fibre mat, the advantages and disadvantages of the production methods, such as time and reproducibility, are also of importance. The chain stitch cannot be applied manually to the hemofiltration fibres (yet) because of aforementioned customized equipment. Due to the nature of the hemofiltration fibres (no continuous fibre but multiple cut fibres) it might not be possible to design the equipment within the given time. For that reason, the use of one of the mould designs for alignment was considered the safest solution for a timely result and is therefore described in the following.

The SLA mould seems most sufficient to achieve the required fibre mat dimensions but is less sufficient in terms of production time. A single mould print takes 8 – 13 hours (incl. wash and cure time) while a single laser cut mould only takes about 15 min. Aside from the mechanical challenges in regards to the moulds, the fibre placement afterwards was also a time consuming process for both methods. Due to the electrostatic effect fibres tend to attract or repel to different objects, e.g. popping out the mould's grooves. Adding water to the moulds helps to keep the fibres inside the grooves but also triggers clustering of the fibres at the endings outside the grooves. The fibres will also cluster in the centre when one fibre escapes from the groove. The depth of the grooves also affect how easily a fibre can pop out. Less fibres popping out during the alignment process also decreases the overall time for fibre placement. Therefore, the SLA mould was the better option in terms of fibre placement. With an SLA mould it takes about 15 – 20 min to create a single hemofiltration fibre mat (± 100 fibres) while with a laser cut mould it takes about 30 – 40 min (± 80 fibres). All in all, the most efficient and feasible method to align the hemofiltration fibres seemed to be the SLA mould.

4.2.2 Fixation

Different types of adhesive methods were compared for the initial fixation of the aligned fibre structures to determine its efficiency, see Table 4-3 test f1 – f5, and Table 4-4 test f8. Silicone seemed like a great option but an estimation of the preparation time, capillary forces after application, and the curing time made it an unnecessarily time consuming process. This is especially the case when compared to the use of tape. The only few downsides of the tape appear to be the ability to: store single mats without the mould attached to it, correct mistakes after tape application without damaging the fibres, and to apply tape on fibres in a wet mould as water adversely affects the adhesion of the tape. Overall, using tape for fixation of the fibres seems to be a faster and more accurate process compared to the silicone but has some downsides to overcome.

The crochet chain stitch from the alignment method does not only align the fibres but fixates them at the same time. As shown in Table 4-4 test f7 and f8, a single row allows for rotational movement around the stitch, while a double stitch prohibits this movement. A double stitch also ensures a correct interspacing over the total length of the object in contrast to a single stitch. Furthermore, compared to hemofiltration fibre mats fixated with tape the chain stitched mats can be stored individually.

4.2.3 Stacking

It is of importance to have an accurate alignment and fixation method to be able to stack an oxygenation and hemofiltration fibre mat. It is also important to have a base to stack (and fixate) the fibre mats onto for insertion into the potting device, a.k.a. a potting cap. Due to (mainly) the first condition only two tests could be made in the allotted time for the trial and error phase. The first stacking test (s1), based on method a1 and f1, used two pins on each side to fixated the mats. This did not work as the hemofiltration mats needed to be perforated and stretched before stacking. This caused deformations of the

hemofiltration fibre mat, making this mat and thus the stacked combination unusable. For the second test (s2) the mould-aligned fibres fixated with tape could be used. The same tape used for fixation could be re-used to fixate the hemofiltration fibres onto the base. With this method it was easy to stack both hemofiltration and oxygenation fibre mats while maintain a correct interspacing.

4.2.4 Conclusion

From this trial and error phase it can be derived that an immediate solution is possible. The fibres could be aligned using a SLA printed mould and are fixated using tape. These hemofiltration mats could then be transferred and taped to a base where oxygenation mats can be alternately stacked on top of that using tape. Limitations to this approach are the minimum interspacing of 0.3 mm and the inability to store individual hemofiltration mats.

Table 4-1: Trial and Error Phase: Alignment (a1 – a5)

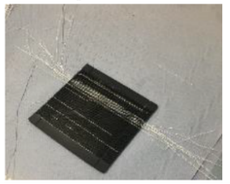
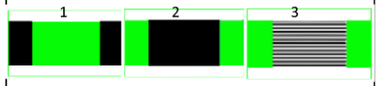
Date	*2021-09-22*	*2021-10-04*	*2021-10-07*	*2021-10-08*	*2021-10-22*
Test	a1	a2	a3	a4	a5
Production Method	Mould with laser cut engravings 	SLA printed mould v1 	Knitting machine 	SLA printed mould v2 	Crochet chain stitch v1 
Settings	 1. Engraving of the spacers grooves (approx. 0.6 mm) Settings: P=40 ; V=10 ; Pulses 500 2. Engrave central zone for depth oxygenation fibres (approx. 0.38 mm) Settings: P=50 ; V=20 ; Pulses 500 3. Engrave fibre grooces for dialysis fibres (approx. 0.26 mm) Settings: P=40 ; V=20	Interspacing: 1 mm Depth: 1mm Width: 1mm	Interspacing: 1 mm	Interspacing: 0.5 mm Depth: 0.5 mm Width: 0.5 mm	 1. start 2. slip knot 3. add pen/fibre 4. pull thread through loop 5. add pen/fibre 6. pull thread through loop 7-8. repeat
Membrane Size (in mm)	60 × 40	80 × 80	N/A	80 × 80	N/A
Pros	• Ensured interspacing • Irregulations visible • Moulds production is time effective • Moulds are cost effective	• Ensured interspacing • Irregulations are visible • Inlays for fibres are clean • Tilted surface seemed to help for inlay of the fibres • No clustered fibres at the edges • Static effect causes fibres to stick (in)to groove surface • Fibres fo not have to be cut in advance • Do not have to touch middle of the fibre • Easy to correct mistakes	• Fast • Immediate fixation	• Ensured interspacing • Irregulations are visible • No clustered fibres at the edges • Static effect causes fibres to stick (in)to groove surface • Fibres do not have to be cut in advance • You do not have to touch the middle of the fibre	• Simultaneous to 3M Membrana Oxyplus Capillary Membranes (fibre mat) • Quick • Individual pens/fibres can be removed • Length mat can be as long as desired • Tightness of the configuration can be controlled by the thickness of the tread and the tightness of the stitch => easy local density variation • No moulds necessary • Immediate fibre fixation
Cons	• Clustered fibres at the end of the engravings • Halfway through placing the fibres clustering over the total length of the fibres increases. • Laser seems to have clouded the engravings. • Fibres are electrostatic => tend to jump out of engraving	• Production time moulds are longer than test a1 • Mould deformed in the SLA printer => deformed part makes it hard to place fibres • Straigtning fibres in groove causes damage => fold • Overhanging fibres need to be cut • Fibres are stuck in grooves => damage and hard to clean the mould	• Minimum interspacing = 1 mm • Fabric needs to be removed afterwards (somehow) • Needle damages fibres • Hard to correct mistakes	• Mould deforemed in the SLA printer => deformed part hard to place fibres • Straightning fibres in groove causes damage => fold • Fibres stuck in grooves (afer removal) => cleaning the mould • Resolution printer is not sufficient for smaller grooves and interspacing (compared to test a2)	• Not manually applicable by hand • Width is limited to the length of the pen/fibre • Tightning the stitch by hand is hard
Future Ideas	• Engravings over the whole length of the mould • 70 × 70 mm mould with equalized length of fibres to avoid clustering • Stackable fibre mat moulds	• At this moment in time the mould has the correct dimensions	• Tie individual fibres together with a knot	Use spikes to allign fibres instead of grooves	• Correct interspacing only applies at point of stitch application (in case of a singular chain stitch line) • Use crochet needle for stitch • Make (semi-)automatic stitching device • Use thinner thread
Notes	• Perpendicular cut engravings seem to increase fibre placement difficulty • What would be the minimum interspacing when placing manually? • Takes about 25 - 30 minutes to create a fibre mat of 60 × 40 mm.	• Took less time to create than test a1 (30 minutes for 80x80 mm => about 15 min. for 80x40 mm).	• Look into interspacing technique of current oxygenator fibre mats	N/A	• The width of th final fibre mat will not exceed the length of the fibres.

Table 4-2: Trial and Error Phase: Alignment (a6 – a10)

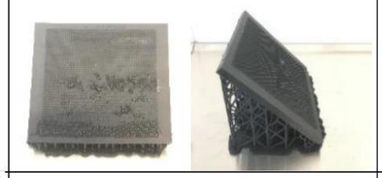
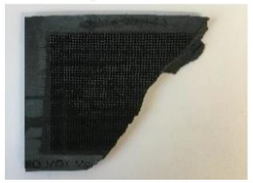
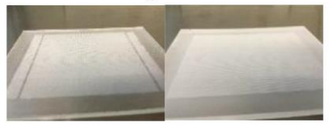
Date	*2021-11-10*	*2021-11-11*	*2021-11-22*	*2021-11-22*	*2021-12-06*
Test	a6	a7	a8	a9	a10
Production Method	Crochet chain stitch v2 	SLA printed mould v3 	SLA printed mould v4 	Laser engraved mould 	SLA printed mould v5 
Settings	 a) start b) forward c) in front d) grab thread e) pull through f) fixate => repeat	Interspacing: 0.4 mm Width: 0.4 mm Depth: 0.4 mm	Interspacing: 0.3 mm Width: 0.3 mm Depth: 1 mm	Settings: P=100 ; V=10 Interspacing: 0.3 mm Width: 0.3 mm Depth: 1 mm	Interspacing: 0.3 mm Width: 0.3 mm Depth: 1 mm
Membrane Size (in mm)	N/A	80 × 80	80 × 80	60 × 60	60 × 60
Pros	• Interspacing along entire pen / fibre (unlike test a5) • Simulteneous to 3M Membrana Oxyplus Capillary Membranes (fibre mats) • Quick • Individual pens/fibres can be removed • Tightness of the configuration can be controlled • Interspacing of the configuration can be controlled by the thickness of the thread and the tightness of the stitch => easy locan density variation • no mould necessary • Immediate fibre fixation	• Ensured interspacing • Irregulations aare visible • No clustered fibres at the edges • Fibres do not have to be cut in advance • Do not have to touch the middle of the fibres • Easier application than test a4 • Better removal than test a4 (decreased contact area)	N/A	N/A	• Ensured interspacing • Irregulations are visible • No clustered fibres at the edges • Fibres do not have to be cut in advance • Application as easy as test a7 • Removal as easy as test a7 • Water does not drain from mould • Shorter print time than test a7 (+/- 9 hours) • Mould deformed less than test a7
Cons	• Not manually applicable to fibres by hand • Tightning the stitch by hand is hard • Going back and forth with the chain stitch makes stitching after the initial chain stitch line harder	• Long print time (+/- 12 hours) • Mould deformed in the SLA printer => deformed part hard to place fibres • Overhanging fibres need to be cut • Water drains from mould	• Printer was unable to print the complere mould • Mould deformed in the SLA printer => deformed part hard to place • Long print time (+/- 12 hours)	N/A	• Ling print time (+/- 9 hours) • Mould deformed in the SLA printer => deformed part hard to place fibres • Fibre is not properly fixated in the middle part
Future Ideas	• Multiple needles with simulteneous stittching	N/A	• Smaller mould • Bigger grooves to enhance printability	• Double engraving for deeper resukts?	• Design solutions to prevent warping • Design solutiond for better fixation in the middle part • Design solutions for betterwater retaining
Notes	• The width of the final fibre mat will not exceed the length of the fibres • Using sparated needles to create multiple rows of the chain stitch simulteneously	N/A	• Most likely the print is too big / heavy for printer • Another probability would be that the resolution of the printer is not accurate enough to print the shallow grooves	• Order matter • 1st grooves, 2nd spikes = 0.75 mm depth • 1st spikes, 2nd grooves = 0 mm depth • Both seem to be unuable as the depth is too shallow for the fibres to stay in place after placement.	• Current potting technique allows for smaller mould

Table 4-3: Trial and Error Phase: Fixation (f1 – f5)

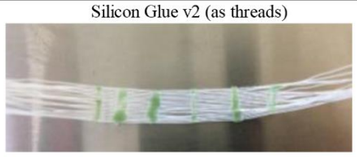
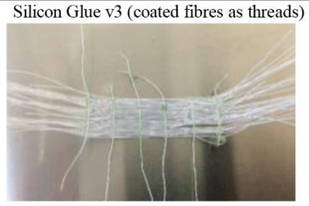
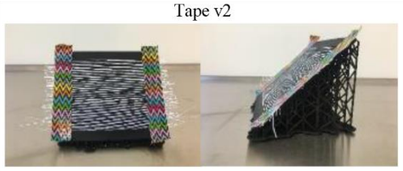
Date	*2021-09-13*	*2021-09-13*	*2021-0924*	*2021-09-24*	*2021-10-04*
Test	f1	f2	f3	f4	f5
Fixation Method	Silicon Glue v1 	Tape v1 	Silicon Glue v2 (as threads) 	Silicon Glue v3 (coated fibres as threads) 	Tape v2 
Allignment Method	a1	a1	a1	a1	a2
Pros	• Properly fixated • Smooth surface • Mould prospectives for future application • Clearly visible area borders • Reusable mould	• Easy fixation • Not messy • Ready-made product • Fast • No capilary forces to deal with	• Fast • Fibres stay in place (interspacing) over complete length • No stretching needed for stacking => less damage	• Fast • Fibres stay in place (interspacing) over complete length • No stretching needed for stacking => less damage • Less surface area covered than test f3	• Fast • Fixated
Cons	• Long curing time • Preparation time • Hard to store for longer period of time • Difficult to distribute evenly by hand • Capilary forces cause difficulties with distibution • Fixation cannot be directly used for stacking • Messy	• Unable to store single mat without attached mould • Difficult to correct mistakes => damages fibres	• Might damage centre of the fibres • Hard to apply in small amounts • Breaks if not enough material is applied • Hard to place • Difficult to remove fibres from mould afterwards • Preparation time • Long curing time • Covers part of fibres (= no diffusion)	• Might damage centre of the fibres • Hard to apply in small amounts • Breaks if not enough material is applied • Hard to place • Difficult to remove fibres from mould afterwards • Preparation time • Long curing time • Covers part of fibres (= no diffusion)	• Grooves are deeper than test a1, causing the tape more trouble to attch to the fibres • Fibres do not want to come out of the grooves => too deep • Stretching tape before placing tape makes the fibre mat curl
Future Ideas	• Pressure/height equalizer is rigid object with a thickness of 0.64 mm	N/A	N/A	• Cover sewing thread instead of fibres to cover less surface areas	• Grooves perpendicular to fibres to be able to press the fibres against the tape • Grooves less deep for a larger/better contact area between fibres and tape
Notes	N/A	N/A	N/A	N/A	N/A

Table 4-4: Trial and Error Phase: Fixation (f6 – f9)

Date	*2021-10-07*	*2021-10-22*	*2021-11-10*	*2021-12-08*
Test	f6	f7	f8	f9
Fixation Method	Sewing machine 	Crochet chain stitch v1 	Chrochet chain stitch v2 	Tape v3 
Allignment Method	a3	a5	a6	a10
Pros	• Fast • Fixated	• 2-in1 method for allignment and fixation • Thread thickness determines coverage of surface area • Fixated • Individual fibres can be removed if necessary • Mats can be stored individually • No additional equipment required	• 2-in1 method for allignment and fixation • Thread thickness determines coverage of surface area • Fixated • Individual fibres can be removed if necessary • Mats can be stored individually • No additional equipment required • No wabbling compared to test f7 • Thread goes in straight line (alternate knit direction) • Correct interspacing over complete length pen / fibre	• Fast • Fixated • Indication to place tape
Cons	• Punctures • Minimum interspacing = 1 mm • Hard to place fibres with consequent interspacing • Flattens fibres (thread too tight) • Hard to regulate (sewing) force	• Singulat fixatoin in the middle of the pens/fibres seems to trigger wabbeling • Thread seems to go into a diagonal direction • Interspacing only remains at point of stitch	• Not manually applicable to fibres by hand • Width is limited to the length of pen/fibres • Tightning the stitch by hand is hard • Going back and forth with the chain stitch makes stitching after the initial chain stitch line harder	• Tape will not stick to fibres is grooves are too deep • Tape will not stick to fibres if the mould is too wet • The fibres will not come out if the mould is too dry • Stretching tape before placing tape makes the fibre mat curl
Future Ideas	• Maybe crochet instead of sewing?	• Apply chain stitch to multiple points on the pen/fibre • Figure out thread direction control	N/A	• Make water frain grooves • Bigger area for tape application?
Notes	• Look into current oxygenator fibre mat fixation	N/A	N/A	Contradictions => use TRIZ contradictions matrix?

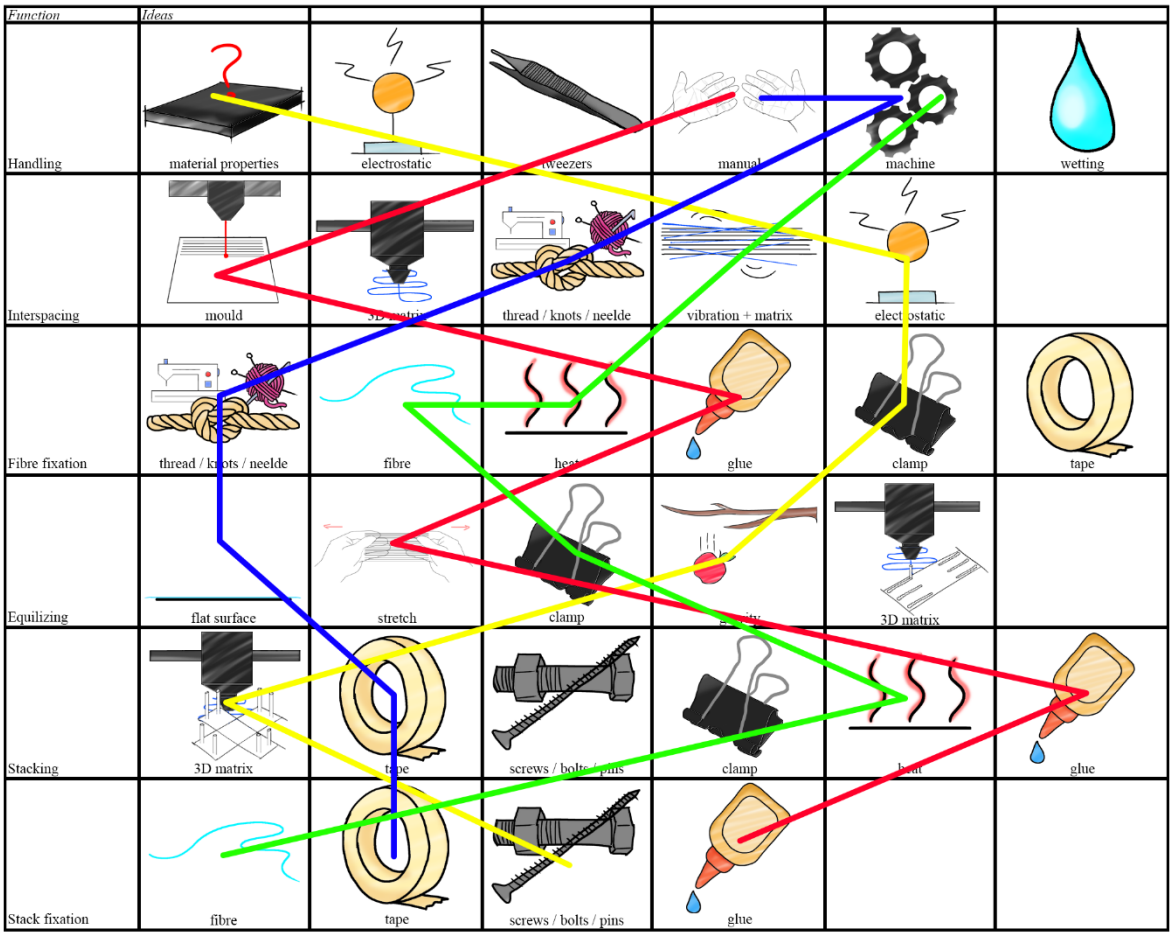
4.3 Ideation

For the ideation phase, the three aspects from the trial and error phase were further detailed into separate functions the final product should take into account. These function are:

- Handling — Handling and processing of the fibres
- Interspacing — Ensure equal spacing between the fibres over the complete length in one layer
- Fibre fixation — Forming a fibre mat by restraining fibre movement to maintain the interspacing
- Equalizing — Ensure fibres are all in the same (horizontal) level
- Stacking — Layering of hemodiafiltration fibre mats and oxygenator fibre mats
- Stack fixation — Restraining the movement of the stacked fibre mats to maintain position

A brainstorming was conducted to come up with solutions to the fulfil these functions. The functions and ideas were then processed into a morphological overview, see Table 4-5.

Table 4-5: An overview of the morphological chart with its solutions and directions. Red: realistic. Yellow: odd but realistic. Blue: Advanced but semi-realistic. Green: Idealistic.



Each direction has its own characteristic: red is a realistic solution, yellow is realistic but odd solution, blue is an advanced but semi-realistic solution, and green is idealistic but most likely not feasible (within the time of the project). For every direction of the morphological chart, two concepts were drawn up.

4.4 Concepts

In concept 1 (Figure 4-4), a mould is used to align the hemofiltration fibres with a predefined interspacing. Subsequently, a lid with two slots is added on top of the aligned hemofiltration fibres. The slots are located at both endings of the fibres and can be used to apply the silicone to fixate the aligned hemofiltration fibres. The endings of the hemofiltration fibre mat is then constrained in a stretching device which is able to stretch the mats by turning a lever. While the hemofiltration fibre mat is stretched, a water-based adhesive is applied on top of the mat. Oxygenator fibre mats can then be stacked on top of the hemofiltration fibre mat. This process is then repeated until the desired fibre mat combination is achieved. Finally, water is applied to dissolve the water-based adhesive, resulting in a potable fibre mat combination.

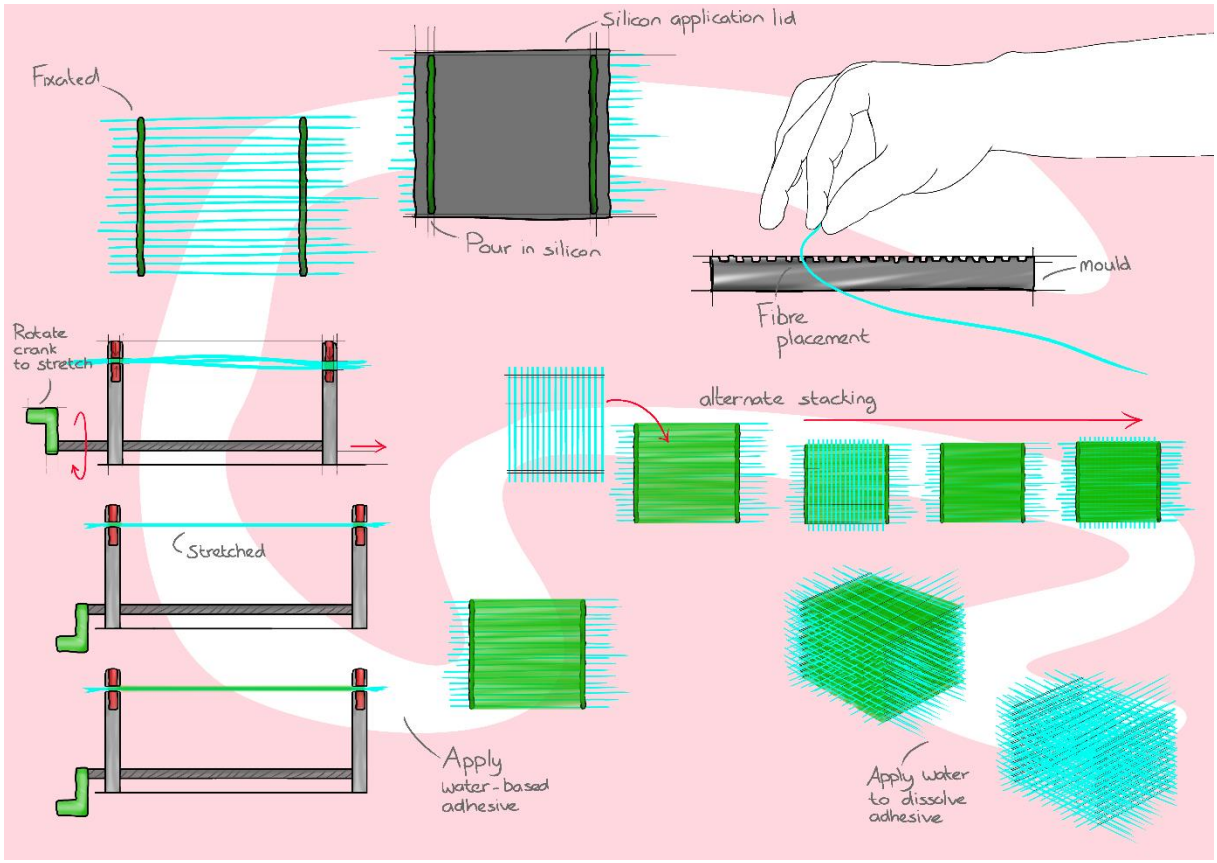


Figure 4-4: Concept 1, a two part mould with silicone application slots for fibre fixation. A stretch device to equalize the mats and a water-based adhesive for stacking.

Concept 2 (Figure 4-5) has a mould that consists of three merged layers: a bottom layer for support, a pillared layer for interspacing and a top layer to apply silicone. The fibres are woven through the pillared layer using a needle-like device. A syringe with silicone is then connected to the top part of the mould and used to fixate the aligned fibres. The silicone spreads through the capillaries, in the top layer, to the correct location on the hemofiltration fibres. After the silicone has fixated the hemofiltration fibres, the mould can be broken and the hemofiltration fibre mat can be removed. A dot of silicone is then applied in each corner of the hemofiltration fibre mat and subsequently a oxygenator fibre mat is stacked on top of this. The process is repeated until the desired fibre mat configuration is achieved.

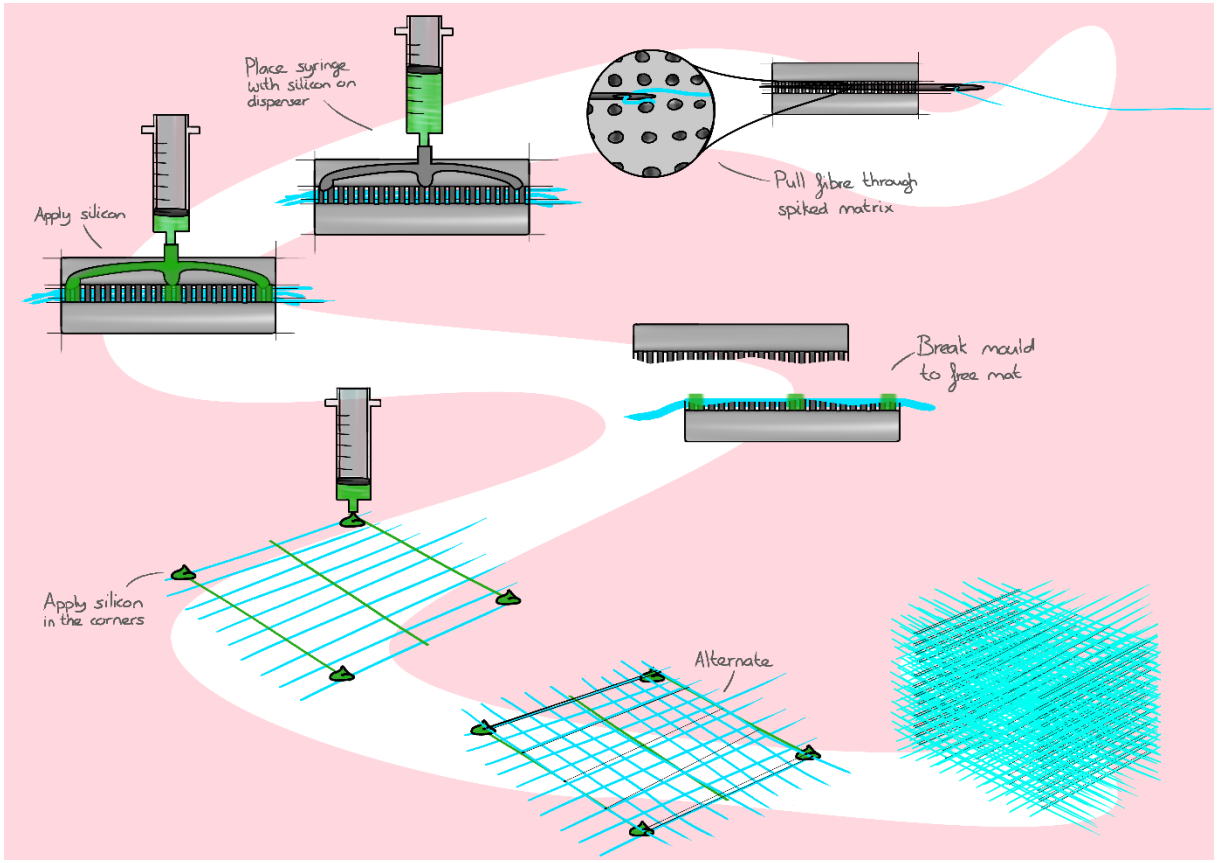


Figure 4-5: Concept 2, a breakable mould using silicone for fixation.

To increase the fibre handling, concept 3 (Figure 4-6) has a mould in which the grooves are coated with a negatively charged material. This coating should enhance the attraction between the grooves and the fibre with the purpose of decreasing placement difficulties and thus increasing speed. After the fibre alignment, a clamp is added to both fibre endings to fixate the fibres. The fibre mat is then removed and hung upon a rack. The oxygenator fibre mats are also fixated in these clamps and the oxygenator and hemofiltration mats will be alternately hung upon the rack until the desired fibre mat configuration is accomplished.

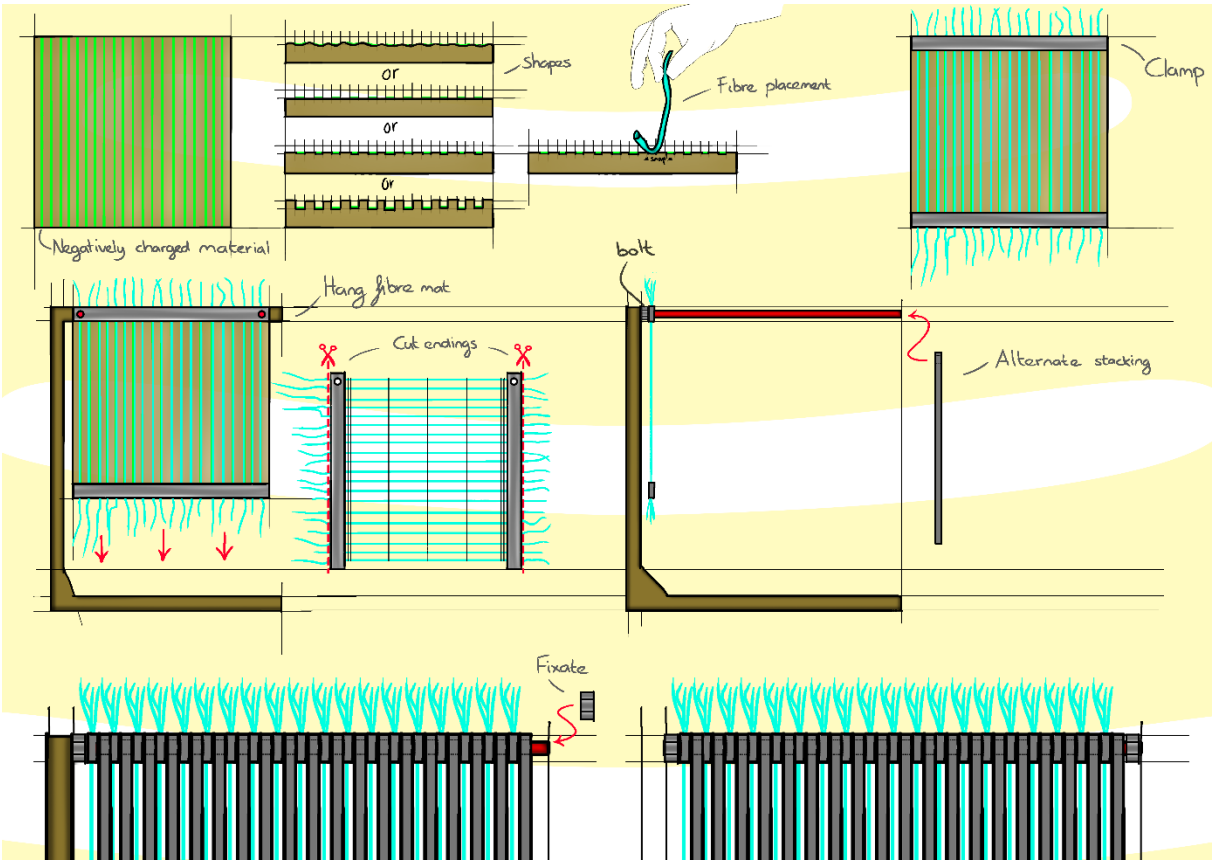


Figure 4-6: Concept 3, an electrostatic mould and rack stacking process.

The use of a regular mould is disregarded in concept 4 (Figure 4-7) as it makes use of two clip-like parts. These clips are placed on opposite sides of the fibre. Hemofiltration fibres and water-dissolvable weft threads are alternately placed within the clips. When the desired hemofiltration mat size has been achieved the clips can be used to fixate the hemofiltration fibres by applying pressure to the clip. Subsequently, one of the clips of the hemofiltration fibre mat is placed in a stacking mill utilizing gravity to straighten the fibres. A clamp is then used to fixate the straightened fibres before the mill is turned by 90° to stack the next layer. An oxygenator mat, fixated using the same clips as with the hemofiltration fibres, is stacked on top of the hemofiltration fibre mat. This process is repeated until the appropriate fibre mat configuration is obtained. Adjustable screws are then used to fixate the corners of the fibre mat configuration and water is applied to dissolve the weft threads, creating the wanted fibre mat configuration.

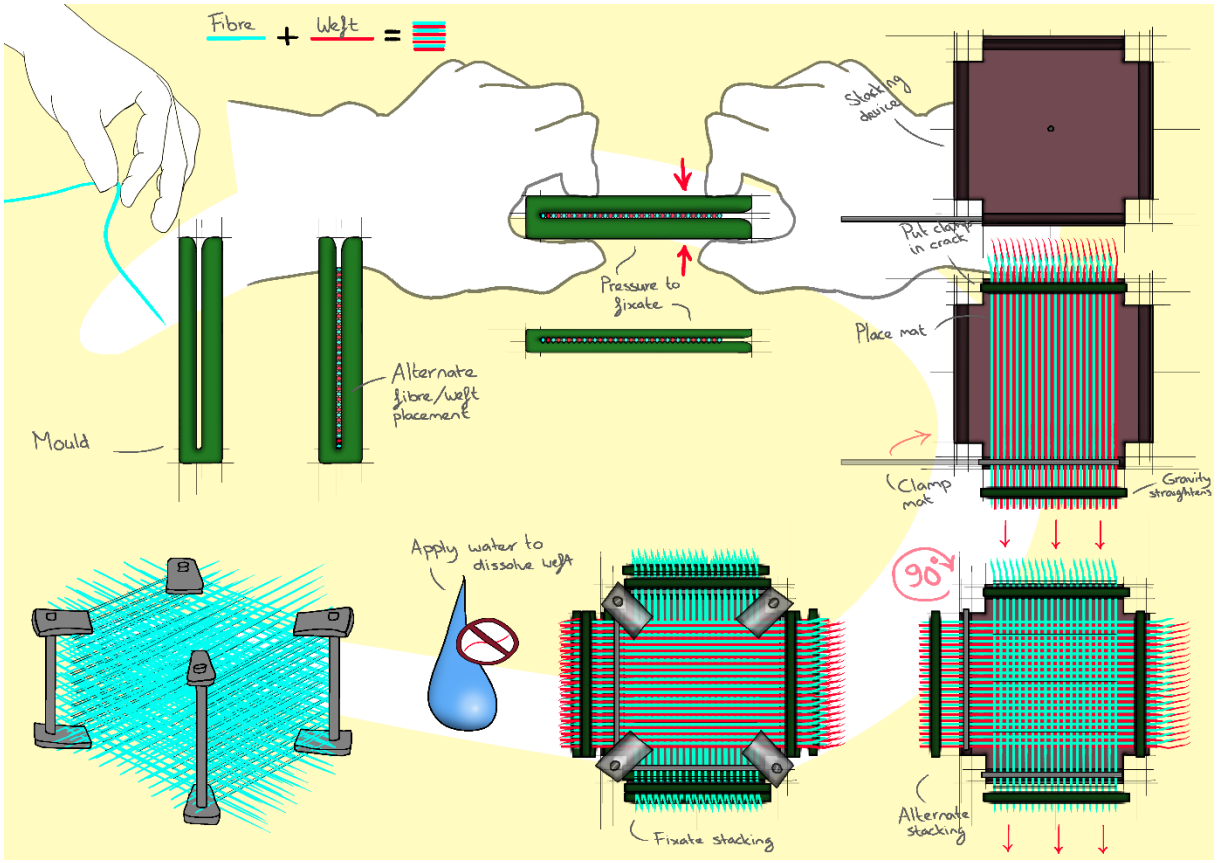


Figure 4-7: Concept 4, a two compressible (aligned) clips using water-dissolvable weft threads for interspacing and the mill stacking technique.

The concepts marked in blue in Table 4-5 are supposed to be semi-automated in terms of handling. Concept 5 (Figure 4-8) therefore makes use of a rotating hook with a sewing thread attached to it. Fibres are fed into the rotating hook by hand, causing the hook to "catch" and loop around the fibre, thus constricting the fibre in the attached sewing thread. This process is repeated until a wanted hemofiltration fibre mat length is realized. The hemofiltration fibre mat is then taped on top of the desired surface and an oxygenator fibre mat is stacked on top of this, also using tape. This process is repeated until the required fibre mat configuration is attained.

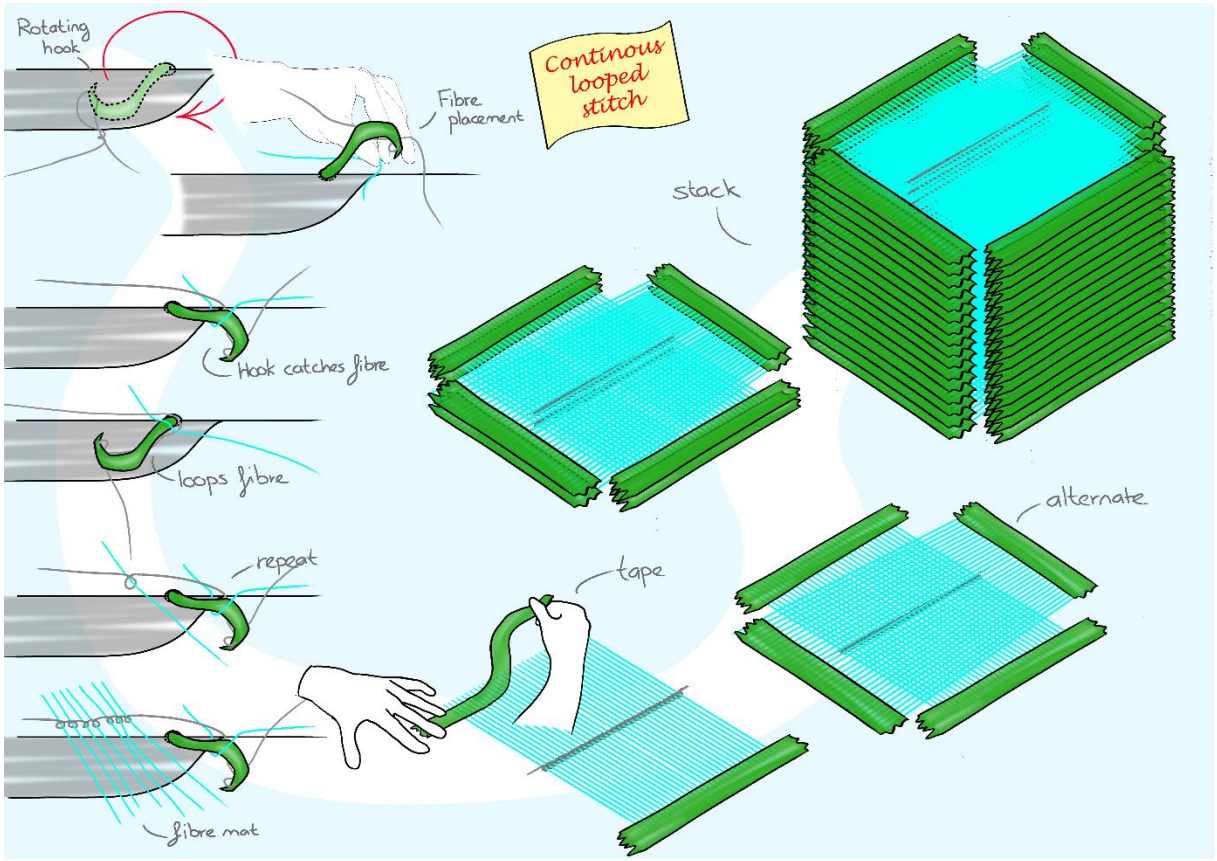


Figure 4-8: Concept 5, continuous loop stitching for fibre alignment and using tape for stacking.

Concept 6 (Figure 4-9) makes use of the chain stitch technique explained in Figure 3-9. A slip knot is created before the start of the knitting process. The slip knot is fixated by a clamp after which the first fibre is manually placed. A crochet needle pushes the other thread through the loop of the slip knot, creating a new loop. The original loop, of the slip knot, is then pulled down to tighten the stitch. This process is repeated with the newly created loop until the preferred hemofiltration fibre mat length is concluded. Like in concept 5, the needed fibre mat configuration is created by alternately stacking hemofiltration and oxygenator fibre mats using tape.

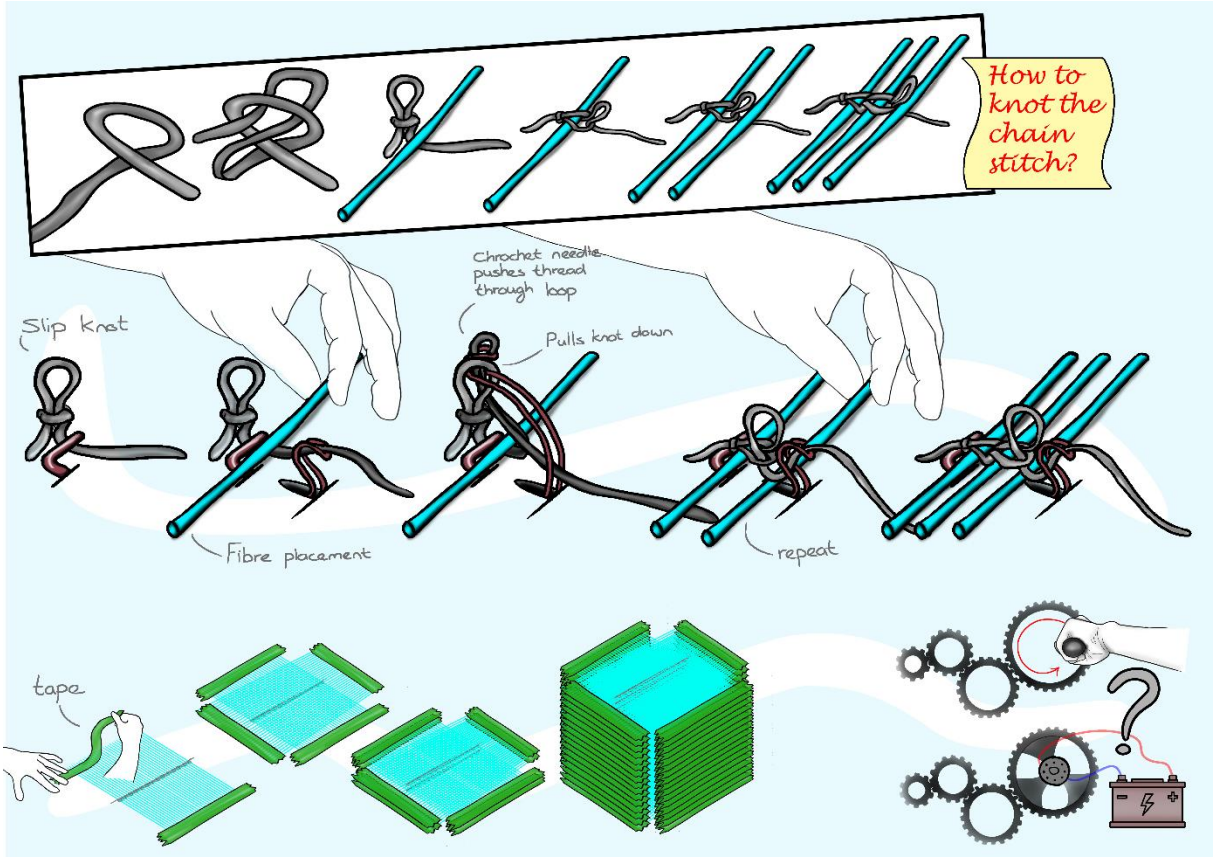


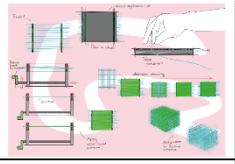
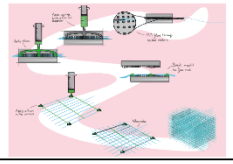
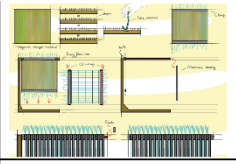
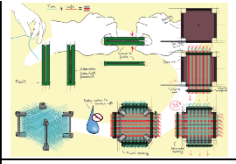
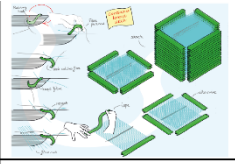
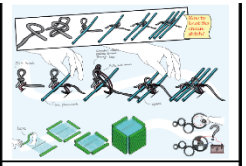
Figure 4-9: Concept 6, chain stitching fibre mats and using tape for stacking.

4.5 Concept Direction Selection

Eventually, the concepts 1 – 6 were evaluated by applying a Harris Profile based on the best judgement of the designer and the daily supervisor of the project. The concepts are compared based on the ten most relevant preferences, at that time, ranked top to bottom by importance. Each concept is ranked using a score from -- very bad, to ++ very good for all the individual preferences. The concept with the highest score is perceived as the most suitable solution. In case it is a tie, the concept with the highest score in the highest ranked preferences wins.

Looking at Table 4-6, concept 6, the chain-stitch based design (CBD), appears to be the most favourable as it scores best on the most important preferences and shows positive scores only. Therefore, it seems that a semi-automated concept using the chain stitch is the ideal solution. However, the implementation of this semi-automated concept is the most complex solution and will most likely cause some complications. And as one of the boundary conditions of this project is to have a working solution by the 24th of March 2022, it is not wise to focus on an idea that might not be feasible in the given time.

Table 4-6: The Harris Profile: ranking concepts based on the current preferences. Each concept is ranked based on relevant preferences, ranked top to bottom by importance. Scores vary from -- very bad to ++ very good, and are assigned per preference per concept using a coloured (grey) square(s). These squares are assigned from the midline up until their gained score. For a quick overview, the total score has been added to the bottom of the Harris Profile. This shows Concept 6 was ranked best as it obtained the highest score.

																									
	Preferences	**Concept 1**				**Concept 2**				**Concept 3**				**Concept 4**				**Concept 5**				**Concept 6**			
		--	-	+	++	--	-	+	++	--	-	+	++	--	-	+	++	--	-	+	++	--	-	+	++
1.	The fabrication method does not increase the chance of damaging the fibres.			■				■			■				■					■				■	■
2.	The fabricated fibre mat combination is easily reproducable.		■					■			■				■					■	■			■	■
3.	The fibre fixation method covers an as small as possible part of the fibre's surface area.			■	■			■				■				■				■	■			■	■
4.	The space between the layered mats is as small as possible.			■				■		■	■					■	■			■	■			■	■
5.	The layered mats do not damage each other throughout the whole process.			■	■			■	■			■				■	■			■	■			■	■
6.	It is easy to control the locally varying fibre density.		■				■				■					■	■			■				■	
7.	The fabrication method takes as little time as possible.	■	■				■			■	■				■					■				■	
8.	After the fixation of the fibres the predefined interspacing cannot be altered.			■	■			■	■		■			■	■					■				■	
9.	The fabrication method should not alter the efficiency of the fibres.		■				■					■	■			■	■			■				■	
10.	It is possible to industrialize the fabrication method.			■				■		■	■					■				■	■			■	■
	Total score	4				6				-6				5				15				16			

In consultation with both project supervisors, it was therefore decided that the CBD was not feasible within the available time for the rest of the project. Therefore, it was discussed that based on all the collective outcomes a Mould Based Design (MBD) (as further described in section 4.6) was the most suitable solution for this moment in time. Although, it is anticipated that the MBD can only be refined while major improvements stay out as the overall process is manual work. Therefore, it is still expected that the final solution of the CBD could be more accurate and efficient compared to the finalized MBD. In addition, the CBD has the opportunity to achieve an interspacing < 0.3 mm, unlike the MBD which is expected to be limited by the resolution and design guides of the SLA printer. Furthermore, the overarching RenOx project will continue for at least 3 years after this (sub-)project has finished. Many fibre mat combinations will have to be made for the duration of the RenOx project. For this purpose, a semi-automated CBD would presumably be the better solution in the long run. A future sub-project of the RenOx project could potentially further detail and develop the CBD.

Thus, further focus of this project was therefore on improving the MBD. The MBD was optimized so that hemofiltration fibre mats could be made and stacked with oxygenation mats before March 24, 2022. The oxygenation and hemofiltration fibre mat combination was then to be potted for a proof of concept. Furthermore, the RIA and DRS based on the MBD provided a basis for the future design of the CBD.

4.6 Mould Based Design

The iterative optimization process of the MBD is concisely describe down below. The final design solution is described in both text and visuals to gain a better understanding of the design itself and the manufacturing process of the combined oxygenation and hemofiltration fibre bundle. The results of the manufacturing process with the final design solution will be further discussed in section 5: Results.

4.6.1 Problem Identification

To further detail the current design, the different problem areas needed to be identified and addressed. To be able to pinpoint these areas and innovate the design even further, the TRIZ innovation method [34] was applied (for more information see Annex A: TRIZ Innovation Method). First, the main parameters of values, system- , super system- , and sub-system components were determined. An interaction matrix (for more information see Annex A, Table 12-1) and function analysis (Annex A, Figure 12-1) was conducted based on the aforementioned information and knowledge about the design so far. All the harmful problems, identified in the function analysis, were ranked against each other to determine the most significant harmful problems, listed in Table 4-7. For each problem, their coupled positive was conducted (Annex A, Figure 12-2) after which the applicable inventive standards were determined (Annex A, Figure 12-3). The applicable inventive standards were applied to each individual problem and a minimum of one solution was generated for each applicable inventive standard (Annex A, Table 12-2, Table 12-3, Table 12-4, and Table 12-5). After this, the insufficient problems of the current design were looked into. A top 3 of the most insufficient problems, based on the assigned insufficiency score in the function analysis, was made as seen in Table 4-7. The Innovation Situation Questionnaire was applied to these problems to distract the key problems and goals. A Root Conflict Analysis (RCA+) was then performed to find any contradicting statements where the 40 inventive principles (40-IP) could be applied (Annex A, Figure 12-4, and Figure 12-5). The correct parameters for the contradictory statements were established, after which it was possible to determine the applicable IPs for each individual contradiction. A minimum of 2 solutions had to be created for each selected IP per contradiction. Both solution

pathways were compared after which 3 new designs were developed (Annex B, Figure 12-6, Figure 12-7, and Figure 12-8).

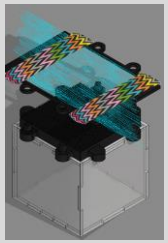
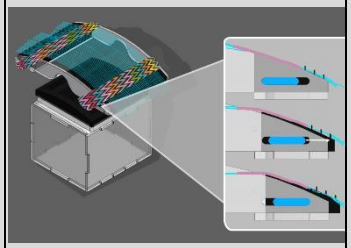
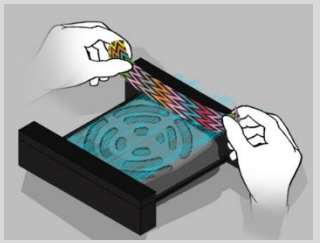
4.6.2 Prototyping and Selection

The new designs were turned into prototypes, tested, and ranked against the aforementioned problems. However, the printer still caused problems printing the pillar structure of the design. This caused a (partly) deformed pillar structure, a completely deformed mould, or a broken mould. Therefore, several samples were printed to optimize the printing process. One of these samples had to determine the minimum printable pillar distance in a single row of the alternately spaced pillars (Annex C: Pillar Print Samples). Another important sample series had to determine the fibre area between the pillar rows for fibre placement (Annex D: Fibre Area Samples). It became clear that the minimum printable pillar distance in a single row was 4.8 mm and the necessary fibre area between the pillar rows was 0.3 mm to be able to place the hemofiltration fibres properly. Furthermore, it was of importance to reduce the weight of the print parts to prevent the print from falling of the build platform. This was achieved by shelling the design and minimizing its size and thus weight. In addition, by reducing the amount of print parts the total production time of the designs was also reduce. All prototypes (Figure 4-10) were therefore made with these dimensions and conditions.

Figure 4-10: Prototypes a) Layered mould, b) Segmented mould, and c) Stretch mould.

Testing of the prototypes was done by both the designer and the daily supervisor of the project as they were most experienced with the manufacturing technique. Each of them tried out a prototype by creating 1/4 of the total surface area of the fibre mat and stacking this mat on top of a mock-up potting cap. The result of the process of creating fibre mats and stacking fibre mats were analysed by comparing them to the identified problems and each other. The applied ranking method, ranks the lowest score to be best as -1 is awarded when a problem has been resolved, 0 when the severeness of a problem has been reduced, and a 1 is given when a problem remains unchanged. After ranking, the scores were added up for each prototype. Table 4-7 shows that the segmented MBD is the best option as this one scores lowest when compared to the addressed problem areas.

Table 4-7: Ranking of the three MBDs based upon identified problems. The designs were assessed on the basis of (previously identified) problems. A score of -1 (resolved), 0 (reduced), and 1 (unchanged) was awarded per concept for each problem. The Segmented MBD came out best as it received the lowest total score (-2).

Problem Type	Nr.	Problem	Layered MBD 	Segmented MBD 	Stretch MBD 
Harmful problem	1	Hemofiltration fibres are stuck in the SLA mould.	0	-1	-1
	2	Hemofiltration fibres pop out of the SLA mould.	1	-1	-1
	3	Tape redirects hemofiltration fibres (after application).	0	0	1
	4	Water flows off SLA mould.	0	1	0
Insufficient problem	5	Hand(s) place hemofiltration fibres (onto mould/potting cap).	1	0	0
	6	Hand(s) remove hemofiltration fibres (from mould).	-1	-1	0
	7	Hand(s) touch SLA mould.	0	0	0
	8	Tape touches SLA mould.	0	0	0
		Total :	1	-2	-1

4.6.3 Segmented MBD Optimization

This design was once again optimized based on the remaining, and newly encountered problems. One of these new problems was the pairing of fibres at the edge of the mould (Figure 4-11a). This was mainly due to the alternated spacing of the pillars. The electrostatic nature of the hemofiltration fibres, enforced by the addition of water to align the fibres in the mould, induced pairing. This caused the interspacing of 0.3 mm between the fibres to become smaller at the area where tape was applied after all fibres had been aligned. After tape application, the fibres had to be stretched before stacking. Fibres that paired up in the mould would regain an interspacing < 0.3 mm. This evidently resulted in a larger interspacing with their neighboured fibres. The result was a hemofiltration fibre mat with multiple fibre pairings (Figure 4-11b and Figure 4-11c), so it no longer matched the predetermined interspacing.

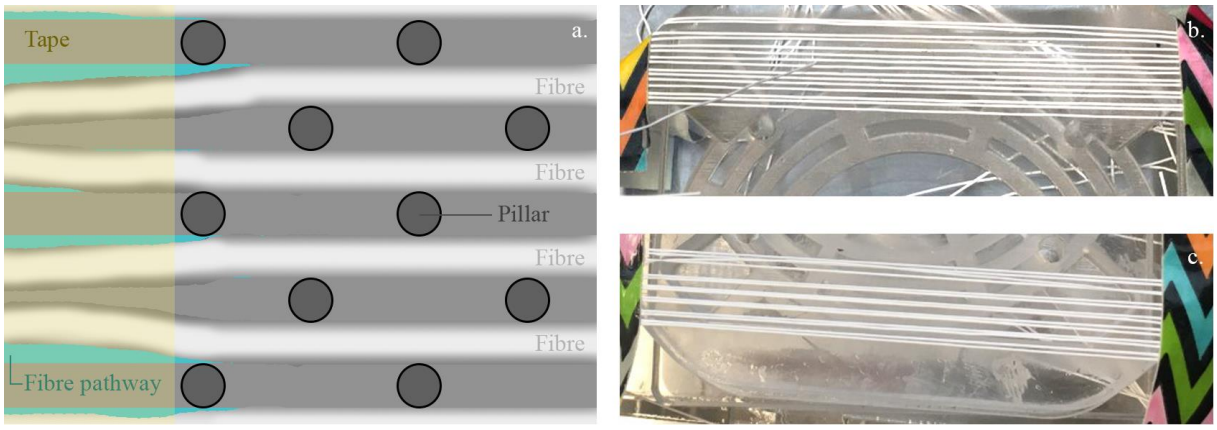


Figure 4-11: Fibre pairing a) where fibres are aligned by placing them between the alternately spaced pillars. Caused by the alternately spaced pillars and the electrostatic effect of the hemofiltration fibres enforced by water. The fibres pair up at the edge of the mould (and edge of the tape). Because of this phenomenon they deviate from the set fibre pathway. Once the tape is placed, the fibres are stretched and stacked upon a potting cap (b and c). It can then be seen that the fibres form pairs and the predefined interspacing is disregarded.

However, the pillars had to be interspaced due to the issues created by the 3D printer. E.g. printing the pillars in parallel would cause a film layer to form between the bottom part of the pillars Figure 4-12.

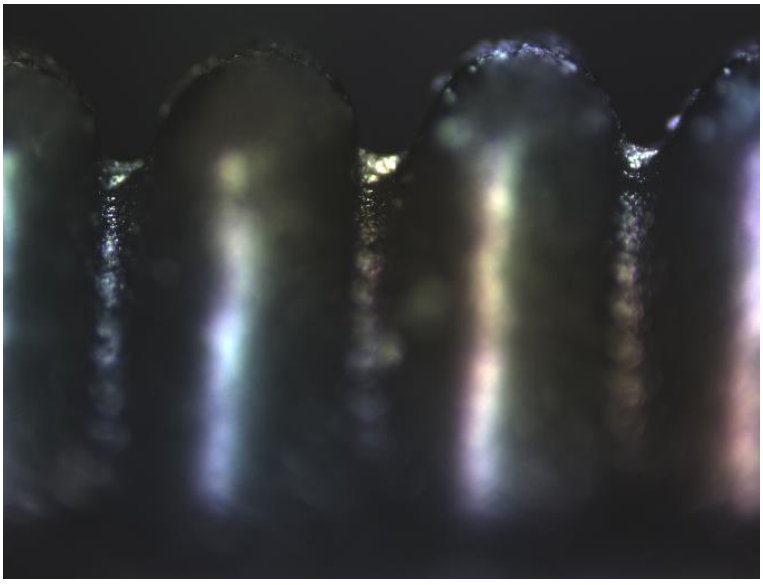


Figure 4-12: Parallel pillars with an aimed interspacing of 0.3 mm. A film layer formed between the pillars. The pillars and interspacing are also out of proportion as interspacing and pillar width should be equal.

This would prevent fibres to be placed between these pillars, thus hinder the creation of the fibre mats. Another issue was the use and application of the tape especially while using water, as water would prevent the tape from adhering to the fibres. On top of that, the lack of application tools seemed to alter the alignment of the fibres as the tape was non-uniformly stretched by hand to apply the fibre mat on the potting cap, thus altering the interspacing. All the old and the new problems had to be addressed to develop an adequate solution.

4.6.4 Optimized Segmented MBD

After several iterations an optimized version of the Segmented MBD was created as shown in Figure 4-13. Instead of using one-sided tape after fibre placement, this design made use of double-sided tape to prevent fibres from pairing. Simultaneously, it avoided the need to spray the fibres with water, because they would remain in place as soon as they adhered to the tape.

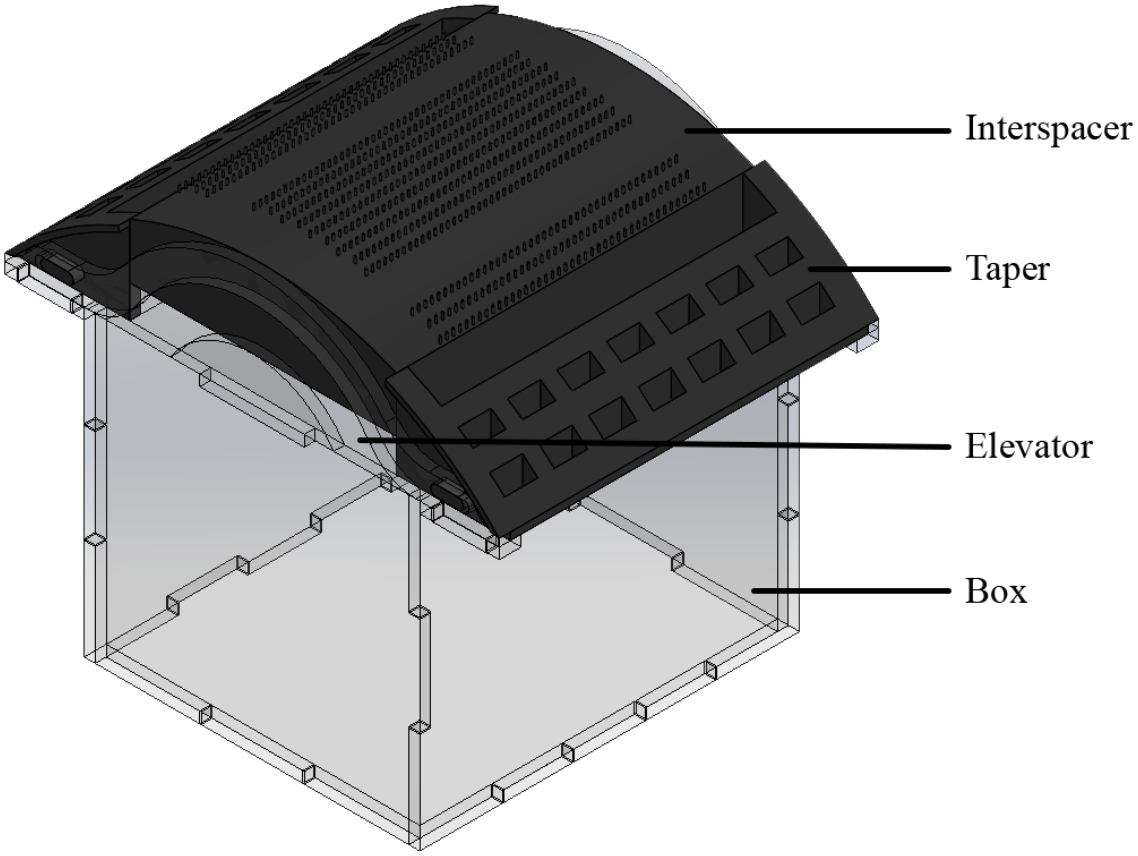


Figure 4-13: A render of the optimised prototype of the segmented MBD. The middle black part is the ‘interspacer’ and the outer black parts are the ‘tapers’. The elevator aligns the surfaces of the interspacer and the taper. The main part of the design rests on top of a box for easier fibre application as hands have now more vertical freedom.

To verify the new design, tests were carried out to check the accuracy of the hemofiltration fibre mats. Three fibre mats were created with this design and compared to a fibre mat created using the alignment method a1 (Table 4-1) and fixation method f2 (Table 4-3). Both moulds aimed at an interspacing of 0.3 mm, hence the reason for a comparison. With the new design it took about 30 minutes to create and stack a single hemofiltration fibre mat. This was longer than expected. It was observed that fibre placement in the middle of the interspacer was not as easy as fibre placement in the top and bottom of the interspacer. After a hemofiltration fibre was placed the double-sided tape kept it in position throughout the whole process. While stretching the hemofiltration fibre mats it was observed that not all fibres were

completely stretched (Figure 4-14a), thus the fibres were not in one horizontal layer (Figure 4-14b). Especially the middle part seemed to remain unstretched while the top and bottom parts were. When the fibres were further stretched by hand, they did seem to align similar to the top and bottom part of the hemofiltration fibre mat. This was undone as soon as the manual stretch was released. These newly identified issues also seemed to derive from the mould itself, and thus the issue originated from the printing process, as it could be seen (by the eye) that not all pillars were of equal height.

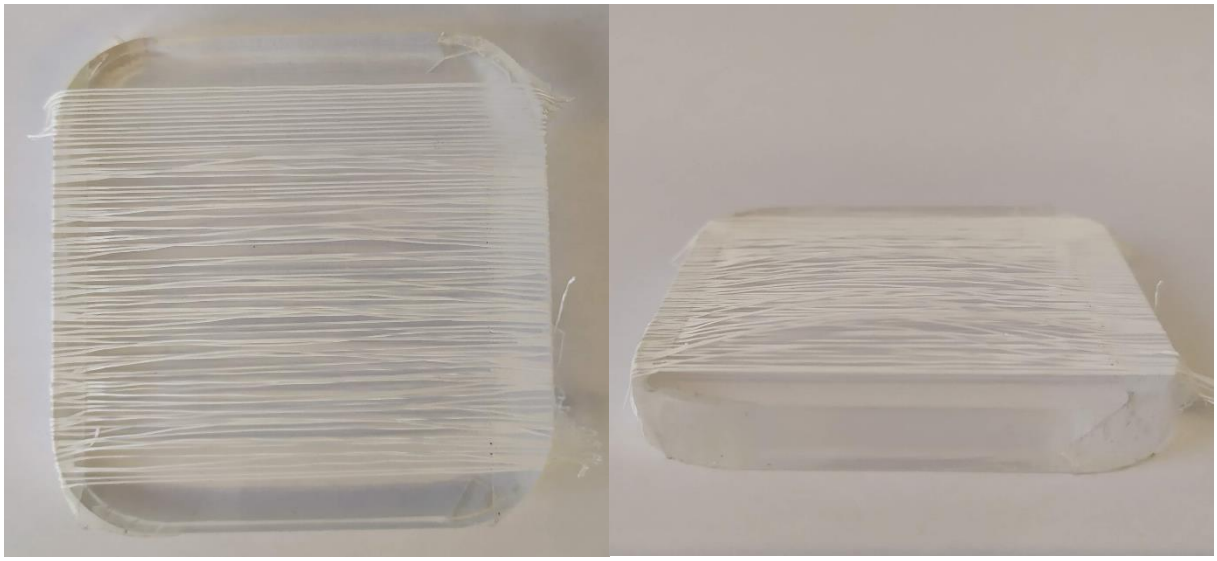


Figure 4-14: Stretched fibre mats with differentiating fibre lengths. The top view (a) show that the hemofiltration fibre mat lower part of the picture is not stretched. The mat in the upper part is stretched more appropriately. A front view (b) shows that the unstretched fibres are not located in the same horizontal layer as the stretched fibres.

To verify the suspected pillar deformation by the printer, the printed interspacers were analysed under the confocal microscope. In Figure 4-15a, pillars resembling the desired measurements for the mould are shown. In Figure 4-15b, it can be seen that the alternately spaced pillars were simplified by the 3D printer. This caused the pillars to gain a more triangular shape in the centre and at the edges of the mould. It also reduces the height of the pillars with the result that fibres are slightly elongated after placement.

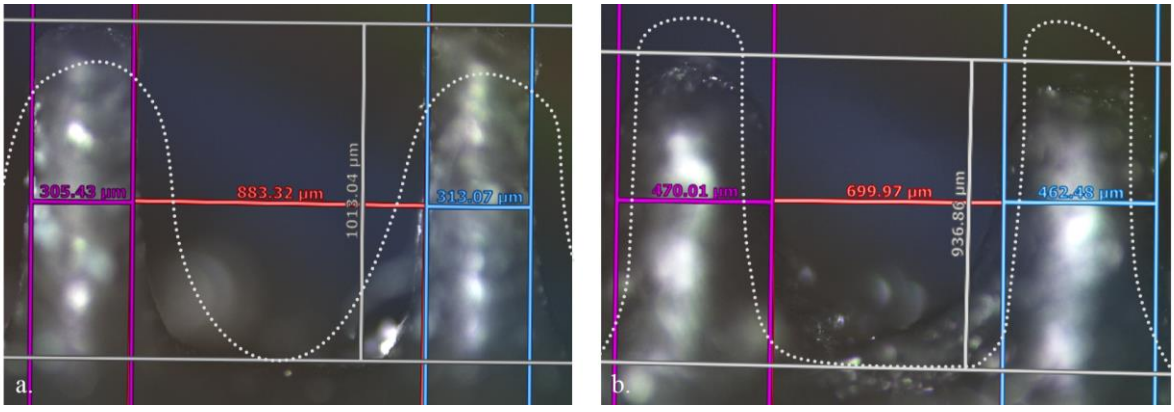


Figure 4-15: Pillar deformation by the Form2 SLA printer where a) shows a pillar that resemble the desired measurements (pillar width: 300 µm; height: 1000 µm; distance: 900 µm) and b) presents deformed pillars. Purple and blue measurements indicate the width of the pillar. Red measurements indicate the distance between the pillars in a single row. Grey measurements indicate the height of the pillars. The dotted line represents the contour of b in a and a in b.

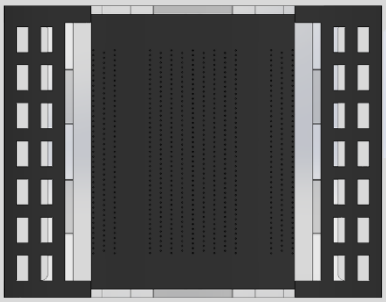
As a result, the area between the pillars decreased as the pillar width increased, making it harder to place the fibres up until the surface of the mould. This would indeed explain why not all fibres were in one horizontal layer after stretching as not all fibres were of equal length. When a fibre is slightly elongated,

a uniform stretch with fibres of the desired length would constrict these fibres from stretching. As shown, this mainly occurred at the middle part of the hemofiltration fibres, indicating a deformed middle part of the mould. This is most likely related to several 3D print parameters (e.g. print time, material thickness, or positioning) more present at the centre of the design. For the parts of the mould that were printed successfully, it seemed that stretching and placing the fibres was accurate.

The evaluate the "stretched" fibre mats, the Sensofar S Neox confocal microscope was used to analyse the interspacing of the stacked hemofiltration fibre mats. Before measurements were made it could already be concluded that the tape was a suitable fixation method. During measurements it became clear that not all parts of the fibre mat were measurable, due to unstretched fibres. Only (nearly) stretched fibres in the horizontal layer on top of the potting cap could therefore be analysed. The hemofiltration fibre mats were divided into four equal areas perpendicular to the fibres. The areas ran from tape edge to tape edge that were located on top of the potting cap. Each side line of these areas were analysed in three different spots. This resulted in a total of 15 obtained measurement points of each mat.

Table 4-8, shows that the mean interspacing obtained by the segmented MBD is more close to 0.3 mm than the mat created by mould a1-f2, indicating more control over the desired interspacing. The segmented MBD does however have a larger standard deviation than mould a1-f2. This is however expected to be caused by the deformations of the shape of the pillars on the interspacer generated by the SLA printer.

Table 4-8: Interspacing results of the created hemofiltration fibre mats.

	Mould a1-f2	**Segmented MBD**
		
Mean interspacing	261.97	285.92
Standard deviation	± 45.19	± 101.92

Based on the results that confirmed the deformation of pillars an attempt to improve the printability by reducing the size of the interspacer was made. Unfortunately, the printer was out of Black V4 resin, so the next best option, Clear V4 resin, was used and analysed. The results were quite surprising as the measurements of the smaller Clear V4 mould were far more accurate than measurements of the current (bigger) Black V4 Mould. As two variables changed (size and resin) it was decided to create another big mould but this time using the Clear V4 resin, so it could be determined which variable allowed for better results. Table 4-9 shows that both Clear V4 moulds are much closer to the desired measurements, except for the pillar height, and has general smaller standard deviations. As the height of the pillars is not crucial for the creation of the fibre mat, this result can be disregarded. This means that using Clear V4 resin for manufacturing the interspacer with the Form 2 SLA printer provided the best possible results.

Table 4-9: Measurements of different moulds and sizes.

Measurements (in µm)	Width pillar		Height pillar		Distance pillar	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Desired results	300	N/A	1000	N/A	900	N/A
Black V4 Mould (big)	374.10	± 49.30	976.28	± 61.84	813.25	± 56.86
Clear V4 Mould (big)	297.63	± 19.53	1080.39	± 30.25	902.22	± 19.58
Clear V4 Mould (small)	291.37	± 9.58	1120.52	± 28.63	909.32	± 13.22

4.6.5 Final Design

Based on the findings in Table 4-9, Clear V4 resin was used for the interspacer of the final design (see Figure 4-17 and Figure 4-18). This design was used for the creation of five hemofiltration fibre mats. These mats were required for the process of alternate stacking of the hemofiltration fibre mats and oxygenation fibre mats with the intend for potting. However, while creating the first mat it became clear that the newly printed mould was faulty (Figure 4-16a) as it can be seen that the pillar rows do not align. This mistake was made by the designer when the interspacer was altered. Due to the remaining time of the assignment, it was decided, in consultation with the supervisor, to continue to make the hemofiltration fibre mats for potting with the faulty design. This would still allow to see if the potting process of the combined membranes would work properly. In the meantime a new interspacer was manufactured (Figure 4-16b) and was used to create one final mat as a proof of concept. This mat was placed under the confocal microscope to determine its accuracy.

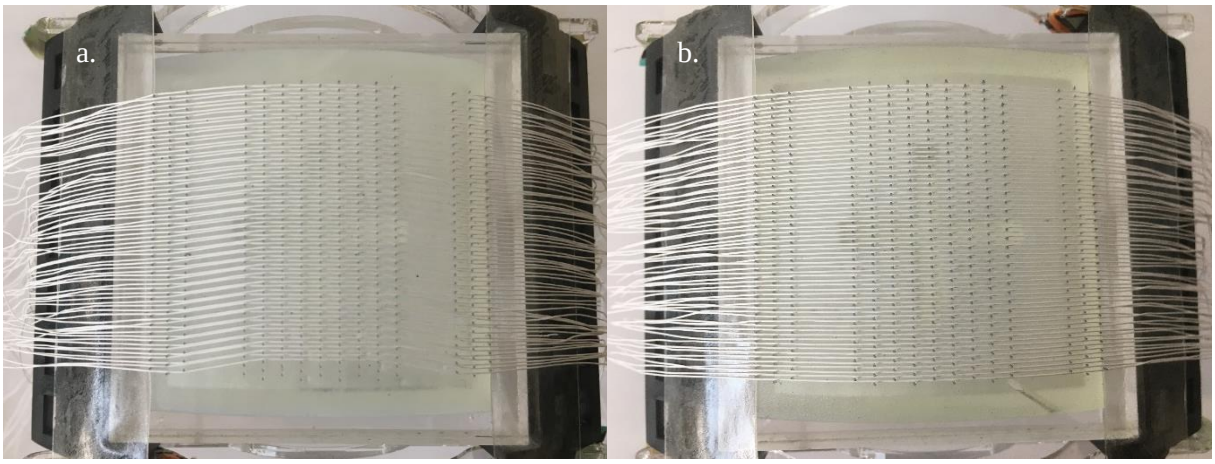


Figure 4-16: Final MBD with a) faulty interspacer and b) correct interspacer.

Mould Based Design (MBD)

Wytze Duinmeijer

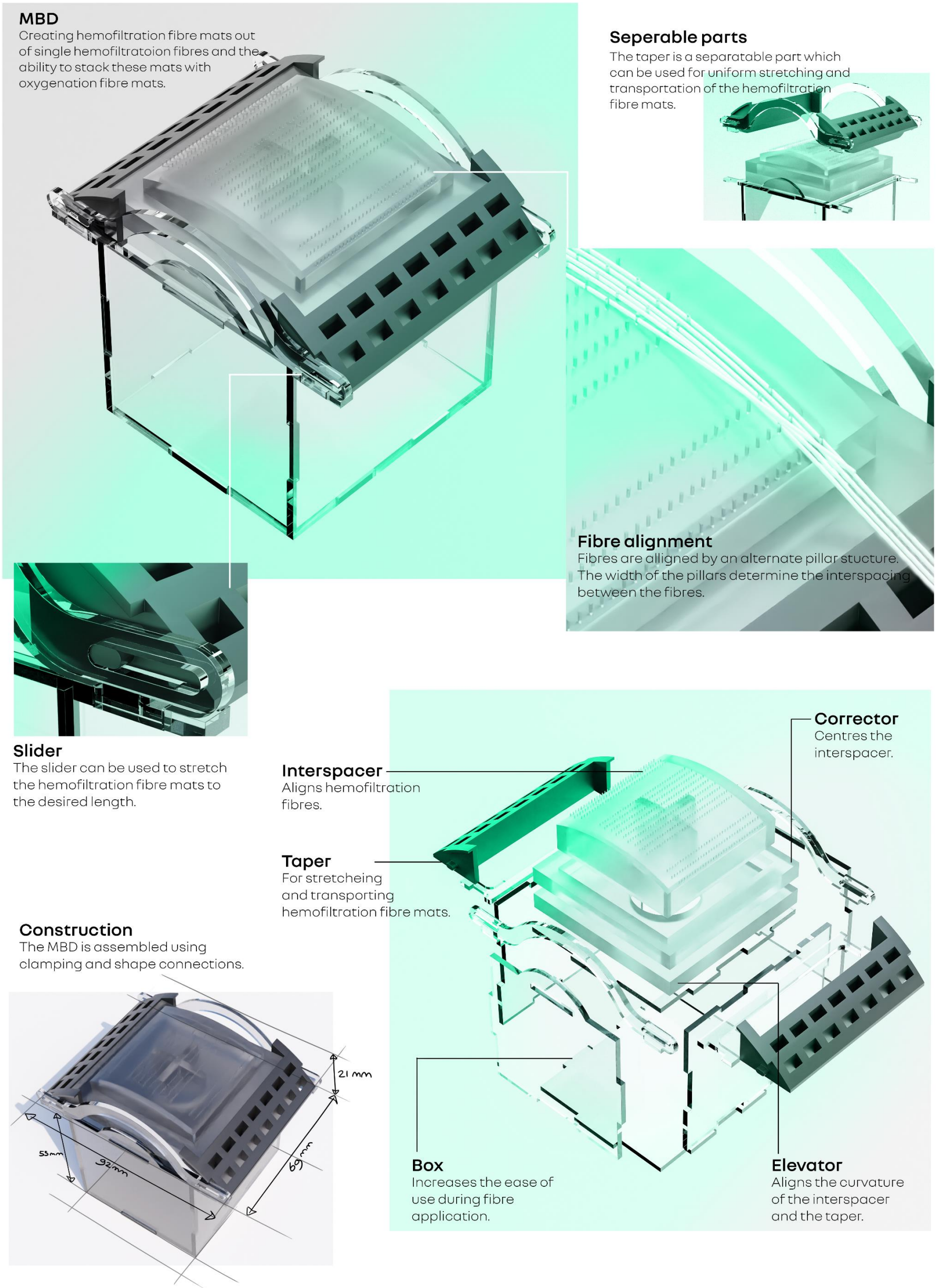


Figure 4-17: Final MBD design with general information about the design.

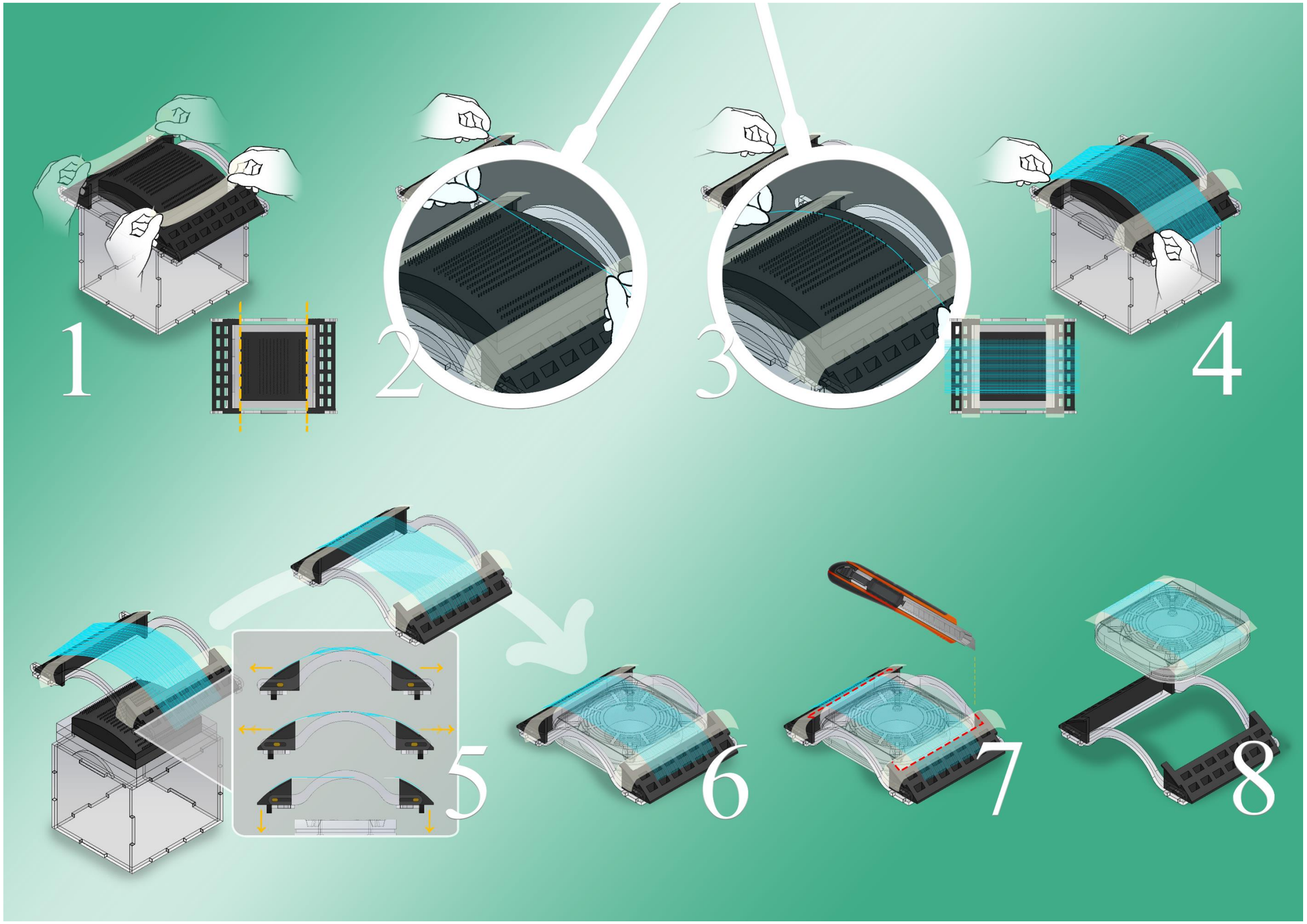


Figure 4-18: Manufacturing process of the finalized MBD design. 1) Double-sided tape is placed alongside the orange lines. 2) A fibre is stretched and curved around the interspacer (3) for alignment until the interspacer is full (4). The taper is then lifted from the box and slid outwards on both sides to stretch the fibres (5). The fibres are then placed on the potting cap (with or without oxygenation fibre mats in place) and fixated by the double-sided tape (6). Excessive tape is cut off using the shape of the taper (7). The fibres are not stretched on top of the potting cap (8) and alternately stacked with oxygenation fibre mats. The process is repeated until the desired fibre membrane bundle configuration is reached.

4.7 Fabrication and Testing

For this project, hemodiafiltration fibres from the ready-made product 3M™ Membrana™ PUREMA™ Capillary Membranes, type S were utilized. Each individual hemofiltration fibre was separated from the bundle to be (re-)used for the creation of a hemofiltration fibre mat. Afterwards, the created hemofiltration fibre mats had to be combined with 3M™ Membrana™ OXYPLUS™ Capillary Membrane mats (60 × 40 mm) using the squared potting technique developed by A.F. Martins Costa [23] to pot the oxygenation and hemofiltration fibre mat combination.

All designs were modelled in SolidWorks® (SW) 2021 student version. Laser cut parts were manufactured using the Trotec Speedy 300. SW-parts were converted to dxf-files and prepared in Adobe Illustrator® 2021. All continuous lines were first joined after which every line thicknesses was set to 0.05 mm. Cut lines were marked red (RGB 255) and engraving parts were marked black (RGB 000). Next, the file was directed to the laser cut machine software JobControl® 1.14 for the final laser cutting preparations. Print parts were manufactured using the Formlabs© Form 2 SLA printer. SW-parts for 3D printing were converted to STL-files. The Formlabs© PreForm 3.23.0 software was used to prepare the prints. The part was rotated in such a way that the contact area with the built platform was minimized. Support structures were automatically generated by the software using a full raft, touchpoint sizes of 0.60 mm, and a material density of 1.00 g/cm^3. The layer thickness was set to 0.050 mm and the layout of the part(s) is centred on the building platform. The file was then uploaded to the Form 2 SLA printer. Before the start of the print, the desired resin and tank were inserted. Thereafter, instructions given by the printer were followed and the print was started. After 3D printing, the parts were washed in the the Formlabs© Form Wash and cured in the Formlabs© Form Cure, using the advised setting by Formlabs©. Subsequently, the support structure was removed and the parts were sanded using P400 sandpaper wetted with water to remove the remaining support marks. All manufactured parts, both laser cut and 3D printed parts, were cleaned for 10 minutes using a VWR USC 600 TH ultrasonic cleaner filled with distilled water before assembling. Parts were assembled using shape fittings and clamping mechanism. In case clamping failed, tape could be used to fixate parts.

The final design consists of a total of 15 production parts, of which 12 parts are manufactured using the laser cutting machine. All laser cut parts were made of Poly(methyl methacrylate) (PMMA) and manufactured using the Trotec Speedy 300 laser cutting machine. Two of these 12 laser cut parts, the connector and elevator, have a 6 mm thickness and the rest has a thickness of 2 mm. The standardized Trotect laser settings for PMMA were used by assigning the correct thickness of the PMMA sheet. For the parts with d = 6 mm an additional double cut was applied. The other three parts were created using the Formlabs© Form 2 SLA printer. The interspacer was created with Clear V4 resin. The other two parts (the tapers) were created using Black V4 resin.

After assembly, the following general production steps were followed to produce a fiber mat made of hemofiltration fibres: Tesa® double sided transparent photo strip tape (width = 15 mm; thickness = 0.16 mm) is applied in vertical direction, along the pillars of the interspacer and over the taper, on both sides (Figure 4-18.1). Hemofiltration fibres are then individually placed in each row (Figure 4-18.2 and (Figure 4-18.3) until the interspacer is full (Figure 4-18.4). The potting cap (with stacked fibre mats) could be placed upon an elevator of 50 × 50 × 100 mm for convenience. The taper is then lifted from the box and the interspacer is carefully removed (Figure 4-18.5). Subsequently, the hemofiltration fibre mat is stretched and stacked upon the potting cap/oxygenation fibre mats (Figure 4-18.6). Excess tape and fibres are removed by a 9 mm retractable blade knife along the inner shape of the tapers (Figure 4-18.7) resulting in a hemofiltration fibre mat with the desired predefined interspacing (Figure 4-18.8).

Finally, an oxygenation fibre mat, if desired, can be stacked perpendicular to the hemofiltration fibre mat using double sided tape. This process needs to be repeated until the desired combined oxygenation and hemofiltration fibre membrane is achieved. The potting cap, with the combined oxygenation and hemofiltration fibre membrane, is then placed inside the potting device for potting according to the protocol of A.F. Martins Costa [23].

The Sensofar© S Neox confocal microscope (EPI 10X) was used to analyse the interspacing of the final hemofiltration fibre mats. The mat was divided into several segments on which different spots were analysed as shown in Figure 4-19. With the Sensofar© SensoSCAN 6.5 software the interspacing and depth of the fibres were measured using the annotations tool. The mean and standard deviation were then calculated to determine the accuracy of the mat.

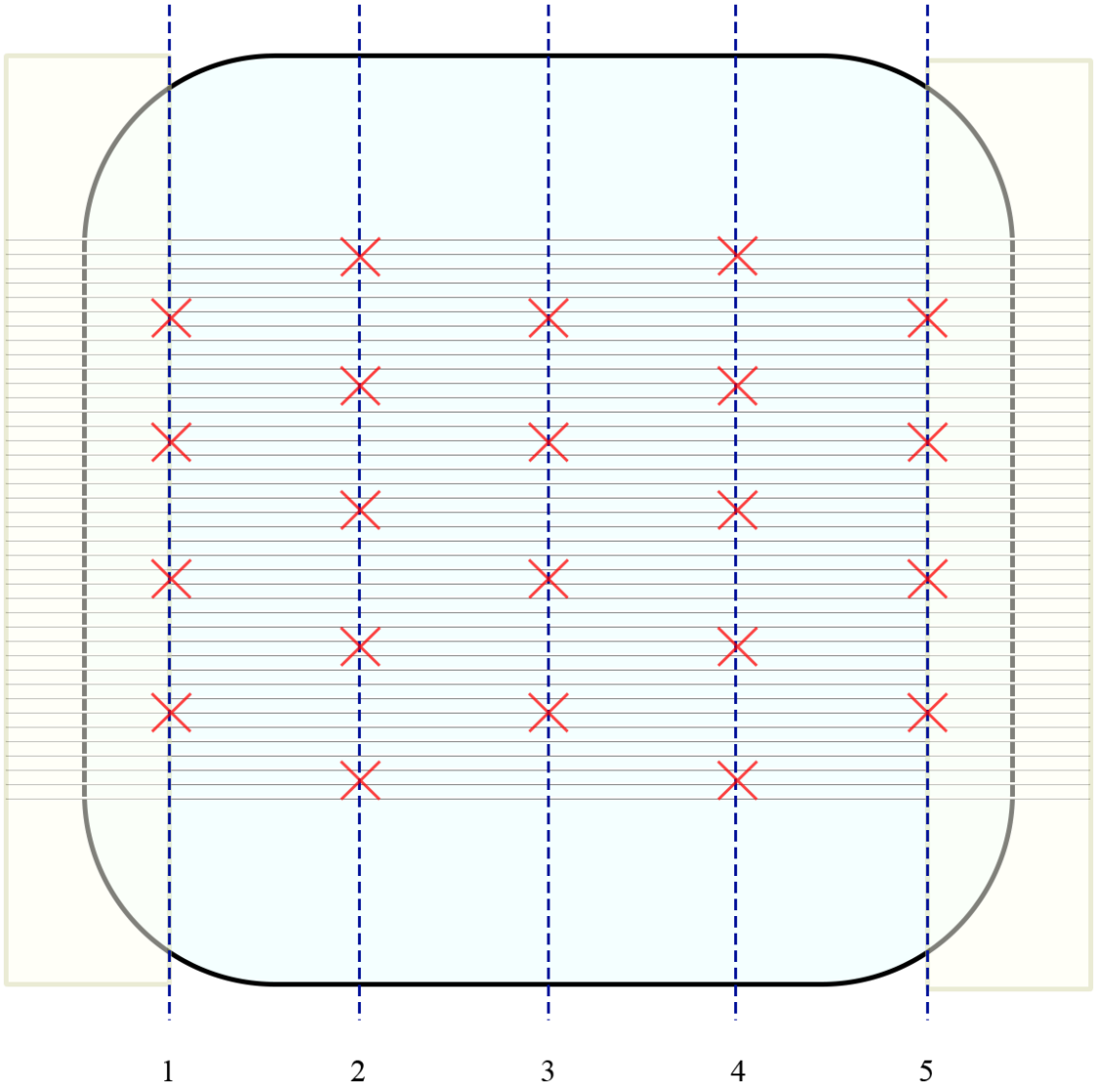


Figure 4-19: Analysis of the interspacing of the hemofiltration fibre mats. The five (imaginary) lines are drawn up starting and ending on the inner tape edge(s). The odd numbered lines were analysed on 4 spots and the even numbered lines were analysed on 5 spots of the line.

5 Results

Results of the final (combined) hemofiltration fibre mat will be presented down below. In the text, the used method will be referred to. Results and its limitations will be further discussed in the Discussion chapter.

5.1 Hemofiltration fibre mat

For the creation of the hemofiltration mat for proof of concept, the finalized design was used (section 4.6.5) with the correct interspacer (Figure 4-16b). After aligning all the hemofiltration fibres (Figure 5-1a) it could be seen that hemofiltration fibres were all neatly placed along the surface (Figure 5-1b). For stacking, the fibres needed to be stretched and placed upon a potting cap (Figure 5-1c). While stacking, all fibres appeared to be in one horizontal layer (Figure 5-1d). After stacking and removal of excess tape and fibres, the fibres remained in a single horizontal layer on top of the potting cap (Figure 5-1e). The fibres seemed stretched and the alignment was present but there were two parts in the fibre mat which were slightly altered (Figure 5-1f).

The created hemofiltration fibre mat was analysed under the confocal microscope and compared to the previously created hemofiltration fibre mat of the segmented MBD (from section 4.6.4). Table 5-1 shows that the mean of the final mould is about as close to 300 µm as the previous design but the standard deviation decreased by 56.41 µm. This suggests that the final mould is more accurate than its predecessor. No visual damages to the fibres itself were observed. The irregularities (Figure 5-1f, red squares) were clustered fibres (Figure 5-1g), which caused an altered interspacing of the involved fibres.

Table 5-1: Interspacing results in µm of the created hemofiltration fibre mats comparing the segmented MBD with the final mould.

(in µm)	**Segmented MBD**	**Final mould**
Mean	285.92	318.26
Standard deviation	± 101.92	± 45.51

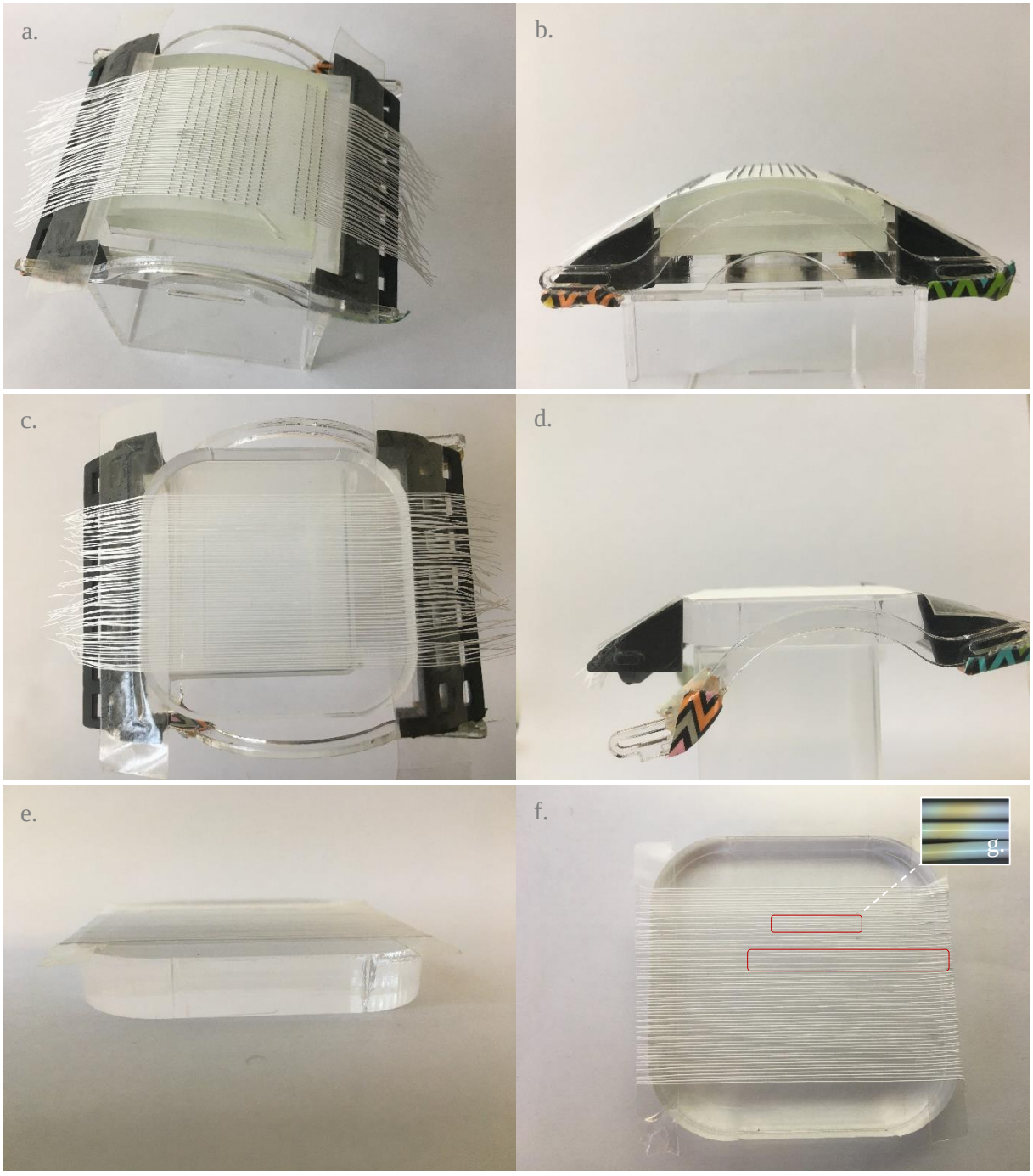


Figure 5-1: Process of the creation and stacking of a hemofiltration fibre mat with the finalized MBD. The hemofiltration fibre membranes are aligned in the mould (a) and curved along the surface (b). The mat is then stretched and placed upon the potting cap (c) where the fibres remain in one horizontal layer (d). After removal of the excess tape and fibres, fibres remained in one horizontal layer on top of the potting cap (e). The alignment of the hemofiltration fibre mat (f) with two irregularities (f, red squares). These irregularities are clustered hemofiltration fibre membranes (g) disrupting the alignment.

5.2 Potting

For the potting, hemofiltration fibre mats created with the final mould (section 4.6.5) and the faulty mould (Figure 4-16a), were used. After a mat was created it was alternately stacked with an oxygenator fibre mat upon the potting cap, see Figure 5-2.

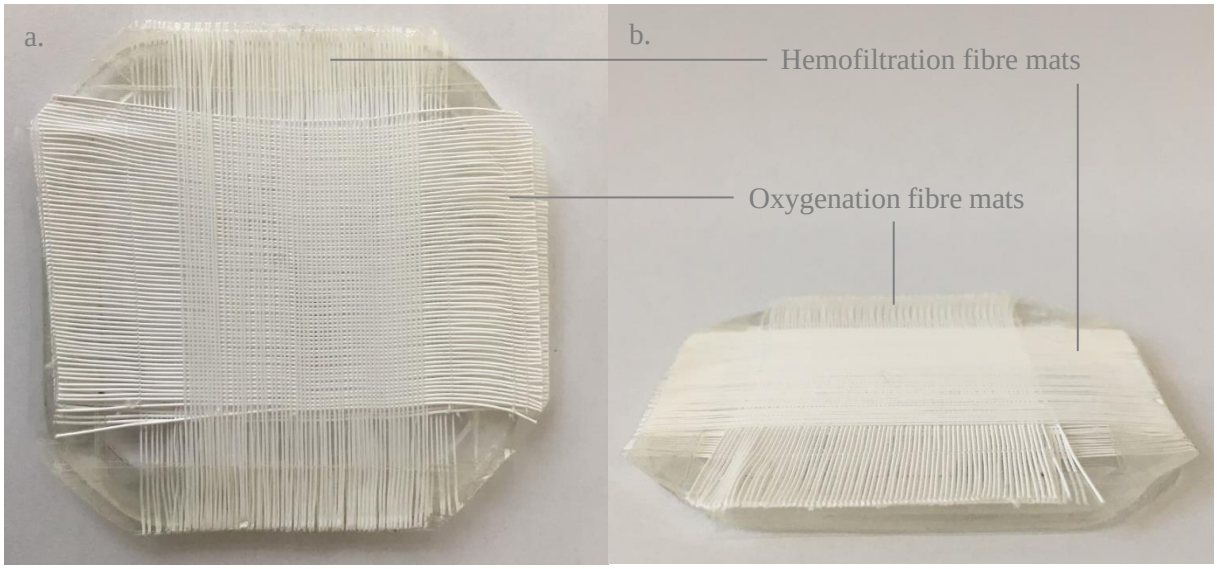


Figure 5-2: Alternately stacking of hemofiltration fibre mats with oxygenation fibre mats on a potting cap. Top view (a) of stacked hemofiltration fibre mats with oxygenation fibre mats. Front view (b) of the combined oxygenation (vertical) and hemofiltration (horizontal) fibre mats.

A combined membrane with a total of nine fibre mat layers containing five hemofiltration fibre mats and four oxygenation fibre mats was created. The combined fibre mat bundle, fixated with double sided tape, was potted using the squared potting technique developed by A.F. Martins Costa [23]. The potted membrane could be removed from the potting device and appeared to be stacked properly (Figure 5-3a). The tape and the taped fibre membranes remained in position and the fixation method did not prevent an even distribution of the silicone (Figure 5-3b). Due to the use of the faulty mould it was unclear and could not be determined whether the hemofiltration fibres remained in the same position. After cutting off the edges, both the oxygenation (Figure 5-3c) and hemofiltration fibres (Figure 5-3d) were open on visual inspection.

Figure 5-3: A potted combined oxygenation and hemofiltration fibre membrane bundle. Uncut top view (a) and bottom view (b). After cutting the oxygenation fibres (c) and hemofiltration fibres (d) were open on visual inspection.

6 Discussion

The results from Table 5-1 indicate that the current manufacturing technique for the creation of hemofiltration fibre mats is more accurate than its predecessor and adequate for its purpose. The mean interspacing approaches the target of 300 µm and is consistent with a standard deviation of 45.51 µm. Unfortunately, an interspacing < 300 µm was not possible to achieve due to the limitations of the Form 2 SLA printer. However, a printer of our project partner in at the Department of Cardiovascular Engineering, Institute of Applied Medical Engineering, RWHT Aachen University (a Stratasys Objet350 Connex3) might be able to manufacture moulds with a smaller interspacing. Future research should show what the possibilities are and whether this would accommodate the printing of a mould with varying density and an interspacing < 0.3 mm. As for the standard deviation, even though the standard deviation in the finally produced fibre mat was significantly smaller compared to the previously produced ones, it is still five times as big as the deviation measured in the oxygenation fibre mats of 3M™ Membrana™ (≈ 6.1 µm). However, the current measurements are based on just one hemofiltration fibre mat. Increasing the quantity of the analysed hemofiltration fibre mats, to e.g. 10, might already alter the results.

The accuracy is also already compromised by irregularities seen in the final hemofiltration fibre mat. Even though it is only present in two parts of it (see Figure 5-1f and g), it could still have a negative effect on the efficiency and therefore the patient: When blood is passing through the combined membrane, a change in fibre distance can alter the flow path and increase stress on the blood cells, thus increasing the chance of blood coagulation or cell damage. These irregularities in fibres alignment might originate from the fact that the hemofiltration fibres are only fixated at the ends. A chain-stitch based design (CBD), like concept 6 (Figure 4-9) would secure interspacing over the total length of the fibre, thus possibly preventing this problem. This technique is also currently used in the 3M™ Membrana™ OXYPLUS™ Capillary Membranes. Mimicking this design, like the CBD, could guarantee a more accurate and more reliable manufacturing process.

The alternative of using a CBD method would also make stretching the fibres superfluous. As stretching might cause damage (invisible to the eye) to the hemofiltration fibre mats, this step could potentially harm the efficiency and thus the patients. As this was not tested during the project, it should be investigated in the future. In any way, removing the stretch step from the manufacturing process will decrease the risk of damaging the fibres while creating a hemofiltration fibre mat, thus improving safety.

Not only would it help to increase accuracy and safety of the hemofiltration fibre mats it might also aid the stability of the combined fibre mat during potting. Even though the silicone was able to reach all the parts of the combined fibre membrane, the rotational forces could have altered the alignment of the hemofiltration fibres. This could not be tested during this project as a faulty mould was used to create the hemofiltration fibre mats used for potting and the potting test could not be repeated due to time restrictions. Subsequent research should determine whether potting further compromises the alignment of the hemofiltration fibre mats.

The faulty mould was a result of human error in the creation of the 3D model. As these types of errors are often too small for the eye, an aid for either error detection or prevention could help. For the latter, this could e.g. be done through the use of algorithmic modelling. This would allow the user to design and create a new 3D model by editing certain predetermined parameters such as interspacing. However, as this manufacturing technique is a mostly manual process it can be said that in general this method is prone to human error. Errors could basically occur throughout the whole process (e.g. during 3D modelling, 3D printing, fibre placement, stretching, and/or taping). Providing the user with a protocol might reduce the occurrence of errors but it does not eliminate them entirely. Therefore, increasing automation

of the manufacturing process would be more beneficial to the result. Creating a crochet like machine to stitch the fibres together would already reduce the user's involvement during the manufacturing process. This way the mats would be manufactured by the machine and for stacking there would be no need for stretching as the fibre mats are aligned neatly without stretching. The stacking process would then be more similar to the current process of solely stacking oxygenation fibre mats, which is a proven method and thus, result in a more reliable manufacturing method.

In the long run, a CBD oriented design will also be easier to adapt to an industrialized manufacturing process in contrast to the MBD design. The industrialized process will likely correspond to the current manufacturing technique used to produce 3M™ Membrana™ OXYPLUS™ Capillary Membranes.

All things considered, the manufacturing process developed in this study suffices, but still has a number of teething problems to look into and/or overcome if it is to be used for blood testing. Therefore, it is hypothesized that a more automated chain-stitch based design might overcome all of these problem and is therefore a more suitable solution, both now and in the future.

7 Summary and Outlook

Patients suffering (primary) from acute respiratory failure, elusive for conventional therapy such as mechanical ventilation, require additional lung support as a bridge to recovery. An extracorporeal membrane oxygenator (ECMO) can be used for this purpose as the device is connected to the bloodstream and not directly to the lungs. This reduces the stress on the lungs which allows for recovery. The oxygenator is the main part of the ECMO and consists of a network of small hollow permeable fibre membranes filled with continuously flowing oxygen-enriched air. As blood flows around the membranes, a partial pressure difference occurs at the boundary layer of the fibres, causing oxygen and carbon dioxide to diffuse.

Due to the lung-kidney crosstalk, acute kidney injury is a complication in ca. 70 % of the patients undergoing ECMO therapy. Simultaneously using an artificial lung and kidney increases the foreign surface area, which is a known trigger for the coagulation cascade, which could lead to serious consequences for the patient (e.g. stroke or death). An ideal solution would therefore be to have a single device for combined pulmonary and renal support. This does however not yet exist. The RenOx project aims at developing such a device but is in need of hemofiltration fibre mats to do so. As these are currently not commercially available, they have to be fabricated out of commercially available hemofiltration fibre bundles. The individual fibres must be separated from the bundle and then aligned at a specific distance to each other.

During the project a manual fabrication method was designed to create these hemofiltration fibre mats with a predefined interspacing and the ability to stack them with oxygenation fibre mats. Based on an iterative process of design and testing a mould-based design was developed.

The final design is a curved mould with alternately spaced pillars for fibre application. The design is able to create hemofiltration fibre mats of 60 × 40 mm with an interspacing between the hemofiltration fibres of 0.3 mm. Double-sided tape was used to fixate the aligned hemofiltration fibres, thus creating a mat. The other side of the double-sided tape was used to stack the hemofiltration fibre mats. This was done by removing the interspacer from the mould, stretching out the fibres, and placing the tape on top of a layer of oxygenation fibre mats. After stacking a sufficient amount of these alternating layers the membranes were potted, resulting in an oxygenation and hemofiltration fibre mat combination.

The V-model was partly applied for the development process. To guarantee the safety of the design, a risk analysis was carried out to identify production-related risks. These risks were then addressed by specifying appropriate design requirements as countermeasures. Due to these precautions the final design satisfies its purpose and provides an adequate and timely solution to the problem.

However, the designed manufacturing process also contains steps which are prone to (human) error. These problems need to be researched further to determine how they affect the results and whether this affects usability of the results. Therefore, it would be wise to test the final results of the hemofiltration fibre mats with a higher quantity to determine its accuracy based on the mean interspacing and its

standard deviation. These same mats also need to be analysed for alternations in alignment and it should be determined if (and how) these alternations would affect the efficiency of the combined fibre membrane. Another test to research whether the stacked hemofiltration fibre mats retain their interspacing after potting should be carried out. These results also influence the assessment of whether the method is adequate for the intended purpose. In case the hemofiltration fibre mats do not retain the predefined interspacing, it is a problem to be solved before it can be used for blood testing. Furthermore, a test to identify if the manufacturing process damaged the hemofiltration and oxygenation fibre membranes needs to be performed. Given all the aforementioned results have a positive outcome, the mould manufactured by the printer in Aachen should be analysed to find out if an interspacing < 0.3 mm is feasible with this technique. This should then also allow an interspacing with a locally varying density between hemofiltration fibres.

As several problems mentioned above might already be solved by applying a chain-stitch based design instead, it would be well worth exploring this option further.

8 Terms and Abbreviations

- AKI – acute kidney injury
- ARDS – acute respiratory distress syndrome
- BE – Biomechanical engineering
- CBD – chain-stitch based design
- CO_2 – carbon dioxide
- DRS – design requirement specifications
- DVVP – design verification and validation plan
- ECMO – extracorporeal membrane oxygenation
- EOST – Engineering Organ Support Technologies (research group)
- IP – inventive principles
- ISO – International organization for standardization
- MBD – mould based design
- O_2 – oxygen
- RIA – risk analysis
- RCA+ – Root Conflict Analysis
- RRT – renal replacement therapy
- SLA – Stereolithography
- SW – SolidWorks®
- TRIZ – Russian acronym for the “theory of inventive problem solving”.
- URS – user requirement specifications
- UT – University of Twente
- VA – veno-arterial
- VV – veno-venous

9 List of Figures

In case a figure is not sourced, the figure has been created by W.C. Duinmeijer.

10 List of Tables

11 References

[1] W. L. Kenney, J. H. Wilmore, and D. L. Costill, "Physiology of Sport and Excercise," in *Physiology of Sport and Excercise*, K. Maurer Ed., 6th ed.: Human Kinetics, 2015, pp. 448-503.

[2] E. N. Marieb and K. Hoen, "Human Anatomy & Physiology," in *Human Anatomy & Physiology*, vol. 9th, S. Beauparlant Ed., 9th ed. New York City: Pearson Education, 2013, pp. 803-849.

[3] G. Rawal, S. Yadav, and R. Kumar, "Acute Respiratory Distress Syndrome: An Update and Review," *J Transl Int Med*, vol. 6, no. 2, pp. 74-77, Jun 2018, doi: 10.1515/jtim-2016-0012.

[4] A. J. Doyle and B. J. Hunt, "Current Understanding of How Extracorporeal Membrane Oxygenators Activate Haemostasis and Other Blood Components," (in English), *Front Med-Lausanne*, vol. 5, Dec 12 2018, doi: ARTN 35210.3389/fmed.2018.00352.

[5] T. V. Brogan, L. Lequier, R. Lorusso, G. MacLaren, and G. Peek, *Extracorporeal Life Support: The ELSO Red Book*, 5th ed. Michigan: Extracorporeal Life Support Organization, 2017.

[6] J. Arens *et al.*, "Toward a Long-Term Artificial Lung," *ASAIO J*, vol. 66, no. 8, pp. 847-854, Aug 2020, doi: 10.1097/MAT.0000000000001139.

[7] R. A. Incalzi *et al.*, "Chronic renal failure: a neglected comorbidity of COPD," *Chest*, vol. 137, no. 4, pp. 831-7, Apr 2010, doi: 10.1378/chest.09-1710.

[8] B. Gjerde, P. S. Bakke, T. Ueland, J. A. Hardie, and T. M. Eagan, "The prevalence of undiagnosed renal failure in a cohort of COPD patients in western Norway," *Respir Med*, vol. 106, no. 3, pp. 361-6, Mar 2012, doi: 10.1016/j.rmed.2011.10.004.

[9] C. Sorino, N. Scichilone, C. Pedone, S. Negri, D. Visca, and A. Spanevello, "When kidneys and lungs suffer together," *J Nephrol*, vol. 32, no. 5, pp. 699-707, Oct 2019, doi: 10.1007/s40620-018-00563-1.

[10] J. T. Kielstein *et al.*, "Renal function and survival in 200 patients undergoing ECMO therapy," *Nephrol Dial Transplant*, vol. 28, no. 1, pp. 86-90, Jan 2013, doi: 10.1093/ndt/gfs398.

[11] S. K. Gadepalli, D. T. Selewski, R. A. Drongowski, and G. B. Mychaliska, "Acute kidney injury in congenital diaphragmatic hernia requiring extracorporeal life support: an insidious problem," *J Pediatr Surg*, vol. 46, no. 4, pp. 630-635, Apr 2011, doi: 10.1016/j.jpedsurg.2010.11.031.

[12] C. Y. Lin *et al.*, "RIFLE classification is predictive of short-term prognosis in critically ill patients with acute renal failure supported by extracorporeal membrane oxygenation," *Nephrol Dial Transplant*, vol. 21, no. 10, pp. 2867-73, Oct 2006, doi: 10.1093/ndt/gfl326.

[13] A. H. Smith, D. C. Hardison, C. R. Worden, G. M. Fleming, and M. B. Taylor, "Acute renal failure during extracorporeal support in the pediatric cardiac patient," *ASAIO J*, vol. 55, no. 4, pp. 412-6, Jul-Aug 2009, doi: 10.1097/MAT.0b013e31819ca3d0.

[14] X. Yan *et al.*, "Acute kidney injury in adult postcardiotomy patients with extracorporeal membrane oxygenation: evaluation of the RIFLE classification and the Acute Kidney Injury

Network criteria," *Eur J Cardiothorac Surg,* vol. 37, no. 2, pp. 334-8, Feb 2010, doi: 10.1016/j.ejcts.2009.07.004.

[15] G. M. Fleming *et al.*, "A multicenter international survey of renal supportive therapy during ECMO: the Kidney Intervention During Extracorporeal Membrane Oxygenation (KIDMO) group," *ASAIO J,* vol. 58, no. 4, pp. 407-14, Jul-Aug 2012, doi: 10.1097/MAT.0b013e3182579218.

[16] S. Hughes, I. Szeki, M. J. Nash, and J. Thachil, "Anticoagulation in chronic kidney disease patients-the practical aspects," *Clin Kidney J,* vol. 7, no. 5, pp. 442-9, Oct 2014, doi: 10.1093/ckj/sfu080.

[17] P. D. Robinson, R. C. Shroff, and H. Spencer, "Renal complications following lung and heart-lung transplantation," *Pediatr Nephrol,* vol. 28, no. 3, pp. 375-86, Mar 2013, doi: 10.1007/s00467-012-2200-2.

[18] M. P. Gallagher *et al.*, "Long-term cancer risk of immunosuppressive regimens after kidney transplantation," *J Am Soc Nephrol,* vol. 21, no. 5, pp. 852-8, May 2010, doi: 10.1681/ASN.2009101043.

[19] I. Rama and J. M. Grinyo, "Malignancy after renal transplantation: the role of immunosuppression," *Nat Rev Nephrol,* vol. 6, no. 9, pp. 511-9, Sep 2010, doi: 10.1038/nrneph.2010.102.

[20] unknown, University of Twente.

[21] B. Wiegmann, A. Maurer, R. Zhang, P. Zardo, A. Haverich, and S. Fischer, "Combined pulmonary and renal support in a single extracorporeal device," *ASAIO J,* vol. 59, no. 4, pp. 433-8, Jul-Aug 2013, doi: 10.1097/MAT.0b013e318292e887.

[22] M. Hormes, R. Borchardt, I. Mager, T. S. Rode, M. Behr, and U. Steinseifer, "A validated CFD model to predict O(2) and CO(2) transfer within hollow fiber membrane oxygenators," *Int J Artif Organs,* vol. 34, no. 3, pp. 317-25, Mar 2011, doi: 10.5301/ijao.2011.6494.

[23] A. F. Martins Costa, "Fiber Potting," University of Twente, Work instruction, 2022.

[24] W. F. Gillis *et al.*, "Carbon fiber on polyimide ultra-microelectrodes," *J Neural Eng,* vol. 15, no. 1, p. 016010, Feb 2018, doi: 10.1088/1741-2552/aa8c88.

[25] N. C. Mat, Y. Lou, and G. G. Lipscomb, "Hollow fiber membrane modules," *Current Opinion in Chemical Engineering,* vol. 4, pp. 18-24, 2014, doi: 10.1016/j.coche.2014.01.002.

[26] U. Baurmeister, "Woven Hollow Fiber Double Weft Tape With Knitted Selvedge," Patent Appl. 654,596, 1991.

[27] J. Tretzel, "Hohlfadenmodul zum Abtrennen von Gas," Germany, 1990.

[28] P. Riesop and A. Wodetzki, "Holhfadenmatte," Germany Patent Appl. 4308850, 1994.

[29] S. Suzuki, T. Torigai, A. Ueno, and S. Nakahara, "HF Sheet," Japan, 2006.

[30] S. Suzuki, S. Nakahara, and I. Kinoshita, "Membrane Knitting Device," Japan, 2006.

[31] H. Yamamori, A. Hoshide, and M. Kobayashi, "Hollow Fiber Membrane Module," United States of America Patent Appl. 09/088,681, 1998.

[32] GV, "The Design Sprint," ed, 2019.

[33] *3D Printing: Manual Guide*.

[34] Y. Salamatov, V. Souchkov, Ed. *TRIZ: The Right Solution At The Right Time: A Guide to Innovative Problem Solving*. Insytec B.V., 1999.

12 Annex

12.1 Annex A: TRIZ Innovation Method

Mould Based Design	Hemofiltration fibres	Oxygenation fibre mat(s)	SLA mould	Stacking base	Tape	Cleaning station	Curing station	Hand(s)	Plier	Potting device	SLA printer	Super sonic cleaning	Water
Hemofiltration fibres		◆◆	◆◆	◆◆	◆◆			◆◆	◆◆	◆			◆◆
Oxygenation fibre mat(s)	◆◆			◆	◆◆			◆◆		◆			◆
SLA mould	◆◆				◆◆	◆◆	◆	◆◆	◆◆		◆◆	◆◆	◆◆
Stacking base	◆◆	◆			◆◆			◆◆		◆			◆◆
Tape	◆◆	◆◆	◆◆	◆◆				◆◆		◆◆			◆
Cleaning station			◆◆					◆					
Curing station			◆					◆					
Hand(s)	◆◆	◆◆	◆◆	◆◆	◆◆	◆	◆		◆◆	◆	◆	◆	◆
Plier	◆◆		◆◆					◆◆					◆
Potting device	◆	◆		◆	◆◆			◆					◆
SLA printer			◆◆					◆					
Super sonic cleaning			◆◆					◆					◆
Water	◆◆	◆	◆◆	◆◆	◆			◆	◆	◆		◆	

Table 12-1: Interaction matrix of the mould based design. Blue diamonds are positive interactions and red diamonds are negative interactions.

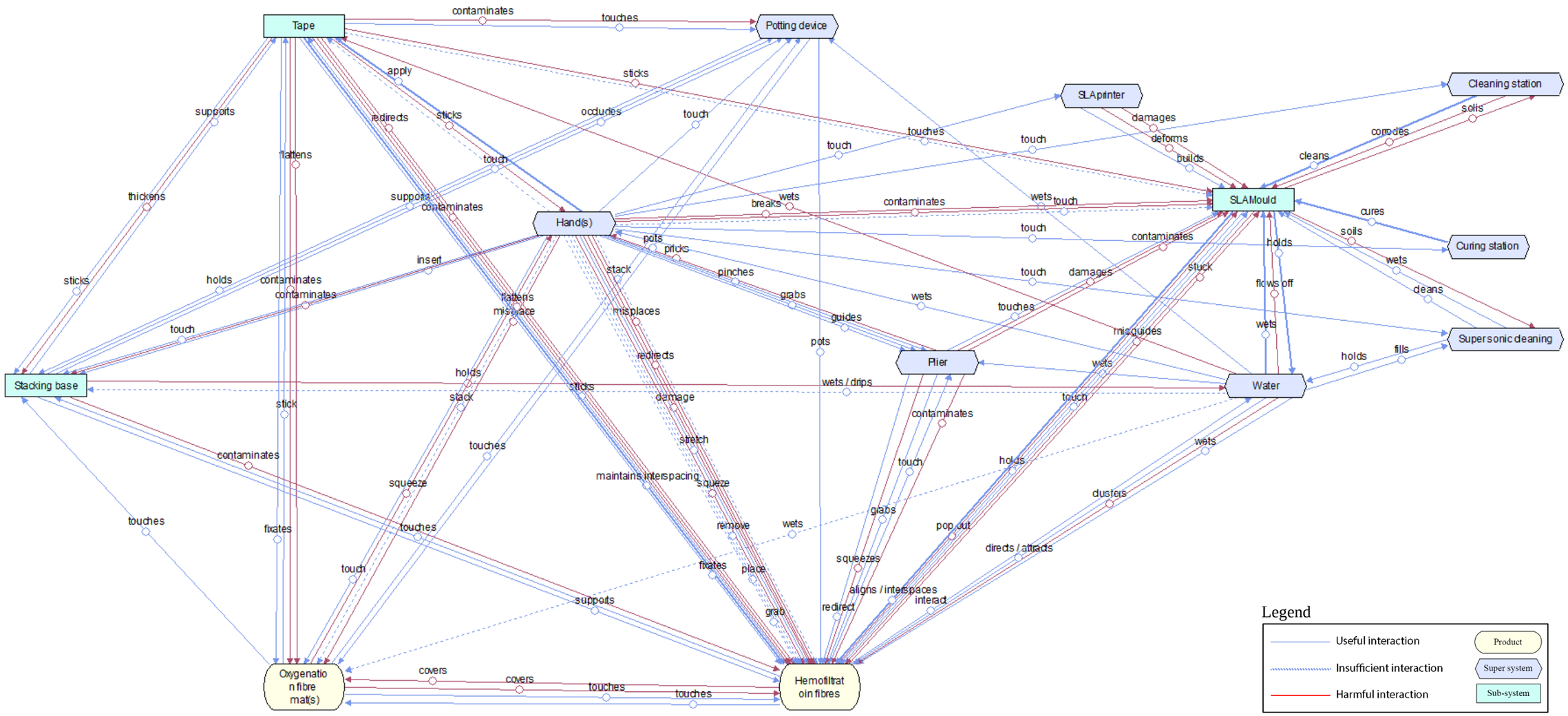


Figure 12-1: Function analysis of the mould based design.

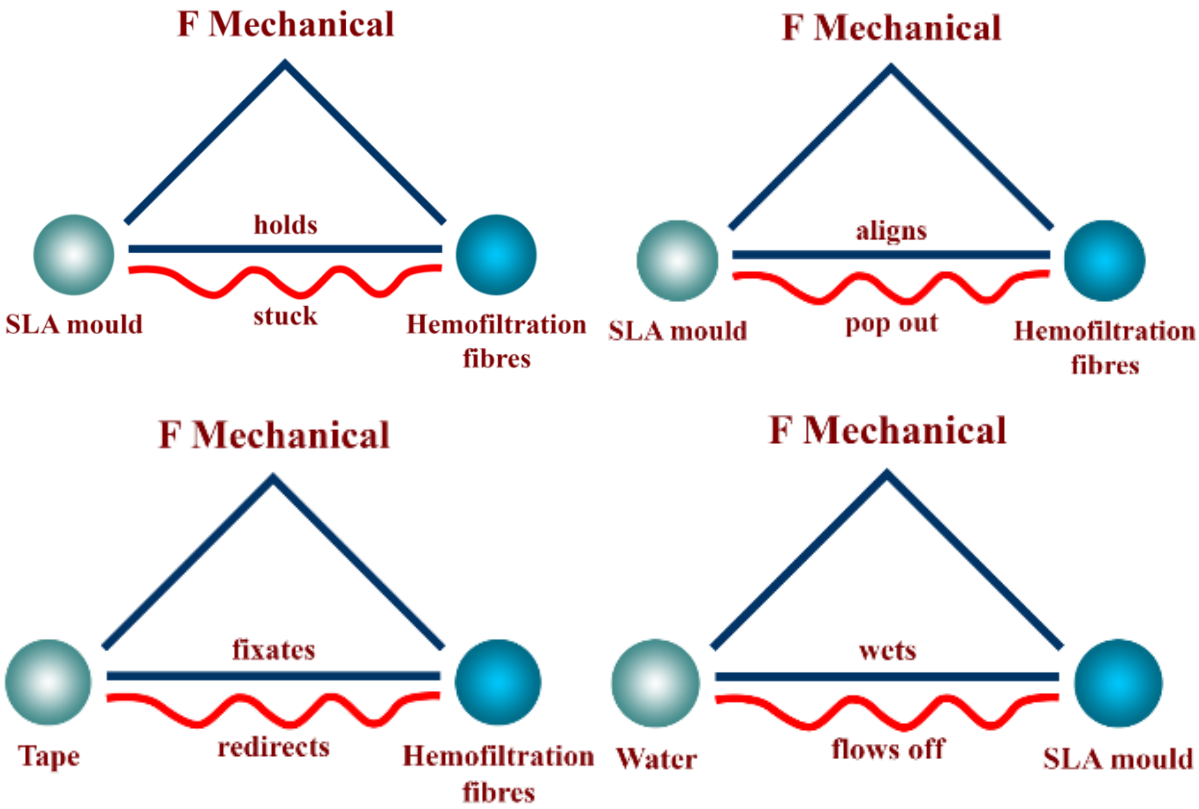


Figure 12-2: Harmful problems and their coupled positives. F stands for field of the problem. The red waving line represents the harmful interaction and the blue line above its coupled positive.

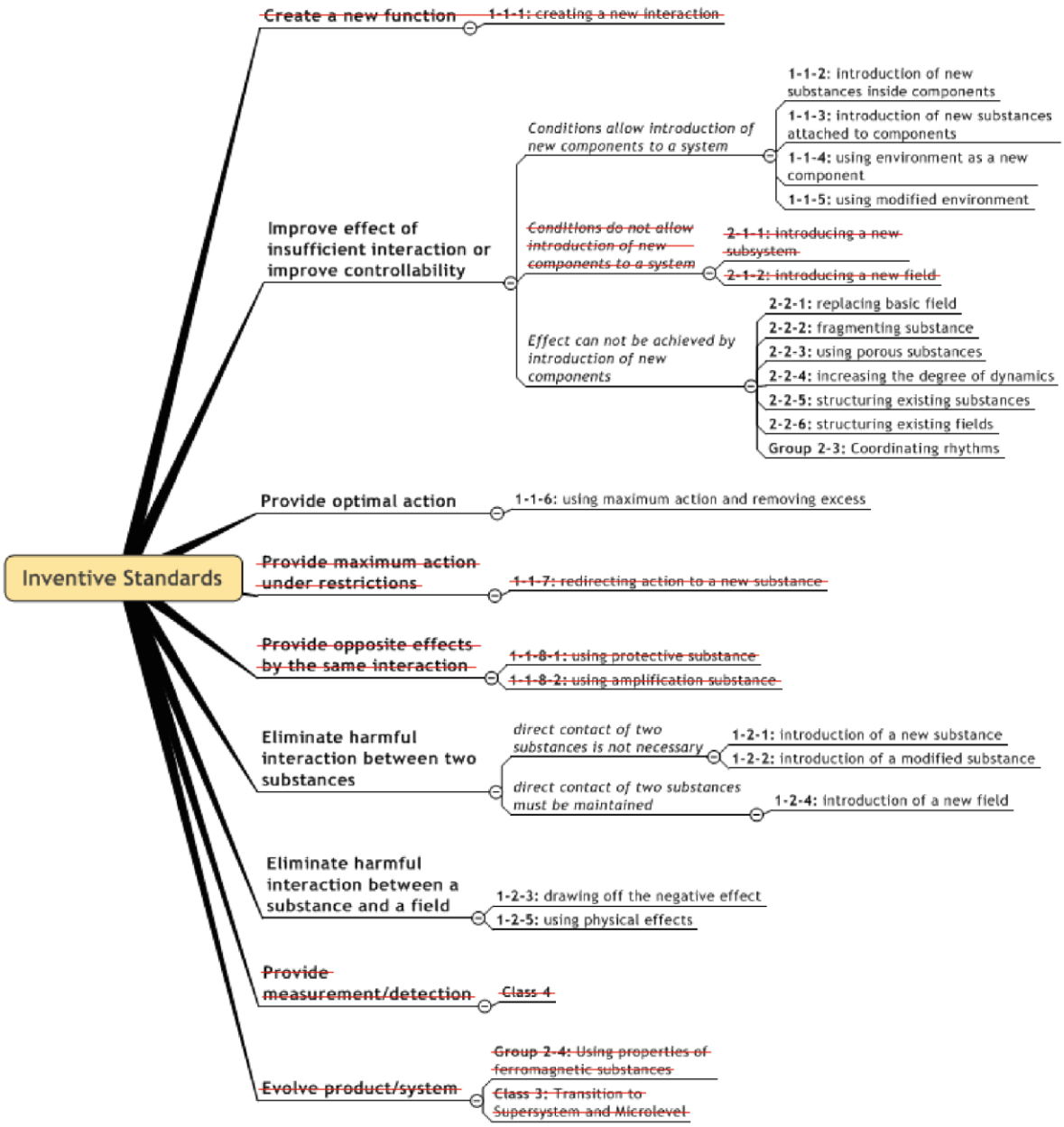


Figure 12-3: Inventive Standard selection for the coupled issues. Disregarded standards are crossed through.

Table 12-2: IS applied to (harmful) problem nr. 1 of Table 4-7.

Inventive Standard	Idea(s)	Note(s)
1-1-2: introduction of new substances inside components	N/A	No new substances can be added inside the component.
1-1-3: introduction of new substances attached to components	~ Add a lubricant to the SLA mould to improve removal of hemofiltration fibres.	N/A
1-1-4: using environment as a new component	~ Dip SLA mould with hemofiltration fibres in water to improve removal. ~ Break spikes of SLA mould on coutertop or with hands.	Breaking spikes is not. desired
1-1-5: using modified environment	~ Use electrostatic gloves to improve removability.	Might not be strong enough.
1-1-6: using maximum action and removing excess	~ Use vibrations to remove the hemofiltration fibres from the mould.	N/A
1-2-1: introduction of new substance	~ A plastic foil is added on top of the SLA mould after which the hemofiltration fibres are placed. The hemofiltration fibres are removed by removing the foil. ~ Top layer of mould is created using silicon and can be removes from base.	N/A
1-2-2: introduction of a modified substance	N/A	Direct contact is necessary for alignment.
1-2-3: drawing off the negative effect	~ Add grooves to mould to keep added water on top of the mould. ~ Add oil or silicon aerosols on top of the SLA mould to reduce friction forces.	N/A
1-2-4: introduction of a new field	~ The SLA mould is charged in such a way that the hemofiltratoin fibres repel	N/A

Inventive Standard	Idea(s)	Note(s)
1-2-5: using physical effects	N/A	No use of magnetic field.
2-2-1: replacing basic field	N/A	Substance field cannot be changed.
2-2-2: fragmenting substance	~ Separating the spikes and the flat surface, making the spikes a removable part. ~ Separating interspacing and stretching, creating a mould that first aligns and then stretches the fibres. ~ Different spike heights to improve alignment and reduce friction forces.	N/A
2-2-3: using porous substances	~ A porous SLA mould with oil or silicon aerosols in cavities to reduce friction. ~ Create a cavity mould to which the hemofiltration fibres are passed.	N/A
2-2-4: increasing the degree of dynamics	~ Creating a flexible/silicon mould to easier remove the fibres.	N/A
2-2-5: structuring existing substances	N/A	Effectiveness of substance field cannot be improved.
2-2-6: structuring existing fields	N/A	Effectiveness of substance field cannot be improved.
2-3: coordinating rhythms	N/A	No rhythms can be applied.

Table 12-3: IS applied to (harmful) problem nr. 2 of Table 4-7.

Inventive Standard	Idea(s)	Note(s)
1-1-2: introduction of new substances inside components	N/A	No new substances can be added inside the component.
1-1-3: introduction of new substances attached to components	~ A lid slides over aligned hemofiltration fibres for temporary fixation. ~ Water-based adhesive is applied to the fibres and can be removed after fixation.	N/A
1-1-4: using environment as a new component	~ Use hand to keep fibres in place.	N/A
1-1-5: using modified environment	~ Use vacuum to keep fibres in place.	Not feasible.
1-1-6: using maximum action and removing excess	~ Add water-based adhesve to hemofiltration fibres to prevent popping out.	N/A
1-2-1: introduction of new substance	N/A	Direct contact is necessary for alignment.
1-2-2: introduction of a modified substance	~ Gravity forces are used to keep the hemofiltration fibres stretched.	Direct contact is necessary for alignment.
1-2-3: drawing off the negative effect	~ A lid slides over aligned hemofiltration fibres for temporary fixation.	N/A
1-2-4: introduction of a new field	~ The SLA mould is charged in such a way that the hemofiltration fibres attract.	N/A
1-2-5: using physical effects	N/A	No use of magnetic field.
2-2-1: replacing basic field	N/A	Substance field cannot be changed.
2-2-2: fragmenting substance	~ Separating interspacing and stretching, creating a mould that first aligns and then stretches the fibres.	N/A

Inventive Standard	Idea(s)	Note(s)
	~ Fixation pillar to be applied on aligned hemofiltration fibre (slides from the side).	
2-2-3: using porous substances	~ Using a capillary mould to align hemofiltration fibres.	N/A
2-2-4: increasing the degree of dynamics	~ Alignment support can be individually tightend.	N/A
2-2-5: structuring existing substances	~ Friction forces are enhanced, decreasing the chance of popping out.	N/A
2-2-6: structuring existing fields	~ Hemofiltration fibres are inserted in a soft material at begin and end of fibre.	N/A
2-3: coordinating rhythms	N/A	No rhythms can be applied.

Table 12-4: IS applied to (harmful) problem nr. 3 of Table 4-7.

Inventive Standard	Idea(s)	Note(s)
1-1-2: introduction of new substances inside components	N/A	No new substances can be added inside the component.
1-1-3: introduction of new substances attached to components	~ Add glue layer lines the SLA mould sides to press hemofiltration fibres into.	N/A
1-1-4: using environment as a new component	~ Reduce alignment support height to allow for easier contact between hemofiltration fibres and tape.	N/A
1-1-5: using modified environment	~ Add tape to mould before aligning hemofiltration fibres so they are fixated immediately.	N/A
1-1-6: using maximum action and removing excess	~ Add a thick soft layer of adhesive that can be pressed into the SLA mould.	N/A
1-2-1: introduction of new substance	~ Add a temporary fixation (e.g. an elestic band) before applying tape to ensure interspacing.	N/A
1-2-2: introduction of a modified substance	~ A lid slides over aligned hemofiltration fibres for temporary fixation.	N/A
1-2-3: drawing off the negative effect	N/A	No negative field effect present.
1-2-4: introduction of a new field	~ Centre of the hemofiltration fibres is put in water and frozen in place.	N/A
1-2-5: using physical effects	N/A	No use of magnetic field.
2-2-1: replacing basic field	~ Replace tape by water freezing to fixate hemofiltration fibres. ~ Pull hemofiltration fibres through grooves on the side of the SLA mould.	Probably affects the hemofiltration fibres.

Inventive Standard	Idea(s)	Note(s)
2-2-2: fragmenting substance	~ Separate centre and outer part of mould. The tape will be applied on outer shape and inner part can be removed, applying outer shape over stacking base. ~ Create a space in which tape can be applied. ~ Stacking base in which spikes of mould fit and hemofiltration fibres can be transferred directly.	Might only work for first layer.
2-2-3: using porous substances	~ Using a capilar mould to align hemofiltration fibres.	N/A
2-2-4: increasing the degree of dynamics	~ Use extendable parts that can press hemofiltration fibres against tape. ~ Use silicon / glue insted of tape.	Tried before and did not work properly.
2-2-5: structuring existing substances	~ Apply tape to mould before aligning hemofiltration fibres for instant fixation.	N/A
2-2-6: structuring existing fields	~ Hemofiltration fibres are inserted in a soft material at begin and end of fibre.	N/A
2-3: coordinating rhythms	N/A	No rhythms can be applied.

Table 12-5: IS applied to (harmful) problem nr. 4 of Table 4-7.

Inventive Standard	Idea(s)	Note(s)
1-1-2: introduction of new substances inside components	~ Adding substances to the water (e.g. sugar) to increase viscosity. ~ Use material with better adhesive properties for SLA mould.	N/A
1-1-3: introduction of new substances attached to components	~ Increase the adhesive properties of the SLA mould by applying a coating.	N/A
1-1-4: using environment as a new component	~ Using a concave sla mould to retain water. ~ Using an alternating concave and convex SLA mould surface to retain water.	N/A
1-1-5: using modified environment	~ Cooling water (either by cooling directly or cooling the SLA mould).	N/A
1-1-6: using maximum action and removing excess	~ Align hemofiltration fibres in SLA mould under water. ~ Centre of SLA mould is covered with water during alignment.	N/A
1-2-1: introduction of new substance	N/A	Direct contact is required
1-2-2: introduction of a modified substance	N/A	Direct contact is required
1-2-3: drawing off the negative effect	~ Use walls instead of spikes ~ Add walls to the sides of the SLA mould.	N/A
1-2-4: introduction of a new field	~ Slight suction from above to prevent water from flowing off. ~ Add airflow from the sides to make sure water will not flow off.	N/A
1-2-5: using physical effects	N/A	No use of magnetic field.
2-2-1: replacing basic field	~ Use adhesive instead of water.	N/A

Inventive Standard	Idea(s)	Note(s)
2-2-2: fragmenting substance	~ Create a layered mould which will be assembled with hemofiltration fibres.	N/A
2-2-3: using porous substances	~ Creating a porous SLA mould with sponge like properties in cavities. ~ Creating a porous SLA mould with water in cavities.	N/A
2-2-4: increasing the degree of dynamics	~ Make (top of) mould out of sponge material which can retain water.	N/A
2-2-5: structuring existing substances	N/A	Substance field cannot be improved.
2-2-6: structuring existing fields	N/A	Substance field cannot be improved.
2-3: coordinating rhythms	N/A	No rhythms can be applied.

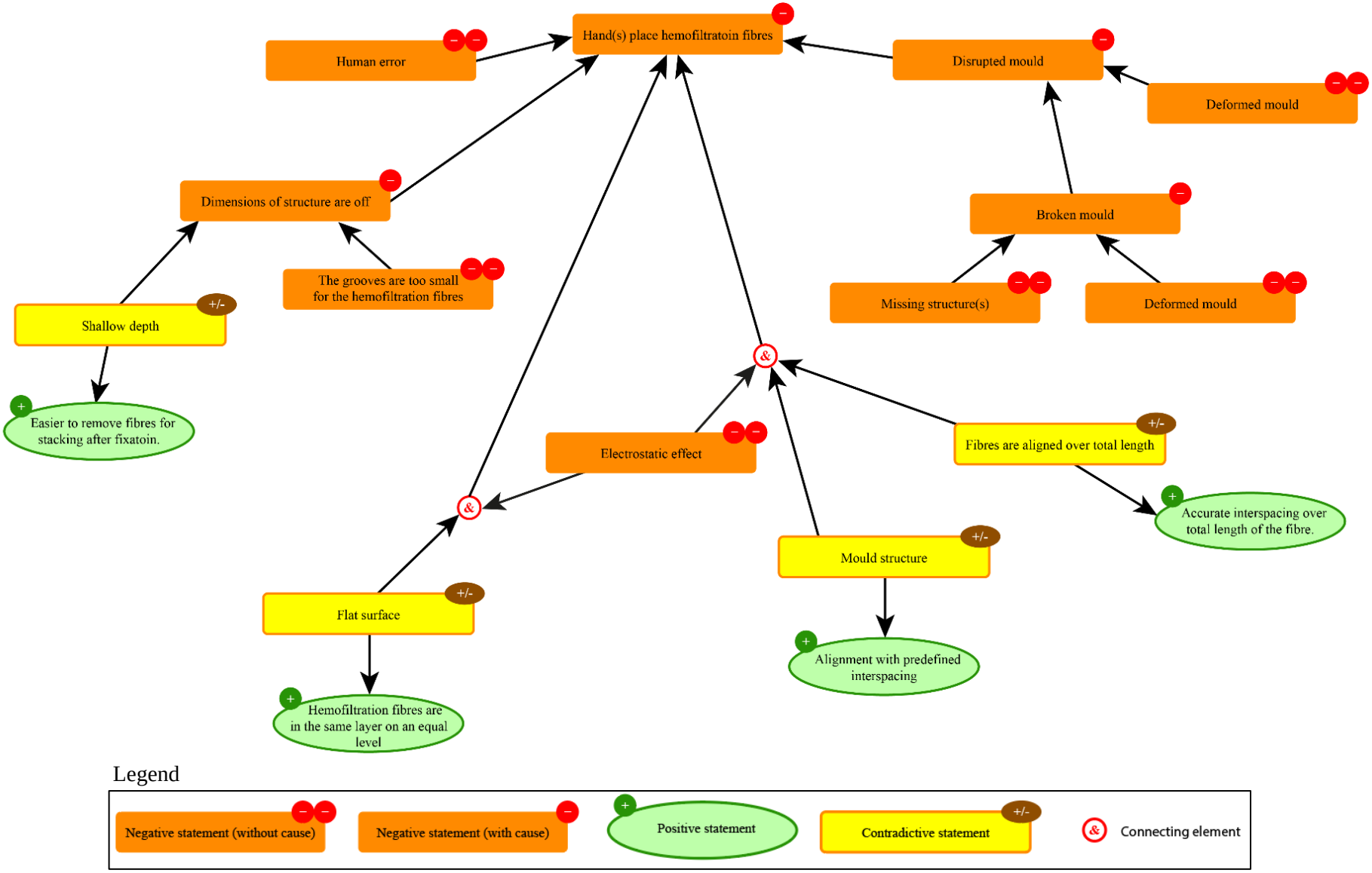


Figure 12-4: Root conflict analysis (RCA+) for (insufficient) problem nr. 5 of Table 4-7.

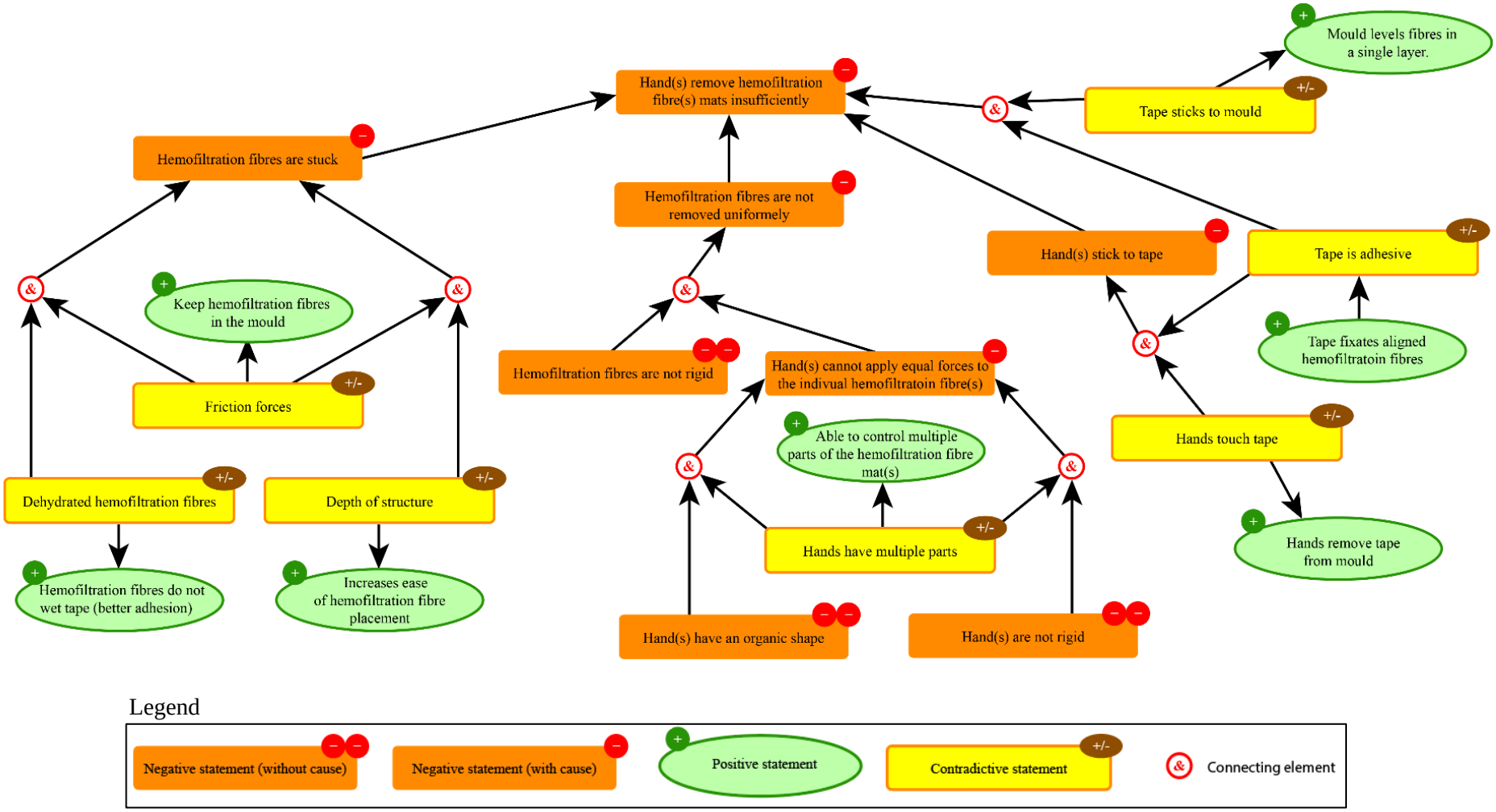


Figure 12-5: Root conflict analysis (RCA+) for (insufficient) problem nr. 6 – 8 of Table 4-7.

12.2 Annex B: Solution Designs After TRIZ

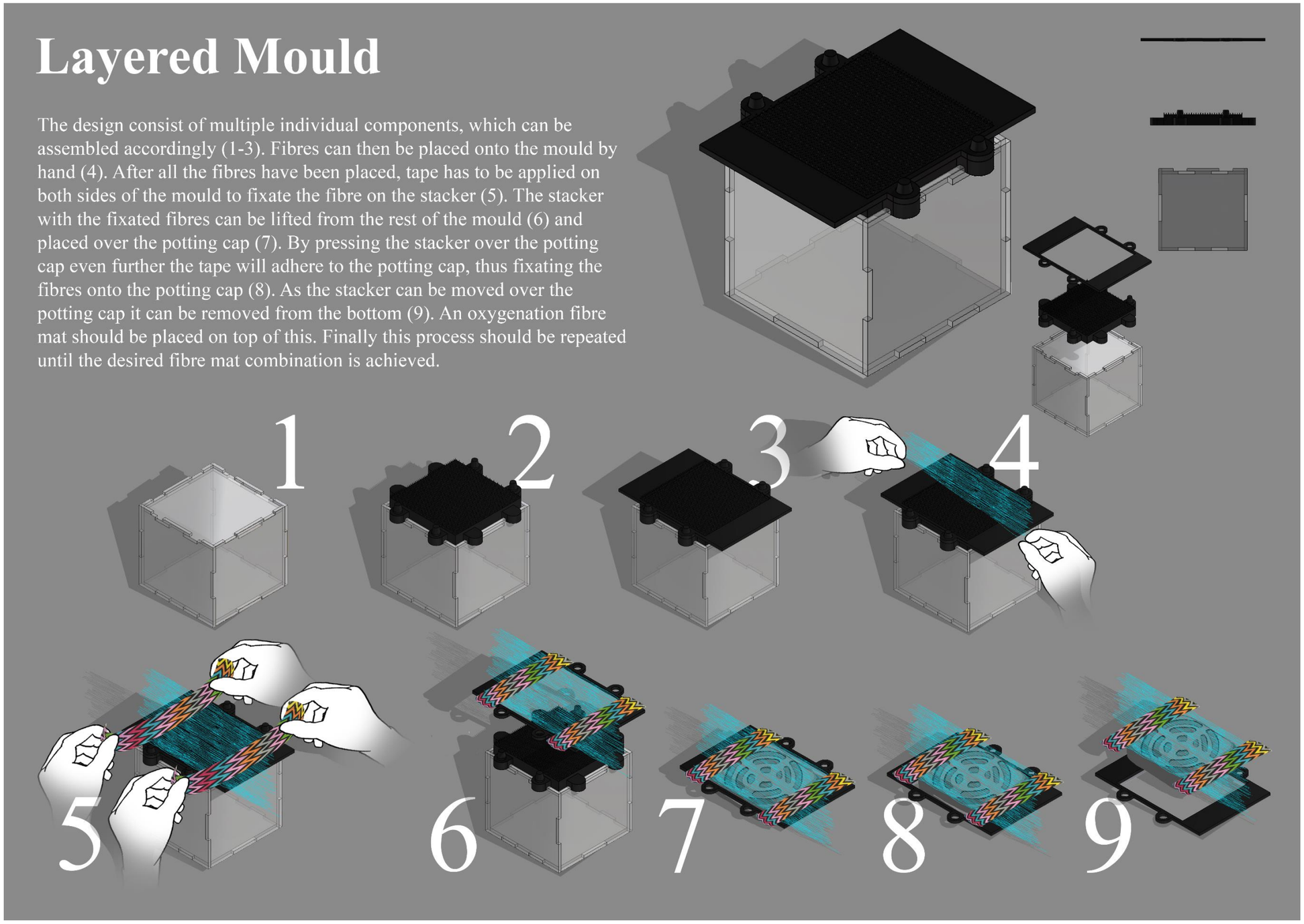


Figure 12-6: Layered Mould Design

Segmented Mould

The fibres are placed between a row of alternately placed pillars which create the interspacing between the fibres (1). As the mould is curved one would start from the middle and is able to guide the fibre around the curve which aids the embedding of the fibre between the pillars (2). Gravity will help to keep the fibres down and water could be used to assist this as well (3). After all the fibres have been placed, tape is applied on the part between the rows of pillars on the side and the middle (4). Now the fibres are fixated the interspacer and support can be removed from the mould leaving the taper with the unstretched fibres. These fibres need to be stretched to ensure a proper interspacing between the fibres (5) as the mould is curved. After stretching the taper can be moved over the potting cap (6). By pressing the taper over the potting cap the tape will stick on the sides of the potting cap (7). The taper can then be removed, leaving the potting cap with a neatly stretched fibre mat on top of it (8). An oxygenation fibre mat can be stacked on top of this using tape after which the process is repeated until the desired fibre membrane combination is aquired.

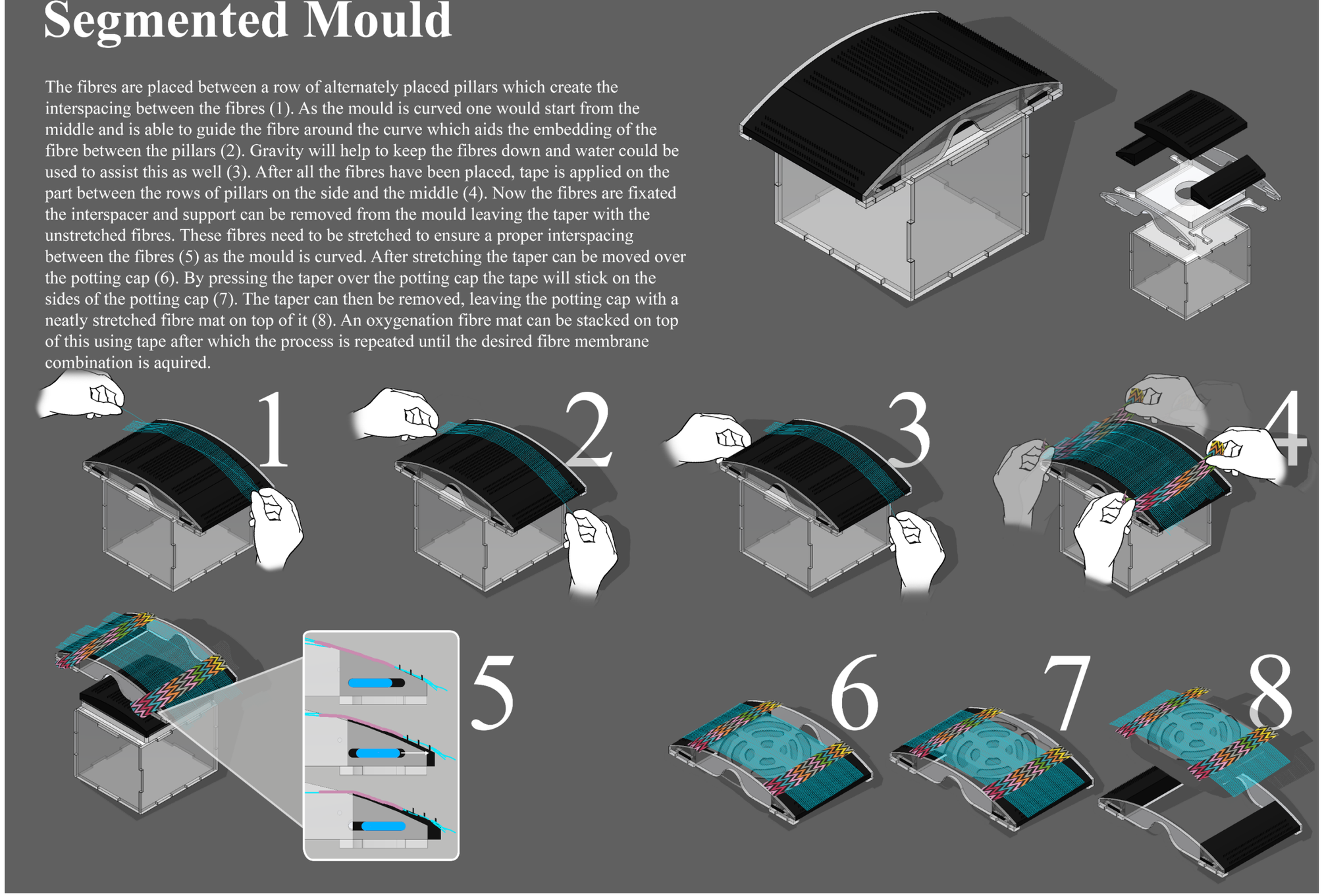
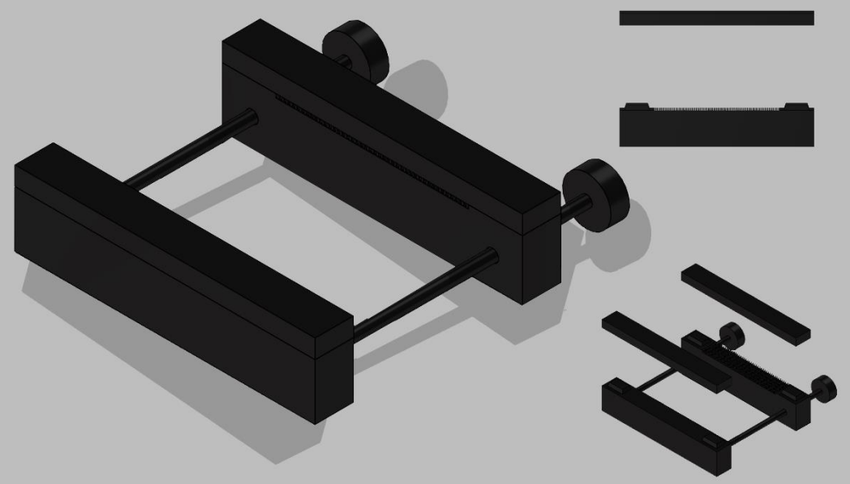


Figure 12-7: Segmented mould design

Stretch Mould

The fibres are place over the two base parts of which one base part has an interspacing created by pillars (1). After the fibre placement, a lid is placed (2) to cover the base parts with pillars (3). Next a second lid is placed on the base without pillars, thus fixating the fibres by clamping the fibres between two surfaces (4). The two base parts can now be parted and the interspacing over the total length of the fibres is aquired by a combing technique (5). Finally the stretch mould is placed over the potting cap and the fibres are taped to its surface (6). An oxygenator fibre mat is placed on top of the haemofiltration fibre mat. This method is then repeated until the desired fibre membran combination is aquired.



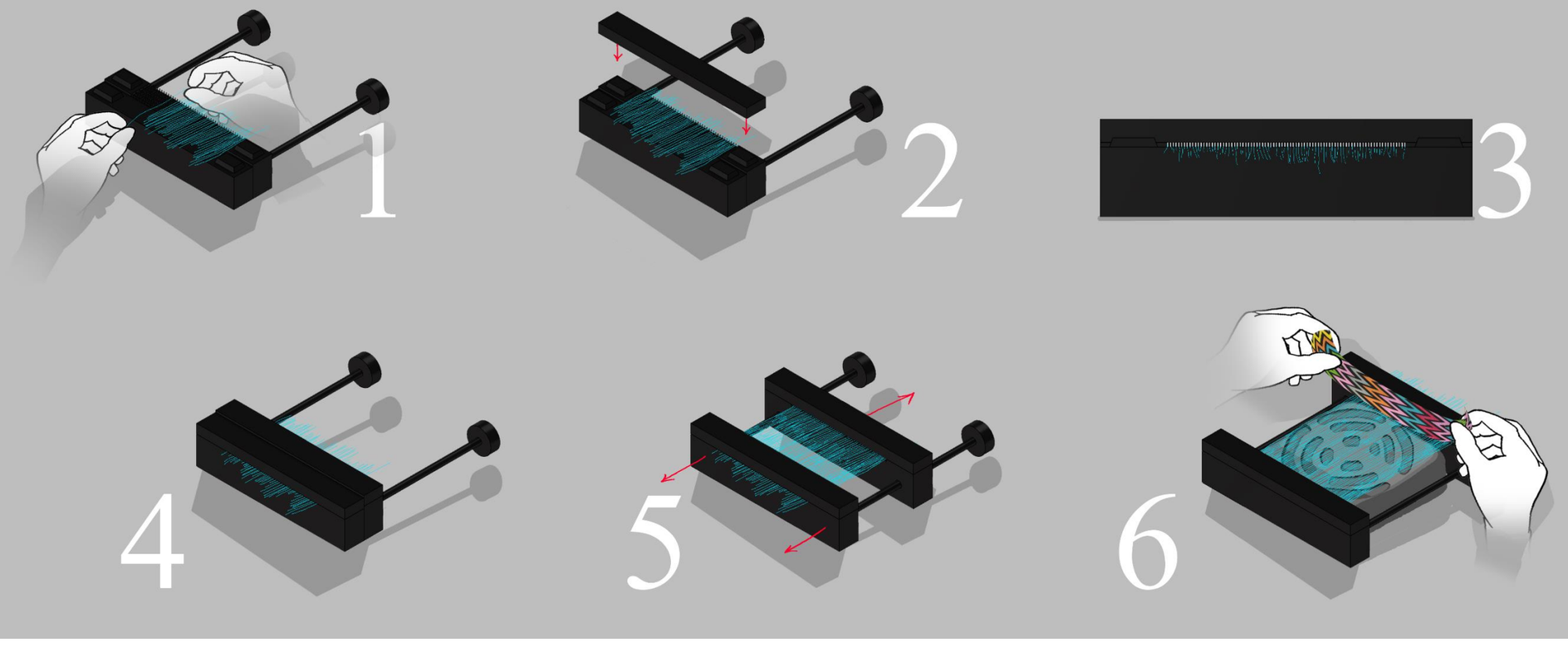


Figure 12-8: Stretch mould design

12.3 Annex C: Pillar Print Samples

Support structures could be removed from all of the samples in Figure 12-9. Failing support structures in a1 and a3 might have influenced warping in the samples. Warping happened in all samples except for samples a2, c3, d2, and d3. As the samples were made smaller to reduce print time (20 × 20 mm with a thickness of 2 mm) it could have initiated warping. Warping could also have happened due to the placement of the print on the built platform. Therefore, these outcomes do not make much difference in the decision.

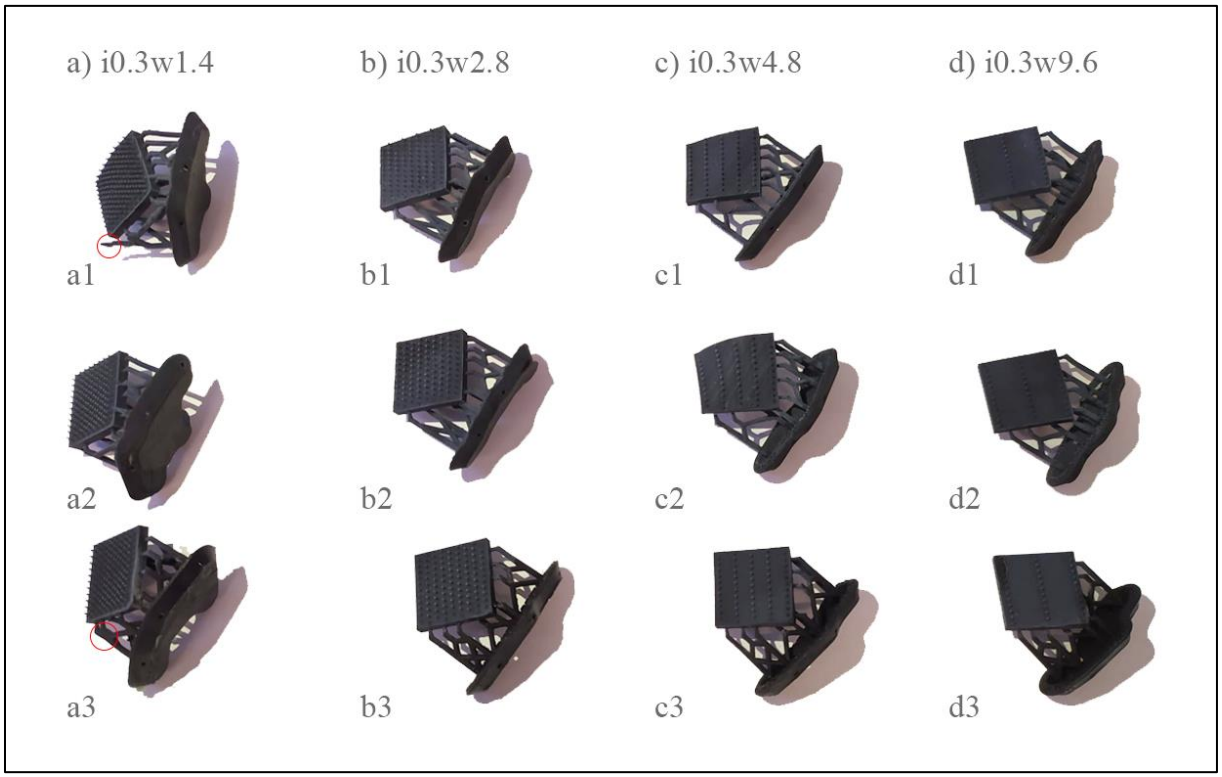


Figure 12-9: Print samples of 20 × 20 mm (with support) with alternately spaced pillars with an interspacing of 0.3 mm (i0.3) and a variating width in distance (mm) between the pillars in single row (w). Support structures in a1, and a3 failed as marked by the red circles. Warping happened in all of the above except in a2, c3, d1, and d2.

Looking at the samples suggested that the pillars were shaped appropriately. The interspacing between the pillars was checked using a calliper and matched the 0.3 mm interspacing. However, in Figure 12-10 it can be seen that samples a1 – 3 and b1-3 have some damages to the pillars. This indicates that these structures are hard to print for the Form 2 SLA printer. Samples c1 – 3 and d1 – 3 were used to test the fibre placement. This test was performed by both the designer and the daily supervisor of the project. It became clear, for both participants, that placing the fibres in samples d1 – 3 was harder than placing fibres in sample c1 – 3. This mainly had to do with the fact that the pillars are alternately spaced. The user therefore needs to be able to locate the next pillar in line by the eye. The distance between the pillars in a single row of samples d1 – 3 (9.6 mm) was bigger than samples c1 – 3 (4.8 mm). This increased difficulty of placement. Due to these results is was determined that the best option was sample c.

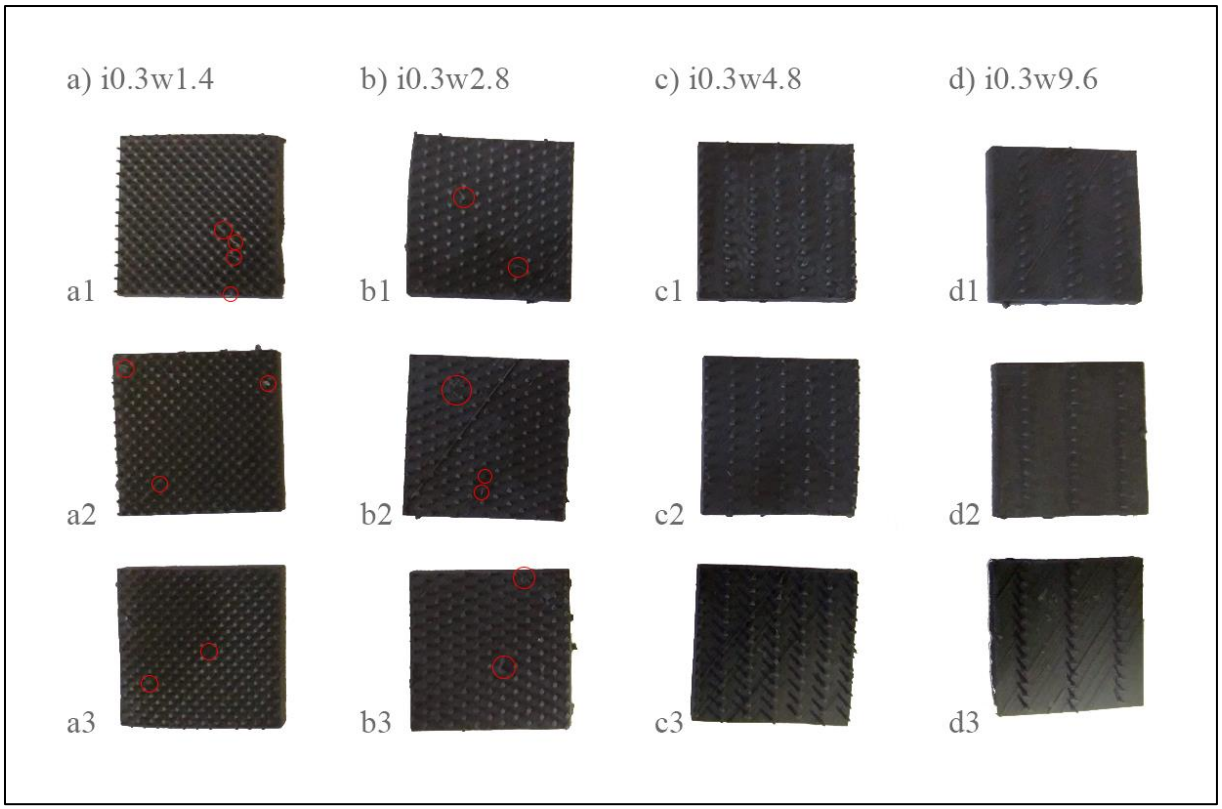


Figure 12-10: Print samples of 20 × 20 mm (without support) with alternately spaced pillars with an interspacing of 0.3 mm (i0.3) and a variating width in distance (mm) between the pillars in single row (w). Damages to the pillars were observed in a1 – 3, and b1 – 3 as marked by the red circles.

12.4 Annex D: Fibre Area Samples

A minimum fibre area between the rows needs to be determined to assure fibres can be placed in the mould. To do so, a small series of samples was made to research this matter (Figure 12-11). As the hemofiltration fibres have a diameter of about 0.26 mm it was decided to try out a sample series of 0.25 – 0.30. Each sample has an intermediate step of 0.01 mm, thus resulting in 5 samples in total. Each sample was tested by both the designer and the daily supervisor of the project. It was evident that placing the hemofiltration fibres in sample ‘a’ and ‘b’ was not possible. Sample ‘c’ showed a waving hemofiltration fibre after the hemofiltration fibre was place. This sample also required some force to be able to place the hemofiltration fibre up down to the surface. Sample ‘d’ also required a slight force and showed waving in some parts of the sample. Sample ‘e’ did not show any signs of waving and it was possible to place the fibres without force.

Figure 12-11: Print samples of 20 × 20 mm (with support) with alternately spaced pillars, an interspacing of 0.3 mm, distance between the pillars in a single row of 4.8 mm and a varying fibre area. Samples with a fibre area of 0.25 – 0.30 mm were conducted. Sample ‘a’ contained a fibre area of 0.25 mm and with an intermediate step of 0.01 mm it increases to sample ‘e’.

12.5 Annex E: Risk Analysis

See e-document:

RO0604_RiskAnalysis-MBD_Rev08_220404.p

12.6 Annex F: Design Requirement Specifications

See e-document:

RO0604_DRS-MBD_Rev11_220404WDr.pdf