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Development of an Economic Benefit and Risk Analysis Automated Tool for Stem Cell Production Laboratory Automation Projects

Florianópolis
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Final report of the subject DAS5511 (Course Final Project) as a Concluding Dissertation of the Undergraduate Course in Control and Automation Engineering of the Federal University of Santa Catarina.
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This work is dedicated to my classmates, my professors
and my dear mother

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ABSTRACT

This thesis presents the development of an economic benefit and risk analysis automated tool for stem cells production laboratory automation projects. This work intents to fill a gap observed in the Automation and Bioscience department of the Fraunhofer IPT regarding a lack of economic and risk analysis methodology to be implemented in the laboratory automation projects, as well as the lack of models in the literature for this kind of project. The tool was implemented in Excel and it aims to, through capital budgeting methods, financial statements, and simulation, provide an economic-probabilistic analysis of returns expected from the project and lay out a cost-benefit comparison between the manual and the automated production scenario. The application of the tool was validated through the analysis of an automation project of an Engineered Human Myocardium production laboratory and in a qualitative perspective by interviewing the end-users of the tool inside IPT. As a result, the tool proved to be truly beneficial to IPT researchers, creating a standard economic benefit and risk analysis for laboratory automation projects.

Keywords: Economic Benefit Study. Economical Risk Analysis. Laboratory Automation.

RESUMO

Esta tese apresenta o desenvolvimento de uma ferramenta automatizada de análise de risco e benefício econômico para projetos de automação de laboratórios de produção de células-tronco. Este trabalho pretende preencher uma lacuna observada no departamento de Automação e Biociências do Fraunhofer IPT em relação à falta de metodologia econômica e de análise de risco a ser implementada nos projetos de automação laboratorial, bem como a falta de modelos na literatura para este tipo de projeto. A ferramenta foi implementada em Excel e visa, através de métodos de orçamento de capital, demonstrações financeiras e simulação, fornecer uma análise econômico-probabilística dos retornos esperados do projeto e estabelecer uma comparação custo-benefício entre o cenário de produção manual e o cenário de produção automatizada. A aplicação da ferramenta foi validada através da análise de um projeto de automação de um laboratório de produção de Miocárdio Humano de Engenharia e em uma perspectiva qualitativa, entrevistando os usuários finais da ferramenta dentro do IPT. Como resultado, a ferramenta provou ser verdadeiramente benéfica para pesquisadores do IPT, criando um benefício econômico padrão e uma análise de risco para projetos de automação laboratorial.

Palavras-chave: Estudo de Benefício Econômico. Análise de Risco Econômico. Automatização de Laboratório.

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LIST OF ABBREVIATIONS AND ACRONYMS

ES	Embryonic Stem
iPSC	Induced Pluripotent Stem Cells
EHM	Engineered Human Myocardium
GMP	Good Manufacturing Practice
NPV	Net Present Value
ROI	Return On Investment
IRR	Internal Rate of Return
PDF	Probability Density Function
CAPEX	Capital Expenditures
OPEX	Operating Expenses
UML	Unified Modeling Language
VBA	Visual Basic for Applications
EUAV	Equivalent Uniform Annual Value
OEE	Overall Equipment Effectiveness

CONTENTS

1 INTRODUCTION

This work describes the development of a tool to automate the study of the economic benefit and risk analysis of laboratory automation projects. The tool was validated using the data from a stem cell laboratory automation project at the Fraunhofer Institute for Production Technology IPT to present a stem cell production partner company with a possible automated production scenario that is economically feasible. Furthermore, this work is intended to shed light on stem cell production from a monetary point of view to make a statement about the economic efficiency of a possible fully automated production plant.

1.1 MOTIVATION AND JUSTIFICATION

Embryonic stem (ES) cells can grow indefinitely while maintaining pluripotency and the ability to differentiate into cells of all the three germ layers, ectoderm, mesoderm, and endoderm, during the gastrulation phase in embryonic development (EVANS; KAUFMAN, 1981). Human ES cells might be used to treat diseases such as Parkinson's disease, spinal cord injury, and diabetes (THOMSON, J. A. et al., 1998). However, there are ethical strains regarding the use of human embryos, as well as the problem of tissue rejection following transplantation. One way to avoid these issues is the generation of pluripotent cells directly from the patients' cells (TAKAHASHI; YAMANAKA, 2006).

In 2006, a major technological breakthrough in science and medicine was made with the report that cells with a gene expression profile and developmental potential similar to ES cells could be generated from mouse somatic cells (such as fibroblasts) by using a cocktail of four transcription factors, introduced as induced pluripotent stem cells (iPSC) (TAKAHASHI; YAMANAKA, 2006). This discovery opens up the unique perspective of manufacturing cell products to test and validate novel drugs and regenerative medicine in tissue, incurable neurodegenerative or cardiac diseases directly in human cells. As known from ES cells, iPSC can be multiplied almost without restriction and differentiate into cell types for all organs of the body (YU, J. et al., 2007).

In particular, it is important to be able to test active substances directly on iPSC-derived body cells of patients (SHI, Yanhong et al., 2017). For diseases of the nervous system and the heart, this approach holds a special fascination since, for non-regenerative tissues, no patient or disease-specific cell sources for drug development have been available so far (HARRIS et al., 2013), (EBERT et al., 2009), (DEVINE et al., 2011).

These exciting new biomedical perspectives demand technologies to generate iPSC and their differentiated progeny, such as neuronal and cardiac cells, in large quantities in a standardised and industrial format (MARX et al., 2013). The basis for research and clinical use of iPSC is a substantial number of cells (approximately seven million

cells per treatment), which must be produced with safety concerns, cost-efficient, and also with a standardised methodology of the production to reduce variability between cell lines (DANISZEWSKI et al., 2018).

Those requirements are not met with manual production. The automation of production, which has already been established in many other industrial fields for years, offers the decisive advantage of reliable reproducibility in addition to cost reduction and increased throughput. In addition, the current coronavirus pandemic has once again shown that automation in the field of bioprocesses is urgently needed to achieve reproducible results and high throughput (NIESSING et al., 2021).

As said, the huge volume of production in a low-cost manner that is required is not met in the actual manual production. With the focus shifting from a production scale for research to a sales scale, iPSC manufacturing can benefit from automation by combining robustness and process adaptivity (KULIK et al., 2016). Through fully automated production, a high and, above all, consistent quality of the manufactured cells can be achieved. The reproducibility of the cell lines produced on the system ensures that the results of subsequent research and applications are comparable, as they are based on the same starting product. The parallelisation of all processes enables the reproducibility of the iPSC cell lines. Such parallelisation is not possible with conventional manual cell culture methods, which gives automated production another qualitative advantage over manual production.

The production quality department of the Fraunhofer IPT has as one of its goals to help companies enter the age of Industry 4.0 through digitalisation and automation projects. One such project, the StemCellFactory (IPT, 2022), created together with partners from research and industry, had the goal of designing and building a production facility that automates, standardizes, and parallelises all necessary iPSC culture steps with comprehensive quality management.

At first, the project had as its goal the development and establishment of an automated process for reprogramming somatic cells, the design and construction of an integrated automated production prototype, and the development of processes for the generation of iPSC and iPSC-based products for the pharmaceutical drug development on an industrial scale and with industrial standards, including all necessary quality controls. Meanwhile, new techniques and technologies were developed in the field of iPSC production, so the project was extended for two more phases, StemCellFactory II and StemCellFactory III, where novelties in the field continue to be implemented until today.

The StemCellFactory projects opened up a new possibility of a portfolio on automation of iPSC laboratories projects for the IPT quality department. The prospecting of these projects started less than a year ago, and there are already two companies that have contracted the consulting service to automate their iPSC laboratories, and

there are a growing number of companies in the pipeline.

However, there was still a lack of methodology to carry out the automation projects in the partner companies' laboratories. The projects include the phases of requirements gathering, definition of automation plans, and cost-benefit studies to give companies an overview of their possibilities. As the institute works mostly in partnership with small and medium-sized, which have limited risk capital to use, the economic benefit study and risk analysis are of great importance.

As the goal of the department is to expand this portfolio of projects, an automated tool that implements a model of economic benefit and risk analysis of those projects will be an essential part to help maintain a standard on the projects and reduce work time.

In brief, the motivation of this work combines the great iPSC market perspective that, together with the StemCellFactory project, created the possibility of a portfolio expansion on laboratory automation with industry for IPT and the lack of economic benefit and risk analysis models to prove to the companies that the automation of the laboratories is worth it.

1.2 OBJECTIVES

The main goal of this work is to create an economic benefit and risk analysis model for laboratory automation projects and to implement this model as a highly accessible automated tool. Such a tool must return the comparison of economic benefit for automated and manual scenarios of iPSC production environments based on production and economic input parameters. Hence, three sub-goals are:

- Creation of a standard economic benefit and risk analysis for laboratory automation projects within IPT;
- Reduce IPT researchers' workload;
- Standardise the data acquisition from the companies, and presentation of the analysis results.

Additionally, this work provides the industry project partners with a functional statement on the absolute and actual economic efficiency of the automation of their laboratory. On the one hand, the aim is to find out whether the operation of the plant is profitable in principle and, on the other hand, to create a monetary comparison between manual a fully automated production, and analyze the economic benefits and risks.

1.3 METHODOLOGIES

This work was developed in seven steps, as presented in Figure 1.

The first step involves the study of the theoretical foundation, both in stem cell laboratories and on methodologies of economic benefit study and risk analysis in the area of project profitability.

In the second step, workshops with the partner company were held to collect information about the current production process, requirements for the automation of the laboratory and requirements for the economic study of the project.

In the third step, a model for the economic benefit study and risk analysis for the automation of laboratories was developed based on the requirements presented by the company and collected from the production quality department of IPT.

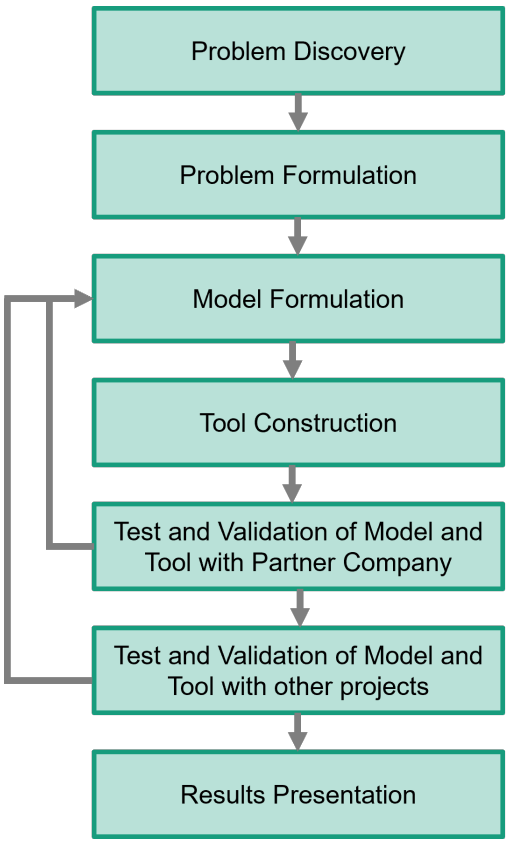
For the fourth step, the automated tool that applies the developed model was built using Excel software as its basis.

Then, in the fifth step, the tool was validated with information from the automation project of the IPT's partner stem cell production laboratory.

For the sixth step, the tool was validated with other projects of automation of laboratories of the production quality department of IPT.

Finally, in the seventh step, the results are presented.

Figure 1 – Methodology of the work developed



Source: Personal Archive (2022).

1.4 DOCUMENT STRUCTURE

This monograph is organised as follows:

- **Chapter 2 - Thesis Context** presents the research institute where the thesis was done, the partner company where the work was validated, its processes and requirements;
- **Chapter 3 - Theoretical Foundation** presents the required technical concepts to better comprehend the covered topics;
- **Chapter 4 - Economic Benefit and Risk Analysis Automated Tool** describes the work performed to obtain the economic benefit and risk analysis model for laboratory automation projects and the implementation as an automated tool;
- **Chapter 5 - Tool Validation** describes the validation of the tool using the economic and risk analysis of the automation of the partner's laboratory and experts interview;
- **Chapter 6 - Conclusion** presents the concluding remarks and future perspectives.

2 THESIS CONTEXT

2.1 FRAUNHOFER INSTITUTE FOR PRODUCTION TECHNOLOGY IPT

The Fraunhofer Institute for Production Technology IPT (Figure 2) develops system solutions for the networked, adaptive production of sustainable and resource-efficient products and the associated services. The main focus is on process technology, production machines, production quality, and metrology, technology management and ranges from the fundamentals to the digital transformation of production. The institute develops and optimises new and existing methods, technologies, and processes for the production of the future developing both highly specialised individual technologies and complete system solutions for sustainable production on behalf of our customers.

The work presented in this thesis was developed in the 312 - Production Quality Department in partnership with an industry partner that has the mission of developing, manufacturing, and commercialisation of iPSC-based tissues for organ repair.

Figure 2 – Fraunhofer Institute for Production Technology IPT logo

Source: IPT

2.2 PARTNER COMPANY

The company[1] with whom this project was developed has the mission of developing, manufacturing, and commercialisation of iPSC-based tissues for organ repair, where the lead commercial product is contractile heart tissue patches - Engineered Human Myocardium (EHM) - for the treatment of patients with advanced heart failure. Through a public/private partnership, it was possible to take the lead in therapeutic products from the research stage through pre-clinical characterisation into clinical development and to establish a solid basis for commercial product development, including:

- Strong analysis for safety, feasibility, and function from pre-clinical models;
- Good Manufacturing Practice (GMP) manufacturing authorisation for EHM investigations of medicinal products;
- Authorisation for the first clinical trial worldwide aiming at sustainable remuscularisation of the failing heart;

[1] The project is under a Non-disclosure agreement, and the company name can't be explicitly announced. Consequently, the code name "company" will be used throughout the document.

- A fully characterised EHM line with the freedom to operate for commercial use;
- Process scale-up for commercial product supply

With the company's lead product entering clinical development and the achievement of important milestones for commercialisation, it has successfully arrived at a value inflection point that warrants further investments to take EHM through clinical development scale and expand it into the market.

2.2.1 Current Processes

Currently, the company has a fully manual production, although currently, it is only producing to adjust its processes to fulfill the GMP requirements and ensure product safety and efficiency through clinical studies and trials. The main processes for EHM production are presented in (Appendix A). The processes are:

P0 - Prepare & Cast
P1.1 - Seeding stroma cells
P1.2 - Seeding Cardiomyocytes cells
P1.3 - Cast Patch
P2 - Medium Change
P3 - Harvest

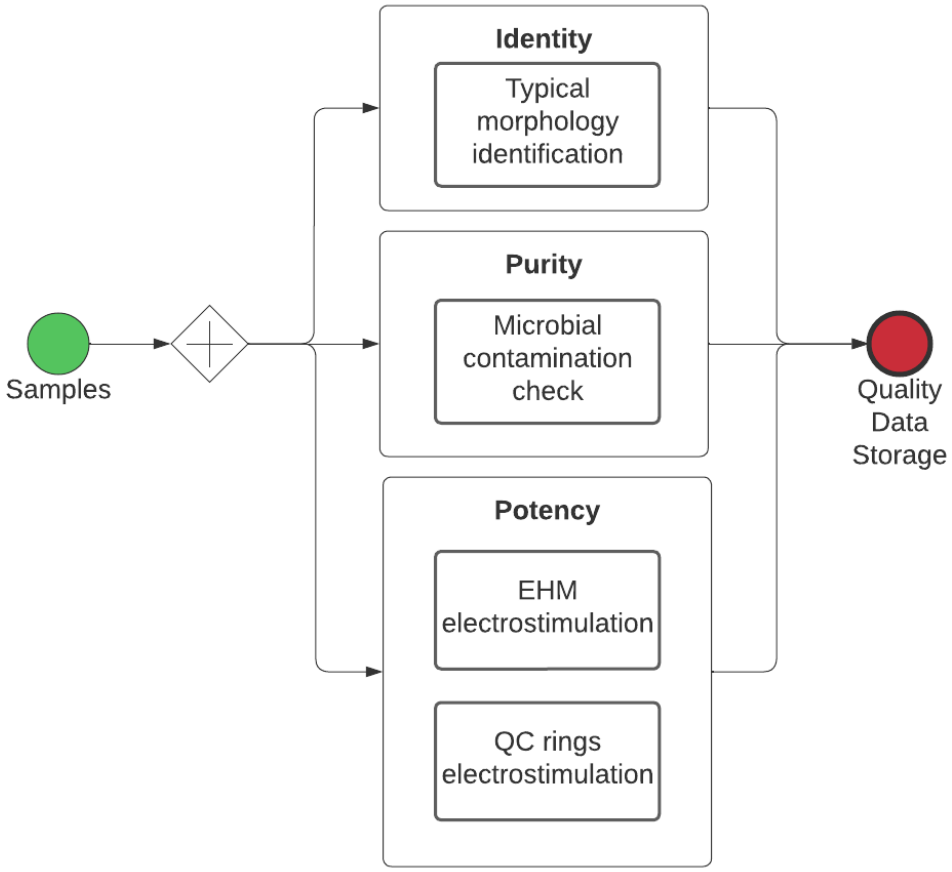
2.2.2 Quality control process

The most important process regarding medical products is the quality control process (Figure 3), where the safety of the product to be used by humans is confirmed. In EHM production, the standards for safety and quality are even higher. For cell-based drug development, the final product must have high safety and high efficacy proven. Manufacturing processes must be based on a foundation of characterisation data to ensure the continuity of quality necessary for GMPs-compliant cell therapy manufacturing (MASON; HOARE, 2006).

To ensure high efficacy and safety, the company performs three assays:

- Identity: to confirm that product contains the intended cellular and non-cellular components.
- Potency: to confirm that the product possesses the inherent or induced biological function(s) that is relevant to treating the intended clinical indication.
- Purity: to confirm that the product does not contain undesired components and that the product is not contaminated with microbes or adventitious agents.

Figure 3 – Quality Control process overview



Source: Personal Archive (2022).

2.2.3 Current Problems

A major challenge to commercialize cell-based therapies is the development of a scalable manufacturing processes while maintaining the critical quality parameters (high safety and high efficacy) of the final live cell product (CARMEN et al., 2012).

Applying current GMPs to the manufacture of living biological drugs is hardly straightforward. Cell culture-based processes are inherently more complex and less well-controlled than small molecule synthesis, and the products themselves, due to their living biologic nature, cannot be fully defined. These difficulties have given rise to a philosophy that "the product is the process" in which manufacturers ensure product consistency, quality, and purity by ensuring that the manufacturing process remains substantially the same over time (CARMEN et al., 2012).

As opposed to traditional industrial processes, where well-characterised production lines are utilised, in the case of EHM production, it cannot be drawn from extensive process know-how. Instead, cell behavior can differ significantly between two batches. This effect is intensified when manual labor due to variations in the handling proce-

dures that can be partly reduced by the application of detailed procedures (KULIK et al., 2016).

The manual maintenance of EHM introduces several limitations for transition into large-scale experiments. First, the maintenance of the stem cell culture to retain pluripotency and for directed differentiation protocols requires highly trained and experienced staff. Moreover, technician variability and human error pose major limitations when high numbers of samples are being processed in parallel. This variability also contributes to significant differences between cell lines generated and maintained in various laboratories (ALLEGRUCCI; YOUNG, 2007).

2.3 REQUIREMENTS FOR LABORATORY AUTOMATION

As the company is ready to scale up the production to enter the EHM market competition, once its production processes are accordingly to the GMP requirements for Advanced Therapy Medicinal Products (GMP, 2022) and its product was approved by clinical studies, its biggest requirement at the moment is to scale up the production with a goal of 10.000 EHM patches per year.

Furthermore, all software components developed for the project should comply with the GAMP Good Practice Guide: GxP Compliant Laboratory Computerised Systems (ISPE, 2012) which contains steps for which scientists, suppliers, and others involved in managing laboratory computerised system acquisition, implementation, and operations should use to verify laboratory systems that fit for their intended use. The Guide provides a practical, risk-based approach for evaluating these systems, thus eliminating trial and error.

Moreover, the company needs the automation of the production to be in compliance with GMP and decrease the variability caused by the operator. As a requirement for the most important process of production, the quality control process, the company requests an inline quality control so that it is not necessary to stop the production for control stages and to minimize the production waste.

3 THEORETICAL FOUNDATIONS

3.1 CELL CULTURE LABORATORY AUTOMATION

In recent years, there has been clinical and commercial interest in generating cell products for therapeutic applications. The major reason is the advances in stem cell research and the progressing clinical studies revealing its potential for regenerative therapy (TROUNSON et al., 2011). To fulfill clinical demand, however, there is a need for reproducible and robust manufacturing processes. To meet the growing need for high-quality cell products many novel challenges yet need to be addressed.

Automation has strongly contributed to revolutionizing many human activities, thus providing unquestionable benefits to system performance (DEKKER; WOODS, 2002). In comparison to other production sectors, such as the automotive and aviation industries, biotechnology is still lagging (KULIK et al., 2016). As opposed to traditional industrial processes, where well-characterised cell lines are utilised, cell culture it cannot be drawn from extensive process know-how. Instead, cell behavior can differ significantly during production. This effect is intensified when manual labor is employed to expand the cells due to variations in the procedures that can be reduced, but not totally, by the application of detailed operating procedures.

In high-wage countries, in particular, automation has been one of the main key factors enabling a reduction in production costs. In addition to potentially reducing the cost of goods, automation also offers enhanced reproducibility, reliability, and increased throughput (KULIK et al., 2016). With the attention shifting from lab-scale to large-scale production, cell manufacturing for regenerative medicine can benefit from automation by combining robustness and process adaptivity.

It is also important to consider the advances in the digitalisation of machines and processes, which no doubt offer new possibilities for data-driven and adaptive production. In this context, the term ‘Industry 4.0’ is often used to summarize these developments. Although this term can be difficult to define, there are essentially nine aspects associated with Industry 4.0: interconnection, collaboration, standards, security, data analytics, information, decentralised decisions, and physical and virtual assistance (SCHENK et al., 2016).

Reproducibility and standardisation can be achieved by the collaboration of various automated devices and sophisticated data analytics. Standardised control hardware in combination with high-grade information acquired from multiple sensors can be utilised to enhance the reliability of technical systems. By using decentralised decisions and interconnectivity of devices, a high degree of adaptivity can be achieved. The combination of traditional automation and Industry 4.0 has the potential to achieve safe and well-defined production of cell products for therapies in the future.

Some improvements in laboratory automation cited (LIPPI; DA RIN, 2019) are:

- Lower costs in the long term;
- Improve efficiency;
- Improve sample management;
- Enhance standardisation for certifications;
- Improve the quality of testing;
- Lower sample volume;
- Staff requalification.

On the other hand, some limitations of laboratory automation cited (LIPPI; DA RIN, 2019) are:

- Higher cost in the short term;
- Increase of fixed costs, as it may demand a bigger infrastructure, maintenance, and energy supply;
- Increase the risk of downtime related to system failures and maintenance;
- Psychological dependence on automation;
- Disruption of trained staff in specific technologies.

3.2 ECONOMIC ANALYSIS OF LABORATORY AUTOMATION PROJECTS

When a manager needs to make a decision, he is faced with four main difficulties, according to (ROLDAN; MIYAKE, 2004): complexity, inherent decision uncertainty, multiple interrelated objectives, and different perspectives that may lead to different conclusions. Faced with this, in the process of choosing the most appropriate path, managers see the need to use a constant and expressive flow of information, and, for this, they use the most diverse tools to analyse their decisions.

In times of burst of the biotechnology bubble, investments in laboratory automation demand justification beyond simple declarations that something is better or faster. Choices need to be analysed to convince that automation makes sense for an organisation. For this purpose, existing economic tools and financial techniques can be used to compare technology and investments based on economic measures of effectiveness.

As highlighted in the previous section, laboratory automation can successfully lower costs. This has been shown by studies as the techno-economic analysis of an automated iPSC production study presented in (NIESSING et al., 2021). It shows a difference of around 40% higher Net Present Value (NPV) of automated stem cell

production compared to manual production. The same advantage is shown in other studies such as (ARMBRUSTER; OVERCASH; REYES, 2014) and (YU, H.-Y. E. et al., 2019).

With the works on automation of stem cell production laboratories found in the literature, no advanced models of economic benefit and risk analysis were found. For instance, some of those studies use NPV to demonstrate the profit or loss of the laboratory automation project, the labor cost as the main driver of the reduction of costs in the long term, and the payback period to show how long it takes for the automated scenario to become more profitable than the manual one. In conclusion, projects are evaluated using methods such as cost-benefit analysis or capital budgeting methods such as payback period and NPV independently, showing a lack of a more in-depth and complete study model applied to this type of project.

3.3 CAPITAL BUDGETING FOR ECONOMIC ANALYSIS

Investments exist in multiple forms: single or multi-purpose, certain or uncertain, isolated or interdependent, with limited or unlimited time horizons, stand-alone or connected with subsequent projects. All must be considered using appropriate investment appraisal methods. These are applied within a decision-making and control approach that primarily focuses on projects or programs, i.e, making decisions about a single investment project or a set of interrelated projects. The decision process usually is called capital budgeting and relates to long-term capital investment programs and projects that must be assessed by capital budgeting methods (GÖTZE; NORTHCOTT; SCHUSTER, et al., 2008).

Investment projects are always connected with risk, and the criteria for the selection of investment projects depend, in the majority of cases, on the level of risk. Therefore it is necessary to use statistical and financial methods to evaluate the investment projects that imply the calculation and analyses of some indicators that will allow emphasising the size, structure, dynamics, and efficiency of using the investment resources.

Capital budgeting methods are tools for decision-making and have been defined in the literature as the methods and techniques used to evaluate and select an investment project (BIERMAN, JR; SMIDT, 2012). Some of those methods are:

3.3.1 Cost Comparison

For the cost comparison method, the target measure is the cost(s) of an investment project. It is assumed when using the cost comparison method that the revenues of mutually exclusive investment alternatives are identical and that only the costs differ. The average costs for the planning period should be determined for each investment

alternative. Adding up all cost components gives a total cost for each alternative investment. (GÖTZE; NORTHCOTT; SCHUSTER, et al., 2008)

This is one of the simplest calculation methods but yet a great appraisal for initial investments when it is known what the required performance is, and it can be achieved with several alternatives. A negative aspect of this method is the static perspective of the cost comparison method since it looks at one 'average' period only. Differences in the timing of costs cannot be assessed, therefore. Such differences can result from changes in prices and/or consumption over time for each cost category.

3.3.2 Average Rate of Return

The average rate of return method combines a profit measure with a capital measure to focus on the return (expressed as a rate of interest) earned on the capital invested (GÖTZE; NORTHCOTT; SCHUSTER, et al., 2008). Therefore, the average rate of return is the average revenue generated over the life of an investment. This rate is calculated by aggregating all expected cash flows and dividing by the number of years that the investment is expected to last.

This method is commonly used when considering multiple projects, as it provides the expected rate of return from each project in a simple manner. The key flaw in this calculation is that it does not account for the time value of money. Revenues in later periods are worth less than revenues in more recent periods.

3.3.3 Simple Payback

The target measure used for the simple payback period method is the time it takes to recover the capital invested in the project (BIERMAN, JR; SMIDT, 2012). Payback periods are typically used when liquidity presents a major concern.

The simple payback period (Equation (1)) of an investment project is the period after which the capital invested is regained from the average revenue generated by the project. The payback period serves not only as a comparison of available alternatives but also as a measure of the investment risk. For this reason, the simple payback period is a good addition to other capital budgeting methods that only assess economic efficiency (NIESSING et al., 2021).

$$\text{Simple Payback period} = \frac{investment}{\text{average revenue}} \tag{1}$$

A major advantage of using the simple payback period is that it is easy to calculate once the revenue forecasts have been established. But there are drawbacks to using the static payback period method to determine capital budgeting decisions. Firstly, the simple payback period does not account for the time value of money, and

secondly, it ignores the cash flows that occur towards the end of a project's life, such as the salvage value. Thus, this method is not a direct measure of profitability.

3.3.4 Return on Investment

Return on Investment (ROI) is an indicator that shows the extent to which the amount invested in a particular action returns as profit or loss. Thus, ROI enables profitability assessment of an amount invested. To calculate ROI, the return of an investment is divided by the cost of the investment. The result is expressed as a percentage or a ratio (FRIEDLOB; PLEWA JR, 1996). The calculation is shown in Equation (2):

$$\text{ROI} = \frac{profit}{investment} x100\% \tag{2}$$

ROI is one of the most popular profitability methods used to evaluate how well an investment has performed because of its simplicity in calculating and because it is a universally understood concept. Some of its limitations are that it does not account for risk or time horizon, and it requires an exact measure of all costs.

3.3.5 Net Present Value

NPV is the difference between the present value of cash inflows and the present value of cash outflows over time. (BIERMAN, Jr; SMIDT, 2014).

NPV is used to analyze the profitability of a projected investment or project. To calculate NPV, it is needed to estimate future cash flows for each period and determine the correct discount rate. The calculation is shown in Equation (3):

$$\text{NVP} = \sum_{t=1}^{N} \frac{R_t}{(1+i)^t} \tag{3}$$

With:

R_t = cash inflow-outflows during a single period t
t = time of the cash flow
i = discount rate
N = Total number of periods

NPV is one of the most detailed and widely used methods for evaluating the attractiveness of an investment that takes into consideration the time value of the money. With this advantage comes the drawback that it relies heavily on assumptions and estimates, so there can be substantial room for error.

3.3.6 Internal rate of Return

The internal rate of return (IRR) method is used to estimate the profitability of potential investments. IRR Equation (4) is a discount rate that makes the net present value

(NPV) of all cash flows equal to zero in a discounted cash flow analysis (DAYANANDA, 2022). Therefore, the IRR is the annual rate of growth that an investment is expected to generate.

$$0 = NPV = \sum_{t=1}^{T} \frac{C_t}{(1 + IRR)^t} - C_0 \tag{4}$$

With:

C_t = Net cash inflow during the period t
C_0 = Total initial investment costs
t = The number of periods

IRR is a very popular metric for estimating a project's annual return. Still, it is not necessarily intended to be used alone. IRR is typically a relatively high value, which allows it to arrive at an NPV of zero. It can be misconstrued or misinterpreted if used outside of appropriate scenarios. In the case of different cash flow signs, the IRR may have multiple values. Moreover, if all cash flows have the same sign (i.e., the project never turns a profit), then no discount rate will produce a zero NPV.

3.3.7 Discounted Payback Period

The discounted payback period gives the number of years it takes to break even from undertaking the initial expenditure by discounting future cash flows and recognising the time value of money (GÖTZE; NORTHCOTT; SCHUSTER, et al., 2008).

The difference between the static payback period method and the discounted payback period method is that the last take the time value of money into account. This means that an earlier cash flow has a higher value than a later cash flow of the same amount (assuming a positive discount rate).

The discounted payback period is calculated by discounting the net cash flows of each period and accumulating the discounted cash flows until the amount of the initial investment is met.

3.3.8 Minimum Acceptable Rate of Return

The minimum acceptable rate of return, also called the hurdle rate, is the lowest rate of return that the project must earn to offset the costs of the investment (DAMODARAN, 1996). When projects are evaluated by discounting future cash flows to the present, they usually use the hurdle rate as their discount rate.

3.4 RISK ANALYSIS

The existence of risk is directly related to the uncertainty of certain future events. In this perspective, risk analysis is a technique that aims to understand the degree of sensitivity of future results to possible changes in critical variables for success.

According to (FERNANDES et al., 2012), the risk analysis can be subdivided into three groups:

- Business, economic or operational risk - respect the uncertainty inherent to the projection of future results and is normally related to the specificities of the developed activities.
- Financial risk - refer to the uncertainty inherent in the projection of return on equity, usually related to financing decisions.
- Global risk - combining the two previous types of risk.

The purpose of capital budgeting is to assess the economic prospects of a proposed investment project. Risk emanates from the uncertainty encompassing the projected variables that are used in the capital budgeting methods (SAVVIDES, 1994). Risk analysis identifies and estimates risks and their level, as well as measures considered to mitigate their negative impact. Quantitative risk analysis is performed to estimate the risk of the project by numeric resources (PLATON; CONSTANTINESCU, 2014).

A risk analysis application utilises a wealth of information, be it in the form of objective data or expert opinion, to quantitatively describe the uncertainty surrounding the key project variables as probability distributions and to calculate its possible impact on the expected return of the project (SAVVIDES, 1994).

Recognising that the values projected are not certain, a risk analysis is usually supplemented to include sensitivity and scenario analysis tests. Sensitivity analysis involves changing the value of a variable to test its impact on the final result. It is therefore used to identify the project's most important, highly sensitive variables. Scenario analysis is a sensitivity analysis that allows a simultaneous change of values of several key project variables, thereby constructing an alternative scenario for the project. A pessimistic and optimistic scenario is usually presented. The use of risk analysis in capital budgeting carries sensitivity and scenario analyses through to their logical conclusion.

The evaluation of project risk depends, on the one hand, on the ability to identify and understand the nature of uncertainty surrounding the key project variables and, on the other, on having the tools and methodology to process its risk implications on the return of the project (SAVVIDES, 1994). In this thesis, the method that implements the risk analysis will be the Monte Carlo simulation method.

3.4.1 Monte Carlo Simulation Method

The Monte Carlo method is a stochastic, e.g., random sampling of inputs, a method to solve a statistical problem, and a simulation is a virtual representation of a problem. The Monte Carlo simulation combines the two to give us a powerful tool that allows us to obtain a distribution of results for any statistical problem with numerous inputs sampled over and over again.

Risk analysis or 'probabilistic simulation' based on the Monte Carlo simulation technique is a methodology by which the uncertainty encompassing the main variables projected in a forecasting model is processed to estimate the impact of risk on the projected results (SAVVIDES, 1994). It allows studying the reflection of uncertainty associated with various cash components. The output from the simulation consists of distributions of net cash flows, which can be used for decision-making and risk management (ROZYCKI, 2011).

Monte Carlo simulation performs risk analysis by building successive scenarios using input values for the project's key uncertain variables, which are selected at random from multi-value probability distributions. It then calculates numerous results, each time using a different set of random values from the probability density function (PDF). Then, it results in distributions of possible outcome values.

By using PDF, variables can have different probabilities of different outcomes occurring. Probability distributions are a much more realistic way of describing uncertainty in variables of a risk analysis. The most used PDF in Monte Carlo simulation for economic studies are:

Log-normal

Values are positively skewed, not symmetric like a normal distribution. It is used to represent values that don not go below zero but have unlimited positive potential. Examples of variables described by log-normal distributions include stock prices and material usage.

Uniform

All values have an equal chance of occurring, and only the minimum and maximum values are needed. Examples of variables that could be uniformly distributed include manufacturing costs and future revenues.

Normal

Also called Gaussian distributions, the data is symmetrically distributed with no skew. When plotted on a graph, the data follows a bell shape, with most values clustering around a central region and tapering off as they go further away from the center. The values in the middle near the mean are most likely to occur. It describes many natural phenomena, for example, height, inflation rates, and stock prices.

The normal distributions have key characteristics that are easy to spot in graphs: The distribution can be described by the mean and the standard deviation. The mean

is a so-called measure of central tendency, represents the more central value of our curve, and is the same as the median and mode. In contrast, the standard deviation represents how dispersed are the values of probability around the central value.

The PDF of the normal distribution is given by Equation (5):

$$F(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$

Source: (VITI; TERZI; BERTOLACCINI, 2015)

(5)

With:

σ = standard deviation
σ^2 = variance
μ = mean

Triangular

Some variables are best modeled via three outcomes; pessimistic (minimum or worst case), most likely or mode, and optimistic (maximum or best case) values of the random variable. The variable may not be symmetric, and it may display a long right or left tail. In such situations, it is desirable to use the triangular distribution.

The triangular distribution, shown in Figure 4, is a continuous probability distribution shaped like a triangle and defined with the minimum value “a” and the maximum value “b”, the location parameters of the distribution, and the mode value “c”, the shape parameter.

The PDF of the triangular distribution is given by Equation (6):

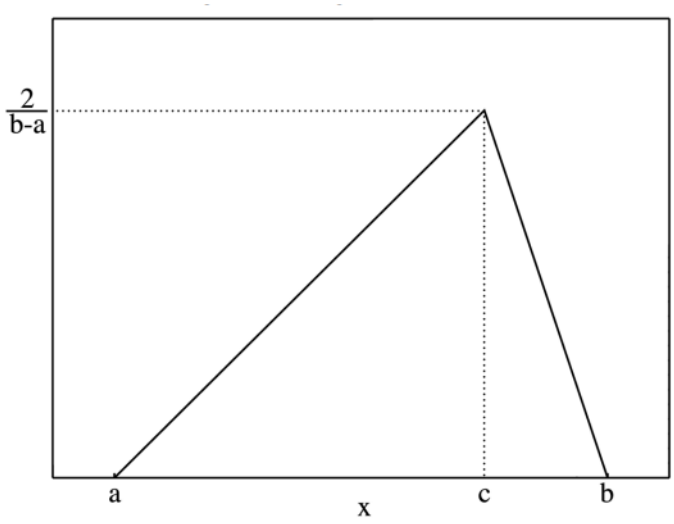
$$f(x) \begin{cases} 0 & x < a \\ \frac{2(x-a)}{(b-a)(c-a)} & a \leq x \leq c \\ \frac{2(x-b)}{(b-a)(b-c)} & c \leq x \leq b \\ 0 & x > b \end{cases}$$

Source: (FAIRCHILD; MISRA; SHI, Yilun, 2016).

(6)

(JUNQUEIRA; PAMPLONA, 2002) used the Monte Carlo Simulation in an economic and financial feasibility study for the implementation of a detergent industry, obtaining as a result probability distributions of NPV and IRR indicators.

Figure 4 – Triangular Distribution



Source: (FAIRCHILD; MISRA; SHI, Yilun, 2016).

3.4.2 Sensitivity Analysis

The sensitivity analysis determines how different values of an independent variable affect a particular dependent variable under a given set of assumptions (CHRISTOPHER FREY; PATIL, 2002). This analysis is also known in practice as the "what if" analysis.

According to (SILVA; QUEIRÓS, 2013), the process consists in identifying the uncertainty variables that are valuable to the investment project (e.g., cost of raw materials, personnel costs, amount of investments, discount rate, etc.), assigning new values to these variables, recalculating the values of cash flows and decision criteria and analyzing the impact on the values of these criteria. This analysis allows to identify the most sensitive variables of the investment and also the critical points and limits of the variables, to keep the project viable.

Usually, the sensitivity analysis will vary each of the variable(s), considered critical, analyzing the impact of this variation on the NPV and/or IRR of the investment.

3.4.3 Scenario Analysis

The scenario analysis is a technique based on a multivariate sensitivity analysis since each scenario can be constructed based on changing the base values of several variables.

The choice of the appropriate scenarios depends on the goals of the project and the context in which this it takes place (KOSOW; GASSNER, 2008), but most often, it is used in at least three types:

- **Base Scenario**: The assumptions under analysis are estimated at their most likely values, so the most likely value and/or profitability of the investment will be identified.
- **Pessimistic scenario**: a pessimistic estimation is placed for the assumptions under analysis. This scenario calculates the NPV and/or IRR that is predictably lower for the investment.
- **Optimistic scenario**: the assumptions under analysis are set at an optimistic level, obtaining the highest NPV and/or IRR of the investment project.

One of the great advantages of scenario analysis is the fact that it allows the analysis of the impact of a joint variation of variables that are considered critical to the success of the investment according to the evolution of the conjuncture. Nonetheless, it has no directly associated probability of occurrence in each scenario.

The scenario analysis is broader than a sensitivity analysis since the first one allows for analysis of the effect of simultaneous interaction of several assumptions (independent variables) on the NPV and/or IRR of the investment (SILVA; QUEIRÓS, 2013).

3.5 COST ACCOUNTING

Cost accounting provides the detailed cost information that management needs to control current operations and plan for the future (VANDERBECK, 2012). It is a process that measures all of the costs associated with production to assist management in decision-making processes that optimize operations based on efficient cost management. The major costs included in cost accounting that will be used for the present work are:

Direct Costs

Direct costs are related to producing a good or service. The cost can easily be traced to a product, department, or project.

Indirect Costs

Indirect costs are expenses unrelated to producing a good or service. An indirect cost cannot be easily traced to a product, department, activity, or project.

Fixed Costs

Fixed costs do not vary with the number of goods or services a company produces over the short term.

Variable Costs

Variable costs fluctuate as the level of production output changes, contrary to a fixed cost. A variable cost increases as the production volume increases, and it falls as the production volume decreases.

Operating Costs

Operating costs are expenses associated with daily business activities but are not traced back to the production itself. Operating costs can be variable or fixed.

To simplify all of these costs, they can be organised under the two most common categories: capital expenditures (CAPEX) and operating expenses (OPEX). CAPEX are major investments a company makes that are designed to be used over the long term. OPEX is the daily expenses that incur to keep the business operational.

3.6 FINANCIAL STATEMENTS

Financial statements are written records that convey the business activities and the financial performance of a company. The three main financial statements are:

- Balance Sheet
- Income Statement
- Cash Flow Statement

3.6.1 Income Statement

An income statement, also known as a profit and loss statement, is a financial statement that presents the company's income and expenditures, showing whether a company is making a profit or loss for a given period.

The income statement focuses on four key items: revenue, expenses, gains, and losses.

Revenue and Gains

- Operational Revenue: Revenue realised through primary activities.
- Non-Operational Revenue: Revenues realised through secondary, non-core business activities such as income from interest earnings and income from patents.
- Gain: These include the net income realised from one-time non-business activities, like the sale of long-term assets.

Expenses and Losses

- Primary Activity Expenses: Expenses linked to the primary activity of the business. They include the cost of goods sold, selling, general and administrative expenses, depreciation or amortisation, research and development expenses, and general operational costs.
- Secondary Activity Expenses: All expenses linked to non-core business activities, like interest paid on loan money.

- Losses: Expenses that go towards a loss-making sale of long-term assets, one-time, or any other unusual costs.

Essentially, it gives an account of how the net revenue realised by the company gets transformed into net income (profit or loss).

3.6.2 Free Cash Flow

Free cash flow represents the cash a company generates after accounting for cash outflows to support operations and capital expenditures. It gives the net cash flow available for distribution to investors after the firm has met all of its operating needs and paid for investments in new fixed assets. (SHRIEVES; WACHOWICZ JR, 2001). This financial statement only encompasses cash transactions, giving a clearer picture of just how profitable a company is. The formula used to calculate the Free cash flow is:

$$\text{Free Cash Flow} = \mathit{IncomeBeforeTaxes} + \mathit{Depreciation} - \mathit{IncomeTaxes} - \mathit{CAPEX} \quad (7)$$

3.7 BREAK-EVEN ANALYSIS

A break-even analysis is a financial calculation that weighs the costs of a new project against the revenue to determine the point at which it will break even, known as the break-even point. In other words, it reveals the point at which it will have sold enough units to cover all of the costs. This is a useful analysis to study the relationship between fixed costs, variable costs, and returns (GUTIERREZ; DALSTED, 1990).

Break-even analysis is performed to determine the value of a variable of a project that makes two elements equal, e.g., production volume that will equate revenues and costs. This is commonly applied to alternatives that serve the same purpose. As a result, break-even analysis is carried out between a common variable of the alternatives. It involves the determination of this variable and the selection of analysis, such as NPV, to be expressed as a function of the common variable.

3.8 REQUIREMENTS ENGINEERING

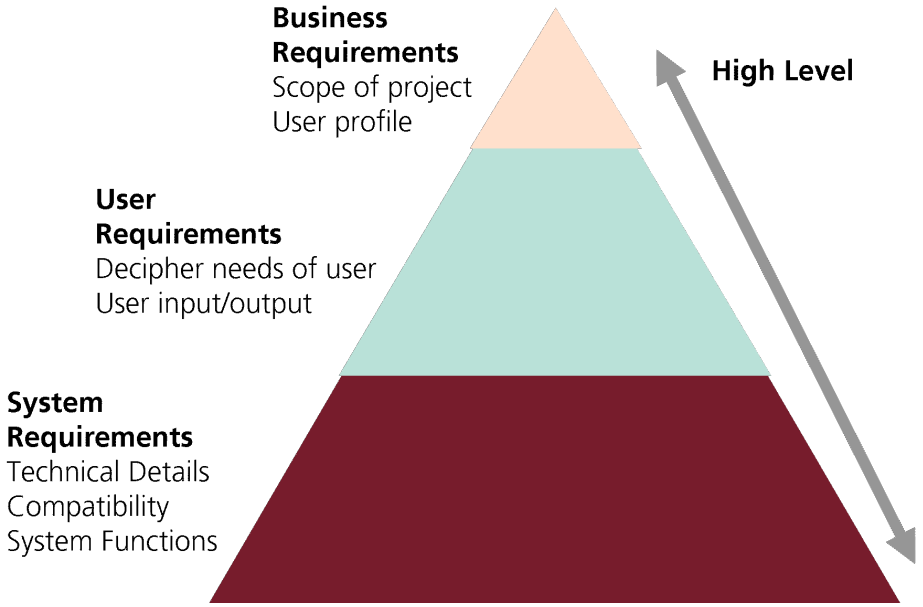
Requirements engineering is concerned with identifying, modeling, communicating, and documenting the requirements for a system and the contexts in which the system will be used. Requirements describe what is to be done but not how they are implemented (PAETSCH; EBERLEIN; MAURER, 2003).

According to IEEE standard 729 (IEEE. . . , 1983), a requirement is defined as follows:

- A condition or capability needed by a user to solve a problem or achieve an objective;
- A condition or capability that must be met or possessed by a system or system component to satisfy a contract, standard, specification, or other formally imposed documents;
- A documented representation of a condition or capability as in 1 and 2.

The requirements in this work were classified into five categories, business requirements, business rules, user requirements, functional requirements, and non-functional requirements, which are comprised of three main categories that can be seen in the requirements pyramid in Figure 5.

Figure 5 – Requirement Pyramid



Source: (GERVASIO, 2022)

- **Business Requirements**: outlines the purpose of a product.
- **Business Rules**: restrictions or constraints under which the system will function.
- **User Requirements**: specifies what the system needs to do. It is written from the point of view of the end-user and does not need to be technical or complicated.
- **Functional Requirement**: defines a system or its component. It specifies what the system should do.
- **Non-functional Requirement**: defines the quality attribute of a software system and how should the software system fulfill the functional requirements.

3.9 UNIFIED MODELING LANGUAGE

A model is an abstract representation of a specification, a design, or a system, from a particular point of view (KOBRYN, 2000). It is often represented visually by one or more diagrams. The Unified Modeling Language, known as UML, is a standardised modeling language consisting of an integrated set of diagrams, developed to help system and software developers for specifying, visualizing, constructing, and documenting the artifacts of software systems, as well as for business modeling and other non-software systems. Using UML helps to validate the architectural design of the software (KOBRYN, 2000).

In this work, it was used the use case and activity diagram, both behavior diagrams which show the dynamic behavior of the objects in a system. The first, the use case model, describes a system's functional requirements in terms of use cases (PODESWA, 2009). It is a model of the system's intended functionality (use cases) and its environment (actors). Secondly, the activity diagram is a graphical representation of workflows of stepwise activities and actions with support for choice, iteration, and concurrency (PODESWA, 2009). It describes the flow of control of the target system, such as exploring complex business rules and operations, describing the use case also the business process.

The structure diagrams, which show the static structure of the system and its parts on different abstraction and implementation levels and how they are related to each other, were not used because the tool developed didn't use extensive code or object-oriented programming.

4 ECONOMIC BENEFIT AND RISK ANALYSIS AUTOMATED TOOL

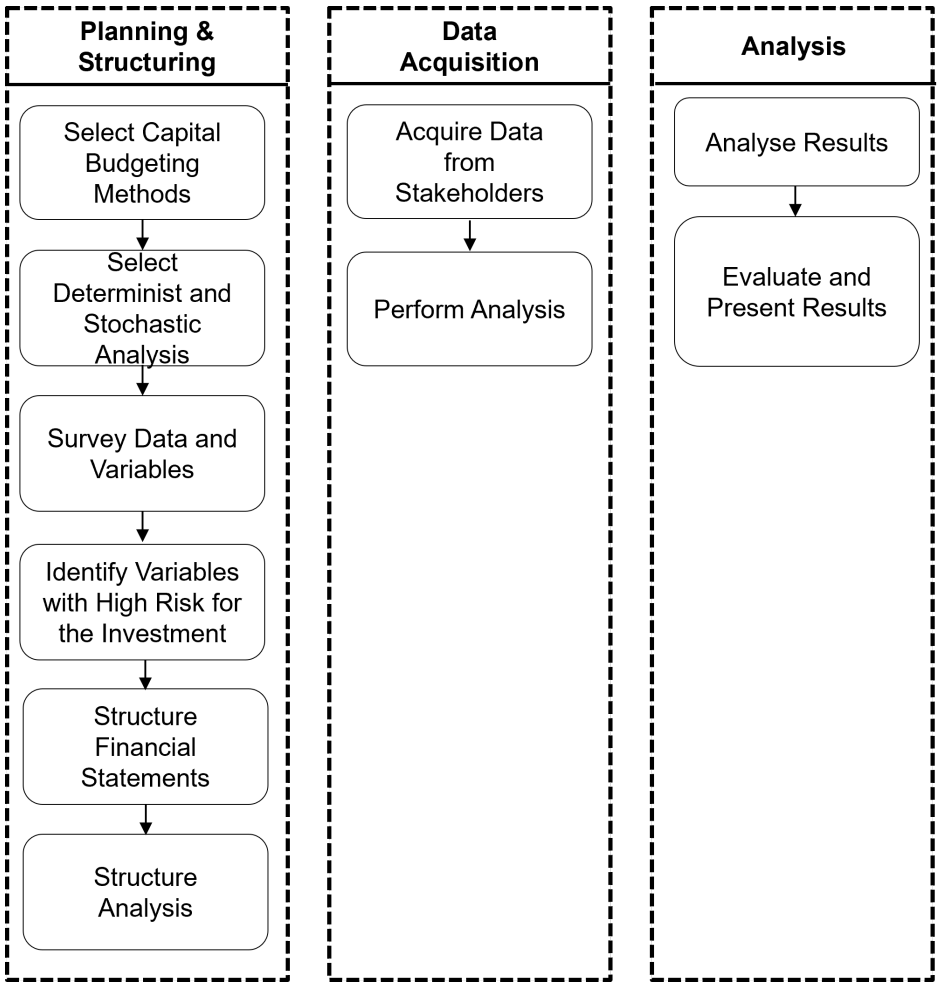
As shown in Section 3.2, the models of economic benefit and risk analysis for automation projects in stem cell production laboratories presented in the literature evaluate the project's profitability with only a few scattered techniques. These techniques do not quantify the economic impact and the risks to which the projects are exposed in an explanatory way, leading to a wrong decision as a consequence of not having access to the dimension of the profitability impact (positive or negative) which is associated with other techniques not applied, such as sensitivity analysis and Monte Carlo simulation.

Therefore, this work proposes the creation of an automated tool to standardize the profitability study of stem cell laboratory automation projects based on a new model of economic benefit study and risk analysis to assist the work of researchers at IPT during the phase of cost-benefit study of the automation projects. The model proposed in this thesis presents three original features:

1. The analysis of multiple capital budgeting methods for a complementary profitability study;
2. The sensitivity and scenario analysis of the economic risk factors;
3. The calculation of the financial result of the project through simulation using the Monte Carlo method, expanding the risk analysis.

The proposed model is detailed in Figure 6 and is divided into three steps: Planning & Structuring, Data Acquisition, and Analysis.

Figure 6 – Economic benefit and risk analysis model



Source: Personal Archive (2022).

In the Planning & Structuring step, the need for IPT to obtain a standard method of economic and risk analysis in laboratory automation projects was identified. For this end, capital budgeting methods were studied and chosen to compose the model. Later, deterministic and stochastic analyses were added to the model to analyse the risks involved in the project. After the choice of the methodologies, a detailed survey of data and variables important for the study was carried out. In addition, the variables of greatest risk to the project were identified. In possession of these data, the structuring of the free cash flow, income statement, and analysis were executed, and the tool was built.

At step Data Acquisition, partner company stakeholders and IPT researchers were consulted to collect project data. Then, the capital budgeting methods of NPV, IRR, ROI, and discounted Payback were used, aiming at obtaining information relative to the economic viability of the project. Besides this, through sensitivity analysis, it was identified the variables that have a greater impact on the project's success, and

later it was estimated the probabilistic variations for the variables. To finish this step, computational simulation was applied based on the Monte Carlo Simulation method, contributing to the analysis of project risks and assisting in further analysis and decision making.

In the third and last step, the Analysis, with the information obtained in Step 2, the feasibility of the project was critically analysed, focusing on economic aspects and risk indicators found. Then, recommendations were made to the partner company regarding the automation project of the EHM production laboratory.

The economic benefit and risk analysis model created was implemented as an automated tool using Excel to facilitate the usability of the model by the stakeholders and thus meet the project's objective of reducing the workload of the researchers and implementing the standard profitability analysis that will be presented to the clients during the stem cell production laboratory automation projects.

4.1 CAPITAL BUDGETING METHODS

The capital budgeting methods, the deterministic methods chosen to be part of the economic benefit model developed were NPV, IRR, ROI, and discounted payback period.

The NPV has been chosen as being the most widely used technique for the economic evaluation of investment viability which clearly shows the profitability of the project considering the time value of money. The technique consists of analyzing the present value generated by the cash flow associated with the project and discounting the amount initially invested. In case the NPV is positive, the invested value is considered recovered and presents profitability equal to the NPV value.

The IRR consists of the rate that equals the project's NPV to zero, indicating the income that should be obtained from its realisation. A project that has an IRR higher than a minimum rate of attractiveness established by the company is considered economically viable. It was chosen to compose the model's arsenal of capital budgeting methods because, as it is presented as a percentage, it facilitates the visualisation and comparison of profitability between projects. Both IRR and NPV can be used to determine how desirable a project will be and whether it will add value to the company. While the first use a percentage, the other is expressed as a monetary figure. While IRR is usually more useful when there is comparison across multiple projects or investments or in situations where it is difficult to determine the appropriate discount rate, when a cash flow associated with a project alternates between positive and negative values, e.g., reinvestment or loss in a certain period, more than one IRR value can be obtained. In this case, it is recommended its substitution by NPV analysis or another investment economic evaluation technique. That is why it is so important to use more than one method of capital budgeting when studying the profitability of a project.

Besides IRR and NPV, the payback period is used to evaluate the attractiveness of projects. Due to the value of money over time, it is convenient to use the so-called discounted Payback. This method was used in the model as well because its main goal is to provide subsidies for choosing the project that returns the investment in the shortest period possible, thus indicating the one that has the lowest uncertainty associated due to the shortest horizon of return. Yet, even though it is a great method to indicate the project that will bring the fastest result to the company, this method should not be used to evaluate the profitability of a project because it does not inform which project best remunerates the investment, only which one returns the capital invested in a faster way, so its focus is on the risk factor. Therefore, this indicator should be used in association with other methods.

Lastly, the ROI, a ratio between net income over a period and costs resulting from an investment, was also incorporated because it is a universally known metric, and even though it has less depth than the others, it was required by the company for being simple and direct. As a performance measure, ROI is used to evaluate the efficiency of an investment or to compare the efficiencies of several different investments. It is a popular metric because of its versatility and simplicity, but in economic terms, it is one way of relating profits to capital invested without consideration of time in the equation, failing to consider the nuances of the value of money over time and the possibility of new investments in the future. For long-term investments, the need for another metric, such as the NPV, is essential, and without it, the ROI is incorrect.

4.2 FINANCIAL STATEMENTS

For this work, the income statement and free cash flow statement were used. The income statement will focus on the project's revenues and expenses in annual periods. Once expenses are subtracted from revenues, the statement will produce the project's profit, called net income. The cash flow statement will measure how well the project generates cash to pay its debt obligations, fund its operating expenses, and fund investments. The balance sheet was disregarded as the overview of the company assets, and liabilities will not have an impact on the calculation of the profitability of the project over time.

The simplification of the income statement used in this work is presented in Table 1.

Table 1 – Income Statement simplification.

Net Revenue
(-) Cost of Sale
(=) Net Profit
(-) OPEX
(=) Gross Profit/Loss
(-) Depreciation
(=) Operating Profit/Loss
(-) Interest
(=) Income Before taxes
(-) Income taxes
(=) Net Income (Profit/Loss)

4.3 ECONOMIC FEASIBILITY RISK ANALYSIS

The capital budgeting methods presented so far share the assumption of deterministic data content, admitting future values as certain, without considering the uncertainties and risks associated with these predictions. Nevertheless, these factors must be considered in the analysis. (SOUZA; CLEMENTE, 2004) differentiate risk and uncertainty. For the author, the risk is defined when future events can be predicted using probabilities. On the other hand, uncertainty is associated with unpredictable future events, either due to a lack of information or due to their random character. Therefore, some stochastic methods have been chosen to deepen the analysis.

The term ‘risk’ is defined in this work as the lack of ability to accurately predict the outcome of a performance measure, therefore, the variables chosen to be analysed in the risk assessments are:

- Production volume;
- Target price;
- Personnel cost variation;
- Material cost variation;
- Fixed cost variation;
- CAPEX variation;
- Interest rate variation;
- Income taxes variation.

The variables were chosen in partnership with the IPT researchers who have already worked on automation projects in laboratories and believe to be the most

unpredictable variables, resulting in risk for the economic evaluation of the project. They can be considered as assumptions of the model.

The sensitivity analysis and the scenario analysis seek to provide subsidies for the risk analysis of an investment (GITMAN et al., 2010). The sensitivity analysis consists of changing key variables individually and observing the behavior of the return associated with the project. It seeks to determine the influence of changing a given variable on indicators, in this work, the NPV. The use of this technique favors the identification of the critical variables to the project, being those that provide a greater relative variation of the NPV, the analysed parameter.

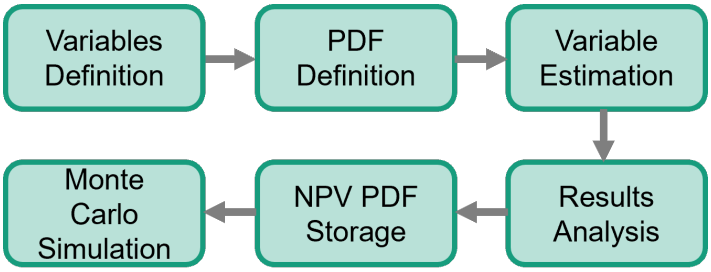
Aiming to complement the sensitivity analysis, it was used the scenario analysis because it enables the variation of more than one variable in each analysis. This way, the problem identified in the sensitivity analysis is minimised, where the variables were considered uncorrelated and analysing them separately.

The Monte Carlo simulation was used to complement the risk analysis described so far. It was chosen to complement the analysis. The method uses known and estimated probability distributions to determine the input variable parameters, thus seeking results in terms of probabilities. The result presented in this model, the NPV, is characterised by an associated probability distribution, highlighting two distinct pieces of information: the mean and the standard deviation.

The stochastic analysis was also performed from the simulation of scenarios using the Monte Carlo method applied using Visual Basic for Applications (VBA). The method used in this study (Figure 7) follows the steps below:

1. Select the input variables. Those are the uncertain parameters of the model, i.e., the parameters that do not have a fixed/established value;
2. Assign a PDF to each variable;
3. Generate N possible values for each input data, using random samples of its PDF;
4. Combine the random samples to get N input vectors;
5. Perform the simulation of the model N times, one for each input vector. At this point, a vector of results is provided, and an input-output mapping of the model is defined;
6. The set of the output data defines the probability density function of the result of the simulation.

Figure 7 – Stochastic analysis model

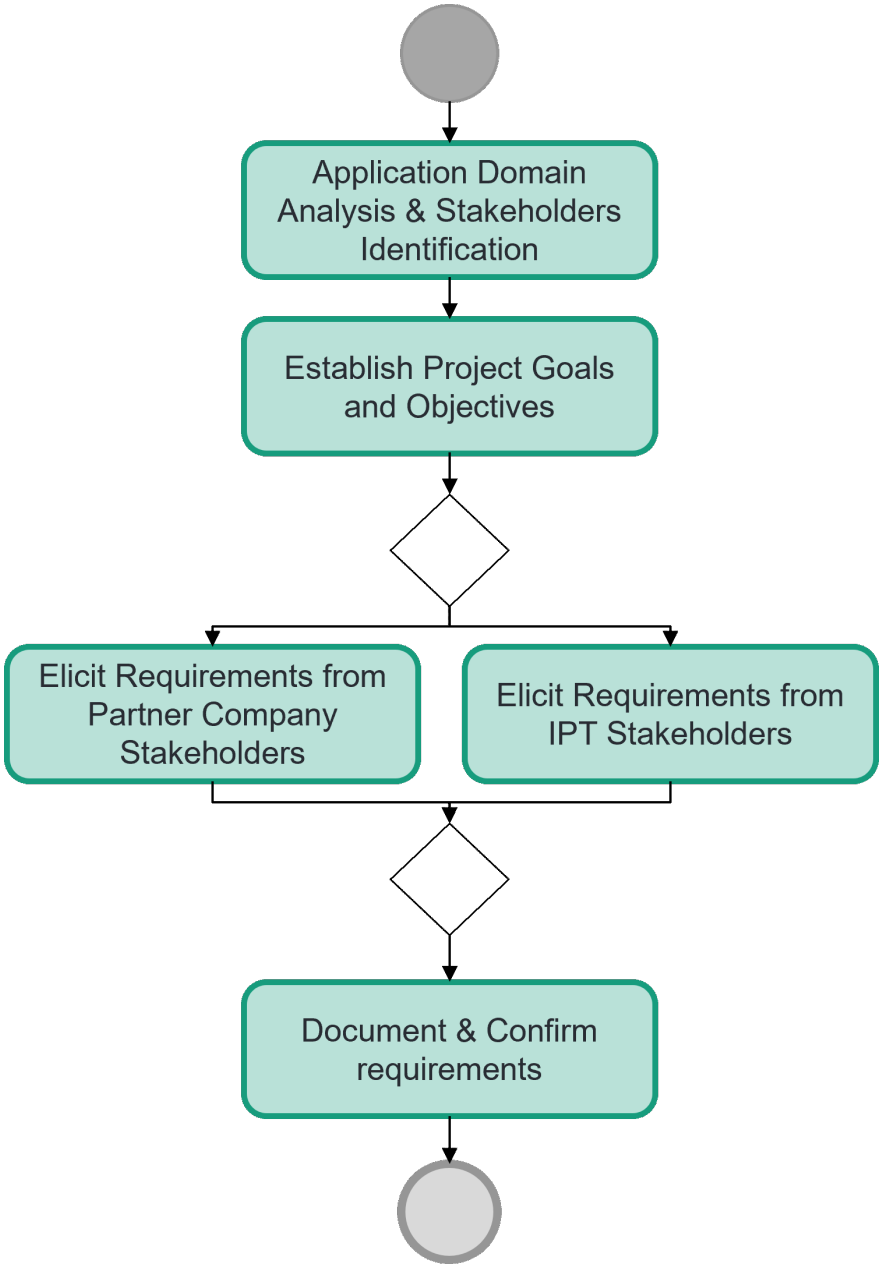


Source: Personal Archive (2022).

4.4 REQUIREMENTS

The requirements for the economic benefit and risk analysis tool were gathered following the steps shown in Figure 8. The application Domain Analysis & Stakeholders Identification was a key phase of the project. During this phase, all of the environmental aspects were determined, understanding the domain concepts of how the tool will be used and who will be the most important user. In the second step, it was established together with the researchers in charge of the laboratory automation project of IPT the main goals of the new tool and how it could be aligned with the department's new objective o having more laboratory automation projects. After that, the requirements were collected from some key researchers in these types of projects inside the IPT through meetings, and the company's requirements were collected through workshops. Finally, the requirements were documented and confirmed with the project's key stakeholders.

Figure 8 – Requirement gathering flowchart



Source: Personal Archive (2022).

4.4.1 Scope of the project

The scope of the project, as shown in Table 2, was defined during the analysis phase and refined after collecting requirements from stakeholders.

Table 2 – Scope of the project

In-scope
Capital budgeting methods: NPV, IRR, ROI, and Discounted Payback Period
Cost and revenue comparison over 10 years
Income statement
Free Cash Flow
Monte Carlo Simulation
Sensitivity Analysis
Price Analysis
Scenario Analysis
Break-Even Analysis
Out of scope
Euro-Dollar exchange
Dollar variation

The main inputs and outputs of the system are presented in Table 3 and Table 4, and the requirements are presented in Tables 5-9.

Table 3 – Inputs of the system

ID	Inputs (I)	Description
I1	Production Values	Information about production
I2	Economic Values	Information about financial and economic indicators
I3	Production Assumptions	Range values to be used when studying the production
I4	Economic Assumptions	Range values to be used when studying the economic aspects
I5	Manual Scenario	Information about the Manual process
I6	Automated Scenario	Information about the Automated scenario
I7	Investment Scenario	Investment costs
I8	Production Process	Production processes
I9	Production Costs	Costs of each process

Table 4 – Outputs of the system

ID	Outputs (O)	Description
O1	Cost Comparison over 10 years	Cost comparison between the manual and automated scenario divided in OPEX (personnel cost, material cost, fixed cost) and CAPEX(initial investment)

O2	Revenue Comparison over 10 years	Revenue comparison between the manual and automated scenario
O3	Personnel Comparison over 10 years	Personnel quantity comparison between the manual and automated scenario for each year depending on the production growth
O4	Net Present Value	Project's profit or loss over 10 years
O5	Return on Investment	Amount of return on the investment relative to the cost
O6	Internal Rate of Return	Rate of growth that the investment is expected to generate
O7	Discounted Payback Period	Number of years it will take to break-even recognizing the time value of money
O8	Break-Even between alternatives of production	Quantity of units needed so that both manual and automated scenarios have the same cash flow (profit or loss)
O9	Break-Even between alternatives on year	Quantity of years needed so that both manual and automated scenarios have the same cash flow (profit or loss)
O10	Project Overview	Overview of units produced, unit price, personnel cost, material cost, fixed cost, investment cost, and revenue over 10 years for each manual and automated scenario
O11	Free Cash Flow	Forecast of Free Cash Flow statement of the project over 10 years for both manual and automated scenario
O12	Income Statement	Forecast of Income Statement of the project over 10 years for both manual and automated scenario
O13	Sensitivity Analysis	Sensitivity Analysis of the project's uncertain variables only for automated scenario
O14	Monte Carlo Simulation	The Monte Carlo simulation using the NPV of the project as an outcome and taking into consideration the project's uncertain variables only for automated scenario

O15	Price Analysis	Equation of the number of units produced and the target price to simulate the cash flow over 10 years, i.e., the profit or loss only for automated scenario
O16	Scenario Analysis	Scenario Analysis of the project to create a worst, average, and best scenario of the cash flow over 10 years, i.e., the profit or loss

In Table 5, the business requirement describes the stakeholder's viewpoint of the system and the business rule, that are the constraints of the business guided the system development are presented.

Table 5 – Business requirements and rules

ID	Business requirements (BR) and business rules (BRL)
BR1	Tool to study the economic viability of laboratories automation project, delivering a report with a comparison of costs and revenues between a manual scenario and an automated scenario and studies of the profitability of the automated scenario
BRL1	The input Excel sent to the partner company cannot have macros enabled, as not all of them are allowed to use them
BRL2	All inputs must be in euros
BRL3	10-years period project study

The user requirements, presented in Table 6, are the requirements set by the end-user, and they express how the stakeholders expect the tool to perform.

Table 6 – User requirements

ID	User requirements (UR)
UR1	The tool must present a cost and revenue comparison between the manual and automated production scenarios
UR2	The tool must present a cost comparison chart separated by personnel cost, material cost, fixed cost, and investment cost between the manual and automated production scenarios
UR3	The tool must have a Monte Carlo simulation that returns the probability distribution of the NPV of the project considering the uncertain variables only for the automated scenario
UR4	The tool must simulate the company's cash flow as a function of the number of units produced and the unit value of the product
UR5	The tool must do a risk analysis with the uncertain variables for the automated scenario
UR6	The tool must show the profitability comparison between the manual and automated production scenarios
UR7	The tool must show the payback period of the manual and automated production scenarios
UR8	The tool must do a break-even analysis between the alternatives
UR9	The final report of the profitability and risk analysis must be saved as a PDF file

In Table 7, the functional requirements, features, and functions that describe the behaviors between inputs and outputs are presented.

Table 7 – Functional requirements

ID	Functional Requirements (FR) for all Inputs (I1-I7)
FR1	The system must add values
FR2	The system should show added values
FR3	The system should edit added values
FR4	The system must delete added values
FR5	The system must generate a report with outputs (O1-O9, O13-O14)
FR6	The system should receive the saving address
FR7	The system must save the report as a PDF at the address

Following, the non-functional requirements are shown in Table 8.

Table 8 – Non-Functional requirements

ID	Non-Functional Requirements (NFR)
NFR1	The system must be developed in Microsoft Excel software
NFR2	The system must have a responsive design

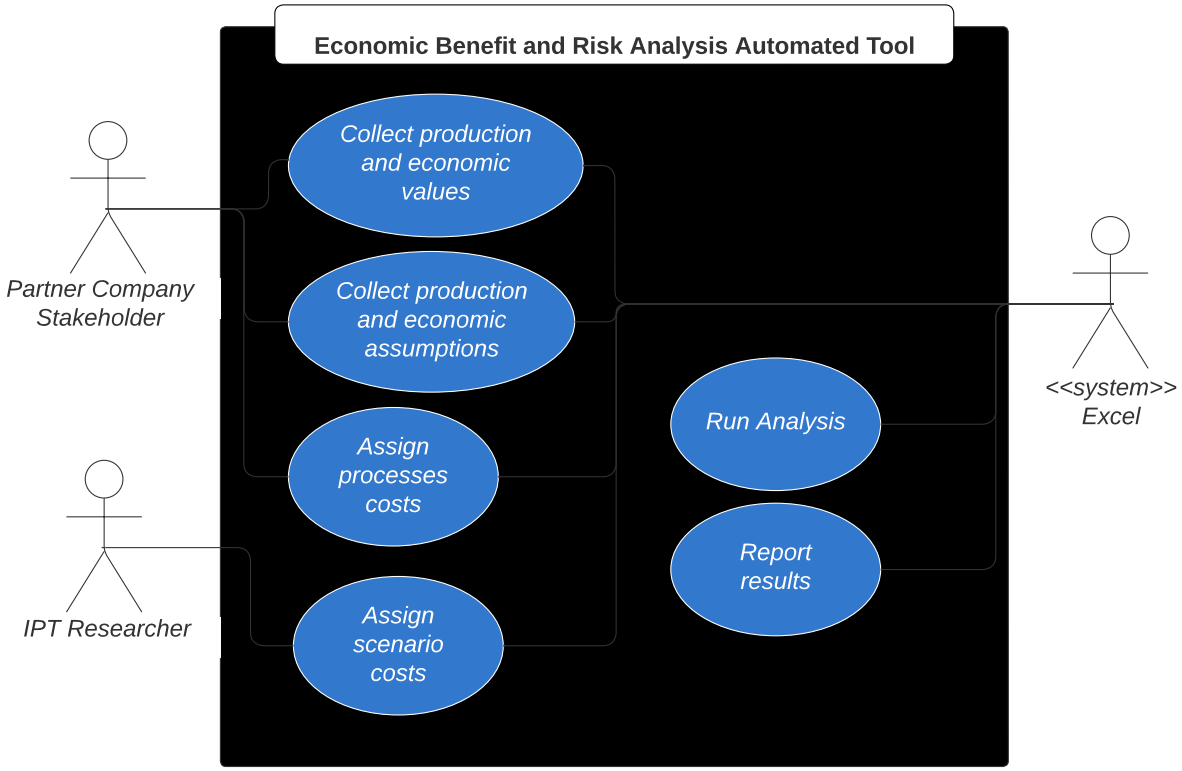
Lastly, some user experience requirements are listed in Table 9 to help the development of the visual interface of the tool.

Table 9 – User Experience requirements

ID	User Experience Requirements (UX)
UX1	All fields with limited/specific entry options should be a list drop input type
UX2	The manual input fields and the automated inputs fields should be differentiated by color
UX3	The tool must have the Fraunhofer IPT color pallet
UX4	The tool tabs should be separated with an input type logic

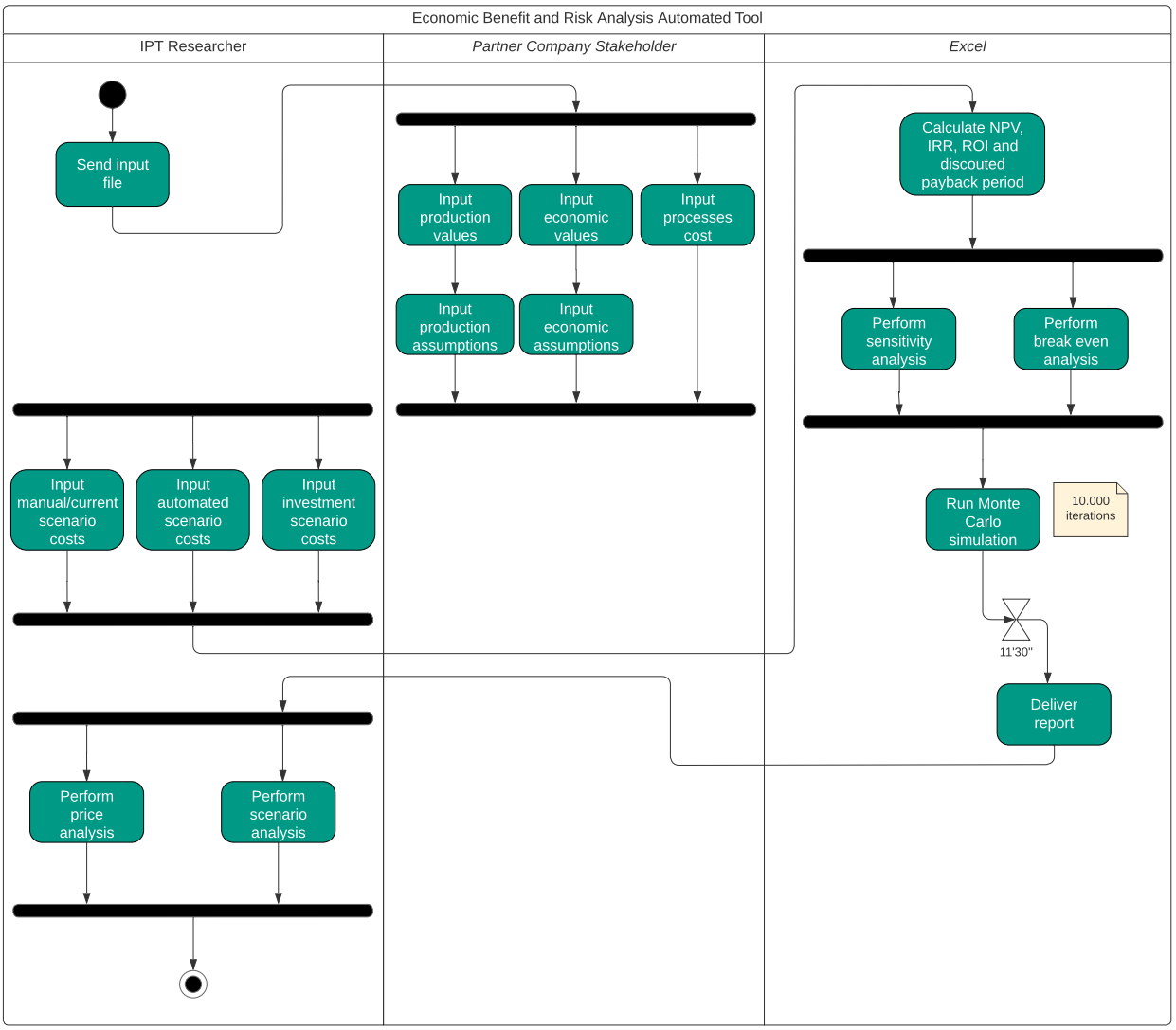
Some UML diagrams were also drawn to facilitate the understanding of the system's usability and to facilitate development. In Figure 9 can be seen the use case diagram. The actors represented in the figure identify the system users, the IPT researchers, and the partner company stakeholder, as well as the excel software where the system runs. Later, in Figure 10, the activity diagram is presented with the flow of information on the system.

Figure 9 – Use case diagram



Source: Personal Archive (2022).

Figure 10 – Activity diagram



Source: Personal Archive (2022).

4.5 BASE SOFTWARE

The Microsoft Excel software was chosen for the development of the tool for being a widely known software of easy usage and maintenance. Excel possesses the necessary functions and functionalities for the elaboration of the economic benefit and risk analysis tool, such as a user-friendly interface, possibly constructed through User Forms, the flexibility of simulations through VBA, and ease creation of visuals through graphs.

One weakness of Excel is that it does not have a built-in function that generates the random value to calculate the probability of a triangular distribution, which can be used to represent the probability distribution of some variables for the Monte Carlo simulation. Some paid software, such as @Risk (PALISADE, 2022), has this kind of

functionality.

4.6 USER FORMS

A User Form is a custom-built pop-up window that can be used to create a custom interface for Excel. This window allows to have a more user-friendly interface and to automate Excel using VBA and macros.

In this work, the User Form was used to create an interface to improve user interaction when collecting data. Without it, the user would have to go into different tabs of Excel where to put the data. The interface created is shown in Appendix B. It was created respecting the user experience requirements UX 1-4.

4.7 INCOME STATEMENT

The income statement built for this work, shown in Table 1, has as its goal to show the progress of revenue after taxes and expenses of the company in the period of 10 years. As well, the income statement calculates the revenue before taxes that is used for the free cash flow analysis.

The interest on the loan was calculated using the French amortisation system, also called Price Table. It is a method used in loan amortisation whose main characteristic is to present equal installments. It uses the compound interest to calculate the value of the installments of a loan and, from this installment, which is the value related to interest payment and which is related to the amortisation of the loan.

4.8 FREE CASH FLOW

The free cash flow, calculated using Equation (7), was used in this work to, besides showing the profitability of the company during the years, calculate the capital budgeting methods chosen for this study which are: NPV, IRR, ROI, and Discounted Payback Period.

The NPV was computed with the build-in function NPV() from Excel. This function uses a rate, in this work, the cost of capital given in the economic values inputs, the values from the cash flow from year one to ten, and discounting the initial investment.

The IRR used a built-in function as well. The IRR() function receives as input the cash flow, including the initial investment as a loss. This function works only with equal-size payment periods, as studied in this work (yearly for ten years), and it only accepts cash flows of the same sign, that is, if there is a year of loss and the others of profit, there will be more than one IRR, and the formula may result in an error. However, as explained in subsection 3.6.2, this is a problem with the IRR method as a whole, and

this thesis proposes to use more than one capital budgeting method to examine the profitability of projects.

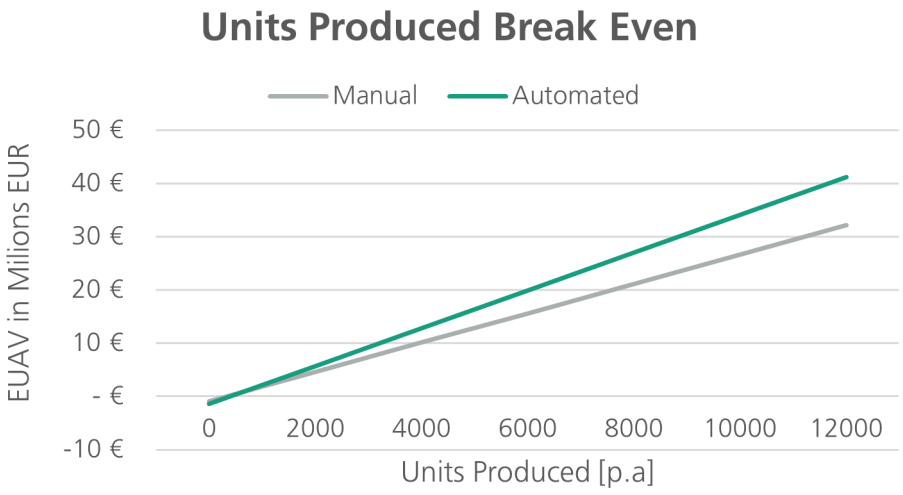
ROI, the ratio between the return and the investment, was calculated using the free cash flow where (Income before taxes + Depreciation) as the return and (CAPEX + Income taxes) as the investment.

Lastly, the discounted payback period was calculated by bringing all the free cash flow values to the present with the Excel formula PV(), using the cost of capital as the rate, and calculating the time when the return exceeds the CAPEX value or initial investment.

4.9 BREAK-EVEN ANALYSIS BETWEEN ALTERNATIVES

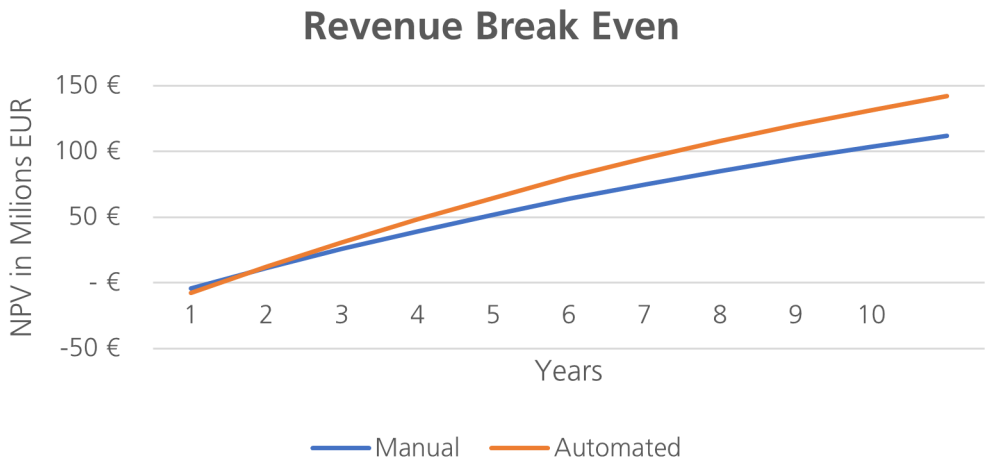
A break-even analysis can be done for a specific project as well as can be used to compare projects to determine the best of two or more alternatives. In the present work, two break even analysis between alternatives, manual scenario, and automated scenario, were carried out. The first one was based on the Equivalent Uniform Annual Value (EUAV) of each scenario, with the common variable between them being the volume of units produced. In addition, a revenue break-even analysis was executed with the common variable being the NPV and comparing the year to break even. In short, the revenue break-even is a graph representation of the discounted break-even point already calculated. Both graphs, with results for illustrative purposes only, can be seen consecutively in Figure 11 and Figure 12.

Figure 11 – Units Produced Break-Even Analysis result graphs



Source: Personal Archive (2022).

Figure 12 – Revenue Break-Even Analysis result graphs



Source: Personal Archive (2022).

4.10 PRICE ANALYSIS

Taking into consideration that the value proposition of iPSC production companies is product leadership because the product is new, different, and unique, the pricing strategy depends on the maturity of the market. As discussed in section 1.1, the iPSC was discovered in 2006, less than 20 years ago. Based on some reports, the global market for iPSC should grow from $2.8 billion in 2021 to $4.4 billion by 2026 (FAN, 2017) and compared to the global pharmaceutical manufacturing market size, which was valued at $405.52 billion in 2020 (SIZE, n.d.), we can assume to be a small market with little competition.

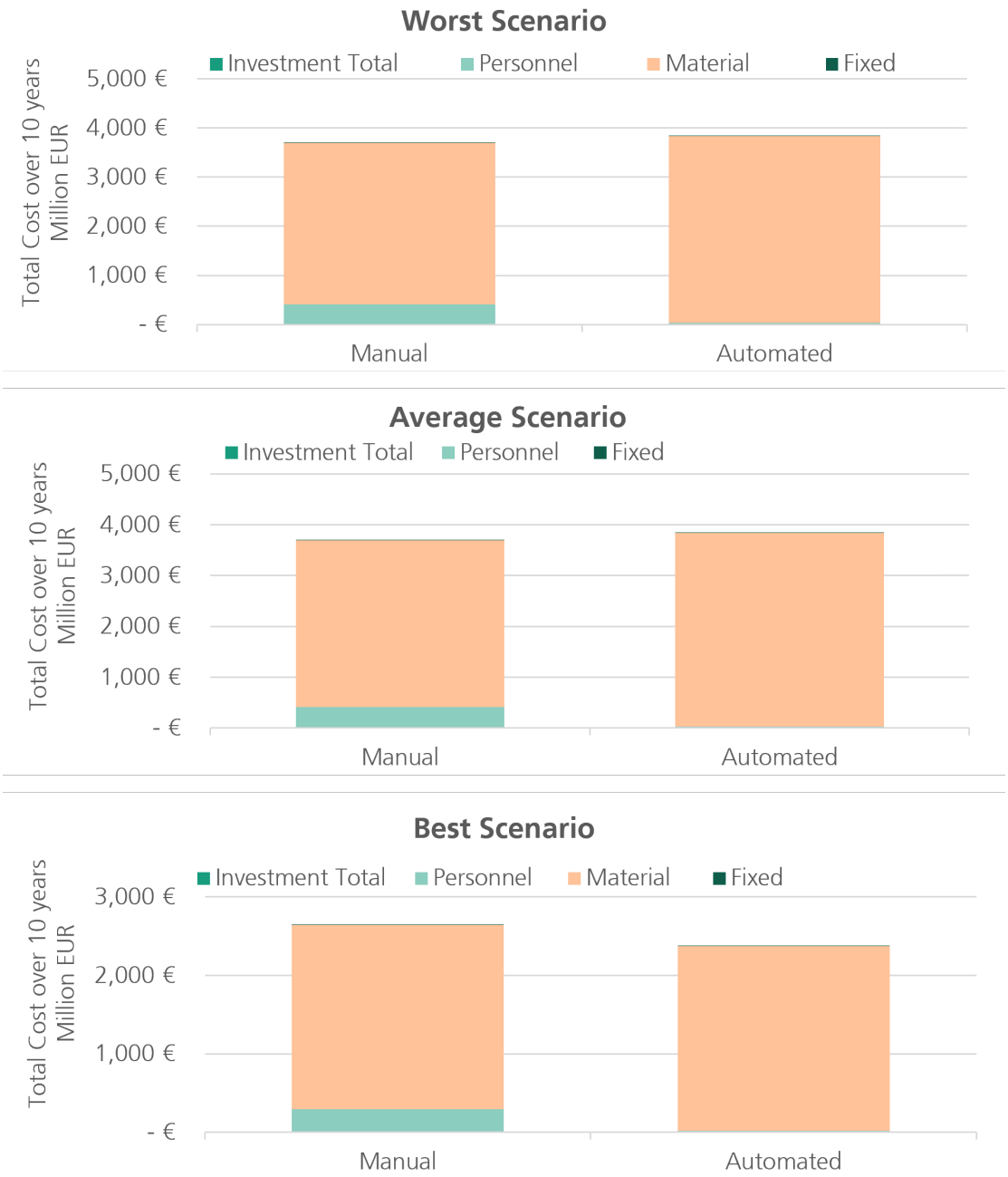
Therefore, the price analysis in this thesis considers the target price and production volume as variables in a cash flow analysis to allow the study of revenue fluctuation when those variables change separately or jointly, intending to calculate the price and volume that will maximize profit.

4.11 SCENARIO ANALYSIS

The key factor analysed in the scenario analysis was the comparison of the cost structure between the manual and automated production scenarios. To create a best, standard, and a worst-case scenario of this cost structure comparison, for the variables production volume, personnel cost, material cost, fixed cost, and CAPEX, a value for the variation in percentage must be input for each case scenario and both manual and automated scheme. As a result (Figure 13), three different graphs are

created to present the cost comparison and highlight the biggest cost driver for each case scenario.

Figure 13 – Scenario Analysis result graph



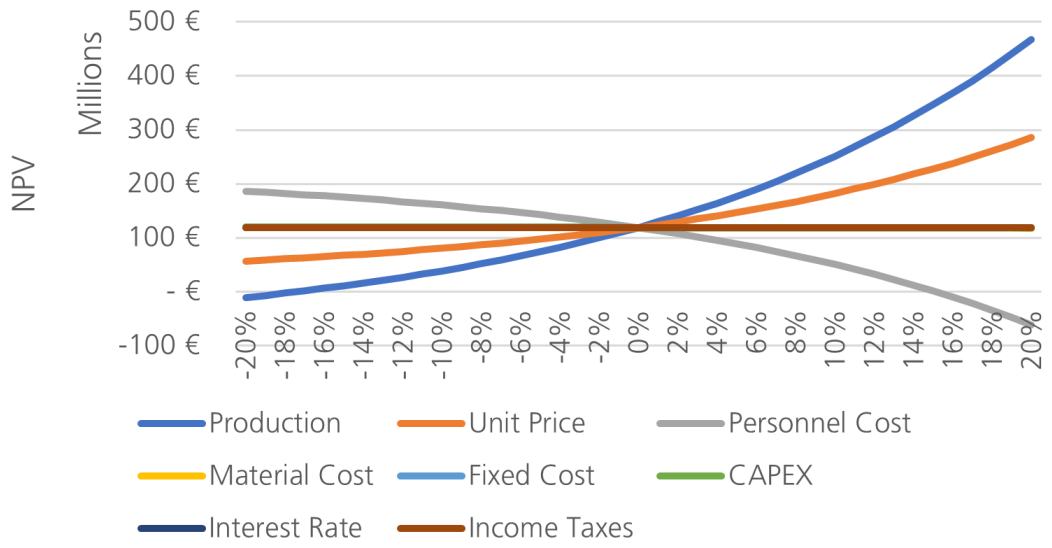
Source: Personal Archive (2022).

4.12 SENSITIVITY ANALYSIS

The sensibility analysis carried out in this work took into consideration the uncertain variables:

A cash flow is set up with these variables with open value, then they are varied in a range between -20% and 20% separately and put into the NPV calculation. The stratification of the variables was done with the help of the Data Table from the What-If Analysis tool of Excel. The result of the sensibility analysis is shown as an illustrative graph (Figure 14) with the NPV in euros on the X-axis and the percentage variation of the variables on the Y-axis.

Figure 14 – Sensitivity Analysis graph



Source: Personal Archive (2022).

4.13 MONTE CARLO SIMULATION

As requested in the user requirement UR3, the Monte Carlo simulation only took into consideration the automated scenario, and the uncertain variables considered were:

- Interest rate variation;
- Production volume;
- Target price;
- Yearly OPEX variation;
- CAPEX variation;
- Income taxes variation.

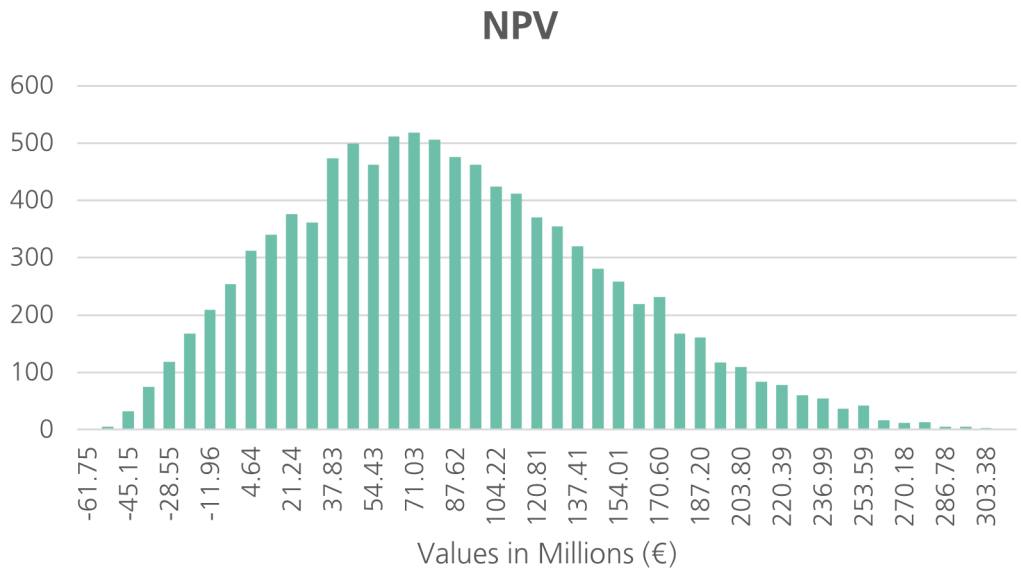
As explained in subsection 3.4.1, the inputs of the Monte Carlo simulation are probability density functions. For this reason, the uncertain variables were transformed into PDFs with the values given in the production and economic assumptions inputs and Excel formulas.

The first variable, the interest rate variation was presumed to be a normal distribution assuming an equal probability of a decrease or increase of the rate of interest starting from the expected value. The sample value used in the simulation calculation was found using the built-in Excel function NORMSINV(), which calculates the inverse of the standard normal distribution with the parameters mean and the standard deviation given.

All other variables were assumed to be triangular distributions because it is a standard distribution and is widely used in situations where little is known about the temporal behavior of the variable, as are the variables in question. Due to the lack of a triangular PDF function in Excel, the stratification of the variables was done using Equation (6) implemented as an Excel function using the minimum, average and maximum values that were input in the assumptions.

A cash flow is set up, and the NPV is calculated with the stratified variables in the Monte Carlo simulation that runs 10000 times, resulting in a PDF shown in Figure 18:

Figure 15 – Monte Carlo simulation result



Source: Personal Archive (2022).

4.14 FINAL REPORT

The final report was created to satisfy the requirements UR1, UR2, UR6, UR7, and UR9, which comprise the outputs to the partner company's stakeholders, and UX3, which comprise the outputs to be required by the partner company's stakeholders.

The final report, which can be seen in Appendix C, includes the results of the economic analysis, with the NPV, IRR, ROI, and discounted payback period, as well as the results of the break-even and sensitivity analysis and the cost comparison between scenarios. Finally, the Monte Carlo simulation results are shown.

5 TOOL VALIDATION

For the quantitative validation of the model and tool, data from the automation project of the EHM production laboratory of the partner company was used.

5.1 AUTOMATED EHM-PRODUCTION LABORATORY PROJECT

Up to now, the production of EHM has mainly been done manually. This can result in differences in product quality, scalability, reproducibility, and economic efficiency of the process and thus endanger the production process. Therefore, automated production processes can counteract this.

The automation project of the EHM cell production laboratory made in partnership between IPT and the partner company was used to validate the automated tool of economic benefit study and risk analysis developed in this thesis. Also, interviews were done with key stakeholders of IPT for qualitative validation of the tool.

5.2 PRODUCTION AUTOMATION PROJECT

The automation project of the EHM production laboratory started with the analysis of flow charts describing the manual process, then the raw materials and equipment that are used, and the general requirements were developed. The next step was to merge the workflows and select devices for each process-cluster that are suited for the automation. After defining all disposable formats, a draft of the machinery concept, including all automation steps, was designed.

Initially, the main idea was to build a modular system so that the production could be upgraded as the company grows. Although all the stations were designed to be modular, the production system could not be modular as a whole because the clean room which encompasses all stations is made to order and is not extendable. Therefore, regarding the main requirements for the automation project, the prototype production system was designed to generate up to 10.000 EHM cell lines per year in parallel, keeping the production GMP compliant. The machine includes the following main stations:

- Formulation: The initial cell is cleaned from the cryopreservation liquid to start the EHM culture.
- Medium Storage: The different kinds of mediums are stored and ready to be mixed into media.
- Mastermix: The different mediums are mixed to become media.

- Media Dispensing: The media is dispensed inside the plates where the EHM cells are cultivated.
- Sterilisation and Glove box: Entry gate for the clean room where all material that enters is sterilised and the glove box where the technicians have manual sterile access to the cells.
- Sampling: The EHM patches are sampled for quality control tests.
- Incubators: The EHM patches are in culture during the periods between media changes.
- Assembly and Packaging: The final EHM patch is transferred from the culture plate to the final package.

The main automation technologies used in this project are firstly the XPlanar (BECKHOFF, 2022), a multi-agent parallel movement robot system, that is modular and contact and dust-free. It is compatible with hygienic environments with the possibility of GMP compliance documentation and will be responsible for the movement of the plates with the EHM patty culture between the stations. Secondly, an automated incubator, with a "self-parking" system for the plates. Next, the Stäubli Sterile Clean Robot (STÄUBLI, 2022), a robot for hygienic environments in charge of the packaging station. Then, a dispensing system, controlled by a programmable logic controller, where the different media will be dispensed on the plates. Lastly, the only inline quality control that was automated in this project is the potency test, where the inherent or induced biological function of the product is confirmed. To automate this test, a camera system will record the EHM patches while medium change and a machine-learning algorithm will be used to identify the quality of the movement of the cell. This machine-learning algorithm will be developed at IPT using the GAMP protocol.

The two main challenges of the automation project are the master mix dispensation system and the packaging. The master mix station still needs validation because the different media react to each other, so the time to mix them needs to be precise to achieve the ideal quality of the final media to be dispensed in the EHM patch culture. Consequently, a viscosity and timing control must be implemented and tested. Similarly, the packaging of the EHM cell needs to be created and validated. The package must be rigid, be able to be filled with media, aseptically sealed, and proven to be aseptic inside. The research on this packaging is out of the scope of the project but needs to be done for the product to be commercialised.

5.3 ECONOMIC ANALYSIS OF EHM PRODUCTION

To compare the manual and automated production scenarios, production data, financial and economic indicators, and assumptions were gathered from the stakeholders of the company in partnership with the IPT researchers. The key production and economic values are shown in Table 10, and the key assumptions, only from the automated scenario, as the analyses by simulation are made only for this case, are shown in Table 11. All values marked with "-" are unknown to the partner company, or it was preferred not to use them, e.g., sale taxes and income taxes, resulting in an analysis less complete than the tool allows but reaching the study requested by the partner company.

Table 10 – Key values for economic analysis of manual and automated EHM production

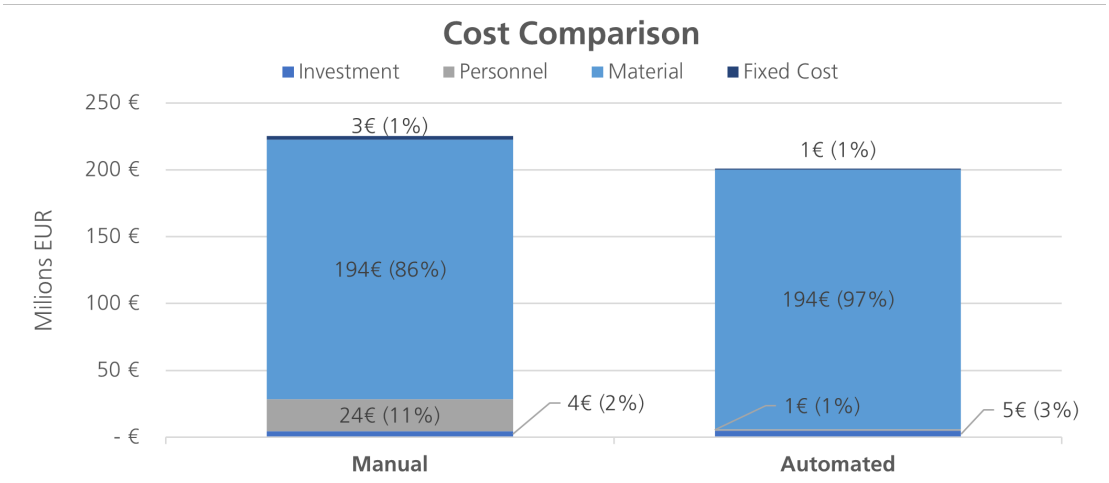
Production Values	**Unit**	**Automated**	**Manual**
Investment Cost (CAPEX)	€	4,752,005	4,365,560
Target Price per Unit	€	5,000	5,000
Annual Growth Rate of Target Price	% p.a	-	-
Personnel Cost	€	128,762	2,402,400
Annual Growth Rate of Wage	% p.a	-	-
Material Cost	€	19,415,150	19,415,150
Fixed Cost	€	72,500	257,200
Total OPEX	€	19,616,412	22,074,750
Working Days	p.a	330	330
Production Cycle Time	days	55	-
Yearly Produced/Sold Units	units p.a	10,000	10,000
Annual Growth Rate of Production	% p.a	-	-
Rejected Units due to Quality Issues	%	-	-
Depreciation Period	years	8	8
Depreciation Method	-	Linear	Linear
Economic Values	**Unit**	**Automated**	**Manual**
Cost of Capital	%	7.3	7.3
Sales Taxes	%	-	-
Income Taxes	%	-	-

Table 11 – Key assumptions for economic analysis of manual and automated EHM production

Production Assumptions	**Unit**	**Min Value**	**Expected Value**	**Max Value**
Investment Cost (CAPEX)	€	3,000,000	4,752,005	7,000,000
Target Price per Unit	€	2,000	5,000	7,000
Total OPEX per Year	€	15,000,000	19,616,412	22,000,000
Yearly Produced/Sold Units	units p.a	5,000	10,000	12,000
Economic Assumptions	**Unit**	**Min Value**	**Expected Value**	**Max Value**
Loan to Execute Project	€	-	-	-
Interest Rate	%	-	-	-
Income Taxes Variation	%	-	-	-

Figure 16 shows the cost distribution of manual and automated EHM production in the first year of production. Overall, manual production is 12% more expensive than automated production. The similarity of costs comes from the biggest cost driver for both scenarios, the material cost, and since both manual and automated produce the same EHM quantity, the cost is equal. This was already expected since the matrix cells, and the medium where they grow are expensive raw materials. Even the investment cost is similar for both scenarios, € 4.4 M for the manual scenario and € 4.8 M for the automated scenario, as the project to increase the current production to 10,000 cells per year demands an upgrade of the current production facilities with expensive devices such as Bio Safety Cabinet, incubators and the design of clean room conditions. The total cost difference is mainly from personnel cost, which is approximately 19 times higher in the manual case.

Figure 16 – Cost distribution in the first year for manual and automated EHM production



Source: Personal Archive (2022).

To calculate the revenue of the scenarios, it was taken into consideration the Overall Equipment Effectiveness (OEE) of both cases, shown in Table 12. It was used

Table 12 – Overall equipment effectiveness of automated and manual production

Level of Utilization	**Automated**	**Manual**
Theoretical Production Days [d/a]	365	365
Theoretical Production Hours per Day [h/d]	24	24
Theoretical Production Time [h/a]	8760	8760
Planned Production Days [d/a]	330	330
Non-productive Days (weekend, maintenance. . .) [d/a]	35	35
Shifts per Day [shift/d]	1	3
Hours per Shift [h/shift]	24	8
Break per Shift [h/shift]	0	1
Planned Production Time [h/a]	7920	6930
Level of Utilization [-]	90%	79%
Level of Performance		
Planned Production Time [h/a]	7920	6930
Days of no Output after Maintenance [d/a]	55	0
Actual Production Time [h/a]	7920	6930
Level of Performance [-]	83%	100%
Level of Quality		
Actual Production Time [h/a]	7920	6930
Rejected Cell Lines due to quality issues [%]	0%	0%
Actual Production Time for Good Parts [h/a]	7920	6930
Level of Quality[-]	100%	100%
OEE	75%	79%

to approximate as close as possible to reality the number of cells that will be commercialised, taking into consideration the losses due to level of utilisation, performance, and quality. The OEE of the manual scenario was 79% and of the automated scenario was 75%. The automated case shows a lower OEE because the maintenance days result in a total stop of the production for an entire cycle, resulting in a lower level of performance than the manual one.

Table 13 shows the results for both scenarios. We can see once again the importance of using more than one capital budgeting method to compare projects. In this comparison between manual production and automated production of the partner company, we can see how close the values of NPV, ROI, and IRR are, which makes a joint analysis of the three even more meaningful.

An IRR greater than the company's cost of capital, in the case of the partner company, 7.3%, can already be considered a profitable project and worth the investment. In this case, we can see that the IRR is extremely high because it is a project with a very fast return, which is proven with a discounted payback period of less than one year. Having this very high IRR and return of less than one year for both cases, the choice of the best project is up to NPV and ROI.

In this case, NPV is the method that indicates the most profitable scenario, which in this case is the automated, despite its IRR being lower. The IRR only indicates if

the alternatives are economically viable or not. Although the automated scenario has a lower IRR, the investment difference for the Manual returns 376%, while selecting the Manual the investment difference would only return the cost of capital.

Thereby, the NPV, the revenue that the project has over ten years discounting the capital cost of the automated scenario, which exceeds the manual scenario by approximately 3 million euros, shows that the automation of the laboratory, besides presenting qualitative and quantitative improvements to the production of EHM, also presents a greater economic potential than the manual production.

The ROI, which measures the amount of return on a particular investment, relative to the investment's cost, is slightly higher in the case of the automated scenario, showing that the proposed automation is more profitable relative to the investment made than the manual proposal. However, the ROI was placed in the economic benefit analysis model proposed in this work because it is a very well-known metric, but it does not take into account the passage of time, so it cannot be the only metric to define which would be the project to be followed.

Another insight from the analysis shown in Table 13 is the number of employees needed in the tenth year, taking into account the annual production growth inputs, where we can see how much more dependent on employees the manual scenario is, needing more than twice as many workers as the automated scenario.

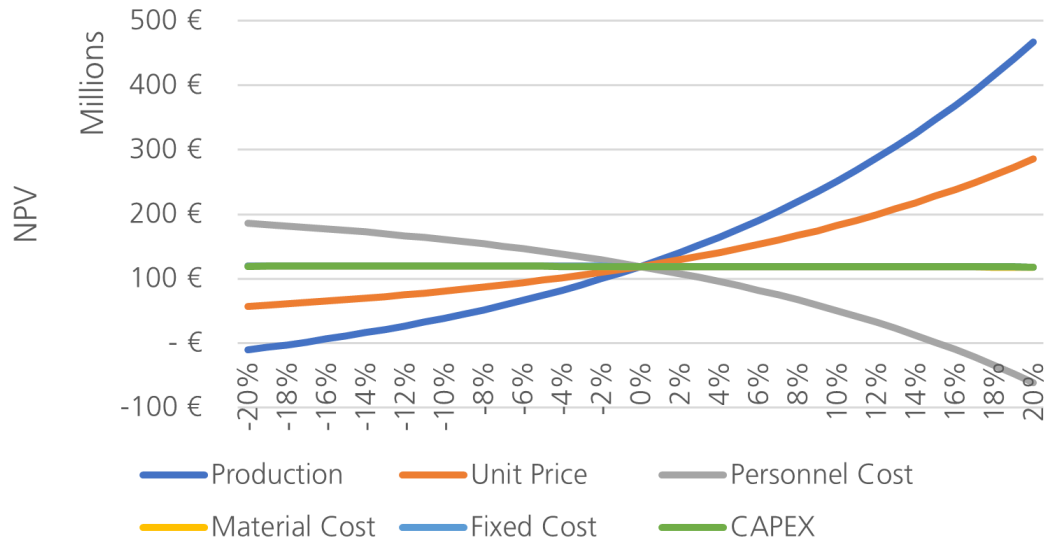
Table 13 – Economic analysis of automated and manual EHM production

	Unit	**Automated**	**Manual**
Initial Investment (CAPEX)	€	4,752,005	4,365,560
Mean costs per year	€	19,616,412	22,074,750
Mean revenue per year	€	37,500,000	39,500,000
Number of personnel in the 10th year	-	5.00	13.00
NPV	€	119,131,324	116,342,763
RoI	%	2.7	2.5
IRR	%	376	399
Discounted Payback Period	years	0.29	0.27

In addition to the economic benefit study, a risk analysis of the EHM production laboratory automation project was conducted. As shown in Figure 17, the variable with the highest impact on the NPV result of the project is the personnel cost. As in the sensitivity analysis, each variable is varied separately while the others remain constant. The analysis of automated EHM production showed that an increase of approximately 14% in personnel costs would already result in a period of loss for the company. However, statistics shown by Germany's Federal Statistical Office ((BUNDESAMT, 2022)) indicate that between 2017 and 2021, the change in labor costs is between 1.6% and 3%, meaning that the likelihood of a 14% abrupt increase in personnel costs is not considered. Therefore, we can consider the production volume as the main risk driver

of this project where a decrease of 20% in production, i.e., producing 8000 units instead of 10000 per year, would already result in a period of loss for the company. Moreover, the target price is also a variable to be monitored, but alone does not show the potential to lead to a period of loss.

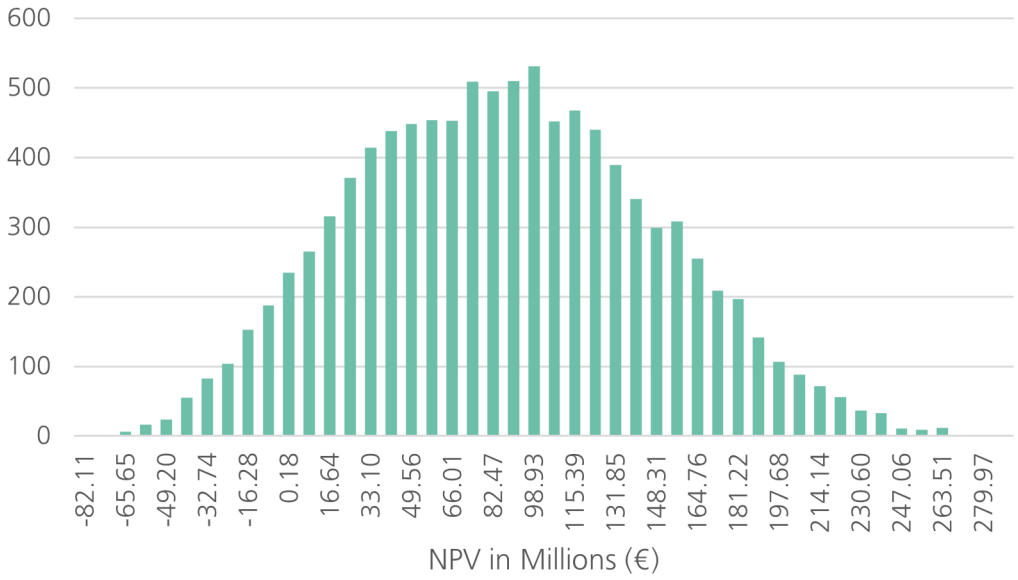
Figure 17 – Sensitivity analysis of automated EHM production



Source: Personal Archive (2022).

Finally, the results of the Monte Carlo simulation, shown in Figure 18 and Table 14, using the intervals shown in Table 11, reveal a low probability of 9% of a negative return for the EHM production automation project. In the worst-case scenario, there is a 10% probability of the project's revenue being less than or equal to approximately €4.6 million, and for the best-case scenario, there is a 10% probability of the revenue being greater than or equal to approximately €164 million. However, the highest probability is that the result is in the 80% left, with the highest probability being around the average, which for this project would be approximately €83 million of revenue. This shows us a closer approximation to the real result of the project. As well, we can see that there is a 27% probability of achieving the expected result of approximately 120 million euros of NPV.

Figure 18 – Monte Carlo Simulation of the NPV of the automated EHM production



Source: Personal Archive (2022).

Table 14 – Monte Carlo simulation of automated EHM production results

Average NPV	83,114,429 €
NPV Standard Deviation	60,640,433 €
Worst Scenario (10%)	4,607,545 €
Best Scenario (90%)	164,248,327 €
Probability of a negative NPV	9%

5.4 FINAL USER INTERVIEW

At last, an in-depth, standardised, open-ended interview was used to evaluate the work from a qualitative point of view. The interview was conducted with three IPT researchers. Two of them, the main stakeholders of the tool and the end-users, are research fellows from the automation and bioscience department at IPT, and the third interviewee is the group leader of this department, who was also responsible for the economic benefit analysis done for the StemCellFactory project published in (NIESSING et al., 2021). For the analysis, they will be called researcher 1, researcher 2, and researcher 3, respectively.

The type of interview, in-depth, standardised, and open-ended, was chosen because it is structured as a conversation between researcher and interviewee asking the same questions, therefore, facilitating a faster interview that can be more easily

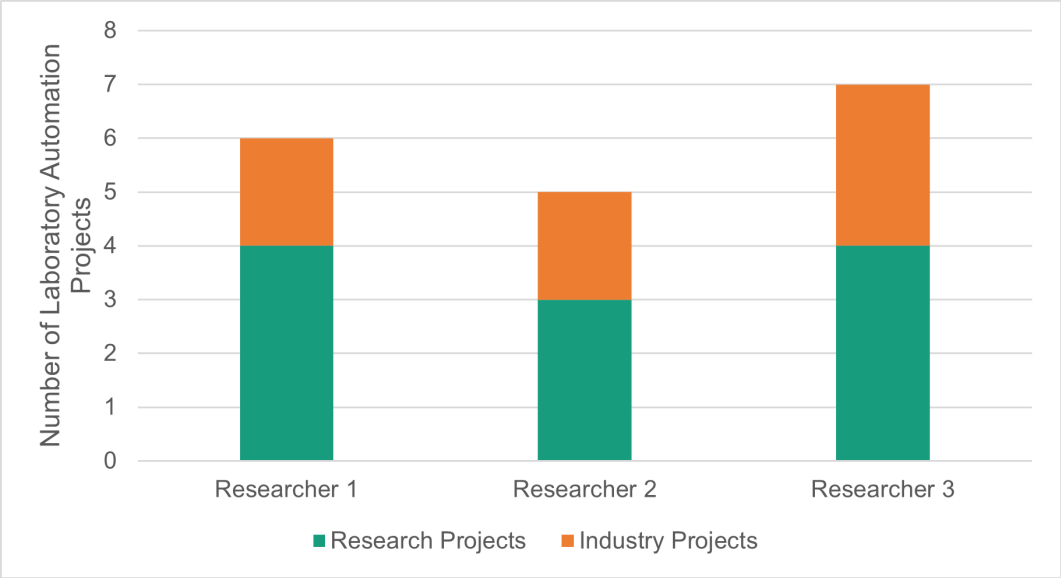
analysed and compared. Before the interview, the tool was fully presented to the interviewees in a standardised way to make sure that everyone had the same knowledge of all the functionalities that were developed and how the tool should be used.

The questions asked are listed below:

1. "How many projects of laboratory automation were you part of here in IPT?"
2. "How many projects of this kind are foreseen to happen of projects in the near future?"
3. "In general, how would you describe how the economic benefit and risk analysis of laboratory automation projects was done in IPT before this project started?"
4. "After having been introduced to the tool, how do you think it will be useful during your work on laboratory automation projects?"
5. "Do you think there is something to improve in the tool or something that it does not fulfill as requested?"

As shown in Figure 19, IPT is still starting in the area of consulting projects for laboratory automation, where its greatest experience so far has been with research projects. The interviewee, researcher 3, with the biggest participation in automation projects by IPT, participated in a total of seven projects, four in research and three with industry. However, for the near future, the researchers emphasised that the goal is to increase this field of action as much as possible, with a target of close to ten new projects with industry in the next two years. It was pointed out by researcher 2 that the goal is to create automation platforms that will help expand even to other types of biotech labs, going beyond those that produce iPSC.

Figure 19 – Interviewees' participation in laboratory automation projects at IPT

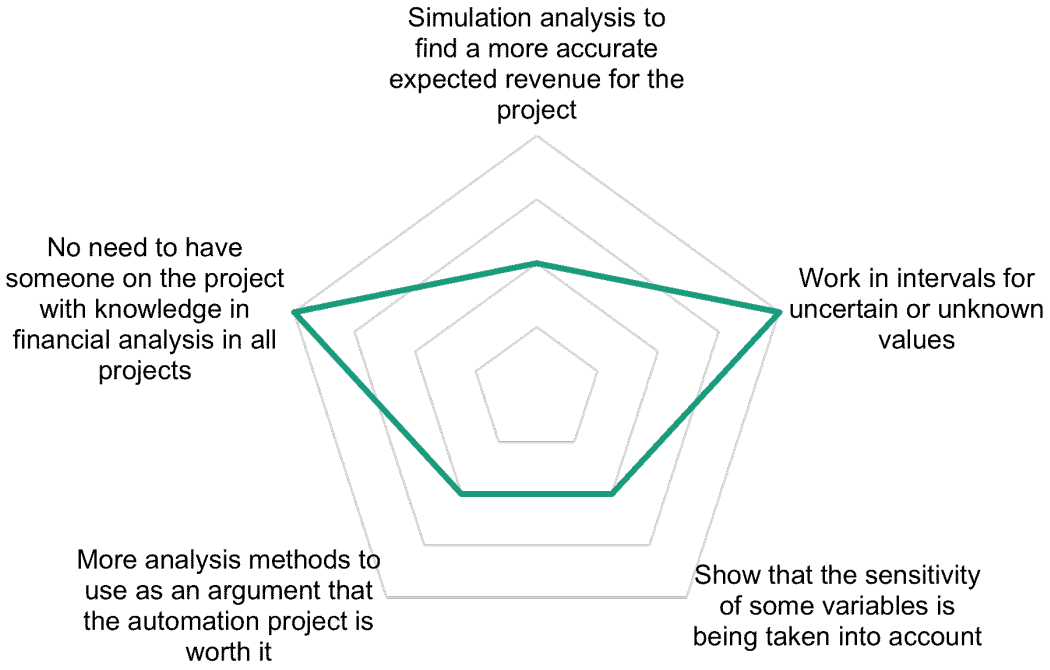


Source: Personal Archive (2022).

To reach this expansion goal, where the major focus is on projects with the industry, a standard economic benefit study and risk analysis of these projects become even more essential. It was pointed out by the researchers that before this work, there was no economic benefit analysis that studied the profitability of the automation of the laboratories. This is because most of the projects were for the purpose of research on the optimisation of automation and not for the purpose of studying how profitable the projects were. Researcher 2 highlighted that the only analysis was the cost of the investment. On top of that, the researcher Researcher 3, responsible for the economic benefit study of the StemCellFactory project, pointed out that his study was based on a master thesis conducted inside the IPT, the only work on the area of profitability analysis of one of the research projects, but yet not involving real data from the industry.

After the presentation of the tool, all the interviewees showed great enthusiasm for the result of the work. IPT's goal of expanding the area of laboratory automation projects to the industry was once again emphasised, leading to the need for a standard economic analysis for them, which the researchers believe will be solved with the use of the model and tool developed in this work. Some of the key benefits that were cited by interviewees can be seen in Figure 20.

Figure 20 – Main benefits of the model and tool developed in this work by IPT researchers



Source: Personal Archive (2022).

The two most quoted were that the tool will allow the data to be analysed in intervals for the simulations, bringing a closer approximation to reality, whereas in most projects, neither the researchers nor the companies have all the exact values. The other point made by the three researchers is that projects like this require experts in the field of automation, and often these people do not have much knowledge in the field of economics. Therefore, now that the projects are going to demand this knowledge, it would always be necessary a new person in the project team to conduct the economic analysis, or the workload of the automation researchers would increase. Therefore, the tool will be of great use and help so the researchers can focus on their area of expertise.

Most of the points for improvement commented by the interviewees are related to the amount of data needed for the analyses. It was emphasised that, even if the model and the tool were built to make an in-depth analysis of the economic benefit and risk of the projects, it would be difficult to collect as much data from the companies, such as tax data and wage growth rates. This is because the current partner companies are leaving the research area to enter the market and do not yet have this information.

Another great point of improvement of the tool mentioned is the non-consideration of inflation. Even though the tool considers an annual wage increase rate and a unit

price growth rate, it does not consider any increase rate for the other costs. Even if before the inflation in Germany could be considered stable, we see that in times of economic instability as we are experiencing, it is extremely necessary to consider the inflation on prices, especially in the cost of materials. And even being considered stable, for long-term projects, as in the case of the one regarded in this work which considers a ten-year life cycle, inflation has an impact and should be considered.

Lastly, another improvement that can be made in the tool is the lack of an analysis of the optimisation potential that the automation of the laboratory will bring. In the analysis that was proposed, both the automated and manual production scenarios, when producing the same amount of units, have equal material costs. This is not always true in reality. Many times, the automation of the laboratory leads to less material waste which can be transformed into a better performance indicator for the automated scenario, which can be used as an argument to justify the project.

6 CONCLUSION

To meet the lack of standard economic benefit study and risk analysis for laboratory automation projects within the IPT research institute and thus reduce the workload of researchers, an automated tool was created in this work. The tool is based on a new model that fills the gap in the literature on economic benefit analysis and risk analysis of automation projects in stem cell production laboratories, meeting the objectives described in section 1.2 and comprising the features and requirements listed in section 4.4.

As a result of a literature survey, it was observed that no economic benefit and risk analysis model for automation projects of stem cell production had been created so far. Some studies from this kind of project show the use of capital budgeting methods individually, with no structured methodology. Besides, few works take into consideration risk analysis.

To address the first problem, the model presented in this paper uses four capital budgeting methods together the NPV, IRR, ROI, and discounted payback period. For the second gap left by the literature, the application of sensitivity analysis of uncertain variables and Monte Carlo simulation were used as risk analysis in the proposed model. Sensitivity analysis helps to understand which variables should be treated with more care because their variations have a great impact on the financial results of the project. Equally important, the Monte Carlo simulation shows an estimation closer to the reality of the project profitability, helping to measure the investment risk.

The automated tool developed based on the proposed model was validated through an EHM production laboratory automation project. The data was collected with the partner company and inserted into the tool by the IPT researchers. The use of multiple methods was proven to be very positive and necessary during the validation of the model, where the comparison between a manual and automated production scenario led to very similar economic results, making each of the capital budgeting methods important to the decision-making process.

Moreover, the sensitivity analysis method pointed out the uncertainty variables production volume and personnel cost as two project risk variables, where a small-scale variations could result in a negative economic outcome. Finally, the Monte Carlo simulation improved significantly the quality of the decision showing that the probability of the NPV of the automation project being around 120 million euros, as expected by the static analysis, is 27%, a good chance, but already making it clear that the real value is likely to be lower. Furthermore, it reaffirmed how favorable the project is, with a chance of loss of only 9%.

To conclude, the model was well accepted by the IPT researchers as it proved to be well structured and easy to understand. On top of that, the automated tool developed

in Excel, in combination with VBA and User Forms, showed that it will be very useful in future projects of laboratory automation within IPT, fulfilling the role of standardising the study of economic benefit and risk analysis with high accessibility, enabling new improvements and maintenance.

6.1 FUTURE IMPROVEMENTS

Although the currently developed tool meets all the requirements and has proven to fulfill its role, a future perspective of the presented work and possible improvements could be to transfer the data to be stored in variables inside the VBA, reducing the use of Excel's primary memory and optimizing the application. For example, currently, the Monte Carlo simulation processing time is around 12 seconds because the result of 10000 iterations is saved in Excel cells. It is believed that this time can be drastically reduced just by changing to save the results in a variable instead of the memory.

To finalize, as commented by the IPT's researchers, stakeholders of the project, during the qualitative validation interviews, inflation should be included in the analysis. This is due to the fact that the analysis considers a ten-year project life cycle, which, even with low inflation, has an impact that must be considered. And also, for moments of economic instability, such as the one that is being experienced nowadays, inflation can have a great impact, mainly on the costs. Another point to be developed in the tool is the creation of an optimisation potential indicator, making it possible to compare, for example, how much less material is being spent to produce the same quantity of units when automating the production.

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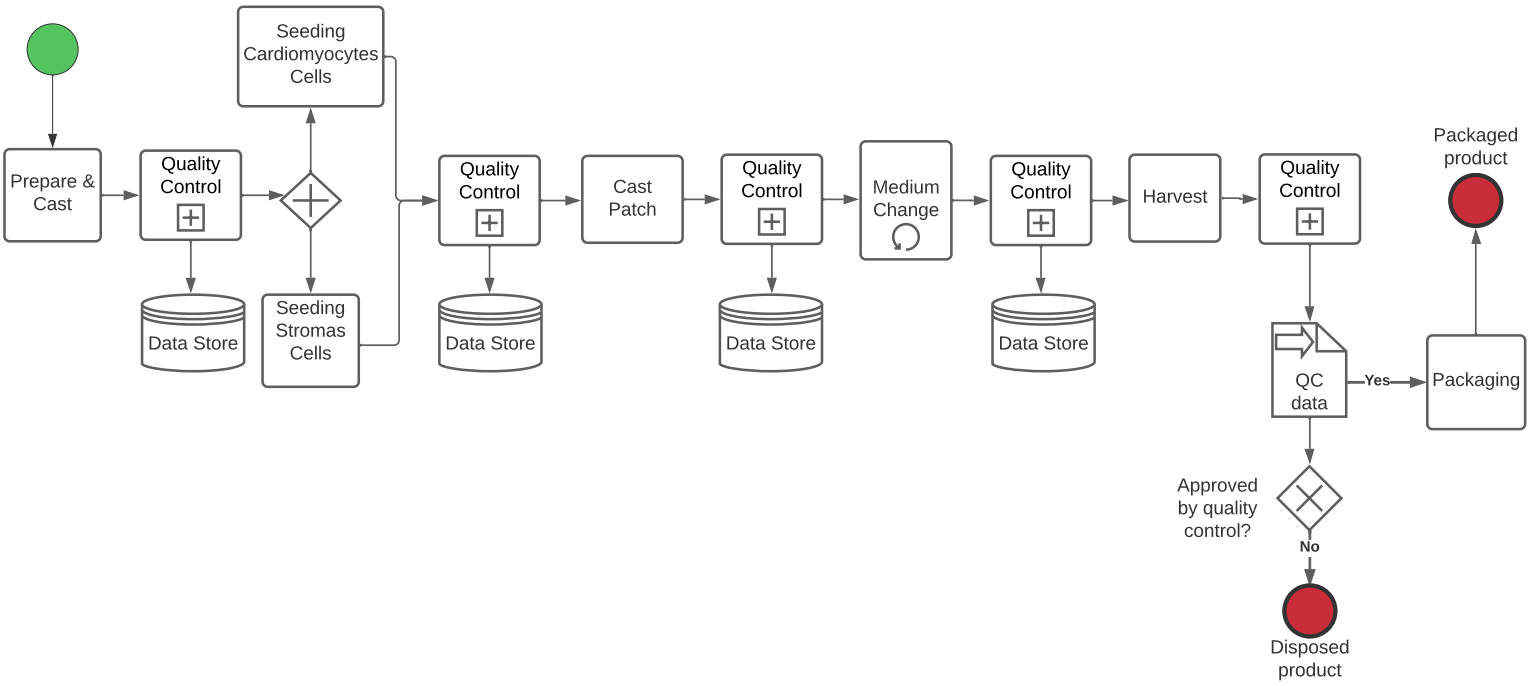
APPENDIX A – EHM PRODUCTION PROCESS



APPENDIX B – USER FORMS

Figure 21 – Initial User Form page screenshot

Figure 22 – Input Values/ Production Values User Form page screenshot

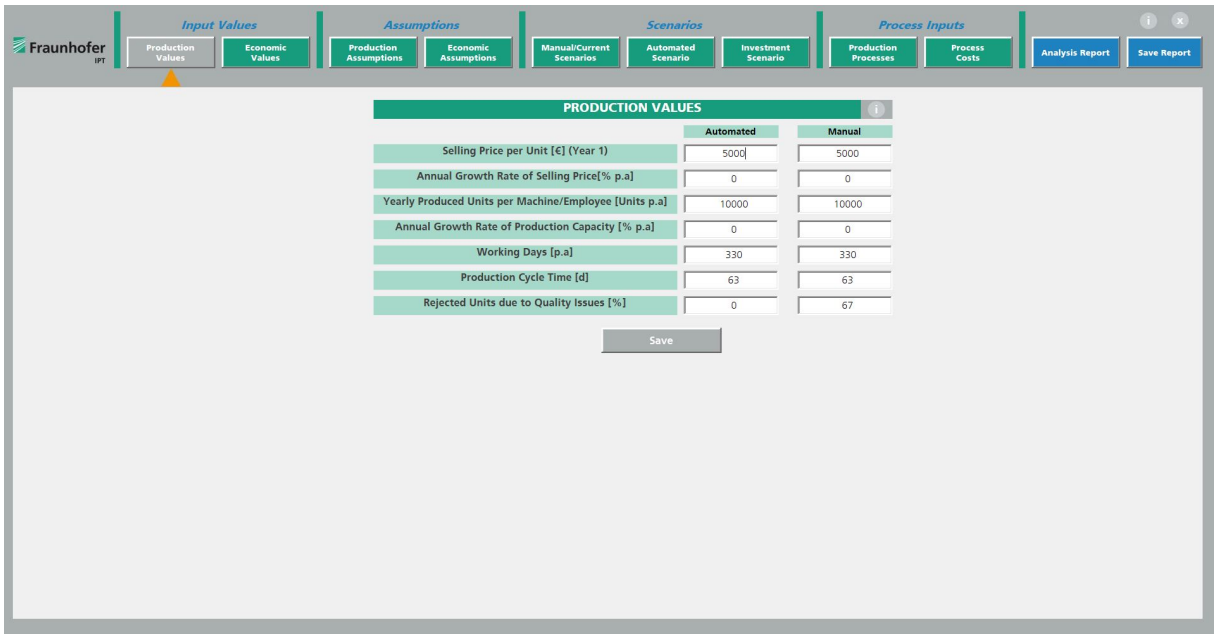


Figure 23 – Input Values/ Economic Values User Form page screenshot

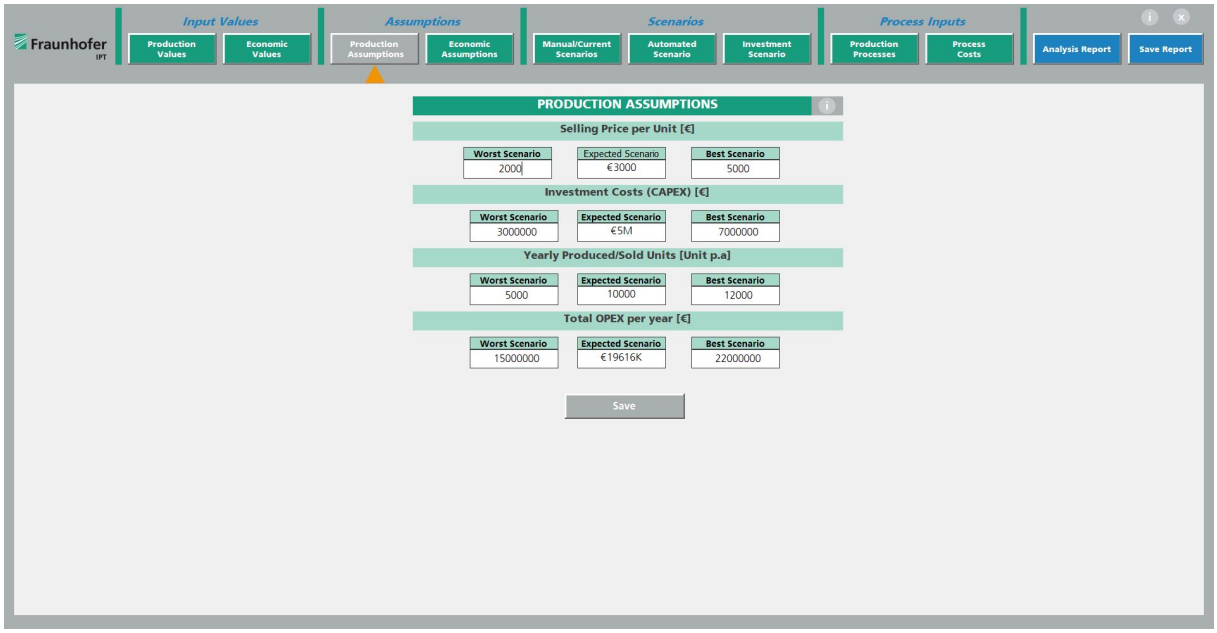


Figure 24 – Assumptions/ Production Assumptions User Form page screenshot

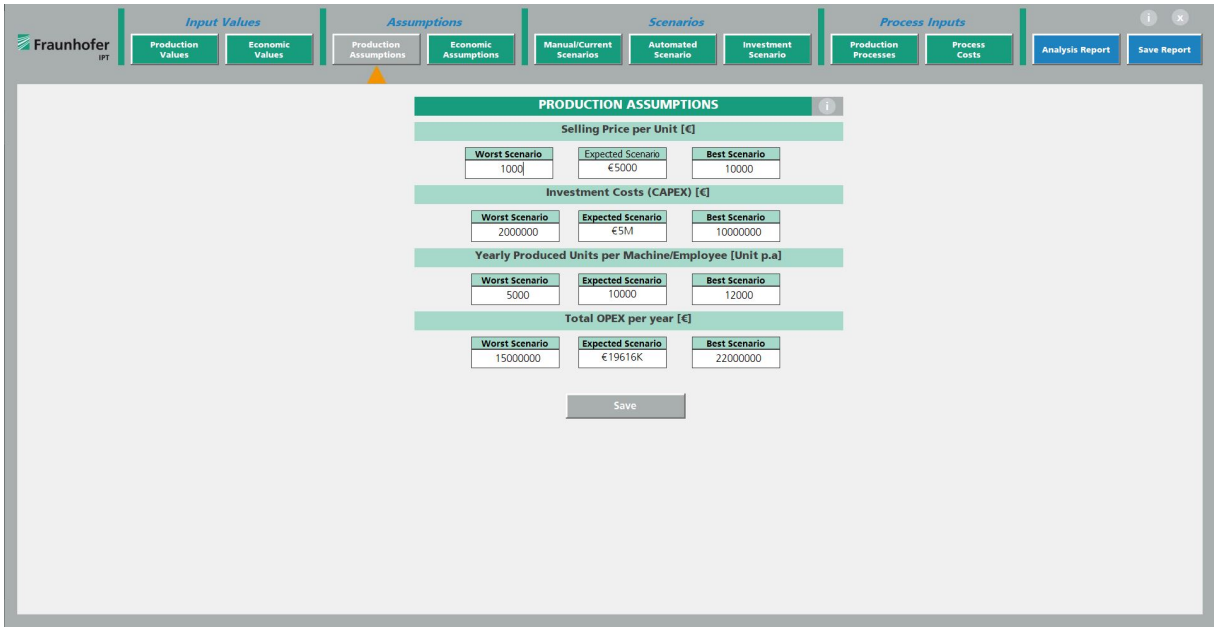


Figure 25 – Assumptions/ Economic Assumptions User Form page screenshot

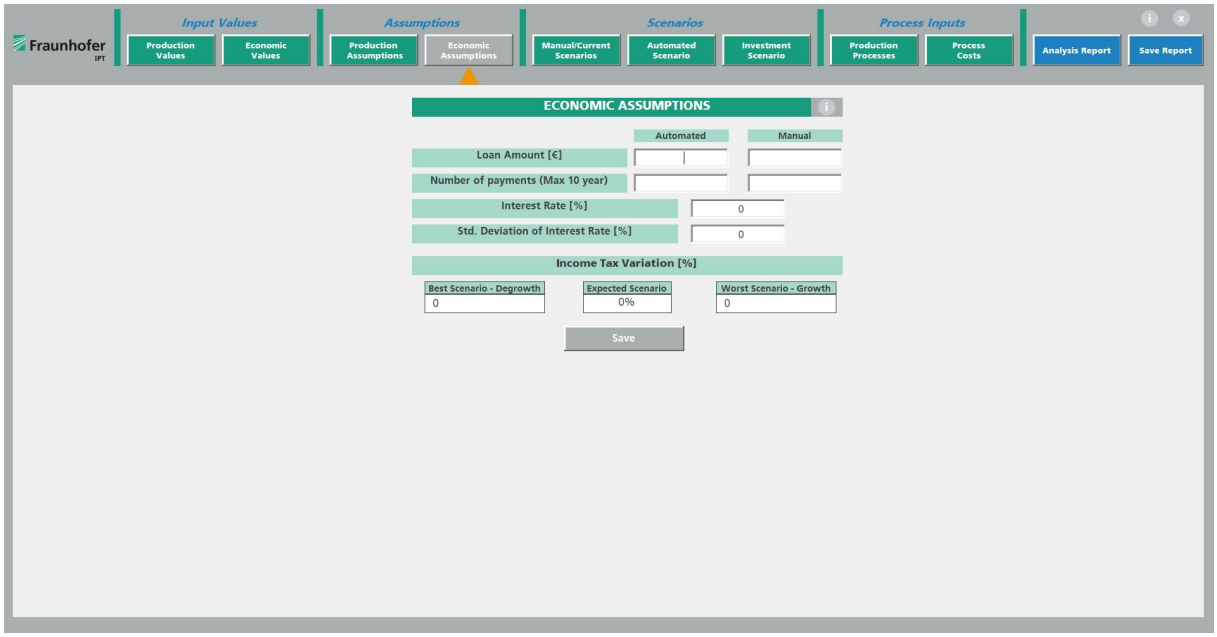


Figure 26 – Scenarios/ Manual/Current Scenario User Form page screenshot

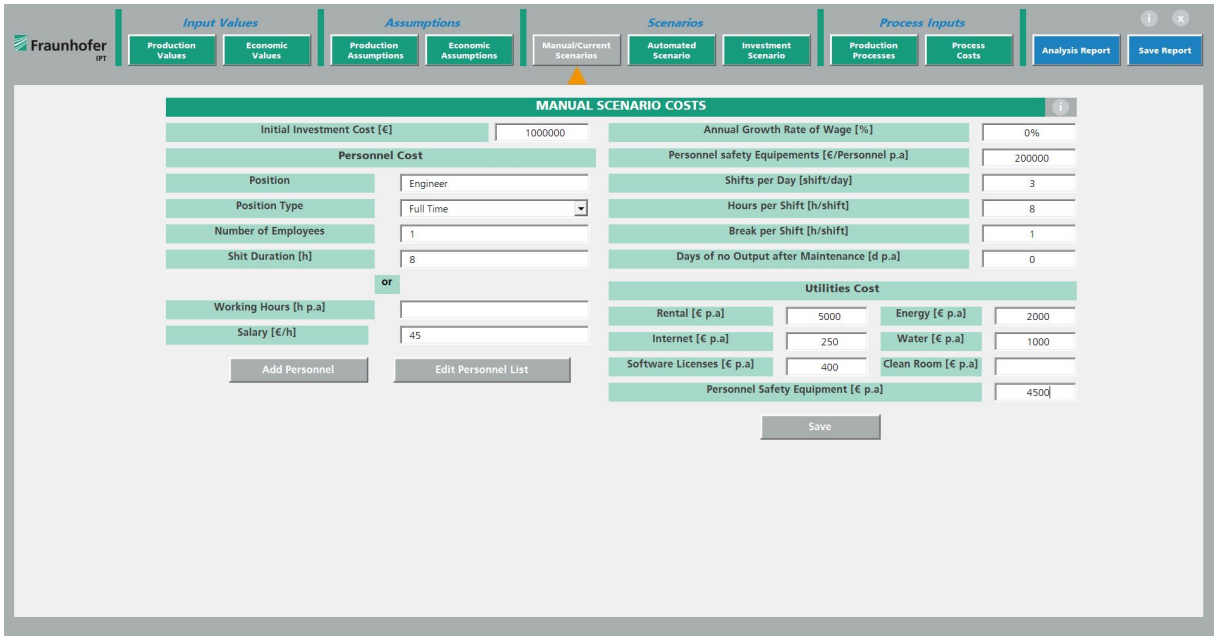


Figure 27 – Scenarios/ Automated Scenario User Form page screenshot

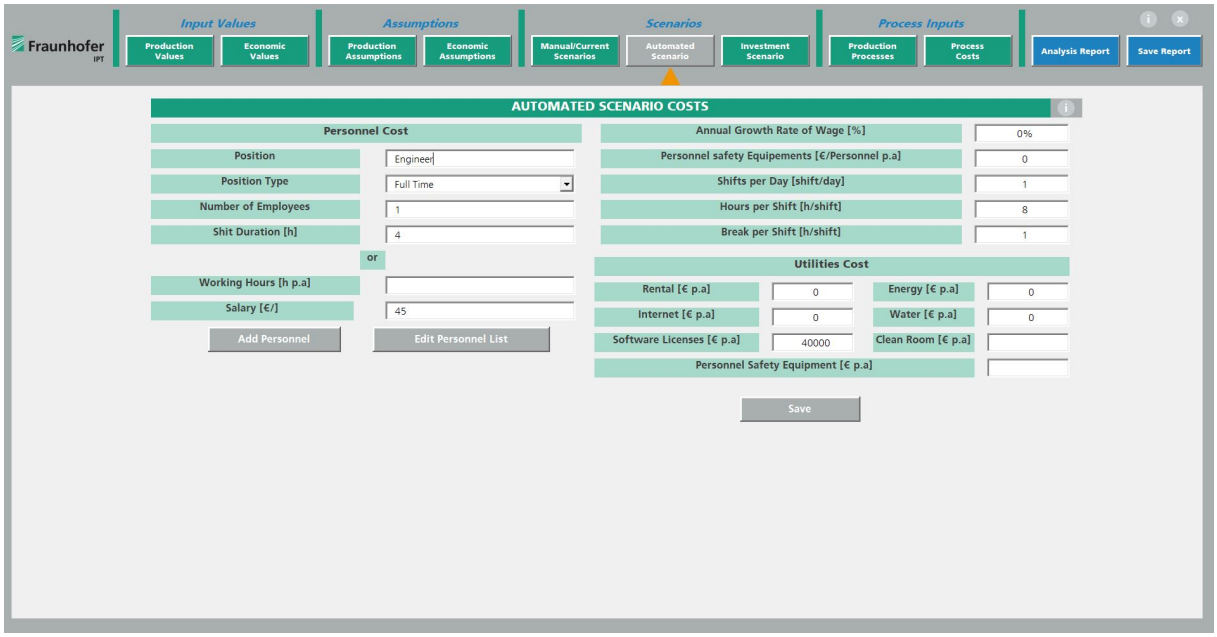


Figure 28 – Scenarios/ Investment Scenario User Form page screenshot

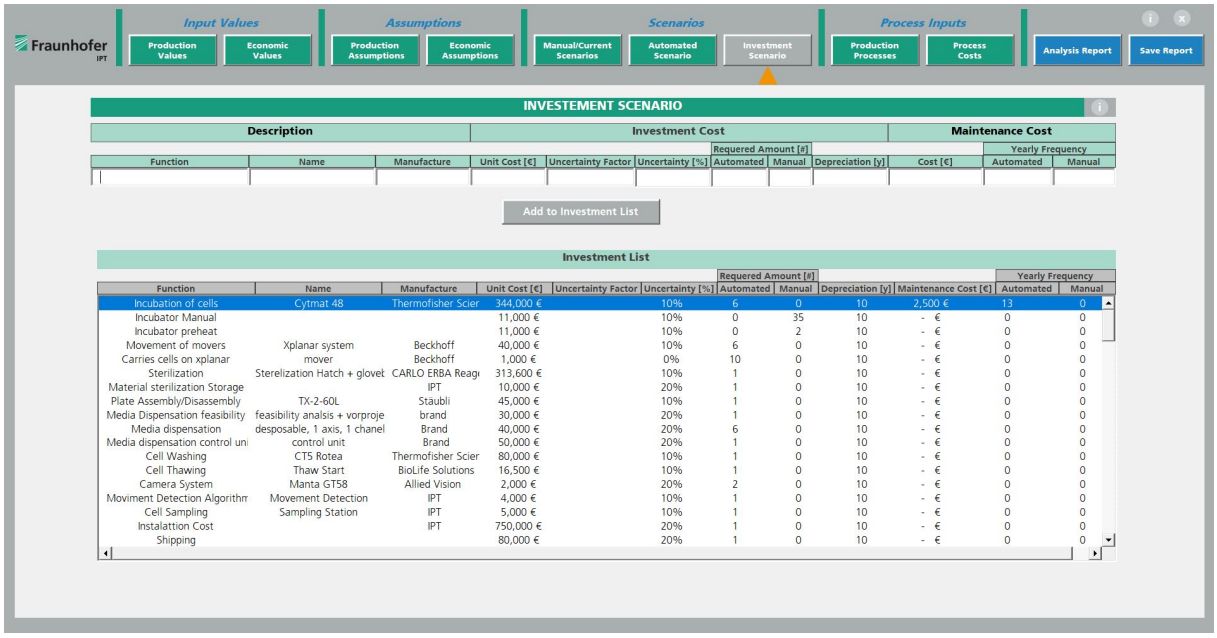


Figure 29 – Process Inputs/ Production Processes User Form page screenshot

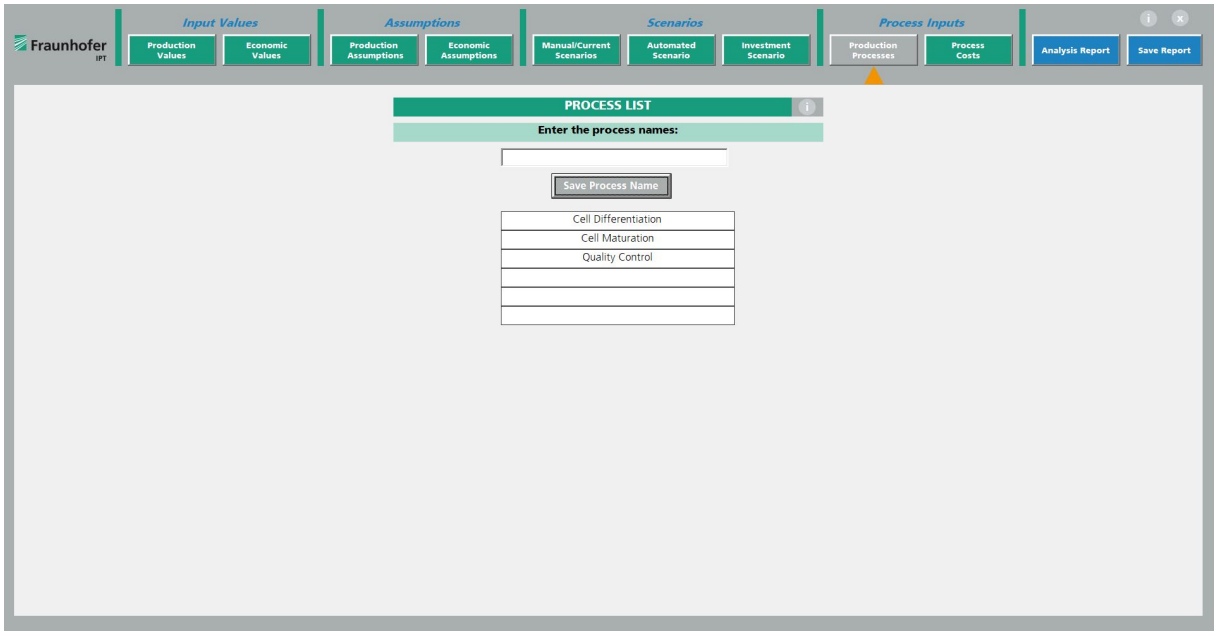
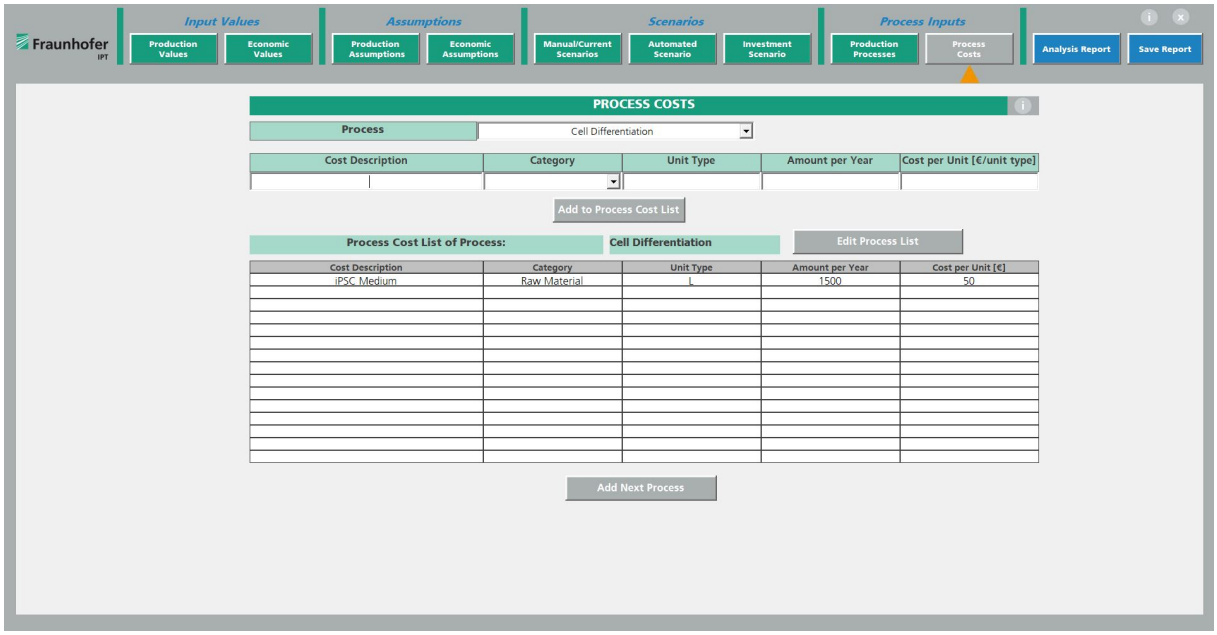


Figure 30 – Process Inputs/ Process Costs User Form page screenshot



APPENDIX C – FINAL REPORT

Fraunhofer IPT

Economic Analysis Results

Static Analysis over 10 years

	Automated	Manual
Initial Investment	4,752,005 €	4,365,560 €
Mean Costs per Year	- 19,616,412 €	- 22,074,750 €
Mean Revenue per Year	37,500,000 €	39,500,000 €
Number of employees*	5.00	13.00
NPV	119,131,324 €	116,342,763 €
ROI	2.7%	2.5%
IRR	376%	399%
Discounted Payback Period	0.29	0.27

*on the 10th year

Net Present Value (NPV)

NPV determine the present value of an investment's future cash flows above the investment's initial cost.

Automated	Manual
119,131,324 €	116,342,763 €

How to interprete? *If NPV is greater than 0, the investment is profitable.*

How to decide? *If both NPV are greater than 0, choose the investment with the higher NPV.*

Return on Investiment (RoI)

RoI measures the amount of return on the investiment relative to the cost.

Automated	Manual
2.7%	2.5%

How to interprete? *If ROI is greater than 0, the investment returns a profit.*

How to decide? *If both ROI are higher than 0, choose the investment with the higher ROI.*

Intern Rate of Return (IRR)

IRR is the annual rate of growth that an investment is expected to generate.

Automated	Manual
376%	399%

How to interprete? *If IRR is bigger than the cost of capital, the investment is worthwhile.*

How to decide? *If both IRR are greater than the cost of capital, choose the investment with the higher IRR.*

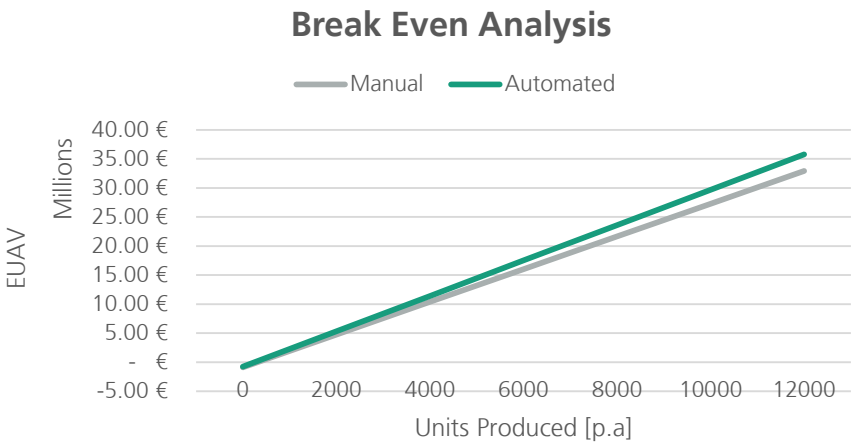
Discounted Payback Period

Discounted payback period gives the number of years it takes to break even recognizing the time value of money.

Automated	Manual
0.29	0.27

How to interprete? *The payback period shows how many year it will take to start making a profit after paying the investment.*

How to decide? *Choose the Investment with the smallest payback period.*



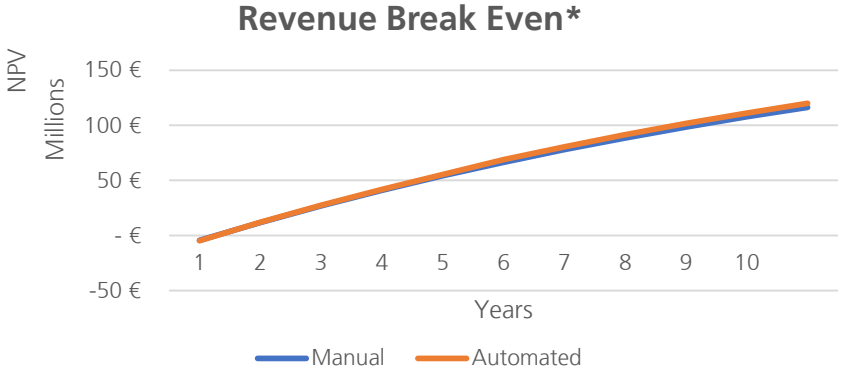
Break Even Analysis

Break even analysis uses the Equivalent Uniform Annual Value (EUAV) as a annual uniform representation of revenue.

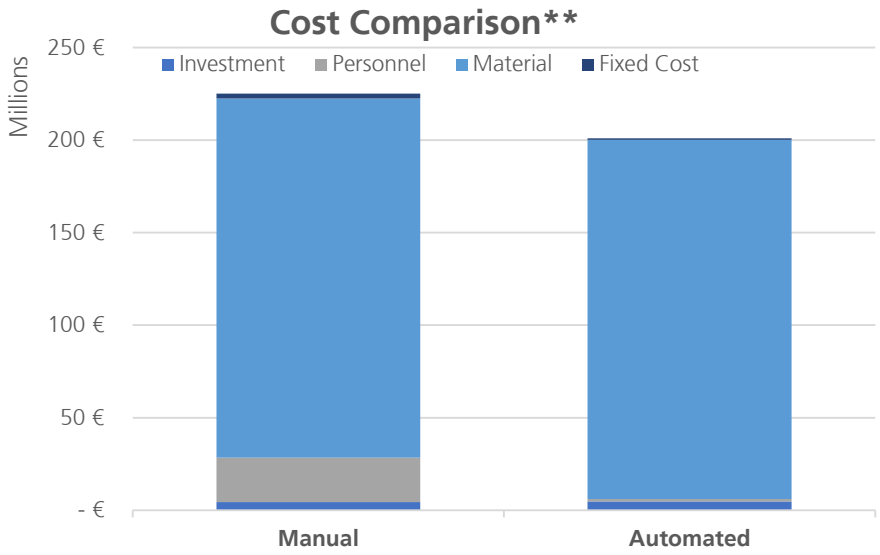
Break Even Point	< 0 Units

How to interprete? *One of the scenario will always be more profitable than the other, unless at the break even point, when both have the same profitability.*

How to decide? Choose the most profitable *scenario on the range of production scale you want to operate.*



*Constant production volume of 10000 units



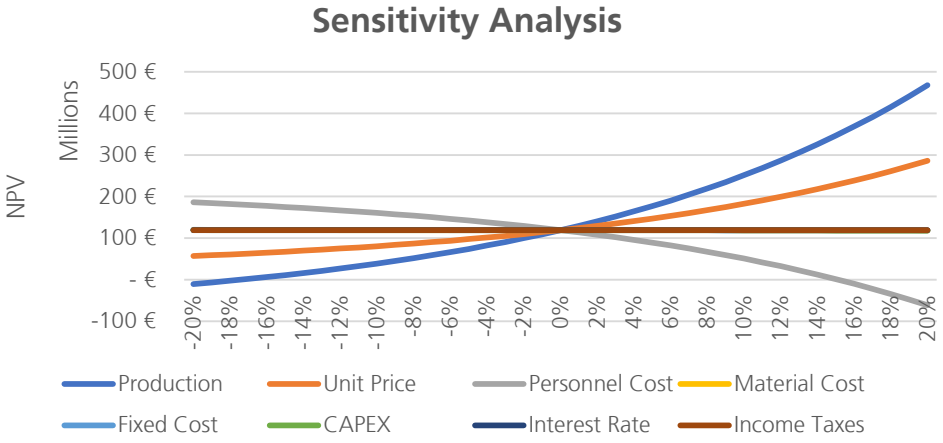
Total	225,113,060 €	200,916,120 €
Investment	1.9%	2.4%
Personnel	10.7%	0.6%
Material	86.2%	96.6%
Fixed	1.1%	0.4%

**Total in 10 year

Sensitivity Analysis

Sensitivity analysis, also referred to as a what-if analysis, study how various sources of uncertainty* in the profitabilty model contribute to the model's overall uncertainty.

How to interprete? *The "What-If" question is: "What would happen to the profitability of the project If one of our uncertainty variables went up or down in a range of 20%?". The variable(s) that have a bigger impact, i.e. results in a larger NPV fluctuation when varied between -20% and 20%., are the most sensitive and most worrying for the project.*



*Uncertain variables of the model: Income tax variation, Interest rate, Production volume per year, Unit sales price, Investment cost and OPEX per year.

The value range of the uncertain variables is a input of the model

Simulation Analysis

Average NPV	83,114,429 €
NPV Standard Deviation	60,640,433 €
Worst Scenario (10%)	4,607,545 €
Best Scenario (90%)	164,248,327 €
Probability of a negative NPV	8.65%

Monte Carlo Simulation

Monte Carlo simulation was used to predict the probability of different outcomes of NPV taking into consideration uncertain variables* into its projection.

How to interprete? *The simulation returns a probability distribution of NPV where the average NPV is 83M € with a standard deviation of 61M € .*

We consider the probability of 10% of the results as the worst scenario possible to happen and the probability of 90% as the best scenario because the beginning and the tail of the distribution is rarefied and liable to be disregarded.