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Reference Model and Methodology to Design Sensing, Smart, and Sustainable Medical Devices

A thesis presented by

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Dedication

To my family, principally my grandparents Eugenia Sandoval and Jorge Olivares, who received me in their arms in times of need and always encouraged me to succeed. Thanks for all your unconditional confidence, support, patience and delicious food. You were my main upkeep for pushing through this work. I thank to my uncle and aunt, who spend quality time with me, especially this last 2 years.

To Alejandra Vega, my principal motivation and partner in this last steep of a journey now to be concluded; whose intelligence and knowledge potentiated the speed of a part of the project. And Kin Gutiérrez that despite being difficult, kept a precise guiding direction, also Stef that is always motivating and helping when in handy. To my mother Nicté Olivares, that even though not being the best effort tried to go through every challenge.

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To the CONACyT who lead and motivate national Research and Development, with government and resource management. Because of institutions like those mentioned, there is still a spark of hope in the national technological and scientific landscape.

Abstract

Recognizing the importance of health care, the dissertation presents the instantiation of a reference model and methodology to design the Sensing, Smart, and Sustainable (S^3) medical devices. The concept of Sensing Smart, and Sustainable is presented as a concept that satisfies the requirements of the new products, aligned with the trends of the Fourth Industrial Revolution (I4.0). New medical devices must be intelligent, patient-focused, flexible to world health changes, data-driven in order to support in the decision-making process such as diagnosis, connected and socioeconomically and environmentally sustainable. Although the integration gap between Life Cycle Engineering (LCE) and Health care is evident; models and methodologies currently applied in LCE can be turned over to medical devices. Moreover, the lack of health policy and management expertise in many countries has impeded progress in building sustainable medical devices. Hence, the intention of the presented project is to enable a model to guide the ideation, design and development of medical devices using the life cycle engineering principles. To support the medical devices development, an instantiated reference model and methodology is proposed based on the Integrated Product, Process and Manufacturing system Development (IPPMD); along with the best practices from World Health Organization (WHO) Research and Development Blue Print and the Biodesign The Process of Innovating Medical Technologies from Cambridge University. The reference model is applied in a case of study: through the application of the IPPMD in the development of an Analogous CPAP for COVID-19 ICU patients. Analysis of the results found the conclusion to further work on the IPPMD reference model and methodology to design the (S^3) Medical Devices.

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Chapter 1

Introduction

The concept of Industry 4.0 (I4.0) arises as the integration of technologies of the last four decades, such as Cyber-Physical Systems (CPS), Internet of Things, Cloud Computing, Artificial Intelligence; among others [1]. Countries as Germany have posed schemes like the High-Tech Strategy 2020 of Fig.1.1 to promote the development and production of I4.0 technology-based solutions in fields of Industry, Energy, Mobility, **Health**, Security and Communication. According to [2], the estimated market value of the I4.0 in 2019 was 71.7 billion USD, and it is expected to grow at a compound annual growth rate (CAGR) of 16.9% from 2019 to 2024, due to the increasing adoption of technology trends [3].

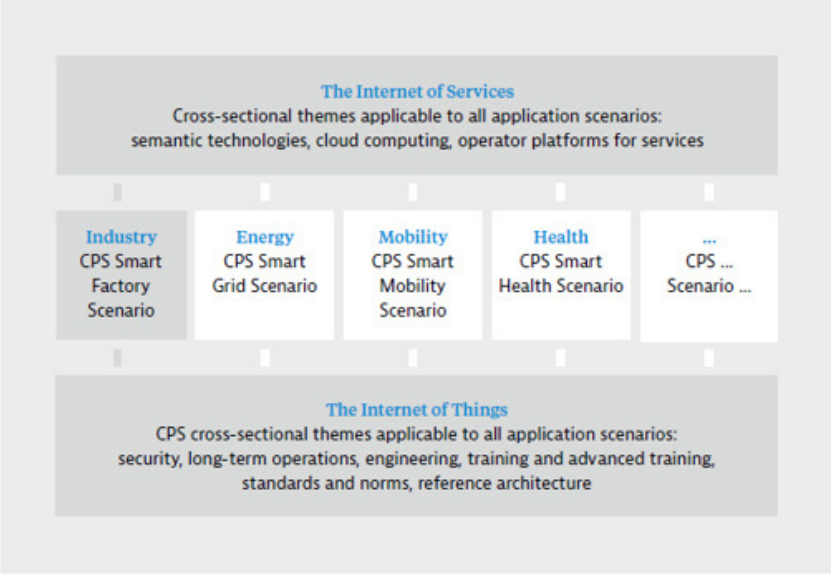


Fig. 1.1: I4.0 to High-tech Strategy 2020 (GTAI, Germany, 2014)

1.1 Motivation

As technology evolves people quality of life improves but also new health challenges appear, driven by the demographic change. According to the United Nations; from 1900 to actual days the life expectancy increased from an average of 46, to above 70 [4]. At the same time, in the last two decades as seen in Fig.1.2, global health expenditure has increased quicker than the economic growth [5, 6], which in time will be untenable. With those challenges for the future enterprises and new product developers, there is a demand of design reference models and taxonomies; such as the Integrated Product, Process and Manufacturing System Development (IPPMD) and the Sensing, Smart, and Sustainable (S^3) from [7], which seek to integrate global trends as sustainability to the aforementioned I4.0 concepts.

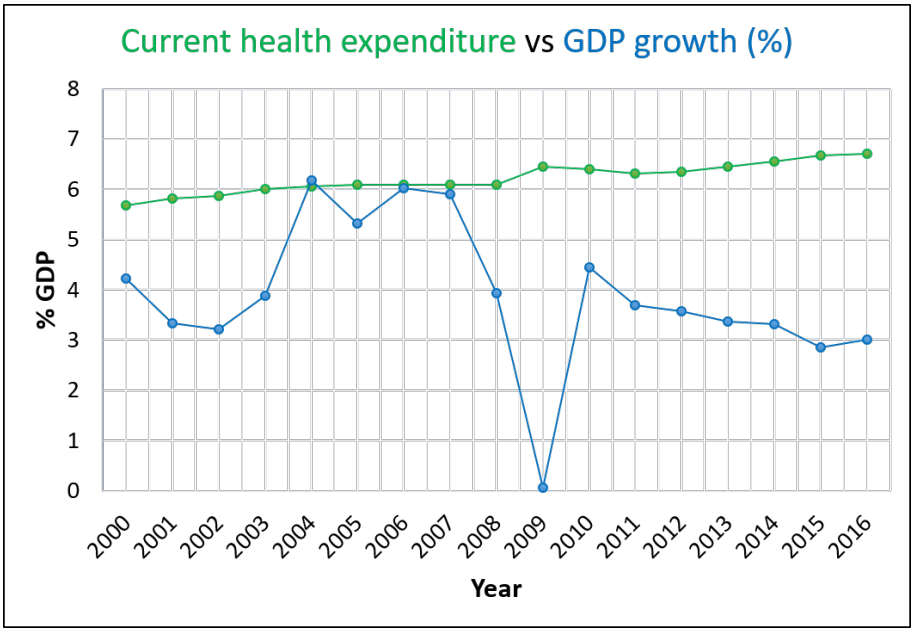


Fig. 1.2: World current health expenditure (% of GDP) vs GDP growth (annual %) from 2000 to 2016 (World Bank and WHO 2020)

Although governments expense in health has increased over the years, currently more than 35% of health spending per country comes from out-of-pocket [8]. The first level of health care, aims to prevent and promote health, delivering services locally to the communities.

However, at least half of the worlds people still lack full coverage of essential health services [9]. According to PwC rising health care cost over facilities have created gaps between customer expectations and the medical infrastructure, for instance the build of new medical facilities presents a significant challenge and the solution could be to bring care directly to the patients [10]. A way to do this is developing affordable medical devices (MD) based on cutting edge technologies such as wearable, big data, artificial intelligence; for any phase of the patient-centred care cycle: prevention, diagnosis, treatment and rehabilitation of illness and disease.

Medical devices (MD) are described as complex systems products; therefore their evaluation and features relevance determination is important from the beginning till their evaluation through their Life Cycle (LC), which can be done with the (S^3) of Fig. 1.3 concept that consist in three main elements: Sensing, Smart, and Sustainability.

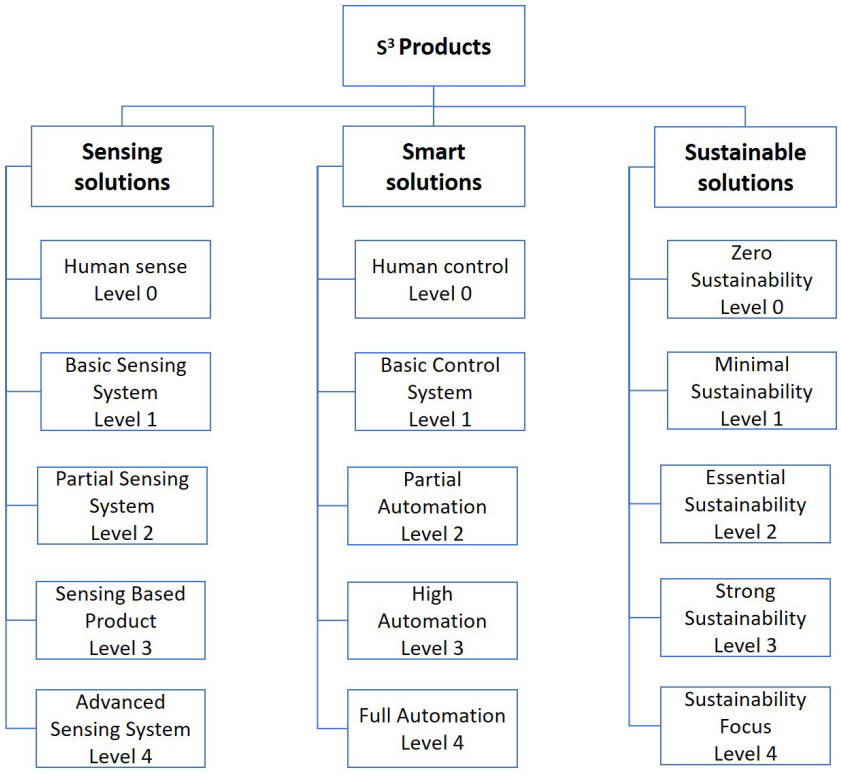


Fig. 1.3: Sensing Smart and Sustainable Taxonomy (Jonathan Miranda, et al., 2019).

Where Sensing stands for the capability to detect physical or virtual variable(s) of an environment, Smart is the property that allows a system to control the state or conditions of a requirement and Sustainability pursuits to cover the current needs without compromising the future. Although (S^3) taxonomy aims to be a general structure scale, the ontology of this concept rises from the query of I4.0 trends impact to the enterprise systems and yet, it does not consider how a product is created [11]. Hence, it cannot be directly applied as it is to the classification/evaluation of products, due to the compatibility lack.

Discussions around automation have reached the expansion and transformation of concepts and taxonomies known as level of automation (LOA), that started to evaluate tasks performance from manually, to fully autonomous systems, later divided in four generic functions: information acquisition, analysis, decision, and action implementation [12]. However, those functions were principally limited around the influence of human factors, and automation is not only about replacing human activities but also to enhance human-machine interaction. Luca Save et al. proposed a cognitive connected LOA taxonomy, which ended up being very complex, to apply it in a general way. Jrgen Frohm et al. proposal in [13] , separates physical elements and cognitive tasks of the system, which is only reliable when evaluating an isolated arrangement. In another perspective, Jian Qin et al. [14] combined perspectives of future manufacturing visions and CPS attributes to propose a categorical framework of manufacturing, but only with Automation and Intelligence components, being unable to apply it generally.

Deficiency in the definition of taxonomy can contribute to the incorrect evaluation of devices, and therefore to the ambiguous application of concepts for product development. The quantitative weighting of qualitative properties is important to size products; especially in the case of a feature concept such as S^3 levels.

To increase quality, reduce time to deliver and decrease cost in health care the global organizations and stakeholders have looked for new concepts, methods and tools which will provide innovative cost-effective patient-centered products. Advantages in medical devices is driven by intelligent systems, patient-focused solutions, flexibility to world health changes, data-driven analysis, connectivity and socioeconomically and environmentally sustainability. The use of big data, embedded systems and cyber-physical systems sets the basis of the fourth industrial revolution (Industry 4.0) as we observe in Fig.1.1, changing also the way medical devices are innovated affecting health care domain [15].

Technological trends, better practices and concepts aim to be pulled together to create total integration of all stages of development through Life Cycle Engineering. Life Cycle Engineering aims to provide a set of reference models, architecture, methodologies, tools and techniques to integrate these important cycles in product design [16]. The Integrated Product, Process and Manufacturing system Development (IPPMD) Reference Model offers a set of general methodologies, tools and activities for all the main elements of the life cycle engineering, allowing to reuse the most relevant for specific applications. Instantiation of a reference model is applied to delimit and specify the activities, methods and tools mostly required in particular areas. Thereby the importance of a correct reference model instantiation, relies in precise the requirements specification for the MD development, to engage the new century and trending health needs of the population.

IPPMD and (S^3) are related in the same way the I4.0 trends were established as base of the technological development goals in Germany, to promote the development and production of I4.0 technology-based solutions. IPPMD aims to support the design and manufacturing of (S^3) technology-based solutions to achieve the (S^3) for Everything in Mexico [17].

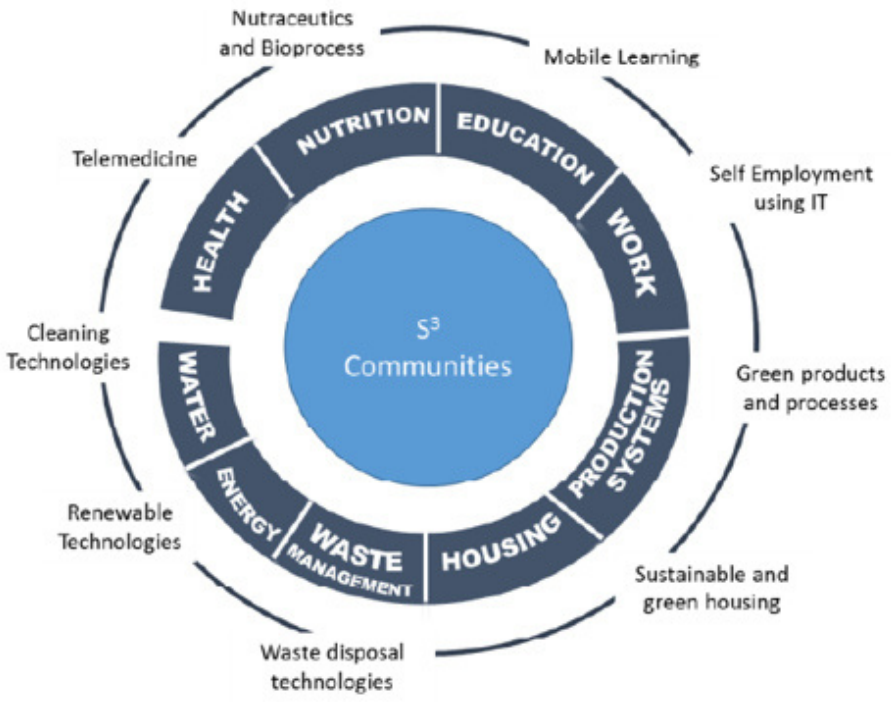


Fig. 1.4: S3 for Everything (Molina et al., Mexico, 2017)
Challenges and solutions for Sensing, Smart, and Sustainable Communities

Where an analysis of principal areas (Products, Processes, Enterprises, Business Ecosystems, Communities and Cities) with the particular requirements was held. Here they talk about the S3 enablers, that are S3 technologies (which can be set as an analogy to the Internet of Things) and Collaborative Networks (which can be related to the Internet of Services).

Facing the emergency of the Ebola epidemic in West Africa, a large amount of professionals and resources came together to find medical technologies to counter the disease and save

lives. Some of the outcomes were effective such as the VSV-EBOV vaccine, others evidenced global scientific research and development (R&D) entities gaps. From the lessons learned WHO members came up with a global strategy and preparedness plan, the R&D Blueprint was received in May 2016 [18]. Joining efforts to develop a standardized a Medical Device Design Methodology, professionals from universities and industry worked in a compendium project along with the Cambridge University Press to publish the Biodesign The Process of Innovating Medical Technology book in 2009 [19]. Those best practices can serve as a basis to instantiate the IPPMD reference framework methodology into an Integrated Product, Process and Manufacturing System Development (IPPMD) Reference Model for medical devices. The aim of these work is to reduce the gap between life cycle engineering and medical devices innovation process and set the basis of a new approach to face the challenges of the recent years with international best practices.

1.2 Problem Statement and Context

Medical device (MD) design methodologies have become important, for instance Cambridge University proposed a model in 2009 to connect health-tech innovation with entrepreneurship [Biodesign 2015]; and after facing Ebola outbreak in 2014-2016, WHO decided to put the acquired lessons in a R&D Blueprint to improve readiness when need [WHO 2016].

However, those methodologies still require integration between enterprise entities of LCE and international trends of I4.0 and SDGs. Solution requirement definition and evaluation can be done applying the (S^3) concepts, leading health technology development through the IPPMD to **improve health problem formulation and solution mechanisms**.

Currently there is no medical device design methodology that involves all the three entities of an enterprise project, which are product, process and manufacturing system. The WHO R&D Blueprint as well as the Biodesign Process of Innovating Medical Technology, contemplate the main elements for medical technology development, such as need screening and priorization, solution criteria to establish product profiles, even business plan; yet, no a complete relation with the production process and manufacturing system. Moreover, the IPPMD has shown to be a successful reference model in the innovation of technology through all the enterprise system entities, however it hasnt been instantiated for the medical device technology.

Having a medical device design methodology and reference model is important to improve quality, fasten development and reduce cost of medical technology in order to generate solutions and make it reach people. In recent years R&D has shown to be of importance in health with the Ebola and the COVID-19 challenges, even the WHO convoked different advisors from academic, scientific, industry and government to participate in the initiative of developing a reference model. Even though, there is still an area of opportunity to integrate lifecycle engineering concepts of the IPPMD with the international best practices of medical technology design; to produce a simplified landed roadmap to serve as a guide to develop complete solutions of medical devices.

The purpose of this project is to instantiate the IPPMD for medical devices, with best practices from the WHO R&D Blueprint and the Biodesign Process of Innovating Medical Technology. This will be done in the presence of a proper taxonomy that allows to asses products in relation to the level of (S^3) reference parameters of human involvement and technology development that can be applied for the valuation of product properties; aligned with the I4.0 trends. Our proposal encompasses the different phases of technological development that start on individual devices and culminates in advanced systems set of applications.

1.3 Research question

Why is important to have a medical device design methodology and reference model with international best practices?. Developing Medical Devices (MD) is not a simple task, because health issues are intertwined with complex characteristics and requirements, therefore deriving the precise health need statement and key features for a solution its necessary for the scientific community, innovation academical research groups and enterprise sector in order to produce solutions that successfully improve patients outcome.

- How can the international best practices from the WHO R&D Blueprint and Biodesign The Process of Innovating Medical Technologies can feed the IPPMD in order to produce the instantiation for MD?

Why is important to reduce time to market when developing medical technology?. Medical technology development is characterized for commonly be expansive and complex, hence it requires a multidisciplinary team to develop it and the time needed from the ideation to the launching is regularly large. When facing a social health outbreaks, it is important to have guidance methodologies to follow in order to reduce time of response in developing solutions.

- What are the most effective strategies from the IPPMD, that can be instantiated to reduce the developing time of medical devices?

How can medical devices innovation process time can be fastened?. It is clear that having clear stages and activities inside the IPPMD reference model serves as a selection toolkit to focus the efforts in developing innovative solutions, and screening seems to be exceptionally important when delimiting the need and solution criteria.

- How does screening/need statement in the instantiation of the IPPMD reference model and methodology for MD may reduce ideation time, hence developing process?

1.4 Hypothesis

Foundation of IPPMD for MD design methodology within international WHO and Cambridge best practices improve integration of medical and engineering disciplines.

IPPMD for MD reference model and design methodology positively influence the health problem formulation to produce solutions that meet health challenges.

Screening and need statement formulation reduce solution options and their parameters specification, as the IPPMD elements to develop MD.

1.5 Objectives

Develop and validate the reference model and methodology to design the Sensing, Smart, and Sustainable (S^3) medical devices (MD) based on the Integrated Product, Process and Manufacturing system Development (IPPMD) and international best practices.

- Enhance the current S^3 taxonomy to allow the valuation of general systems, including products; taking in count the relation of human involvement and industrial revolutions technological progression.
- Syntheses the R&D Blueprint and the Biodesign process of innovating medical technology key elements, to set the basis of the instantiation of the IPPMD.
- Select the activities, methods and tools from the IPPMD toolbox to support the MD design and development best practices feeding the IPPMD for MD roadmap.
- Conduct the "Analogous CPAP for COVID-19 ICU patients" case study to validate the IPPMD for MD, applying the S^3 assessment of principal components.

1.6 Solution Overview

The aim of this project is to provide the scientific world with a reference model and methodology to face the new century technological and social demands in the development of medical devices as in Fig.1.5 by instantiating the general IPPMD reference model, by selecting the stages related to the health problem formulation and finding of solution mechanisms.

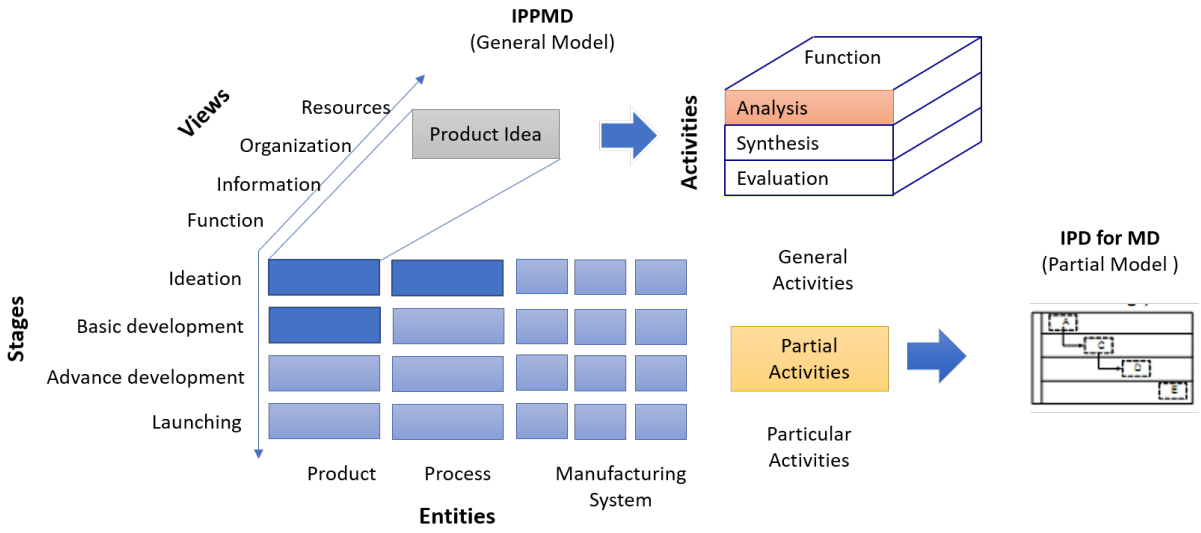


Fig. 1.5: IPPMD Instantiation

To do so, the stages (Product Idea, Concept Design and Components Specification) from the general IPPMD model where selected to develop a partial model for MD through the instantiation process, where:

Product Idea: Systematic search for selection and development of promising product ideas. It is obtained both technically and economically viable applications.

Conceptual Design: The collection of information about constraints and customer requirements to be part in the solution proposal.

Components Specification: The concept should provide a structure with elements, from where a list with particular information about materials and dimensions is generated.

Activities pulled from the IPPMD toolbox and the international best practices, Screening from WHO and Need Statement from Cambridge; where chosen to propose the toolbox for the development of medical devices. The technology requirement for solution is proposed as the S3 assessment, where a Care cycle analysis and a S3 level requirement are held.

Screening: A health challenge or set of health problems are analyzed to prioritize the must relevant issue, in order to focus the resources and efforts in finding a solution.

S3 Assessment: The proposed application of the S3 taxonomy, with a care cycle analysis to identify possible technologies that support in the prevention, diagnosis, treatment, management and rehabilitation of the patient; and then a S3 level requirement where the selected technologies are evaluated to set the reference of the expected solution.

Need Statement: research is held to finish the delimitation of the health problem, population and expected outcome, improvement in the patients condition.

Furthermore to validate the partial model IPPMD for MD, a case study Fig.1.6 is to be held with the proposal of a roadmap to design a mechanical ventilation machine to face the global situation of COVID-19.

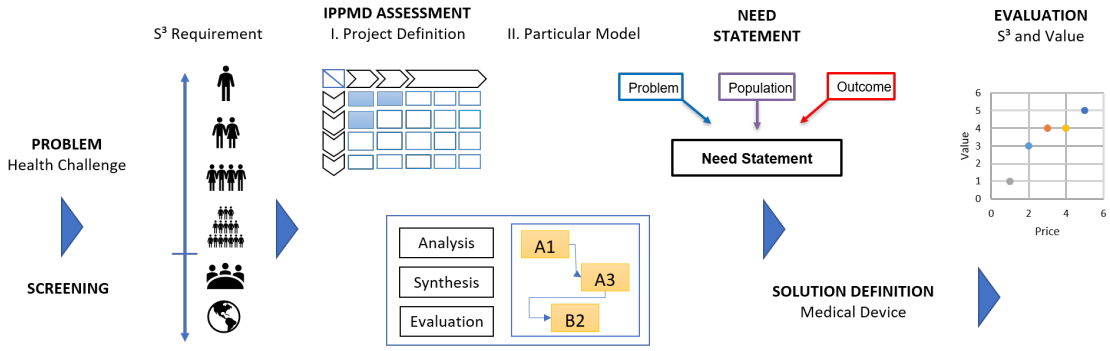


Fig. 1.6: IPPMD for MD Case Study

The characteristics of the product will be classified for its evaluation with respect to the S^3 taxonomy, and subsequent evaluation of features relevance, finalizing with the suggested process for its development.

1.7 Main Contributions

The IPPMD for MD is a reference model and methodology to support the design/development of med-tech products that allows the rapid implementation of R&D activities when required. Its aim is to fast-track the availability of effective methodologies, tools and activities that can be used in the development of med-tech solutions to support the patient-centric care cycle. With a multidisciplinary international urgency case of study as convener, the broad national coalition of professionals who have contributed to the IPPMD for MD come from medical, scientific and regulatory areas of expertise. The main contributions of this project will be in Life Cycle Engineering (LCE), Design of medical devices (MD), Industry 4.0 (I4.0), Levels of Automation (LOA), Sensing, Smart, and Sustainable S^3, Biomedical Engineering.

1.8 Dissertation organization

Exploring the S^3 Taxonomy, the authors faced controversial definitions of the levels, related to enterprise allusions; hence, Section 2 sought to find major events and properties from the Industrial Revolutions, Human Factor and Level of Automation to function as a reference of the S^3 Automation taxonomy for Industry 4.0. IPPMD describes the characteristics that define the general reference model to develop innovative high-tech devices, and Medical Devices Design Methodologies gather the international best practices the WHO R&D Blueprint and Biodesign ”The Process of innovating Medical Technology”. Section 3 proposal defines the IPPMD Reference Model for Medical Devices, which gives rise to the Section 4 Case Study Analogous CPAP for COVID-19 ICU patients. The COVID-19 subchapter analyses the physiopatholog of COVID-19 infection, and the need of an alternative to mechanical ventilation devices, to deal with the local shortage or unavailability in the healthcare system. Moreover, Epidemiology analysis serves for a requirement expectation and the S^3 features classification to propose a IPPMD particular roadmap for its creation. Discussion and conclusions of this work are entwined in Section 5, to finally suggest the future endorsement.

Chapter 2

Literature Review

2.1 Industrial Revolutions

The fourth industrial revolution was formulated and presented in 2016 by the founder of the world economic forum Klaus Schwab, who describes it as an era of the technological revolution that is clearing off the limits between physical, digital and biological areas [20]. Technologies like CPS, Artificial Intelligence (AI), Autonomous vehicles; are becoming entwined in our day to day lives. In order to understand it better, its important to highlight the main technological contributions that can be observed in Fig.2.1, as well as the impact in the human capabilities, described below as in [2].

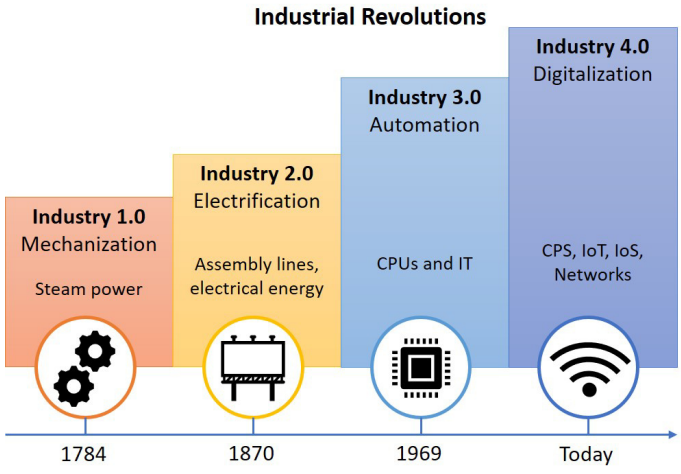


Fig. 2.1: Main aspects of Industrial Revolutions

The first industrial revolution started in Great Britain in the late 18th century, powered by the major invention of the steam engine in 1784; which, resulted in new manufacturing processes, the creation of factories and the upswing of the textiles industry, shifting from an agrarian economy to one based on mechanical production [21].

The second industrial revolution around the 1870s, was marked by mass production and some material/energy industries such as steel, oil, and electricity; deriving in some of the major technological contributions like the light bulb, the telephone, and the internal combustion engine, ushering affordable consumer products for the mass consumption era [22].

The third industrial revolution, also known as the digital revolution due to the development of information and telecommunications (IT) technologies, took place on the second half of the 20th century, and within just a few decades it produced the invention of semiconductors, computers, and internet.; which impacted business, industry, products, and society, connecting people in a common environment to meet an age of optimized and automated production [23].

From that on, technology (CPS, IoT, Cloud Computing) happens to be merging more in human life, and the development of applications and devices have fastened more than ever. Some of the key factors of the fourth industrial revolution are shown in Fig. 2.2.

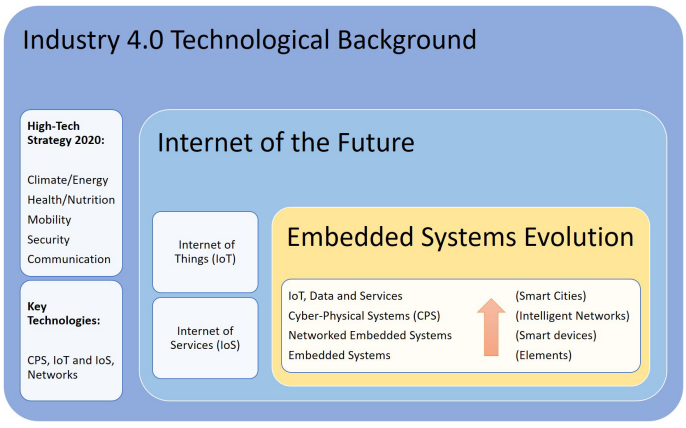


Fig. 2.2: The fourth industrial revolution principal components (GTAI)

Embedded systems that operate to process information and control functions inside a product, interact with the exterior through sensors and actuators, interconnected between them and also to the virtual network of the internet, which gives the capability to use data to provide online services, conform CPS [2]. Thus, the evolutionary development of embedded systems culminates networking over the internet, as the Internet of Things (IoT) and the Internet of Services (IoS), breaking existing models to new service applications, production value chains and business models [24]. Additionally, decentralized control assist building networks and encourage process management independence, powered by the relation between real and virtual worlds.

2.2 Human Factors Engineering

The capabilities to support human activities have been also improved; as new tools, methods, and procedures emerged. Nevertheless, in order to talk about the technology development, it should be first discussed about the human factors of Fig.2.3, which are those related to the capacities to interact with, perceive and sense the environment. Fig.2.2.

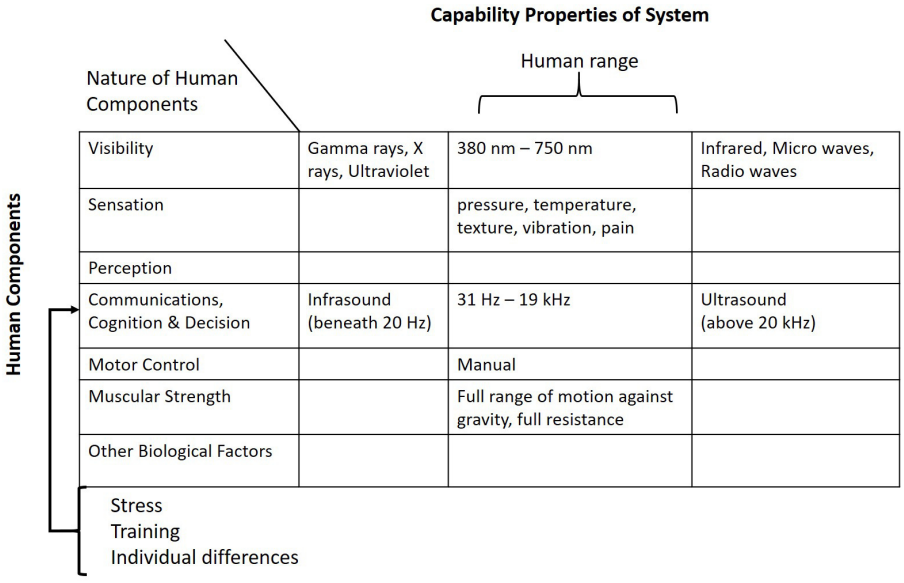


Fig. 2.3: Human factors matrix (modified from the original of Christopher-D.-Wickens [11]).

Across the top of the matrix, there is a range that allows distinguishing the limits within which

the human operates with their senses and capabilities. At the left, there are some of the system environment activities (areas), to which an operator focus; that can be affected by stress, training, and differences in skill or capability [25]. With this established, it can be postulated that there can be technological elements with wider, similar and narrow amplitude than the human element.

For individual processes, the human factors can be applied directly; but as the industrial revolutions came by, the tasks biding and the amplitude of organization grew. Therefore, the next level of human involvement was the control and administration of systems, which can be manual activities automatized, or any combination of activities and series of procedures; for instance, talking about chain production and production lines in factories. With the ability of machines to perform human activities, the concept of automation was coined in the 1950s by Diebold, to denote both automatic operation and the process of making things automatic.

2.3 Levels of Automation

Many operations previously performed by humans were taken over by machines, reducing the time of production, hence increasing productivity and improving quality; due to precision and accuracy enhancement. Moreover, the role of the operator changed from manual production to supervisory activities; with the objective of improving the systems with more intellectual or cognitive tasks like planning, diagnosis and problem solving [26]. Those roles and activities, as well as the interaction between the humans and the systems, have been embodied by different taxonomies among them, the Levels of Automation (LOA) specify the automation degree of involvement as shown in Fig.2.4. Moreover, analyzing those automation pyramids, we realized that they mainly focus on production, which is the goal of the industry. Thus, to apply the same scheme to the products, the main core should be the principal activity of employment for which the product was developed.

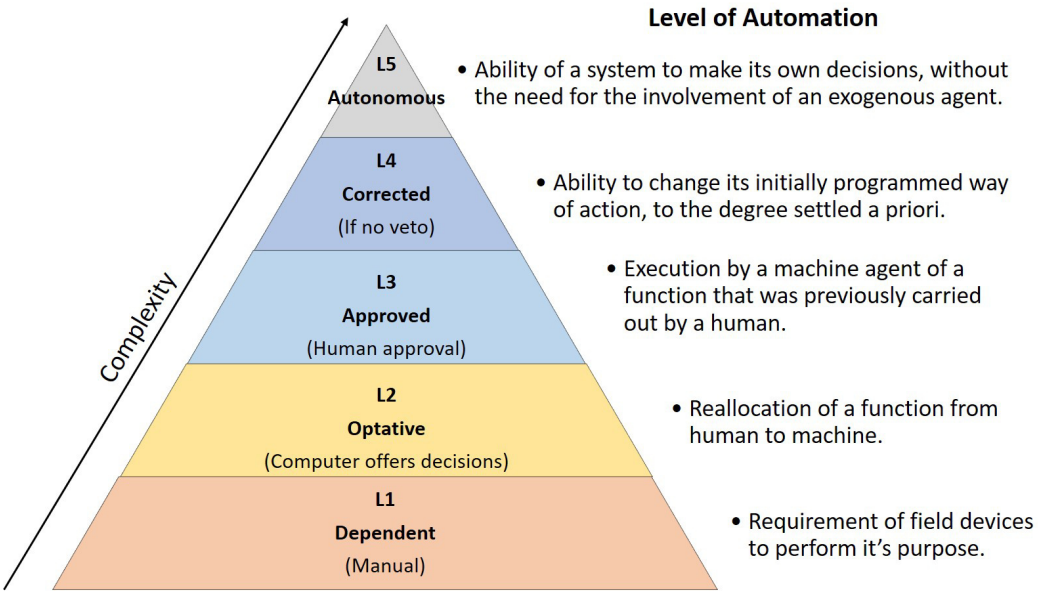


Fig. 2.4: LOA taxonomy.

Currently, there is no taxonomy or feature evaluation scale for products that relates to industrial revolutions, therefore in the same way that the LAOs are established for production systems, the S3 taxonomy addresses the enterprise perspective, yet none of them achieving the suitability for products.

2.4 Sensing, Smart, and Sustainable

Applying principles from systems and product life cycle engineering the Sensing, Smart, and Sustainable S^3 was developed to promote the integration of I4.0 trends in a model that can tackle the new century challenges [27]. One of the main characteristics of this model is that it seeks to encompass the evaluation of systems in a general way, and which can be applied not only in products development but also to production processes and manufacturing systems, even though there is a dispute around its general applicability due its seminal references, which are mainly focused on an enterprise features levels, as analyzed in Fig.1.3.

Therefore, for the S^3 conceptualization:

Sensing was conceived from the expected impact of the Internet of Things on businesses, and the need for transformation into organizations with the capacity to sense, analyze and seize information intelligently, supporting the decision-making process [11].

Smart is a control classification by LOAs, which takes into account the main characteristics of various authors [26], but still being an industry oncoming, not generally applicable for products.

Sustainable is typically divided into three main pillars which are the social, economic and environmental impact. Looking over this impact, tools like Life Cycle Assessment (LCA), Carbon Footprint, and others are applied. Although this is a modern perspective, and the world still has ancient levels of response to this topic [28].

Henceforth, human senses are capable to perceive a range of physical variables as posted in the human factors matrix of Fig.2.3, the sensing characteristic ought not to be established as a human capability in the zero level because there could be devices with lower potential than the human factor. Likewise, for the smart zero levels, human capability is one of the greatest goals of automation and artificial intelligence, in order to substitute human activities to help beating challenges; furthermore, some technologies overcome the human competence, so a more robust approach could be to establish the reference baseline of human skills right inside the extremes of the taxonomy.

2.4.1 Suggested update S3 Taxonomy

As described in Human Factors; there are technologies that have superior, equivalent or lower capabilities than the human being. Therefore, a way to improve the Sensing scale, based on history and human sensing adaptations, could be relating the technological evolution to the current definitions.

Additionally, previous study cases showed that there are mainly three elements around the automation scale concept portrayed in Fig.2.5 Human (user/operator), Mechanical System and Control System [29].

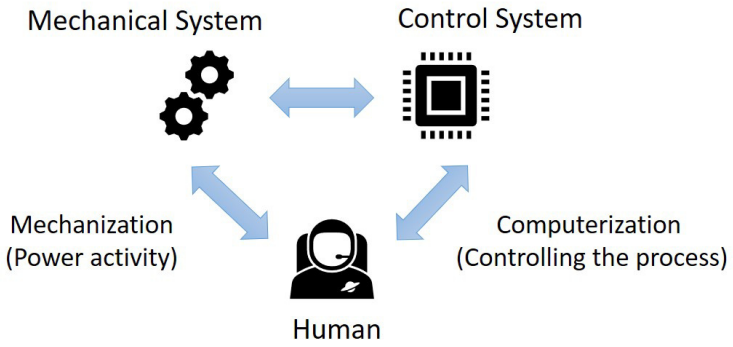
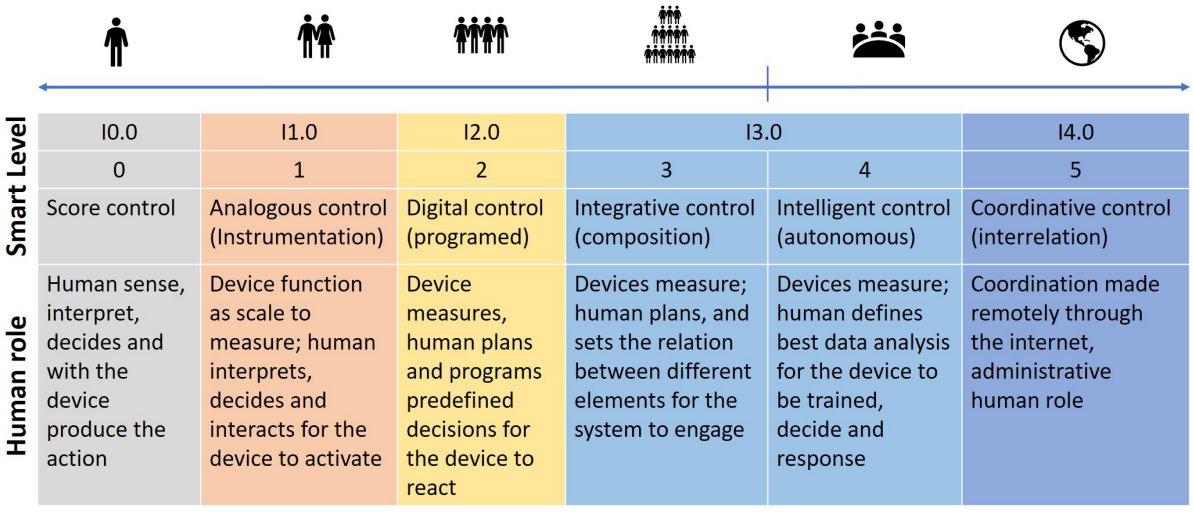


Fig. 2.5: Separation of functions into mechanization and computerization (Frohm et al. 2005).

Where mechanization refers to the replacement of human power such as material/energy transformation, and computerization to the cognitive sensory process and mental activity (Frohm et al. 2005). This means that the human involvement rather than being in just one level, changes of role as technology develops as seen in Fig.2.6.



	I0.0	I1.0	I2.0	I3.0		I4.0
Smart Level	0	1	2	3	4	5
	Score control	Analogous control (Instrumentation)	Digital control (programed)	Integrative control (composition)	Intelligent control (autonomous)	Coordinative control (interrelation)
Human role	Human sense, interpret, decides and with the device produce the action	Device function as scale to measure; human interprets, decides and interacts for the device to activate	Device measures, human plans and programs predefined decisions for the device to react	Devices measure; human plans, and sets the relation between different elements for the system to engage	Devices measure; human defines best data analysis for the device to be trained, decide and response	Coordination made remotely through the internet, administrative human role

Fig. 2.6: Human role variation in the Smart levels

Unlike Digitization (I4.0) that seeks to virtualize, the objective of Automation (I3.0) is to relieve the activities of the human being for technology capable of doing the same with equal

and/or better efficiency. With this in mind, we can establish reference order for the levels of our proposal; as a historical, technological evolution [30]. The reference point requires to be universal; human capabilities are well characterized, so are the industrial revolution timelines.

2.5 S3 Automation Taxonomy for I4.0

A taxonomy is proposed based on the capacities, virtues, and limitations of the human, such as sensory, information processing, decision making capability, among others. Simultaneously the historical development is considered to improve the structural order from the S^3 original taxonomy. With this foundation, a reference can be achieved to weight technologies with wider, equal and/or minor capacities than those of the human being. The proposed taxonomy to define the Sensing, Smart, and Sustainable levels for products is presented in Fig.2.7.

Industrial Revolution	Level	Sensing	Smart	Sustainable
I0.0	0	Perception (ambiguous)	Score control	Landfill, Incineration
I1.0	1	Analog (comparable)	Analogous control (Instrumentation)	3R (product focus) reduce, reuse, recycle
I2.0	2	Digital (transduction)	Digital control (programed)	6R (manufacturing) + recover, redesign, remanufacture
I3.0	3	Multisensing (discretization)	Integrative control (composition)	Nuclear (local)
	4	Collective sensing (uncertainty reduction)	Intelligent control (autonomous)	Communal (national)
I4.0	5	Crowdsensing (collaborative)	Coordinative control (interrelation)	Global (international)

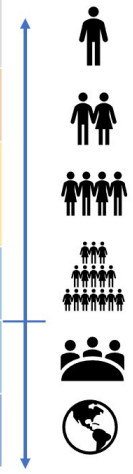


Fig. 2.7: Levels of S3 Taxonomy.

The proposal makes a combination of the industrial revolutions, the S^3 features, and human capabilities. At the left side in the first and second columns from Fig.2.7, the relation between industrial revolutions and the levels of S^3 characteristics (found in products) is presented, which comes from the historical precedents and the human involvement. Meanwhile, the

indicators of the right side of the Fig.2.7, show how the proposal moves forward from the physical limits to the individual replacement and beyond. To clarify the proposed taxonomy levels from Fig.2.7, each level is described below:

Level 0 - At the beginning of the industrial era, there was no such thing as a sensor and the measurements were made with the perception of the senses; control was carried out through scores based on intuition and accumulated experience and the waste management consisted of recollection and incineration.

Level 1 - Following, the first measurements were made in a comparative way with analogous elements, the control from devices was manual and waste problems were tackled by reducing, reusing and recycling materials.

Level 2 - Technological advances made possible to transduce from any energy to electricity, programs and manufacturing enterprises then set control commit in the residual 6r methodology to recover, redesigning and remanufacturing products that normally would pollute.

Level 3 - Discretization made possible to save data in memories; the control systems started to gather in the PLCs the minimal connections and ports to enable communications with the machines on the shop floor, residual waste programs engage people to separate its garbage at home before recollection.

Level 4 - Massive data can be merged to reduce uncertainty and improve the accuracy of measurements; artificial intelligence gave autonomous capabilities to the products and community policies promote social participation to achieve sustainability goals.

Level 5 - Nowadays, computers, smartphones, and social media applications are entwined within a global network that can be handled to provide context-aware features, control is also coordinating interrelated intelligent devices and there is a need to tackle sustainability problems on a global scale.

2.5.1 Levels of Sensing features in Products

Sensation has three main characteristics, transduction that changes physical energy from one type to another, an adaptation that decreases the response overexposure and a relation against perception converting information into experience [31].

Level 0 - Perception: Without an element to recognize and measure the environment for the system, sensing relies on human senses and its interpretation; this can be imprecise and can lead to an error (ambiguous).

Level 1 Analog: The first way to measure anything is by comparing elements of the same physical property and establish a scale (comparison).

Level 2 Digital: With electricity started the transduction from one type of energy to another, regularly electricity. (transduction).

Level 3 Multisensing: With the creation of semiconductors the possibility to save data emerge and the discretization of the analogous information (discretization).

Level 4 Collective sensing: Combining information from multiple sensors and machines increases the data quantity, which can be used to produce a statistical relation to producing a more accurate measure (uncertainty reduction).

Level 5 Crowdsensing: With the internet, mobile systems and cloud computing, there is a capability to measure simultaneously, share data in real-time, and process the information to boost novel sensing applications in areas such as environmental monitoring, transportation and traffic planning, urban dynamics, location services and more.

2.5.2 Levels of Smart features in Products

In order to perform their tasks, technology has been developed with the aim to be autonomous, which is the capacity to be independent and self-governing. However, this capacity has different levels of smartness, going from a dependent system to an intelligent product, capable of making choices [32].

Level 0 Score control: The activity or performance of the product, relays solely on human involvement, experience, and interpretation.

Level 1 Analogous control: The device can perform certain actions, but to do so, it requires the control and operation of an individual. (Instrumentation).

Level 2 Digital control: Elements fed with electrical power capable of performing predefined electromechanical activities. (programmed).

Level 3 Integrative control: Several components and/or devices connected to a master programmable controller, able to record instructions and execute assignments. (composition).

Level 4 Intelligent control: Programmed to think like humans and mimic not only their actions but the decision-making process; to diminish exogenous intervention. This level requires a junction of different knowledge areas, in a common ground base such as Artificial Intelligence. (autonomous).

Level 5 Coordinative control: Government is made virtual, simulations, and cloud computing intensify the amplitude of coordination and concepts as swarm autonomous vehicles, business analytics, data science, arise. Human interaction plays a more administrative role. (interrelation).

2.5.3 Levels of Sustainable features in Products

From the United Nations Sustainable Development Goals established in 2005 emerge the social, economic, social and environmental Fig.2.8 pillars of sustainability. Technology transactions come as an unbalanced economical exchange, which in time leads to gaps and differences between countries. Every product has its impact not only helping to solve problems or covering needs but improving the lives of the people and community in the present to preserve the future. Moreover, all of these balancing the resources to prevent the destruction of the environment [33]. Where the combinations result as:

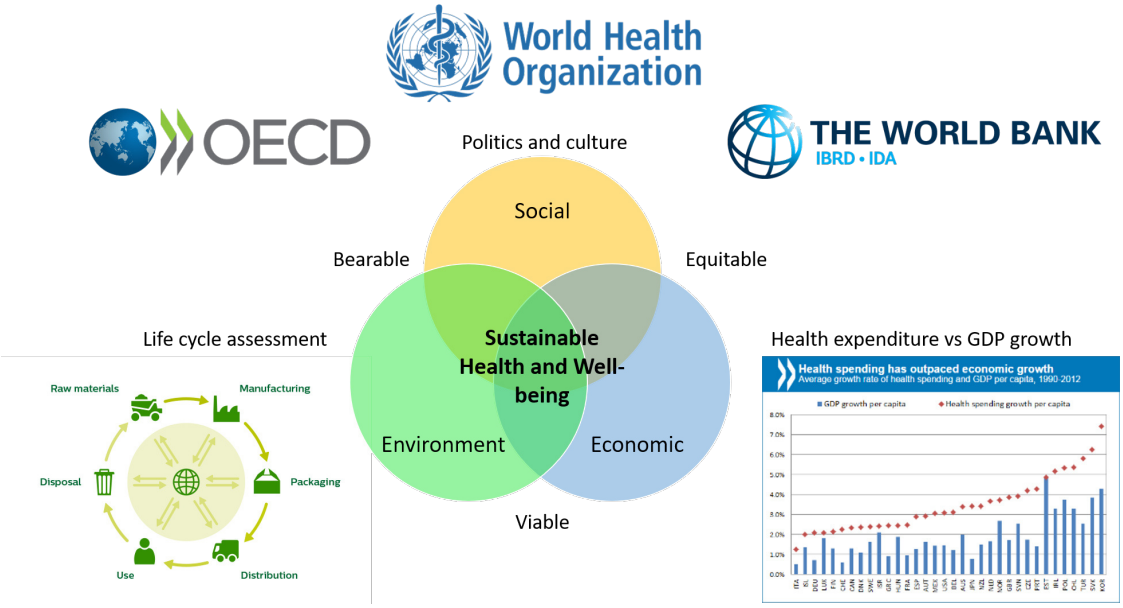


Fig. 2.8: Sustainability pillars and its implications
(Motivated on UN, WHO, OECD,The World Bank, LCA from KWEBA).

Bearable where the social and environment meet to produce something that may be unpleasant but its tolerable at certain point, but not in long term; for instance the gap from health spending and economic growth. **Viable** solutions that are in economic equilibrium with the environment, but perhaps are not very social; for example a business that has it's workers in bad conditions, or does not respect human rights, extra limits the working hours. **Equitable** for solutions that take in account social requirements and are economic stability; but do not relate with the materials or waste result from its origin, use, til disposal.

The Sustainable scale translates its levels as a **magnitude of impact**, first talking about the evolution of waste disposal; from waste, to product to manufacture, and then as an amplitude of the context for local, national and international:

Level 0 Landfill, Incineration: With zero sustainability, waste management consist in gathering the residuals and sometimes disposed of, for example, with fire (waste focus).

Level 1 3R product reduce, reuse, recycle: The very first way to diminish waste, is not producing at all; so, reduction comes first. Then reuse the product, for instance, when talking about imperishable things. Furthermore, its elements, the case of a material like the metal; can be melted and remolded to recycle (product focus).

Level 2 6R manufacturing recover, redesign, remanufacture: Waste management should not be made only in the final disposal of a product; it can be recovered, redesign and remanufactured; in the case where the material does not get to be recycled yet (manufacturing).

Level 3 Nuclear: It is important that the product complies with the rules and corresponds to the principles of the organization, group or family (local impact).

Level 4 Communal: The production business affect workers, employers, and communities. Therefore, it is important to expand sustainability to a collective level (national impact).

Level 5 Global: From the planet we get resources that seem to be endless, but in the long run, the way we consume and pollute is unsustainable. Meeting international sustainability standards will aid in reaching solutions in accordance to this domain (international impact).

2.6 Medical Device Design Methodologies

2.6.1 WHO R&D Blueprint

Medical Device (MD) Technology evolve as scientific discoveries happen, procedures are related to outcomes, health issues are broken into categories and solutions are tested. Even though, while in 2014-2016 Ebola outbreak in West Africa resulted in global efforts that culminated in solutions such as the VSV-EBOV vaccine; some other R&D community efforts were not that effective. Hence in May 2016 at the World Health Assembly, WHO decided to put those acquired lessons into the Fig.2.9 Blueprint to support readiness when needed.

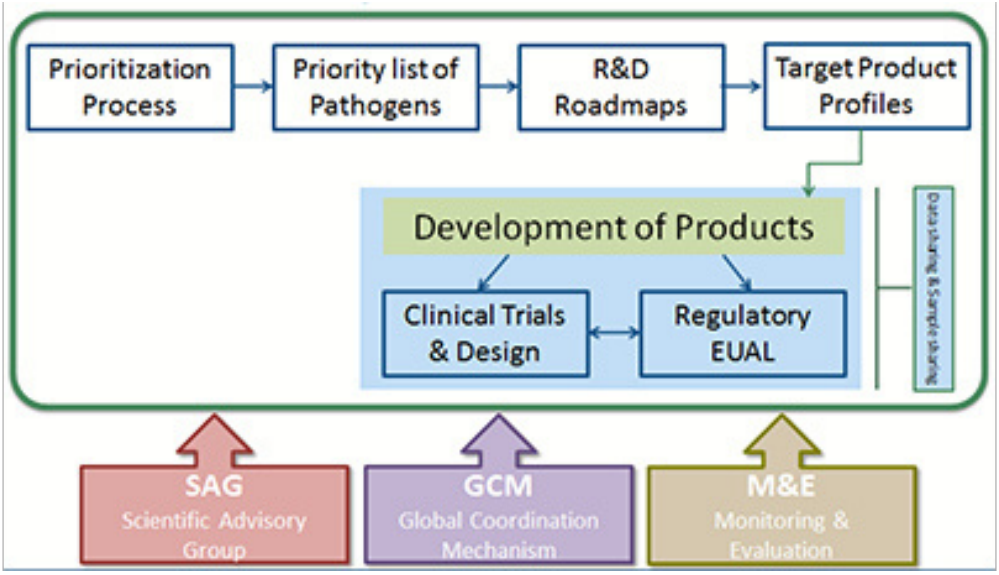


Fig. 2.9: R&D Blueprint (WHO, 2016).

Nine months after the outbreak was declared a global public health emergency, three rapid diagnostic kits to detect the infection and a number of potential vaccines, medicines and blood products were being assessed in clinical trials. Moreover, it was learned that the traditional R&D model can be adapted and accelerated, provided partners work together in a coordinated way and share information.

The intention of the developed R&D roadmap for emergency situations, was to establish clear rules and guidelines toward safe and accelerated discovery, development, assessment and access to safe and effective health technologies in the context of infectious disease outbreaks. This R&D Blueprint consists in a two phase or state suggested series of actions seen in Fig.2.10, before and during epidemic, where:

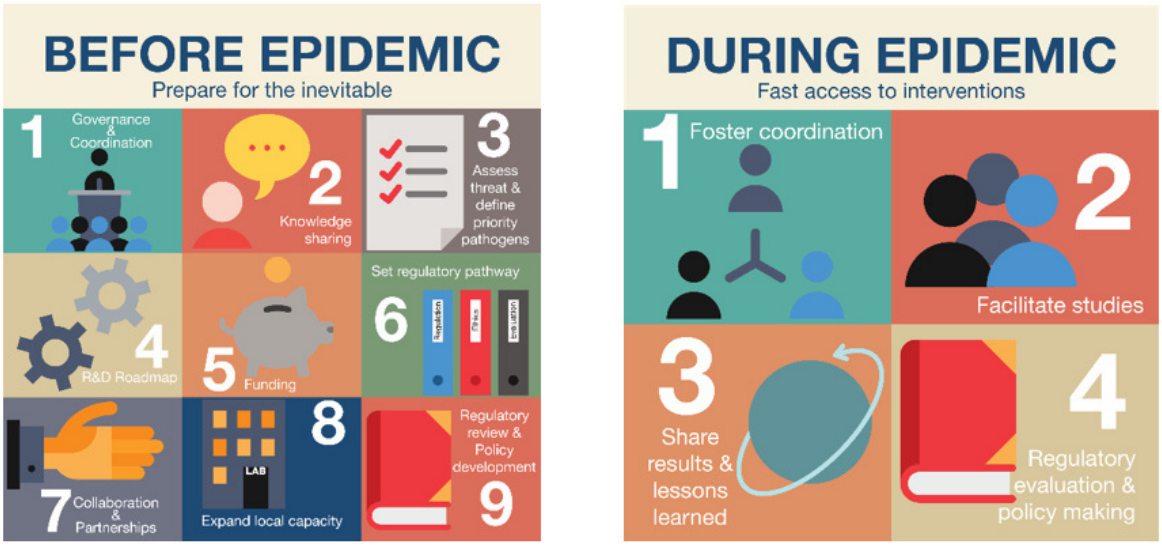


Fig. 2.10: Before and During an epidemic suggested scheme of action (WHO R&D Blueprint, 2016)

- **Preparation** consist in governance and coordination, knowledge sharing, asses threat & define priority pathogens, and the definition of clear R&D Roadmaps for each of the top critical cases, look for founding resources, set a normative and regulatory pathway, propitiate international collaboration and partnerships between governments, scientific communities and private industry, to expand local health care capacity (R&D labs, diagnosis clinics, prognosis, treatment, health supplies production, etc.), regulatory review and policy development.

- **Fast intervention** that requires foster coordination, studies promotion, results sharing & learned lessons documentation, regulatory evaluation & policy making.

According to the analysis, the most relevant features of this methodology include the prioritization before R&D, where importance of disease affections spot the focus of the consecutive actions; such as inversion of efforts and resources, collaborative coordination and subsequent documentation for international technology and knowledge sharing.

2.6.2 Biodesign "The Process of Innovating Medical Technologies"

Biodesign, the process of innovating medical technologies is methodology guide of best practices created by a collective of academical, industrial and innovative sectors within one of the better universities worldwide, the Cambridge University. The objective of this methodology is to provide the medical technology inventors and innovators with the resources to guide them through the innovation process, in a more successful way in order to bring products to the market that improves patients outcomes. The secondary objective is to support innovation courses, such as the one given in Cambridge with this methodology as a standard process. It involves different areas such as bioengineering, medicine, business which are involved in interdisciplinary projects such as biomedical innovation, medical device manufacturers industry, entrepreneurship.

The aim to provide the foundation and the framework for medical technology entrepreneurship, is because there are references of medical technology innovation, and entrepreneurship separated; but it is probably the first time that those are merged in such a complete way. The field of technological entrepreneurship became linked to Bio X initiative, that aim to bring together different parts of university to focus in problems of biomedical technology, and to Silicon Valley which helped validating more than 40-50 case studies. Collaboration of this project has been delivered across the world, from U.S. market, India, Europe, China, and other countries to achieve global success stories.

The material is committed in a three principal steps proven of successful innovation process, where identify consists of screening the need and defining possible solutions with all its required properties, invent is set by a series of activities to consider in the landing concept, and implement delimits the context to user requirement to deliver the projects.

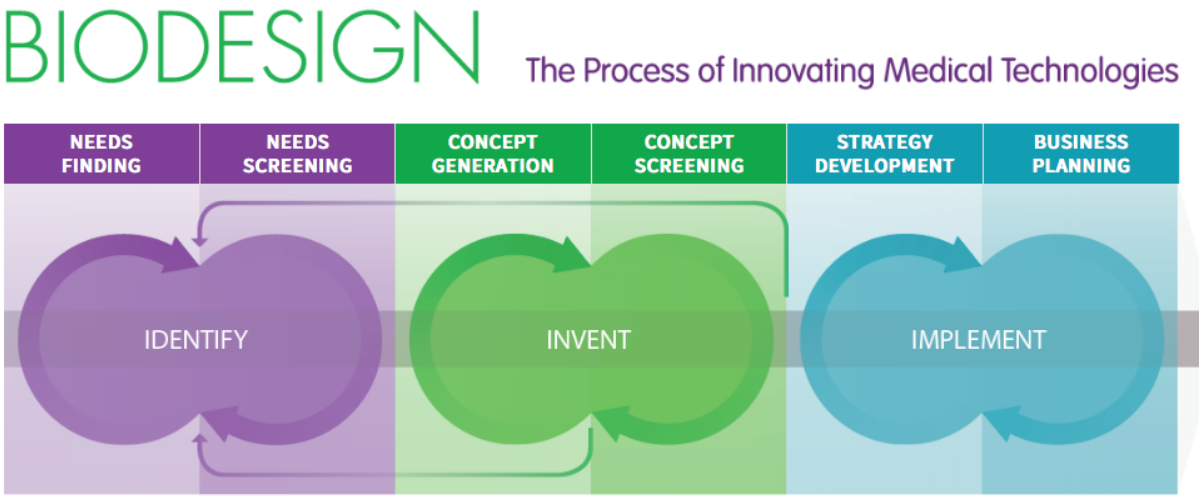


Fig. 2.11: Biodesign process to innovate medical technology (Cambridge Press, 2015)

Beneath the steps, it is commonly reformulated the drafting of preliminary needs where the goal is to establish the requirements as broadly as possible, while keeping it linked to a specific, validated problem. This type of scoping exercise allows the innovators to methodically revisit the assumptions they have made in developing the needs statement in a way that results in the optimal framing for the need, so it is detailed and actionable without being too limiting.

It is also important to consider how the problem is branched, because the further away innovators work from the root of a problem, the more likely it is that the branch where their innovation exists could be cut off or superseded by another invention that solves the problem from a previous level.

Too often innovators incorporate elements of a solution into their need statements because they quickly envision ideas to solve the problems they observe. This is tempting when a key opinion leader (KOL), offers a solution for how to approach the need area in question. Embedding a solution into a need statement seriously reduces the range of possible opportunities that are explored, constrains the creativity and places unnecessary boundaries on the potential market. So, if the problem identified through observation is an issue about which the target population is not readily aware, it can be more challenging for the innovators to validate the need.

Solution is to be related closely to target population needs, hence talking with members of the target population, it is essential to ask them exactly what results they would want, not how to achieve them, focusing the discussion around the need and deconstruct the problem breaking it down to each component to ensure that it is understood at every level. Make sure to understand any possible interactions between the various components of the problem and develop hypothesis for the root causes of each component that can be validated or refuted by the target audience. Then, using input from the target population, seek to identify the key elements that an ideal solution would have to include to satisfy them (ideally, these elements should be linked back to the root causes likely to address)

A well characterized target population, would result in a precise definition of solution criteria, for example for a low income, remote located, not technical users kind of population will need in general this kind of properties entwined a solution:

- Inexpensive
- Locally manufactured
- Able to withstand though environmental conditions
- Operational despite inadequate infrastructure
- Usable with minimal specialized skills or training
- Secure
- Easily repaired (with accessible replacement parts) or substituted

The complete research, information analysis, market study, users experience and need definition, those first Identify concepts to find and screen a requirement are of such importance to define with precision a problem and the characteristics of the solution, that is commonly mention that:

A well-characterized need is the DNA of a great invention

2.7 MD Best Practices

2.7.1 Screening

The common characteristic inside both references is the Screening, where a list of health issues or one general health problem is analyzed to prioritize the most relevant priorities, population and requirement. It is important to apply an information treatment, to delimit the expected statistical requirement and the features that will feed for the solution proposal.

By definition, screening is the act of separating something from a whole; that in the particular case of the design and development methodologies of medical equipment, it serves initially to prioritize relevant health problems. And later to select the most convenient from a series of possible solutions. In the R & D Blueprint we find it in the Prioritization Process and in Biodesign inside Identify in Needs Screening.

Screening is an Analysis kind of activity; relating it to the IPPMD principles.

Starting from a series of health problems, or a big problem; it can be specified until you have a well-defined situation and population. For this it is important to carry out analysis activities such as investigation of medical aspects of different areas, such as Physiopathology and Epidemiology to mention some.

2.7.2 Need Statement

A refined need statement is then constructed by needs scoping and needs validation, to construct it with three main elements of Fig.2.12:

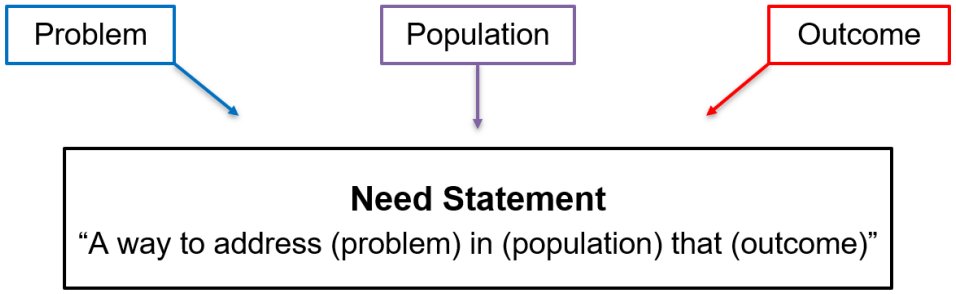


Fig. 2.12: The three principal components of a Need Statement (Biodesign, 2015)

Where the **problem** communicates the health-related dilemma that requires attention. The **population** clarifies the group that is experiencing the problem (and potentially foreshadows the market for the solution). The **outcome** specifies the targeted change in outcome, against which the solution to the problem will be evaluated.

Need Statement is an Synthesis kind of activity; relating it to the IPPMD principles.

An example of a need statement can be found in the successful story of HICARE LIMO, where a Standford India Biodesign fellowship worked in a project for the All India Institute of Medical Sciences to reduce wound aggravation of limb after a trauma, the result need of statement was: *Improving limb immobilization (problem), in trauma patients (population) to prevent the aggravation of their wounds during transfer (outcome).*

Chapter 3

Proposal

3.1 IPPMD reference model for Medical Devices

Integrating IPPMD key concepts (Life Cycle Engineering, System Modeling, and Instantiation), with international best practices to develop medical devices from WHO (Screening) and Cambridge (Need Statement), plus the Automation taxonomy for I4.0 S^3 approach; the IPPMD reference model to design the S^3 MD proposal is presented in Fig. 3.1:

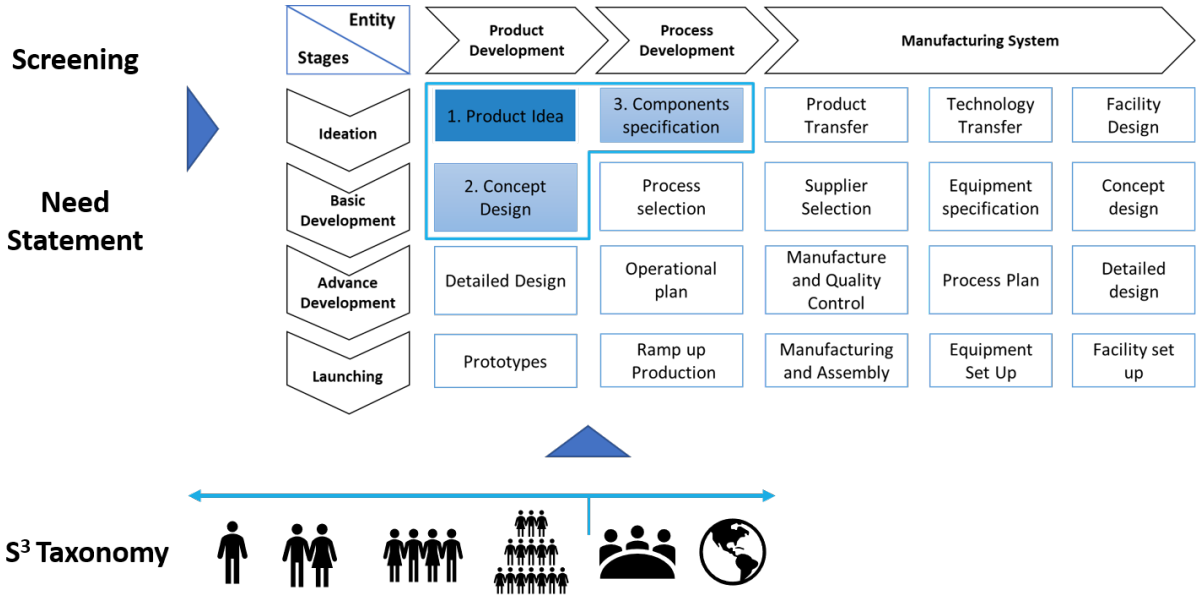


Fig. 3.1: IPPMD reference model to design the S^3 Medical Devices (Motivated on the IPPMD from Molina et al., the WHO R&D Blueprint and Cambridge Biodesign).

Where the Screening and Need Statement, support the Product Idea as well as a proposed S3 assessment further described; the model and methodology provide a reference to improve health problem formulation and solution mechanisms. The stages described in Tab. 3.1, are related to the problem analysis and requirement (Product Idea), current solutions comparison to provide a proposal (Concept Design), and the definition of elements to develop the medical device (Components Specification):

Stage	Entity	
	Product	Process
Ideation	Product Idea: Systematic search for selection and development of promising product ideas. It is obtained both technically and economically viable applications.	Components Specification: The concept should provide a structure with elements, from where a list with particular information about materials and dimensions is generated.
Basic Development	Conceptual Design: The collection of information about constraints and customer requirements to be part in the solution proposal.	

Table 3.1: IPPMD selected stages for health problem formulation and solution mechanisms to development MD (IPPMD, Molina et al.).

The S^3 Taxonomy feeds to the Product Idea in the assessment of technology levels of solution requirement and once again in the Evaluation of the proposal at the end of the development of the health problem formulation and finding of solution mechanisms to develop MD.

The development of the proposal is accompanied with the suggestion of a toolbox (series of tools, methods and applications) that can help to develop the activities that are to be selected for each of the described engineering stages.

3.2 Instantiation, IPPMD model configuration for MD

From the general model of the IPPMD we feed with best practices, industrial, marketing, business information of Medical Device sector; to produce a partial model that aims to support in the development of solution proposals to overcome health challenges. The configuration of particular model for MD requires three phases Fig. 3.2:

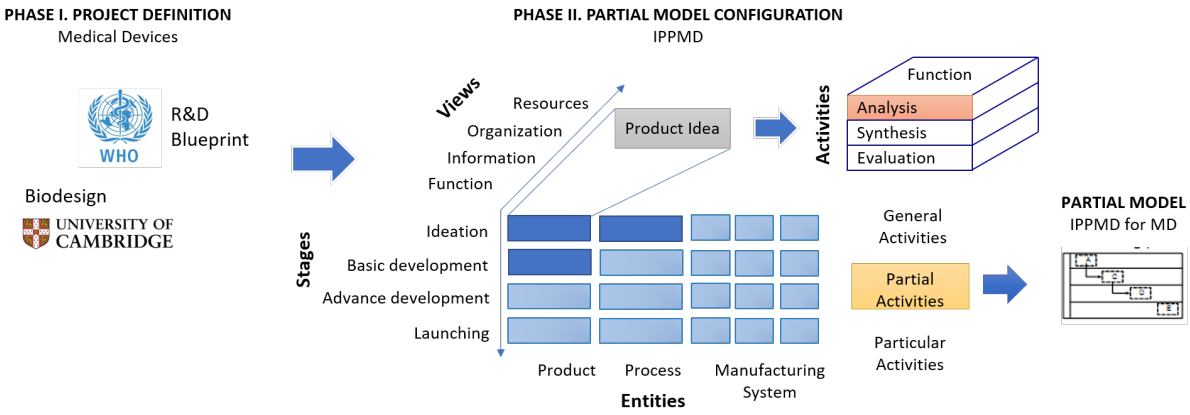


Fig. 3.2: Phases for IPPMD model configuration (IPPMD, Molina et al.).

I *Project Definition*: The requirements of Medical Device industrial sector are identified for the scope to be established within the reference model map, in our case we use the **Market** (buyers and users), **Industry** (producers), **Business** (enablers).

II *Partial Model Configuration*: Collection of tools and methodologies can be set for the industrial sector. For instance the **WHO and Biodesign elements**, can serve to provide some of the stages and activities to support the selection of MD requirement.

III *Particular Model Activities Selection*: The particular model is established by specifying the characteristic activities for the type of project, in this case **Screening** from WHO that require analysis kind of activities, **Product Idea** that require the IPPMD assessment to have the Solution Requirement S^3 Technology Level and the **Need Statement** (problem, population, outcome) formulation; as well as the Evaluation, Alternatives Comparison, etc to lead to the **Conceptual Design** and **Components Specification**.

3.3 Phase I - Project Definition

As a health area of problems, to design medical devices require the identification of requirements through sciences such as anatomy, physiology, epidemiology, to mention some. To complete this, three task had to be realized for the outcome of a process Fig. 3.2:

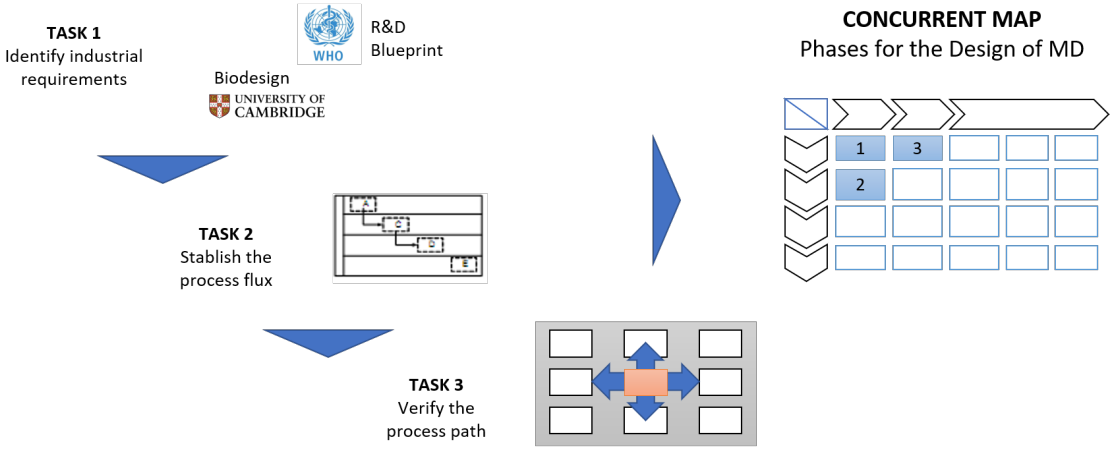


Fig. 3.3: Model Configuration I. Project Definition: Tasks and tollgate (IPPMD, Molina et al.).

Where important phases of Product Idea, Concept Design and Components Specification are set to serve as a guide for the particular model to develop solution proposal of MD. WHO and Cambridge will also feed in the stages for the partial model roadmap.

3.3.1 Task 1. Identify Industrial Requirements

Requirements from the MD market, industry and business are presented in Tab. 3.2:

Market	**Industry**	**Business**
Certification	Standards	Protocols
Security	Traceability	Data management
Equitability	**Viability**	**Profitable**
Local distribution	**Local production**	**Local administration**
User friendly	Flexibility	Adaptability
Precision and efficiency	Integration	Continuous growth

Table 3.2: Medical Device sector requirements.

Where the first are related to the licensing to produce, next security aspects, and highlighted **Sustainability features** that are of great importance for universal health care, usability aspects as well as flexible production lines with adaptable business, and finally but not less important relevant characteristics for the functionality of the systems (Product, Production and Management) [34], [35], [36], [37].

Hence the partial model scope for the MD sector, is to produce and provide technology that is licensed, secure, sustainable, patient-center focused and adequate to solve health challenges.

3.3.2 Task 2. Identify Process Trajectory

The proposed process consist in the next prioritized elements of Fig. 3.4:

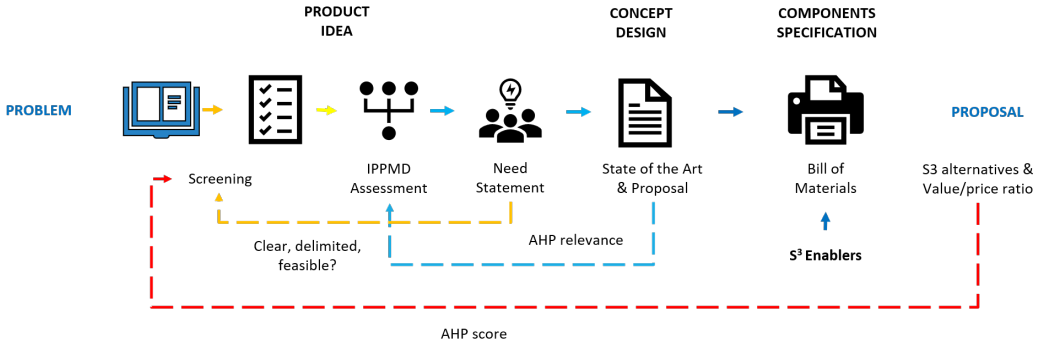


Fig. 3.4: Process Trayectory for MD project development of Solution Proposal.

Starts with a Problem, to be specified through Screening, then develop the Product Idea (IPPMD Assessment and Need Statement), Concept Design, Components Specification to generate a Proposal to be evaluated.

General health problem or set of health problems, are delimited to one priority health challenge, develop and compare alternatives to finishing with a viable solution proposal.

3.3.3 Task 3. Verify Process Path Information

Recurring to the WHO R&D Blueprint and the Biodesign from Cambridge as well as the IPPMD reference model, the information path can be verified with the relations in Tab 3.3:

Stages		Information path	Document Type
From	**To**		
Screening	Product Idea	Health problem analysis report	Record
Product Idea	Concept Design	S3 requirement level of technology Need statement paragraph	Record Format
Concept Design	Component Specification	Proposal Concept diagram Functional Decomposition Morphological Matrix	Instructive Format Format
Component Specification	Development	Bill of Materials	Format

Table 3.3: Stages relation of information document types.

Screening to Product Idea, a **health problem analysis report** with symptoms and population definition. Product Idea to Concept Design, the **S3 requirement level of technology**, the **need statement paragraph**. From Concept Design to Component Specification, a **Proposal Concept diagram**, which can be feed with information from Functional Decomposition and Morphological Matrix. The Component Specification delivers a **Bill of Materials** that is based on the Schematic, result of the Product Architecture and the selection of S^3 enablers.

3.3.4 Project Definition Tollgate: Concurrent Map

We already defined the Medical Device requirements to produce a Process Trajectory with Product Idea which inside contains the international best practices of Screening and Need Statement, Concept Design and Components Specification.

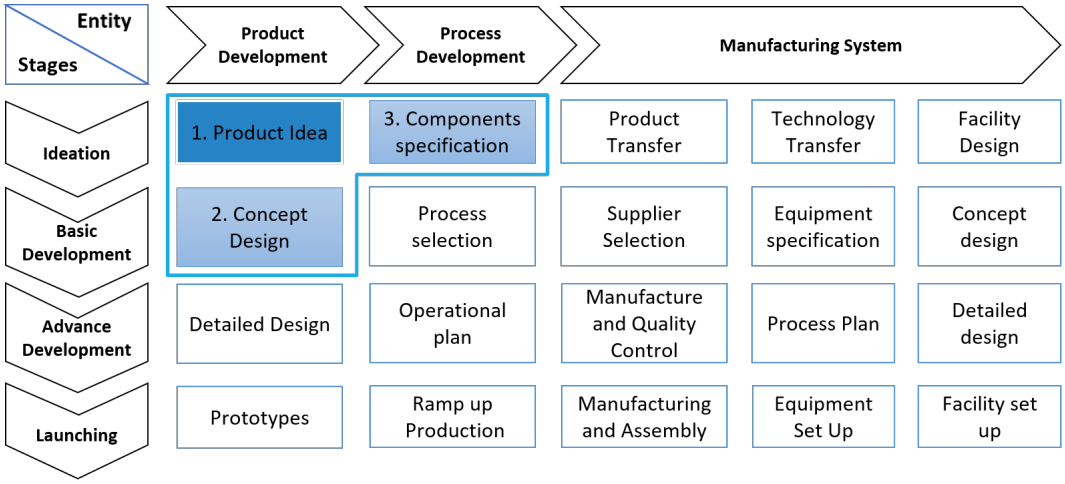


Fig. 3.5: IPPMD Councurrent Map for solution proposal of MD to be complemented with international best practices (IPPMD, Molina et al.).

Hence selecting from the IPPMD general reference model, the selected phases Fig. 3.5, will reflect the order of interaction for the execution of the IPPMD engineering stages for MD.

3.4 Phase II - Partial Model Configuration

Once defined, selection of activities is held in Fig. 3.6 to establish a reference for MD:

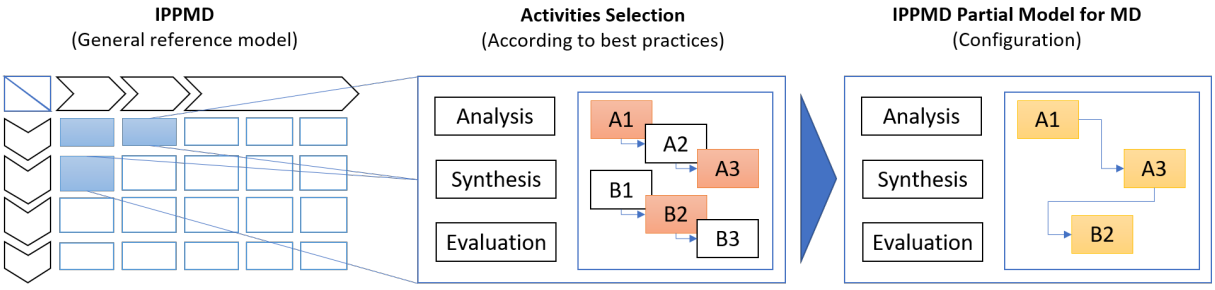


Fig. 3.6: Phase II- Partial Model Definition (IPPMD, Molina et al.).

Where activities are related to each stage as road for the MD industrial sector project development, as for Screening and Need Statement to be considered for Product Idea.

3.4.1 Task 4. Activity Breakdown and Selection

With the process flow established and the activities interaction verified is important to describe each activity inside the reference model using the process path. It is important to mention that those activities from Tab.3.4 are to be enabled with a suggested toolkit for MD, where:

Stage	**Activities**		
	Analysis	Synthesis	Evaluation
Product Idea	1. Screening	Epidemiology model	Prediction vs real
	2. S3 assessment Care cycle technology		S3 level requirement
		3. Need Statement	Is it clear? Delimited?, Feasible?
Concept Design	4. State of the art Functional Decomposition	Solution criteria Morphological Matrix 5. Proposal	AHP relevance
Components Specification	Product Architecture 6. S3 enablers selection	System Schematic Bill of Materials	7. S3, AHP and Value

Table 3.4: IPPMD Stages and selected Activities for MD.

1. **Screening**; is the analysis of the health issue considering the related medicine areas to prioritize relevance or delimit health problems to one (WHO R&D Blueprint).

Physiopathology analysis: Information around the disease from its origin, agent, symptoms and how may be treated.

Epidemiology model: A model is to be created with global statistical data, distribution and local demographics. Then a required quantity estimation can be done, if you have a resource quantity, with the model you can predict when the solution will be required.

Prediction vs Real, the model prediction may be compared against real.

2. **S3 assessment**, a care cycle analysis to establish the technologies that solve the health problem and then S3 level requirement to evaluate the technology for the solution.

Care cycle analysis, related to the patient focus stages of prevention, diagnosis, treatment, management where technologies that support each stage are to be selected.

S3 level requirement, technologies from the care cycle are located in the scale from the taxonomy, in order to set the reference for the solution development.

3. **Need Statement**, one paragraph should embody the characteristics of the required solution, the specific problem, delimited population and expected outcomes (Biodesign).

Is it clear?, Delimited?, Feasible?, need statement may be redefined as many times as , necessary; to avoid misleads, generalities and expectations outside the achievable reality.

4. **State of the art**, the research of past, current developments, and cutting edge technology to compare approaches.

Solution Criteria, is the sum of general characteristics that are suggested for a technology to solve the problem, which may involve security, categorical price, usability, etc.

Analytic Hierarchy Process (AHP) is a multi-criteria decision making method, that works through pairwise comparisons by experts to derive priority scales [38].

5. **Proposal**, the schemes to define the functions, elements and alternatives; to select and describe the solution concept (IPPMD).

Functional Decomposition is a method of analysis that dissects a complex process to show its individual elements, to understand the principles required for its complete functionality.

Morphological Matrix is a representation of the functions and possible solution alternatives for each element of the complete system.

6. **S3 selection** of technology enablers to produce the characteristics of the required S^3 level of the solution, from diagrams that represent the elements and the connections of the system.

Product Architecture is a diagram that represents the minimal elements that compose a product [39] in terms of their role (protect, supply, connect, interact).

System schematic represents the system with all the elements connected for the product to

function with the patient, it contains technical data of physical variables.

Bill of Materials from the schematic, one can get the quantity components and the technical information to be loaded on the list to select the manufacturing process.

7. **S3 and Value** of the proposal is to be made with a S3 level and Value/price ratio comparison of alternatives, to select the best for the particular challenge.

S3 alternatives & AHP score is the comparison from the required level, against the alternatives inside the S3 scale definitions, which can be seen in a 3D representation (relevance of S3 components is considered as priority). Then to to calculate the AHP score.

Value/price ratio of how well the alternatives meet the challenge and their market price, set from qualitative to qualitative spectrum a relation similar to cost-benefit.

3.4.2 Partial Model Configuration Tollgate 1: Partial Model

The IPPMD partial model for MD, consist in the architecture Fig. 3.7 of the selected stages of Product Idea (with international best practices of WHO and Cambridge), Concept Design and Components Specification; that support with suggested activities and tools, the particular configuration to develop health technology projects:

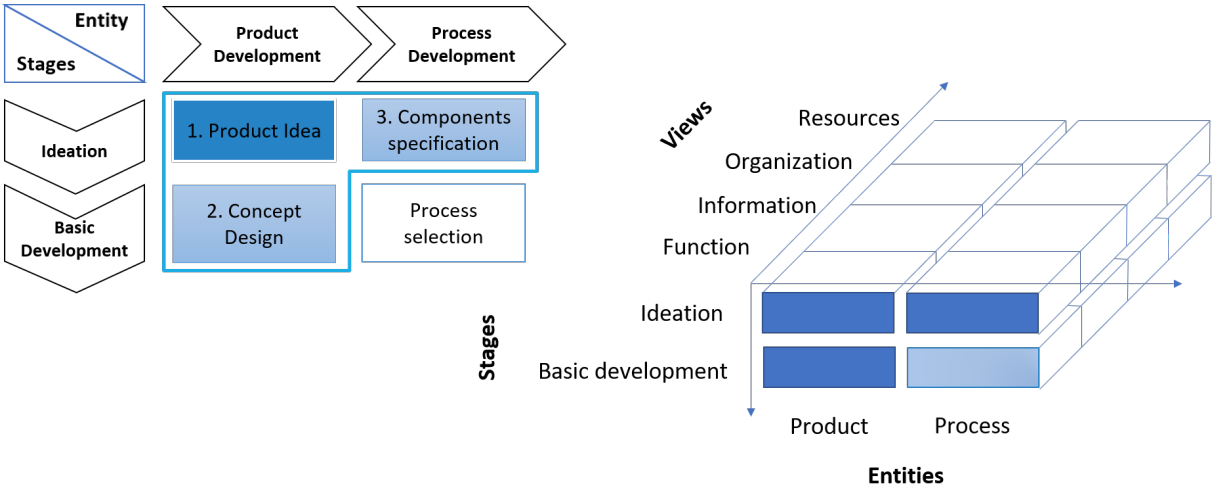


Fig. 3.7: IPPMD partial model for MD (Modeling views on Appendix B).

The IPPMD methodology for MD, consist in a road-map Fig.3.8 that includes the most relevant phases for Medical Devices sector and integrates the activities of Screening (WHO, R&D Blueprint) and Need Statement (Cambridge, Biodesign) in the definition and development of technological solution proposals to face health challenges:

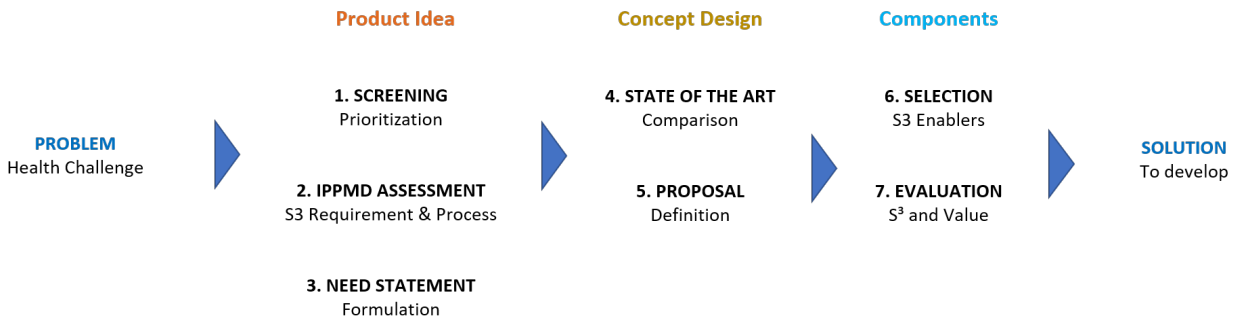


Fig. 3.8: IPPMD for MD methodolgy.

3.4.3 Partial Model Configuration Tollgate 2: Toolkit

The set of technological resources and methodologies to support the activities execution is defined in Tab. 3.5 by engineering stage, where the tools to support MD development are:

Stage	Activity	Tools
Product Idea	1. Screening	Physiopatology, Epidemiology, Biomechanical, Biochemistry
	2. S3 Assessment	Care cycle, S3 level, Disease cycle, IPPMD reconfiguration
	3. Need Statement	Research, Market study, Clinical protocol
Concept Design	4. State of the art	Patents, Open source database, Scientific articles
	5. Proposal	Functional decomposition, Morphological Matrix, QFD, AHP relevance
Components	6. S3 Selection	Classification database fed from books, manuals, datasheets
	7. Evaluation	S3 level and Value, Viability, ROI, AHP score

Table 3.5: Technological resources to support the IPPMD for MD reference model and methodology (An expanded version of the Toolbox can be find on Appendix B).

I **Screening tools** of structural, chemical, pathological and statistics medical analysis.

II **S3 Assessment tools** carried out within the care cycle phases and technology solutions which can be valuated with the S^3 taxonomy.

III **Need Statement tools** are related to any valid source of information, to establish the definition of the principal components for the solution.

IV **State of the art tools**, information sources of developments and possible solutions.

V **Proposal tools** are the ones that produce functional descriptions and alternatives which contemplate principal components.

VI **S3 Selection tools** will be any source of information that may feed possible components for the particular project, which will be classified with the S^3 taxonomy.

VII **Evaluation tools** in addition to the S^3 level requirement graphics, value/price ratio can be feed with expert knowledge as a cost/benefit criteria.

Chapter 4

Case Study

Coronavirus Disease 2019 (COVID-19) is an illness that affects principally the respiratory system caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). It can generate fever, tiredness, and dry cough and in some severe cases breathing difficulties that evolve into pneumonia, severe acute respiratory syndrome and even death [40]. It propagates when someone sick cough or sneeze and produce droplets with the virus, which can infect other people by breathing the particles or contaminating surfaces that other people may touch, then leading their hands to their eyes, mouth or nose[41]. The virus, presented in Fig.4.1 has a protective glycoprotein layer, which is destroyed in the presence of soap and water, the WHO Hand Wash protocol can be consulted in [42].

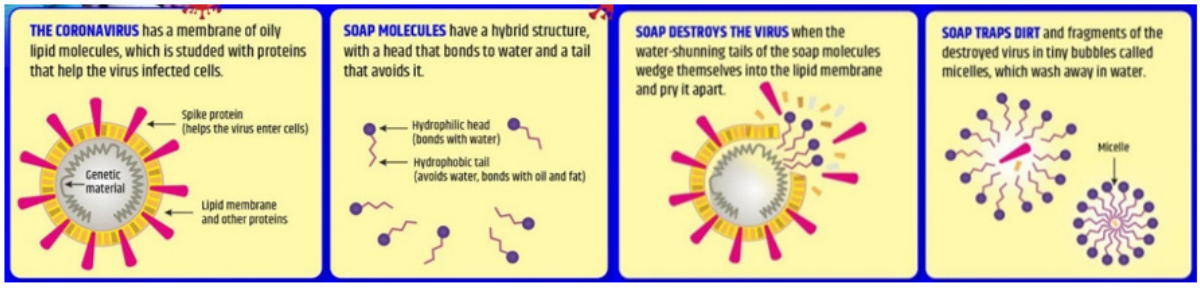


Fig. 4.1: SARS-CoV-2 glycoprotein surface vulnerability to water and soap (Adopted from Dr. Harsh Vardhan, 14th Mar, 2020).

The reason of being a virus mutation that is new in human affection, necessarily require for COVID-19 health perspective, problem analysis Fig. 4.2. Besides from the respiratory compromise of the patients, health care professionals notice that possible solutions are well defined through the patients care cycle [43], [44].

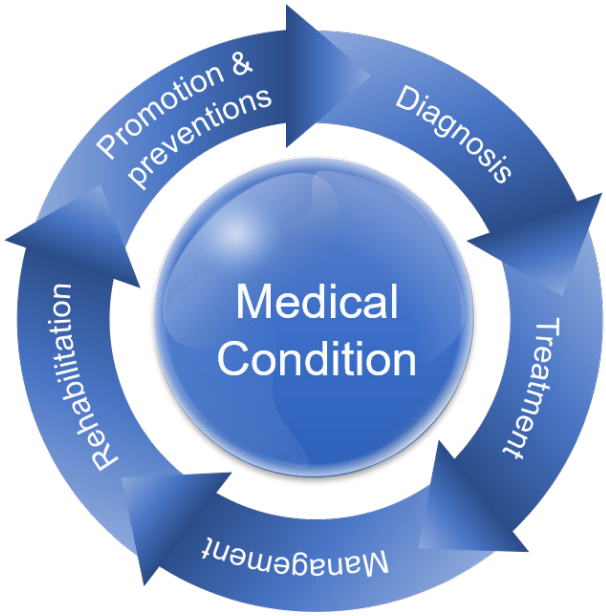


Fig. 4.2: Patient centered care cycle.

More detail around WHO suggested strategy can be found on [45]. There is mentioned that until a vaccine or medicine are successfully approved, the first countermeasure is to low the spreading behaviour which is known as flattening the curve [46].

1 **Vaccine** (Preventive): Still in development.
2 **Washing hands** (Preventive): A modification in the protocol would reduce re-contamination.
3 **Distance** (Preventive): Studies suggest that COVID-19 particles travel more than 2m.
4 **Test** (Diagnosis): Develop a cheaper, faster and precise method to isolate cases.
5 **Medicament** (Treatment): There are some alternatives, but still in test.
6 **CPAP** (Treatment): Severe cases need O2 and positive pressure airflow.
7 **Mechanical Ventilation** (Treatment): Critical cases need intubation and ventilation.
8 **Isolation** (Management): To avoid the health system from being surpassed.

4.1 Product Idea

4.1.1 Screening

Physiopathology analysis is presented in Fig. 4.3, where the affection [47] and case severity distribution [48] feed the physiology requirement of **Oxygen** to compensate the gas exchange deficiency and **Positive pressure** facilitates respiration by preventing alveoli from collapse.

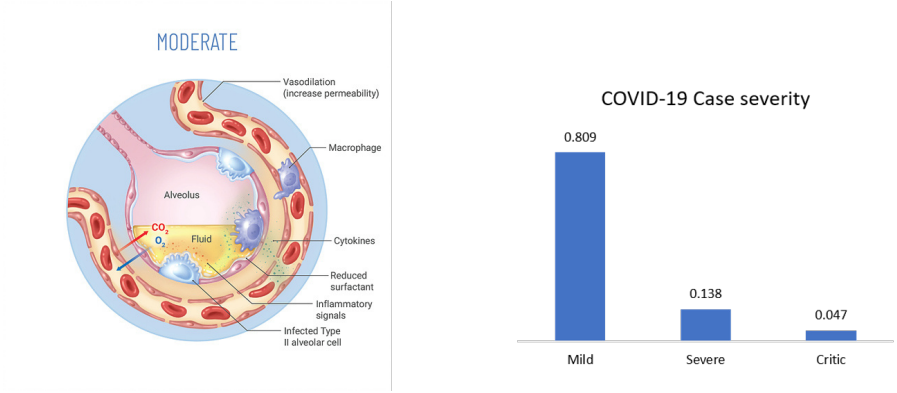
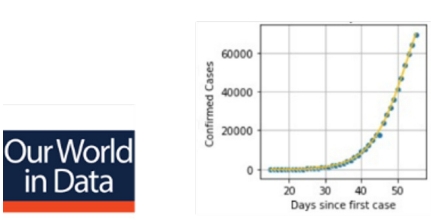


Fig. 4.3: COVID-19 effect on the alveoli (Avesta Rastan, 2020).
COVID-19 case severity in China (China CDC,11 February 2020).

Epidemiology analysis was implemented as in Fig. 4.4, with a world dataset [49] and Mx population [50], to treat information [51] and model the trending. It needs an **Easy to produce** device to cover the required quantity, **Cheap** to assure every population stratus, **Easy to use** for any healthcare provider, and already **Certified** to easier local approval.



Age	MX Population	ICU admission
0–19	34.53%	0.00%
20–44	38.12%	2.20%
45–54	11.59%	7.90%
55–64	8.15%	7.95%
65–74	4.70%	13.45%
75–84	2.16%	20.75%
≥85	0.76%	17.65%

Fig. 4.4: Epidemiology analysis of COVID-19 in Mexico (Our World in Data, United Nations, USA CDC, 2020).

4.1.2 S3 Assessment

In order to make the S^3 assessment, it is important to review all the characteristics that are implied in the problem. As mentioned in [45] it was declared pandemic, which implies that it affects to all the people; hence the solutions must cover every social stratus. Also it is important to understand the distribution, health impact and spreading behaviour from the screening; dividing by severity, the **care cycle analysis** is made with Fig. 4.2 to produce Tab. 4.1:

Severity	Mild	Severe	Critic
Health impact of the COVID-19 infection	Fever, cough and fatigue	Sore throat, difficulty to breath Pneumonia	Acute respiratory distress syndrome Low gas exchange
Diagnosis	Body temperature Pulse oximetry	X-ray (Radiography) Viral test	Ultrasonography (USG) Antibody test
Management	Isolation	Hospitalization	ICU care
Treatment	Antipyretic Analgesic	Positive pressure + O2 Inmunosupresor	Intubation Respiratory support
Technology	Thermomether Oximeter	Medical gas installation Air/Oxygen blender Oxygen analizer	Vital sign monitor Mechanical Ventilation

Table 4.1: COVID-19 care cycle - technology analysis.

Solutions are classified as technology and a technological **S3 level requirement assessment** of Tab. 4.2 can be made applying the S^3 taxonomy of Fig. 2.7. Is important to mention that for severe and critic case, health care system resources are limited. And the infected quantity typically doubles every 3-4 days before reaching its peak.

Technology	Sensing	Smart	Sustainable
Thermometer Oxymeter	1. Analogue 2. Digital	1. Analogous control, is not programmed	5. International Every clinic should have this elements
Medical gas installation Air/Oxygen blender Oxygen analizer	1. Analog 2. Digital	1. Analogous control because it is manual setup	4. National It is required by 13.8% of the COVID-19 cases
Vital sign monitor Mechanical Ventilation	3. Multisensing	3. Integrative control	3. Local Just 4.7 % requires

Table 4.2: S3 Assessment for COVID-19 technological requirements.

The epidemiology estimation showed the importance of response protocols, including methodologies to develop quick medical device alternative solutions, due to the risk of exponential propagation. In case health system is surpassed, the 5,523 mechanical ventilators reported on March 24th [52] could be insufficient; hence an strategy is to alternatively attended severe cases, to limit ventilators assignation for the critical cases.

The required S^3 levels to attend the COVID-19 severe cases with technology are:

- **Sensing Level 2 - Digital.** Requires to sense pressure and oxygen.
- **Smart Level 1 - Analogous control.** Manual control of air and oxygen blend and flow.
- **Sustainable Level 4 - National.** It has to be economically viable and equitable.

Sustainability is the principal differentiator, if a technology is to expansive; not every body will be able to buy it, and if its acquired; there wont be enough for every patient to use it.
In this particular problem the relevance of sustainability results to be priority, so;

The defined project is to use the partial model IPPMD for MD to generate the roadmap plan to develop a positive pressure air/oxygen blender system,that can reach every population stratus.

4.1.3 Need Statement

As mentioned above, a significant feature of the problem is the exponential spreading of the disease and hence at some point in time the lack of resources; particularly mechanical ventilators, that ideally should be assigned to support critical patients, will result insufficient.

As in Fig. 2.12, the problem delimits the characteristics of the solution, for the particular population to produce an expected condition improvement in the health state of the patient.

The **problem** **population** the **outcome**	is to assist with oxygen and positive air flow, is the severe cases of COVID-19 and is to improve gas exchange and prevent alveoli from collapse;
complement of the **problem** for the **population** **outcome**	is that is has to be a rapidly producible and economic, of Mx, in order to have an that overcome the limited resource of mechanical ventilators.

Table 4.3: COVID-19 severe cases need statement analysis (Biodesign structure).

Hence, to solve the COVID-19 with a preferable strategy, we need:

A device that can assist with oxygen and positive pressure air flow the respiratory system in COVID-19 severe cases (ICU patients) to improve gas exchange and prevent alveoli from collapse, with a rapidly producible and economic solution to overcome the limited resources of mechanical ventilation in the health system of Mexico.

4.2 Concept Design

4.2.1 State of the art

International initiatives have worked in the develop of valve bag based ventilation systems, however few have been validated by government entities for their production or use in patients, until now. Because valve bag-based ventilatory support systems can cause barotrauma and pneumothorax Fig.4.5 if they do not have good pressure, flow or volume control [53]. Additionally, there are tests to be held for medical devices powered by electricity (IEC 60601).

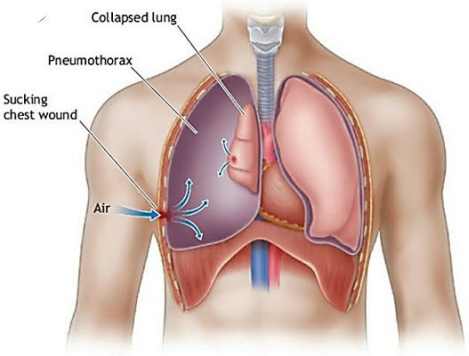


Fig. 4.5: Barotrauma and Pneumothorax.

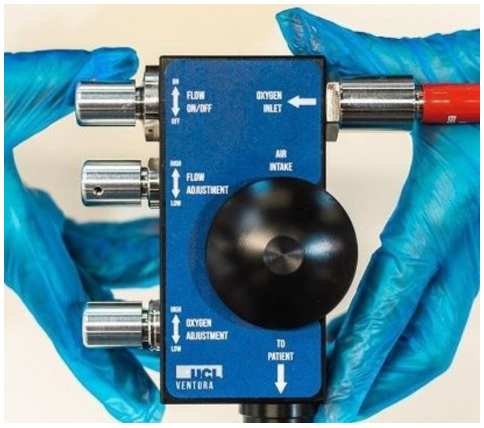


Fig. 4.6: UCL Ventura CPAP

On the other hand England, the Formula 1 team and University College London developed a CPAP that was tested and has already been approved by the Medicines and Healthcare products Regulatory Agency (MHRA) for production and use in patients. The team received orders from the British government to produce more than 10,000 fans. At the moment they have a production capacity of 1000 units per day [54].

What is best for a solution?

Merging all the previous requirement analysis, it may be synthesized a solution criteria with the most relevant features for the COVID-19 severe cases and limited ventilatory resources:

1. Precise, **2. Secure**, **3. Analogue**, **4. Easy to use**, **5. Cheap**, **6. Easy to produce**

Analytic Hierarchy Process

Developed by Thomas L. Saaty, mathematic from the University of Pittsburgh; to support in the relevance definitions from the solution criteria features.

The three principal steps for AHP are described on Fig. 4.7 as:

1. Hierarchical structure, where the objectives to achieve a goal in a project are established.
2. Relative importance relation, where the weights of the features are calculated.
3. Consistency evaluation to confirm if the evaluation was done correctly.

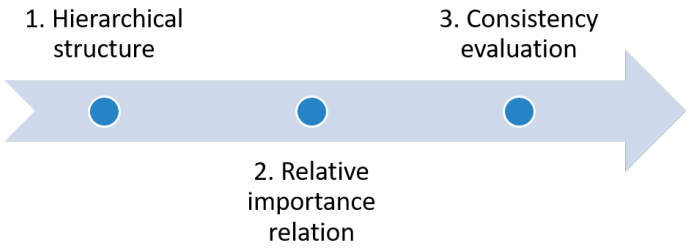


Fig. 4.7: AHP steps (Motivated on Saaty et al.).

1. Hierarchical structure

The goal is to evaluate the relevance features for the CPAP to deal with the COVID-19, so we require the relevance of the S3 components in Fig.4.8 then to locate the solution criteria.

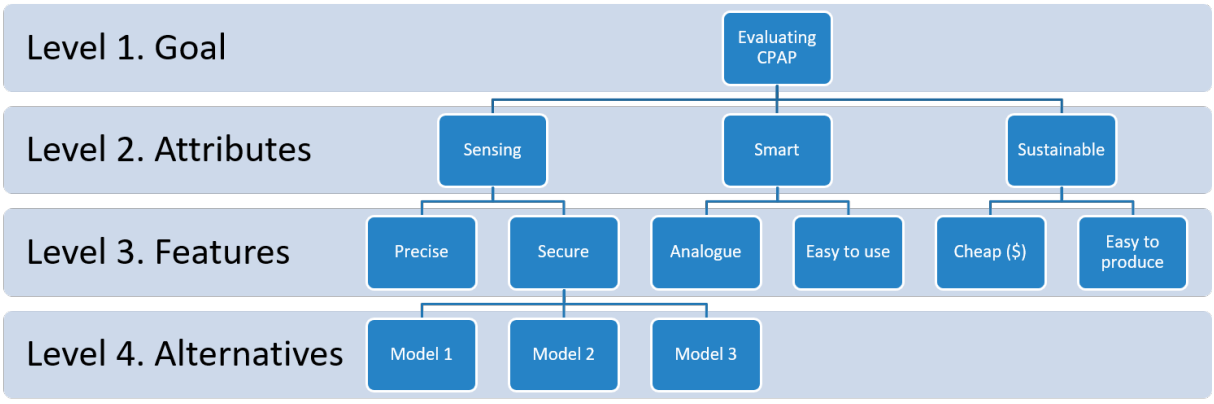


Fig. 4.8: AHP Heriarchical structure (Adapted from Saaty et al.).

2. Relative importance relation

In order to compare the features, is is required a scale of values; to establish, how important is one feature over other; in Fig.4.9 for instance, the arrows relate how important is Cheap feature with respect of Easy to produce.

Intensity of importance on an absolute scale	Importance
1	Equal
3	Moderate
5	Strong
7	Very strong
9	Extreme
2,46,8	Intermediate values

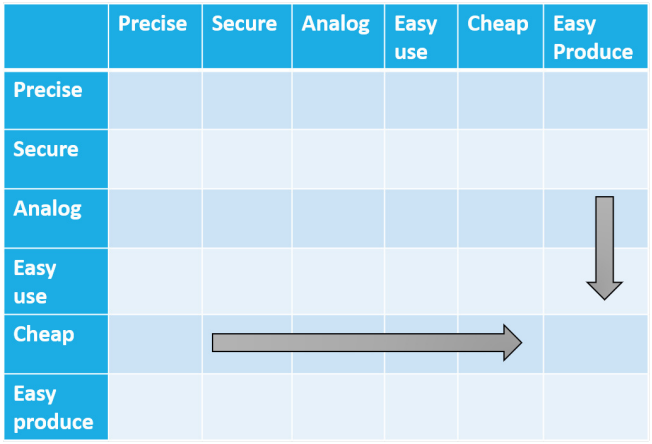


Fig. 4.9: AHP fundamental scale and Pair-wise comparison matrix (Adapted Saaty et al.).

So for us, security come first over precision; being then the must relevant of all both cheap and easy to produce, over the rest; leaving to the Fig.4.10 next result:

	Precise	Secure	Analog	Easy use	Cheap	Easy produce
Precise	1	1/2	3	3	0.5	0.5
Secure	2	1	5	5	1	1
Analog	1/3	1/5	1	2	1/6	1/6
Easy use	1/3	1/5	1/2	1	1/3	1/3
Cheap	2	1	6	3	1	1
Easy produce	2	1	6	3	1	1
∑	7.67	3.90	21.50	17.00	4.00	4.00

Fig. 4.10: Normalization of pair-wise comparison matrix (Motivated from Saaty et al.).

To normalize, we require to calculate:

$$Criteria(i)' = Criteria(i) / \sum Criteria$$

This is the normalized matrix Fig.4.11, which values we can use to calculate the criteria weight; that we can translate as percentage in the final result if it is validated.

	Precise	Secure	Analog	Easy use	Cheap	Easy produce	Criteria Weighs
Cheap	0.130	0.128	0.140	0.176	0.125	0.125	0.144
Secure	0.261	0.256	0.233	0.294	0.250	0.250	0.261
Analog	0.043	0.051	0.047	0.118	0.042	0.042	0.065
Easy use	0.043	0.051	0.023	0.059	0.083	0.083	0.044
Cheap	0.261	0.256	0.279	0.176	0.250	0.250	0.243
Easy produce	0.261	0.256	0.279	0.176	0.250	0.250	0.243

Fig. 4.11: Weights calculation (Saaty et al.).

With the normalized value, we can calculate the Criteria Weights:

$$Criteria\ Weight(j)' = \sum Criteria(j)/n$$

3. Consistency evaluation

To calculate the consistency ratio Fig. 4.12 we require the maximum principal eigen value, then the consistency index to finally divide it between a consistency from a random judgement.

	Precise	Secure	Analog	Easy use	Cheap	Easy produce	Weighted Sum	λ
Precise	0.152	0.077	0.471	0.397	0.313	0.313	1.097	7.209
Secure	0.304	0.154	0.785	0.662	0.625	0.625	1.905	12.381
Analog	0.051	0.031	0.157	0.265	0.026	0.026	0.503	3.205
Easy use	0.051	0.031	0.078	0.132	0.052	0.052	0.292	2.209
Cheap	0.076	0.038	0.942	0.397	0.156	0.156	1.453	4.360
Easy produce	0.076	0.038	0.942	0.397	0.156	0.156	1.453	7.267

$$\lambda(j) = \frac{Weihted\ value\ (j)}{Criteria\ Weight(j)}$$

$$\lambda_{max} = \frac{\Sigma\lambda}{n} \qquad \lambda_{max} = 12.381$$

$$Consistency\ Index = \frac{\lambda_{max} - n}{n-1} \qquad C.I. = \frac{12.381 - 6}{5} = 0.02109 \qquad C.R. = \frac{0.02109}{1.24} = \mathbf{0.0170} \qquad C.R. < 0.10$$

$$Consistency\ Ratio = \frac{Consistency\ index}{Random\ index}$$

n	1	2	3	4	5	6	7	8	9	10
Random consistency index (R.C.I)	0	0	0.58	0.9	1.12	1.24	1.32	1.41	1.45	1.49

Fig. 4.12: Weights calculation (Saaty et al.).

Consistency Ratio resulted minor than 0.1 or 10%, then the evaluation resulted to be correct.

4.2.2 Proposal

The proposal is to replicate the continuous positive airway pressure (CPAP) device developed by the University College London and the Mercedes-AMG High Performance Powertrains team from the Formula 1. In order to do so, a **Functional Decomposition Diagram** (FDD) is carried out in Fig.4.13 and 4.14 as part of the selected analysis activities from the IPPMD:

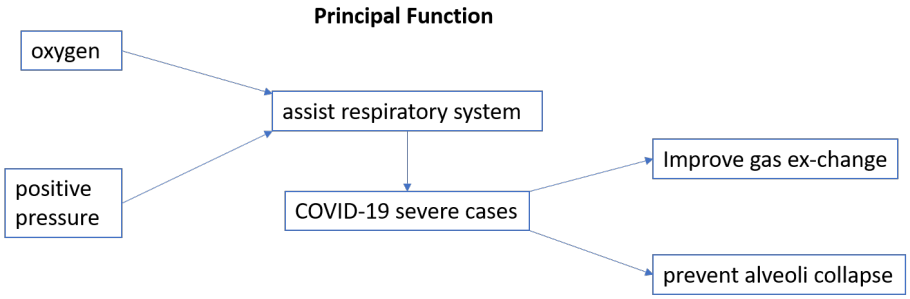


Fig. 4.13: Principal function of the CPAP
(IPPMD, Concept Design Toolbox, Molina et al.).

Once the principal function is defined, the secondary and tertiary functions are established; for instance to improve gas-exchange is required to blend air with oxygen, to prevent alveoli from collapse is important to increase the pressure inside the; and so on:

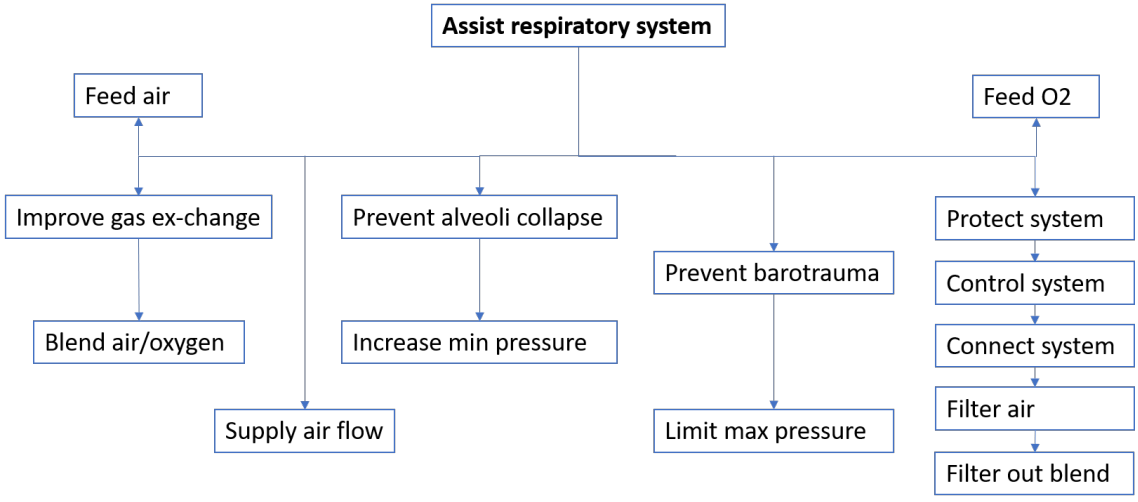


Fig. 4.14: Functional Decomposition Diagram of the CPAP
(IPPMD, Concept Design Toolbox, Molina et. al.)

With the FDD, a **Morphological matrix** is filled to generate a series of possible solution alternatives, with components that can carry out the functions on the left of Fig.4.15:

Functions/Solutions	S1	S2	S3	S4
Protect internal components	Plastic	Stainless Steel	Al	Ti
Control: On/Off, O2%, Flow	Solenoid valve	Mechanical valve		
Filter: Air input, Air/O2 output	Nonwoven fabric	Carbon	Hypochlorite sodium	
Set Min & Max Pressure	Plastic	Stainless Steel	Al	Ti
Measure O2%	Oxygen analizer			
Measure Pressure	Analogue gauge	Digital gauge		

Fig. 4.15: Morphological Matrix for the CPAP
(IPPMD, Concept Design Toolbox, Molina et. al.)

Mixing components, three concepts of solution alternatives are presented in Fig.4.16, where:

A **Concept, consist in a plastic pressure fixed CPAP**, producible in a 3D printer, disposable; but not very sustainable material.

B **Concept, consist in a Stainless steel electric controllable CPAP**, which may be reliable but would require IEC 60601 certification.

C **Concept, consist in a Aluminium analogue controllable CPAP**, with CAD files its parts should be easy to be produce on the CNC machines and then assembled.

Functions	Concept A	Concept B	Concept C
Protect internal components	Plastic	Stainless Steel	Al
Control: On/Off, O2%, Flow	No control	Solenoid valves	Mechanical valves
Filter: Air input, Air/O2 output	No filter	Hypochlorite sodium	Nonwoven fabric
Set Min & Max Pressure	Plastic	Stainless Steel	Plastic
Measure O2%	Oxygen Analyzer	Oxygen Analyzer	Oxygen Analyzer
Measure Pressure	Analogue Gauge	Digital gauge	Analogue Gauge
Sensing	2. Digital	2. Digital	2. Digital
Smart	0. No control	2. Digital control	1. Analogue control
Sustainable	0. Landfill	3. Local	4. National

Fig. 4.16: Solution Alternatives for the CPAP
(IPPMD, Concept Design Toolbox, Molina et. al.)

Remembering that **the S3 level requirement is 2,1,4; the alternative of concept C, suits better than the others**. It is a device that can sense pressure and oxygen in a digital way, the control does not require electricity so it can work any where with just a concentred Oxygen supply such as a concentrator or a medical gas tank, and due to its materials it can be disposed to be recycled completely and as social it can reach a national context if produced to to it's price and reduced cycle time for its production.

From now on, the selected concept C and proposal will be known as:

Analogue CPAP for COVID-19 ICU patients.

4.3 Components Specification

4.3.1 S3 Selection

With the concept, it's necessary to define the elements of the **Product Architecture** for the CPAP in Fig.4.17, that is the functional elements and physical components of products to define in words of Ulrich and Eppinger in 2000, *the basic physical building blocks of the product in terms of what they do and what their interfaces are to the rest of the device*.

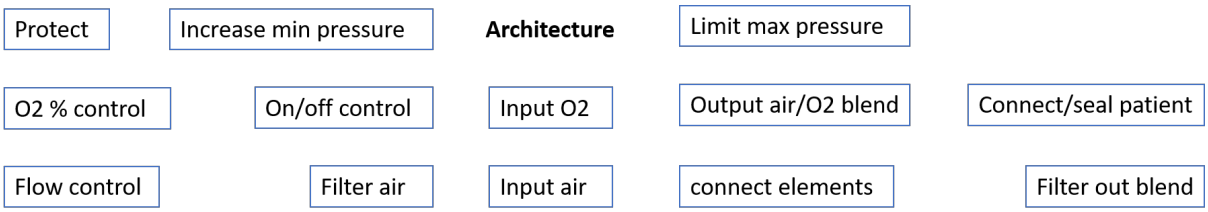


Fig. 4.17: Analogue CPAP architecture
(IPPMD, Toolbox, Molina et. al.)

As we can see there are some repeated elements: the Filter for Air and the Filter for the Air/O2 blend; and the components that limit max and min pressure, which can be similar.

With the Product Architecture, we can also produce a **Schematic Diagram**, to describe how the elements are connected, the Fig. 4.18 shows the connection of the complete system:

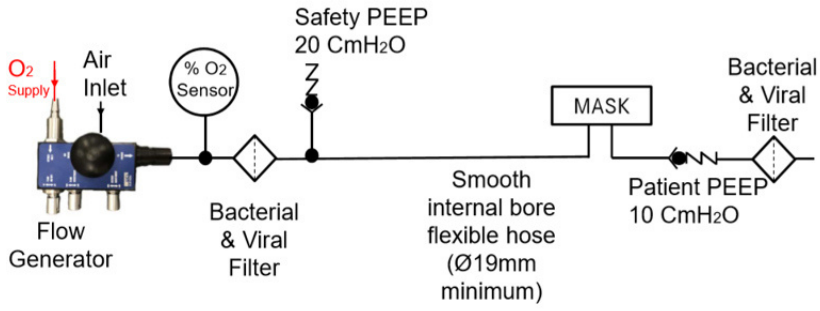


Fig. 4.18: CPAP System schematic (UCL, 2020).

With the diagram, we can define a **Bill of Materials** (BOM) that is required for the complete CPAP system to function in Tab. 4.4, with the description and quantity:

Part	Description	Quantity
Mechanic Valve	On/Off O2% Air/O2 Flow	3
Medical gas connector	Oxygen	1
Cloth filter	Air input Patient output	2
Closed face anesthetic mask	Sealed 2 connections	1
PEEP Valves	Max 20cm H2O pressure Min 10cm H2O pressure	2
O2% Analyzer	Resolution: 0.1% Precision: +- 2% over the lecture	1
Pressure gauge	From 0 to 30cm H2O	1

Table 4.4: Bill of Materials for the CPAP.

4.3.2 Evaluation

Advantages and disadvantages of some initiatives and commercial devices where embodied in the **S3 level** matrix of Tab.4.5 is made to enhance a comparison between initiative devices; where mechanical ventilator, valve bag ventilation systems, plastic 3D printed CPAP's, digital apnea CPAP machines and the UCL-Ventura device are to be evaluated.

Medical Device	**Sensing**	**Smart**	**Sustainable**
Mechanical ventilator	3	3	1
Valve bag system	2	2	3
Plastic 3D printed CPAP	2	0	1
Digital CPAP	3	2	2
Analogue UCL-Ventura CPAP	2	1	4

Table 4.5: S3 Level of initiative and commercial devices.

According to the problem analysis and solution criteria, previously held, the S^3 components require: **Sensing 2** - Digital, **Smart 1** - Analogue Control, and **Sustainable 4** - National.

AHP relevance to selection

We also have the relevance from the Concept Design, in the State of the art evaluation activity of Analytic Hierarchy Process 4.19 by summing the weighted values of each feature that correspond to the S3 component. In order of relevance, the S3 components are:

CRITERIA WEIGHTS

Attribute	Features	Criteria Weights
Sensing	Precise + Secure	0.4047
Smart	Analog + Easy use	0.1089
Sustainable	Cheap + Easy produce	0.4864

RELEVANCE

1. Sustainable: 48.64%
2. Sensing: 40.47%
3. Smart : 10.89%

Fig. 4.19: Weights calculation (Saaty et al.).

1 **Sustainability**, because it is pandemic, affects everyone, the solution should be also demographic; as local innovation principle, to be produced inside the nation.

2 **Sensing**: This is the less important because pressure gauges are easy to find, as well as oxygen analyzers. And the functionality of the device does not rely on those sensors.

3 **Smart**: For this is important to have a low level, this way wont require electricity to function and is less susceptible to fail in use.

AHP score

With this information, we can calculate the score Fig. of each of the alternatives; as the distance from the level of the feature to the objective in each component of the S3, and then the sum of product against the percentages of relevance:

Device	Sensing	Smart	Sustainable	Score
Objective	1	1	1	100
Mechanical Ventilator	0.8	0.6	0	58
Valve bag system	1	0.8	0	88
Plastic 3D printed CPAP	1	0	0	69
Digital CPAP	0.8	0.8	0	70
Analogue UCL-Ventura CPAP	1	1	1	100

SCORE

1. Analogue CPAP: 100
2. Valve bag system: 88
3. Digital CPAP: 70

Fig. 4.20: AHP scores to select the medical device to develop.

Where the equations for distance and score are:

$$Distance(i)\ S(j) = 1 - Abs(Device(i)\ S(j) - Objective\ S(j)$$

$$Score(i) = (\sum Distance(i) * Weight\ S(j)) * 100$$

So related to the Sensing, Smart, and Sustainable components of Technology level, the evaluation showed that the best option from the requirement is the Analogue CPAP, followed by the valve bag systems (even though there is a risk of Barotrauma).

Value/price ratio

Alternatives evaluation, that is similar to the Benefit Cost Ratio (BCR) from cost-benefit analysis to analyze how profitable is a project. A scale from 0 to 5 is proposed in Tab.4.6, where Value is the capacity to solve categorical variable for the health problem and price is an approximation of the acquisition cost from the market.

Value	Description
0	Does not solve
1	Solves incorrect, imprecise or risky
2	Solves in a estatic way
3	Solves in a flexible manner
4	Solves more than required
5	Solves the problem and serves to other issues

Price	Description
0	Free of cost
1	Cheap
2	Economic
3	Cost-effective
4	Expansive
5	Very expansive, for some it is unaffordable

Table 4.6: Value price scale definition.

With the scale definition, an expert analysis is required to assign the alternatives to the Value/Price Matrix according to it's characteristics of capacity to solve and cost of acquisition. Evaluation of the CPAP and the other Air/O2 blending systems is embodied in Tab. 4.7 where the ratio is calculated resulting in the nex values:

Where V/P ratio shows that the Analogue CPAP contribution is higher than the other devices.

To represent this, a graph Fig. 4.21, it can be seen the position graph of value vs price of medical devices for the particular COVID-19 severe cases.

Medical Device	Price	Value	V/P ratio
Mechanical ventilator	5	5	1
Valve bag system	3	4	1.33333
Plastic 3D printed CPAP	1	2	2
Digital CPAP	4	4	1
Analogue CPAP	2	3	1.5

Table 4.7: Value, Price and Value/Price ratio S3 assesment.

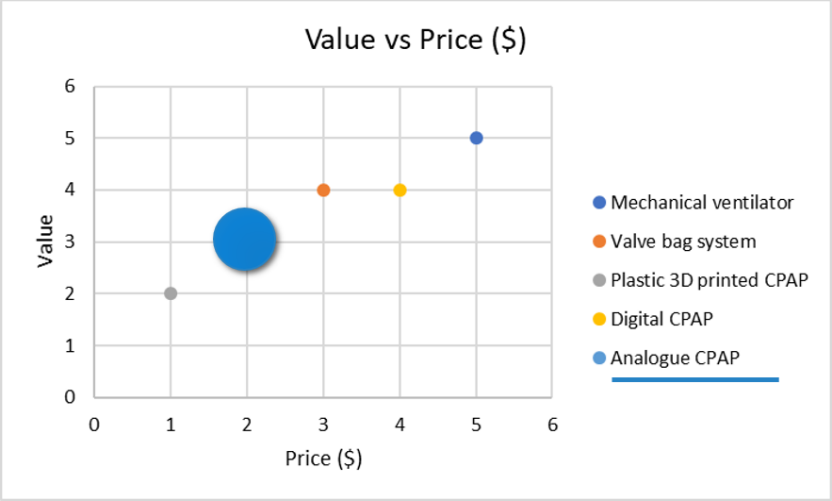


Fig. 4.21: Value vs Price medical devices for COVID-19 severe cases evaluation graph

In the particular case, higher value is not necessarily better; because the solution aim to reach everyone, so is better a lower price such as the here validated Analogue CPAP.

Chapter 5

Discussion

5.1 Recapitulation

Medical device design methodologies are ever more important; however they lack from I4.0 and SDG trends Fig.5.1 which can be find in the Sensing, Smart, and Sustainable concepts and taxonomy to evaluate technological level.

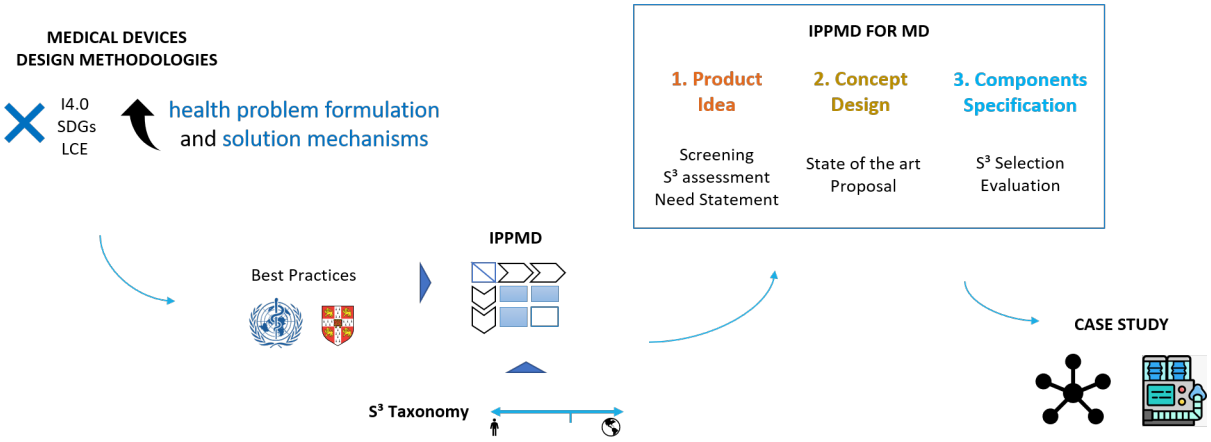


Fig. 5.1: IPPMD reference model and methodology to develop the S3 MD project.

IPPMD principles of LCE, System modeling and Instantiation, may also feed and serve as a basis in the development of Medical Device design methodologies to improve health problem

formulation and find solution mechanisms. Align with best practices from WHO and Cambridge; the proposal resulted in a three stage road map, where:

1. Product Development consider the activities of Screening (WHO) to analyze and prioritize health problems, a proposed S^3 assessment with the application of the developed taxonomy, and Need Statement (Cambridge) to formulate the specific problem for a delimited population with the expected outcomes.

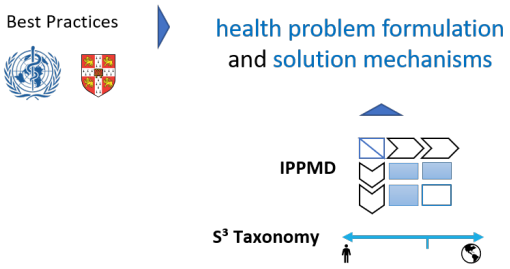
2. Concept Design, contemplates a research of the state of the art to analyse possible solutions and compare in order to find the best alternatives; with methodologies to portray function principles and characteristics.

3. Components specification, then gather the information from previous to deposit in an architecture and a schematic that defines the components required as well as the connection of the elements for the system to function. An finally places the information in a bill of materials to continue the development. The analysis is held with a S^3 evaluation and a Value/price ratio to look for the device that not only meets the requirement of technological level, but also produces the greatest benefit.

The case Study was then held to prove the methodology, the COVID-19 was the health problem; it was delimited to the severe cases. The application of the IPPMD for MD resulted in the formulation of the requirements of O2 and Positive pressure, and the proposal of develop of an Analogue CPAP.

5.2 IPPMD for MD features

The proposal is now compared in Fig.5.2 with the next elements:



Feature	WHO Blueprint	Cambridge Biodesign	IPPMD for MD
Priorization	✓		✓
Roadmaps			✓
Integration	✓	✓	✓
I4.0, LCE			✓
Sustainability	✓		✓
Flexibility		✓	✓
Feedback		✓	✓
Automatable			✓

Fig. 5.2: Medical Device Design Methodologies analysis

Where the best practices feed the health problem formulation and the IPPMD model and S^3 taxonomy feed in the solution mechanisms. Analysing the methodologies, we have:

Prioritization, is a term used by the WHO; which consist in analyze a health problem or several to select the must relevant or delimit the aspects of one.

Road maps are the activities workflow and reference direction to develop a project, WHO and Cambridge only propose one; IPPMD generates each time a development is to be held.

Integration means the involvement of different scientific fields, important in the MD area.

I4.0 and LCE concepts continuous evolution of technology; and the importance of developing a project within the approach of its complete life cycle and components.

Sustainability, importance of the three pillars for the world; social, economic, environment.

Flexibility is related to the capacity of reconfiguration.

Feedback to constantly reformulate the project in a continuous improvement mechanism.

Automatable with the correct knowledge base Fig.7.1, the S^3 taxonomy could support in the requirement analysis and the selection of components.

Chapter 6

Contributions

In the research and analysis of medical device design methodologies, I expected to find a simple and well defined structures to develop medical technology. However WHO R&D Blueprint displayed low methodological information (it is more related to health management, guidance and governance suggestions) and Cambridge Biodesing turn up to be a vast compendium with definitions, processes and examples; that may not all be required by a developer to produce innovation.

The IPPMD methodology in this case was easier to follow, but the model aspect is more related to computational systems; hence it may serve well to build up applications that are related to health data analysis for patients and information management for life cycle platforms in the development of products. Thus IPPMD flexibility to support any kind of technology project, result in a differentiator that was exploit to build the proposal within it's borders.

Integration of so many components Fig.6.1 was not an easy task, but the relations were well posted and the definitions from the basis, the IPPMD and S^3 taxonomy helped in the allocation of the selected new components of best practices activities and proposed applications of the taxonomy; that helpfully will aid in the creation of healthcare technology.

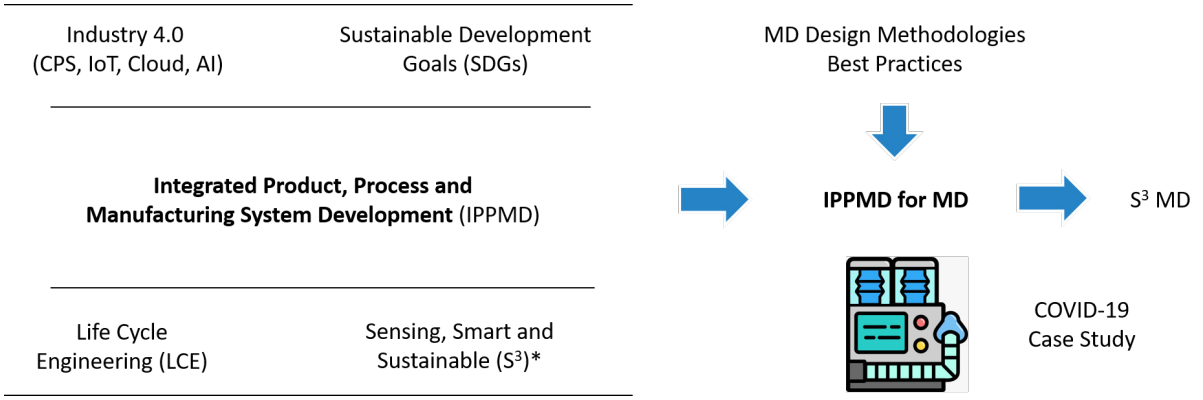


Fig. 6.1: Research structure IPPMD refernece model to design the S3 MD

The research questions where asked: the importance of MD design methodologies relies on the readiness to take action when it is required, instantiation showed to be a crucial in the integration of the best practices of the MD sector inside the proposed methodology. However there was a misleading in the developing time feature for MD that was initially considered.

Contributions are described below:

1. **Instantiation of the IPPMD for MD**:
As we mention in the problem formulation, till the instantiaton of the reference methodology to design medical devices proposal from the project; previously, there was no MD design methodology that entwined LCE principles, I4.0 and SDGs.

In the development of the IPPMD reference method to design the S^3 medical devices, the integration of the WHO and Cambridge international key elements to design MD, showed to be principal components inside the proposal to *delimit health problems*; and the IPPMD structural scheme and wide set of resources, resulted to be fundamental for the selection of *solution mechanisms* to support in the development of health technology.

2. **S3 taxonomy update**:

What we accomplished was an update of the S^3 level definitions, related to historical evolution of technology and human capacities as a reference; with the impact graduation for the sustainable component. The improvement is that previous it that had a established relation to enterprise systems by its origin and now is focused on capacities of products and their influence when combined, spread and collaboration.

3. **S3 assessment activity**:

With the taxonomy, we apply a care cycle analysis for health challenges, to feed the S3 level requirement evaluation; to set a reference for the technology parameters of the solution that will be developed within the rest of activities of the IPPMD for MD.

4. **Validation of the IPPMD for MD**:

The case study served as a validation opportunity for the application of the reference methodology and the proposed taxonomy update; where even a novel activity, the S^3 assessment, to apply in the Product Idea stage was checked.

Even though the reference methodology for MD was developed and applied, there is still an area of opportunity in the classification of technology to build a data base within the S^3 taxonomy, where if programmed; the requirement input could be replied with a solution level criteria to be developed. Thus the same principle may be focused on the classification of several technological components, according to features of relevance such as precision, resolution, capacity, price, to mention some; which also according to the objective may be clustered to feedback with a filtered technology suggestions to facilitate in the selection.

Chapter 7

Conclusions

The integration of medical device development best practices from WHO and Cambridge within a flexible, configurable reference the IPPMD; resulted in a well defined and structured model and methodology to support the health problem formulation and finding of solution mechanisms. Where the Screening (WHO) and Need Statement (Biodesign) help in the analysis of the challenge, to propose a precise description of a delimited population and expected outcome. Then IPPMD elements and S^3 taxonomy propitiate the finding of requirement and hence solutions with the adequate characteristics.

The hypothesis was proved to be correct, as the proposed reference model and design methodology positively influence the health problem formulation as described with the activities selected from the international best practices and the proposed S^3 assessment within the care cycle analysis. As well it may produce adequate solutions from a criteria of technology level as guideline to develop a proposal with this purpose, of meeting the requirement level.

Screening and Need Statement do reduce solution options and parameters specifications, by delimiting health problems to singular demographic and affection characteristics; that was proved in the case study, where once a proposal was developed the evaluation showed that

there are technologies that overcome the challenge in a superior manner and others fall short compared to the requirement.

The S^3 taxonomy showed to be a potential parameter of technology evaluation and classification; that aligned with project objectives, serves to clear a path for the development of products. The application seems to be easy to follow, however it may require a improvement in the Smart element; where the characteristic is focused on control, nevertheless technology may have other types of intelligence for example to classify different elements from a data set, or to provide suggestions over decision making process.

The suggestion then is to change the Smart component from the S^3 taxonomy from control specification, to a intelligence kind of concept; it is also important to increase the concept with technology classifications to produce a base of knowledge, that may open the engineering landscape to other borders.

7.1 Further outcomes

Adhesion of new stages for the development of MD in Fig.7.1,

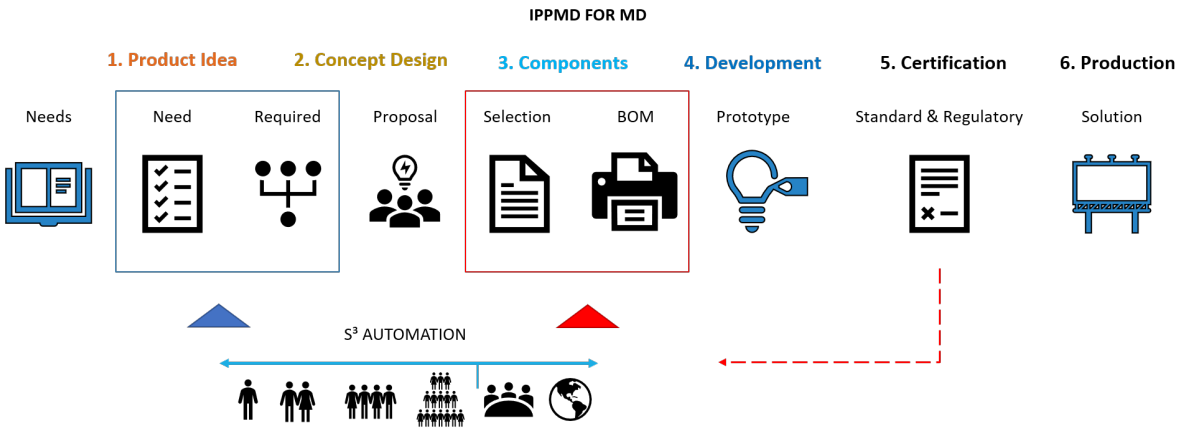


Fig. 7.1: Further outcomes for the IPPMD for MD

The certification process should feed back to the S^3 requirement evaluation to improve the solution definition in order to be approved and accepted for production to be use on patients.

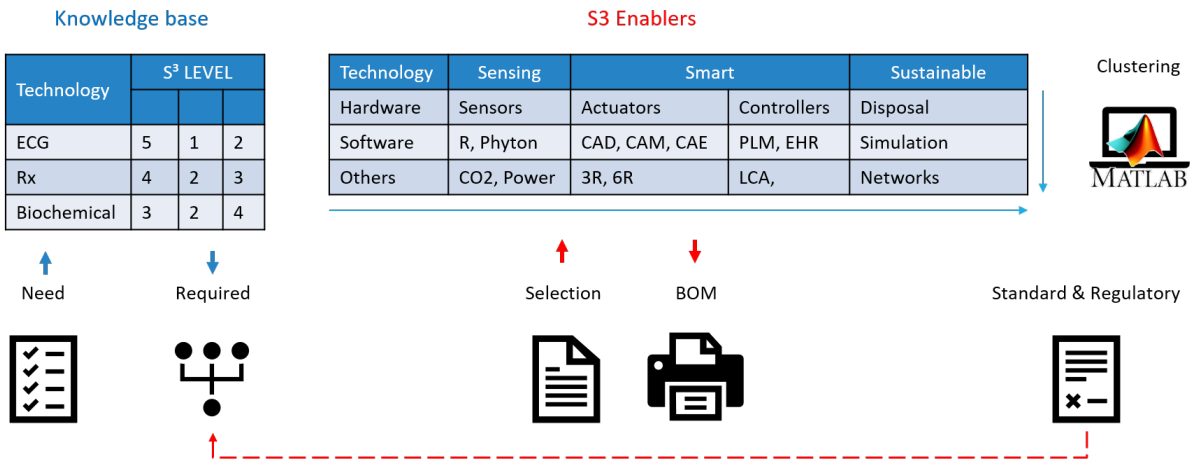


Fig. 7.2: Value vs Price medical devices for COVID-19 severe cases evaluation graph

The S^3 taxonomy could be automated, with the creation of a database to support in the requirement evaluation as in Fig. 7.2 which also can serve as a repository of components information to be classified and then with a program like matlab a Classification method can be held as the K-NN or Principal Component Analysis, in order to reply in the search of a certain level of properties (for example precision, or price) and order the results with relevance in the features searching objective.

Appendix A

Abbreviations and acronyms

AI - Artificial Intelligence

BOM Bill of Materials

CAD Computer-Aided Design

CAE Computer-Aided Engineering

CAGR - Compound Annual Growth Rate

CAM Computer-Aided Manufacturing

CANVAS Business model canvas

CNC Computer Numerical Control

CPAP - Continuous Positive Airway Pressure

CPS - Cyber Physical System

CRM Customer Relationship Management

ERP Enterprise Resource and Planning

GERAM - Generalised Enterprise Reference Architecture and Methodology

GDP - Gross Domestic Product

ICT Information and Communications Technology

IoT Internet of Things

IPPMD - Integrated Product, Process, and Manufacturing System Development

I4.0 - Industry 4.0

LCE - Life Cycle Engineering

LCA - Life Cycle Assessment

LOA - Levels of Automation

MD - Medical Devices

OECD - Organization for Economic Co-operation and Development

PDM Product Data Management

PLC - Product Life Cycle

PLM Product Lifecycle Management

RFID Radio-Frequency Identification

R&D - Research and Development

S^3 - Sensing, Smart and Sustainable

SCADA Supervisory Control and Data Acquisition

SDGs - Sustainable Development Goals

SRM Supplier Relationship Management

UN - United Nations

UML Unified Modeling Language

WHO - World Health Organization

Appendix B

System Modeling

A health tech project is usually of high complexity, it involves multiple disciplines such as medicine, biomedical engineering, electronics, physics; and in order to successfully be implemented, the strategy should be clear for all the involved elements. Thus, it is important to have a representation of the model in different views, such as Fig. B.1

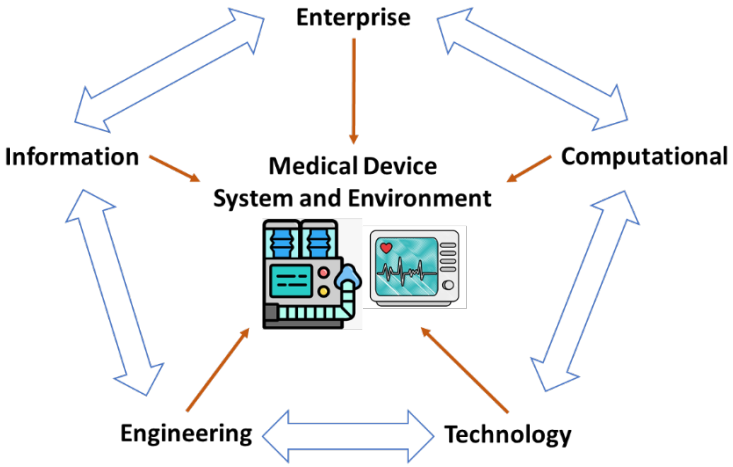


Fig. B.1: IPPMD Medical Device System and Environment modeling views (Adapted from RM-ODP).

The ISO TR9007 (International Organization for Standardization) Reference Model for Open Distributed Processing (RM-ODP) specifies this set of viewpoints for software/hardware systems [55], which normally health tech requires; however the most common applications are

related to Product Life cycle Management software and Electronic Health Record with the Health Level Seven (HL7) Reference Information Model.

The aim of the RM-ODP is to reduce problems that may come from the design, by providing an integration of commonly separated aspects. In the case of Health Informatics, it is referred as as a revolutionary approach with exclusivity characteristics provided by the interrelationship and knowledge representation[56].

- Enterprise view is related to the business objectives and process, its relations, involvement and roles of human resources within an organizational structure. It is established from levels and areas which is useful to define or identify key participants / responsibilities in the decision-making process, but also in the engineering process that requires supervising and liberation of activities.
- Information view specifies data to feed the product data management (PDM) and other applications enterprise resource management such as enterprise resource planning (ERP) or the manufacturing execution system (MES).
- Computational view presents functional structure of the system to produce interactions from the core business, such as product development process, instructions processing. Also, supplier / client relations are established.
- Engineering view collaborates in the mechanisms that serve as basis of the interactions, that is functions and protocols.
- Technology view helps in the election of tools to accomplish the system implementation and communication between the rest of the components.

To capture all the important elements of a MD development project as functions, business, and organization; a set of specific representations can be used such as Flow Diagrams, Canvas, Organizational Structure, to refer some; toolbox with technological resources is set on Tab.B.1

Technological approuch	Objectives	Tools and methods, resources
Screening	To prioritize and define the problem requirements for the solution.	Physiology analysis Epidemiology analysis Need Statement Solution Criteria Literature Review S^3 Level Requirement
Invention	To propose a solution that is feasible.	Best practices Megatrend and market study Reverse Engineering Computer Aided Design (CAD) Electrical Computer-Aided Design (ECAD) Digital Twin (Product Simulation)
Abstraction	To define the concept of the proposal.	Functional Decomposition Product Architecture Elements Product Scheme Diagram Control Diagrams Morphological Matrix Production process
Integration	To setup the technical features of the product, bill of materials and so on.	Quality Function Design (QFD) Failure Mode and Effects Analysis (FMEA) Computer Aided Manufacturing (CAM) Computer Aided Engineering (CAE) Digital Twin (Process Simulation) Product Life Cycle Management (PLM)
Validation	To confirm the characteristics of the project.	Prototype Characterization Regulatory and Clinical strategy Quality Control Digital Twin (Production Simulation)
Implementation	To establish goals, resources and interactions.	Business plan (CANVAS) Production plan, Distribution Layout design Workflow diagrams Procedure Manual
Management	To deal with the control of the elements of the project.	Enterprise Resource Planning (ERP) Supply Chain Management (SCM) Customer Relationship Management (CRM) Quality Management System (QMS)

Table B.1: Technological resources to support the IPPMD for MD reference model.

Bibliography

[1] E. Oztemel and S. Gursev, "Literature review of Industry 4.0 and related technologies," *Journal of Intelligent Manufacturing*, vol. 31, pp. 127–182, 2020.

[2] S. Manufacturing, "Industrie 4.0,"

[3] "Industry 4.0 Market | Size, Share, system and Industry Analysis and Market Forecast to 2024 | MarketsandMarkets."

[4] "Life Expectancy - Our World in Data."

[5] "Health resources - Health spending - OECD Data."

[6] "GDP growth (annual %) — Data."

[7] C. Vallejo, D. Romero, and A. Molina, "Enterprise integration engineering reference framework and toolbox," *International Journal of Production Research*, vol. 50, no. 6, pp. 1489–1511, 2012.

[8] "Countries are spending more on health, but people are still paying too much out of their own pockets."

[9] "World Bank and WHO: Half the world lacks access to essential health services, 100 million still pushed into extreme poverty because of health expenses."

[10] N. Health, "Global health's new entrants: Meeting the world's consumer," no. March, 2015.

[11] G. Santucci, C. Martinez, and D. Vlad-Clcic, "The sensing enterprise," *Proceedings of FInES Aalborg Workshop*, no. September 2012, pp. 1–14, 2012.

[12] L. Save and B. Feuerberg, "Designing Human-Automation Interaction: a new level of Automation Taxonomy," pp. 978–0, 2012. ISBN: 9780945289449.

[13] J. Frohm, V. Lindstrm, J. Stahre, and M. Winroth, "Levels of Automation in Manufacturing," p. 29.

[14] J. Qin, Y. Liu, and R. Grosvenor, "A Categorical Framework of Manufacturing for Industry 4.0 and Beyond," *Procedia CIRP*, vol. 52, pp. 173–178, 2016.

[15] C. Thuemmler and C. Bai, eds., *Health 4.0: How Virtualization and Big Data are Revolutionizing Healthcare*. Springer International Publishing, 2017.

[16] P. Bernus, L. Nemes, and G. Schmidt, *Handbook on Enterprise Architecture*. Springer Science & Business Media, Dec. 2012. Google-Books-ID: JS7yBwAAQBAJ.

[17] D. Chavarra-Barrientos, L. M. Camarinha-Matos, and A. Molina, "Achieving the Sensing, Smart and Sustainable Everything," in *Collaboration in a Data-Rich World* (L. M. Camarinha-Matos, H. Afsarmanesh, and R. Fornasiero, eds.), IFIP Advances in Information and Communication Technology, (Cham), pp. 575–588, Springer International Publishing, 2017.

[18] "About R&D Blueprint." Library Catalog: www.who.int.

[19] "Biodesign: The Process of Innovating Medical Technologies." Library Catalog: www.gsb.stanford.edu.

[20] K. Schwab, *The Fourth Industrial Revolution*. USA: Crown Publishing Group, 2017.

[21] R. C. Allen, *The British Industrial Revolution in Global Perspective*. Cambridge University Press, Apr. 2009. Google-Books-ID: O6MlPo2zNkIC.

[22] A. Chin, C. Juhn, and P. Thompson, "Technical Change and the Demand for Skills during the Second Industrial Revolution: Evidence from the Merchant Marine, 18911912," *The Review of Economics and Statistics*, vol. 88, pp. 572–578, Aug. 2006. Publisher: MIT Press.

[23] J. Rifkin, *The Third Industrial Revolution: How Lateral Power Is Transforming Energy, the Economy, and the World*. New York: St. Martin's Press, first printing ed., Sept. 2011.

[24] J. M. Velsquez-Bermdez, M. Khakifirooz, and M. Fathi, eds., *Large Scale Optimization in Supply Chains and Smart Manufacturing: Theory and Applications*. Springer Optimization and Its Applications, Springer International Publishing, 2019.

[25] C. D. Wickens, ed., *An introduction to human factors engineering*. Always Learning, Harlow: Pearson Education, 2. ed., pearson new internat. ed ed., 2014. OCLC: 881359037.

[26] M. Vagia, A. A. Transeth, and S. A. Fjerdingen, "A literature review on the levels of automation during the years. What are the different taxonomies that have been proposed?," *Applied Ergonomics*, vol. 53, pp. 190–202, Mar. 2016.

[27] J. Miranda, P. Ponce, J. Molina, and A. Molina, "Taxonomy of Levels of Sensing, Smart and Sustainable Products to support New Product Development," *IFAC-PapersOnLine*, vol. 52, no. 13, pp. 2384–2389, 2019.

[28] A. Jayal, F. Badurdeen, O. Dillon, and I. Jawahir, "Sustainable manufacturing: Modeling and optimization challenges at the product, process and system levels," *CIRP Journal of Manufacturing Science and Technology*, vol. 2, pp. 144–152, Jan. 2010.

[29] J. Frohm, M. Bellgran, and V. Lindstrm, "A model for parallel levels of automation within manufacturing," *18th International Conference on Production Research*, no. February 2017, 2005.

[30] C. Freeman, F. Louca, F. Lou, F. Loua, and F. Lou, *As Time Goes by: From the Industrial Revolutions to the Information Revolution*. Oxford University Press, 2001. Google-Books-ID: K3_nCwAAQBAJ.

[31] D. Pari, "Sensores y acondicionadores de senal ramon pallas areny," *S.A. MARCOMBO*, 2005.

[32] S. Russell and P. Norvig, *Artificial Intelligence A Modern Approach Third Edition*. Prentice Hall, 2010. ISSN: 0269-8889 Publication Title: Pearson _eprint: 9809069v1.

[33] B. Purvis, Y. Mao, and D. Robinson, "Three pillars of sustainability: in search of conceptual origins," *Sustainability Science*, vol. 14, pp. 681–695, May 2019.

[34] J. L. Martin, D. J. Clark, S. P. Morgan, J. A. Crowe, and E. Murphy, "A user-centred approach to requirements elicitation in medical device development: A case study from an industry perspective," *Applied Ergonomics*, vol. 43, pp. 184–190, Jan. 2012.

[35] A. S. Baluch, "Angstrom Medica: Securing FDA Approval and Commercializing a Nanomedical Device," *Nanotechnology Law & Business*, vol. 2, p. 168, 2005.

[36] A. K. Chatterji, K. R. Fabrizio, W. Mitchell, and K. A. Schulman, "Physician-Industry Cooperation In The Medical Device Industry," *Health Affairs*, vol. 27, pp. 1532–1543, Nov. 2008. Publisher: Health Affairs.

[37] A. Rudorfer, T. Stenzel, and G. Herold, "A Business Case for Feature-Oriented Requirements Engineering," *IEEE Software*, vol. 29, pp. 54–59, Sept. 2012. Conference Name: IEEE Software.

[38] E. B. Sloane, M. J. Liberatore, R. L. Nydick, W. Luo, and Q. B. Chung, "Using the analytic hierarchy process as a clinical engineering tool to facilitate an iterative, multidisciplinary, microeconomic health technology assessment," *Computers and Operations Research*, vol. 30, no. 10, pp. 1447–1465, 2003.

[39] P. Gu, "Product Architecture," in *CIRP Encyclopedia of Production Engineering* (L. Laperrire and G. Reinhart, eds.), pp. 987–991, Berlin, Heidelberg: Springer, 2014.

[40] W.-j. Guan, Z.-y. Ni, Y. Hu, W.-h. Liang, C.-q. Ou, J.-x. He, L. Liu, H. Shan, C.-l. Lei, D. S. Hui, B. Du, L.-j. Li, G. Zeng, K.-Y. Yuen, R.-c. Chen, C.-l. Tang, T. Wang, P.-y. Chen, J. Xiang, S.-y. Li, J.-l. Wang, Z.-j. Liang, Y.-x. Peng, L. Wei, Y. Liu, Y.-h. Hu, P. Peng, J.-m. Wang, J.-y. Liu, Z. Chen, G. Li, Z.-j. Zheng, S.-q. Qiu, J. Luo, C.-j. Ye, S.-y. Zhu, and N.-s. Zhong, "Clinical Characteristics of Coronavirus Disease 2019 in China," *New England Journal of Medicine*, vol. 382, pp. 1708–1720, Apr. 2020. Publisher: Massachusetts Medical Society _eprint: https://doi.org/10.1056/NEJMoa2002032.

[41] "Facts and figures about the coronavirus disease outbreak: COVID-19." Library Catalog: www.doctorswithoutborders.org.

[42] World Health Organization, "Hand Hygiene: Why, How & When?," *World Health Organization (WHO)*, no. August, pp. 1–7, 2009.

[43] CDC, "Coronavirus Disease 2019 (COVID-19)," Feb. 2020. Library Catalog: www.cdc.gov.

[44] W. Alhazzani, M. H. Mller, Y. M. Arabi, M. Loeb, M. N. Gong, E. Fan, S. Oczkowski, M. M. Levy, L. Derde, A. Dzierba, B. Du, M. Aboodi, H. Wunsch, M. Cecconi, Y. Koh, D. S. Chertow, K. Maitland, F. Alshamsi, E. Belley-Cote, M. Greco, J. S. Morgan, J. Kesecioglu, A. McGeer, L. Mermel, P. E. Alexander, A. Arrington, J. Centofanti, G. Citerio, Z. A. Memish, N. Hammond, F. G. Hayden, and L. Evans, "Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)," *ccmjournal.org*, p. 101, 2020.

[45] "WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020." Library Catalog: www.who.int.

[46] "These simulations show how to flatten the coronavirus growth curve." Library Catalog: www.washingtonpost.com.

[47] "Azuravesta Design | COVID-19 Pandemic." Library Catalog: www.azuravesta.com.

[48] "China: distribution of novel coronavirus patients by symptom severity 2020." Library Catalog: www.statista.com.

[49] "Coronavirus Source Data." Library Catalog: ourworldindata.org.

[50] "World Population Prospects - Population Division - United Nations."

[51] CDCMMWR, "Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) United States, February 12March 16, 2020," *MMWR. Morbidity and Mortality Weekly Report*, vol. 69, 2020.

[52] I. d. S. p. e. Bienestar, "El Pulso de la Salud | 24 de marzo de 2020." Library Catalog: www.gob.mx.

[53] A. Khoury, S. Hugonnot, J. Cossus, A. De Luca, T. Desmettre, F. S. Sall, and G. Capellier, "From mouth-to-mouth to bag-valve-mask ventilation: Evolution and characteristics of actual devices - A review of the literature," *BioMed Research International*, vol. 2014, pp. 1–7, 2014.

[54] "UCL-Ventura breathing aid (CPAP) Design and manufacturing package available from Covid-19 Research."

[55] A. Vallecillo, "RM-ODP: The ISO Reference Model for Open Distributed Processing," *DIN Edition on Software Engineering*, vol. 3, no. January, pp. 66–69, 2001.

[56] L. Bos, *Medical and Care Compunetics 3*. IOS Press, 2006. Google-Books-ID: 0vHjxr2G0CEC.