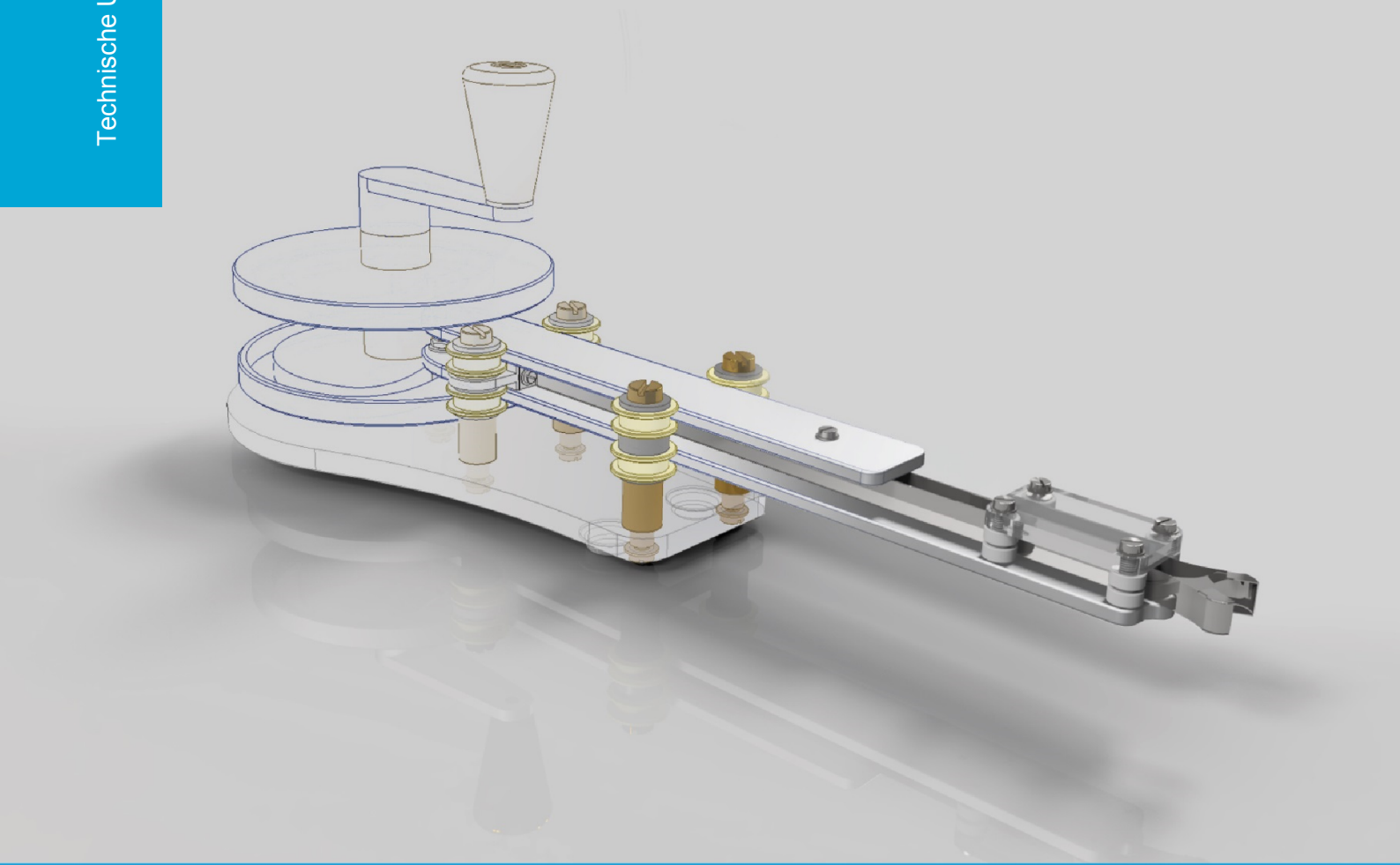
Design of a novel cardiac bioptome tip

A design study

Ruben Rink

Technische Universiteit Delft



TU Delft

Design of a novel cardiac bioptome tip

A design study

by

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in partial fulfilment of the requirements for the degree of

Master of Science
in Mechanical Engineering

at the Delft University of Technology,

Main supervisor:	Prof. dr. ir. P. Breedveld	TU Delft
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Preface

This report on the design of a novel cardiac bioptome tip forms the final result of my master Mechanical Engineering at Delft University of Technology. The report explains the need for a novel instrument and covers the development by showing concepts that ultimately lead to the design and development of a prototype that is validated by an experiment. Furthermore, the report includes a discussion and conclusion, as well as relevant drawings and calculations.

First of all, I am grateful to God for life, health, and the ability and opportunity to complete this study. I would also like to thank my daily supervisor Awaz Ali for her great effort in the guidance and support during my graduation, Paul Breedveld for his always critical and clear advice and Gerwin Smit for his support during the design process. I would also like to thank Remi van Starkenburg and David Jager from DEMO for their technical support, especially Remi for manufacturing parts of the prototype. Additionally, I would like to thank the staff from IWS for advice and support to manufacture multiple parts myself. Last, but not least, I owe thanks to my parents, siblings, housemates, and friends for their support and interest during my study and graduation in Delft.

The development of the new design is done with great pleasure and I hope that my work will be used for further development in the field in cardiac surgery or perhaps other fields.

The committee members for my graduation:

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Ruben Rink
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Abstract

A heart biopsy is also known as an endomyocardial biopsy (EMB). The method is used for surveillance of cardiomyopathies, myocarditis, and possible rejection after a heart transplantation. A cardiac biopsy is a relatively simple procedure but not free of risks. Despite the fact that new techniques were developed to improve EMB in the past years, a number of challenges still remain. Due to the number of prescribed samples, it is required that the bioptome moves to the biopsy site multiple times. As a result, not only the risk of damage will increase multiple times, but the instrument must be reoriented and repositioned after each removal and insertion again. Therefore, the main goal was the design of a method for storing multiple samples (minimum of five) in a single heart bioptome without sample loss.

The main goal was subdivided into eight functions. For these eight functions the best solutions were selected and two concepts were designed. The best concept was then chosen and converted into a final design. The final design comprises a bioptome with a square cross-section of a width of 6 mm with a compliant gripper with a valve (scraper) inside that closes off the opening and prevents sample loss. Actuation takes place by two cam discs that control the elements inside the tip of the bioptome. The cams are rotated by a crank on top, and upon carrying out a full rotation with it, one sample is taken and stored. To validate the working principle of the new design a prototype, the MultiBite, was built and a proof-of-concept test was conducted. The prototype was able to take a sample piece and store it inside the instrument. Because the scrapers did not fully close during the test, caused by a manufacturing difficulty of the scrapers, small sample pieces remained in the gripper or slipped through the scrapers.

The new design has shown potential to take five biopsy samples and store it inside the instrument. However, the scraper manufacturing has to be optimised for optimal and safe functioning of the prototype. In addition, more research and testing is needed to convert the new design of the prototype into smaller and flexible instruments. It is believed that continued research and development of the new design may improve the EMB procedure.

1. Introduction

1.1. Background

1.1.1. Minimally invasive biopsy

The word biopsy is of Greek origin and refers to 'bios' and 'opsis' which means 'life' and 'a sight'. The aim of biopsy is to see and examine a piece of tissue (life). A biopsy is a medical test involving extraction of sample cells or tissue for examination. The objective of a biopsy is to research the properties of the tissue to determine the presence or extent of a disease. When performed in a minimally invasive way it is called minimally invasive biopsy (MIB). Biopsies are mostly performed to gain insight into cancerous and inflammatory conditions.

A biopsy can be either optical when light properties are used to scan the tissue's surface or physical when the tissue cells are extracted for examination [1]. In this report the focus is on physical biopsies. The used biopsy technique strongly depends on the organ or area to examine, because the tissue type, tissue structure, and location differs per organ. We can discriminate between the two most common biopsies: needle and surgical biopsies. Biopsy needles are used to obtain tissue or fluid samples from, for instance, muscles, liver, lungs and bone marrow [2-4]. Surgical biopsies may be necessary at hard-to-reach areas in the body or in situations in which a needle biopsy poses too many risks. Surgical biopsies include the use of endoscopes, laparoscopes, and catheters.

1.1.2. Endo-myocardial biopsy

A heart biopsy, a surgical biopsy, is known as an endomyocardial biopsy (EMB). The technique is used for surveillance of cardiomyopathies (deterioration of the heart muscle), myocarditis (inflammation of the heart muscle), and a possible rejection after a heart transplantation (a process in which the immune system of a transplant recipient attacks the transplanted heart).

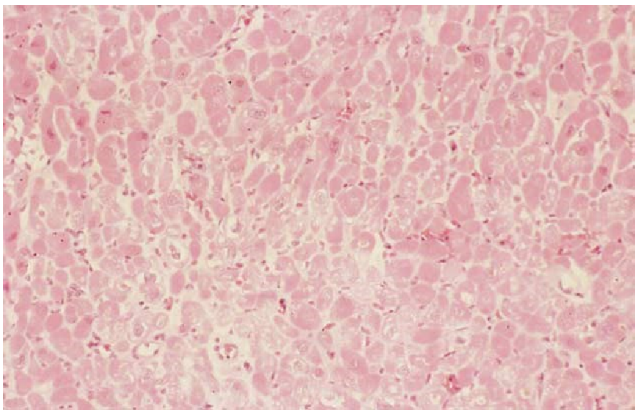


Figure 1 A normal endomyocardial biopsy showing no signs of rejection [5].

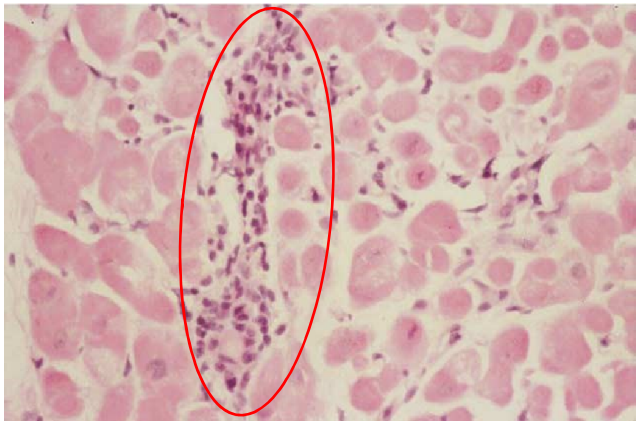


Figure 2 Myocardial biopsy showing acute cellular rejection (inside red oval) [5].

The preferred access site for EMB is the right internal jugular vein, see Figure 3. The right and left ventricle can also be accessed through the right femoral vein and femoral artery, respectively. The right ventricular free wall is too thin to conduct biopsies on, therefore obtaining biopsy specimens from this area is dangerous. Biopsy samples should therefore be taken from the interventricular septum. To increase the likelihood of a diagnosis, a minimum of five samples is commonly taken [5]. The procedure generally consists of the following steps:

1. First the patient's right internal jugular vein is searched by means of an echography device.
2. The insertion place is then anaesthetized.
3. A guidewire is inserted into the right internal jugular vein and advanced to the superior vena cava.
4. A sheath is inserted over the guidewire.
5. Before the bioptome is inserted, the tip is slightly curved to make it easier to pass the tricuspid valve.
6. The bioptome is inserted into the sheath.
7. Depending on the situation, echocardiography or fluoroscopy guidance may be used as the preferred method to visualize the heart. In some cases, a combination of both may be used [6, 7].
8. The interventionist passes the tricuspid valve, using both tactile and visual feedback.
9. The bioptome is moved around until small arrhythmias occur. This indicates that the intraventricular septum is contacted.

10. The bioptome opens, is pushed against the intraventricular septum, and closes.
11. After the bioptome closes it must remain closed until it is retracted. This is to prevent sample loss.
12. Once closed, the bioptome will cut off a sample.
13. The bioptome and sample are retracted.
14. The sample piece is moved off the bioptome.
15. The sample is stored in a solution that depends on the clinical question to be answered.
16. The process is repeated until the required number of samples is collected, which is generally five.

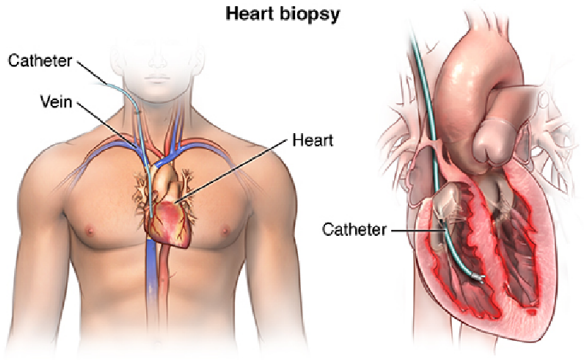


Figure 3 Schematic overview of a heart biopsy, figure taken from [8].

1.1.3. Endo-myocardial biopsy instruments

The first flexible biopsy catheter dates from the 1960's, see Figure 4. This instrument was designed because a needle biopsy was not applicable for use in the heart. With a fine needle it is impossible to obtain enough heart tissue. In addition, with a needle entering the heart from the outside the most important endocardial tissues will not be obtained [7].

The basic principle of contemporary biopsy instruments are similar, however new manufacturing techniques allow more precise parts. An overview of commonly used cardiac bioptomes can be seen in Figure 5. The basic parts of a biopsy forceps instrument consist of a long flexible spiral wire with on one end the forceps and at the other end a handle to actuate the forceps by means of a cable.

In some cases, a longer sheath is preferred and will be inserted in the heart and through the tricuspid valve to prevent damage. By using this

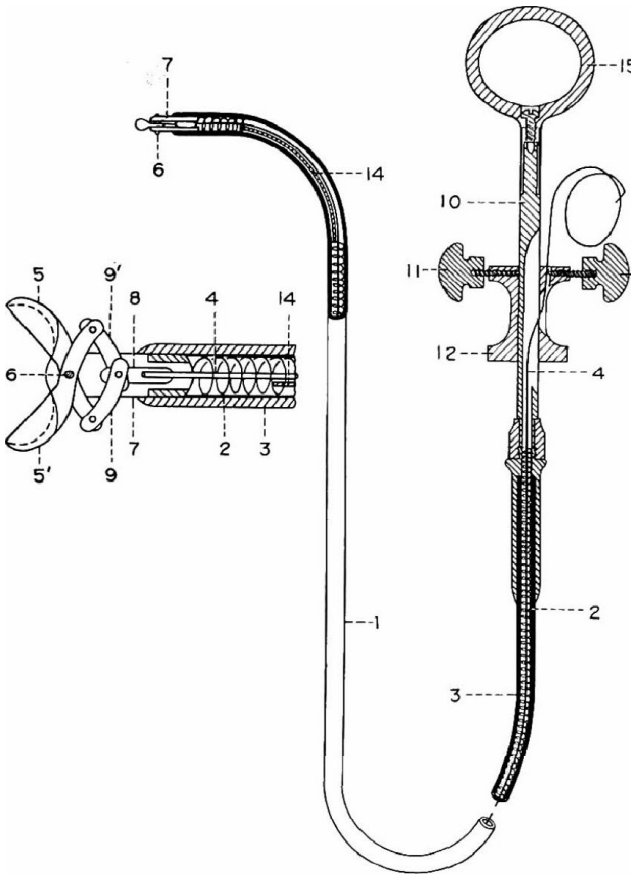


Figure 4 One of the first cardiac bioptomes [9].

technique, the tricuspid valve has to be passed only once during a single intervention. Insertion of the bioptome becomes much easier in this way. Insertion becomes even easier with a steerable sheath [10]. A steerable FlexCath® (Medtronic) sheath was successfully used by Tanawuttiwat *et al.* [11] to retract lead remnants from the heart. A steerable bioptome is another option to make it easier to pass the tricuspid valve, also manoeuvring to the right spot on the intraventricular septum becomes easier. Steerable bioptomes are not commercially available, but the idea is present in patents [12-15].

Konecny *et al.* [16] showed that it is feasible to integrate an electrode in a standard endomyocardial bioptome tip in a safe way. They recommend to investigate if it could increase the safety and diagnostic yield of cardiac biopsies. An electrode in a bioptome tip could improve safety, because more insight in the correct area to take a sample from is provided. The technique has not been applied to commercially available bioptomes yet.

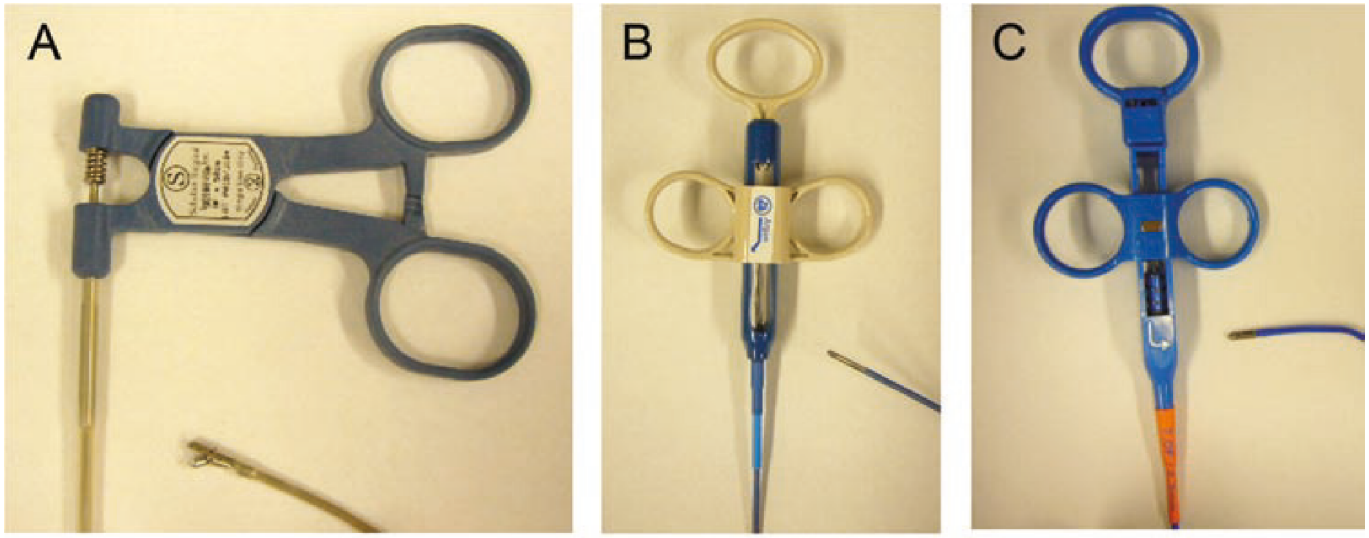


Figure 5 Overview of commonly used cardiac bioptomes. A) Single-use 50-cm Novatome (Sholten Surgical Instruments, Inc, Lodi, CA) with a 2.3-mm tip that requires a 9-F sheath. B) Argon endomyocardial biopsy forceps (Argon Medical Devices, Inc, Athens, TX) with a 1.8-mm tip that requires a 6-F sheath or a 2.3-mm tip that requires a 7-F sheath. C) Bipal 7 bioptome, 50 cm and 104 cm (Cordis Corp, Miami Lakes, FL) with a 2.3-mm tip that requires a 7-F sheath [10].

Ratnakar [17] describes a patent for a biopsy catheter with means to obtain multiple tissue specimens during a single operation of a biopsy catheter. The biopsy catheter comprises a shaft with multiple forceps along its length which allows for multiple biopsy samples. Storing multiple samples in the forceps is brought up in a patent by Slater *et al*. [18]. They describe an endoscopic multiple sample bioptome in which a jaw assembly can displace axially along an outer member. This axial movement brings the jaw cups together, and the hollow design allows for the storage up to six sample pieces in the forceps. None of the idea's and patents mentioned above are tested, nor available at the market.

1.1.4. Clinical complications

Even though EMB is a safe procedure, it is associated with both a risk of procedural complications and long term sequelae [10]. The role of EMB in the diagnosis and treatment of cardiovascular diseases is sometimes reviewed as controversial. The difficulty is that in order to choose for EMB only clinical data is available to make the decision, the pathological data is not available until after the EMB procedure has been performed [6].

A cardiac biopsy is a relatively simple procedure but not free of risks. The most severe complication is a ventricular perforation. This may occur when a sample is taken from an incorrect location such as the right ventricular wall that is too thin. This will possibly result in a pericardial tamponade. The death rate of EMB is associated with this complication [7, 19]. Reported rates of a cardiac perforation are 0.05% by Saraiva *et al.* [20], and 0.0% - 3.3% by Fiorelli *et al.* [7] in a comparative study.

Other complications include atrial fibrillation, ventricular arrhythmia, local pain, tricuspid valve damage or regurgitation, and pulmonary embolization. [6, 7, 10, 20, 21]. The total complication rate varies between <1% and 9.2% [7]. Damage to the heart can occur by mispositioning the bioptome. The tricuspid valve can get damaged by manoeuvring the instrument through the valve. The valve itself or the muscles and chordae tendineae can get damaged leading to regurgitation at worst or only damage to the valve without noticeable consequences. The complication rate of tricuspid regurgitation (TR) is reported as 1.1% by Saraiva *et al*. [20]. Earlier studies by Braverman *et al*. from 1990 showed a rate of 6.2% [22].

A pulmonary embolism is a blockage in the pulmonary artery and is caused by a clot of blood or a loose sample piece travelling to an artery in the lungs. Pulmonary embolism can be life-threatening. Most common signs include shortness of breath and chest pain [23]. To prevent this from happening, a bioptome may never be opened inside the heart once it has been closed already, regardless of whether a sample has been acquired or not. A sample is taken from the intraventricular septum. By touching it, the conductivity changes slightly which causes an arrhythmia. Even though this is an indication for the interventionist that he has reached the correct location, it can cause discomfort for the patient.

1.1.5. Technical challenges

Finding the right location in the heart to take a biopsy sample from can be a challenge, thus care must be taken to ensure adequate tip visualization. However, the resolution of current 2D echocardiography is insufficient to visualize the chordae tendineae, which can be damaged during the EMB-procedure. Fluoroscopy generally provides more information about the course of the bioptome and biopsy site. [10] [24].

Insertion of the catheter may lead to discomfort of the patient, especially when the interventionist has trouble finding the right biopsy site and when the bioptome has to be inserted and retracted multiple times during the biopsy procedure to collect five samples. Incorrect operation of the bioptome may cause a loose sample piece in the blood circulation. Therefore, a bioptome may never be opened inside the heart once it has been closed already.

1.2. Problem definition

Despite the fact that new techniques were developed to improve EMB in the past years, a number of challenges still remain. Due to the number of prescribed samples, it is required that the bioptome moves to the biopsy site multiple times. As a result, not only the risk of damage will increase multiple times, but the instrument must be reoriented and repositioned after each removal and insertion again. Having a bioptome which could store multiple samples would have the advantage that it can remain inside the heart during the intervention. The bioptome will then enter the heart and pass the tricuspid valve only once. Additionally, it will reduce the time of the intervention since no time is lost with inserting and retracting the instrument and reorienting the position of the tip inside the heart. The reduced invasiveness and reduced time will also lead to more comfort of the patient.

1.3. Goal of this study

The main goal of this study is to design a sample storage mechanism (with a minimum of 5 samples) in a biopsy device intended for endo-myocardial biopsy. Included is the design of a mechanism that prevents sample loss. The design of the new bioptome tip will be evaluated by building a proof of principle prototype, on the scale of standard minimally invasive surgery instruments, to validate the working principle.

1.4. Layout of this report

This report shows the entire process of the design of a novel cardiac bioptome tip, from literature study to testing the prototype. In Chapter two, design requirements are presented, and the main problem is divided into smaller sub-problems. Chapter three covers the conceptual design of the instrument and at the end a final concept is selected. In Chapter four the final concept is designed into a prototype, which is tested in a proof-of-concept test. The report discusses the results in Chapter five and gives a conclusion of the work done in Chapter six. Bibliography and relevant appendices are included at the end.

2. Design requirements

2.1. Bioptome requirements & wishes

This chapter analyses the problem and sets design requirements that describe and define the desired instrument. The goal is to design a cardiac bioptome that is able to store multiple biopsy samples. The requirements are first divided into different categories. The requirements are all quantified and measurable. The wishes are not quantified and are not necessary for the functioning of the design.

2.1.1. Mechanical requirements

1. The bioptome must be able to cut a piece of soft material, this resembles the basic feature that the instrument should have and that all heart bioptomes have.
2. The bioptome must be able to take biopsy samples that contain a minimum surface area of 8 mm^2, this is needed to have sufficient myocardium for research.
3. The maximum bioptome diameter or width is 6 mm, this is larger than current heart bioptomes; however, in this study we focus on the standard size for minimally invasive surgery instruments, which is 6 mm.
4. The maximum length of the (rigid) functional parts in the tip is 40 mm. A longer tip will decrease the dexterity of the instrument, while with a 40-mm rigid tip enough freedom of movement remains. This length is comparable to that of other bioptomes.
5. The bioptome must be able to store a minimum of five samples. Five samples are needed to increase the likelihood of a diagnosis [5]. Storage of the samples

inside the bioptome is the main design goal.

6. Once a sample has been retrieved, sample loss must be prevented 100%. Sample loss is generally a harmful event, often leading to embolism in which partial, or total blockage of important blood vessels may occur.
7. The bioptome (tip) must be shaped in such a way that it will not damage the veins, tissue and other body material. Similar to current instruments the outer surface must be smooth without any protruding parts.

2.1.2. Control requirements

8. The bioptome must be simple to control, which means that it must be controlled by a single person, as is the case in the current situation.
9. No more than two actions should be required to grasp one biopsy sample. Similar to current bioptomes that have two actions as well (open and close).
10. The maximum control force should not exceed 10 N, per element to control. This is well below the maximum push and pull force an average index finger can exert [25]. A force of 10 N is therefore considered as a comfortable force.

2.1.3. Production wishes

11. The bioptome should have as few parts as possible, this keeps the instrument and its manufacturing simple.
12. Costs should be as low as possible.

2.2. Bioptome actions

Before starting the design process, it is important to identify the actions that the novel bioptome is required to undertake. The bioptome should be able to undertake the following actions:

1. The bioptome takes a biopsy sample by cutting and/or grasping tissue.
2. The sample should not leave the instrument at any time. Hence the cut sample should be closed off or be transported through the instrument.
3. Once it is ensured that a taken sample cannot leave the instrument, a next sample can be taken.

3. From functions to final concept

3.1. From functions to solutions

3.1.1. Function generation

The overall design problem concerns the design of a heart bioptome having a mechanism for the storage of multiple samples while preventing sample loss. This main problem is subdivided into eight sub-problems, so called functions. Defining these functions makes it easier to solve the main problem. For each of the functions at least one solution will be chosen. Some solutions to a function may exclude solutions to a next function. Therefore, the order of functions is important and should be maintained during the design process. Additionally, using this method will allow us to create a morphological scheme in which a number of solutions can be presented for each of the functions, hence allowing the best possible solution to each sub-problem being selected. The morphological scheme is shown in Table 2.

Table 1 Overview of the design requirements and wishes.

Mechanical requirements		
1.	Cutting	The bioptome must be able to cut a piece of a soft material
2.	Sample size	The samples that the bioptome takes must have a minimum surface area of 8 mm^2
3.	Diameter	The maximum diameter or width is $6\ mm$
4.	Length	The maximum length of the functional parts in the tip is $40\ mm$
5.	Storage	The bioptome should be able to store a minimum of 5 samples
6.	Safety	Sample loss must be prevented 100%
7.	Exterior	The bioptome must be shaped in such a way that it will not damage the veins, tissue and other body material
Control requirements		
8.	Usability	The bioptome must be simple to control, it must be controllable by one person
9.	Control actions	No more than two actions should be needed to grasp one biopsy sample
10.	Control force	The control force per element should not exceed 10 N.
Production wishes		
11.	Number of parts	The bioptome should have as few parts as possible
12.	Costs	Costs should be as low as possible

The eight functions are listed below:

A. Cutter position

The cutter position describes where the cutter is located. This can be at the top or on the side of the instrument. A cutter position on top will allow better pressure against the cardiac wall, whereas a cutter on the side will offer more freedom for cutter morphology.

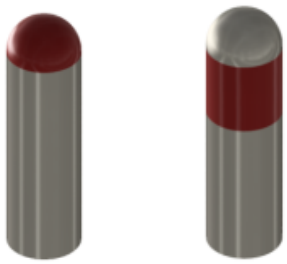


Figure 6 Solutions to cutter position, being: on top or on the side.

B. Cutter shape

The cutter shape defines the shape of the cutter; spherical, flat, cylindrical, or conical. Naturally, cutters with a shape in between flat (zero angles) and cylindrical (infinite angles) can be made, for instance a triangular cutter. However, in this case only the primary shapes are listed. The method by which the cutter will move is defined by the shape of the cutter.

Figure 7 Solutions to cutter shape: spherical, flat, cylindrical, and conical.

C. Cutting method

Three different solutions can be found for the cutting method, being: sliding, grasping, and penetrating. Sliding uses a cutter and an anvil to cut. Grasping uses two cutters on both sides of the tissue. For these two solutions, a relatively rough surface is needed. Penetrating is the preferred option for smooth surfaces in which the cutter is pushed into the tissue and a sample is taken. Sliding and grasping have in common that the action and reaction force are integrated in the instrument. The penetrating method does not necessarily have the reaction force integrated in the instrument, hence the cutter can be emitted in the tissue under high speed to prevent the tissue from being pushed away.

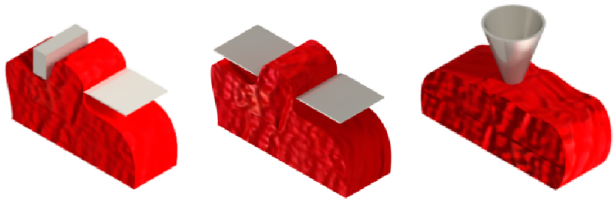


Figure 8 Solutions to cutting method: sliding, grasping, and penetrating.

D. Cutter direction

The cutter direction defines the direction of the cutter while taking a sample. This can be axial, radial, and tangential. The pictures show the axis over which the cutter can move. In combination with cutter movement it describes the full motion.

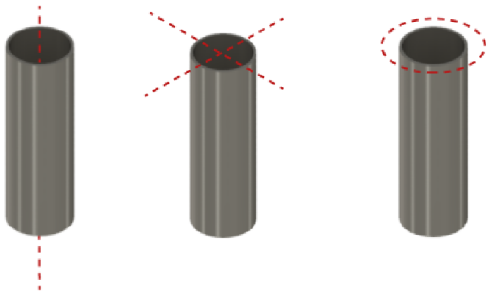


Figure 9 Solutions to cutter direction: axial, radial, and tangential.

E. Cutter movement

Cutter movement describes how the cutter moves over an already defined axis; translational or rotational. Combined with cutter direction this gives the full motion of the cutter.

Figure 10 Cutter movement solutions: translational and rotational.

F. Multiple sample handling

This function defines solutions for how to handle a minimum of five samples (one of the main requirements). This can be realized by using multiple bioptome tips, storage of samples in the tip, storage in the lumen, or by transport through the lumen. Storage in the tip or lumen creates the need for a mechanism that prevents the loss of retrieved samples, this is covered by the next sub-problem. Multiple bioptome tips on one instrument is a combination of multiple 'standard' bioptomes, actuation will be a challenge for this option. Transporting the sample through the lumen needs an extra source of energy to move the samples through the lumen.

Suction, being a solution to transport the sample trough the lumen, is excluded from the options, because it is considered unsafe. There is a potential risk to suck out (too much) blood out of the patient's heart and disrupt the blood pressure inside the heart.

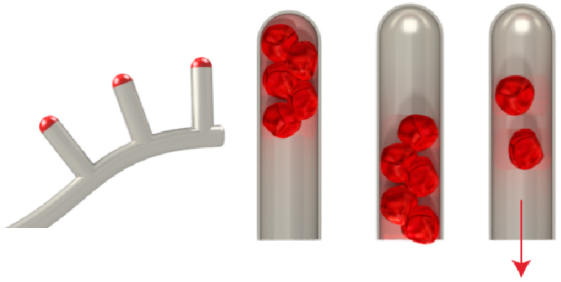


Figure 11 Solutions to multiple sample handling: multiple tips, storage in tip, or lumen, and transporting the sample through the lumen.

G. Preventing sample loss

Sample loss prevention is required to make sure that no biopsy samples are lost inside the heart or elsewhere in the body. This function becomes important only when a bioptome is required to take more than one sample, since it will remain in the heart for multiple samples whereas a standard bioptome takes one sample and is retracted directly. Preventing sample loss can be realized by using a one-way mechanism, an external force that pulls the samples through, or a valve system that closes and opens the opening at set times.

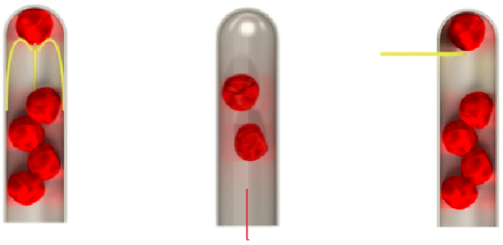


Figure 12 Solutions to preventing sample loss, being: one-way mechanism, an external force, and a valve.

H. Tissue stabilizing

Tissue stabilizing defines how the bioptome is held against the tissue wall. The instrument can be pushed on the heart wall (pressure), using impact by shooting the cutter in the heart wall, or by grasping the tissue. Pushing the instrument on the heart wall requires enough stiffness of both the instrument, and the heart wall at that point. Grasping does not need a stiffness of the heart to function, because action and reaction forces are integrated in the instrument. Discharging the cutter in the tissue (impact) is based on inertia (and therefore mass) of the heart tissue.

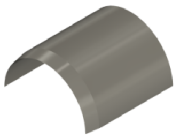
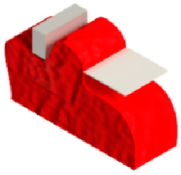
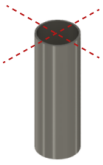
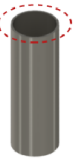
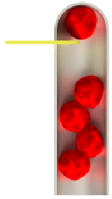
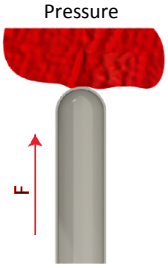
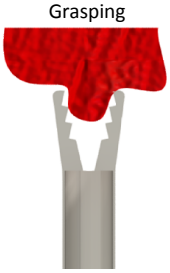
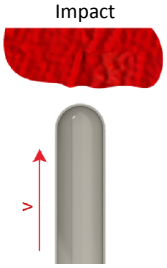
Figure 13 Solutions to tissue stabilizing, being: pressure, grasping, and shooting.

3.1.2. Combination of functions analysis

With the solutions to the functions of the last paragraph, a morphological scheme is generated. Before the solutions to each function are discussed six combinations from the morphological scheme are generated, they are called pre-concepts. The selection of solutions to these pre-concepts are indicated in the morphological table. The six pre-concepts are used to show some of the many design possibilities and to gain extra insight into the interaction between the functions, feasibility, simplicity, and safety. In appendix A the six pre-concepts are analysed and a final score is given, based on six parameters.

From the analysis, it becomes clear that the greatest challenge is to design a sophisticated solution for the function of preventing sample loss. The pre-concepts are not further developed, instead new concepts are derived from the solutions to functions, given in the next paragraph.

Table 2 Morphological scheme showing functions and solutions. The coloured dots show the selection of the six pre-concepts.

Functions	Solutions			
Cutter position	On the side 5 	On top 1 2 3 4 6 		
Cutter shape	Spherical 	Flat 	Cylindrical 	Conical 
Cutting method	Sliding (nibbling) 	Grasping 	Penetrating 	
Cutter direction	Axial 	Radial 	Tangential 	
Cutting movement	Translational 	Rotational 		
Multiple sample handling	Multiple bioptome tips 	Storage in tip 	Transport through lumen 	Storage in lumen 
Preventing sample loss	One-way mechanism 	External force 	Valves 	
Tissue stabilizing	Pressure 	Grasping 	Impact 	

3.1.3. Function discussion

To select which functions to continue with, all functions are discussed separately and a selection is made by considering the simplicity, requirements (if applicable), and interaction with mutual functions. Because the size, in particular the diameter, is limited, positioning the parts in the longitudinal direction is preferred. To pass through the samples the inner diameter inside the tip should be kept free.

A. Cutter position

Literature proves that the majority of used instruments in interventional cardiology have their functional site at the top/front of the instruments [9, 10, 26, 27]. The cutter position on top is the best option, because it allows for easier positioning of the instrument and because interventionists are used to the main functions being available on top of the instrument. Another disadvantage of the cutter location being on the side of the instrument is the fact that when rotation of the tip is required, the orientation of the functional part will not be clear directly.

B. Cutter shape

Because it is important to keep the inside diameter of the tip open, a hollow cutter is the preferred option. Whereas a conical cutter is the best suitable for a shooting mechanism, the option does not suit the requirements for this instrument. Since the mechanism was initially designed for smooth and flat tissue, it is therefore less suitable for the heart's tissue as it has the potential risk of perforating the heart.

Considering the option of a cutter positioned at the top of the instrument, some of the potential cutter shapes become less suitable, such as for instance the flat cutter. The best option is therefore a hollow cutter that has no hinges, but is instead an articulating cutter made out of single piece. This results in either a spherical or a cylindrical cutter.

C. Cutting method

With rejecting the shooting method and therefore the conical cutter shape, the penetrating cutting method can also be discarded. This leaves grasping and sliding. Grasping will enable more grip to the tissue because both cutting edges are sharp, and is therefore preferred. This will be useful especially when applied on the textured cardiac tissue.

D. Cutter direction

The cutter direction is in particular defined by the cutter shape. To obtain a clear opening some options are discarded, for instance the tangential cutter direction that is practically impossible to apply with an open tip. This would mean a decrease in sample surface area and grasping the tissue becomes more difficult. A radial cutting direction is the best option here to combine with grasping.

E. Cutting movement

The cutting movement depends on the chosen cutter shape and must not be complex to actuate. For the spherical, or cylindrical cutter shape in combination with a grasping cutter on top a translational cutting movement is preferred.

F. Multiple sample handling

Multiple bioptome tips is the option that is least preferred. The reason is that this method is too complex to insert it in the heart and manoeuvre it to the right place. In addition, actuation of multiple tips will become a difficult task.

Storage in the tip or in the lumen are similar regarding the basic principle, since only the distance over which the biopsy sample has to move is larger in the case of storage in the lumen. Therefore, storage in the tip is preferred. Transporting the sample through the lumen could be an option in combination with suction; however, suction is left out of the scheme for safety reasons.

G. Preventing sample loss

Safety is for the major part defined by the function of preventing sample loss. This function must have a sophisticated mechanism that will work for small and bigger samples, and without gravity. In case of a one-way mechanism the biopsy sample has to be pushed through the opening to work and smaller sized samples can slip through it.

Adding an external force to prevent sample loss makes the design extra complex and adds an additional problem, because it blocks the way for a new sample. The valve system is a good option; however, the work space for this is limited. A valve system that fully encloses the sample could solve this issue. The valve system is therefore the most promising option for this function.

H. Tissue stabilizing

Stabilizing is coherent with the cutting method. Impact is needed for the crown cutter, but not for a spherical, or cylindrical cutter. Therefore, the option of impact is discarded. Pressure is needed if the tissue is not pulled in the bioptome by the cutter mechanism. Grasping is the best option in this case, because it is the only option in which the action and reaction force are integrated in the tool. This will prevent high forces on the surrounding tissue.

3.1.4. Selection of solutions to functions

In conclusion, the following solutions were selected for the final pre-concept, see also Table 3:

- Cutter position: on top
- Cutter shape: spherical or cylindrical
- Cutting method: grasping
- Cutter direction: radial
- Cutter movement: translational
- Multiple sample handling: storage in tip
- Preventing sample loss: valve
- Tissue stabilizing: grasping

3.2. From concepts to final concept

3.2.1. Design rationale

With the selection of the solutions to the functions concepts can be constructed which will be closer to the final working design. A fundamental difference with a standard bioptome is that the retrieved sample has to pass through the tip or lumen before the next one can be taken. To achieve this, the instrument is hollow and the different parts need to be located lengthwise in the outer shell, behind the tip or in the handgrip.

Also, a valve should be integrated into the shaft to prevent sample loss. The valve should not extend outside the instrument to prevent the bioptome from damaging the heart or getting blocked in the heart muscle. Gravity to push multiple samples inside the instrument cannot be used, because the orientation of the bioptome tip constantly changes and the blood in the heart will nullify the effect of gravity. Moreover, the samples may stick to the surface.

Two concepts are covered in the next section. For these two concepts a compliant gripper is used. The gripper is open in neutral position and closes by sliding a tube over it. When the tube is removed, the gripper opens again, because the side of the gripper acts like a leaf spring. This mechanism allows a hollow tip.

3.2.2. Concept 1: Scraper bioptome

Gripper

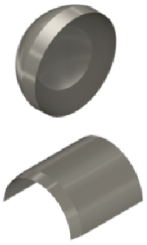
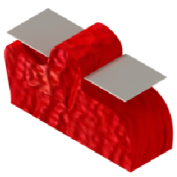
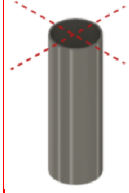
This concept is based on a square bioptome tip and a grasper on top. Figure 14 shows an impression of this concept. The grasper is made from one piece of metal with compliant joints. When the outer tube slides over it, the gripper will close. To make this principle work, the bioptome tip has a square cross-section.

Valve mechanism

The instrument has an extra valve to prevent the sample loss. A thin, flexible sheet is placed inside the bioptome to clear out the gripper by moving inwards along the inner gripper wall. This part is called the scraper. The bending of the scraper only works at single curved surfaces, similar to the gripper design. The scraper is guided on the inside of the gripper by two side panels.

The scraper starts as a straight sheet on one side of the instrument, in this case the right side. When the gripper is shut, the scraper can move upwards. As soon as it enters the curved shape inside the gripper, it will follow it and curve all the way along the surface until it makes a 180° turn. At the left side, it attaches to the left side panel to make sure it remains closed when the gripper opens.

Table 3 Final choice for the eight functions.

Cutter position	Cutter shape	Cutting method	Cutter direction	Cutting movement	Multiple sample handling	Preventing sample loss	Tissue stabilizing
On top	Spherical/ cylindrical	Grasping	Radial	Translational	Storage in tip	Valves	Grasping
							

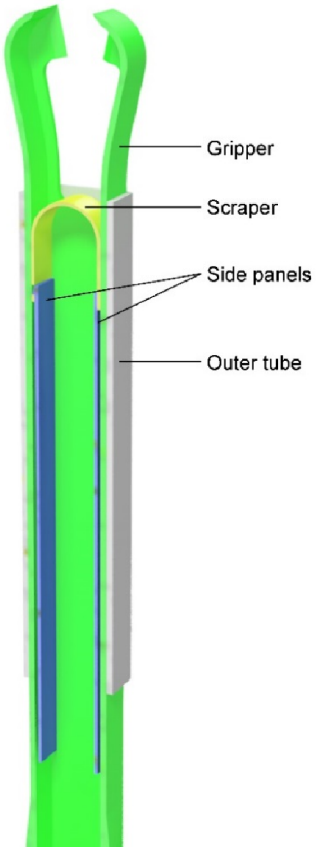


Figure 14 The valve bioptome with scraper.

The scraper can be retracted from the right side by pulling it downwards. At first the part inside the curve moves. Then the angle between the scraper and the left side is getting bigger which causes the scraper to detach from the left side panel. Once detached the scraper folds back to its original shape and gets back to its initial position. This scraper sequence is shown in Figure 15.

Sequence

The sequence of the instrument as a whole is shown in Figure 16. The six steps are given below:

1. The gripper is open and is pushed against heart tissue. The scraper is closed.
2. The outer tube slides forward and the gripper closes and cuts the biopsy sample. The scraper is still closed.
3. The scraper opens by pulling the right side of the scraper down.
4. The scraper is fully retracted on the right side.
5. The outer tube and side panels move a little bit forward. The scraper is pushed around the sample. The scraper connects to the left side panel.
6. The sample is pulled inside the instrument by sliding the outer tube back. At the same time the gripper opens.

Actuation

The outer tube has to move with respect to the grasper. This can be realized using a push-pull cable trough the instrument or by extending the outer tube towards the proximal end of the instrument. The scraper moves with respect to the gripper, as well as the two side panels. Actuation from the handle can be done with a push-pull cable. Another possibility is to use a spring between scraper and inner hub. The timing is then controlled inside the handle. The timing of actuating both the tube to close the gripper and the scraper determines the safety of the bioptome. Opening of the gripper and scraper at the same time should be avoided.

Challenges

The actuation of the scraper can be difficult, because it may be blocked in the curve where the two gripper parts meet. In addition, bending of the scraper can be a difficulty too, because of the relatively small bending radius in combination with a 180° curve.

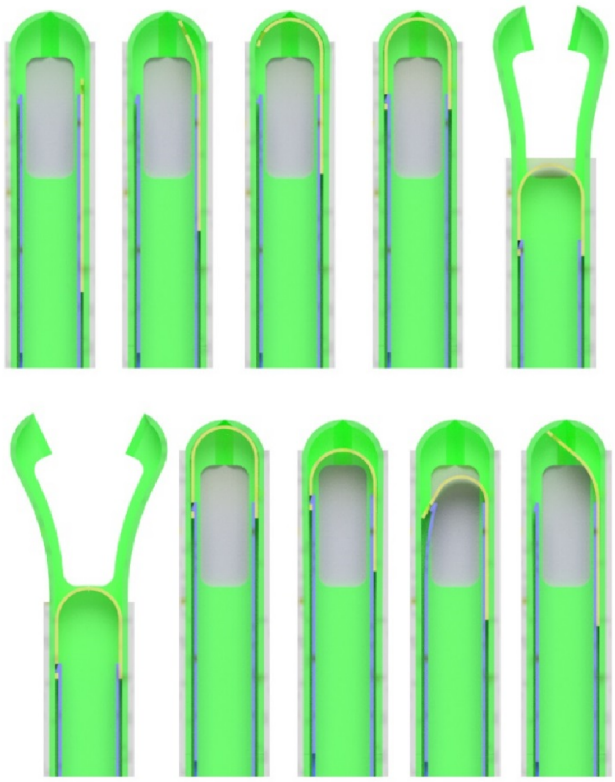


Figure 15 Sequence of the scraper inside the instrument.

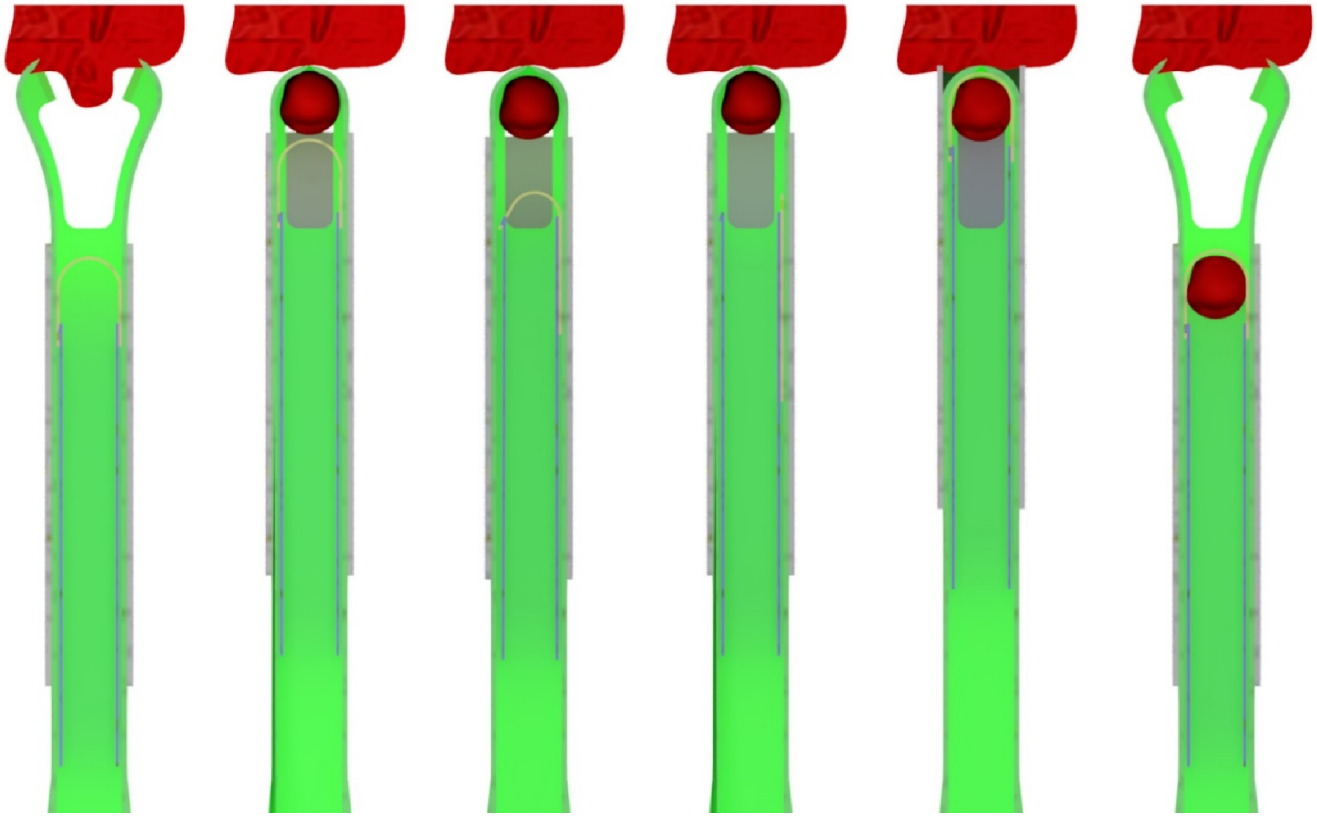


Figure 16 Sequence of the scraper bioptome in six steps.

3.2.3. Concept 2: Cross bioptome

Gripper and valve mechanism

This bioptome concept has two grippers, the working principle of both is identical to the scraper bioptome. They are open in neutral position and close by sliding a tube over it. The green gripper still works as a standard gripper, but the in gripper (yellow) is placed inside the outer gripper, under a 90° angle, and functions as a valve and takes over the cut sample from the outer gripper. The grippers are closed by one square tube with slots to close the individual grippers in a specific order.

This concept has a square cross-section as well, similar to the first concept. A cylindrical bioptome would not work in this case because the two grippers cannot be shaped in a manner that has the similar working principle. Another option is to fit the instrument with multiple grippers in a telescopic way (under 0° instead of 90°). However, this would increase the difficulty of actuation. It becomes even more difficult since the inner gripper should grasp first and in order to make it happen all outer grippers have to move out before it can.

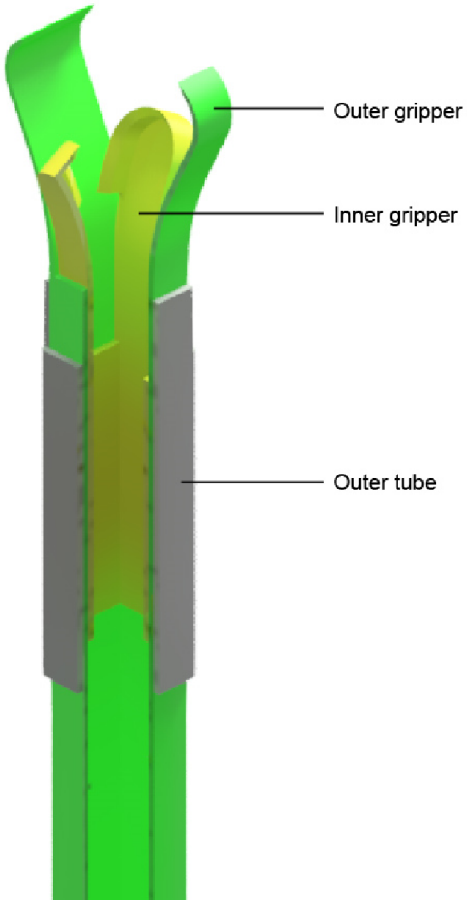


Figure 17 The Cross-bioptome with two grippers.

Sequence

The sequence of this concept is shown in Figure 18. The 5 steps are given below:

1. The gripper is in its neutral position. The inner gripper is closed. The instrument is positioned against the tissue.

2. The outer tube moves upwards and starts to close the gripper, at the same time the inner gripper moves upwards and opens.
3. The gripper is now fully closed and a sample is cut. The inner gripper is moved to the same position as the main gripper and is still open.
4. The inner gripper is closed by moving the inner gripper further upwards. The inner gripper grabs around the taken sample.
5. The biopsy sample is brought downwards by the inner gripper. The next sample can be taken.

Actuation

The outer tube has to move with respect to the outer and inner gripper, independently. The inner gripper has to move with respect to the outer one.

Challenges

Construction of outer gripper is weak, because the sides are missing in order to accommodate the inner gripper. Between step 2 and 3 both grippers are not fully closed. The mechanism is therefore not optimal, regarding sample loss prevention.

3.2.4. Final concept selection

The scraper bioptome allows for a fully closed area of the mechanism to prevent sample loss, where the Cross bioptome is not able to remain entirely closed during step 2 and 3 of the sequence. In addition, the construction of the gripper of the Cross-bioptome instrument will be weak, as the sides are missing, this may cause the gripper to collapse or misalign with the second gripper. The gripper of the scraper bioptome allows for more morphological freedom, so the sides can be closed. Actuation is a challenge in both cases, because two elements need to be controlled independently. For both improvement is needed to make it easier to operate.

The scraper bioptome will be elaborated further. This option has the most promising working principle and safety features based on the fundamental mechanical working principle, meaning that the Cross-bioptome is inferior to the scraper bioptome. In the next chapter, the scraper bioptome is further developed. The main components of the instrument are designed into detail and a final design is presented. A prototype is built at the end.

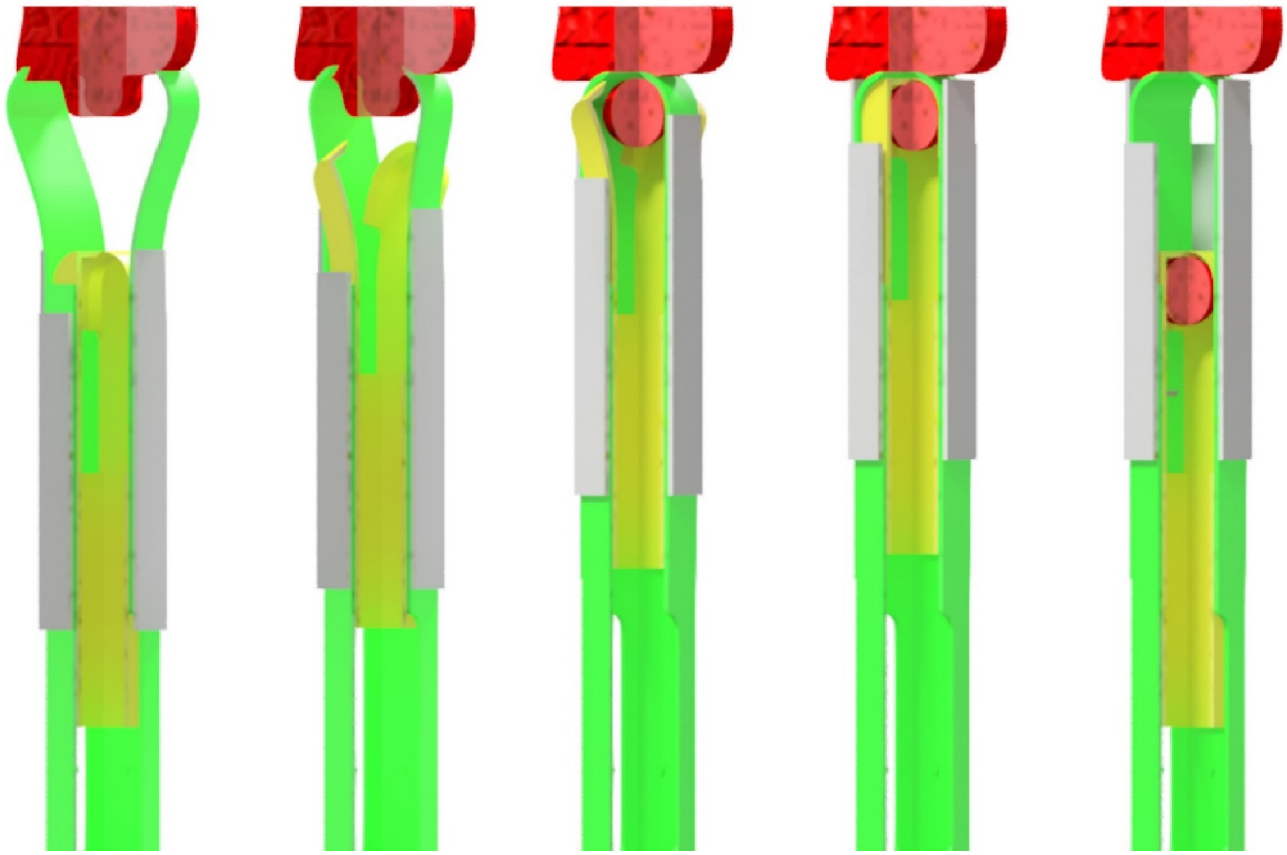


Figure 18 The sequence of the Cross bioptome showed in 5 steps.

4. From prototype to test

4.1. Tip design

4.1.1. Gripper design

The gripper is designed such that the scrapers will fit. The gripper should be hollow to pass the samples through and the gripper hinges should act like a spring. To ensure the sample is as big as possible, the open gap between the two gripper parts must be 6 mm or larger.

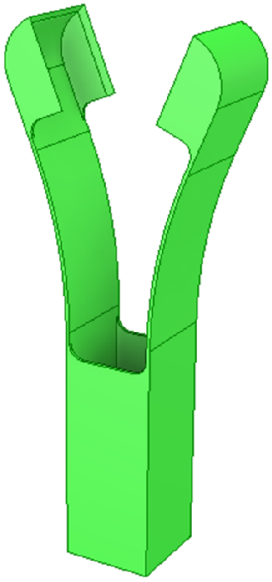


Figure 19 A 3D model of the optimized gripper.

The basic shape is a hollow square tube with wall thickness of 0.2 mm. To calculate the geometry needed to make the gripper work like a spring it is needed that the bending part of the gripper is as flexible as possible. The material composition, geometry and thickness determine how the gripper will bend. The following formula gives is used to calculate the relation between the radius and thickness of the material [28]:

$$\epsilon = -\frac{y}{\rho} \qquad 4.1$$

Where,
$\epsilon =$ strain [-],
$y =$ distance from the neutral plane [m],
$\rho =$ radius of curvature [m].

The maximum strain will always occur at the maximum distance from the neutral plane, in our case: $y = \frac{1}{2}t$. The radius of curvature is equal to the radius: $r = \rho$. This gives:

$$\epsilon = -\frac{y}{\rho} = -\frac{\frac{1}{2}t}{r} = -\frac{t}{2r} \rightarrow r = \frac{t}{2\epsilon}$$

The minus in the formula is omitted, because the strain will be equal, but opposite to each other. The radius of the gripper 'hinge' can be calculated with:

$$r = \frac{t}{2\epsilon} \qquad 4.2$$

Where,
$t =$ the thickness [m],
$\epsilon =$ the maximum strain [-].

The maximum strain of a material is equal to

$$\epsilon = \frac{\sigma}{E} \qquad 4.3$$

Where,
$\sigma =$ the yield strength [Pa],
$E =$ the E-modulus [Pa].

This only applies to materials with a linear stress-strain curve, like most metals. For stainless steel this results in a radius of $25\ mm$ being required for the chosen geometry and material, (assuming a maximum strain of $0{,}4\%$). A more flexible material will allow a smaller radius or a greater thickness. More flexible materials include plastics or special metal alloys like Nitinol. Plastics are not chosen because they are not strong enough, even with a greater wall thickness, and lack the hardness needed to cut the tissue. Nitinol is not chosen because it is difficult to work with and is more expensive.

To check if the design is feasible, the required forces are calculated. The goal is not to exactly calculate the internal force, because more factors are involved, but to give the order of magnitude of the forces. To calculate the force required to close the gripper, the following formula is used (one of the basic beam deflection formulas) [28]:

$$P = \frac{3vEI}{L^3} \qquad 4.4$$

Where,
$P =$ the applied force [N],
$v =$ the deflection [m],
$E =$ the E-modulus of the material [Pa],
$I =$ the moment of inertia [m^4],
$L =$ the length of the beam [m].

The force P is the force required to straighten the gripper hinge, this force depends on the position of the tube (L) and the deflection (v). When analysing this force as a function of L and v, Figure 21 is acquired. Note that P and v depend on the postion of the tube (L), see Figure 20.

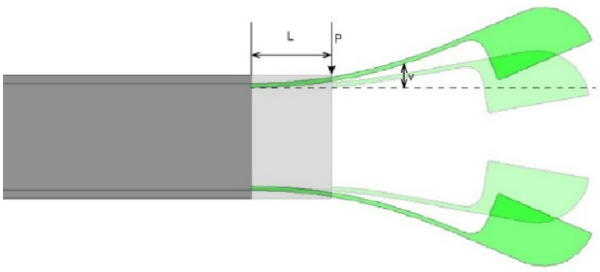


Figure 20 Schematic of force applied on gripper.

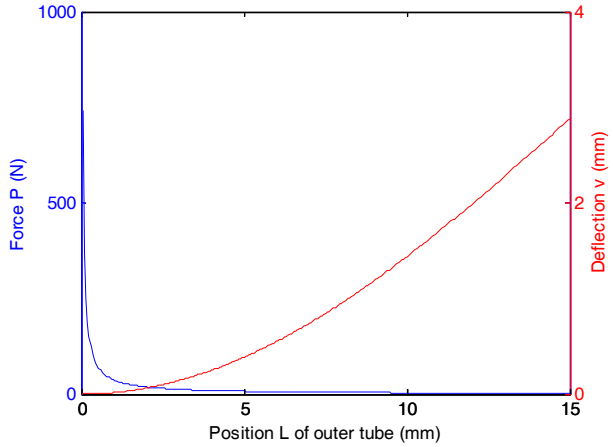


Figure 21 Force and deflection versus position of outer tube relative to gripper.

It can be seen that the force at the start, where L approaches zero, is very high and will be infinitely high when L reaches zero. However, the force drops significantly when L increases. When P is $20\,N$ the deflection v is $0.054\,mm$. The coefficient of friction is assumed to be $\mu_s \leq 1$. A force of $20\,N$ (on both sides of the grippers) is a force on the outer tube in axial direction of maximum $40\,N$.

To avoid the high forces above $40\,N$ at the start a minimum play of $0.054\,mm$ between the gripper and outer tube should be used. To lower the friction forces between the gripper and outer tube for the prototype, a new design is used that minimizes the friction force by using roller bearings to close the gripper. The estimated rolling resistance is ≤ 0.1. This results in an actuation force of $\leq 4\,N$, below 10 N as required by requirement 10.

To show the working principle, the gripper is left open on one side and is covered with an acrylic glass (PMMA) cover. In this way, the working mechanism of the scrapers can be seen, as well as the stored samples.

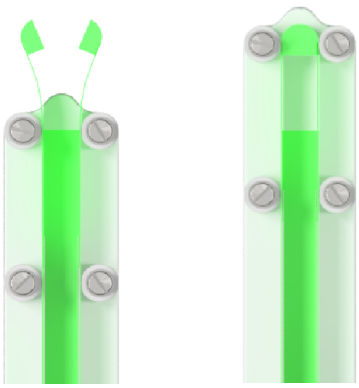


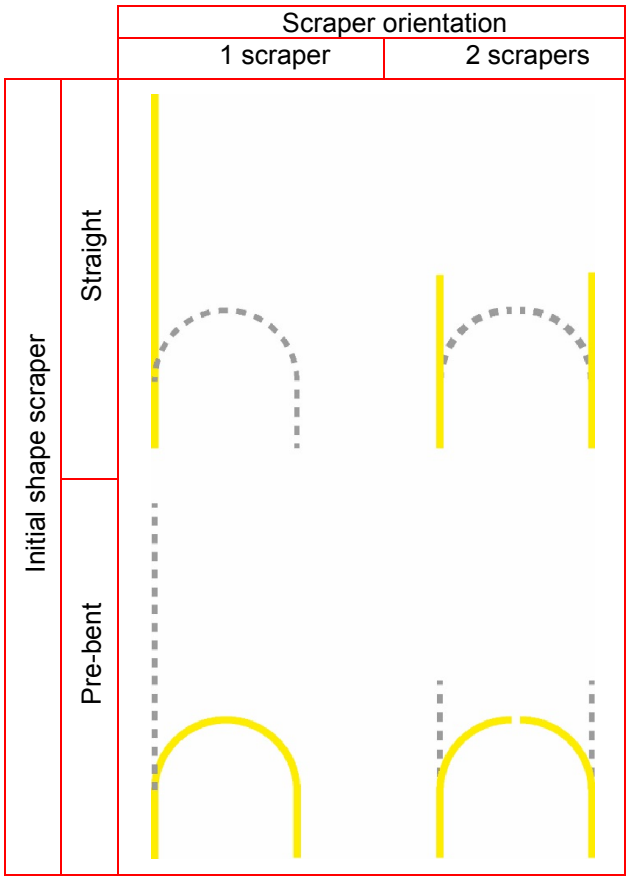
Figure 22 The gripper with closing mechanism, left: the gripper opened, and right: the gripper closed.

4.1.2. Scraper design

The scraper mechanism is chosen as a second valve in this design. The scraper should guarantee a reliable and safe working. The scraper mechanism as introduced in chapter 3 consists of one scraper, but more options are available. Four different options are presented in Table 4.

One option is to use two scrapers instead of one. This prevents the scraper from getting jammed at the point where the two gripper parts meet. Consequently, the scrapers will open as soon the gripper opens and results in two open valves at same time which is not allowed.

Table 4 Four options for the scraper mechanism configuration.



Pre-bending the scraper into the bend of the gripper results in a scraper mechanism that is standard closed. To open, the scraper needs to be pushed straight. The pre-bending can be applied to a single scraper and double scraper configuration as well. The way and simplicity of the actuation also depends on the scraper option. The double, pre-bent scraper mechanism is the best option, because the mechanism is standard closed and will not be blocked in the middle of the gripper which is a risk for the single scraper. To bend the scrapers straight (to open) a tube is needed to push the scrapers to the wall.

The curve the scraper is required to bend has a (average) radius of $2.7\ mm$. The scraper has to bend multiple times, and to make sure it does not fail by fatigue we have to make sure the material reamains in the elastic area. That means that for a stainless steel scraper we need a thickness of $0.0216\ mm$.

The scraper needs to withstand the applied actuation forces. A lack of stiffness and strength will result in wrinkling of the material. A too stiff material will cause too much friction and the mechanism will be blocked. Therefore, we need a material that is flexible, yet has sufficient bending stiffness to withstand buckling.

Nitinol is an alloy that consists of around 50% (of the mass) nickel and 50% titanium. The alloy is well known because of the shape memory effect where the material can be deformed at one temperature and then recovers its original shape by elevating the temperature. Besides that, Nitinol is biocompatible [29]. Another property of Nitinol is its super-elasticity, which occurs at a small temperature range, in which the material exhibits a flexibility a factor 10 or higher than (stainless) steel. The stress-strain curve is shown in Figure 23. It can be seen from the graph that Nitinol exhibits a non-linear behaviour. Around 1% of strain the curve's slope changes and the Nitinol changes from the austenitic phase to martensitic phase.

Because Nitinol is more flexible than stainless steel, or spring steel, the maximum thickness is ten times higher; $0.216\ mm$, assuming a maximum strain of 4%. For the prototype a thickness of $0.127\ mm$ has been chosen, due to availability and costs. Further calculations are also based on this thickness. The bending stiffness, given by multiplication of the E-modulus and moment of inertia, is around 100 times higher than steel, because of the greater thickness.

To check if the design is feasible, the needed forces are calculated, the goal is not to exactly calculate the internal force, because

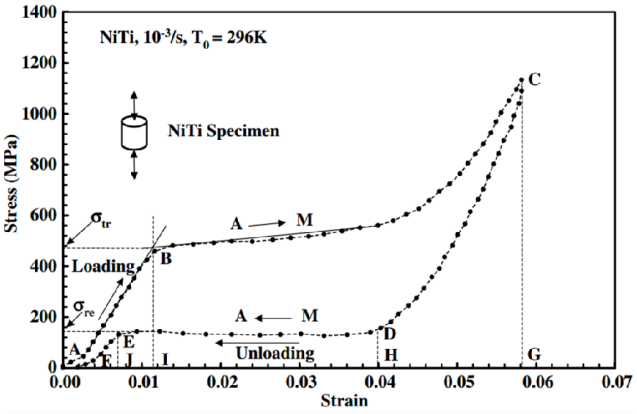


Figure 23 Stress-strain curve of Nitinol showing the non-linear behaviour and transformation from the austenitic phase to the martensitic phase [30].

more factors are involved, but to give the order of magnitude of the forces. To calculate the force needed to straighten the scraper the same formula as used for the gripper is used: $P = \frac{3vEI}{L^3}$. Note that this formula is not accurate for large deflections, the scraper undergoes a large deflection, so the results for the maximum deflection will not be very accurate. But, we know from the calculations done for the gripper the highest forces occur at the start of the bending, where the formula is still accurate.

For the E-modulus the average is determined from Figure 23. An E-modulus of $12.5\ GPa$ is determined, this applies to the area of $0-4\%$ strain. The graph shows the same characteristics as for the gripper. A force of $10\ N$ is reached at $L = 0.2750\ mm$. The deflection at that point is only $0.0060\ mm$. In order to find the axial force on the tube we need the friction force between the inner hub and the scrapers. This is assumed, similar to the calculations of the gripper to be $\mu_s \leq 1$.

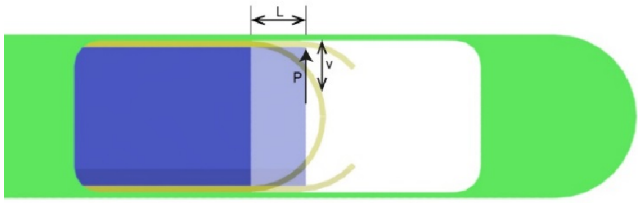


Figure 24 Schematic of force applied on scrapers.

In this design, there is no place to implement roller bearings similar to the gripper design, to lower the actuation forces. The space inside the instrument is needed to store the sample, so this cannot be used. Instead, lubrication is used to lower the friction coefficient. The estimated friction coefficient is $\mu_s \leq 0.3$. This results in a maximum axial force of $\leq 6\ \mathrm{N}$. This is considered as a force still easy to actuate and below 10 N, as required by requirement 10.

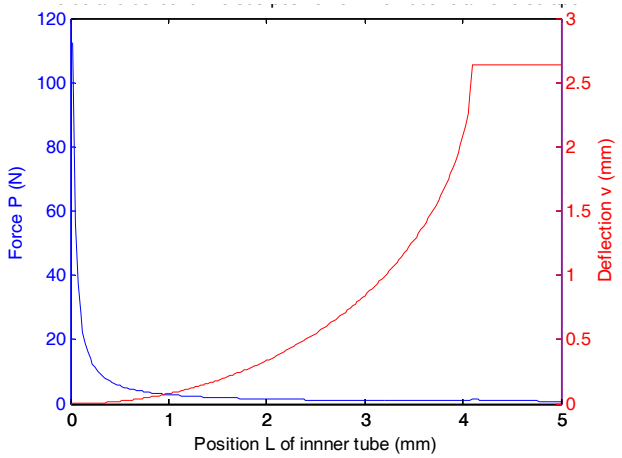


Figure 25 Force and deflection versus position of inner tube relative to scraper.

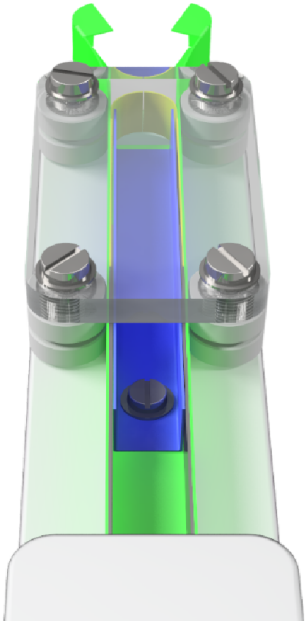


Figure 26 Overview of the main components of the prototype.

4.1.3. Sequence

For the sequence analysis, the gripper is assumed static (which means the base does not move). To make the instrument work three objects have to move; the gripper closer, the scrapers, and the inner tube that opens and closes the scrapers. When looking closely at the sequence of these objects it becomes clear that the inner tube and the gripper closer have the same sequence, so they can be connected. This leaves two objects to actuate. The sequence can be seen in Figure 27 and includes the following steps:

1. The gripper is open. The instrument is pushed against the heart tissue. The scrapers are closed.
2. The outer and inner tube are pushed up, the gripper is partly closed. The scrapers are still closed.
3. The gripper closer and inner tube are pushed up further, the gripper is now fully closed and a sample is taken. The scrapers start to open, because the scrapers are hold back with respect to the position of the inner tube.
4. The gripper closer and inner tube are pushed upwards to the maximum position. The scrapers are fully open.
5. The scrapers close by moving upwards.
6. The gripper closer and inner tube move downwards, along with the scrapers. The grippers start to open again.
7. The biopsy sample is brought downwards. The gripper is fully open. A next sample can be taken.

We discriminate between the gripper closer and inner tube, and scrapers. The position is shown. In Table 5. The positions correspond with the sequence shown in Figure 27.

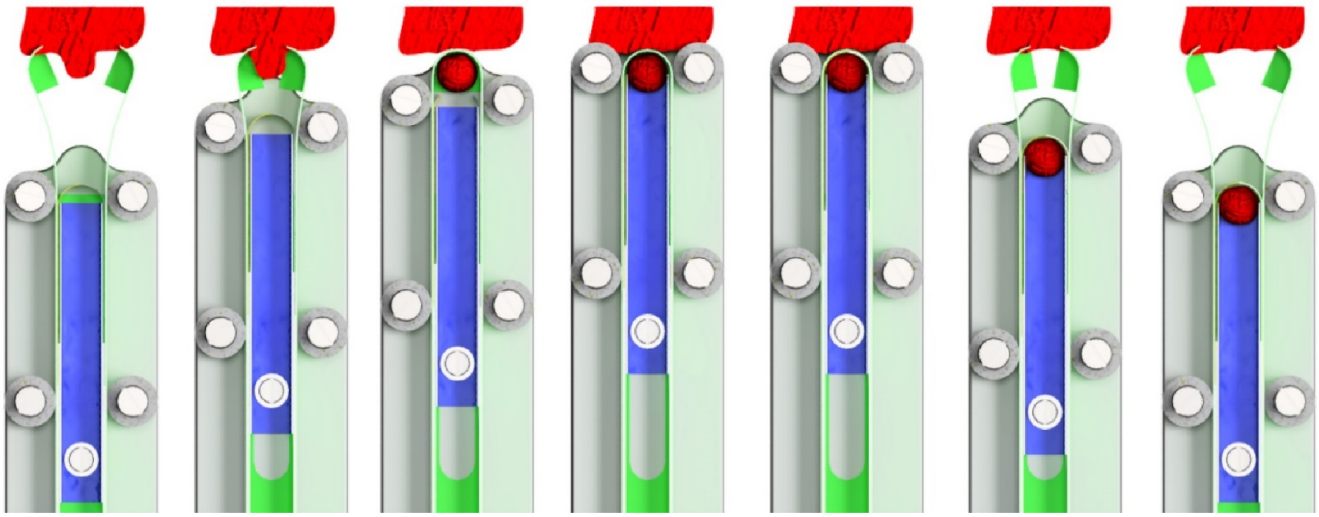


Figure 27 The sequence of the scraper bioptome with two pre-bent scrapers showed in seven steps.

4.2. Actuation design

4.2.1. Actuator selection

From the analysis of the sequence in the last paragraph we know two elements need to be driven independently. The difference with respect to usual, standard bioptomes is that we now have not only a gripper, but also a scraper that needs to be actuated. We also know that the actuation should be suited for multiple grabbing actions sequentially.

The simplest option is to use two separate handles to actuate each element individually. However, this will result in a complex actuation sequence for the operator. Opening both valves (gripper and scrapers) at the same time is possible, resulting in an unsafe situation, because loss of sample is possible. A second option is to use a mechanism that also uses two handles, but one of the handles is locked in position at certain points to prevent unsafe situations in the sequence. For example, the gripper can only open when the scrapers are closed, if the scrapers are open the gripper closer is locked.

The best option is to use a mechanism that automatically synchronizes the two motions to assure safety of the instrument, is simple to operate, and which allows for sequential use. A solution to this is the cam mechanism. A rotating cam in combination with cam followers turn a rotational motion into a reciprocating motion. For the final design this option was chosen.

4.2.2. Final actuator design

The cam mechanism needs to be designed specifically to work for the novel bioptome tip. Because we have two objects that need to move independently, we need two cam discs. Each cam disc has its own specific shape, according to the positions shown in Table 5. For the actuation also multiple options are available; a simple crank, an electric motor or a mechanism that translates a linear motion into a rotating motion. A simple crank is considered as the best option, because it is simple to control, it has no need for an extra power source and there is more feeling with the instrument involved. In addition, the angle of the crank automatically provides visual feedback for the user. To cam discs are designed to rotate clockwise. To prevent anti-clockwise rotation inside the hub a one-way bearing is placed that only allows a clockwise rotation.

To make sure the cam follower follows the cam usually a spring is used to press the cam follower against the cam. A disadvantage of that is that the cam follower may be blocked as a result of the higher friction force between cam and follower. For the prototype a cam mechanism is used in which the cam followers follow a groove in the disc cam (also called a face cam). In this way, the cam followers are not restricted in one direction, but two. This makes the use of springs unnecessary. The cam followers are fitted with a small roller bearing that fits in the groove.

The angle of the crank for each step is shown in Table 6. One full rotation will result in one full sequence of the device. The sequence can be roughly divided into four steps: closing the gripper, open the scrapers, close the scrapers, and open the gripper. From earlier analysis we know that opening the scrapers will require the highest force. To keep the torque, required on the crank, evenly distributed over one full rotation, the opening of the scrapers, relative to the displacement of the cam follower, has the largest angular rotation, about $115°$. The

Table 5 Position of the two elements to control for each step.

	Gripper closer and inner tube (mm)	Scrapers (mm)
1	0	0
2	6	6
3	10.5	8.5
4	15	10.8
5	15	15
6	7.5	7.5
7	0	0

Table 6 Crank angle for the seven steps.

	Crank (degrees)
1	0
2	120
3	150
4	225
5	300
6	330
7	360

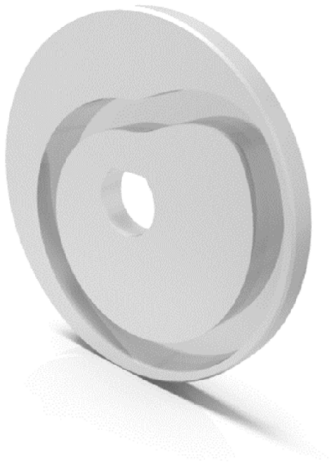


Figure 28 The disc cam for the positioning of the gripper closer and inner tube.

last step, in which the gripper opens again takes only 60°, because the scrapers remain closed and will only move back and the gripper opens again to its neutral shape.

The cam follower mechanism consists of a strip placed in a linear guide. To prevent the guide to jam by tilting (“schranken” in Dutch) the linear guiding is chosen as 50 mm, more than three times the displacement of the cam followers (15 mm). In addition, the guiding is positioned as close as possible to the cam wheels. The two strips can slide through nylon wheels which lower the friction forces.

4.3. Final design

The main functional parts are the gripper with closer, inner tube and scrapers. The gripper is made longer than necessary to look more like an instrument, but is still rigid. In addition, the top of the model is left open to make the working principle and the samples visible.

The two strips, the cam followers, are placed underneath and above the gripper. The lower one actuates the gripper and inner tube. The one on top is connected to the scrapers. The two cams rotate about the same axis, with the slots opposite to each other.

The assembly is put on an acrylic glass (PMMA) plate which holds together the sub-assembly of cams and the pins that guide the two strips. To cope with inaccuracies in the manufacturing process, possibly leading to malfunctioning of the prototype, the positioning of the main parts are made adjustable, this means that the position of the inner hub, scrapers and gripper can be fine-tuned to the right position.

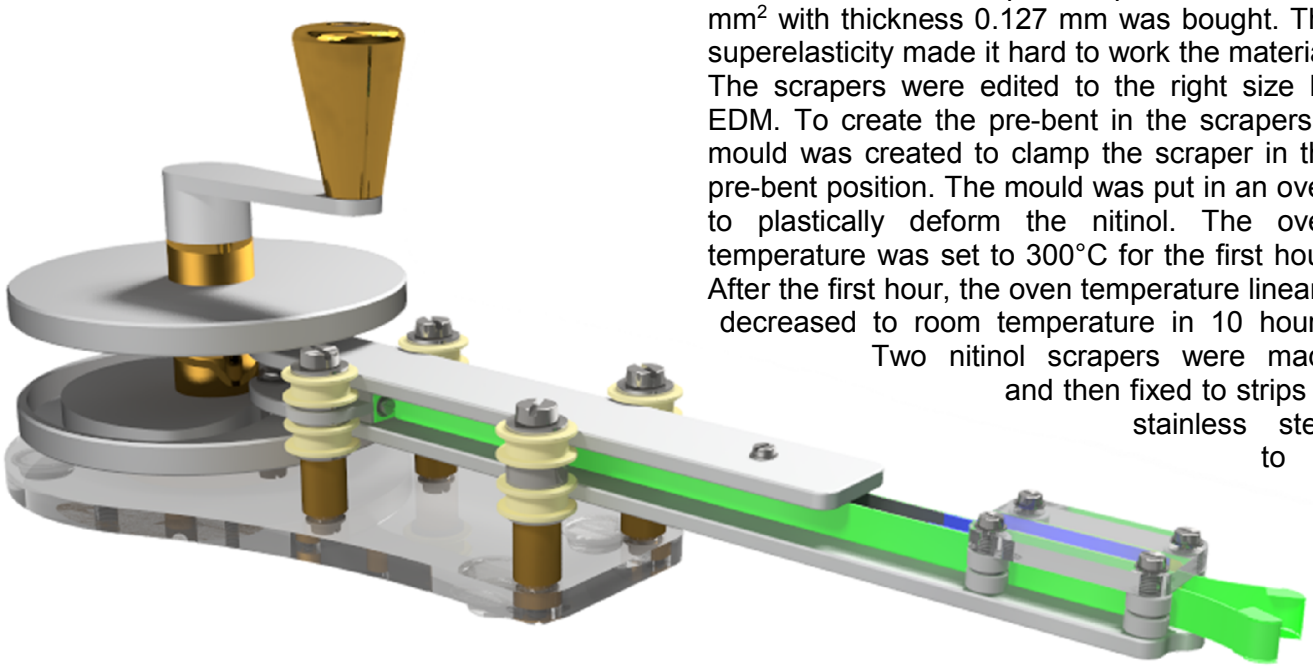


Figure 30 A 3D model of the final design of the prototype.

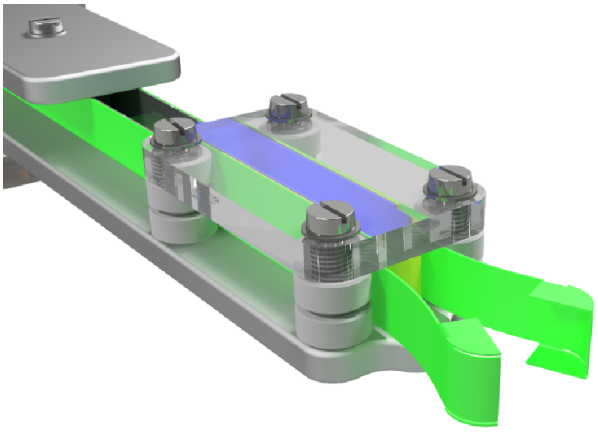


Figure 29 A visualization of the tip of the proof of principle prototype.

4.4. Prototype

4.4.1. Manufacturing process

The parts were partly made in the workshop at mechanical engineering (IWS) and at DEMO. Multiple manufacturing methods were used, like turning, (CNC) milling, laser cutting, and EDM (Electric Discharge Machining). Parts with a small wall thickness were made by EDM for high precision. The minimum radius with EDM is about 0.1 mm, the same as our smallest wall thickness. An important aspect to deal with is that with most manufacturing techniques a radius in the corners is left. Especially with an instrument with a square cross-section and this small scale it is something to take into account.

The gripper was made of a stainless steel sheet of 0.2 mm thickness. The sheet was cut out by a laser cutting machine. The sheet was then soldered and bent into the gripper. Nitinol was used for the scrapers, a piece of 25 x 25 mm^2 with thickness 0.127 mm was bought. The superelasticity made it hard to work the material. The scrapers were edited to the right size by EDM. To create the pre-bent in the scrapers a mould was created to clamp the scraper in the pre-bent position. The mould was put in an oven to plastically deform the nitinol. The oven temperature was set to 300°C for the first hour. After the first hour, the oven temperature linearly decreased to room temperature in 10 hours. Two nitinol scrapers were made and then fixed to strips of stainless steel to

extend the scrapers to the sliding strip. The three main functional parts can be seen in Figure 32. In the Appendix B a list of all parts can be found

4.4.2. Assembling process

On the acrylic glass (PMMA) ground plate everything was fixed. The four slider pins and the pin for the cam wheels were screwed onto the ground plate. The ground plate has four rubber feet that prevent the ground from slipping away. The two cam discs slide over the camshaft with spacer rings. Inside the camshaft the one-way bearing was press-fitted. On top of the camshaft the crank is positioned and fixed with a set screw.

The two sliders are guided by nylon wheels that rotate on the four slider pins. In between the gripper is fixed. Inside the gripper, the scrapers and inner hub are placed. The scrapers extent to a small block that connects to the slider on top. The tip assembly was covered with an acrylic glass (PMMA) plate. The bearings on the side roll over the gripper when the slider moves and close the gripper. Figure 31 shows an exploded view of the prototype.

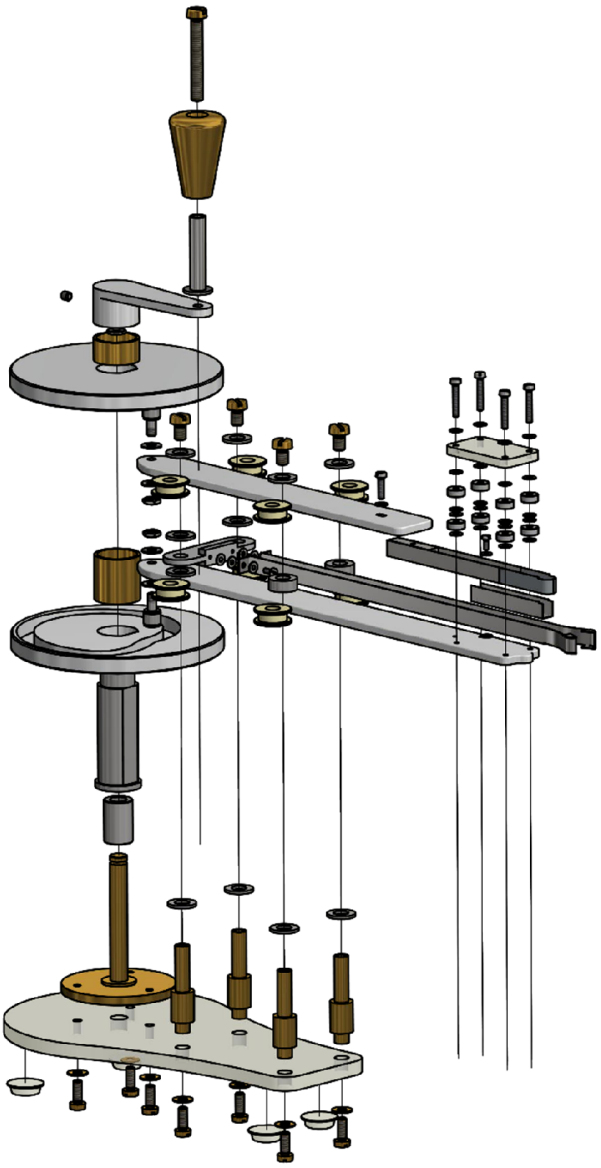


Figure 31 Exploded view of the prototype.

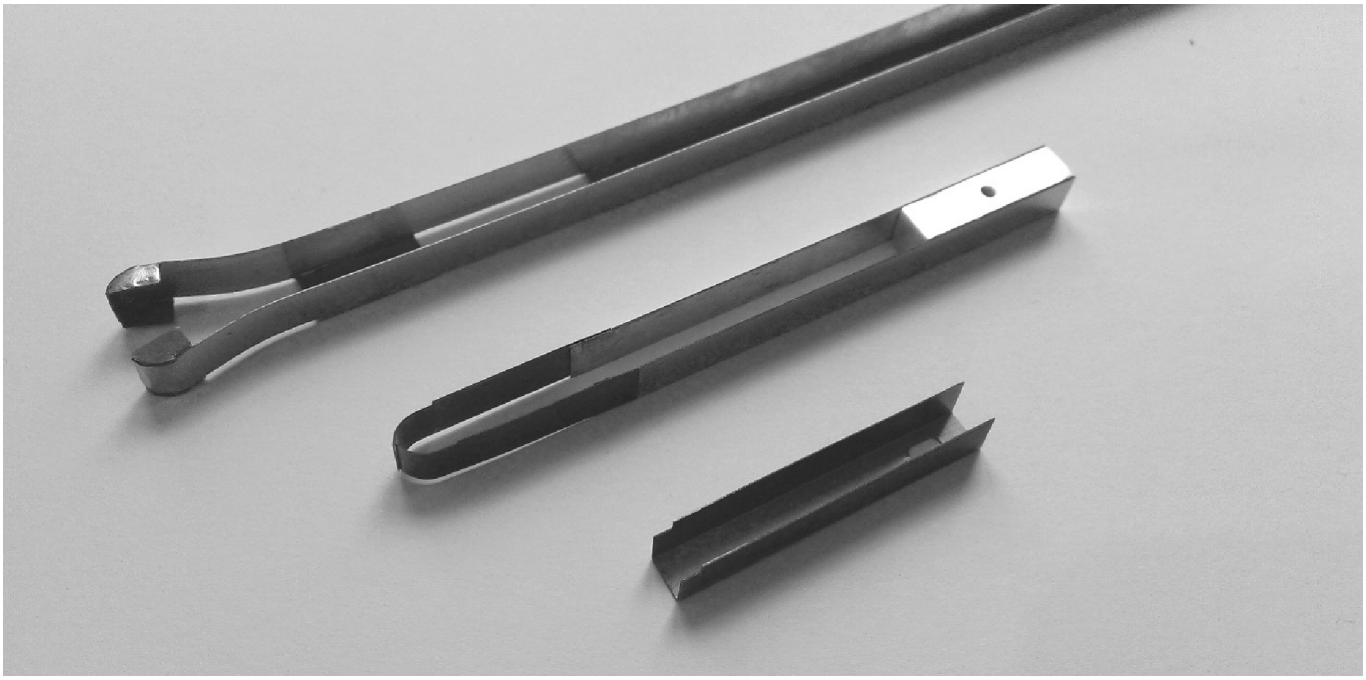


Figure 32 The three main functional parts; the gripper, scrapers and inner hub (from left to right).

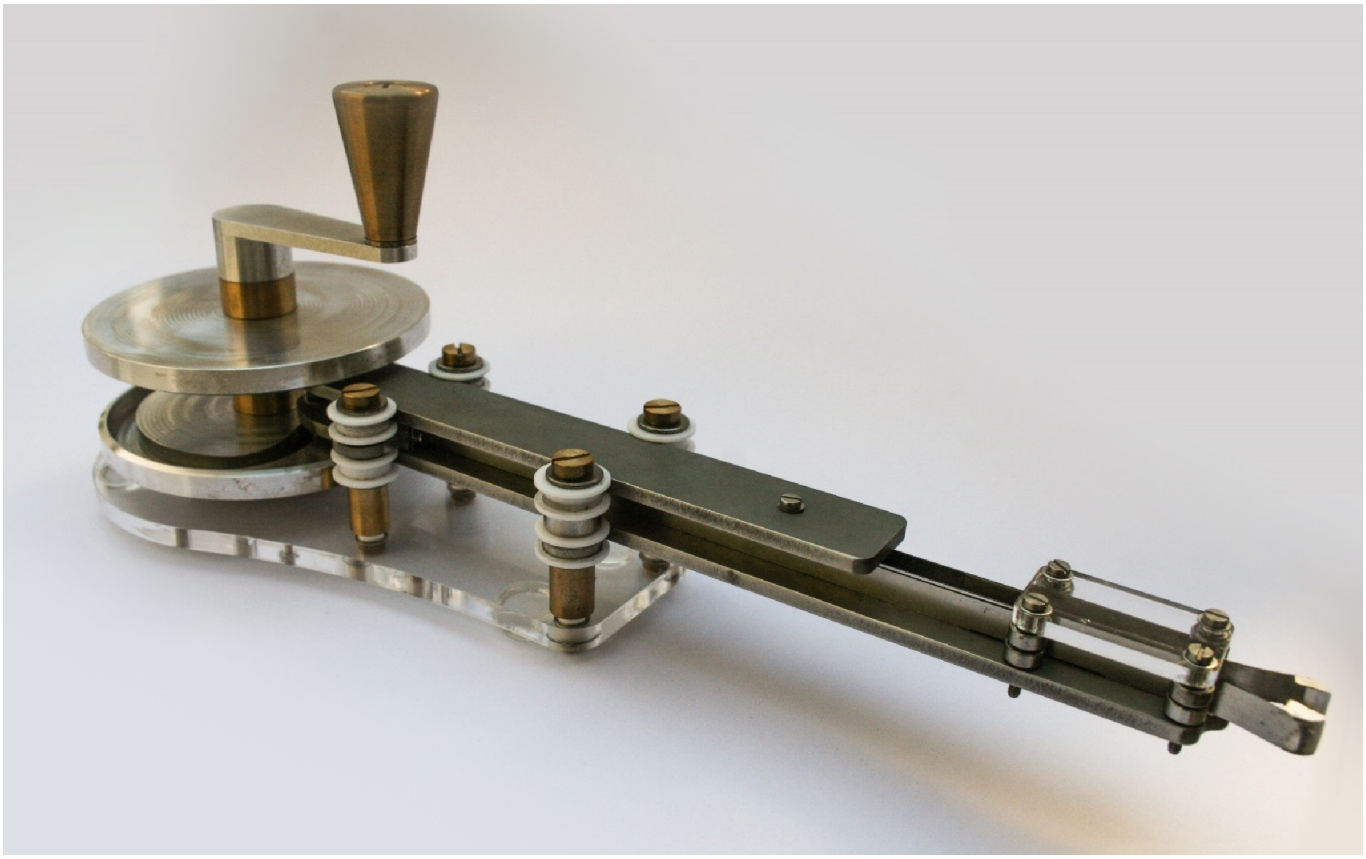


Figure 33 The proof-of-principle prototype, called MultiBite.

4.5. Proof-of- concept test

4.5.1. Aim of the test

A first step to validate the proof-of-principle of the instrument was to test the prototype. The instrument was tested to validate the functioning of the actuation mechanism and the functioning of the working principle. The first test to test the actuation mechanism was done to check the mechanical functioning of the actuation. In order to test the working principle, samples of both gelatine (test 2) and sausages made of mechanically separated meat (MSM) (test 3) were performed.

The aim of the test was not to test if the instrument is able to take a real cardiac biopsy sample, but merely the mechanical working principle, because that is the goal of this study. In addition, the gripper of the prototype has not been sharpened and is therefore not suited to take samples of though materials. Therefore, gelatine was chosen, because it is a soft material that has a homogenous structure. For the next test a different material was used: a sausage consisting of MSM (also known as a 'frikandel' in Dutch) because the structure is tougher compared to gelatine, but still has a homogenous structure. The following tests were performed:

1. Functioning of the actuation mechanism;
2. Functioning of the working principle by taking gelatine samples;
3. Functioning of the working principle by taking MSM samples.

The functioning of the working principle was tested by examining the sample handling and the safety of the mechanism to prevent sample loss.

4.5.2. Materials & methods

Test 1

The following materials were used during the first test:

- Prototype (fully assembled, clean, and functional);
- Table;
- Video camera with tripod.

For the test the assembled prototype was put on a table. A video camera was put on the tripod and captured the test with a top down view. The following protocol was then performed:

1. The crank of the prototype was tried to rotate in both directions;
2. During the operation, the following details were checked:
    - Is the crank able to rotate in the (anti)-clockwise direction?
    - Do the sliders follow the slots in the cam wheels?

A video camera captured the movements of the crank and sliders. The backlash of the instrument was estimated by hand.

Test 2

For the second test the following materials were used:

- Prototype (fully assembled, clean, and functional);
- Table;
- Gelatine in 5 different colours (red, green, yellow, blue and orange);
- Video camera with tripod;
- Photo camera.

The gelatine (brand: Dr. Oetker) was prepared according to instructions on the package. The gelatine was poured into five plastic cups. After adding dye (brand: Dr. Oetker) to the five cups to acquire the colours red, green, yellow, blue, and orange, the gelatine was placed in the fridge for 12 hours.

The setup is illustrated in Figure 34. For the test the assembled prototype was put on a table together with the gelatine with different colours. A video camera was put on the tripod and captured the test with a top down view. During the test the following steps were performed:

1. The open gripper of the prototype was pushed against the gel.
2. The crank of the prototype was rotated a full rotation clockwise.
3. During the operation the following details were checked:
    - Does only one valve (gripper or scraper) open at the same time?
    - Is there any material left (gelatine) in the gripper after the scraper closes inside the gripper?
4. Point 2. and 3. were performed 5 times in total, every time with a different colour: in the order of red, yellow, green, blue and orange.
5. The whole procedure was performed 6 times.

The working principle of the tip was tested by taking 6 x 5 samples. After each series of 5 samples a picture was made of the tip of the instrument. During the experiment the instrument filled up with gelatine samples. The samples that where pushed far enough through the tip were picked out of the instrument. During the test a camera filmed the prototype from above. From that, the total time and the time per sample was analysed. After each series of 5 samples the inside of the grasper (when it opens again) was checked for residual gelatine,

Figure 34 The experimental setup with the MultiBite prototype, camera and gelatine to test the working principle.

pictures were made of this. To check if the scrapers and gripper (fully) closed, the gap size was measured in case of a noticeable gap.

Test 3

- Prototype (fully assembled, clean, and functional);
- Table;
- Deep fried sausage consisting of mechanically separated meat (MSM), also known as frikandel;
- Video camera with tripod;
- Photo camera.

For the test the assembled prototype was put on a table. The MSM was held in place by two protruding screws in a small slat. The crust of the MSM sausage was removed to obtain a homogenous structure. A video camera was put on the tripod and captured the test with a top down view. The following steps were performed:

1. The open gripper of the prototype was placed against the MSM.
2. The crank of the prototype was rotated a full rotation clockwise.
3. During the operation the following details were checked:
    - Does only one valve (gripper or scraper) open at the same time?

- Is there any material left in the gripper after the scraper closes inside the gripper?

4. Point 2. and 3. were performed 5 times in total.
5. The whole procedure was performed 6 times.

During the test a camera filmed the prototype from above. After each series of 5 samples the inside of the grasper (when it opens again) was checked for residual meat, pictures were made of this. To check if the scrapers and gripper (fully) closed the gap size was measured in case of a noticeable gap. The working principle of the tip was tested by taking 6 x 5 samples. After each series of 5 samples a picture was made of the tip of the instrument. During the experiment the instrument filled up with MSM samples. After each series of 5 samples, the samples were picked out of the instrument.

4.5.3. Results

Test 1

The functioning of the actuation mechanism was checked by rotating the crank in both directions, the crank was only able to rotate clockwise, because of the one-way bearing. Rotation in the anti-clockwise direction was restricted, even with a considerable higher amount of torque the crank did not rotate in the wrong direction. In addition, the backlash was determined to be less than one degree. The two sliders were connected to the slots in the cam wheels and the cam wheels were rotated by rotating the crank. The two sliders followed the slots in the cams and little effort was required to actuate the mechanism.

Test 2

The gripper and scraper were able to open and close at the designed positions. The instrument was able to take a sample of the gelatine sample and the scraper took over the sample when the gripper closed, see Figure 35. Some samples were (partly) pressed out the gripper during the gripping action and also during the scraper action, see Figure 36. After a series it was noticed that small pieces of gelatine remained in the inner wall of the gripper. A gap size was noticed between the two scrapers and was approximately 1 mm, see Figure 38. The perspex cover on top leaked some gelatine too. An overview of the taken samples can be seen in Figure 37. The samples differ in shape and size. The average time to take one sample measured over 6 series is 16.3 s, with a standard deviation of 1.3 s. The time slowly decreased during the 6 series.

Figure 35 Overview of stored samples in the tip after the first series.

Figure 36 Overview of stored samples in the tip after the sixth series.

Test	Total time (s)	Time/sample (s)
1	88	17.6
2	90	18
3	83	16.6
4	78	15.6
5	78	15.6
6	71	14.2
Average	**81.3**	**16.3**
SD	**6.47**	**1.29**

Table 7 Overview of time duration of test 2.

Test 3

The gripper was able to take a sample of the MSM sample and the scraper took over the sample when the gripper closed. An overview of the stored samples can be seen in Figure 40. Figure 39 shows the overview of the taken samples. The samples differ in shape and size, but show more consistency compared to the gelatine samples. The gelatine leaked out of the instrument, but the MSM remained in the tip, it was not pressed out of it. Similar to the gelatine small pieces kept sticking to the inside of the gripper at the end of a series. The MSM remained more compact during the tests.

Figure 37 Overview of taken gelatine samples.

Figure 39 Overview of taken samples of MSM.

Figure 38 Front view of prototype tip; clearly visible is the gap between the scrapers.

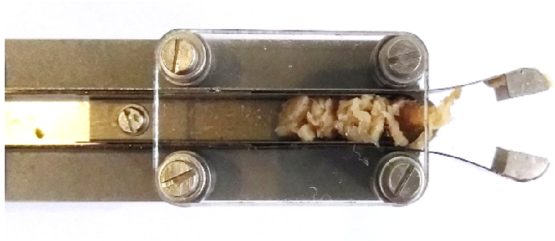


Figure 40 Overview of stored samples in the tip of the prototype after the test with MSM.

5. Discussion

Background

For cardiac biopsies a minimum of five biopsy samples are retrieved from a patient's heart during one intervention. To lower the complication rates associated with cardiac biopsy procedures a novel heart bioptome is designed that can store five biopsy samples without sample loss. It is expected that this will reduce the complications associated with heart biopsies.

Design & requirements

The proof of concept experiment with the prototype was successful and has brought further development and possible appliance to a heart bioptome a step further. The prototype showed that it is possible to store biopsy samples in the instrument within the limited dimensions.

The functional parts in the tip have a length of 38 mm, but this is when the inner hub is pushed forward towards the gripper head. The inner hub itself is 35 mm long to accommodate 5 samples, each with a diameter of slightly less than 6 mm. When the inner hub moves back, for example when the gripper opens, the rigid length of the functional parts becomes larger than 40 mm, it reaches over 53 mm.

To actuate the bioptome three parts need to be positioned: the gripper closer, the inner hub and the scrapers. By connecting the gripper closer and inner hub the complexity for the control is lowered. The cam discs that drive the elements in the tip is simple to actuate, it only needs to be rotated to perform the right sequence. Rotation in the wrong direction is inhibited by a one-way bearing.

Design recommendations

A compliant gripper is used to leave space for the scraper mechanism and samples. The gripper is closed by a slide assembly with ball bearings. The closing angle of the gripper is determined by the extent to which the sliding element is put forward. In the commonly used heart bioptome the gripper is actuated by a cable. The cable is connected to the handle and the force is directly transferred to the gripper. This is not the case with the new instrument; the gripper force cannot be increased when the sliding element is in the farthest position. This can be an issue when a tough tissue needs to be cut.

Another difference with the regular bioptome is the maximum opening angle of the bioptome. This is a consequence of the choice for a compliant design instead of a hinged construction. Regular bioptomes have a maximum opening angle of more than 90°. The new instrument has an opening angle of only 46°. However, the opening gap of the new design is still above the maximum sample size but it may affect the grasping ability of the instrument. Increasing the opening angle would mean a longer tip. Another solution can be found in the use of a more flexible material of the bending gripper part.

The radius of the scraper was designed to fit the inner radius of the gripper perfectly. To enhance the scraper action and therefore the safe working of the bioptome one could choose to increase the radius slightly. This affects the position of actuation (closing of the scrapers) and the volume inside the scrapers. Figure 41 shows a schematic of this principle.

The square shape of the instrument can be seen as a disadvantage. It makes the mechanical tolerances more complex, due to the radii of the parts as a result of manufacturing limitations. A circular design with the same working principle can be designed by decreasing the width of the scrapers and use 4, or more, scrapers. The scrapers then act like fingers and grasp around the tissue. A side effect is that multiple small scrapers will not perfectly close the area and thus will be less safe. Note that the gripper also needs adjustments in order to function in a circular design. The current design of the flexible hinges will only work in a single curved surface.

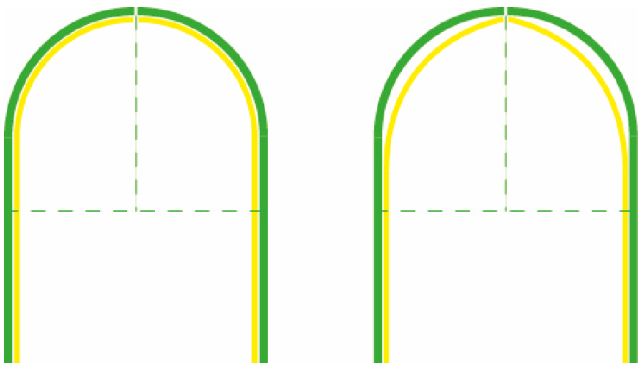


Figure 41 Gripper and scraper combination. Standard scraper radius (left) and increased scraper radius (right) may enhance the scraper principle.

Manufacturing

During the design process the manufacturing of the prototype was kept as simple as possible. However, multiple different manufacturing techniques were needed for the prototype, mainly because the small scale. Initially, the manufacturing process of the gripper was chosen to be bending. The flat pattern was cut with a laser cutter in a stainless steel metal sheet. The low thickness (0.2 mm), in combination with a lack of the right tools at the DEMO workshop to bend thin metal sheets, resulted in a wrinkled product. Therefore, instead of bending, the different elements of the grippers were soldered together, this gave the sophisticated result.

The nitinol scrapers required a special heat treatment to make the pre-bent. Cold working is hard because of the super elasticity the alloy exhibits. In order to attain the right end product, the right bending radius in the mould has to be chosen in combination with the right heat

treatment. By checking the nitinol scraper by hand a difference in stiffness was noticeable. The heat-treated scrapers were stiffer than the original piece of nitinol. Also, the length of the bent part of the scraper was too short, resulting in a gap between the scraper of approximately 1 mm. More research is needed to investigate the right heat treatment for nitinol to attain a scraper of the right dimensions without altered mechanical properties.

Proof-of-concept test

The working principle was validated by the test. The samples were grasped by the gripper and the scraper opened and closed at the right time. The samples were pushed into the tip with every new sample.

Some gelatine was pressed out of the gripper during the tests. This was caused by taking a sample that is too big by applying too much force on the prototype while taking a sample. Gelatine was also pressed out the scrapers when they closed, the reason for that is the gap between the scrapers, as seen in Figure 38. Because of the gap, gelatine was not kept inside the tip. The open gap (about 1 mm) was caused by a manufacturing difficulty.

It was also noticed that small pieces of gelatine remained inside the tip after the scraping motion, caused by too much space between the scrapers and inner wall. A design recommendation is given and can be seen in Figure 41. When more samples are stored inside the tip it becomes harder to push a new sample further into the tip because the gelatine takes over the shape of the tip which cause the pressure to increase. That caused the leakage on top between the gripper and perspex cover at the end of the test, see Figure 36.

The average time to take one sample was 16.3 s. It was measured that the total time of one series decreased during the experiment, possibly because the learning effect. With real tissue, in vivo, more time will be needed, because vision in this experiment was close to optimal, whereas the in vivo biopsies depend on auxiliary visualization devices.

The test with the MSM sausage showed the difference in material toughness. Because the higher toughness, the sample material was not pressed out the gripper and storage compartment. Similar to the test with gelatine, some small pieces remained on the inner wall of the gripper and it was noticed that some samples were not inside the tip, but in between the scrapers, see Figure 40. The reason is the same as for the gelatine test; the optimal functioning of the scrapers.

It was noticed that the gripper hinges (the parts that bend) when the gripper is closed, tend to curve inwards. They push the scrapers inwards to the inner hub. This did not affect the working of the prototype, but it is something to keep in mind. The gripper was bent open by hand and it was expected to return to its original, straight shape, by exerting a force in the opposite direction. When this effect would be larger it may have affected the working of the scrapers, because of the high friction forces of the scrapers with the inner hub on one side and the gripper hinge on the other side.

Experimental recommendations

To improve the experiment, it is recommended to mechanically improve the scrapers by using a better manufacturing technique that does not change the stiffness of the nitinol. During the test with the gelatine the taken samples were not directly removed from the instrument. More samples impede the passage of sample, because the pressure increases. Because a minimum of 5 samples are required, no more than 5 have to remain in the instrument. Therefore, it is recommended to remove the samples from the storage after each series of 5 samples to simulate the heart biopsy procedure in which only 5 sample are taken during one intervention.

Future vision

A next step in the design of the bioptome would be to downsize it to the scale of current cardiac bioptomes. That requires a 3 mm, or smaller, diameter. In addition, the rigid part of the tip needs to be minimized to 20 mm and should be fitted onto a flexible catheter. This redesign includes the use of biocompatible materials.

The instrument designed has a square cross-section, the only possible solution in combination with the gripper and scraper mechanism. However, for an instrument that is inserted into the vascular system a round shape is preferred. The tip can be made square and the flexible part round, but that will increase the outer diameter when it has to fit in a circular sheath.

The prototype that has been built is a not a handheld prototype. One of the steps to take is to design a handle so it can be used as a handheld instrument. Figure 42 shows an example of the prototype turned into a handheld device. The actuation is the same as the proof of concept prototype, with rotating cams. A difference is the fact that his one is fully enclosed, so taken samples cannot be seen. Note that the shaft is still rigid. In order to

Figure 42 A visualization of a handheld prototype with a rigid shaft.

remove the taken samples the tip has to be taken of and the scraper, together with the sample can be pulled out.

A flexible shaft is necessary for a commercial bioptome device. To transfer the forces through the flexible shaft it requires a change in the design of transferring these forces. At the heart of a standard flexible catheter is a coiled steel wire surrounded by a plastic protection layer. This gives flexibility in radial direction and stiffness in the axial direction. By fitting a sliding outer tube over the standard coiled wire the gripper (and inner tube connected) can be actuated. To actuate the scrapers a steel cable in the centre of the catheter can be used. A cross-section of this design is shown in Figure 44. The current actuation mechanism for the scrapers exerts both push and pull forces on the scraper. Because a cable is less suited to transfer push forces, a spring should be fitted to the scraper to push open the scraper (by sliding the inner tube forward), by pulling the cable the scraper can close. Another option is to use a push-pull cable construction which requires no spring in the scraper mechanism. However, this is not preferred due to the higher friction forces and backlash and play that will occur, in particular with a flexible shaft of more than 1 metre. Figure 43 shows a visualization of a 3-mm flexible bioptome connected to a handle for actuation. A full rotation of the knob is one gripping action, the orientation of the knob is marked to provide feedback for the user.

Current bioptomes are designed for single, disposable use. Making the instruments reusable would save a lot of costs and material. To accomplish this, (dis)assembly of the instrument must be simple, so the interventionist can take it apart and clean it. Partly disassembling the novel bioptome is already required to take out the samples. If the removal of the samples can be combined with the cleaning of the instrument in a straightforward way this gives possibilities to design a completely reusable instrument.

Other fields of application

Initially, the instrument is designed for cardiac use. However, the working principle could be applied to other biopsy devices for soft tissue material, like the liver, kidney, prostate and lungs. In some cases there is no need for a flexible instrument, because they have no vascular approach, so the instrument can remain rigid. The new design can be seen as an intermediate form between a standard biopsy device that can take one single biopsy in a safe

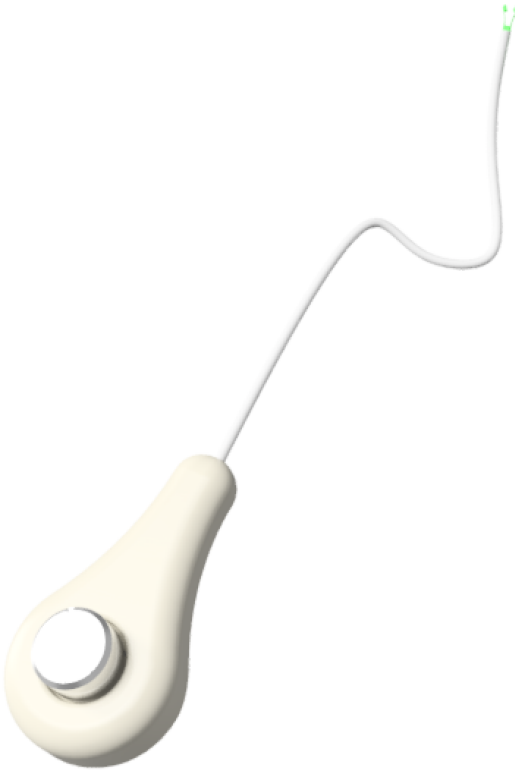


Figure 43 Visualization of a flexible 3 mm bioptome with handheld actuation.

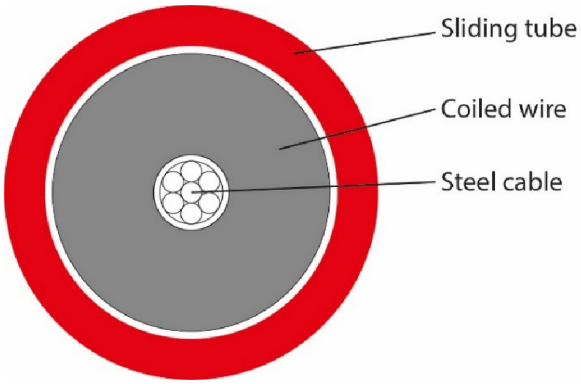


Figure 44 Cross-section of a flexible shaft design.

way and a morcellator that is designed to remove large amounts of tissue. With the new design, more tissue can be removed, compared to a standard biopsy device. In contrast to a morcellator, it is performed in a safe way.

Study limitations

The fabrication of the prototype turned out to be time consuming, it took 10 weeks to manufacture and fully assemble the prototype. The gripper and scrapers were the most difficult parts to manufacture. For reasons of simplicity the gripper was not sharpened, which means the gripper is not suitable to grasp tough tissue material.

6. Conclusion

The main goal of this study, to design a sample storage mechanism (with a minimum of 5 samples) in a biopsy device intended for endo-myocardial biopsy, was subdivided into eight functions. With these eight functions, new concepts were composed. This conceptual approach led to the design of the scraper bioptome. A proof-of-concept prototype, the MultiBite was developed to validate the working principle.

The experiment showed the prototype is functional and the main principle, the storing of five samples in combination with the gripper, worked. Because the scrapers did not fully close during the test, caused by a manufacturing difficulty of the scrapers, small sample pieces remained in the gripper or slipped through the scrapers. For the eventual working on heart tissue no conclusion can be drawn.

To convert the results of this study into a contribution to the design of a commercial (heart) bioptome it is suggested to downscale the design to 3 mm or smaller and continue the development and testing.

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A. Combination of functions analysis

In this appendix six different combinations of solutions are generated from the morphological table. These combinations are called pre-concepts and are discussed by means of six specifications. The *number of parts* describes the number of (the same) parts for each of the pre-concepts. This is a measure for the complexity of the design. Complexity refers to the degree of intelligibility and simplicity of the working principle. In general, more parts will make a design more complex because more parts have to interact with each other and will increase the risk of a failing design. Additionally, the manufacturing and assembly process becomes more complex with increasing number of parts. The *smallest dimension* defines the smallest dimension that each of the pre-concepts contain, measured in mm. This is a measure for the feasibility. Feasibility is defined by the degree of difficulty to fabricate the parts and practical realisation of it. In general, parts with smaller dimensions are more difficult to fabricate. Besides that, parts with smaller dimensions will have a lower strength and stiffness which can lead to a failing part.

The number of *elements to control* relates to the ease of control. More elements to control will make the control more difficult and design more complex. Because more elements to control will require more parts and positioning the parts to perform a certain sequence will be more difficult. The *open area* is measured relative to the full open area of a circular surface with a diameter of 6 mm. For example, a surface area with a diameter of 4 mm has a relative open area of 44%. The *sample volume* is measured relative to a sphere with diameter 6 mm, resulting in a volume of $113\,mm^3$ and gives the biggest theoretical sample size possible with the chosen cutter. The *open area of mechanism to prevent sample loss* is also measured relative to the full open diameter of 6 mm. An open area of zero percent means that the mechanism can fully close and that no sample will be lost. An open area bigger than 0% means that sample loss is still possible.

Pre-concept 1

Pre-concept 1 uses a conical cutter on top that penetrates the tissue. The conical cutter has a similar working principle to the prototype described in a study by Jelinek *et al.* [1]. Inspired by a mechanism of the sea-urchin, the authors developed a spring-loaded, crown-shaped cutter that can be released into body tissue. The device comprises a preloading, locking, and actuation mechanism. The cutter direction and movement are axial and translational, respectively. The sample is stored inside the lumen after which the bioptome can cut a second sample. The tissue is stabilized by the principle of impact, because the conical cutter is shot into the tissue to cut. Barbs are located inside the lumen to prevent the samples from going back in the heart.

The crown cutter is complex because it consists of 6 parts, the total design consists of 8 parts. Also, the cutter was initially designed for flat, smooth tissue which is too hard to grasp. This is not the case with heart tissue because it is not smooth, but sufficiently rough to grasp a biopsy sample of the right size. This principle will work in the heart, but has the risk to cut too deep in the heart tissue. This design has only one element to control, the cutter. The control requires a mechanism that shoots the cutters into the tissue and then can retract without opening the cutters and reload again. 64% is the relative open area that can be used to put through a biopsy sample. The maximum sample size is limited to 37%, due to the conical cutter.

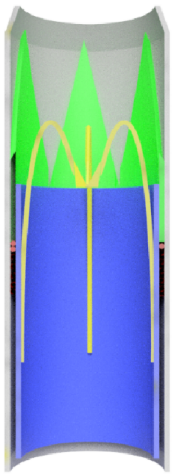

Figure 45 Cross-section of pre-concept 1, a conical cutter.

The smallest dimension is the diameter of the barbs (0.2 mm). The barbs will only work with a full-size biopsy sample, but smaller pieces will still pass it, the open area of the mechanism is 89%.

Pre-concept 2

A ball on top, with a cutting cavity is used in this concept. The ball can rotate and retrieve a sample when it is pressed against tissue. Subsequently it moves the sample inside the lumen where the hook picks out the sample from the rotating ball. After that it rotates back for the next sample. The ball can be driven by a cable by a groove in the ball. The cable at one end is connected to a spring, the other end to a handle, in that way it can rotate forward and backward by pulling the cable.

The spherical cutter on top is simple to actuate, because it only needs to rotate in a single direction. But, slip can occur in the cable groove, which will cause position loss. The cutting area is smaller than average, so the maximum area is limited to 40%. The maximum relative sample volume therefore is 25%. The pre-concept consists of 4 parts which makes this design relatively simple. A yellow hook, also containing the smaller dimension of 0.2 mm, is placed below the sphere to pick out the sample, but will not work for smaller samples, because they will slip through it. The open area of the mechanism to prevent sample loss is the largest of all; 95%.

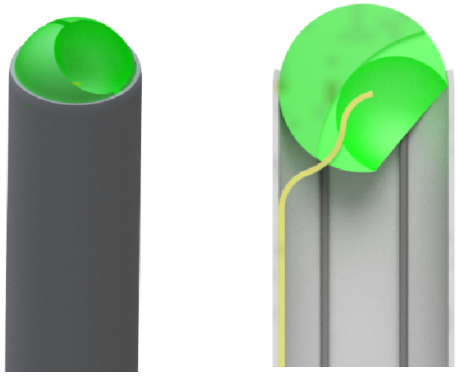

Figure 46 Pre-concept 2 uses a cutting sphere.

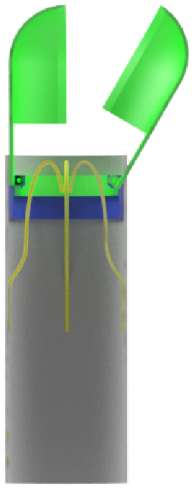

Figure 47 Pre-concept 3 has a 'standard' gripper on top.

Pre-concept 3

Pre-concept 3 looks similar to the nowadays 'standard' heart bioptome [2]. It uses a gripper on top with spherical cutters with the hinges placed close to the inner wall so the lumen is still open. By placing the grippers on a sliding ring the grippers can close by pulling them inwards. The samples are stored inside the lumen by retracting the grippers into the lumen through the barbs.

This pre-concept uses a gripper like the 'standard' bioptome, but with the hinges on the outer area. This causes the hinges of the grippers to be very thin. Current bioptomes use the full diameter for the hinge construction [3]. So, feasibility will be an issue for this design. Because the grippers close by pulling them inwards the biopsy sample is pulled through the barbs at the same time, resulting in only 1 element to control.

Because of the grasping method, the instrument has the ability to take a sample from the heart's tissue with a high maximum sample volume of 81%. The open area is 87%. Because this pre-concept also has barbs to prevent sample loss the same applies as for the other pre-concepts. It will not be safe for smaller sample because they can still pass the barbs, the open area of the mechanism is 92%.

Pre-concept 4

This device has the cutter on top which is a flat diaphragm-shaped (shutter) cutter that is located inside the tip. In order to cut the tissue, it closes the tip. The cutter is actuated by a slotted ring connected to a Bowden cable. The cutter automatically springs back to the open position by a spring. Inside the lumen a suction tube is located (external force) that pulls the sample down to prevent sample loss.

The shutter-like cutter on top is highly complex and not feasible at this scale. The total design has 21 parts and the parts for the cutter (15) need to be very thin ($\leq 0.1\ mm$) in order to cut and have overlap with

adjacent cutter parts. The cutter uses a large part of the outer periphery as well, resulting in a 44% open area, limiting the relative sample size to 30%.

The suction tube that pulls the sample down does not make the pre-concept any simpler, this requires an extra part to control, resulting in 2 elements to control. Another problem with the suction tube is that it is supposed to transport the samples to a ‘safe’ place but the suction tube must pass the sample to pick up the next one. One advantage is the large area it covers, leading to a 10% open area. A blunt tip makes the cutting more difficult, because the instrument must be pushed against the tissue.

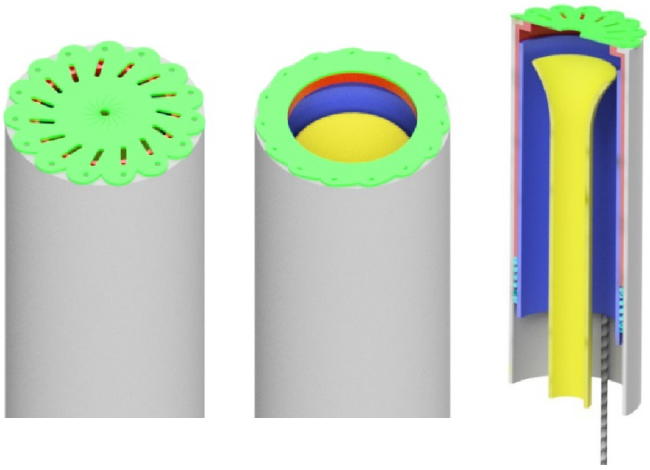

Figure 48 Pre-concept 4 uses a diaphragm shaped cutter.

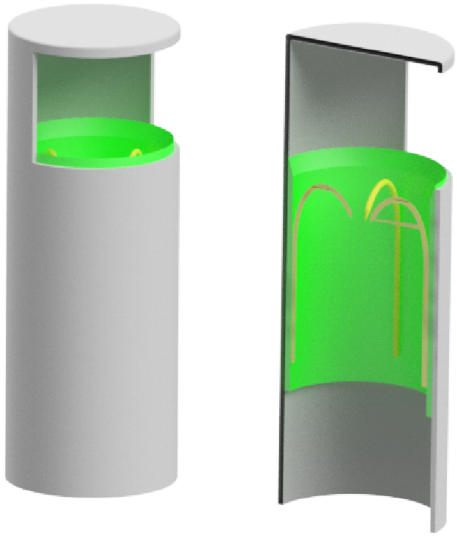

Figure 49 Pre-concept 5 has the cutter on the side.

Pre-concept 5

The fifth pre-concept uses a side-cutter with the sliding principle. The cutter translates in the axial direction. The samples will be stored in the lumen. The tissue sample will remain in the cutter because of the barbs. This pre-concept has the cutter on the side. This enables a cylindrical cutter, but positioning the cutter right with respect to the heart wall becomes more difficult.

One advantage is the relatively large opening, resulting in a 100% open area and 100% maximum sample size. The design is simple and relatively simple to build, because it has only 6 parts and only 1 element to control. Moving the cutter up and down is enough to control the bioptome. This pre-concept uses barbs too, which results in an open area of the prevention mechanism of 93%.

Pre-concept 6

The helical screw cuts the tissue while rotating in one direction. Rotation is done by a slotted ring which results in a half rotation every downwards motion. When in lowest position the ring shoots back to the upwards position (because of the inside spring and open slots in the tip). In that way multiple samples can be taken and will be stored in the coil.

This pre-concept makes use of Archimedes' screw. One disadvantage is that only half of the top surface area is used, limiting the sample size to 35%. This principle was designed for liquids where the screw has an inclined angle to transport the goods to a higher point. Transporting tissue without gravity pulling it down is different matter, which means that a cut sample is not transported down but will remain in the higher part of the instrument. That means that the mechanism to prevent sample loss will not work for heart tissue. The open area of this mechanism is 76%. The design consists of only 5 parts, but the part with the helical screw has a complex shape. In addition, the mechanism to convert a linear motion into a rotating motion has complex shapes too.

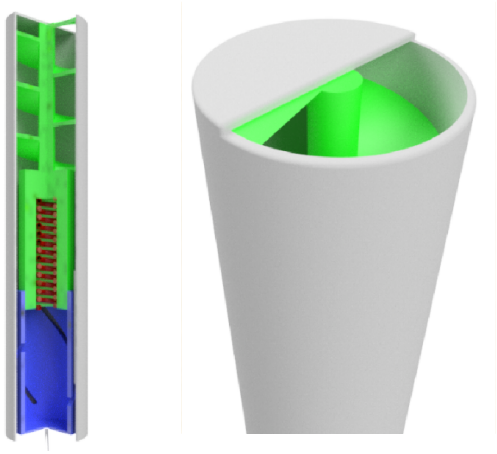

Figure 50 Pre-concept 6 uses a helical screw to cut.

Conclusion

From the discussion of the six pre-concepts it becomes clear that less parts are preferred, this reduces the complexity of the design. All pre-concepts are able to reach the minimum required surface area of $8\ mm^2$, even the ones with a smaller diameter. The open area of the mechanism that prevents sample loss needs to be minimized to 0% to ensure the sample will not slip out of the instrument, especially when it concerns smaller size biopsy samples. It becomes clear that the safety needs to be improved, this is related to the mechanism to prevent sample loss.

The properties and scores of the six concepts are shown in Table 8. For each parameter, a maximum of 10 points can be given. Concept 5 gets the highest score. The design of concept 5 is simple and is simple to control, resulting in a score of 48.2 points. The greatest challenge is to design a safe mechanism to prevent sample loss (open area of the mechanism that prevents sample loss = 0%). Concept 3 is second with 44.1 points. The maximum sample volume is slightly less compared to concept 5, and it also lacks a sophisticated sample loss preventing mechanism.

	1		**2**		**3**		**4**		**5**		**6**	
Number of parts	8	*6.5*	4	*8.5*	8	*6.5*	21	*0*	6	*7.5*	5	*8*
Smallest dimension of part (mm)	0.2	*10*	0.2	*10*	0.2	*10*	0.1	*5*	0.2	*10*	0.2	*10*
Elements to control	1	*10*	1	*10*	1	*10*	2	*5*	1	*10*	1	*10*
Open area (%)	64	*6.4*	40	*4*	87	*8.7*	44	*4.4*	100	*10*	50	*5*
Sample volume (%)	37	*3.7*	25	*2.5*	81	*8.1*	30	*3*	100	*10*	35	*3.5*
Open area of mechanism to prevent sample loss (%)	89	*1.1*	95	*0.5*	92	*0.8*	10	*9*	93	*0.7*	76	*2.4*
Total score		***37.7***		***35.5***		***44.1***		***26.4***		***48.2***		***38.9***

Table 8 Overview of measurable properties and the score of the six concepts.

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B. Table of parts of prototype

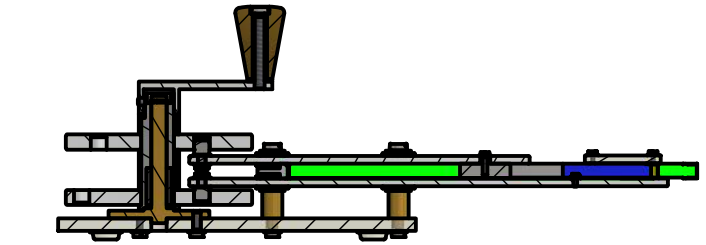
Item	Part Number	Fabricated by	QTY	Description	Material	Production method
1	Gripper_sheet_metal	DEMO	1		Spring steel	Laser cutting/bending
2	Inner hub	DEMO	1		Steel	EDM
3	Scraper_bend	DEMO	1		Nitinol	Cutting or EDM
4	Scraper_bend_MIR	DEMO	1		Nitinol	Cutting or EDM
5	Scraper_extension	DEMO	2		Steel	EDM
6	Ground_plate	Ruben	1		Perspex	Laser cutting/milling
7	Ground_pin	Ruben	1		Brass	Turning
8	Tip_2	Ruben	1		Perspex	Laser cutting
9	Tip_2_under	Ruben and DEMO	1		RVS 304	Laser cutting/milling
10	Slider_scrapers	Ruben and DEMO	1		RVS 304	Laser cutting/milling
11	Pin_sliders	Ruben	4		Brass	Turning
12	Wheel_bearing	DEMO	8		Nylon	Turning
13	Spacer_pin_slider	Ruben	2		RVS 304	Turning
14	Auxillary_slider_scrapers	DEMO	1		Aluminium	Milling
15	Strip_gripper fixation_2	DEMO	1		Aluminium	Milling
17	Cam shaft	Ruben	1		RVS 304	Turning/milling
18	Spacer_camshaft	Ruben	1		Brass	Turning
19	Spacer_camshaft_2	Ruben	1		Brass	Turning
20	Crank	DEMO	1		Aluminium	CNC milling
21	Hub	Ruben	1		RVS 304	Turning
22	Handle_2	Ruben	1		Brass	Turning
23	Disc cam_1	DEMO	1		Aluminium	turning/CNC milling
24	Disc cam_2	DEMO	1		Aluminium	turning/CNC milling
25	HFL0615-KF	Purchased	1	One way bearing 6x10x15		
26	MR62	Purchased	8	Bearing 2x6x2,5		
27	CFS 3	Purchased	2	IKO CFS 3 Cam bearing		
28	Foot	Purchased	4	TOOLCRAFT 2125C60-C		
29	ISO 1207 - M1,6 x 4	Purchased	3	Slotted Cheese Head Screw		
30	DIN 125 - A 1,7	Purchased	8	Washer		
31	DIN 84 - M2 x 8	Purchased	1	Slotted Cheese Head Screw		
32	ISO 1207 - M2 x 12	Purchased	4	Slotted Cheese Head Screw		
33	DIN 433 - 2,2	Purchased	21	Washer, extra small od		
34	DIN 913 - M3 x 3	Purchased	1	Hexagon Socket Set Screw		
35	ISO 1207 - M3 x 8	Purchased	7	Slotted Cheese Head Screw	Brass	
36	DIN 125 - A 3,2	Purchased	11	Washer		
37	DIN 439 - M3	Purchased	2	Hex Nut		
38	ISO 1207 - M4 x 6	Purchased	4	Slotted Cheese Head Screw		
39	ISO 1207 - M4 x 30	Purchased	1	Slotted Cheese Head Screw		
40	DIN 125 - A 5,3	Purchased	16	Washer		
41	DIN 7993 - A 6	Purchased	1	Round Wire Snap Ring		

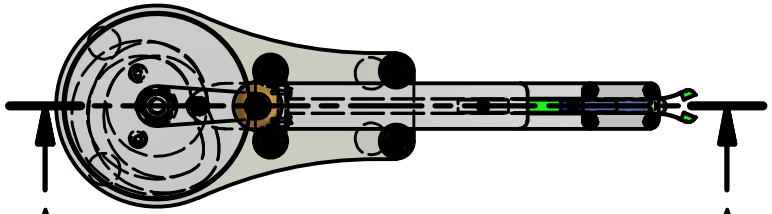
C. MATLAB script for force analysis

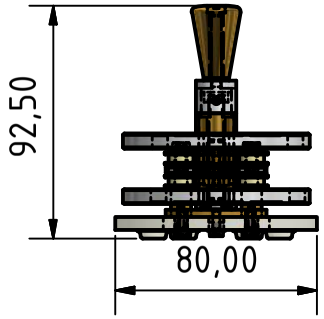
```
clc
close all
%% 6 mm
%% gripper

L=0:0.05:15;
EI=784;
for i=1:length(L)
y(i)=2.88*(sin((L(i)/30*pi)+((3/2)*pi))+1);
P(i)=(3*y(i)*EI)/((L(i))^3);
end
figure
[hAx,hLine1,hLine2] = plotyy(L,P,L,y);
set(hAx,{'ycolor'},{'b';'r'})
set(hLine1,'color','blue')
set(hLine2,'color','red')

title('Force and deflection versus position of outer tube relative to gripper')
xlabel('Position L of outer tube (mm)')

ylabel(hAx(1),'Force P (N)') % left y-axis
ylabel(hAx(2),'Deflection y (mm)','color','red') % right y-axis


%%scraper
Ls=0:0.025:5;
EIs=11.9;
for i=1:length(Ls)
ys(i)=-sqrt(6.97 - (Ls(i)/1.55)^2) +sqrt(6.97);
Ps(i)=(3*ys(i)*EIs)/((Ls(i))^3);
end
figure
[hAxs,hLine1s,hLine2s] = plotyy(Ls,Ps,Ls,ys);
set(hAxs,{'ycolor'},{'b';'r'})
set(hLine1s,'color','blue')
set(hLine2s,'color','red')

title('Force and deflection versus position of inner tube relative to scraper')
xlabel('Position L of innner tube (mm)')

ylabel(hAxs(1),'Force P (N)') % left y-axis
ylabel(hAxs(2),'Deflection y (mm)','color','red') % right y-axis

```

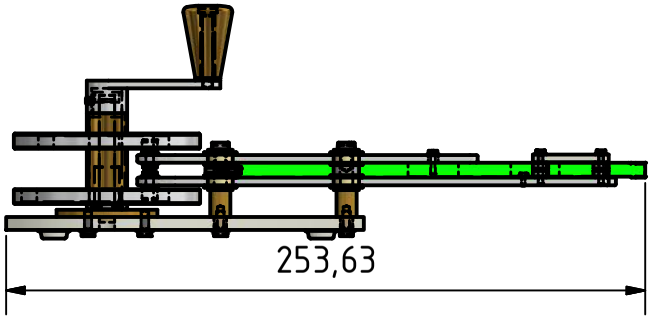
D. Technical drawings of prototype

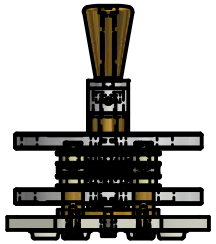
A-A (1 : 3)











					Date	Name
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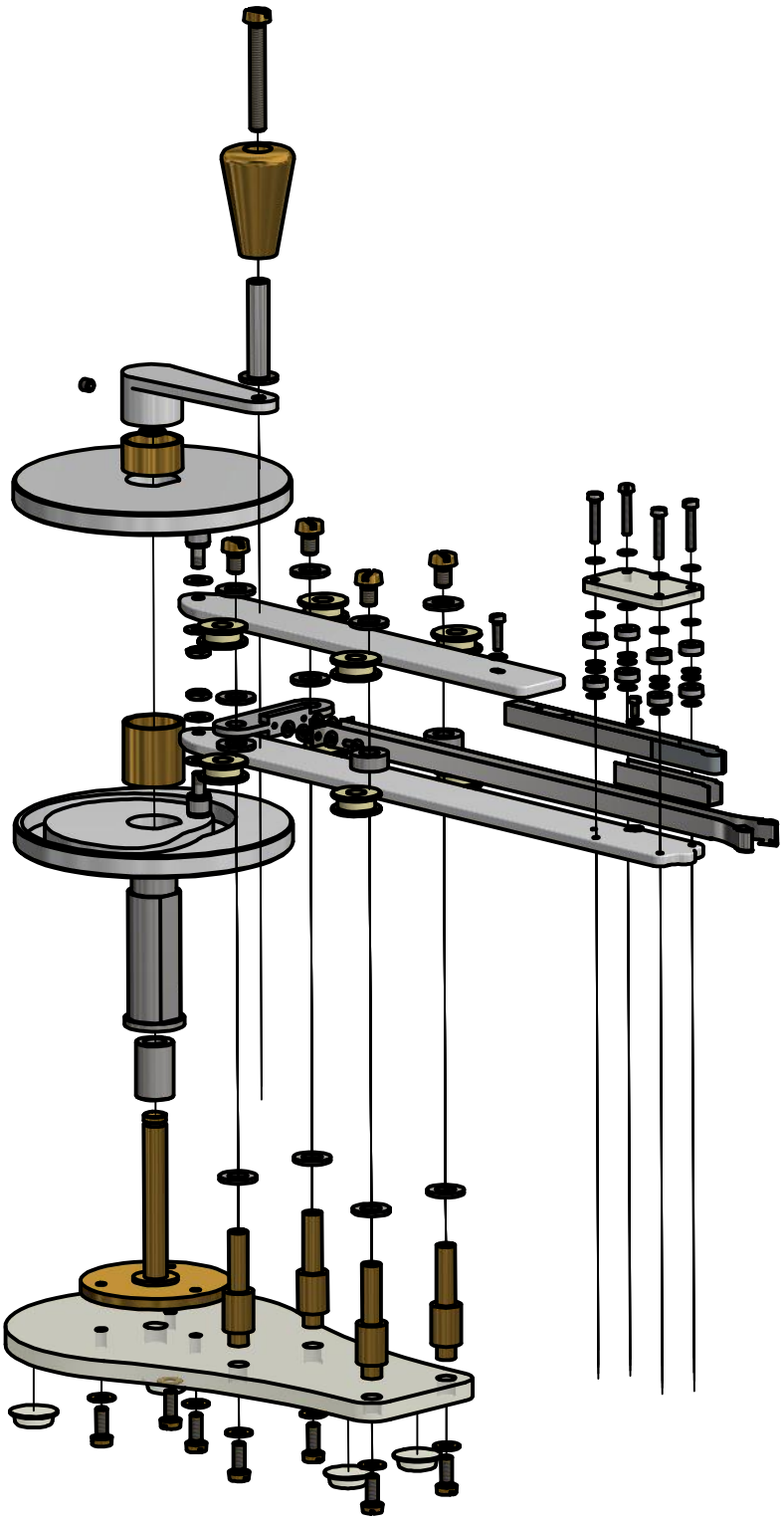
				Checked		
				Standard		
State	Changes	Date	Name			

Pre_bend_scraper_demonstratio

1

A4



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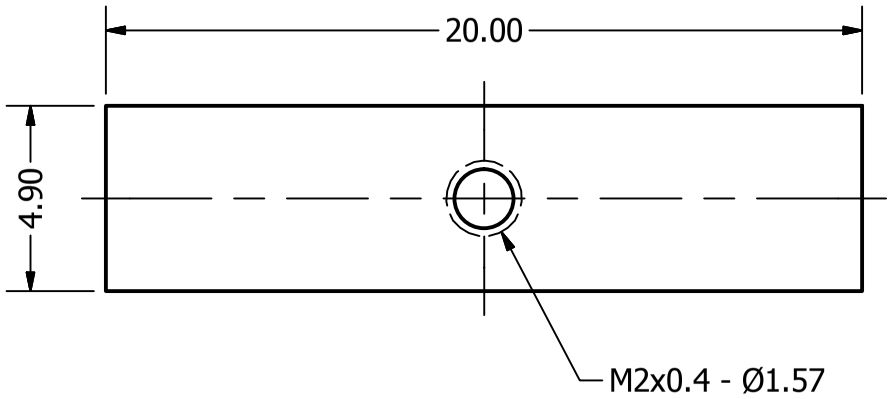
				Checked		
				Standard		

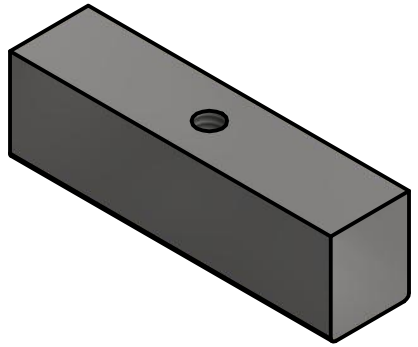
Pre_bend_scraper_demonstratio

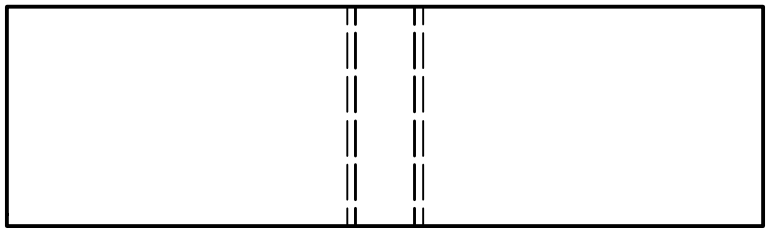
1

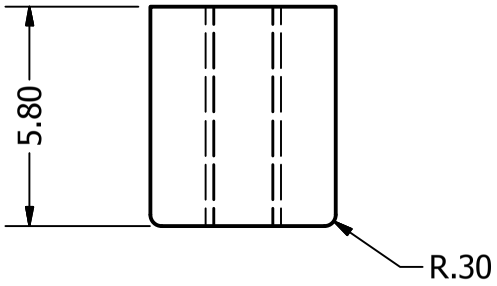
A4

State	Changes	Date	Name









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CHECKED		TITLE		
QA				
MFG				
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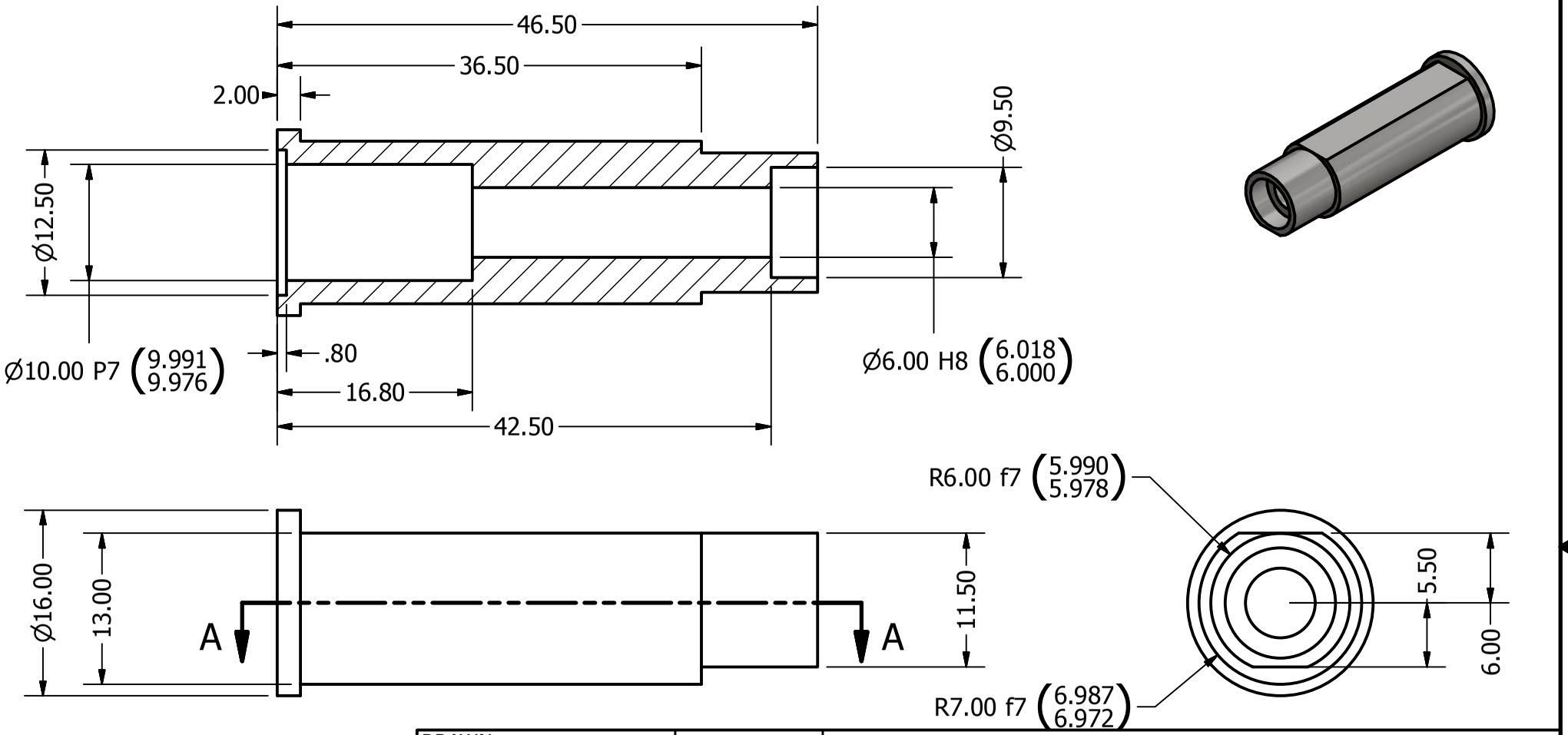
		SCALE 5 : 1		SHEET 1 OF 1



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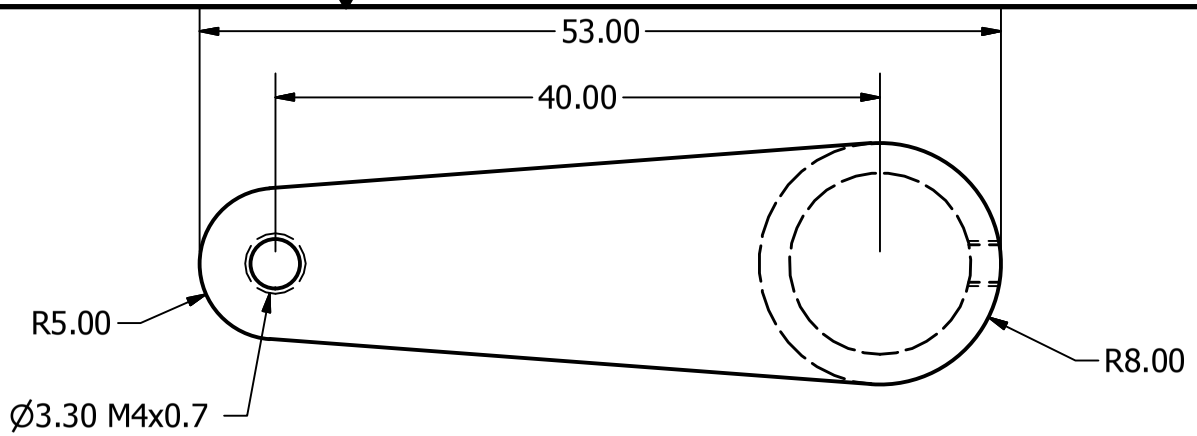
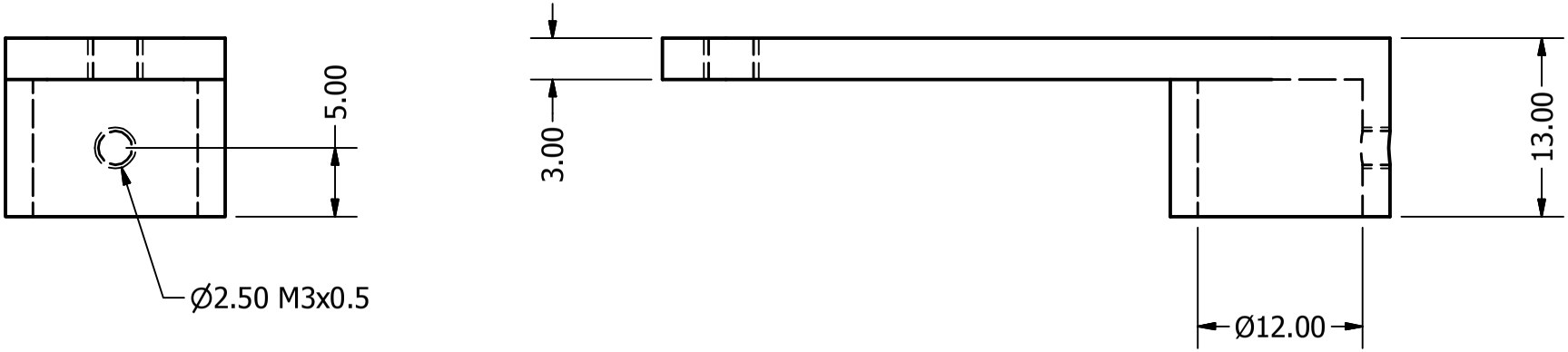
CHECKED		TITLE
QA		
MFG		
APPROVED		
		SIZE A4 / DWG NO Cam shaft / REV
		SCALE 2 : 1 / SHEET 1 OF 1





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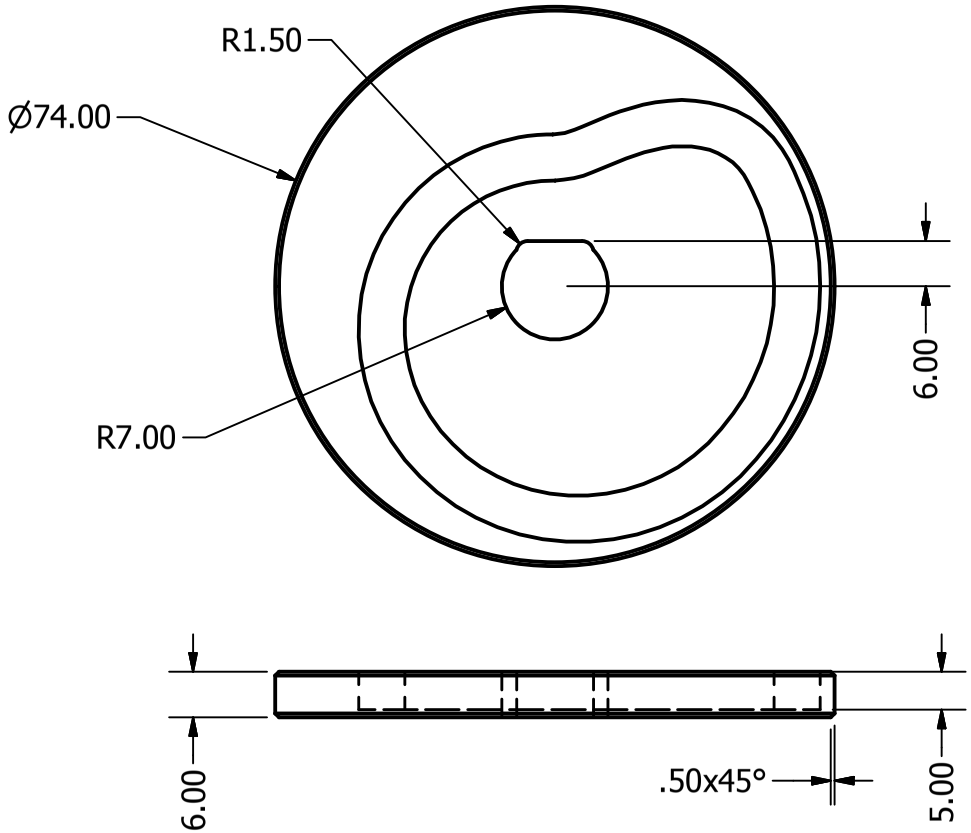
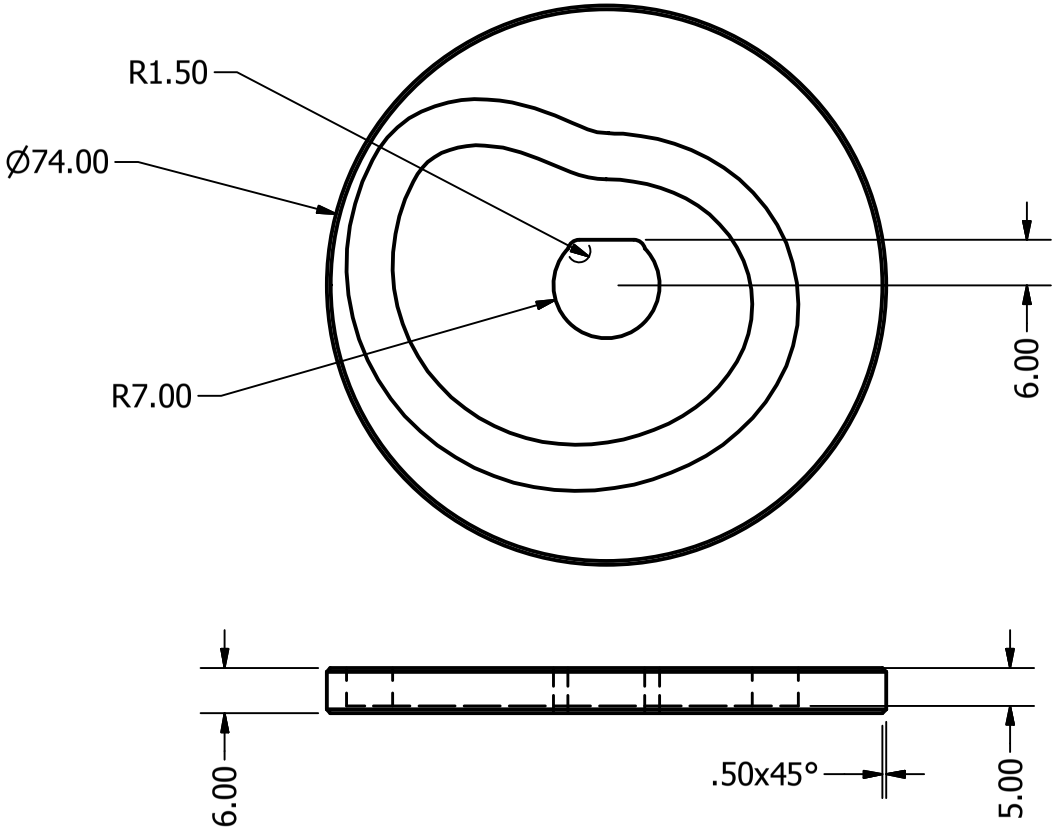
CHECKED		TITLE		
QA				
MFG				
APPROVED		SIZE A4	DWG NO Crank	REV
		SCALE 2 : 1		SHEET 1 OF 1



DRAWN Ruben Rink	9-12-2016	
CHECKED		TITLE
QA		
MFG		
APPROVED		
		SIZE A4 / DWG NO Disc Cam1 / REV
		SCALE 1 : 1 / SHEET 1 OF 1



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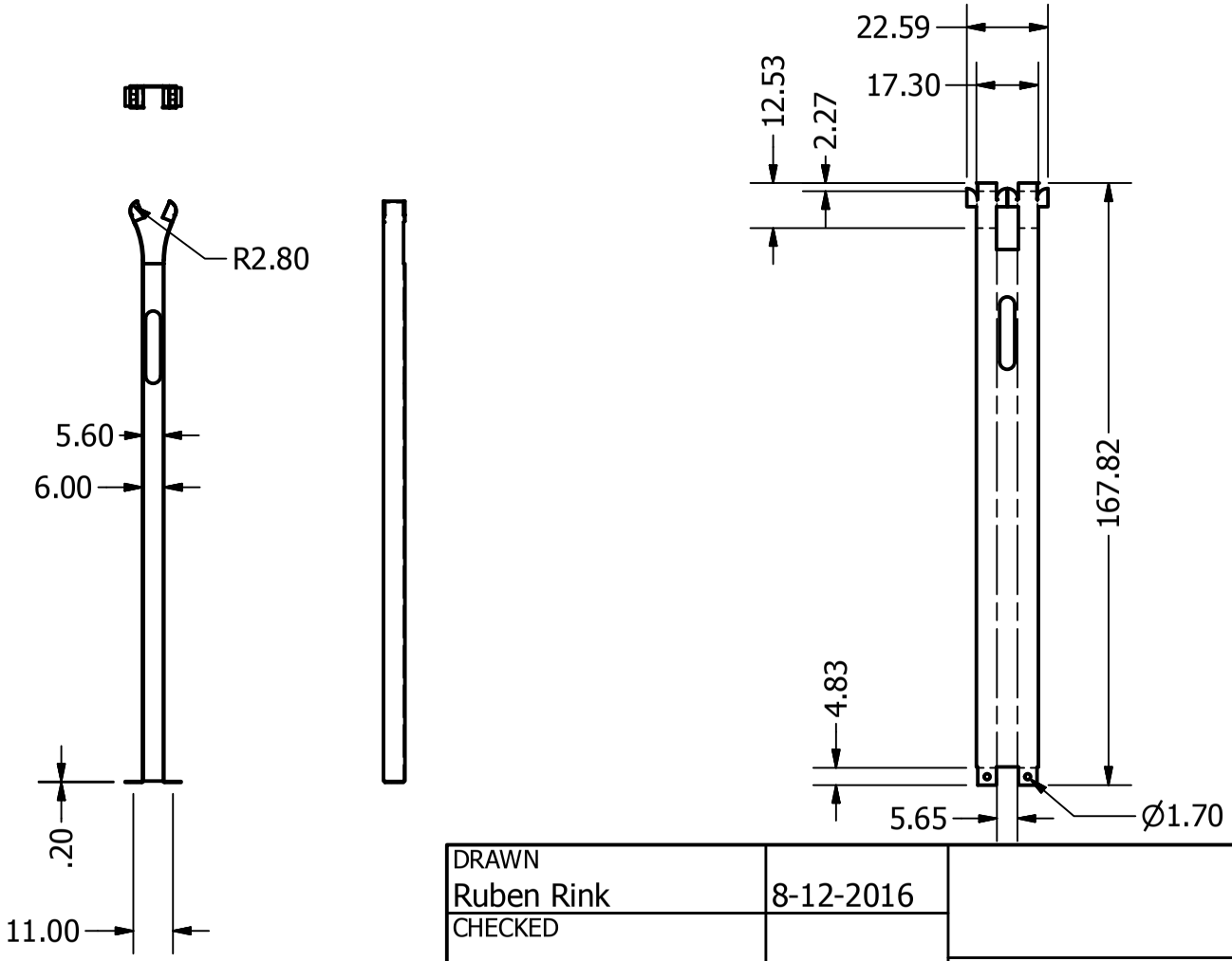
CHECKED		TITLE		
QA				
MFG				
APPROVED		SIZE A4	DWG NO Disc Cam2	REV
		SCALE 1 : 1		SHEET 1 OF 1



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CHECKED		TITLE
QA		
MFG		
APPROVED		
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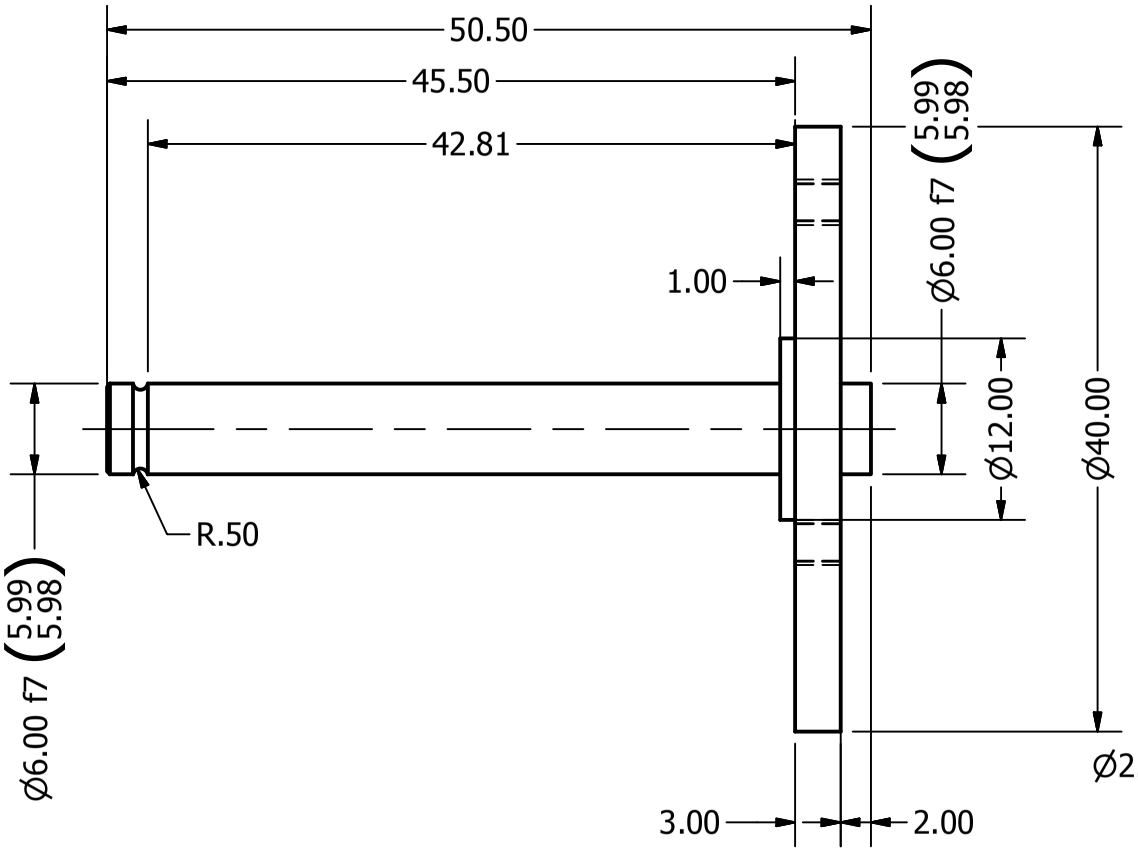
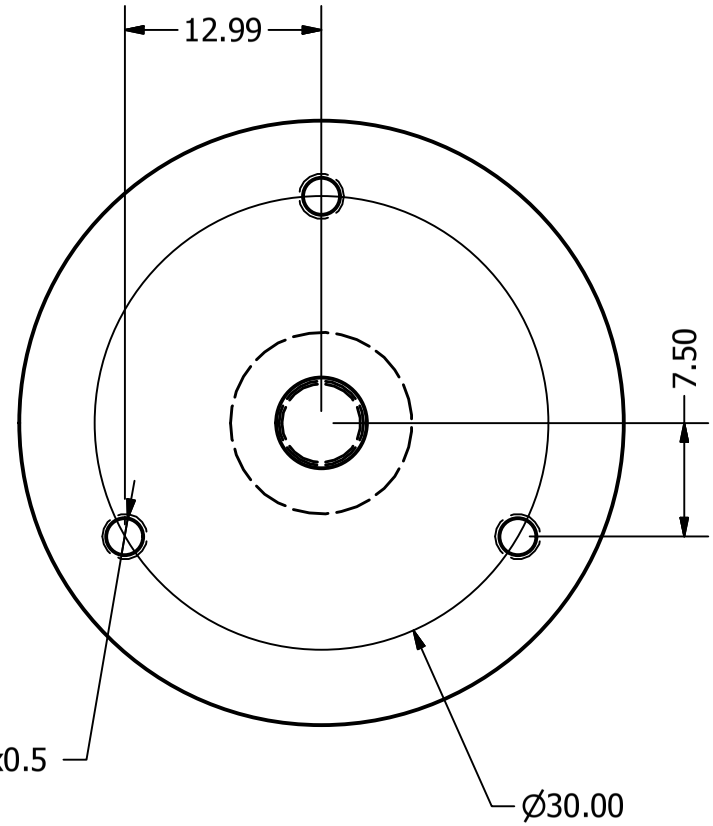
		SCALE 1 / 2 / SHEET 1 OF 1





DRAWN Ruben Rink	8-12-2016	
CHECKED		TITLE
QA		
MFG		
APPROVED		
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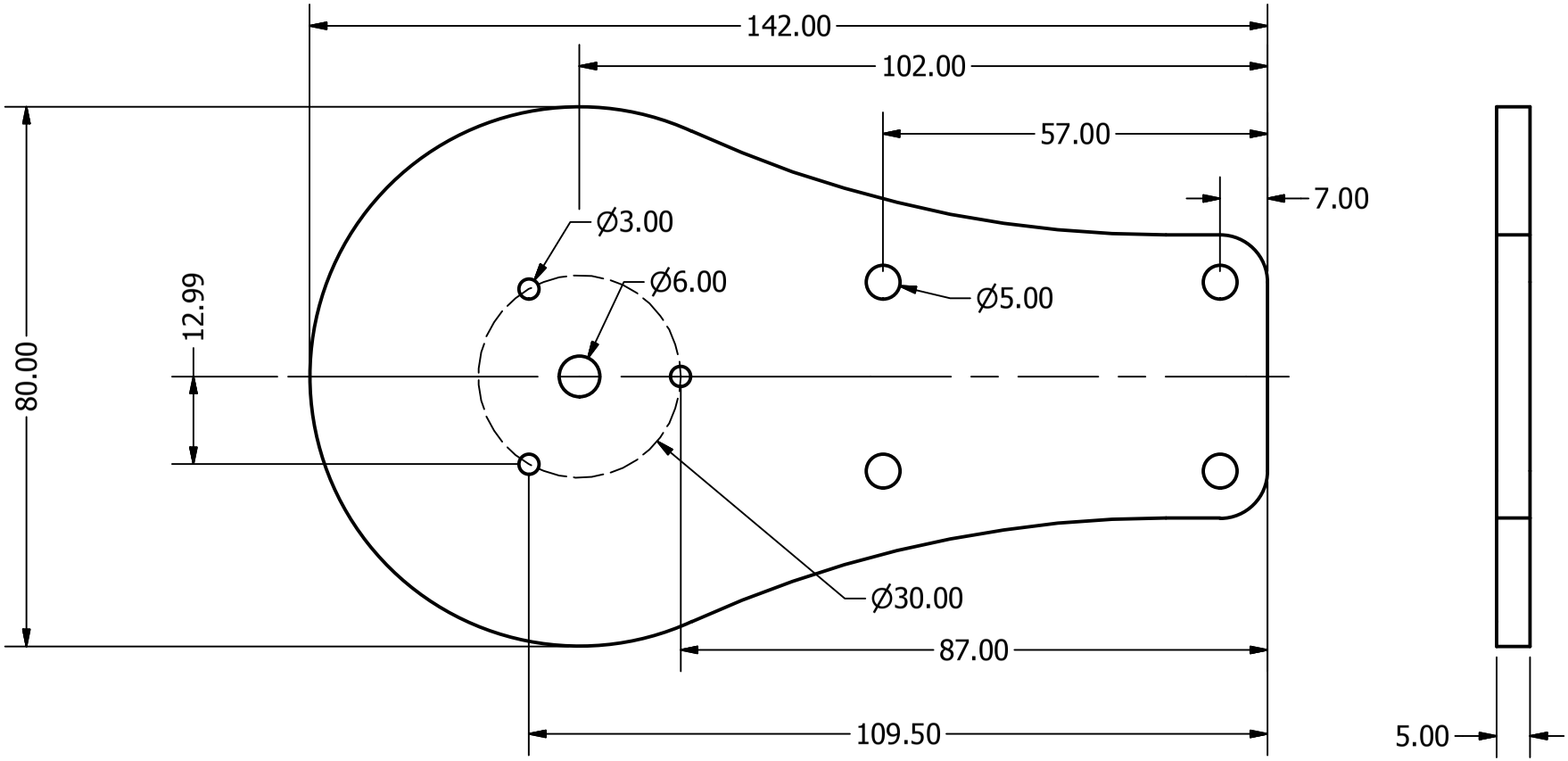
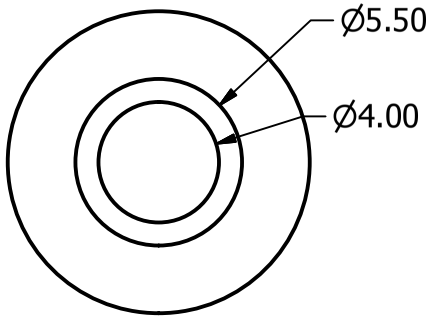
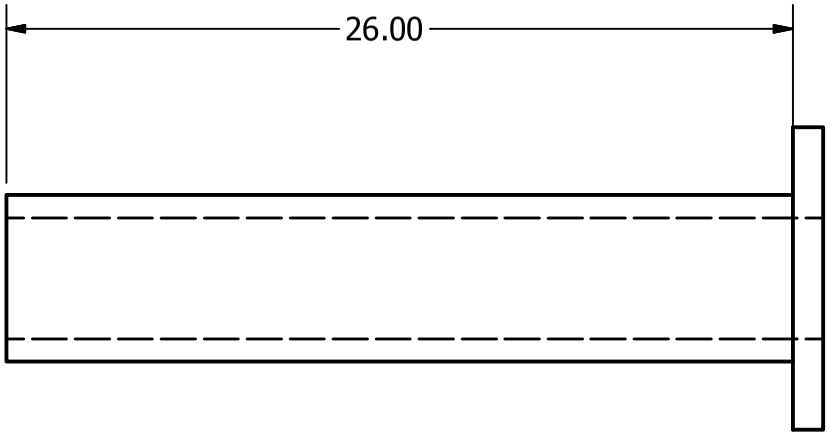
		SCALE 2 : 1 / SHEET 1 OF 1



DRAWN Ruben Rink	8-12-2016			
CHECKED		TITLE		
QA				
MFG				
APPROVED		SIZE A4	DWG NO Ground_plate	REV
		SCALE 1 : 1		SHEET 1 OF 1





DRAWN Ruben Rink	9-12-2016				
CHECKED		TITLE			
QA					
MFG					
APPROVED					
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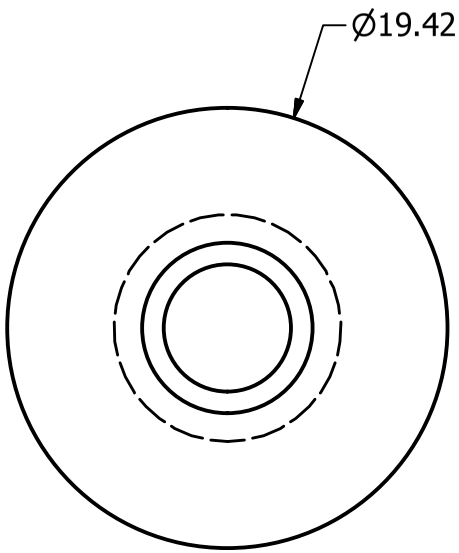
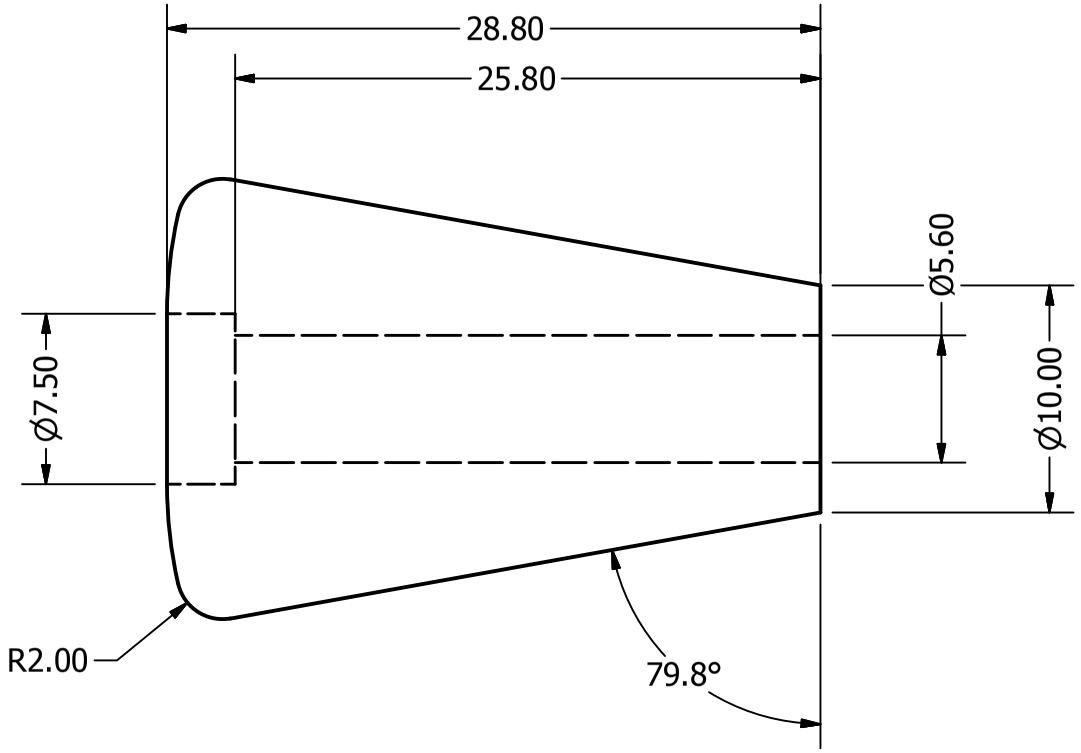
		SCALE 4 : 1		SHEET 1 OF 1	





DRAWN Ruben Rink	9-12-2016	
CHECKED		TITLE
QA		
MFG		
APPROVED		
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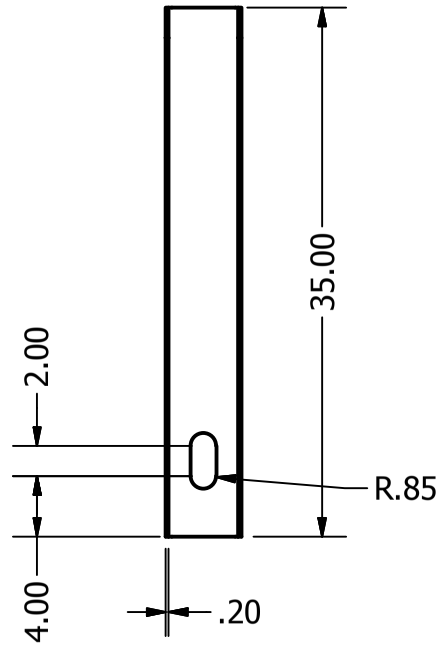
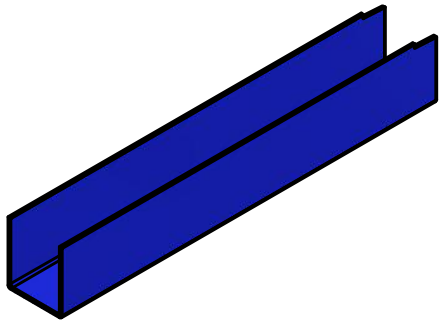
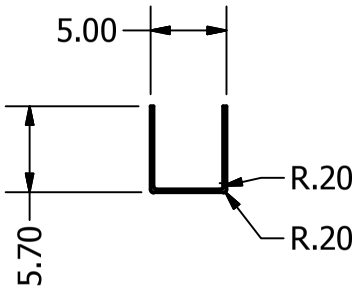
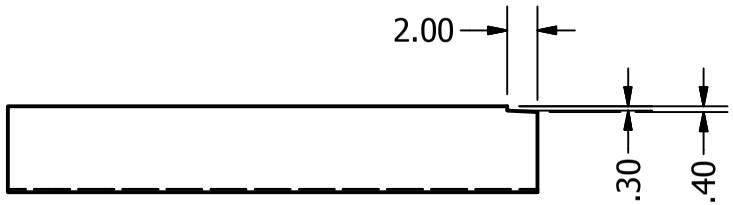
		SCALE 3 : 1 / SHEET 1 OF 1

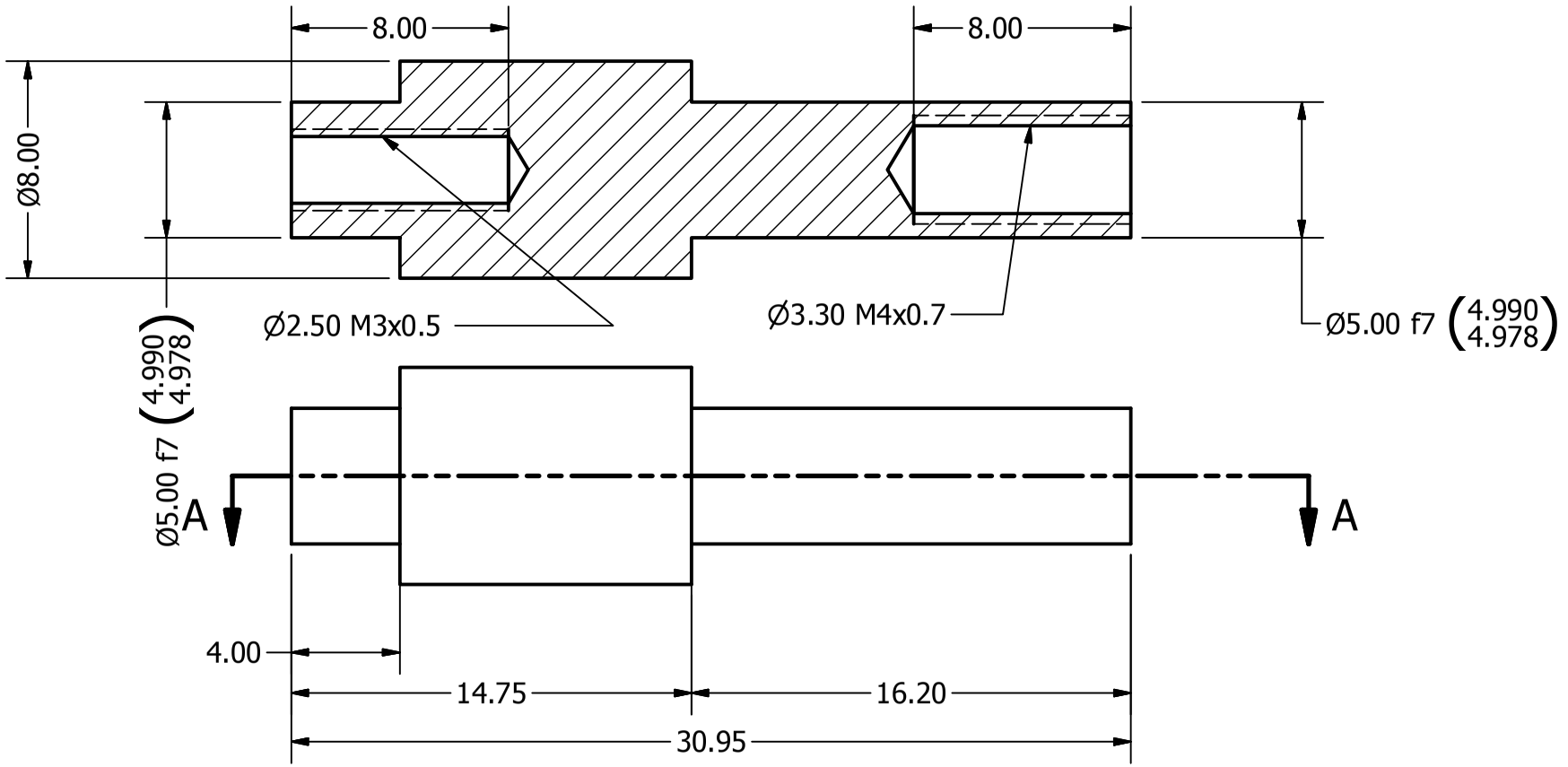




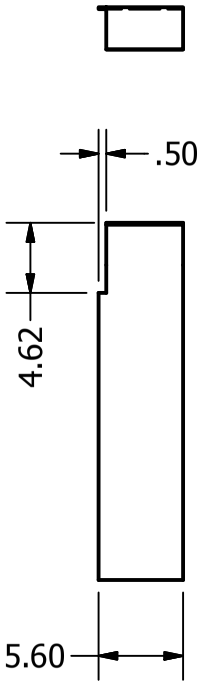


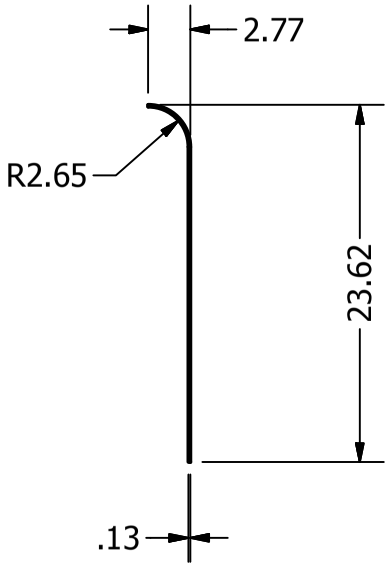


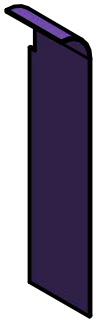
DRAWN Ruben Rink	8-12-2016	
CHECKED		TITLE
QA		
MFG		
APPROVED		
		SIZE A4 / DWG NO Inner hub / REV
		SCALE 2 : 1 / SHEET 1 OF 1



DRAWN Ruben Rink	8-12-2016	
CHECKED		TITLE
QA		
MFG		
APPROVED		
		SIZE A4 / DWG NO Pin_sliders / REV
		SCALE 4 : 1 / SHEET 1 OF 1

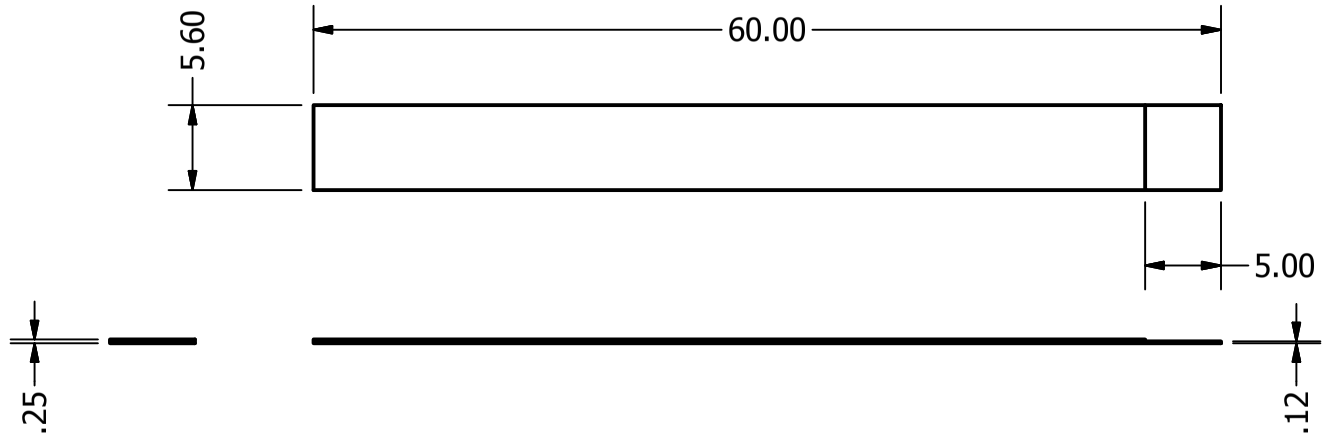






Unbent length: 25 mm

DRAWN Ruben Rink	8-12-2016	
CHECKED		TITLE
QA		
MFG		
APPROVED		
		SIZE A4 / DWG NO Scraper_bend / REV
		SCALE 2 : 1 / SHEET 1 OF 1



DRAWN Ruben Rink	8-12-2016			
CHECKED		TITLE		
QA				
MFG				
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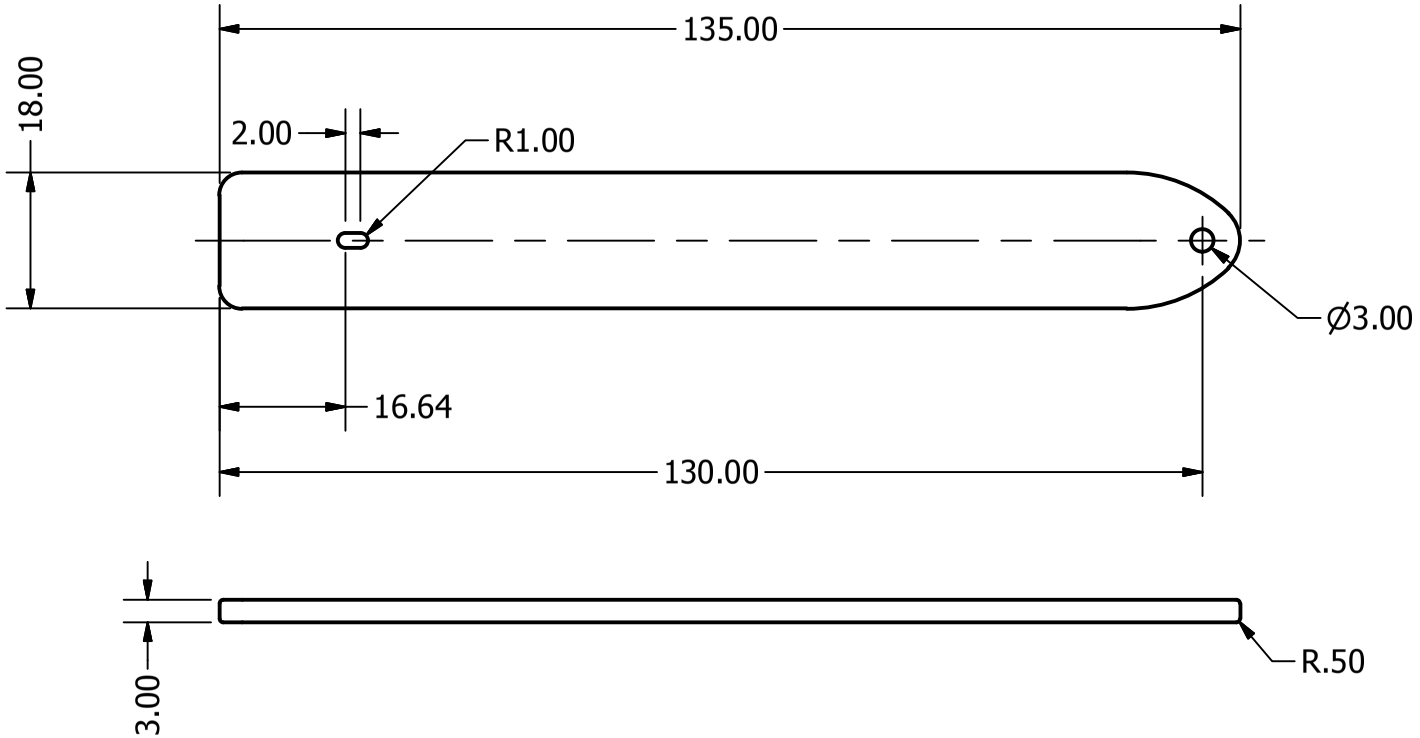
		SCALE 2 : 1		SHEET 1 OF 1



DRAWN Ruben Rink	8-12-2016	
CHECKED		TITLE
QA		
MFG		
APPROVED		
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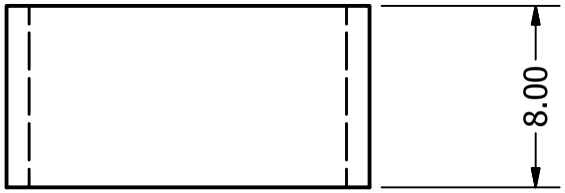
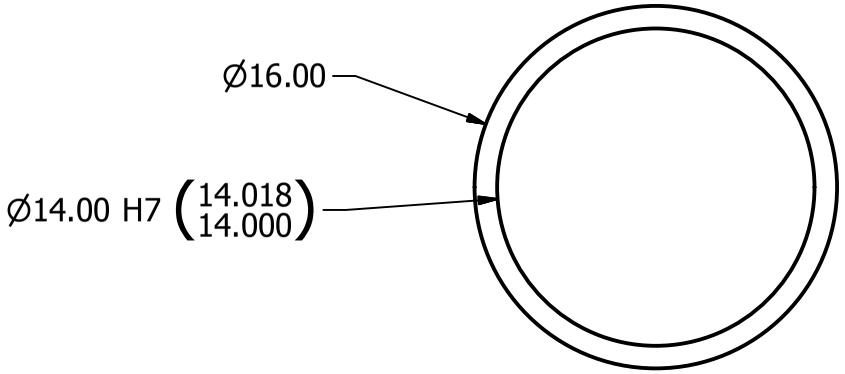
		SCALE 1 : 1 / SHEET 1 OF 1





DRAWN Ruben Rink	9-12-2016	
CHECKED		TITLE
QA		
MFG		
APPROVED		
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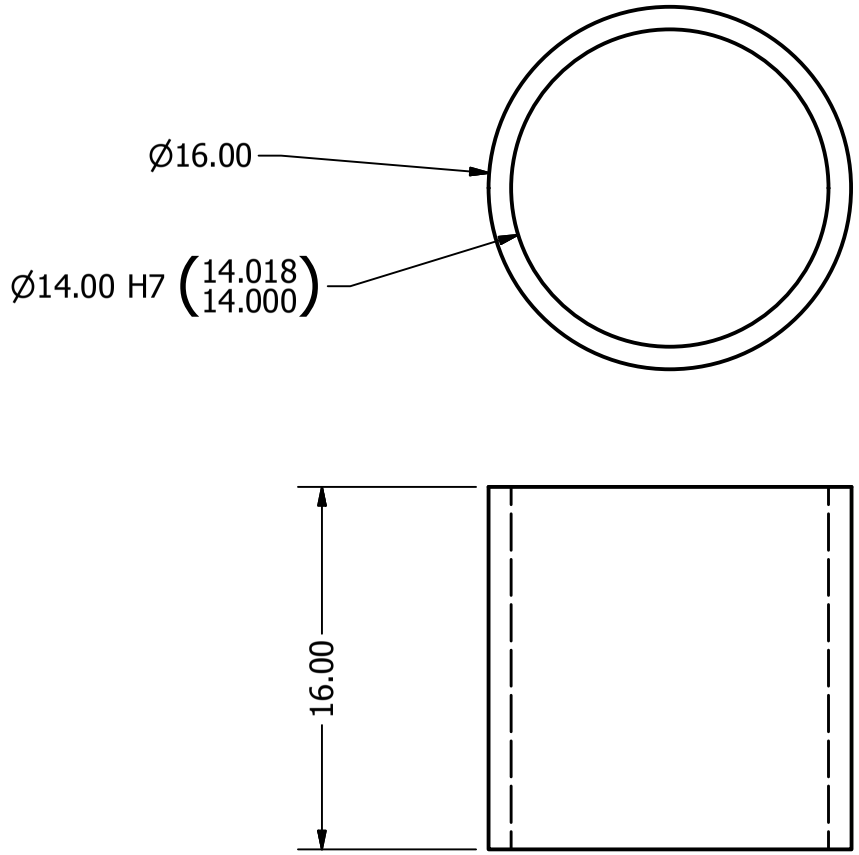
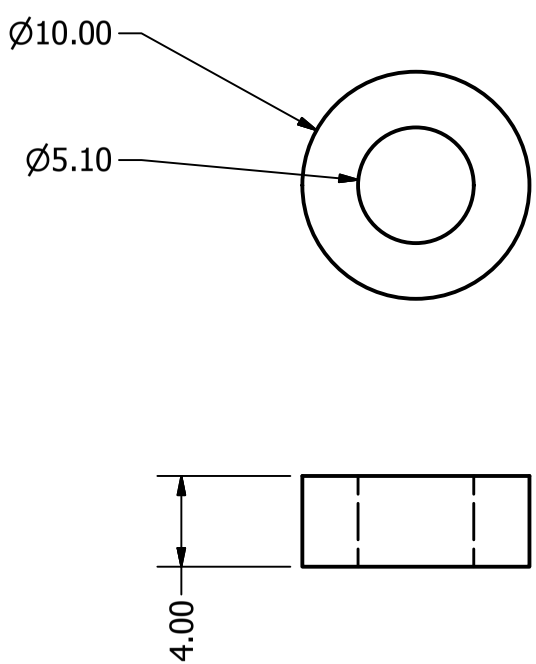
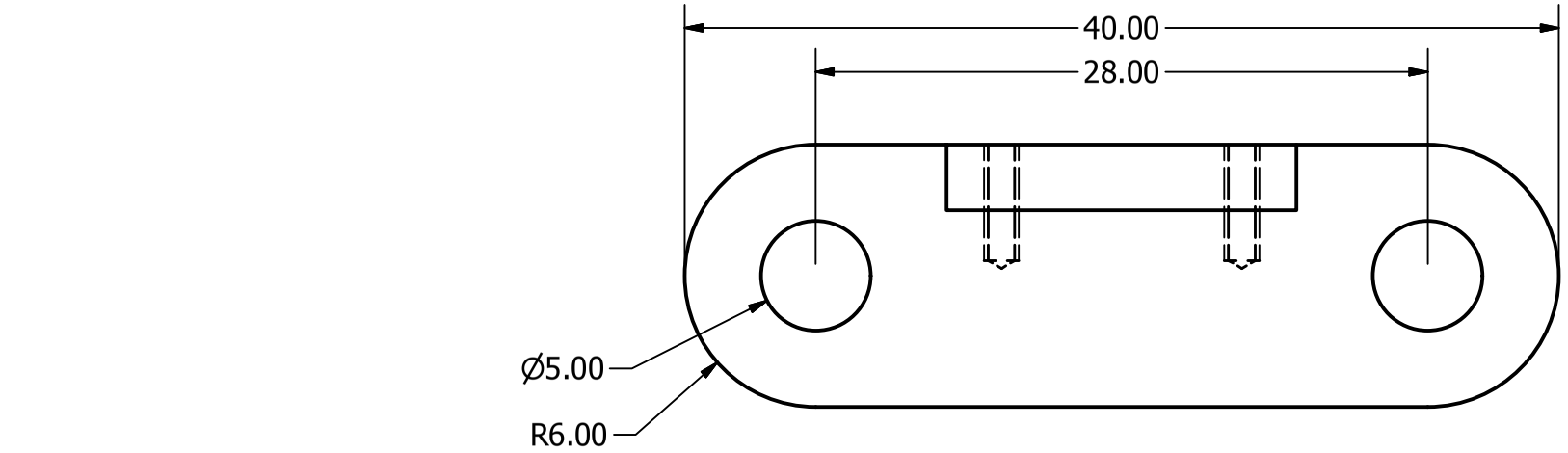
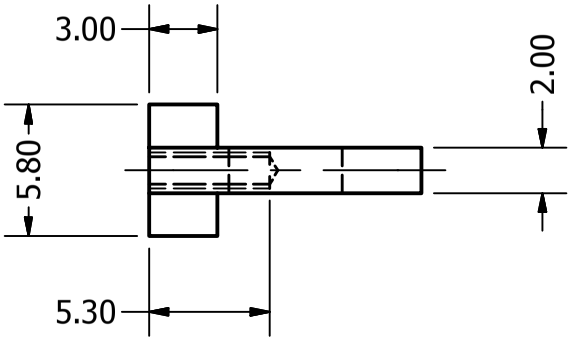


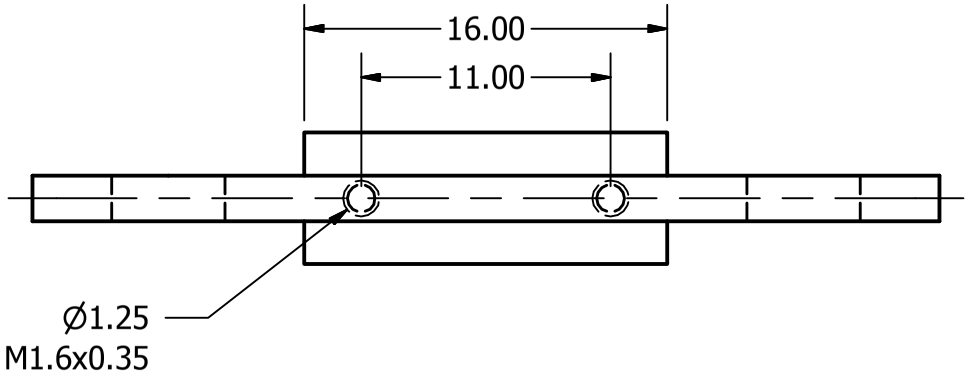
DRAWN Ruben Rink	9-12-2016			
CHECKED		TITLE		
QA				
MFG				
APPROVED		SIZE A4	DWG NO Spacer_camshaft_2	REV
		SCALE 3 : 1	SHEET 1 OF 1	



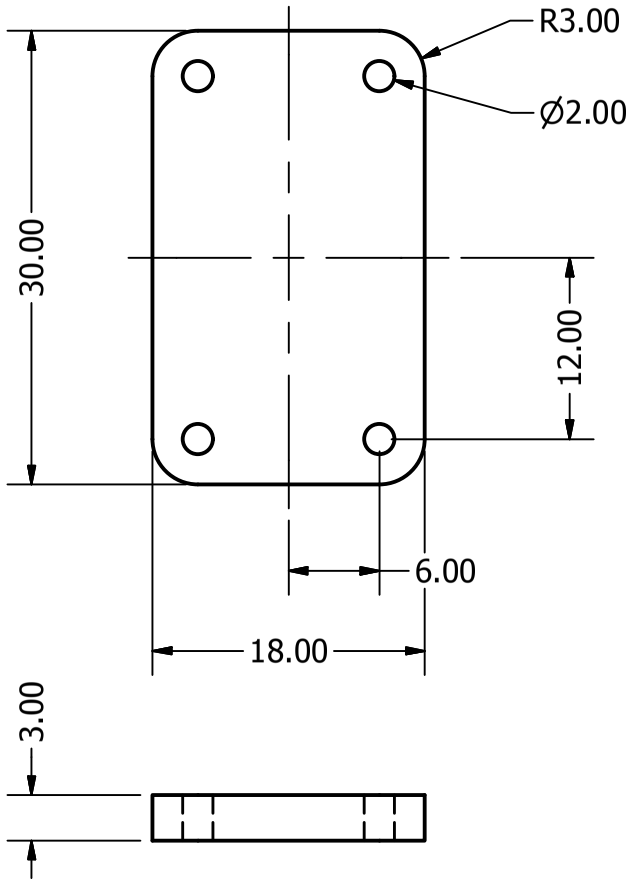
DRAWN Ruben Rink	9-12-2016	RVS, 2x
CHECKED		TITLE
QA		
MFG		
APPROVED		
		SIZE A4 / DWG NO Spacer_pin_slider / REV
		SCALE 3 : 1 / SHEET 1 OF 1







DRAWN Ruben Rink	9-12-2016	
CHECKED		TITLE
QA		
MFG		
APPROVED		
		SIZE A4 / DWG NO Strip_gripper fixation_2 / REV
		SCALE 3 : 1 / SHEET 1 OF 1



DRAWN Ruben Rink	8-12-2016	
CHECKED		TITLE
QA		
MFG		
APPROVED		
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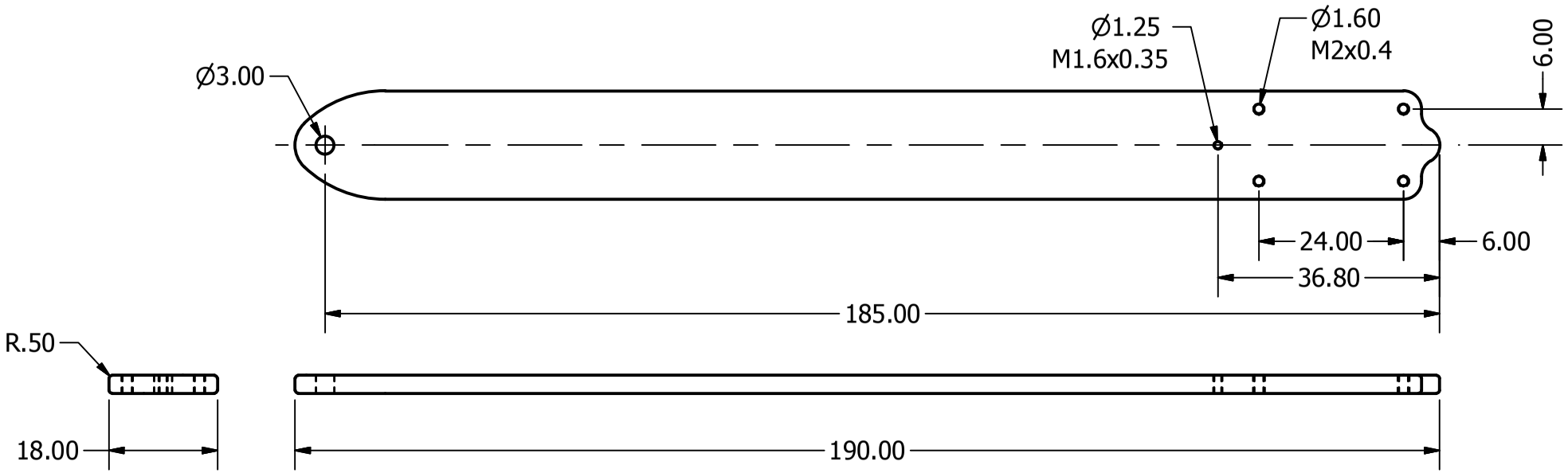
		SCALE 2 : 1 / SHEET 1 OF 1



DRAWN Ruben Rink	8-12-2016	
CHECKED		TITLE
QA		
MFG		
APPROVED		
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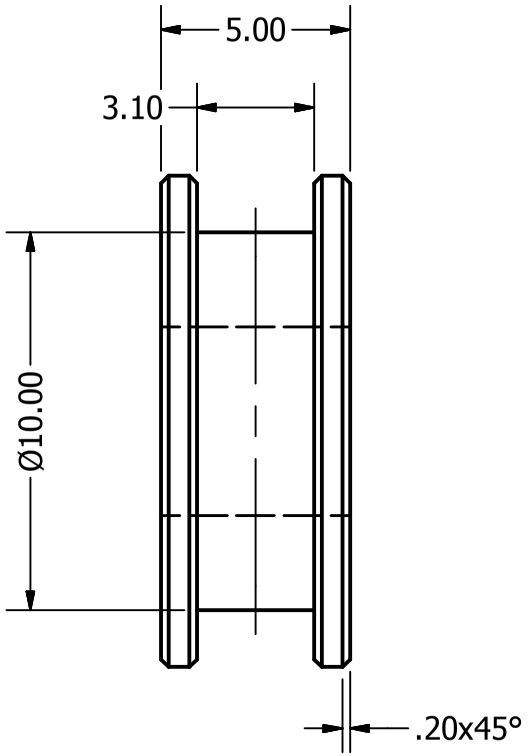

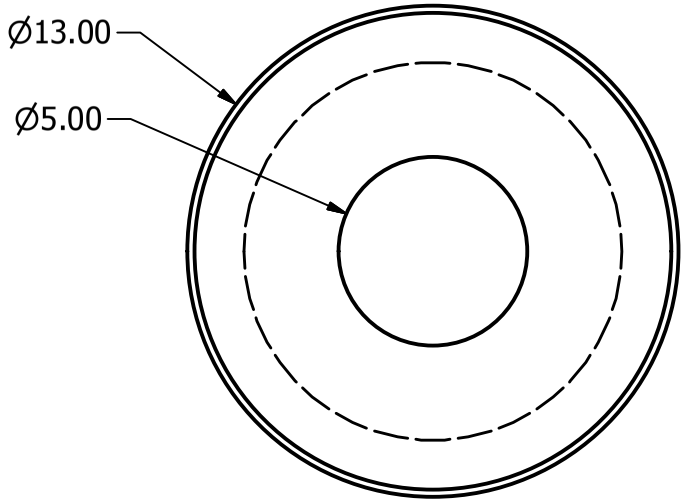

DRAWN Ruben Rink	9-12-2016	
CHECKED		TITLE
QA		
MFG		
APPROVED		
		SIZE A4 / DWG NO Wheel_bearing-1 / REV
		SCALE 5 : 1 / SHEET 1 OF 1