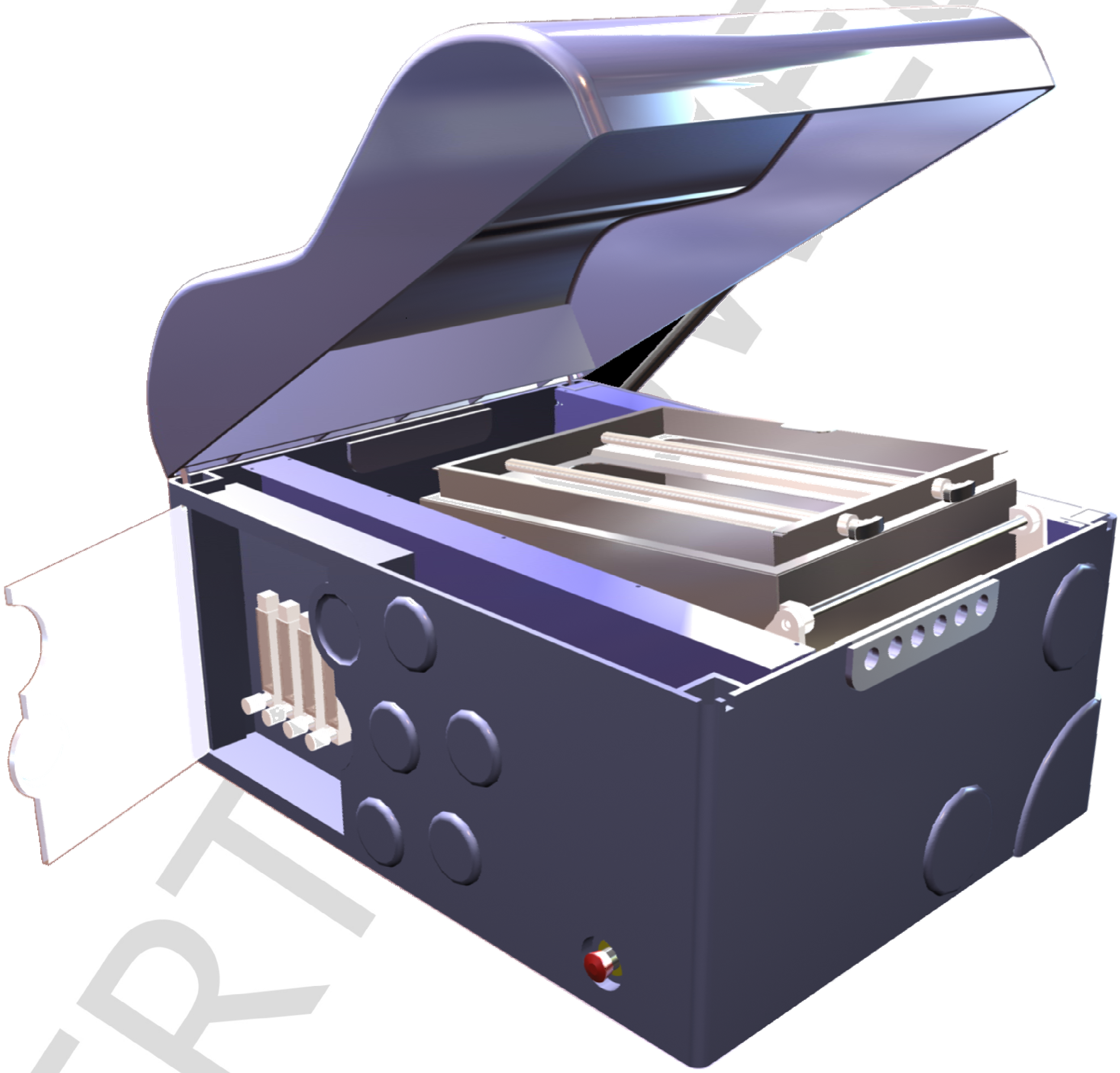
T. Gorter

Let's rock!



Bachelor assignment 2006
Industrial Design

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Let’s rock!

Bachelor assignment 2006 Industrial Design

CELLution Biotech
Groningen, The Netherlands

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Summary

This rapport with the bachelor assignment ‘shaker’ handles the complete design route from prototype to the final concept. The assignment was done with a company, CELLution Biotech, which specializes in developing bioreactors. They have developed the CELL-tainer^{TM}, a bioreactor which uses disposables.
Chapter 1, *Introduction*, tries to explain what bioreactors are, how difficult it is to cultivate certain organisms and how the planning for the assignment was set up.
Chapter 2, *Market research*, describes a market research done under different kinds of bioreactors. There are 2 main different types: stirred tanks and those which are capable of working with disposables, just like the CELL-tainer. The machines looked at are mainly made from stainless steel or plastics, to increase cleaning capabilities.
Chapter 3, *Designroute*, contains the list of requirements, stated by CELLution Biotech for developing the first prototype, and supplementary requirements for the housing of the prototype. This chapter also contains an usage research to explain what could be altered to the prototype and to record timings for sampling. Furthermore are the working principles handled and the use of linear motors and the benefit of using these. Before the designs are presented, an ergonomic overview is shown, which have to be considered during the design process. From all the concept, a concept derived from a photo-copier-a-like draft was chosen to continue working on. After the decision of what concept to work further on, several subparts are discussed.
Chapter 4, *List of requirements review*, reviews the requirements stated in chapter 3 with the current concept. Several requirements were not met, due to lack of time or the missing of an actual prototype of the model.
Chapter 5, *Conclusion*, holds the conclusion and the recommendations for further development. The conclusion says that the design is approved by CELLution, but that the recommendations have to be looked at very specifically to meet all the requirements stated in chapter 3.
Chapter 6, *Supplement*, describes a variation of the final concept described in chapter 3, which was altered 2 weeks before finishing the assignment.

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Explained vocabulary

CELLution	CELLution Biotech BV. The company which develops bioreactors and has commissioned the assignment.
Bioreactor	A cultivation system for cells.
Disposable	Disposable bag which functions as reactor chamber.
CELL-tainer™	A machine developed by CELLution for cultivating biological cells with the use of disposables.
Shaker	A type of bioreactor, using wave agitation to improve the oxygen transfer, making it suitable to cultivate cells.
PLC	Programmable Logic Controller: a 'computer in a chip' for controlling several processes.
Inoculum	The cells that will be inserted in a cultivating process.

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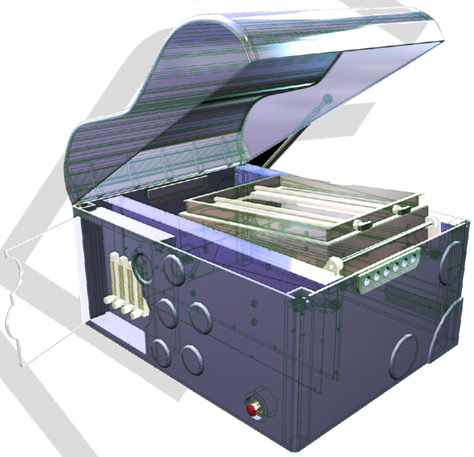
Introduction . 1

Assignment ‘shaker’



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1.1 Method of approach

Before starting with the assignment, a method of approach was formulated. This method is presented to CELLution and approved. Along with the method of approach, a timeschedule was made (figure 1.1, page 3).

Project environment

CELLution is active on the biopharmaceutical market and will soon introduce the CELL-tainer^{TM}, a machine capable of working with disposable bioreactors. The reactor is part of a line of products varying from 20 to 500 litres scalable capacity without losing performance. Momentarily, working principles are proven and one of the next aims of CELLution is the design of the housing for the CELL-tainer^{TM}.

Aim

The result should be a design of a housing for the existing prototype. Part of the assignment is to find suitable forms, fitting the machine and in which market segment it will be placed, considering the functions of the machine.

At the end of the 12 weeks of the assignment, a suitable design which fulfils the wishes of CELLution has to be presented and may serve as a basis for further development of the CELL-tainer^{TM}.

Before the assignment was started, several questions have to be considered during the assignment:

Central question 1:

What is the current state of the machine?

- what materials were used?
- Which functions are present?
- What are the working principles?

Central question 2:

Which machines with corresponding functions are on the market?

- what are the differences between them and the CELL-tainer^{TM}?
- What do they look like?
- What materials are used?
- How does the machine interact with the user?

Central Question 3

What are the demands related to the final design?

- what are ergonomic demands?
- What are the demands for use in a laboratory?
- How does the machine fit within the current market?
- How is design of the machine related to secondary equipment?
- Which secondary equipment is connected?
- What are the demands of CELLution?

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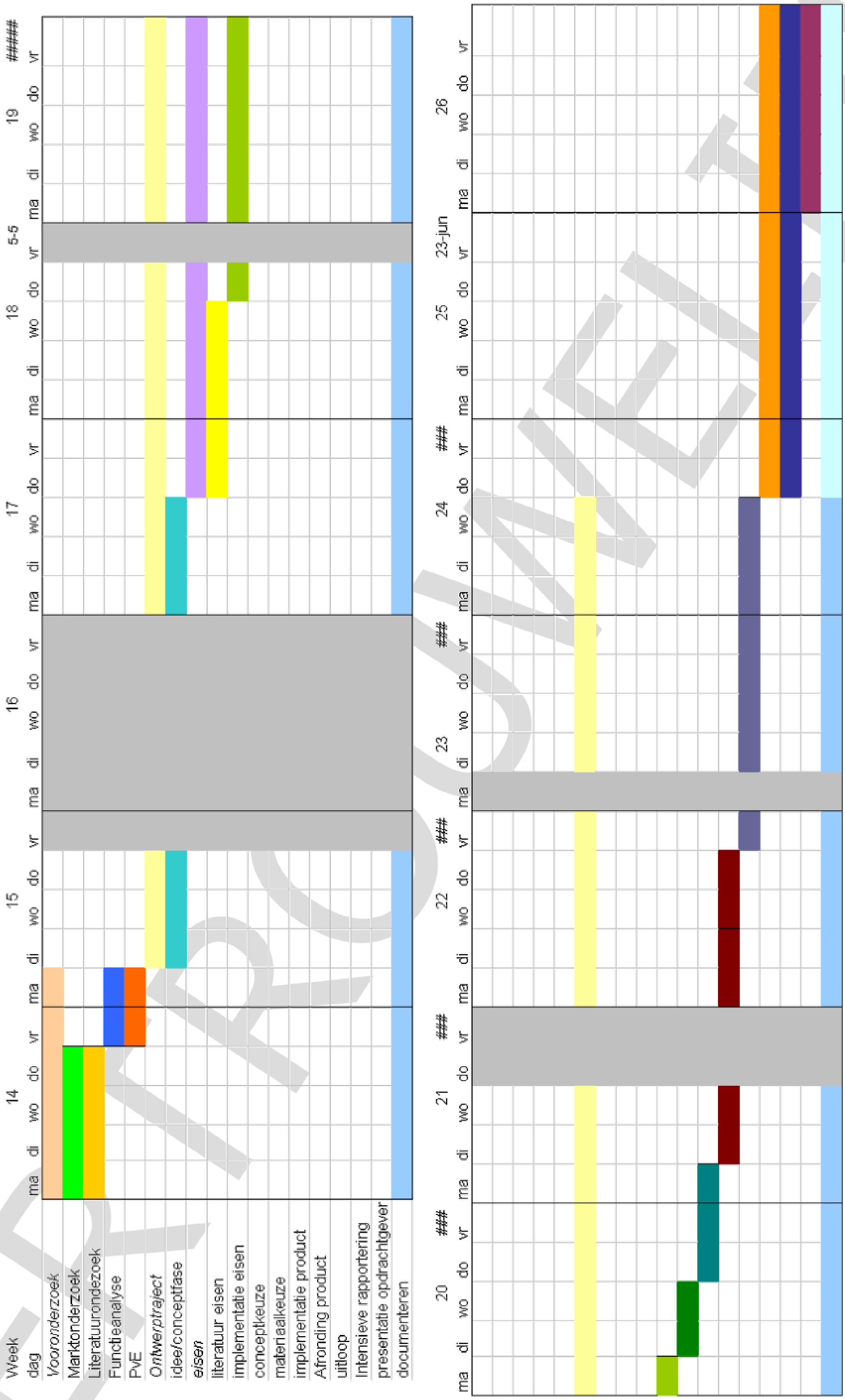

Figure 1.1: Timeschedule Bachelor assignment

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CELLution BIOTECH

1.2 Introduction

This rapport was written by order of the University of Twente and CELLution Biotech, commissioner of the assignment. The main task is to develop a design of their new rocking bioreactor, intended for use on the commercial market. This introduction will hold a short explanation of what a bioreactor is, and in which circumstances it is used. Also some different types and working principles will be discussed. This section has a overlap with the next section, *Market Research*, but is added to the report to greaten the understanding of cultivating cells.

1.2.1 Fermentors

Biotechnology is the application of biological organisms, systems or processes in manufacturing industries. There are many areas of application of biotechnology, for example:
- Fermentation technology
- Enzyme engineering
- Waste technology
- Environmental technology
- Renewable resources technology
- etcetera

CELLution Biotech is engaged in fermentation technology. Their main goal is to develop more efficient fermentors to cultivate micro organisms, such as mammalian cells.
Bioreactors range from simple stirred tanks to complex integrated systems. There are two types of bioreactors. The first are non-aseptic systems where it is not necessary to operate with strictly pure cultures of micro organisms. The other type of fermentor is used for production of such compounds as antibiotics, amino acids, etcetera. The object of any fermentor is to optimize the growth of the organism or of a product produced by the organism. To obtain such conditions, the following must be taken into consideration:
- an energy source
- essential nutrients to satisfy the needs of the organism
- a lack of inhibiting compounds in the medium
- a reliable inoculum
- the most advantageous physicochemical conditions

Two types of fermentation systems exist: batch or perfusion. A batch system implies that all the nutrient components are added at the beginning of the fermentation process and, as a result, the growth rate of the contained organisms will eventually proceed to zero due either to diminishing nutrients or accumulation of toxic waste products. A modification of the batch process is the fed batch system. Here, volumes of nutrients may be added to augment depletion of nutrients. Overall, the system, however, remains closed and there is no continuous flow. In contrast to the above types, in the perfusion system, organisms and nutrients can continuously enter and leave the bioreactor.

So far, biotechnology has been considered with respect to two characteristics: obtaining the best catalyst and the best environment. The most effective, stable and convenient form for the biocatalyst is a whole organism. In most cases, this could be some type of microbe like a bacterium, yeast, or mold. Originally, these micro organisms were extracted from the natural environment, but today, scientists can genetically alter these into superior organisms. This is a practice that is being carried out by most biological-based industries and is direct result of the close cooperation between technologists and geneticists.

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Normal cell lines can be split only a finite number of times before ageing and death. Genetic transformation, whether spontaneous or induced, can give rise to continuous cell lines.

The fermentation process looks as follows (schematic):

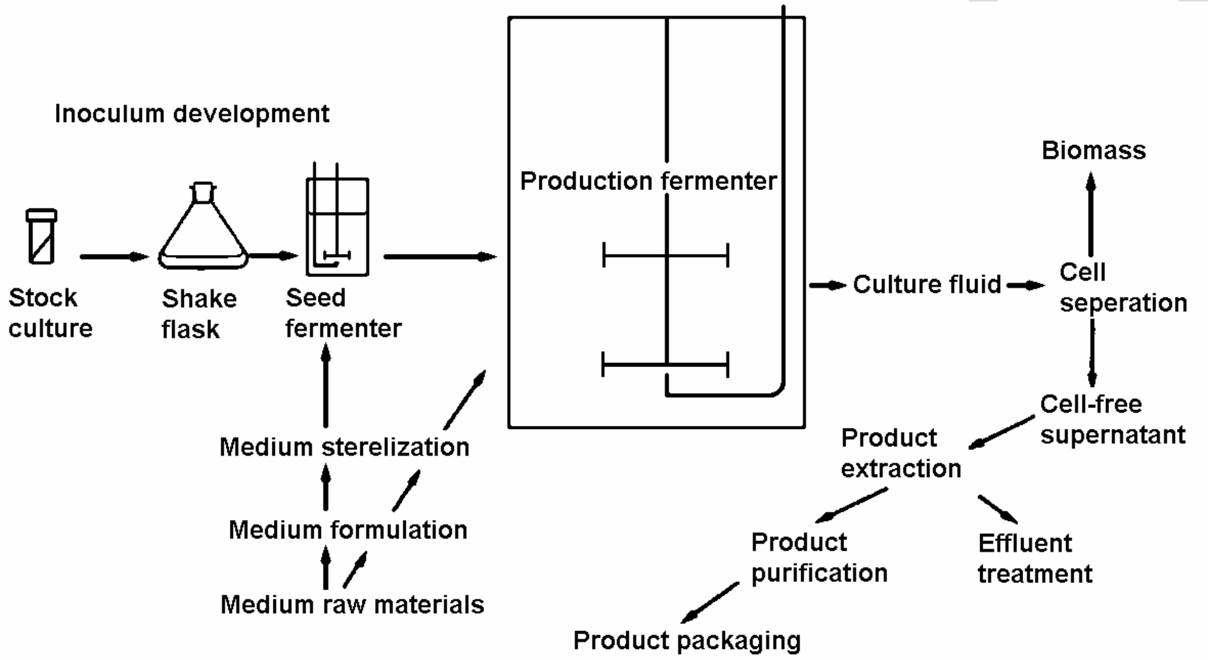

Figure 1.2: schematic representation of the cultivating process of cells

Stock culture
This is the collection of cells which have to be cultivated. These cells are already altered to give rise to continuous cell lines.

Shake flask
the stocked cells are contained in the shake flask. In this environment however, the cells cannot multiply efficiently. But cells need a minimum density to start multiplying.

Seed fermentor
In a little seed bioreactor, the cells will grow until they reach a certain density after which more medium can be added to raise the cell population. This process can be repeated until a desired volume of medium with cells is reached.

Production fermentor
Finally, the cells are added to a production bioreactor for large grow batches.

1.2.2 Cell cultivating

This is a brief overview of the fermentation process. More or less, there is a difference between fermentation and cell cultivation[1]. Fermentation is used with prokaryotes: cells with a simple metabolism and no cellular core (figure 1.3). In case of cell cultivating, then eukaryotes are involved (figure 1.4): cells with a much more complex structure.
Because of their characteristics, prokaryotes are easy to handle in the fermentation process. Eukaryotes on the other hand, are fragile and need to be handled with care and cannot be cultivated in the way prokaryotes are. A ‘standard’ cultivator for prokaryotes is a vessel with

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a stirring unit. The stirring unit improves for example the transfer of oxygen and the suspension of cells. But in such an environment the eukaryotes can not survive, due to shear, so other types of cultivating methods are developed, and are still under development.

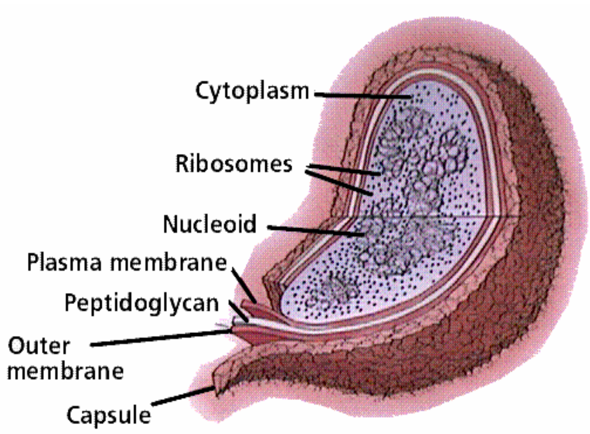

Figure 1.3: schemetic presentation of a prokaryote

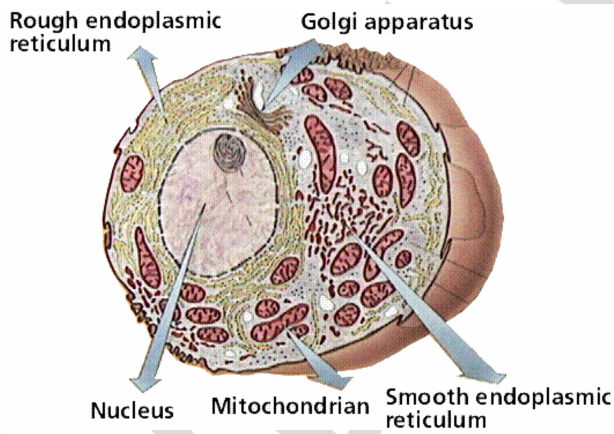

Figure 1.4: schemetic presentation of an eukaryote

Developing a bioreactor is a complex task. Under ideal circumstances, cells can grow with great efficiency. That's why environmental conditions of the reactor, like the presence of oxygen, nitrogen, carbon dioxide and suitable flow rates etc. must be at an optimum at all times, and therefore accurately controlled. Most industrial bioreactors have a container with sensors, controllers and a regulator with a PLC (Programmable Logic Controller). Bioreactors with the purpose of cultivating mammalian cells, have a different design than the regular reactors. Mammalian cells need a medium to grow on and are very fragile, therefore cultivating in a normal reactor is not preferred, while the cells will easily be damaged.

1.2.3 Disposables

In order to prevent contamination while starting or during the fermentation process, disposable bags were developed in the early 90s[2]. Although disposable materials are used as long as there is medicine, the use of disposable bags in combination with cultivating cells is still in its infancy. Using a disposable as reactor chamber has certain advantages, as well as disadvantages.

Advantages:
- Single use operation eliminates need for cleaning and sterilization procedures
- Functionality designed into the disposable component simplifies requirements for reusable hardware
- Single use eliminates chance for cross contamination between batches and products
- Decreased engineering complexity may decrease set up time.

Disadvantages:
- Cost per batch of disposable components
- Greater dependence on outside vendors
- More material compatibility questions
- Scale limitations

Although not listed with 'advantages', these disposables lends themselves to cultivate mammalian cells. As mentioned before, mammalian cells can not grow efficiently in a stirred

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tank. Disposables can not be stirred (because inserting a stirring unit could contaminate the sterile environment) but have to be shaken. By creating a waveform inside the disposable, inserted gasses can mix with the medium and maybe absorbed by the cells. This method is not as aggressive as stirring the medium. So Mammalian cells have a better viability, which is determined by the total amount of living cells divided trough the total amount of cells present.

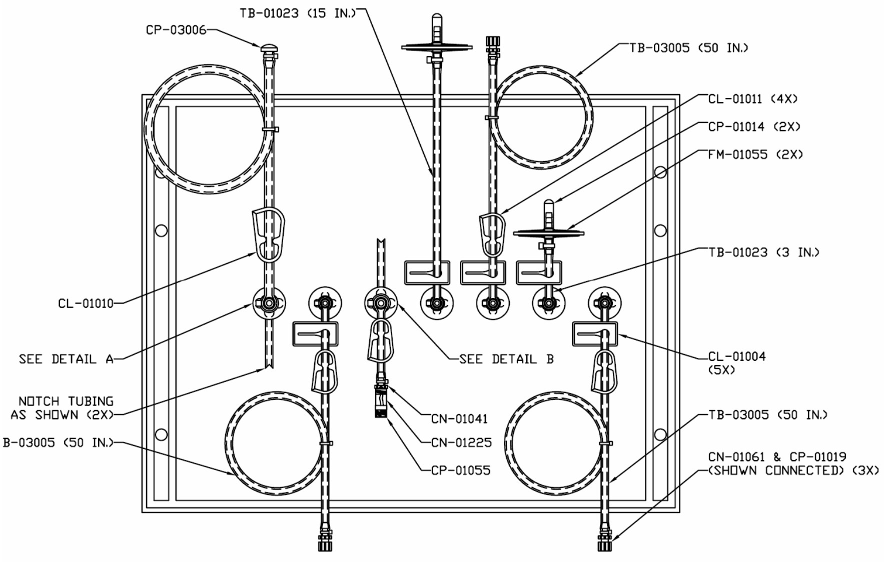

Figure 1.5: a disposable and its connection points locations

Connecting tubes for leading gas into the medium can easily be done with commercial Tubing welders, which have the ability to make a sterile connection in a non-sterile environment. The CELL-tainer^{TM}, developed by CELLution Biotech, is a bioreactor with the purpose of cultivating cells. CELLution is specialized in developing equipment for cultivating mammalian cells. The prototype uses a platform on which the disposable lies. This platform is shaking in a certain way in order to generate a continuous wave in the disposable. The platform is driven by a combination of gears, axles and a motor. Momentarily, the prototype is suitable for a disposable with total volume of 20 liters, containing 10 liters of medium. Figure 1.5 shows a technical drawing of a disposable.

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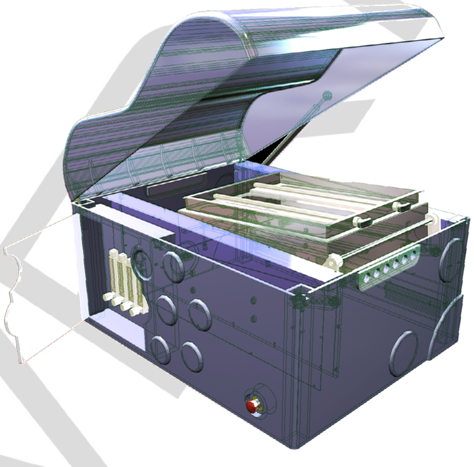
Market research . 2

Assignment 'shaker'



2.1 Market research bioreactors and related

The working prototype, which is currently used by CELLution, is mainly constructed of stainless steel. It is a model, intended to proof the working principles. The appearance however, is poor. With its current 230 kilograms (to shake approximately 10 kilos of medium), the machine is over dimensioned.
Because the eventual model has to find its way on the commercial market, it is very important that it will fit in the line of products now available used for the same purposes. Not only products made by the competition, but the controllers for example, can have influence on the eventual design of CELLution's shaker.

2.1.1 Market Research

Figures 2.1 and 2.2 are impressions of bioreactors made by the competition. Figure 2.1 is a shaker developed by Applikon[3]. On the left of the image is the shaker with a disposable bag (red medium), on the right the biocontroller, flow rate controller and PLC. The computer is to program the PLC and perhaps read data from it to visualize certain parameters. The shaker is made from plastic, but the container for the disposable is made of stainless steel. Except for the emergency button, the machine is entirely closed and easy to clean.

Figuur 2.1: Applikon shaker

Several flexible tubes stick out from the disposable and are connected to the controllers.
Bioreactors which use regular containers, are almost completely made of stainless steel and the cultivation chamber itself is made of glass. Figure 2.2 is an image of a bioreactor from New Brunswick Scientific[4]. Just like the Applikon bioreactor, this one also uses several controllers. The main difference however is that this reactor does not use a disposable as a cultivation chamber. Therefore it has to be cleaned (extremely well) so there is no risk of contamination.

Figuur 2.2: bioreactor

One would expect that this method is not accepted, but there is a wide variety of similar solutions. The reactor in figure 2.2 is small, but reactors do exist which are huge. The volume of the container can be as large as 10.000 liters[2]!
Conventional reactors look complicated (figure 2.3, image left and image right). The reactors in the middle image are from Wave[5], and have a more friendly look. As told before, stainless steel is commonly used in available commercial products. But smaller reactors, working with disposables are often made of plastics (for a large part). In this case, the shakers from Wave Biotech are made of stainless steel. The shaker, in which the disposable lies, can be

closed with a cover for safety and to keep direct sunlight from the medium. A console is located on the right of every shaker (with emergency button) which contains the PLC, flow controllers etc. The reactors look very practical in use.

These new types of reactors and shakers are distinct from the other types with a stylized design. For users, the modern shakers will look friendlier than the older ones, which are saturated with tubes. Not only the bioreactor defines the look towards the user, but also the controllers. Therefore such controllers are also evaluated. For example, figure 2.5 and 2.6 are images of an flow regulator, controller and reactor from Applikon. Notice that figure 2.3 also shows a controller from Applikon.

Figure 2.4 is an image of a controller from Biospectra[6]. The machine looks modern, stylish, and has an easy-to-use appearance. In comparison with the controller from Applikon, the machine looks more user-friendly. It seems though, no tubes are connected (or doesn't need to be connected), but connections are located at the back of the machine. For the appearance towards the user it is better. The three little boxes in front of the machine, are peristaltic tubing pumps.

Figure 2.3: Several bioreactors

Figure 2.4: Biospectra controller

Figure 2.5: Applikon controller

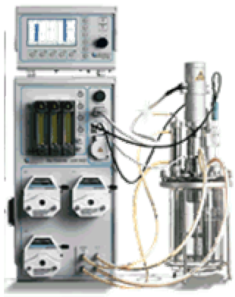


Figure 2.6: flow regultor, controller and reactor

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Website

Furthermore, a copy of CEL-Lutions[7] website gives some information about the desired style of the company (figure 2.7). The first impression gives a no-nonsense policy. The main color is blue. Information is direct and not ambiguous. The site is stylized. Considering this, the design and appearance of CELL-tainer™ , should have these impressions: no nonsense, stylized, perhaps blue tinge.

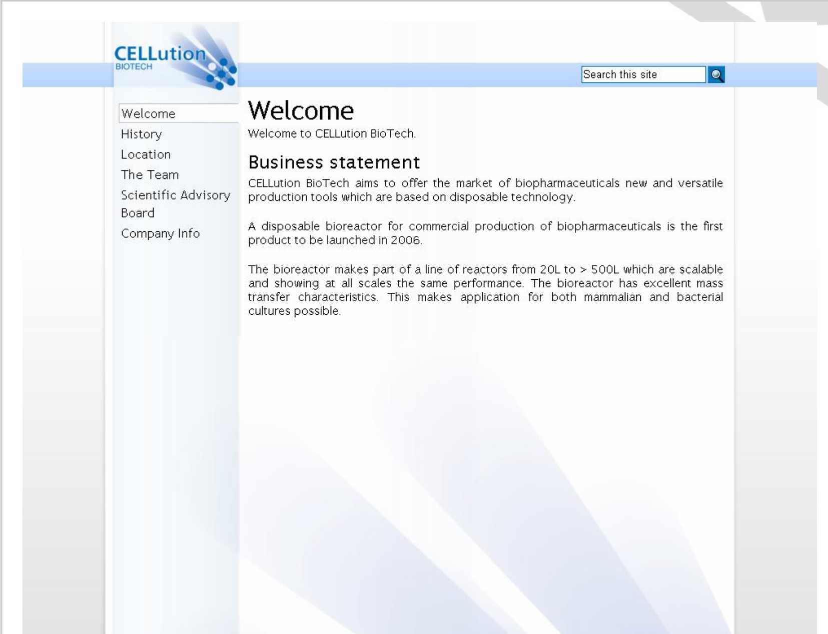


Figure 2.7: CELLutions website

2.1.2 Stakeholders

To distinguish the users who have to work with the machine (in this case the CELL-tainer™), it is necessary to write down the stakeholders.

Stakeholders are as follows:

- Producers
  - assembly workers
  - company which assembles the product

- Consumers
  - company that buys the product
  - installer of the product

- Users
  - laboratory worker
  - cleaner

2.1.3 Collage

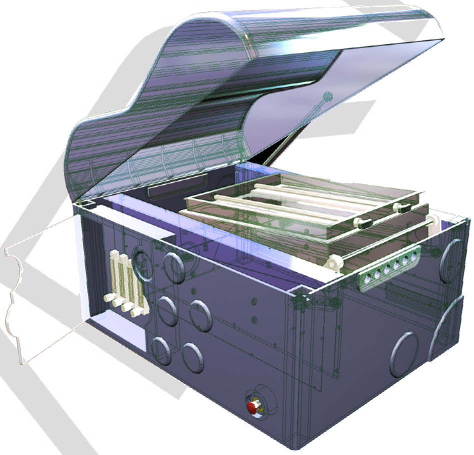
A collage is printed on the next page, to get an impression of used materials and design in commercial bioreactors and controllers.

2.2 Collage

Figure 2.8: collage with the market research

Desingroute . 3

Assignment 'shaker'



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3.1 List of requirements

The prototype of the CELL-tainer™ is manufactured on the basis of a list of requirements, described in 'Shaken, not Stirred: the development of a scaleable wave-induced disposable bioreactor' by Ir. P. van der Heiden[8]. Those requirements are as follows:
- complete disposable cell culture system
- to prevent contamination
- to create a wave for better oxygen absorption
- linear and parallel scalable
- suitable for different types of cell cultures
- same working principles as other wave creating machines
- easy to use
- reliable and robust

With these requirements, the prototype of the CELL-tainer™ was successfully built. This assignment states that a user friendly design must be added to the machine, ready for commercial use. Therefore, a new set of requirements is drafted. Earlier requirements applying to the working principles are included as: 'current working principles may not be altered or hampered by the new design'. It is not necessary to fully understand or explain the requirements stated above.

The list of requirements for the design process is stated as follows:

Requirements related to guidelines and legislation:
- the CELL-tainer™ must apply to the GMP guidelines.
- the CELL-tainer™ must apply to the CE hallmark class 1 and therefore apply to the European machinery directive.

Requirements related to working principles
- current working principles may not be altered or hampered by the new design.
- temperature of the medium must be controllable during cultivation at all times.

Requirements related to the CELL-tainer™ :
- the CELL-tainer™ may not weigh more then 30 kilograms, medium not included.
- maximum cleaning time of the CELL-tainer™ may not exceed 5 minutes.
- the CELL-tainer™ must contain a disposable measuring 72 x 56 x 16 centimeters.
- sampling time may not exceed 10 minutes.
- the CELL-tainer™ must be at standing height for the user.
- the CELL-tainer™ must have connecting capabilities for a controller and a flow regulator.

Requirements related to the disposable:
- Inserting and removing the disposable may not cause any damage to the disposable
- during the cultivation process, the disposable must be fixed in place at all times.
- Inserting time of the disposable may not exceed 5 minutes, adding the medium not included

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3.2 Usage research

For better understanding of the usage of the machine, a usage research was set up to acquire information about taking samples, the time this takes and more related information. The photos were made at Imenz in Groningen, the Netherlands. This was the second location were the machine was placed for experimental purposes during the assignment. Its first location was at DSM, also in Groningen.

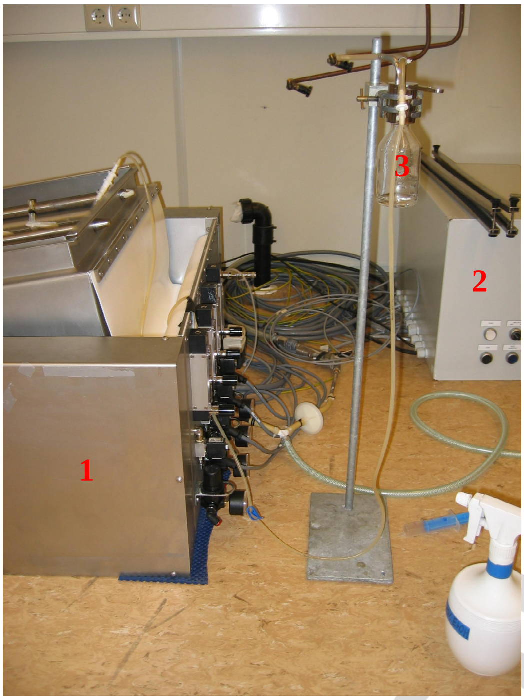

Figure 3.1: CELL-tainer™ with controller

Figure 3.1 shows the experimental line-up with the CELL-tainer™ prototype [1], the controller [2] and a temporary solution to take samples from the medium [3].

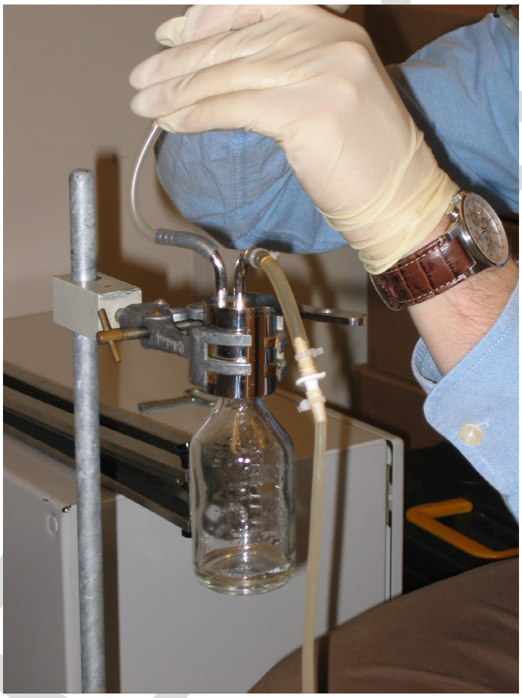

Figure 3.2: taking samples.

To take samples from the medium in its current state, first the tube has to be filled with medium which contains (growing) cells. Then a small amount of medium can be extracted and put in a sterile jar. But some medium remains in the tube and every time, the tube must be emptied before extracting new medium. In Figure 3.1 it can be seen how long the tube is (from the CELL-tainer™ [1] to the clamp with the jar [3]).

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Figure 3.3: sampling by Applikon reactor

The Applikon reactor has a more efficient way to take samples from the medium. The jar in which a sample is collected, has a very short tube to the medium. Therefore samples can be taken easier.

Figure 3.4: Ir. P. van der Heiden taking samples

Figure 3.4 shows Ir. P. van der Heiden taking samples from the CELL-tainer™. Although it is a more complex process with the current line-up, it does not take a long time to collect samples (about 3 minutes). Notice that the posture is very unstable. Goal is to place the CELL-tainer™ at a height at which an operator can do his jobs standing.

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3.3 Working principles

In the next section, it is in order to understand the outcome of the concepts necessary to get an impression of the working principles of the prototype of the CELL-tainer™ before the ideas, drafts and concepts will be discussed The working principles will not be discussed in detail, but superficially. Knowledge of how the prototype works, helps to explain the choices made in the design process.

A simple representation of the machine is as follows:

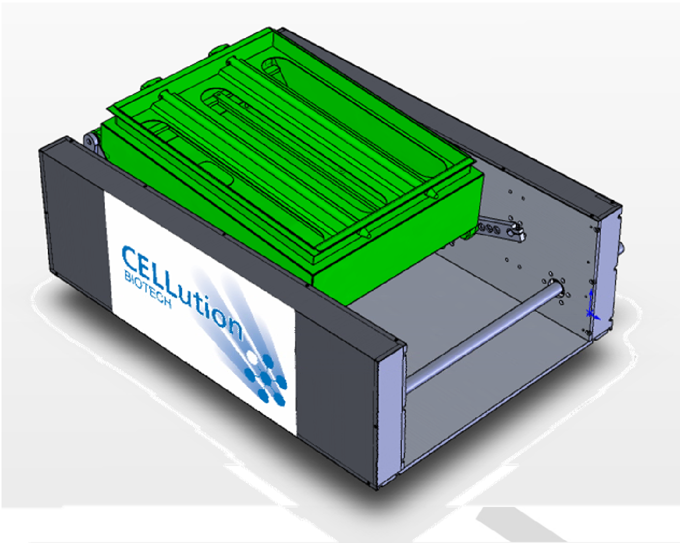

Figure 3.5

The model, created in Solid Works, consists roughly of four different sub-systems.
On the left, the holder for disposables (green) is shown. This is the actual part which shakes the disposables.

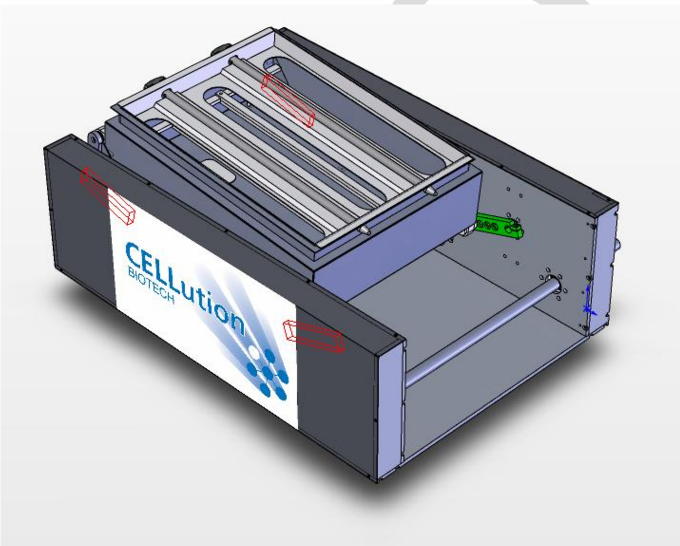

Figure 3.6

In figure 3.6 the suspension for the disposablesholder is shown (green or red-boxed). The position of the holder is variable, but in this case is in its maximum configuration.

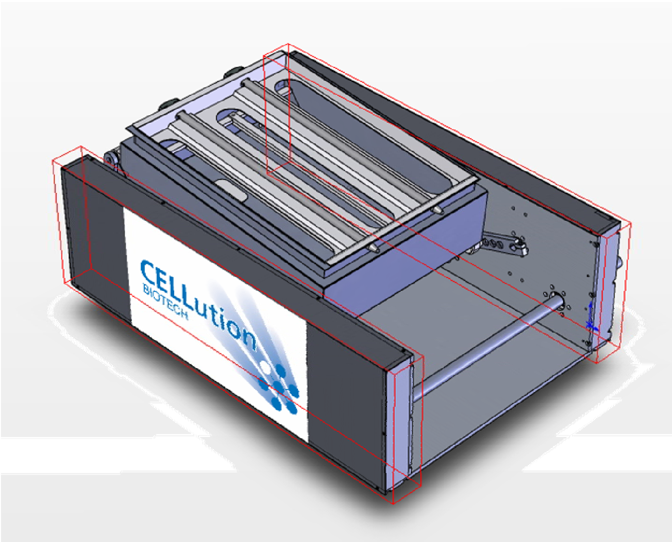

Figure 3.7

The suspension is connected to a transmission, which consists of the prototype of several gears. These gears lie on the left and the right of the disposableholder (red-boxed).

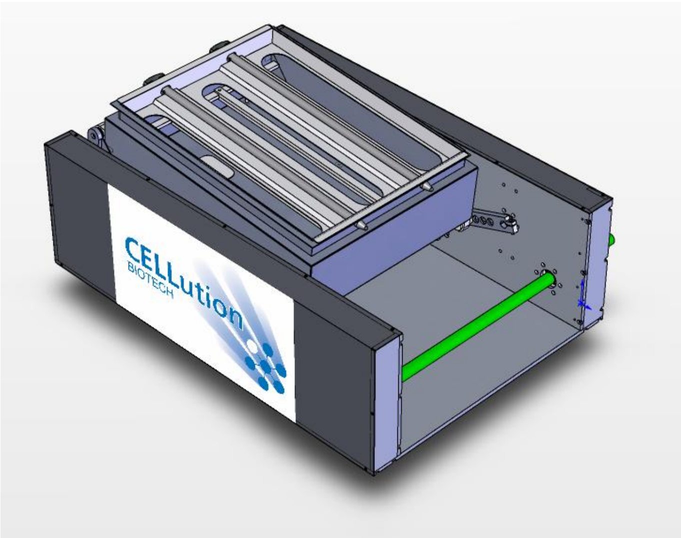

Figure 3.8

The gears are driven by a central axle, which is directly connected to a motor (with its own transmission). The motor is positioned behind the prototype.

With the current combination of axles, arms and motor, the schematic representation of the movement of the disposableholder in relation to the suspension of the drive looks as follows:

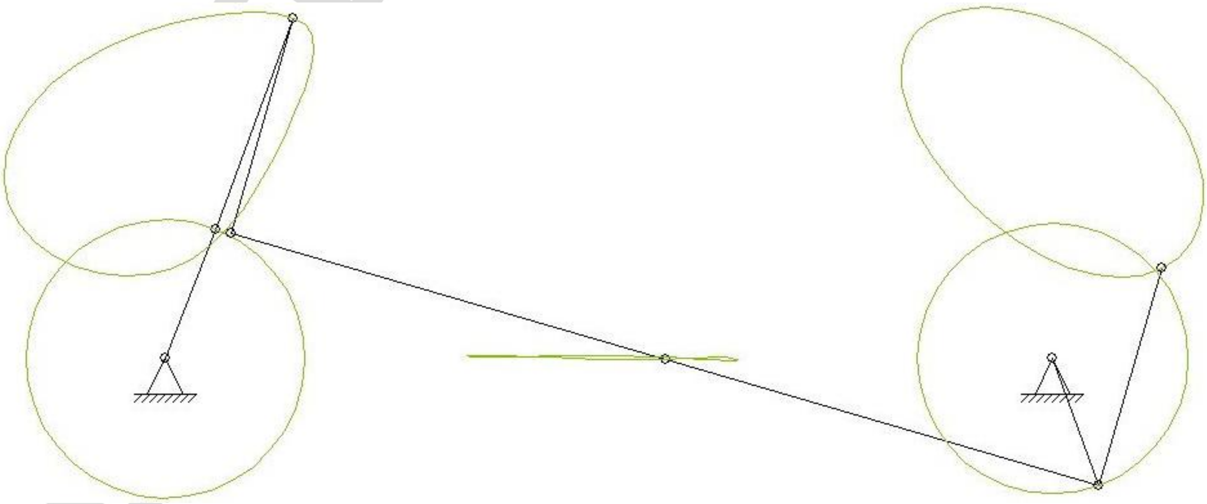

Figure 3.9: schematic representation of the movement of the disposable holder.

Although the movement caused by the combination of a motor, gears and axles is proved, in a future design, the use of two linear motors is planned. Detailed plans are not made yet, but the components will be placed more or less as shown in the basic draft below:

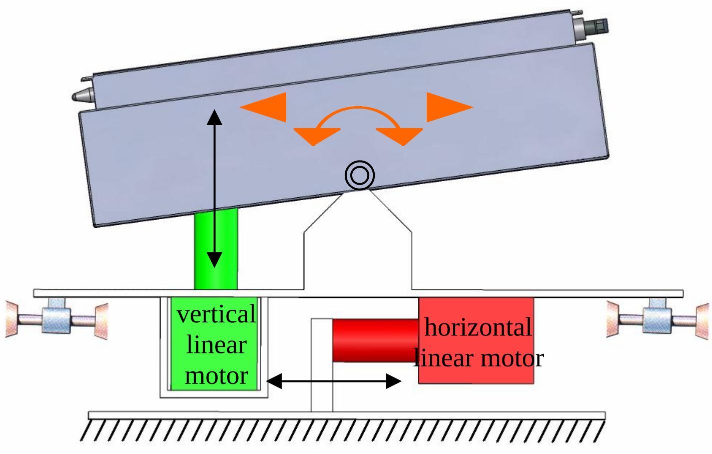

Figure X3.10: schematic representation linear motors

The red, or horizontal, linear motor sets the second plane moving in horizontal direction. With the movement of the plane, the green, or vertical, linear motor will move along, because it is assembled on this second plane. The vertical linear motor is assembled to the disposable holder. The holder is connected to an axle.
With these two motors, the same motion can be obtained as in the prototype with axles, gears and arms.

In both cases (with the use of linear motors or a rotating engine with transmission) the motion of the disposable holder should be the same (figure 3.9).

Further development with linear motors is important, because in its current state the machine (using gears, transmissions etcetera) uses a lot of unnecessary space. The linear motors will be placed under the disposable holder and therefore some space is gained at the sides of the machine.

With basic knowledge of the machine, how it functions and which components are used, some ideas are generated. The ideas which are created are mostly constructed conform the current system and the working principles used, but in every case, with simple modifications, it will be easy to adapt from the old construction to one with linear motors.

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3.4 Ergonomics

With the design of a working space, where a operator has to do his job standing, there are several points to consider:

- correct working height
- sufficient space for feet and knees
- correct reaching distances
- good overview off the working area

Some dimensions have to be considered, during the designing process. These considered dimensions can be found in Appendix A.2, which are underlined. Although operators do not have to stand by the machine for extended times, it will be much more comfortable for the operator to work at the cultivator if the machine itself will not obstruct the task being performed. It will also save time and therefore cost if the machine has an ergonomic design, due to working efficiency during operation.

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3.5 Ideas and drafts

In this section, several ideas and drafts will be discussed.

Conform to the agreements with CELLution, several ideas were presented. These ideas, and the drafts resulting from them, are made without considering any particular demand or wish. Although the list of requirements was kept in mind, the ideas were generated on ‘just draw and we will see’ base. Because CELLution offers a new line in disposable bioreactors with their CELL-tainer™, it was not easy to develop different kinds of concepts. Finally, three different presentations of different types of design, usage and application were generated. These ideas were further developed from several rough drafts. Figures 3.10 to 3.17 are images of such drafts:

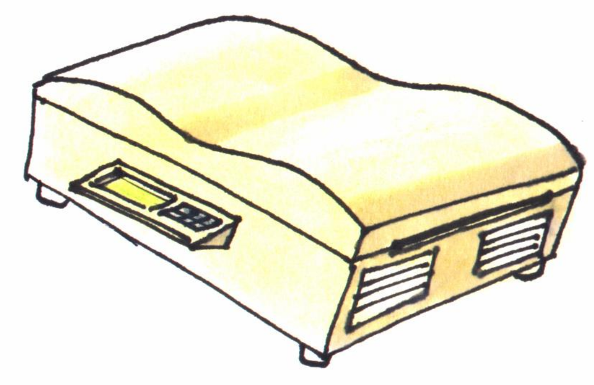

Figure 3.10

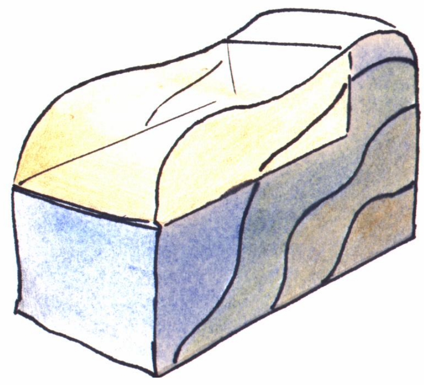

Figure 3.11

Comments with figure 3.10:
This sketch tries to underline the function of the machine: the machine was designed to generate waves, which causes a larger surface for gasses to mix with the medium. The cover follows the movement of the shaker.

Comments with figure 3.11:
Figure 3.11 also tries to underline the function of the machine: generating waves. On top of the machine is a transparent cover, trough which the movements of the machine can be seen.

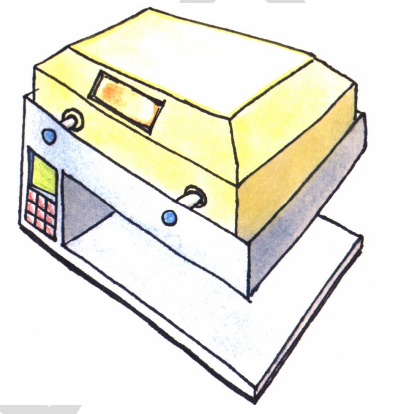

Figure 3.12

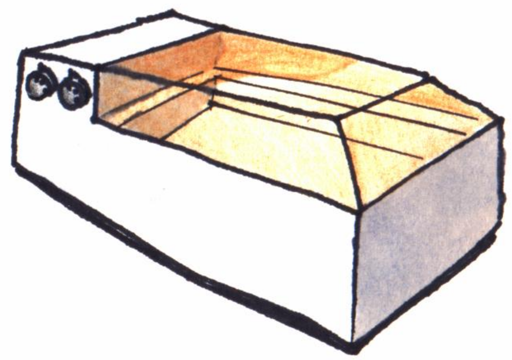

Figure 3.13

Comments with figure 3.12:
A concept in which the shaker is on top of a console. A lot of space is created under the shaker to put workingmaterials etc. Construction needs some adjustment.

Comments with figure 3.13:
Same idea as figure 3.11, but a more stylized look without waves. It’s a (common) disadvantage when actuators etcetera are located behind the shaking unit. below it would be better.

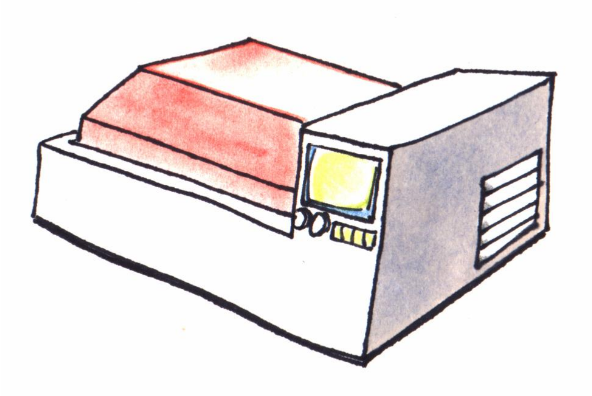

Figure 3.14

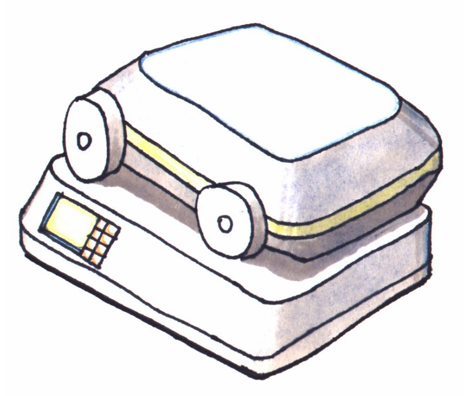

Figure 3.15

Comments with figure 3.14:
Basic idea of this sketch is to leave room for the controllers, next to the shaker unit. The shaker has its own cover which can be closed.

Comments with figure 3.15:
In this one, the movement of the shaker is underlined by placing the shaker between four wheels, which are in fact houses for the axels.

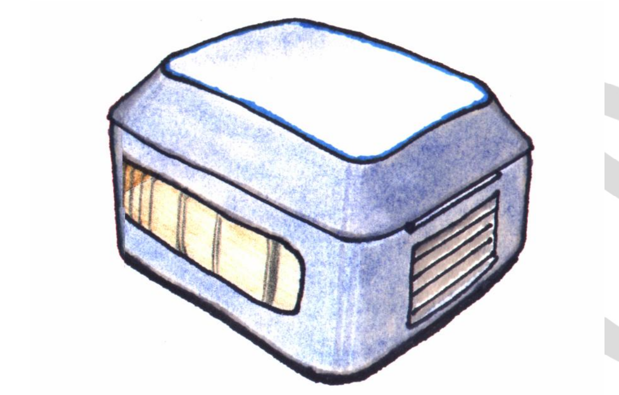

Figure 3.16

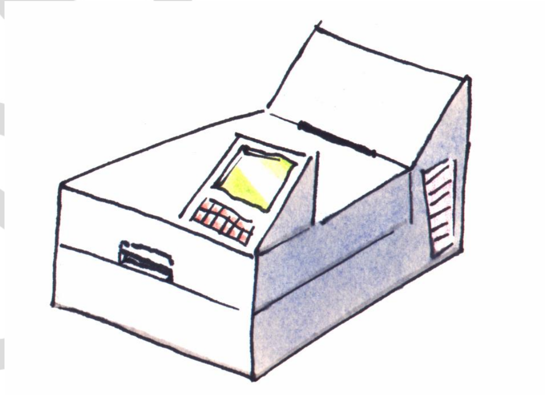

Figure 3.17

Comments with figure 3.16:
Figure 3.16 shows a house for the shaker and its mechanisms. Trough a transparent window it is possible to watch the shaker move.

Comments with figure 3.17:
This concept is a very stylized unit, in which the shaker is housed. An interface is located on top of the cover. At the back is the form of the interface repeated.

Some of the designs from the sketches have advantages as well as disadvantages. Some advantages of one design are added to another and so several early designs which led to the final concept were generated.
The final concepts, which only fulfills the design demands, were represented in three presentation drawings. The drawings are shown in Figure 3.18 to 3.21 (see the following pages).

These three presentation drawings were presented to N. Oosterhuis (Technical Director at CELLution Biotech) and P. van der Heiden (Development Engineer). After reviewing the presentations and consultating with other members of the company, they wished for an extra concept, with more detailed drawings. Although it looks like a photocopier, the concept from figure 3.10 had drawn the attention. Based on this concept (which clearly states the movement of the shaker) a fourth presentation drawing was made (figure 3.21, page 24). After showing the drawing it was decided to further develop this concept.

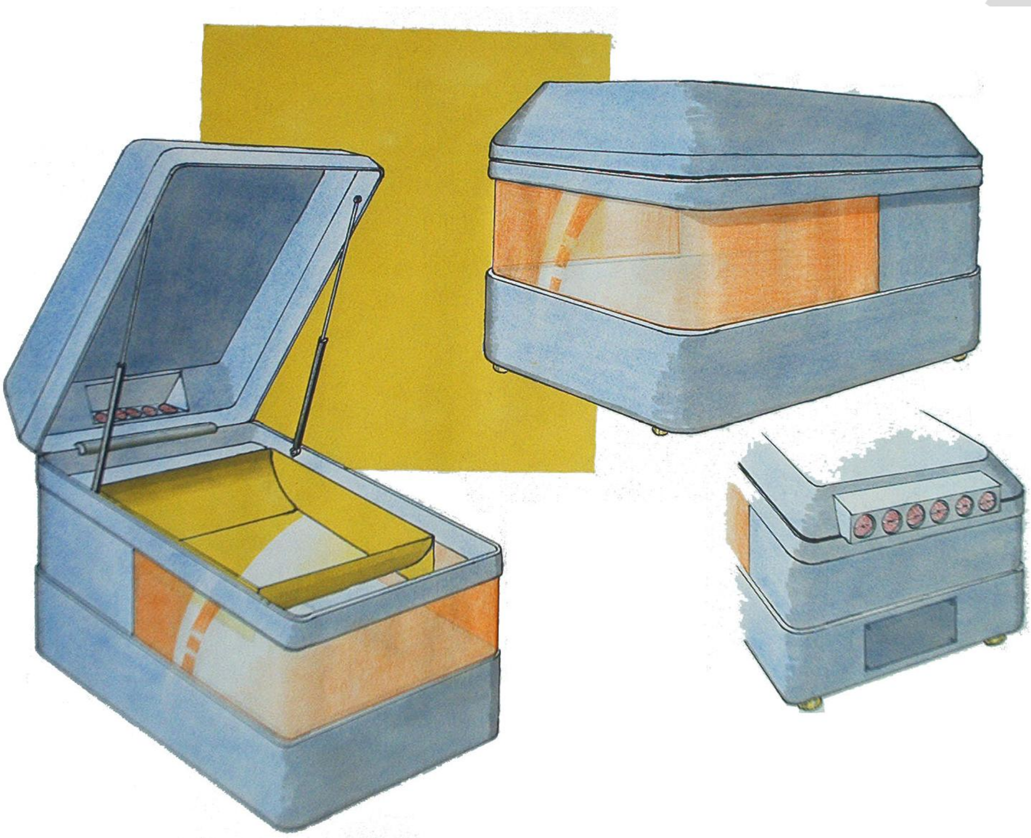

Figure 3.18: Presentation drawing 1

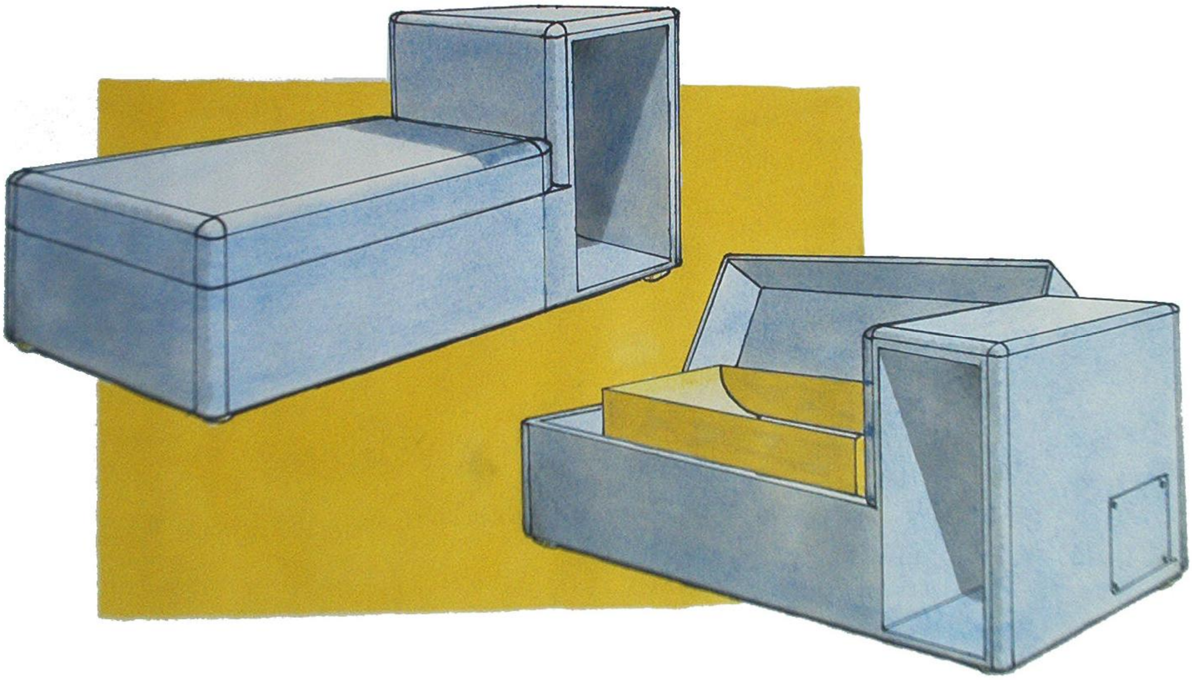

Figure 3.19: Presentation drawing 2

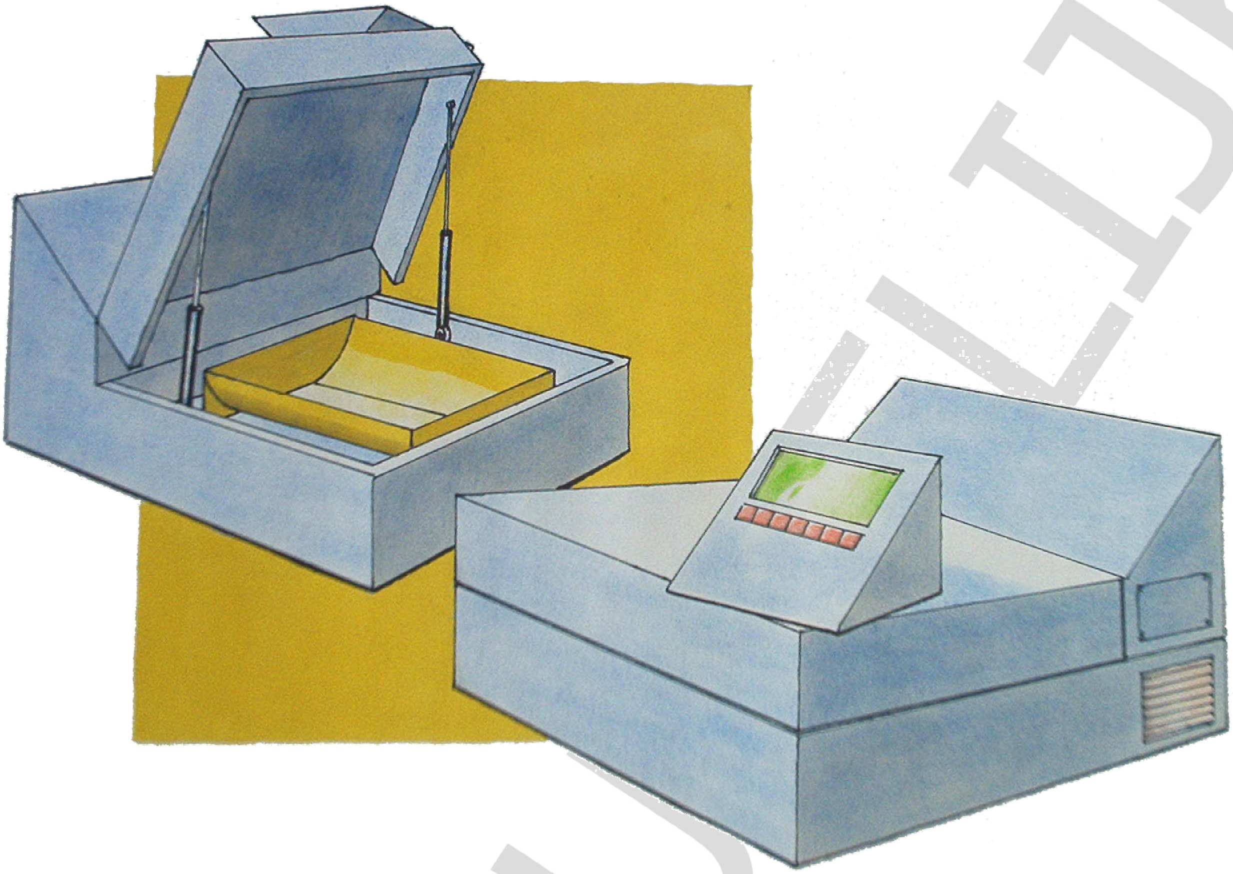

Figure 3.20: Presentation drawing 3

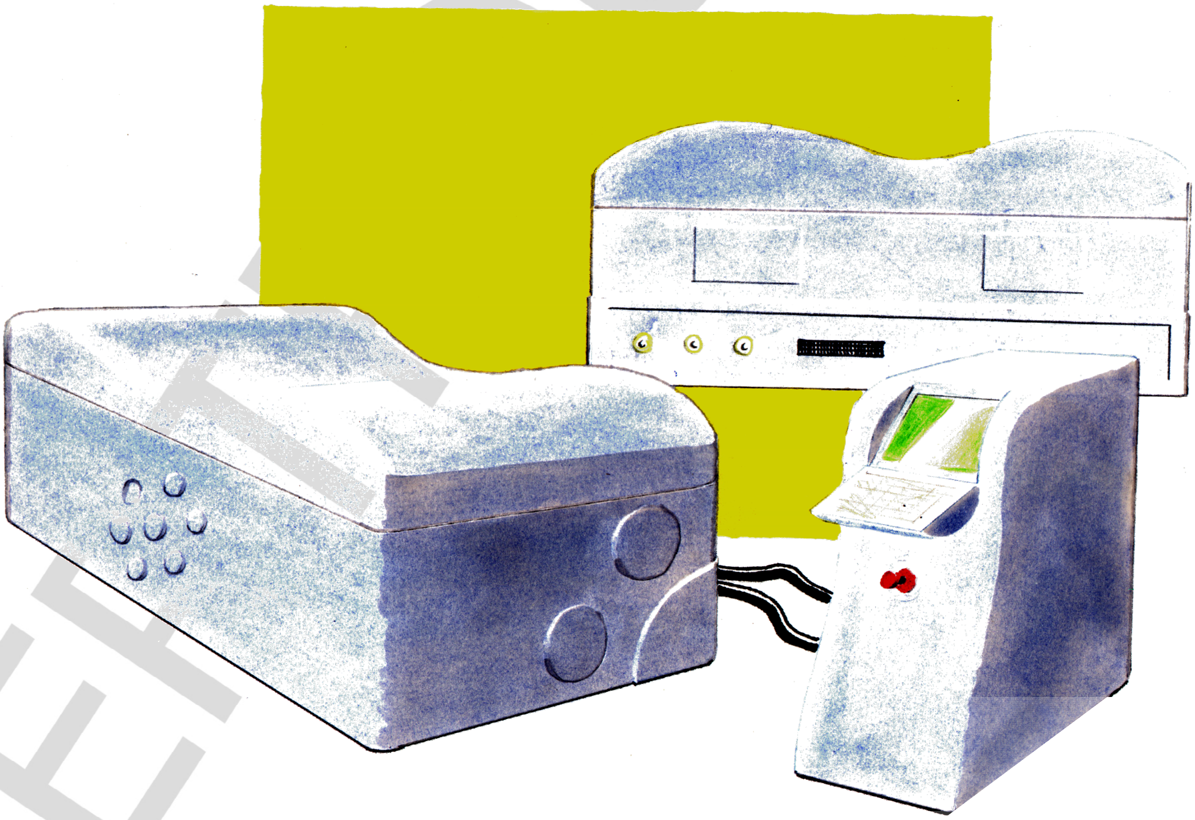

Figure 3.21: Presentation drawing 4.

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3.6 Detailled development

The argument used by choosing particularly this concept was mainly the form of the hood. With its rounding, the movement of the machine is underlined, which is very attractive.

To determine the rounding of the hood (which is very important, because the holder is moving under the hood and at all times it must do this without any hindrance), the schematic presentation of the movement (Figure 3.9, page 18) is used to find the maximum extended positions, which are measured by simply connecting (red) lines between dots. The result is as follows:

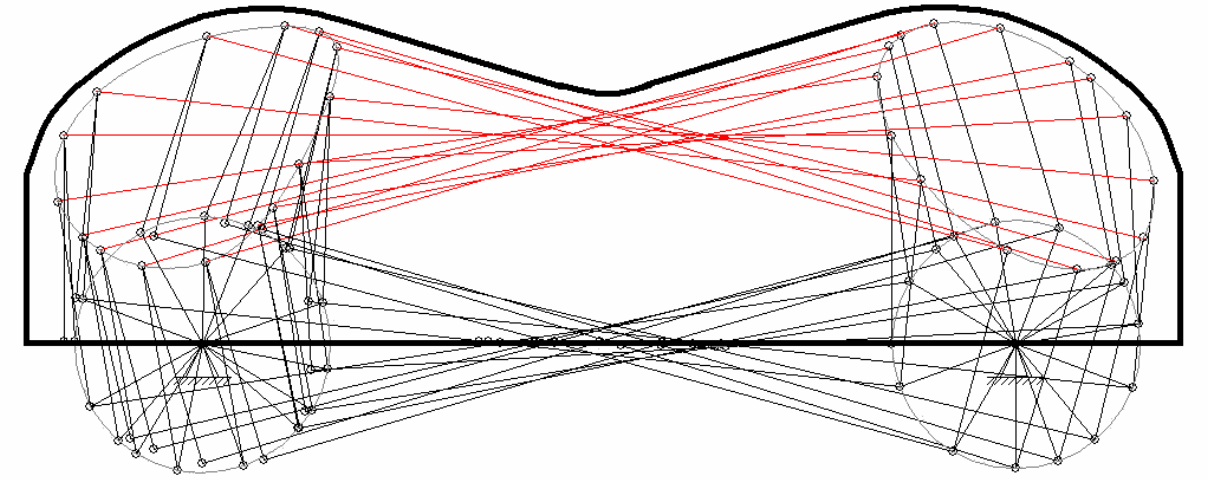

Figure 3.22: determination of the rounding of the hood.

So, for the holder to move freely, the inner distances from holder to hood must be more than the black line seen in figure 3.22. In a presentation draft, these distances can be ignored, but when the model is drawn in a 3D program, for example Solid Works, these distances do matter.

From the first concept to the presentation drawing, some adjustments were already made. This can be seen on the next page.

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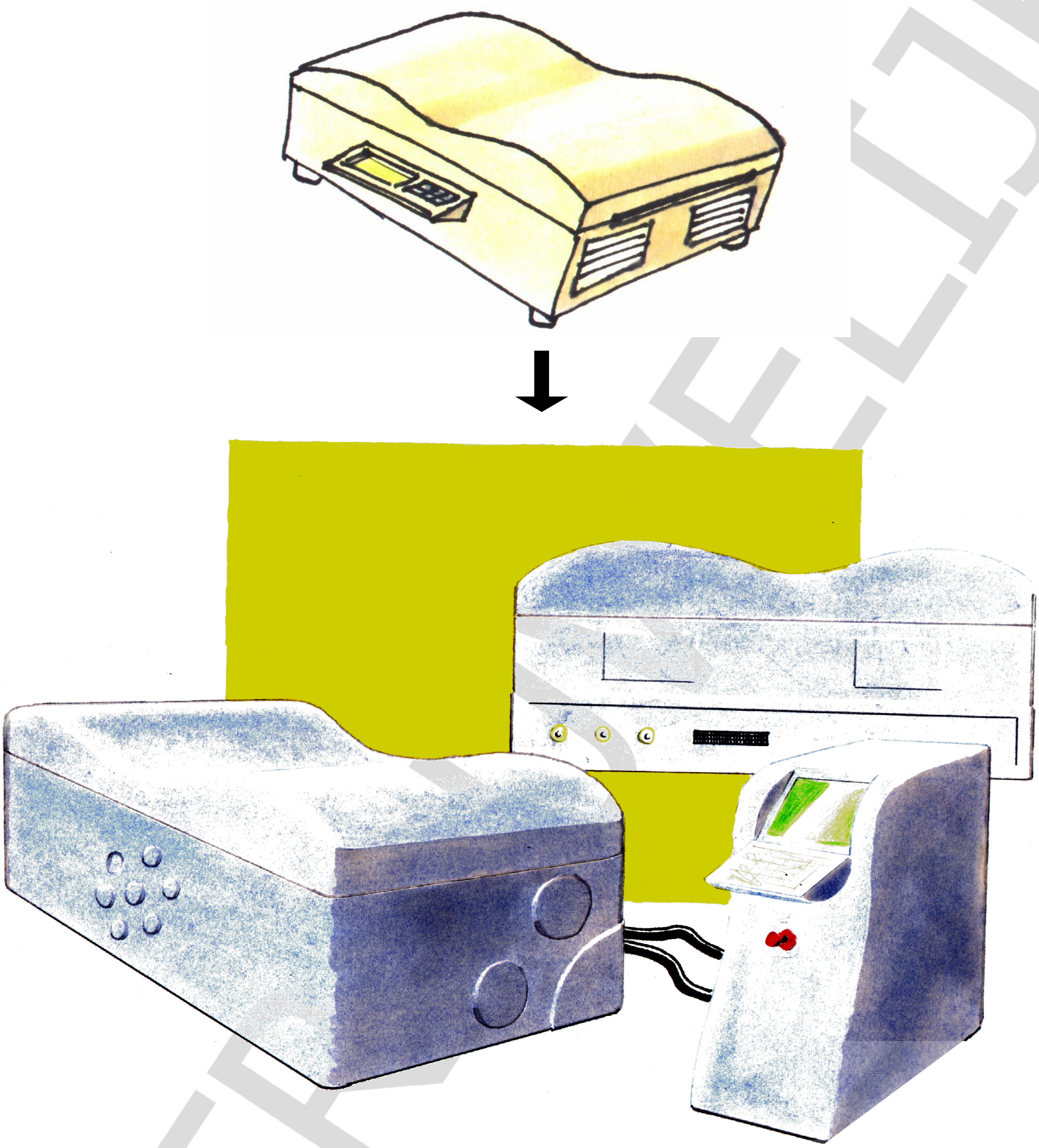

Figure 3.23: From draft to presentation drawing 4.

The controller interface is not connected to the machine itself, but is in a separate console. This choice is made, because with one controller, multiple bioreactors can be controlled. Furthermore, the height of the machine is increased. The holder for disposables will be on top and underneath is room for motors, transmissions (not in the case of a linear motor solution), flow regulators etcetera.

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In presentation drawing 1 (Figure 3.18, page 23), a sort of tube transit is represented, with which it is possible to have a static tube at the outside of the machine and a dynamic tube at the inside. This idea is used in the final concept.
A material with high friction coefficient encloses the rubber tube, but will not pinch off the tube. When the holder is rocking in the machine, the tubes can freely move between the disposable and the tube transit. From the outside, it looks like several tubes inserting the machine.

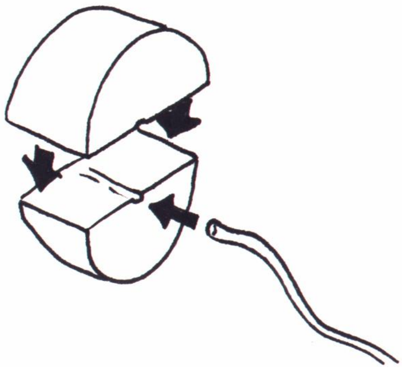

Figure 3.24: tube transit

Because multiple tubes are used, an array of this tube transit must be placed somewhere logical, for example in the hood, so it will be easy to lead the tubes through the transits. In Figure 3.25 is an example of this idea. In the detailed design, the two halves are replaced by one full circle, with a groove to lead the tube in. The tube, along with its transit, can be placed in a holder, which lies in the body of the machine. Why the array is moved to the body, and not any longer a part of the hood, will be discussed later.

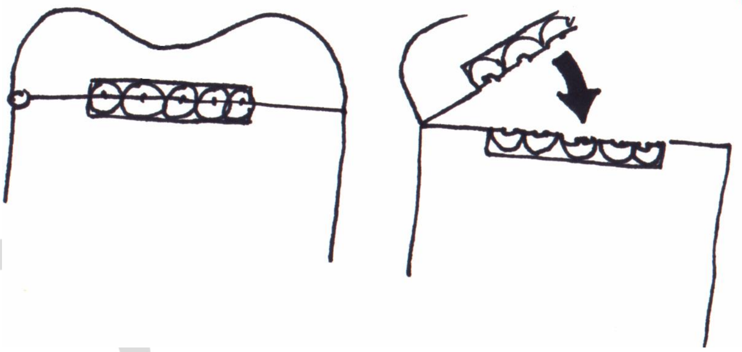

Figure 3.25: array of tube transits in the hood

One of the wishes of CELLution Biotech is the possibility to scale up the production. In this case it means that several bioreactors are put together and controlled with one controller. Logically, these several reactors will be placed together. To increase the functionality and ease of operation of the machine, the hood can be placed in two ways, so it can open clockwise or counterclockwise. It started with the idea of simply placing the hinges on the left or right of the hood. But it seems easier to fix the hinges on the hood, ant turning the hood for placement. Because the hood will be turned, it is not desirable to have a cut-away on both sides of the hood. That’s why the tube transit array is kept in the lower part of the body, instead of one half in the body and the other half in the hood.

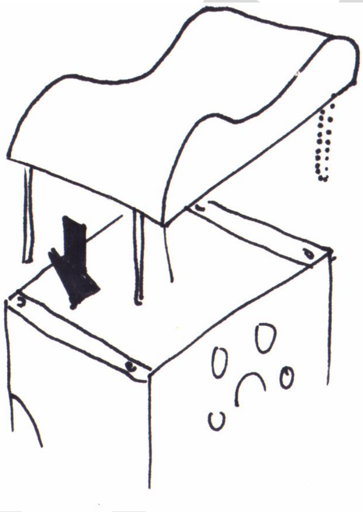

Figure 3.26: placement of the hood

On the next page, several 3D modeled views are shown, to visualize the final concept in its early state.

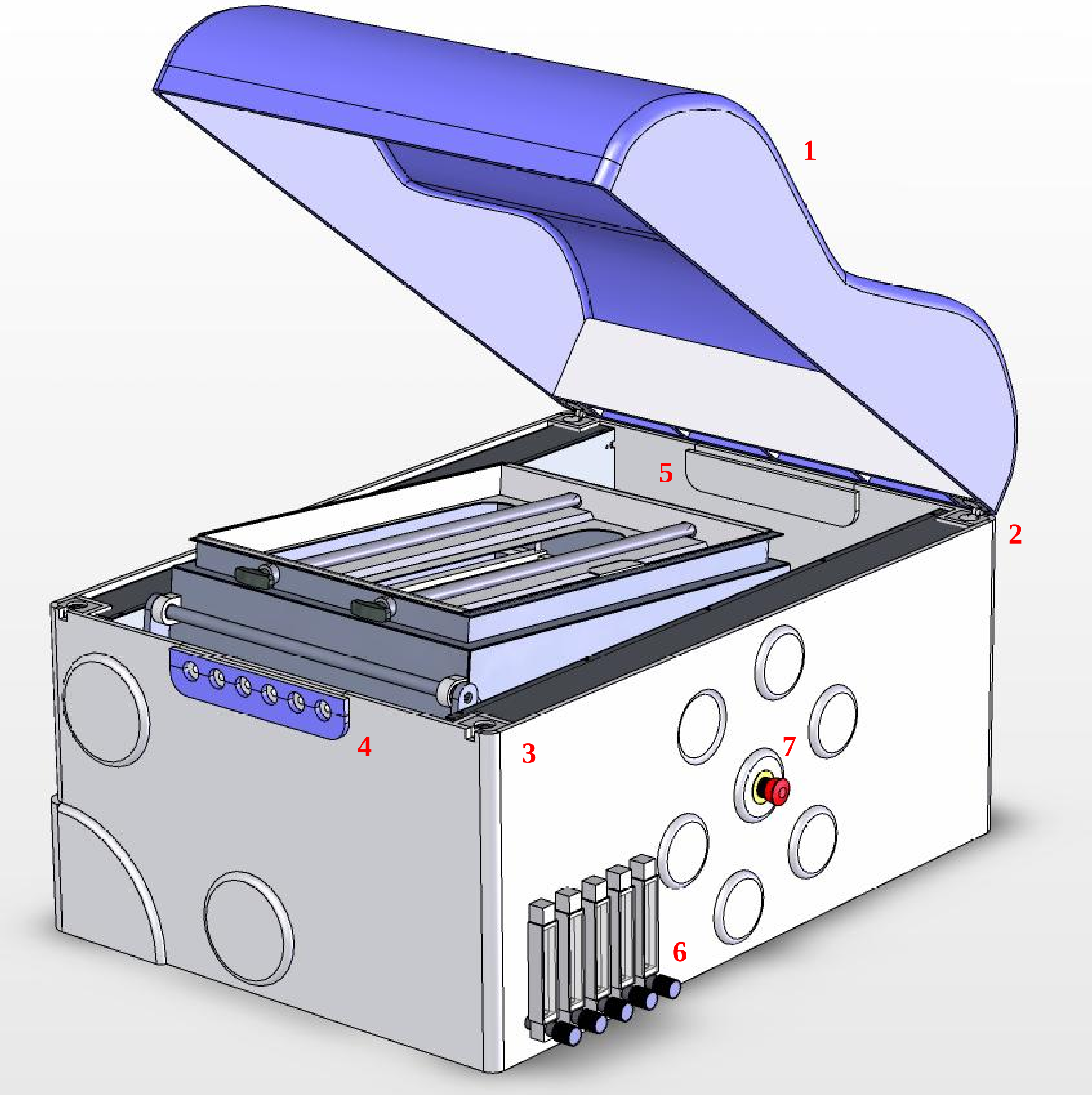

Figure 3.27: 3D representation of the final concept in an early state.

The representation in figure 3.27 was used for early impressions of the state of the design route. The rounding of the hood [1] exactly follows the minimum distance line from figure 3.9, page 18. The hood is fixed at the right of the body [2]. The other connection points are on the left [3]. The tube transit is also on the left [4], and a dummy is on the right to fill the hole [5]. Although the flow regulators are placed at the lower left side [6], this is not the final position. The emergency button is integrated with the logo from CELLution [7], but at this moment also, a better place has to be found for the button. Perhaps several buttons will be placed on the machine. Obviously, when someone is working behind the machine, the button cannot be reached.

Some states of the design process are printed on the next page, in which the concept changed.

From the presentation drawing (Figure 3.21, page 24) to the final concept, several different concepts were presented towards CELLution. It is not necessary to discuss these transitional states of the concept, but underneath is a global summary of the different concepts.

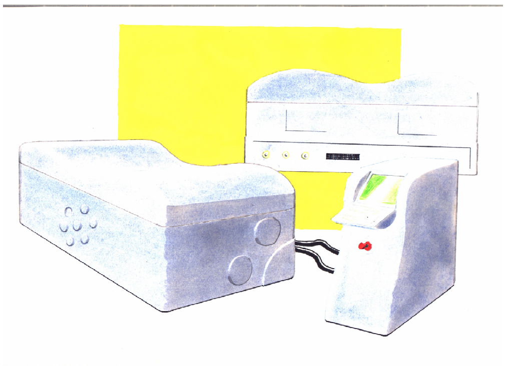

Figure 3.28: Presentation drawing of the final concept

Figure 3.28 shows the presentation drawing which led to the final concept (next page).

Figure 3.29 is one of the first results of a model derived with Solid Works. Placement of the emergency button and flow regulators were debatable at the time.

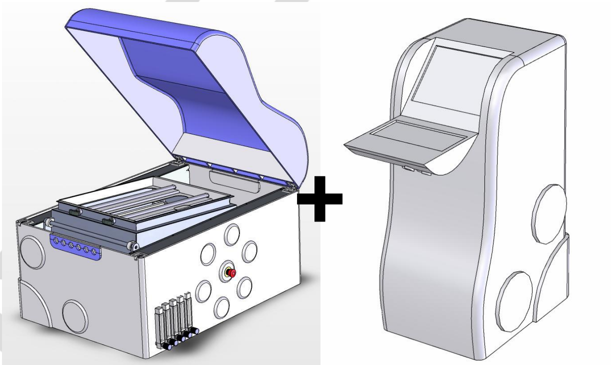

Figure 3.29: Solid Works impression of final concept in early stage

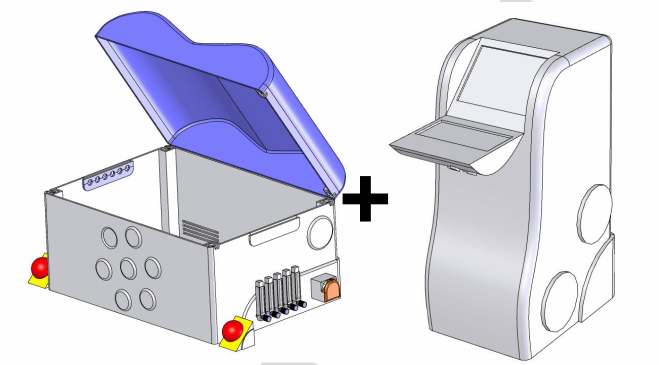

Figure 3.30: Solid Works impression of final concept in early stage

Figure 3.30 shows another placement of the flow regulators and two emergency buttons, placed on the left and the right of the machine. To avoid unnecessary hindrance with the cover, the hinges were placed at the back of the machine.

Figure 3.31 is the concept with a drawer to house the flow regulators. The emergency button is also placed on the drawer. The flow regulators are on a board which can topple over, so there is enough space to close the drawer.

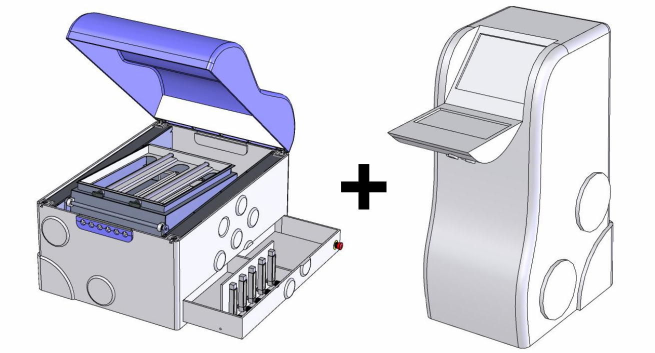

Figure 3.31: Solid Works impression of final concept in early stage

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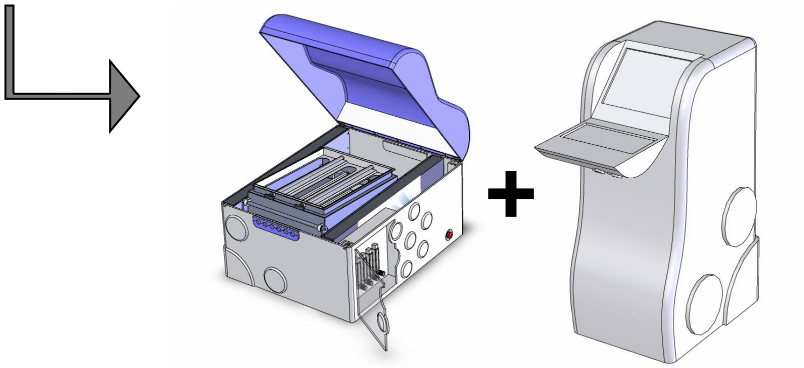

Figure 3.32: Solid Works impression of the final concept

Figure 3.32 shows the final concept. The width of the housing has increased with 10 centimeters. Therefore space is created in which the flow meters are located. The increased width can be undone by placing linear motors underneath the rocking plane, instead of having gears on the sides of the plane.

Figure 3.32 shows the final concept. Although the housing has a lot of familiarity with the early stage of this concept, some major differences have been made.
The flowmeters are placed in a special space, which can be closed with a transparent door. The flowmeters can easily be read through the transparent material. But if an operator has to make adjustments to the meters (for example, changing the flow rate), the operator can open the door and perform his tasks.
The emergency button is not placed directly on the outside of the housing, but is recessed slightly. Therefore it is still prominently present, but not in a disturbing way. This solution will not effect the use of the button in a negative way (problems with reaching etcetera).
The controller design has not been altered.

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3.7 Added elements

In the next paragraphs, some elements which are added to the machine will be discussed.

3.7.1 Tube Transit

The tube transit was developed to lead the tubes, transporting gasses from the disposable to the outside of the machine. But the holder for the disposable is rocking, so the tubes are in constant movement inside the machine. The tube transit uses a rubber, high friction material, in which the tubes lie. Therefore the tubes inside the machine are moving, outside the machine, they are static.

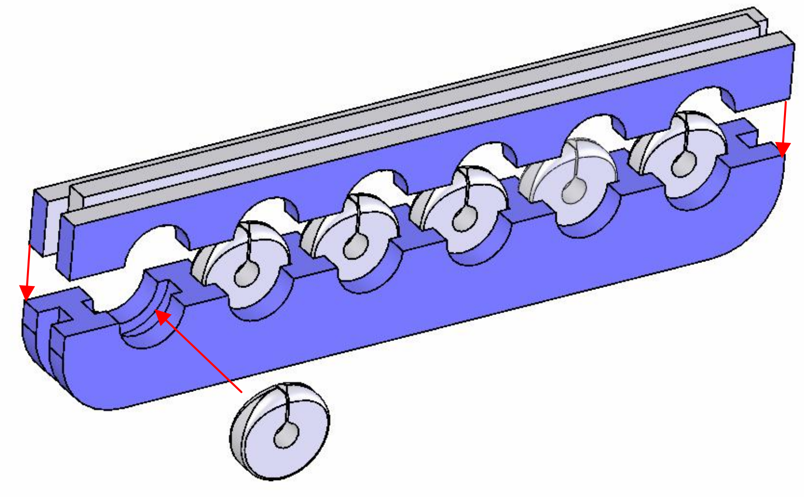

Figure 3.33: The tube transit, consisting of 2 parts and six (or more) flexible high friction materials.

The tube transit consists of two parts (figure 3.33), which can be put together in a space kept open in the machine. Between the two parts is room for (in this case) six flexible high friction cylinders. In the center of the cylinder is a hole, to hold the rubber gas tube.
The gas tube is first mounted to the cylinder. Then the cylinder, holding the tube is inserted in a space in the lower part. The top is mounted on the lower part.

The parts are already mounted in the machine (figure 3.34) as seen in this close up.

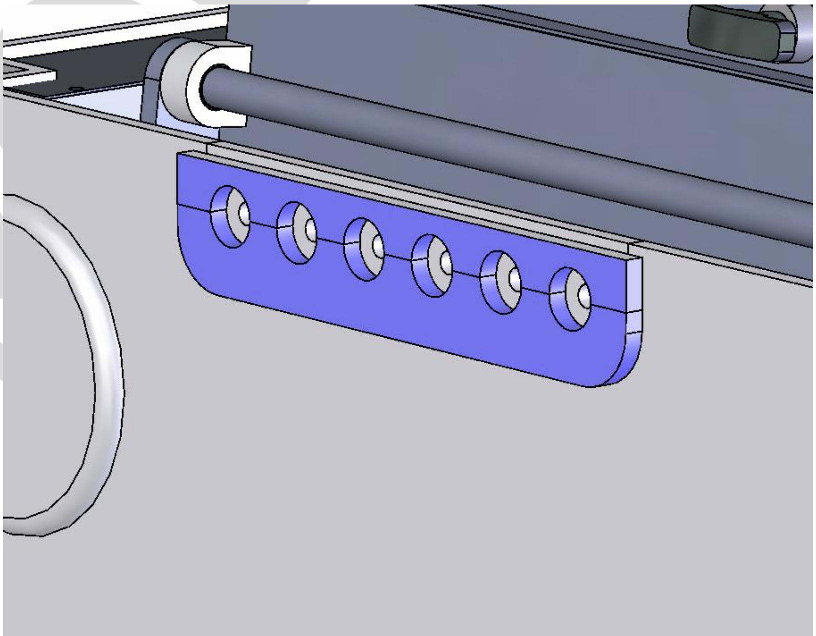

Figure 3.34: the tube transit mounted on the machine.

3.7.2 Construction of the cover hinges

The hood of the machine can be placed on the machine in two different ways, so it can open clockwise and counterclockwise. This decision was made, because of the wish to put two machines together. When two machines are put together (or placed near each other), the covers can be opened in two ways for better functionality. With little effort, the position of the cover can be changed, with the use of pins with hinges, which can be placed on the left or the right side of the cover (Figure 3.35).

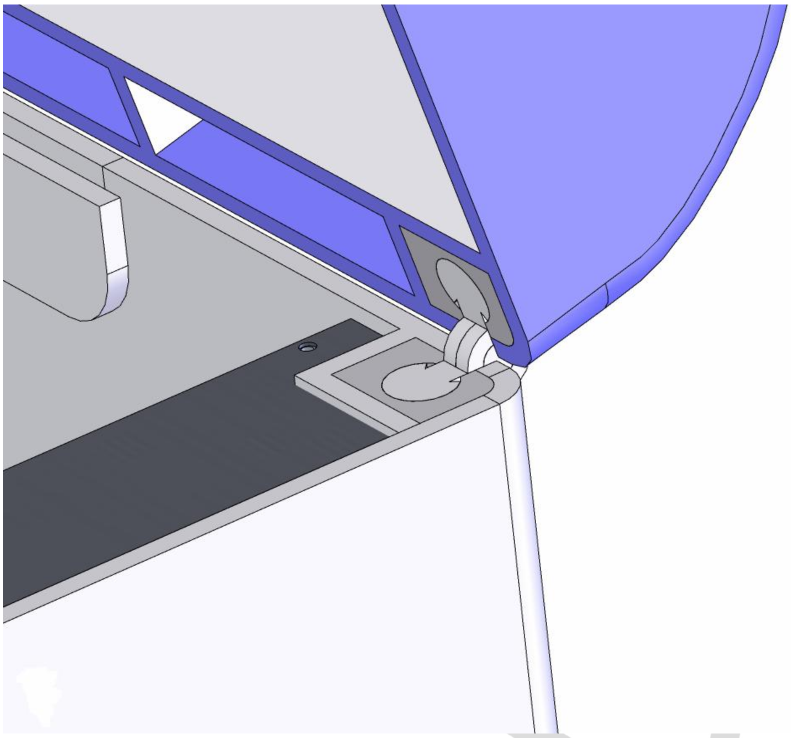

Figure 3.35: construction of the cover hinges.

The idea behind the concept of the hinges, is that it can be made from as few parts as possible, to lower production costs. By making the parts symmetrical (except for the ring in which part two is inserted), it can be used on the left and on the right side of the machine.

Figure 3.36 shows the construction of the hinges with its parts in an exploded view.

Part 1 is permanently mounted on the cover, part 2 is a hinge pin on which part 1 and part 3 can move freely. Part 4 holds the hinge assembly.

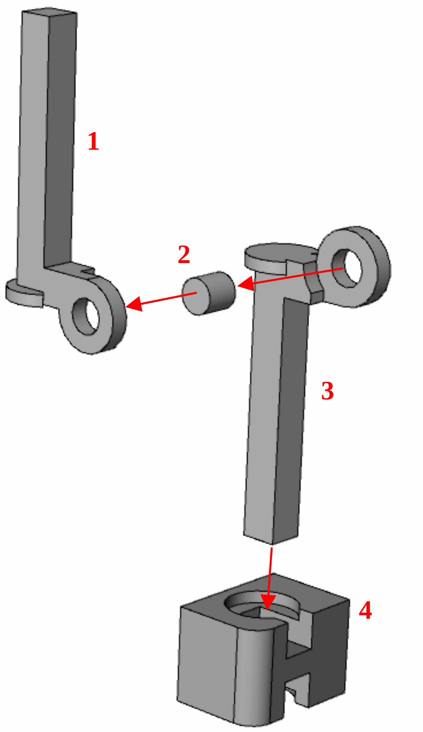

Figure 3.36: exploded view of the hanging

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3.7.3 Controller

To increase scale up possibilities (two or more CELL-tainers™), an external controller is designed (some images of it were printed earlier). In future developments of the fermentor, several machines with limited capacity should have link abilities. In the design process for the fermentor itself, this is translated in a variable cover. Because it is possible to have two or more fermentors connected to a controller, it would be inefficient to add a controller to every single fermentor. Therefore the choice was made to develop a stand-alone controller. In the section *Market research bioreactors and related*, several controllers are mentioned (Applikon, BioSpectra). Although these should work fine with the fermentor from CELLution, they preferred a controller of their own, fitting with the design of the cultivator(s).

Figure 3.37: controller from CELLution

Figure 3.37 shows the controller currently used by CELLution in combination with the CELL-tainer™ prototype. The controller holds the PLC, which communicates with an external personal computer. Notice that the emergency button is located on the controller. In this case, its placement is well chosen, but for future design, the emergency button must be mounted on the CELL-tainer™.

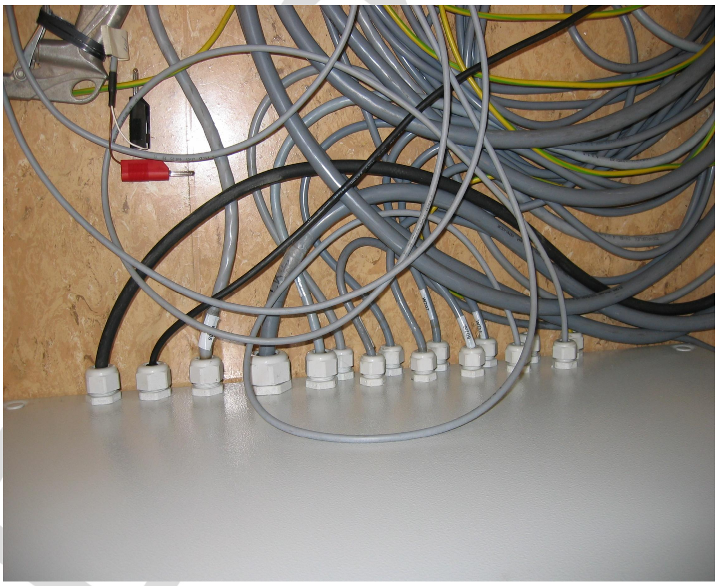

Figure 3.38: Connection wires to the controller

Figure 3.38 shows the different connections from the controller. Connections are for valves, sensors and to control the motor. In future designs, perhaps one or two connectors, in which all the connections are integrated, can be used to enhance connectability.

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When an external controller is used with the CELL-tainer™, it is desirable that the controller fits with the style of the cultivator. To make this happen, several characteristics were taken over from the design of the cultivator.
The CELL-tainer™ design has a curved cover. This is repeated in the front of the controller. A part of the logo from CELLution is used on the left and the right, just like in the CELL-tainer™ design.

The controller has a screen on top with a keyboard to read and interpret data or to feed data into the process. But when the controller is not in use by an operator, it can be closed to prevent it from getting dirty (figure 3.40).

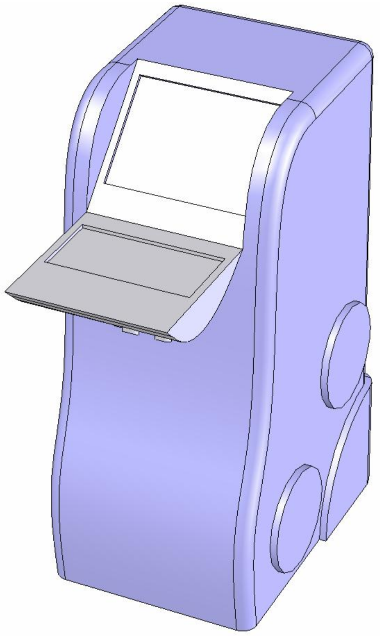

Figure 3.39: Controller

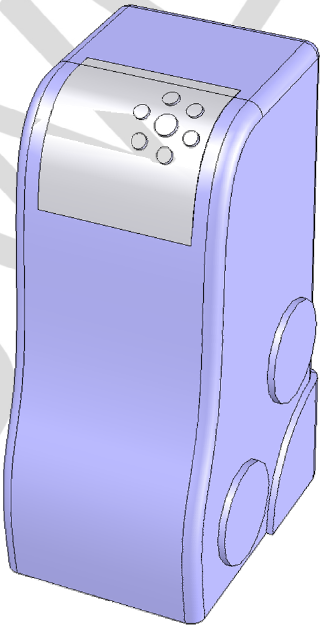

Figure 3.40: Controller

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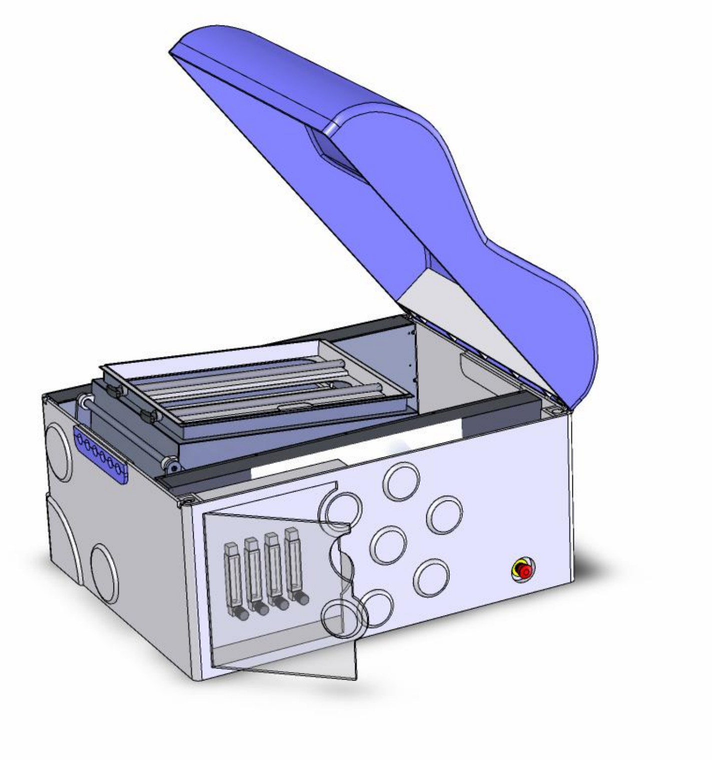
3.8 Final concept

In this section, the final concept will be discussed in detail.



The final concept distinguishes itself from the early developed concepts with its transparent door. On the right of the door, it follows the rounding of the spare circle. The circle in the lower left corner of the logo is placed on the door, so when closed, it forms a part of the logo of CELLution. Behind the transparent door is place for the flowmeters. To make room for this space, the width of the housing has been increased by 10 centimeters.
The tube transit is still in the same place (on the left or the right of the machine) and nothing has changed in the design of the cover. The cover can still be placed on the left or the right side of the machine, whatever may suit the operator.

Figure 3.41: The final concept

These impressions were made with Solid Works, which does not have the capability of advanced shading techniques while rendering. On page 38, some images of the machine made in Maya, a program used to create photo-realistic images, are displayed.

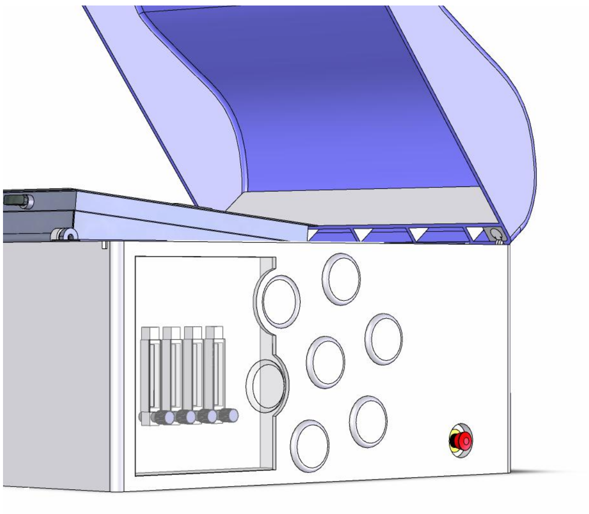


Figure 3.42: a close-up of the transparent door and emergency button

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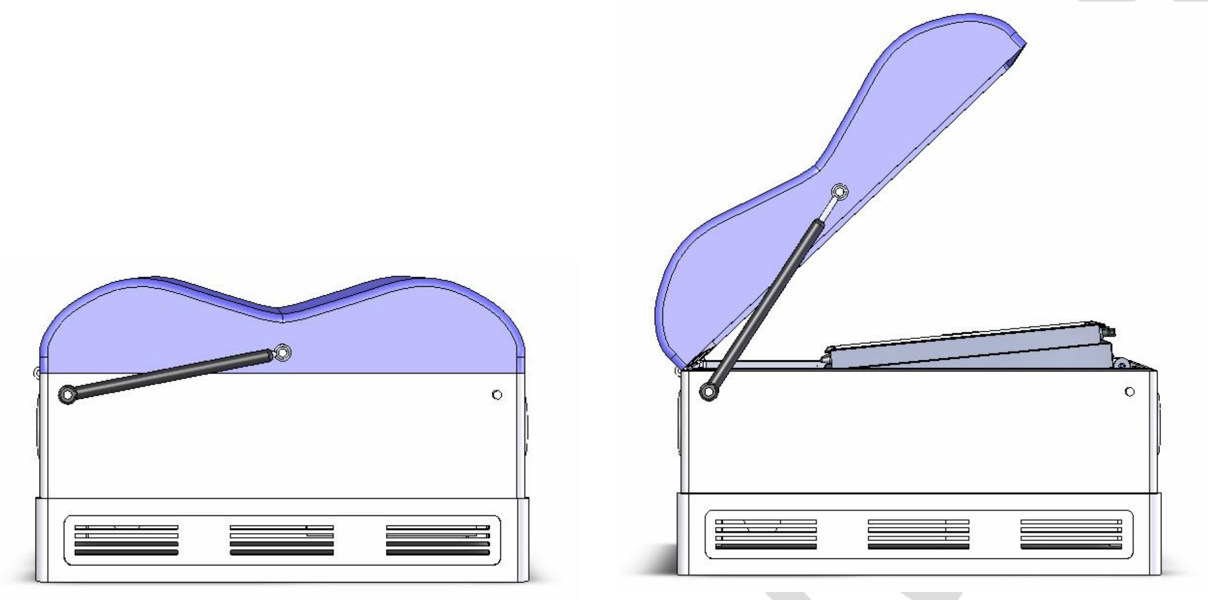

Figure 3.43: an impression of the cover with its pneumatic spring

On the back, a removable pneumatic spring has been added to facilitate the opening of the cover. Because the cover can open in two ways, the pneumatic spring can be placed both left or right of the machine. When the operator is working with the machine, it is desirable that the hood stays in his opened position.

Figure 3.44 shows the concept in closed and open state with its dimensions.

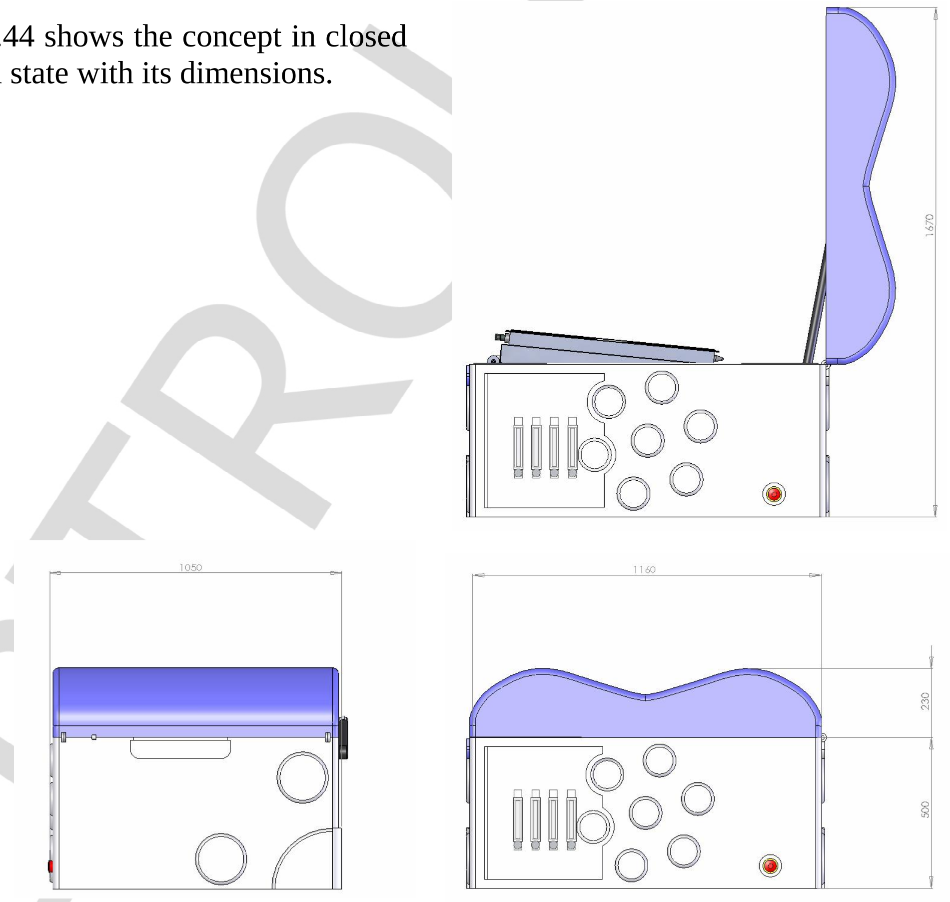

Figure 3.44: the concept and its most relevant measures

More or less, the machine exists out of 5 parts:

- 4 faces (front, back, left, right)
- cover.

The cover and the faces are connected with each other with the hangings (page 32).
At this time, it can not be said in which manner the 4 faces will be connected to each other. That depends on the way how the inside of the machine will look like.

The front face will contain a transparent door, through which the flow meters can be read. This door has a minimum size of 40 x 44 centimeters. This would leave enough space to place 4 flow meters and valves.

The pneumatic spring must have a minimum length of 40 centimeters, but may not exceed 50 centimeters, to prevent it from hampering with the cover.

More technical details of the housing are given in Appendix A.1.

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Figure 3.45 and 3.46 shows the final concept as it is now.

Figure 3.45: the concept in its final stage.

Figure 3.46: Another presentation of the final concept

CELLution BIOTECH

3.9 Choice of material

Outside of the machine
The commonly used Acrylonitrile-butadiene Styrene (ABS)[9] has very good specifications for use as a material for the outside parts. Although it is very hard, its scratch resistance is poor[10]. New Polypropylene/Polystyrene (PP/PS) composites, intended for use in the automobile industries, delivers the same performances as ABS but with high scratch resistance. The scratch resistance is a must to decrease cleaning times. Once a scratch is formed, dirt will nestle in the scratch, which makes it hard to clean[11, 12].
Of these new PP/PS blends, all types can be compounded ready for injection moulding[13]. If desired, PP/PS blends can be heat and UV stabilized and already pigmented in the desired colours.
The costs of a PP/PS blend is less than € 1,60 per kilogram.
On the inside of the machine (parts etc), the same material can be used. A composite of PP/PS is also preferred in the inside of the machine, because it has to be kept clean as well as the outside.

An other good alternative would be stainless steel. Stainless steel has a very high scratch resistance and is also very easy to clean.

The design has one part, which can not be made from PP/PS: the transparent door in front of the flowmeters. PP/PS can not be delived transparent and therefore polymethylmethacrylate (PMMA) is the best choice to make the door from. PMMA has also good UV resistance and is used, for example, in safety glass. It can also easy be moulded, just like PP/PS. A slight disadvantage are the costs of the material: somewhere between € 1,60 euro and € 4,00 per kilogram.

At this time it is not clear what material to use, because it depends on how many units of the CELL-tainer™ will be produced in the future. When these numbers are known, a suitable mould can be designed, fitting the needs of CELLution. In larger batches, plastics are preferred to lower production prices.

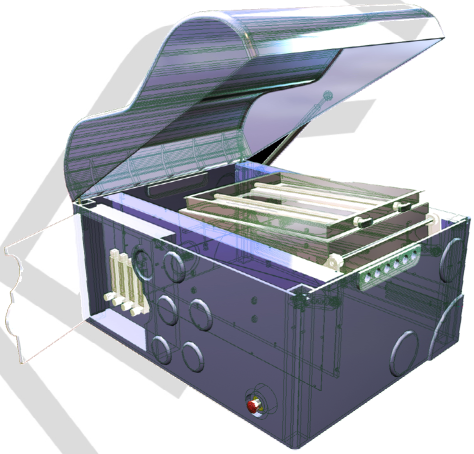
Inside of the machine
Some parts need to be made from stainless steel, considering the forces they are exposed to. Especially the hinge of the cover has to be very stiff to withstand the moment exerted on the hinges. Also the shaft in which the hinge of the cover is inserted needs to be from stainless steel in order to support the forces which are exerted on the shaft.

When using plastics for the housing, any specific color can be added to the housing. When using stainless steel instead, coloring could bring problems.

VERTROUWELIJK

List of requirements review . 4

Assignment 'shaker'



VERTROUWELIJK

4.1 Implementation of requirements

In the section *List of Requirements* on page 14, the requirements to which the final concept must apply, are stated. Every separate demand will be discussed referring to the concept, presented in the section *Choice of final concept*, page 35.

Requirements related to guidelines and legislation:

- *the CELL-tainer^{TM} must apply to the GMP guidelines.*

Although the GMP guidelines were looked at, due to lack of time it was not step by step looked over considering the design of the machine.

- *the CELL-tainer^{TM} must apply to the CE hall-mark class 1 and therefore apply to the machinery directive*

When comparing the results of the project with the European Machine Directive, most demands are fulfilled. But several demands stated in the directive concerning the writing of a userguide, are not conform the directive[14, 15]. This was also not part of this assignment.

Requirements related to working principles

- *current working principles may not be altered or hampered by the new design.*

The working principles of the prototype were not altered, modified or hampered in anyway whatsoever. In fact, the prototype was used as a basis round which the final design was developed.

- *temperature of the medium must be controllable during cultivation at all times.*

The temperature can be controlled during the cultivating process at anytime, using a heated blanket, controlled by the PLC.

Requirements related to the CELL-tainer^{TM} :

- *the CELL-tainer^{TM} may not weigh more then 30 kilograms, medium not included.*

Although an actual prototype of the final design was not made, it is estimated that the final design will exceed its maximum weight of 30 kilograms, looking at the shapes of the machine en the estimated materials that will be used (*choice of material*, page 38). But after consulting CELLution, this was not a major problem.

- *maximum cleaning time of the CELL-tainer^{TM} may not exceed 5 minutes.*

In this case also, an actual test to prove its maximum cleaning time could not be done due to absence of a prototype, but according to design, and looking at machines of approximately the same size, the maximum cleaning time should not exceed 5 minutes.

- *the CELL-tainer^{TM} must contain a disposable measuring 720 x 560 x 160 millimetres.*

As mentioned before, the final design was developed from the prototype. The prototype could contain a disposable of given size, therefore the final design can do this too.

- *sampling time may not exceed 10 minutes.*

Sampling time never took more than 3 minutes during the usage research on the prototype. It is expected that in the final design the sampling time will not exceed this 3 minutes, and therefore apply meets demand.

- *the CELL-tainer^{TM} must be at standing height for the user.*

With the development of an under-carriage, the machine can be made at any specific height and therefore applying to the demand.

- *the CELL-tainer^{TM} must have connecting capabilities with a controller and a flow regulator.*

Connections for flowregulators, the controller and power are present.

VERTROUWELIJK

Requirements related to the disposable:

- *Inserting and removing the disposable may not cause any damage to the disposable*
- *During the cultivation process, the disposable must be fixed at all times.*

The disposable will and can not be damaged during inserting, because no sharp tips or other damaging units are near the disposable inserting place.

- *Inserting time of the disposable may not exceed 5 minutes adding medium not included.*

This demand could not be proven during the assignment, because of the absence of a prototype, but the expectation is that inserting a disposable will not exceed the maximum of 5 minutes.

4.1.1 Ergonomics

Several diemsions are given on page 20, related to a population of men and women, describing arm lengths, reaching depths etc. In case of the CELL-tainer^{TM}, these measures are applicable.

The height of the machine is about 50 centimeters, given or taken, dependable on the current position of the shaking platform. When standing on a lab table, the working height would be over 130 centimeters (80 centimeters for the table and 50+ for the machine). This is too high (118 for P_{50}), according to the dimensions on Appendix A.2. But the machine is not an 8 hour workplace for an operator, therefore it is questionable if this would be a problem.

All the other dimensions are within the given distances. Only the reaching depth does not cover the total distance for P_{50} (726 millimeters), but the machine has a maximum depth of 105 centimeters, therefore the connections on the disposable are more or less of half that distance (Figure 4.1). Even P_5 with 650 millimeters can reach the connection points.

It is thinkable though, that a short operator (<P_5 of height), with a small reaching distance (<P_5) could not work with the machine properly. But it is questionable if the machine needs to be adapted for such situations.

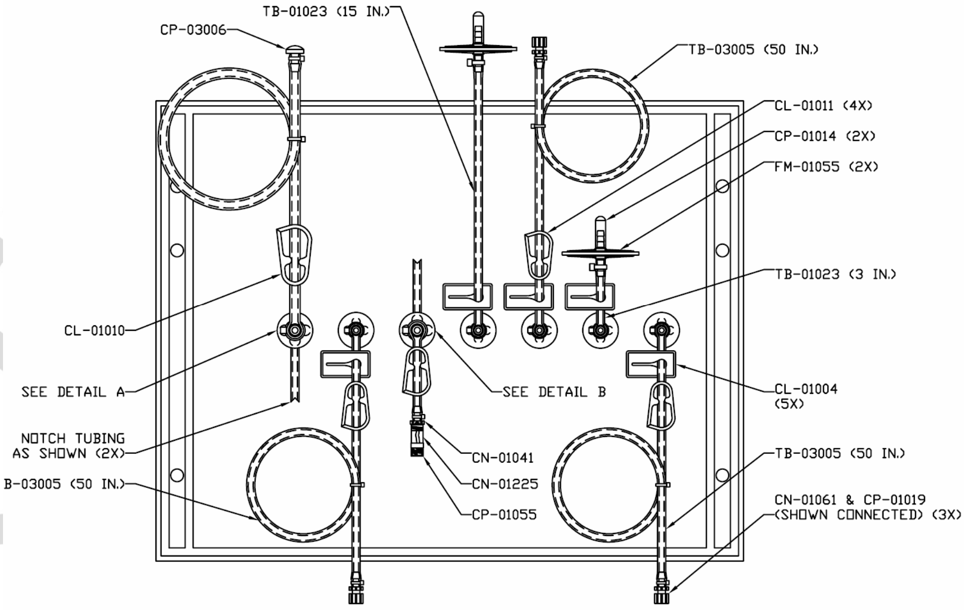
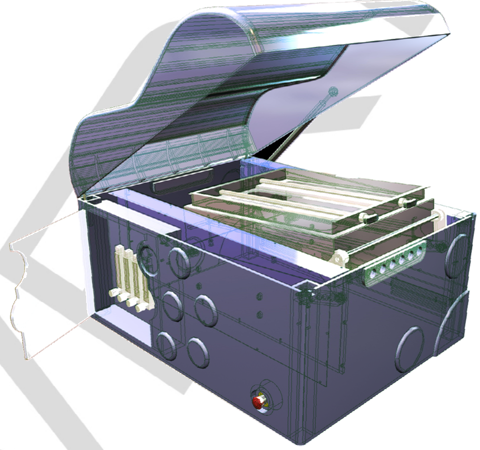


Figure 4.1: a disposable and its connection points locations

Conclusion . 5

Assignment ‘shaker’



VERTROUWELIJK

5.1 Conclusion

The aim of the assignment was to design a housing for the existing prototype. And also to find suitable forms, fitting the machine and in which market segment it will be placed, considering the functions of the machine.

The final concept fulfills the wishes and the demands of the assigner, CELLution Biotech. Most requirements will be met, except for the ones that could not be proven during the assignment (*implementation of requirements*, page 41) Furthermore, the model fits within the new looks of the modern cultivators, is easy to assemble and does not require extreme valuable parts.
Several points, like production and materials, are mentioned, but were not part of the task. But during the design process it is (almost) necessary to keep these in mind.

The central questions were all brought up in this rapport. It was more or less the guideline for the planning made, and according to the planning the research was done and the design evolved.

In the next chapter, *recommendations*, several points are mentioned, which need to be adressed in further research.

VERTROUWELIJK

5.2 Recommendations

First of all, it is important to build a prototype to easily discover any defects, following from the design presented in this rapport. Doing a users research is also easier with a prototype.

To meet the requirements from the American GMP and European CE guidelines, these need to be examined more detailed to apply them to the current design.

In further research on the machine it is important to do a market research on how many machines need to be produced in future manufacturing processes. Results from such a research, can give information on what the most suitable materials will be for production and the related costs.

The final concept can be placed on a lab table, but it is not unthinkable to create a undercarriage for the machine. This is in any case insuperable for the concept presented on page 46.

Furthermore, the controller needs a suitable interface for a user to work with. This would be a user interface for working with the PLC.

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5.3 Supplement

In the last 2 weeks during the assignment, some major changes were made and other requirements were set-up for the CELL-tainer^{TM} by Cellution Biotech
As the assignment started, the main idea was a machine for cultivating cells with a maximum capacity of 20 liters total volume, with 10 liters of medium. The dimensions of the disposable are 720 x 560 millimeters. To increase production capacity, several machines could be linked to a single controller.
At this point, this idea has been rejected and a single machine of 50 liters total volume will be developed instead. This machine can also contain 2 x 20 liter disposables. The plateau which will support these bigger disposables, measures 1000 x 750 millimeters. The rocking movement remains the same. Because the machine has an increased total volume, the controller will be integrated in the machine. So every single machine has its own controller.

Although the assignment was to design a cultivating unit, with scale up possibilities and a controller, CELLution has asked if it was possible to make some presentations of a 50 liter cultivator. The results are shown in figures 5.1 to 5.3.

Notice that this final design, derived from the final concept from section 3.6, has many familiarities with Figure 3.27 on page 28.

Figure 5.1: impression of the 50 liter cultivator

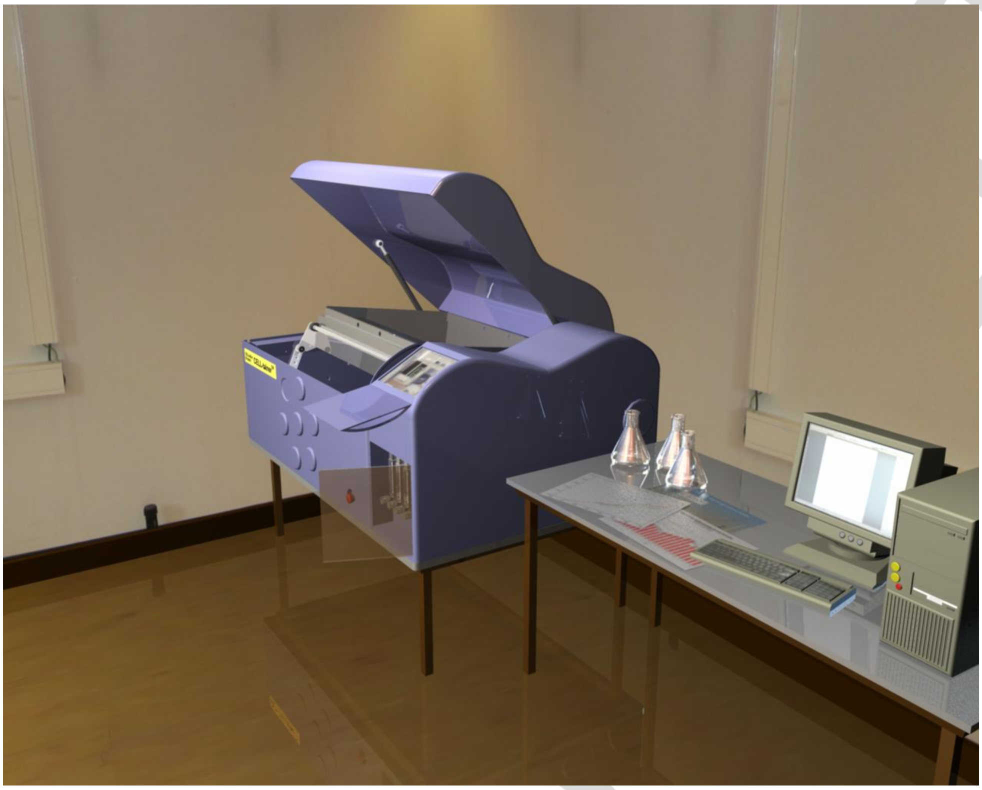

Figure 5.2: close-up of the 50 liter cultivator

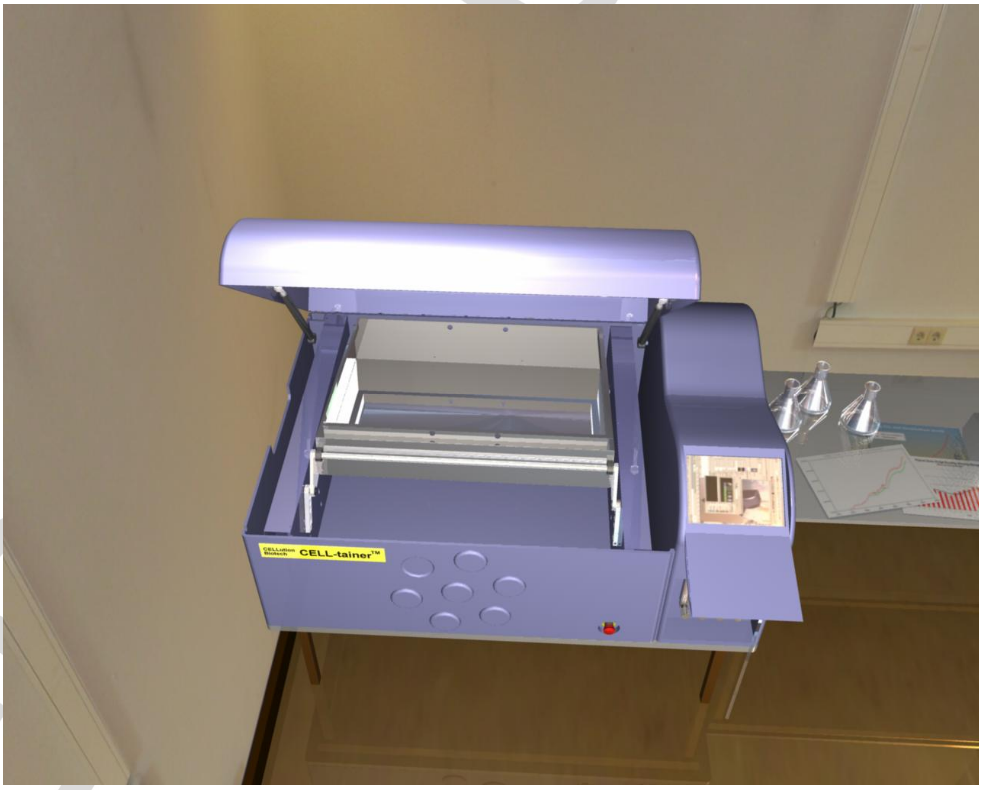

Figure 5.4: close-up of the 50 liter cultivator

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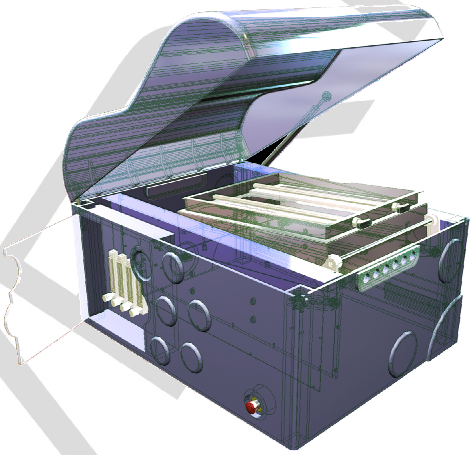
Appendices

Assignment ‘shaker’



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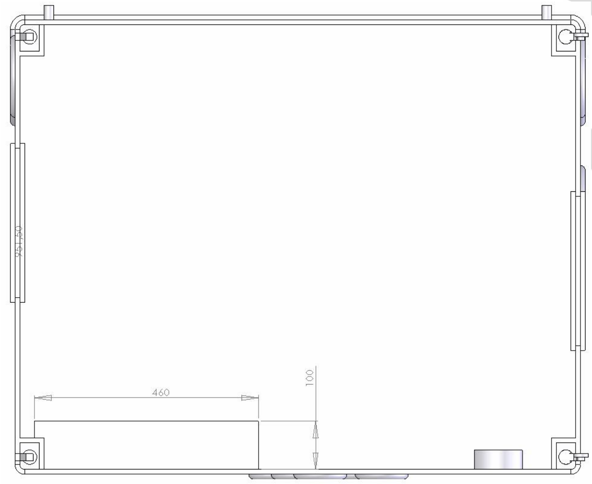
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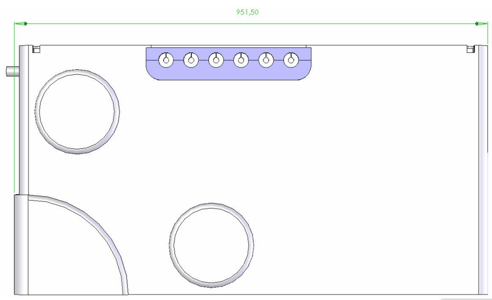
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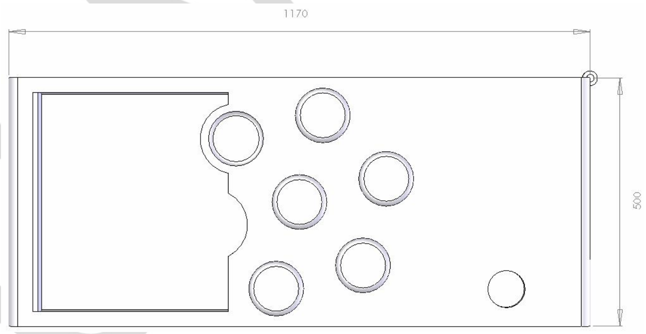
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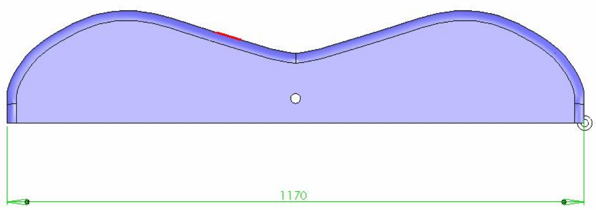
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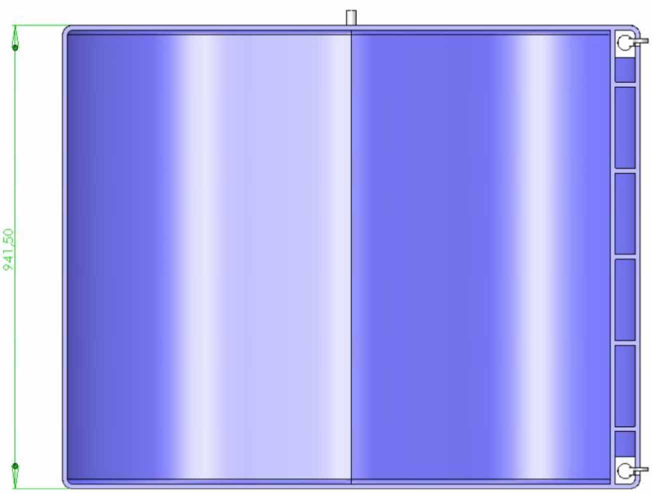
941,50

To determine applicable working heights, table A1 shows some heights, derived from a population of males and females wearing foot-wear[16].

Percentile	Males (mm) P_5, P_{50}, P_{95}	Females (mm) P_5, P_{50}, P_{95}	Mixed (mm) P_{50}, P_5, P_{95}
Working height	1130, 1230, 1320	1040, 1130, 1230	1180, 1080, 1280

Table A1: basic working heights for standing duties (*Handboek Ergonomie 2002*)[14]

Tabel A2 shows some dimensions, also applicable to the design, derived from a population of males and females, without clothing[17].

	Males (mm)	Females (mm)	Mixed (mm) P_{50}, P_5, P_{95}
Standing measures			
Body length	1794	1651	1723, 1565, 1881
Reaching depth	747	704	726, 650, 820
Breast depth	286	291	289, 236, 342
Reaching height arms	2123	1907	2015, 1789, 2241
Eye height	1669	1532	1601, 1449, 1753
Shoulder height	1496	1366	1431, 1286, 1576
Elbow height	1134	1051	1093, 991, 1195
Fist height	794	753	774, 705, 843
Hips width	356	365	361, 321, 401
Shoulder width	412	362	387, 336, 438
Hand measures			
Fingertips width	19	15	17, 14, 20

Table A2: basic dimensions for applicable widths and heights (*Productergonomie*)[15]

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