National University of Science and Technology POLITEHNICA Bucharest

Faculty of Automatic Control and Computer Science

PhD Thesis Summary

PhD Field - Systems Engineering

A Digital Twin Model for e-Health Systems and Personalised Medicine

Model de reprezentare digitală pentru sisteme de e-sănătate și medicină personalizată

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Contents

Abstract

The thesis proposes the development of an architectural framework for "Digital Twin" representation systems in e-health and personalised medicine, facilitating the representation and aggregation of data from multiple sources, as well as structuring and correlating this data for the identification of pathologies and the development of personalised treatment plans. The work includes a study of existing contributions from the literature regarding the concept and applications of the "Digital Twin". An important part of the study was dedicated to the applicability in the medical field, with a focus on e-health systems. Following the study, an architectural framework for digital representation in e-health and personalised medicine systems was proposed, complemented by a risk analysis model and ethical considerations related to the application of the "Digital Twin" in the medical domain. The modeling of functional, physical, and data levels was achieved using SysML diagrams, thus facilitating the management of complexity. The architectural framework was customized for ophthalmology, and validation was carried out in collaboration with specialist physicians by implementing basic blocks of the "Digital Twin" type digital representation system. These systems process clinical and imaging data collected from various medical equipment, using artificial intelligence algorithms to identify glaucoma, contribute to the creation of personalized treatment plans, and simulate scenarios for the progression of pathologies.

1 | Introduction

1.1 The current context

With the rapid evolution of technology, particularly driven by advancements in artificial intelligence, big data processing, and bioinformatics, the medical field is becoming one of the sectors where digitalization and the optimization of health systems are being pursued intensively. One of the emerging concepts facilitating the development of e-health systems and personalized medicine is Digital Twin. Digital Twin systems are digital representations of physical or biological systems used for modeling, monitoring, simulating, and optimizing complex systems.

A digital representation model for e-health systems and personalized medicine focuses on outlining a general modeling framework associated with a health system, a patient, an organ, or a pathology that allows for the collection, storage, processing, modeling, and analysis of health data. This facilitates diagnostic accuracy and supports the clinical decision-making of medical staff. Integrating personalized medicine into the creation of digital representation models aids in developing personalized treatment plans by incorporating information from multiple sources, including the patient's genetic data from DNA sequencing, demographic factors, and lifestyle analysis.

Following a study, the need for the development of personalized diagnostic and treatment methods in various clinical fields was identified. The analysis conducted on the applicability of Digital Twin in medicine revealed that one of the promising research directions is ophthalmology, a specialty exemplified in the case study of this work. Given that one of the primary causes of blindness worldwide is glaucoma—an initially asymptomatic condition that progresses gradually—this work aims to create a digital representation model, or Digital Twin, for e-health systems and personalized medicine, focusing on identifying predispositions to this pathology.

Starting from the general context and the identification of the previously mentioned problem, this chapter will present the objectives, methodological approaches used in the research, and the structure of the work.

1.2 The objectives of the thesis

In this section, the main research directions that contribute to the development of a general modeling framework for e-health systems and personalized medicine are presented and structured.

The general objective of the thesis consists in the development of a modeling framework for Digital Twin type digital representation systems for e-health and personalized medicine, with the goal of facilitating the representation and aggregation of patient data in a virtual environment, as well as structuring and correlating this data within diagnostic and treatment models. The implementation of systems in accordance with the proposed modeling framework brings benefits to the process of identifying the early stages of pathologies and contributes to the development of personalized treatment plans in clinical fields. The validation of the proposed general modeling framework was carried out through the implementation of a specific modeling framework in ophthalmology for the identification and management of ocular pathologies such as glaucoma.

The specific objectives include:

- *Conducting a study on the current state of Digital Twin systems, including concepts, definitions, classifications, architectural models, methods of integration, and their application in various fields such as manufacturing systems, smart cities, education, and energy systems*
- *Analyzing the use of Digital Twin systems in medicine*
- *Developing a generic modeling framework for the implementation of virtual representation systems based on Digital Twin concepts in medicine*
- *Developing a specific modeling framework for ophthalmology to implement virtual representation systems based on Digital Twin concepts in medicine*
- *Validating the modeling framework in the clinical field of ophthalmology by developing components of the Digital Twin system that integrate clinical and imaging data, and detect the presence of glaucoma using artificial intelligence algorithms and convolutional neural networks*

Thus, the objectives of this thesis are focused on the development of a general modeling framework for e-health systems and personalized medicine, as well as medical-predictive models that facilitate early diagnosis of pathologies through the use of artificial intelligence algorithms and contribute to the shaping of personalized treatment plans.

1.3 Research Methodology and Structure of the Thesis

In this section, the research methodology used for creating digital models intended for e-health systems and personalized medicine will be presented. The thesis was developed following the methodological approaches illustrated in Fig. 1.1, with the objective of ensuring a coherent structure built through well-defined stages, adapted to the research process.

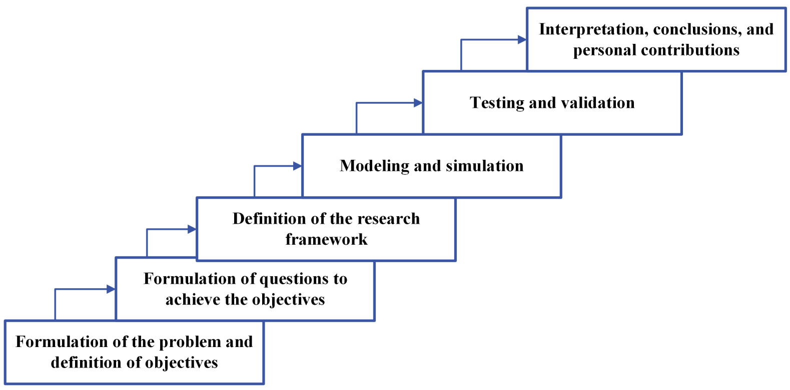


Figure 1.1. Research Methodology of the Thesis

The first stage of the research methodology consisted of formulating the problem and defining the objectives that served as the starting point for the construction of the thesis: the lack of precise and personalized methods for identifying pathologies, managing them, and developing personalized treatment plans. At this stage, the need to develop digital models that integrate the aforementioned functionalities and lead to an improvement in the patient's quality of life was identified.

The second stage of the research methodology involved formulating questions aimed at clarifying, from this point, how the project components contribute to achieving the objectives, in order to provide a clear and unified direction for the thesis.

The first question focused on the concept of Digital Twin - ***How has the concept of Digital Twin evolved, and what are the future perspectives regarding its adoption, existing models and architectures, associated technologies, and applicability in various fields, considering the benefits and challenges encountered?*** Thus, in Chapter 2, the results of a study based on the specialized literature will be presented to identify the evolution of the Digital Twin from concept to architectural model. In Section 2.3, the definitions and classifications associated with the Digital Twin concept will be mentioned, along with a comparative analysis of architectures. Additionally, in Section 2.4, the applicability, advantages, and challenges related to the use of Digital Twin in various fields will be presented.

Another aspect of the research stemmed from the following question - ***How can a general modeling framework be created to facilitate the integration of Digital Twin into e-health systems and personalized medicine?*** Thus, in Chapter 4, Section 4.2, the development of a general, robust architectural framework structured on five levels of representation will be presented, aimed at identifying the presence of pathologies and suggesting optimal personalized treatment options.

The third question focuses on the integration of the Digital Twin in ophthalmology - ***How can the general modeling framework be adapted to the clinical field of ophthalmology for identifying glaucoma and providing personalized treatment?*** Thus, Chapter 5 will focus on the integration of the Digital Twin in ophthalmology. In this chapter, the integration of systemic and personalized medicine information into the Digital Twin will be addressed (Section 5.2), along with considerations regarding the evolution of diagnostic and treatment techniques in ocular pathologies (Section 5.2.1). The adaptation of the general architectural framework for glaucoma identification will be presented in Section 5.4, and the modeling of its components will be detailed in Subsection 5.4.1.

Since modeling represents one of the fundamental aspects of this thesis, the fourth question highlights the use of SysML diagrams for the construction and integration of the Digital Twin in ophthalmology and other related medical fields - ***How can the SysML diagram contribute to the efficient representation of medical processes in ophthalmology, and how can it be integrated into other related fields such as cardiology?*** - Also within Chapter 5, in Section 5.3.1, the process of obtaining the SysML diagram, which ensures the efficient integration of the Digital Twin system in the clinical field of ophthalmology, will be detailed. In Section 5.3.2, the previous diagram will be adapted for the diagnosis and real-time monitoring of cardiovascular pathologies.

The use of the Digital Twin system in the medical field brings numerous benefits, but ethical aspects and risk management must also be considered. These form the basis of the following question - ***What are the ethical aspects and risks that may arise at each layer of the general architectural framework, and how can Digital Twin systems be used in ophthalmology to ensure patient safety and data confidentiality?*** The ethical aspects and risk management will be presented both in Chapter 4 and Chapter 5. A risk analysis for each layer of the architectural framework will be outlined (Subsection 4.3), and the ethical aspects related to the use of Digital Twin in the medical field, specifically in ophthalmology, will be discussed (Subsection 4.3.2, 5.5).

The penultimate question focuses on the validation of the model through the implementation of components of the Digital Twin system for ophthalmology - ***What materials and methods are used for glaucoma detection and personalized treatment?*** In Chapter 6, the materials and methods used for glaucoma detection will be presented (Section 6.2): the datasets for creating pathological patterns and identifying glaucoma through ophthalmic image processing (Subsections 6.2.1, 6.2.2), as well as the integration of the electroretinogram into the Digital Twin (Subsection 6.2.3). The choice of treatment method will be described in Section 6.3.

The final question focuses on the use of the Digital Twin at the level of individual clinics and hospitals, as well as the opinions of medical specialists regarding the integration of the Digital Twin into medical practice - ***What are the medical staff's opinions on the use of the Digital Twin, and what is the optimal context for its use – at an individual level or in hospitals?*** In Section 5.5, the limitations related to the use of the Digital Twin in ophthalmology will be discussed, both from the perspective of the challenges influencing the process of identifying ocular pathologies and from the perspective of physicians, who recommend making clinical decisions in an ethical and responsible manner, considering that, in this context, the Digital Twin system serves merely as a decision support tool.

The questions formulated during the second stage of the research methodology formed the foundation for structuring the thesis, by integrating the components in a unified manner that contributed to achieving the established objectives. These specific questions ensured a coherent approach, aimed at facilitating the attainment of the desired results.

The modeling and simulation of the Digital Twin system represented another stage of the research methodology. The development and modeling of the Digital Twin system for ophthalmology were carried out according to the architectural framework presented in Section 5.4. The Digital Twin collects, processes, and integrates data from various sources, facilitating the identification of the pathology and the creation of personalized treatment plans. Simulations of different clinical scenarios anticipate various ways the pathology may evolve depending on the treatment provided, contributing to the validation of the model. Testing and validation of the model will be conducted through the implementation of components of the Digital Twin system for ophthalmology, utilizing convolutional neural networks and artificial intelligence algorithms.

The validation of the model, from a medical perspective, was carried out with the support of the ophthalmologists involved in the study, who contributed not only through their clinical expertise but also by participating in the scientific papers published during the doctoral studies. Among these specialists was Dr. Costin-Traian MITULESCU, a medical doctor in ophthalmology at the University Emergency Hospital of Bucharest and a faculty member at the "Carol Davila" University of Medicine and Pharmacy. Dr. Mitulescu contributed to this study by constructing and adjusting pathological patterns, interpreting data, ensuring the correctness of the workflow from a medical standpoint, and methodologically validating the model. Our professional collaboration materialized in the scientific papers mentioned in Section 7.4.

The final stage of the research methodology involved the interpretation of results, drawing conclusions, and highlighting personal contributions, all of which are presented in Chapter 7.

2 | Current State of Digital Twin Systems - Concepts, Models, Architectures, Applications

2.1 Introduction

With technological advancements, the Digital Twin has made significant progress and has been widely applied across various fields, aiming to improve operational efficiency and effectiveness. Starting from the definition of a Digital Twin as a virtual replica of physical objects, systems, or processes, it enables modeling, simulation, model updates based on the behavior of its physical counterpart, as well as real-time monitoring and analysis of the system's evolution.

This chapter presents the evolution of the Digital Twin, starting with the definition and classification of the concept and continuing with the exploration of its applicability in various fields such as manufacturing systems, medical systems and e-health, smart cities, education, and energy production.

2.2 Methods of Study and Analysis of Contributions from the Literature

The Digital Twin is in a continuous process of development and promises a promising evolution that brings benefits across various fields. The research methods used highlight a comprehensive approach, starting from the definition of the Digital Twin concept, its classification based on various parameters, the proposed architectures, and exploring its applicability in areas such as manufacturing systems, healthcare, education, and smart cities.

The databases used for conducting this study are Web of Science (WoS), IEEE Xplore, Scopus, and Google Scholar. [1]

In Fig. 2.1–2.4, the number of articles obtained from a search on Web of Science, IEEE Xplore, Scopus, and Google Scholar for the concept of "Digital Twin" over an 8-year period, starting from 2015 and up to the end of 2023, is presented.

Analyzing the evolution of the number of articles published between 2015 and 2023 highlights a significant increase in research interest in this field. In 2015, Digital Twin was found in 21 articles published on IEEE Xplore, 85 articles on Web of Science, 1,393 articles on Scopus, and 28,199 articles on Google Scholar. In the following years, a strong upward trend is evident, reaching the peak number of articles in 2023, with 59,717, indicating a consolidation of research interests in this area. The stabilization over the past 3 years reflects a focus on implementation. Digital Twin is poised for a remarkable development trajectory, redefining existing paradigms and supporting the digital transformation process. [1]

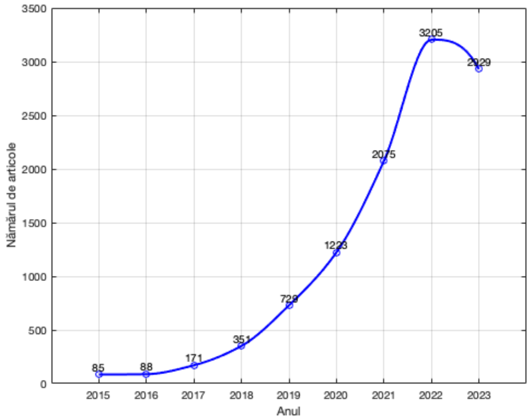


Figure 2.1. The number of articles about Digital Twin published on Web of Science between 2015 and 2023

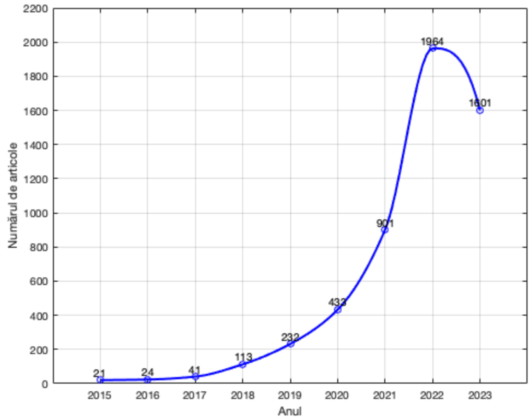


Figure 2.2. The number of articles about Digital Twin published on IEEE Xplore between 2015 and 2023

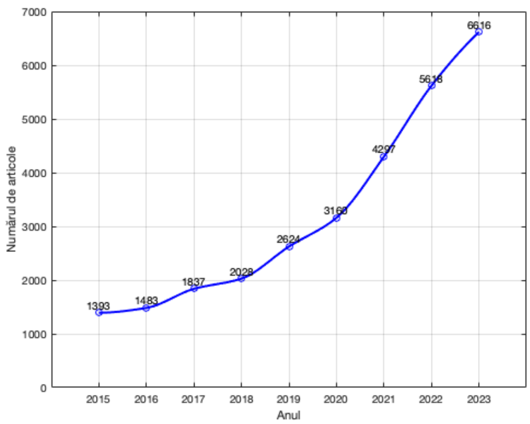


Figure 2.3. The number of articles about Digital Twin published on Scopus between 2015 and 2023

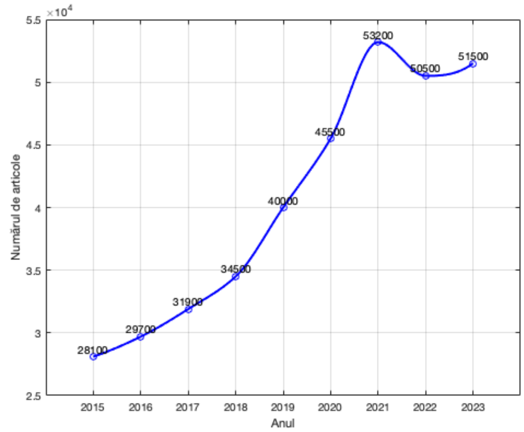


Figure 2.4. The number of articles about Digital Twin published on Google Scholar between 2015 and 2023

The study method consists of synthesizing 115 scientific papers, providing a comprehensive overview for understanding the concept of Digital Twin from various perspectives. An extensive analysis of the Digital Twin concept was conducted, beginning with the identification and selection of definitions, classifications, and architectures integrated into this study. [1]

In conducting this study, regarding the applicability of Digital Twin, related fields such as manufacturing, medicine, smart cities, education, and energy production were selected, with an emphasis on manufacturing and medicine. Thus, the systematic review of the literature was highlighted using the Prisma framework in Fig. 2.5, with the proposed methodology offering a holistic approach to the concept of Digital Twin. [1]

The study was conducted in four stages, starting with the identification of definitions from the specialized literature, as well as examining the applicability of Digital Twin in various fields such as manufacturing, healthcare, smart cities, and education. Another key aspect was the selection of available architectures that offer flexibility and adaptability in implementation, as well as opportunities for generalization. Additionally, emphasis was placed on identifying the advantages and challenges arising from the use of Digital Twin in the aforementioned fields. [1]

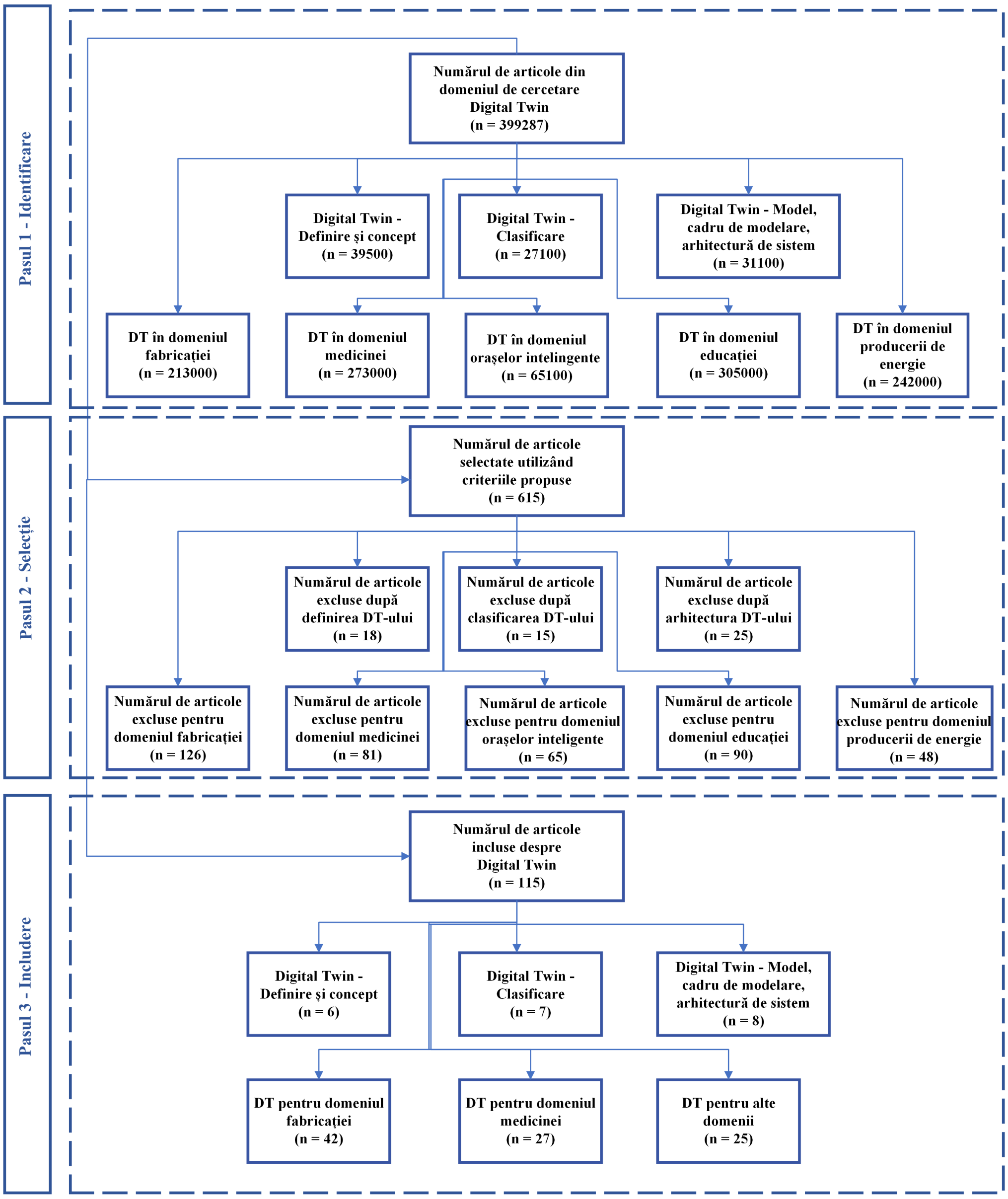


Figure 2.5. Systematic Review of the Literature Using the Prisma Framework

2.3 Digital Twin - From Concept to Architectural Model

2.3.1 Defining the Concept of Digital Twin

Digital Twin is a digital representation of a process, product, or service, and it is considered one of the technologies with significant potential for use. The development of the Digital Twin concept was initiated by Grives [3], when he aimed to create "a virtual representation of a physical product." In fact, the origin of Digital Twin is attributed to the National Aeronautics and Space Administration (NASA) [8], as well as the Air Force Research Laboratory (AFRL).

2.3.2 Classification of the Digital Twin Concept

In [4], Singh et al. provided a classification of the "Digital Twin" concept, taking into account the time of its creation, the level of integration, applications, hierarchy, and maturity level. These classifications will be presented in this section. Thus, a classification of the "Digital Twin" concept was proposed based on several parameters to offer a comprehensive view of how information is stored, managed, and interpreted. According to the classification by Singh et al., an ontology was created, as shown in fig. 2.6.[1]

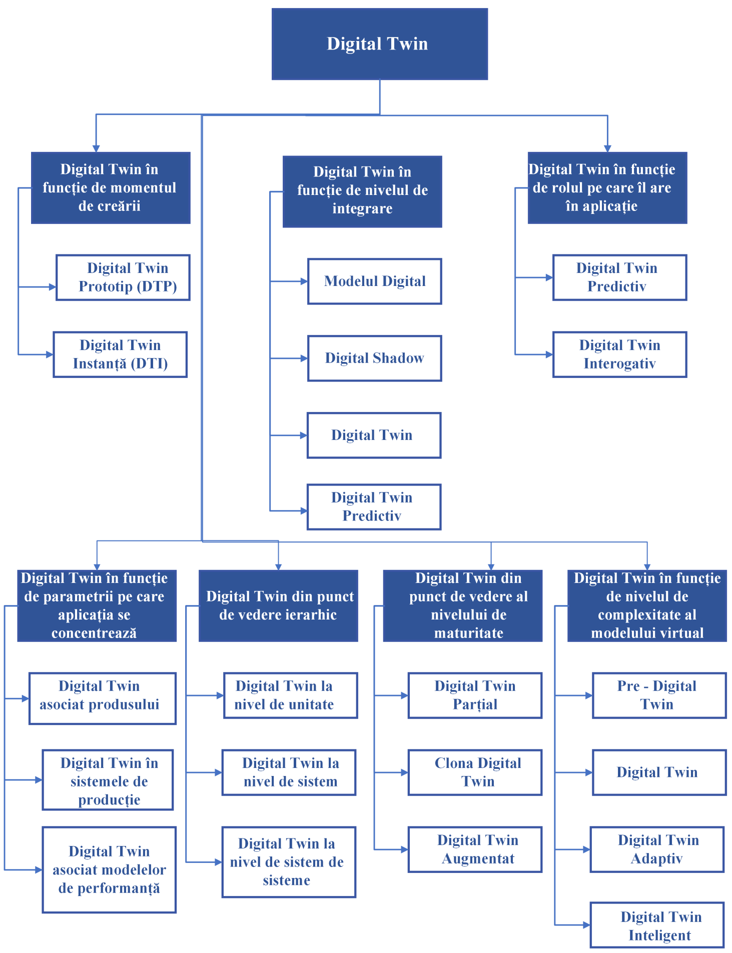


Figure 2.6. Classification of the Digital Twin Concept

2.3.3 Comparative Analysis of Digital Twin Architectures

Over time, numerous Digital Twin frameworks, models, and architectures have been proposed to provide a holistic view from different perspectives. Given the varied fields of application, there are multiple categories of architectures and approaches that inherently focus on different aspects. Digital Twin essentially represents a combination of models and algorithms, which facilitates a differentiated approach to certain aspects. [1]

One of the reference models considered for this study was developed by Lu et al. [5]: a reference model based on physical objects, Digital Twin, and the level of communication between the two parts. In a similar manner, Alam et al. [6] demonstrated that bidirectional connections between a physical and virtual representative can be achieved through cyber-physical systems, while Bevilacqua et al. [22] presented a reference model of Digital Twin for risk reduction in processing facilities.

Table 2.1 presents a comparison of the architectures discussed in [5, 6, 7] based on various criteria such as the field of application, the technologies used, and the operational requirements that ensure the proper functioning of the Digital Twin. [1]

2.4 Analysis of the Integration and Use of Digital Twin in Various Fields

In the real world, there are three types of entities: those related to the human component, those related to technology, and those related to processes. Through digital transformation, identical digital representations are created for human components, the process component is abstracted in the form of a Digital Thread, and the technology elements are associated with the concept of the Digital Twin.

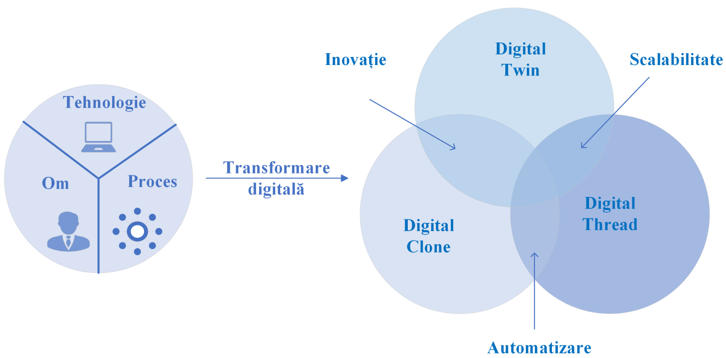


Figure 2.7. The Process of Digital Transformation of Real-World Entities

Digital Twin has begun to be used in the vast majority of fields. Section 2.4.1 highlights the use of Digital Twin in manufacturing systems, while Section 2.4.2 focuses on the application of Digital Twin in related fields such as smart cities, education, and energy production. Additionally, Chapter 3 will present a study that focuses on the integration of Digital Twin into e-health and medical systems. [1]

Table 2.1. Comparație la nivelul arhitecturilor prezentate în [5, 6, 7]

Caracterisitici	**Lu et al. [5]**	**Alam et al. [6]**	**Aheleroff et al. [7]**
Domeniul de aplicare	Fabricația inteligentă, convergența dintre spațiul digital și cel fizic	Sisteme Ciber-Fizice bazate pe Cloud, Aplicații telematice	Transformare industrială, Individualizare în masă
Tehnologii și metode utilizate	Tehnologii pentru procesarea datelor și a modelului informațional	Cloud Computing, Rețele Bayesiene , Logică Fuzzy	Cloud Computing, Internet of Things, Realitate Augmentată, ThingWorx, Vuforia
Aspecte cheie	Fabricație inteligentă bazată pe date, Sistem decizional inteligent la nivelul fiecărei etape a fabricației	Asistență în conducerea bazată pe telematică	Monitorizare în timp real, control la distanță, predicție
Modelul arhitectural	Propunerea unui model de referință al "Digital Twin" în contextul fabricației inteligente	Model de referință pentru arhitectura ”Digital Twin” bazat pe Cloud (C2PS)	Adoptarea Referențialul Arhitectural pentru Industria 4.0 (RAMI) și metodologiei Agile pentru integrarea diferitelor niveluri ale ”Digital Twin”.
Relația cu Industria 4.0	Integrarea ”Digital Twin” în operațiunile de fabricație inteligentă	Integrarea Cloud Computing și controlul la nivelul senzorilor fizici	Utilizarea tehnologiilor din Industria 4.0
Sursa datelor	Captarea informațiilor de la dispozitivele fizice și integrarea lor în procesul de fabricație	Captarea informațiilor de la dispozitivele fizice	Integrarea datelor din surse diverse
Adaptabilitatea	Adaptabilitatea la nevoile variate de producție	Adaptabilitatea la schimbările de mediu	Adaptabilitate în implementare și integrare
Securitatea	Implementarea măsurilor de securitate și control în contextul fabricației inteligente	Implementarea și respectarea standardelor de securitate a datelor în Cloud	Utilizarea tehnologiilor de securitate la nivelul ”Digital Twin” ca Serviciu (DTaaS)
Interoperabilitatea	Conformitatea cu standardele ISO și compatibilitatea cu sistemele existente	Integrarea cu alte sisteme și conformitatea cu standardele	Abordare Agile pentru diferite niveluri de integrare
Provocări și direcții viitoare de cercetare	Standardizarea protocoalelor de comunicație, procesarea datelor în timp real, precizia și acuratețea modelelor, fiabilitatea	Scalabilitatea și realizarea interacțiunilor dintre sisteme, Integrarea cu Blockchain și cu Inteligența Artificială	Niveluri de integrare, Individualizare în masă, Reziliența Digital Twin

2.4.1 Manufacturing Systems

In manufacturing systems, the integration of Digital Twin represents a significant step and is closely linked to concepts such as Product-Service Systems (PSS) and Cyber-Physical Systems (CPS). The synergistic interconnection between Digital Twin, PSS, and CPS helps redefine the way products are designed, while also opening new horizons for providing personalized services and optimizing resources. [1]

Following the search for the concept of *"Digital Twin in manufacturing"*, the minimum number of articles was identified on IEEE Explore - 1,497, followed by Web of Science - 2,272, Scopus - 20,205, and Google Scholar - 213,000. Therefore, the number of identified articles highlights that manufacturing is one of the areas of interest for the application of Digital Twin. [1]

2.4.2 Smart Cities, Education, and Energy Systems

With the rapid evolution of technology, Digital Twin has been applied in various fields such as smart cities, energy production, the oil industry, and education. This section will present the applicability of Digital Twin in the aforementioned areas, starting with the modeling of urban infrastructures and continuing with the optimization of energy production, reduction of gas emissions, and exploration of innovation in education.

In fig. 2.8, the number of articles specific to each field is highlighted, obtained from scientific database searches of the concepts: *"Digital Twin for smart cities"*, *"Digital Twin in energy production"*, *"Digital Twin in the oil industry"*, and *"Digital Twin in education"*. The results emphasize that Digital Twin has significant potential in the development of these fields. [1]

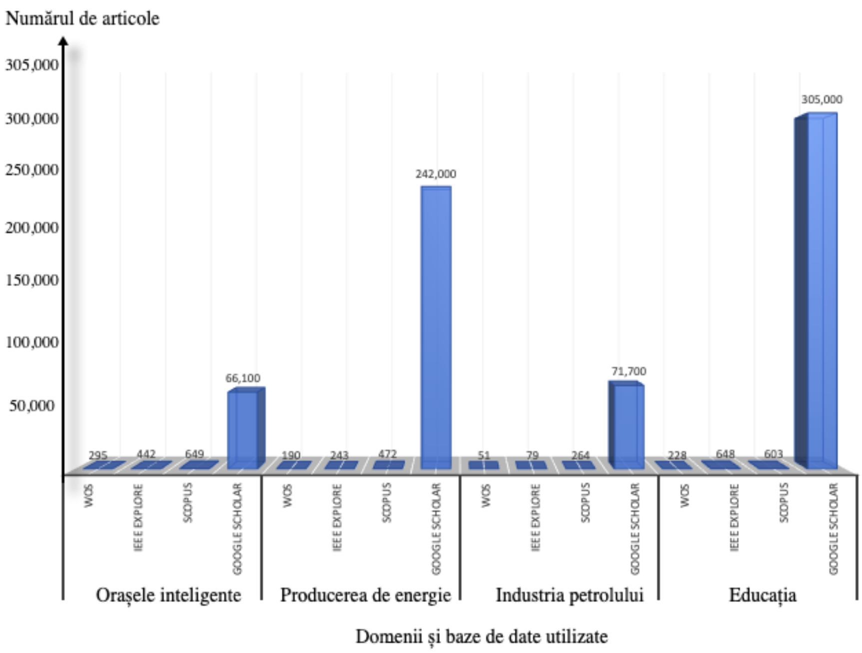


Figure 2.8. The Applicability of Digital Twin in Various Fields

In Table 2.2, the application domains of Digital Twin discussed in this paper are summarized, along with the corresponding bibliographic references. [1]

Table 2.2. Application Domains of Digital Twin

Application Domain of Digital Twin	**References**
A. Manufacturing Systems	[28] - [63]
B. Various Domains - Smart Cities, Energy Production, Oil Industry, Education	[64] - [87].

2.5 Conclusions

The concepts, models, and technologies associated with Digital Twin are increasingly being used on a large scale for modeling, monitoring, simulating, and optimizing complex systems across a wide range of fields such as industry, education, smart cities, and energy production. [1]

In this chapter, an analysis of the concept of Digital Twin has been conducted, exploring its evolution, current state, and future development prospects. The study aimed to create a detailed overview of the applicability of Digital Twin, focusing on objectives such as the current stage of Digital Twin adoption, existing models and architectures, associated technologies, applicability in various fields, and the benefits and challenges involved. [1]

By integrating technologies and applicability across various fields, the study highlights the significant potential of Digital Twin in fostering innovation and efficiency. Digital Twin represents a digital replica of a physical system, process, or product, allowing for the monitoring, simulation, and analysis of its behavior in real-time. Digital Twin not only facilitates decision-making based on the processing and analysis of real-time data but also contributes to optimizing system performance. The selected architectures and detailed classifications provide a solid foundation for further research, opening doors to innovative applications and contributing to the improvement of system performance. [1]

3 | Study and Analysis of Contributions in Digital Twin Systems in E-Health

Another area of interest that highlights the applicability of Digital Twin is medical systems and e-health. Digital Twin contributes to the development of personalized medicine by continuously monitoring the patient's health and identifying pathologies in their early stages. Another functionality offered by Digital Twin is the simulation of disease progression and the suggestion of treatment options. A search of scientific databases for the concept of *"Digital Twin in medicine"* yielded a minimum number of articles: IEEE Explore - 114, Web of Science - 161, Scopus - 307, and Google Scholar - 273,000 articles. Thus, the presence of a total of 273,582 articles suggests a growing interest in personalized medicine. [1]

In this study, ***Digital Twin in e-health and personalized medicine*** will be analyzed. Fig. 3.1 presents the fundamental aspects that formed the basis of this study.

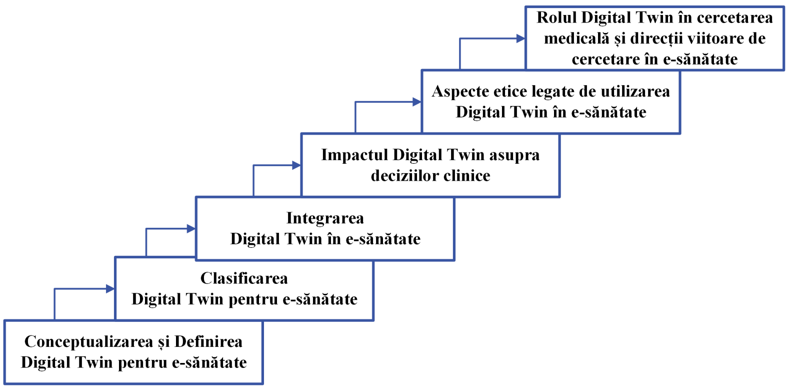


Figure 3.1. Fundamental Aspects of Applying Digital Twin in E-Health

The next step is represented by ***the identification of different types of Digital Twin and their integration into e-health***, based on complexity and the desired purpose. Thus, Digital Twin contributes to the modeling and simulation of various medical scenarios, facilitating the creation of the following types of digital representations:

- *"Digital Twin" at the organ level* - Represents digital models of organs, used for monitoring their functioning, identifying structural and functional anomalies, and evaluating the response to treatment. These models are continuously updated with data transmitted from sensors, thus providing a real-time representation of the organ.
- *Digital Twin at the pathology level* - Represents digital models of pathologies built on medical knowledge and pathological patterns, aimed at identifying early-stage changes that indicate the worsening of diseases.
- *Digital Twin for surgical intervention simulation* - Represents digital models of the patient that allow medical personnel to simulate surgical interventions in order to explore different

approaches and assess risks. The Digital Twin system contributes to increased precision and optimized planning, thereby ensuring the success of the surgery.

The final stage focuses on the ***role of Digital Twin systems in medical research*** and on the ***identification of emerging trends and future directions for the development of Digital Twin in e-health***. Digital Twin can be used in the validation of virtual clinical trials, providing medical staff with the ability to test various medical interventions without involving real patients. This accelerates the research process while also reducing the risks associated with conducting tests on human subjects.

- ***Integration of Digital Twin in Medicine***

One of the fields increasingly benefiting from the use of Digital Twin is the medical domain, through the existence of smart wearable devices that monitor individuals' health in real-time. By combining engineering knowledge with medical expertise and integrating data, the foundations of a connected healthcare system have been established, as presented in [88]. In [89], Digital Twin is defined as a digital representation of the dynamic characteristics of an individual in terms of the evolution of their health over time, starting from the molecular level and providing an overall picture of their lifestyle.

Future research directions include the integration of Digital Twin in medicine, particularly in ophthalmology, for the identification of pathologies that may occur in the visual system, such as glaucoma, cataracts, and macular degeneration. In this way, personalized treatment plans can be developed, simulating patients' reactions to proposed medication and assisting medical staff in decision-making. This comprehensive approach highlights the transformative potential of Digital Twin in personalized medicine. [1]

Based on the insights gained from this analysis, the development of a general modeling framework applicable in medicine, particularly in ophthalmology, is being pursued. This modeling framework aims to integrate data from various sources, use advanced analysis and prediction techniques, while ensuring system interoperability, performance, security, and reliability. The proposed framework will facilitate precise and personalized medical care, necessary for the detection and management of pathologies. [1]

4 | General architectural framework for Digital Twin representation systems in e-health

4.1 Introduction

In terms of the application of the Digital Twin in medical systems and e-health, one of the central characteristics that played an important role in shaping this study was specificity. Unlike other application fields such as manufacturing, energy production, or smart cities, the application of the Digital Twin in medicine involves creating a complex image of the entire organism seen as a system of systems, where each system represents an organ.[114]

According to the definitions presented earlier, creating a human Digital Twin involves integrating various data sources (biological data, genetic data, biomarkers, phenotypic and psychosocial characteristics) and emerging technologies (machine learning and cloud computing) to obtain a holistic view of the human body. Thus, the Digital Twin is not merely a virtual representation of the human body, but serves as a dynamic reflection of the patient's health status and the evolution of their pathologies in real time.

4.2 Architectural framework of the Digital Twin for e-health systems

Based on a rigorous analysis of the specialized literature regarding the concepts of *development framework, architecture, architecture framework*, and *data model*, several definitions were selected to justify the choice of proposing a modeling framework for e-health systems and personalized medicine in this paper.

The architectural framework (Figure 4.1) proposed in this section is based on the architecture presented in [128] and facilitates the construction of a Digital Twin for e-health systems, with the goal of identifying the presence of pathologies and suggesting optimal personalized treatment options. However, it must be noted that the role of the Digital Twin system is not to replace medical staff, but to provide decision support. Structurally, the architectural framework is built on five layers: *Data Acquisition and Dissemination*, *Data Management and Synchronization*, *Digital Twin System Creation*, *Virtualization and Accessibility*, *Ensuring the Security of the Digital Twin System*.

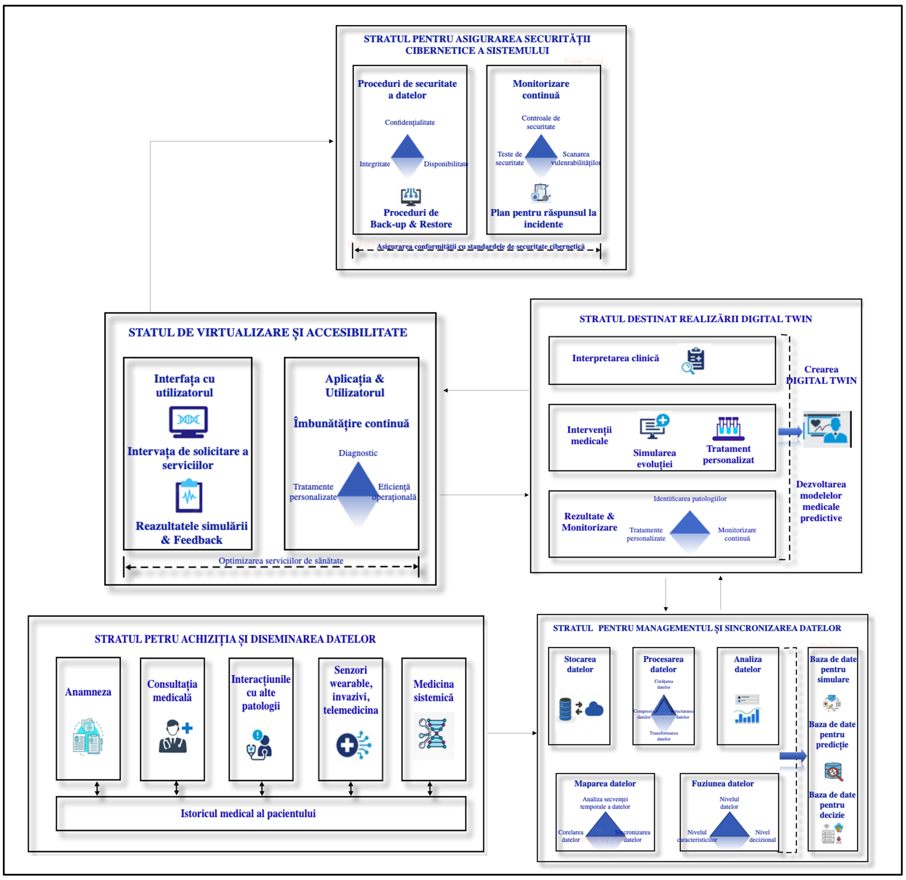


Figure 4.1. Architectural framework of the Digital Twin for e-health systems

The first layer is represented by *Data Acquisition and Dissemination*. At this stage, the focus is on data acquisition from: *Anamnesis*, *Medical consultation*, *Interactions with other pathologies*, *Data from wearable or invasive sensors, remote monitoring or telemedicine*, *Systems medicine*.

All this data will be integrated into the construction of the Digital Twin system, which will identify the presence of pathologies in the human body and allow continuous monitoring of the patient's health, facilitating efficient and personalized management of treatments and medical interventions.

Once this data is acquired, it is transmitted to the *Data Management and Synchronization Layer*, where data storage, processing, mapping, and fusion take place. To ensure the security, authenticity, and integrity of the data, encrypted communication protocols, such as TLS 1.1 (Transport Layer Security) at a minimum, are used. Additionally, at the database level, it is recommended to implement backup and data restoration procedures. [114]

The first stage involves storing the data in the utilized databases, which are subsequently preprocessed to remove redundant information. The cleaning methods used include techniques for data compression, reduction, and transformation. One of the reasons justifying the data cleaning process is to ensure its quality by eliminating deficiencies and inconsistencies that arise during the collection process. Data standardization involves transforming it into a unified format, necessary for its integration into the prediction algorithms used by the Digital Twin.

In the third layer of the Digital Twin for e-health systems - *Digital Twin System Creation Layer*, medical predictive models will be developed by integrating the information obtained after data processing, which is carried out in the *Data Management and Synchronization Layer*, into artificial intelligence algorithms. The medical predictive models are initially formed based on medical knowledge and are updated through a complex process structured into three fundamental stages: *Outcomes and Monitoring*, *Medical Interventions*, and *Clinical Interpretation*.

The first stage involves integrating the information obtained at the previous level into artificial intelligence algorithms built on medical knowledge and pathological patterns to identify anomalies that lead to the detection of pathologies. The artificial intelligence algorithms analyze the data to detect the presence of risk factors that favor the onset of pathologies. Following the identification of the pathology, the medical predictive models are used to propose personalized treatments, which are then adapted to the patient's genetic profile.

The second stage involves using medical-predictive models to simulate the evolution scenarios of the patient's health and adjust the treatment based on detected co-pathologies. The simulations are carried out using neural networks and machine learning techniques, with the Digital Twin system generating health evolution scenarios depending on the absence or administration of specific treatments, or the performance of surgical interventions. This provides doctors with the opportunity to observe the outcomes of various therapeutic options before applying them in the physical plan.

The third stage is represented by clinical interpretation. The results of the health simulations, based on the personalized medical treatment constructed with the help of medical-predictive models, are interpreted in a clinical context. This process emphasizes the continuous improvement of medical-predictive models by integrating suggestions provided by the specialist doctor.

The fourth layer of the architectural framework for pathology identification - *Virtualization and Accessibility Layer* - contributes to improving operational efficiency and facilitates the process of identifying, diagnosing, and shaping personalized treatment plans. It consists of two blocks: *User Interface* and *Application and User*.

The *User Interface* includes a service request interface through which both medical staff and patients can track the updates made. Additionally, an interface is implemented that allows the management of services and the platform, providing users with the opportunity to monitor the diagnostic methods used and the treatment suggestions.

Application and User provides users access to interact with various CloudDTH platforms, while also supporting the efficient coordination of tasks [130]. Thus, end users, entities, and processes can access and view the simulation results from the digital models, facilitating the decision-making process regarding the monitoring of pathology evolution. By utilizing various methods for data visualization and accessibility, the Digital Twin contributes to the optimization of healthcare services. [114]

The *Security Assurance Layer for the Digital Twin System* represents the final layer of the proposed architectural framework. It focuses on ensuring the security of the entire system, the platform, and the network, including user data. It also aims to ensure compliance with security standards that guarantee data confidentiality, integrity, and availability. Data security procedures are implemented at this layer for user authentication, encryption, monitoring, and data auditing, managing the data life cycle. Security controls are implemented to protect against cyberattacks, with periodic security testing recommended to identify potential vulnerabilities at each layer of the Digital Twin system. [114]

Thus, the architectural framework provides a modular vision of e-health systems and personalized medicine. The initial layers focus on collecting and managing patient data, while in the later layers, this data is used to build the Digital Twin system by integrating parameters for pathology diagnosis. The final layer of the architecture emphasizes the security of the entire system, aiming to ensure the confidentiality, integrity, and availability of user data. All these layers provide a robust framework for building the Digital Twin system in e-health.

4.3 Ethical Aspects and Risk Management

4.3.1 Risk Analysis Associated with Digital Twin for E-Health Systems

Creating a risk analysis for the use of a Digital Twin in medical and e-health systems involves establishing a structured and detailed framework, following the stages outlined in Figure 4.2.

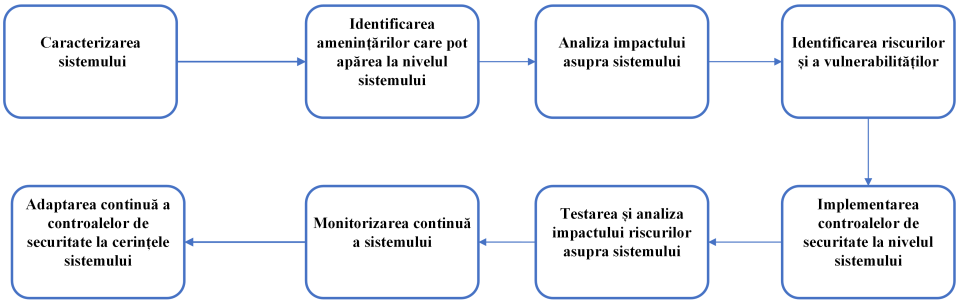


Figure 4.2. Stages Necessary for Creating a Risk Plan

Regarding the impact analysis of the system, the following factors will be considered:

- *the impact on patient safety*
- *the impact on data confidentiality*
- *the impact on system availability*

From the information presented earlier, a risk response strategy has been outlined — Figure 4.3—which contributes to ensuring robust security for the Digital Twin system with applicability in the medical field. This strategy ensures that patient data is protected, maintaining the integrity and functionality of the system. [131]

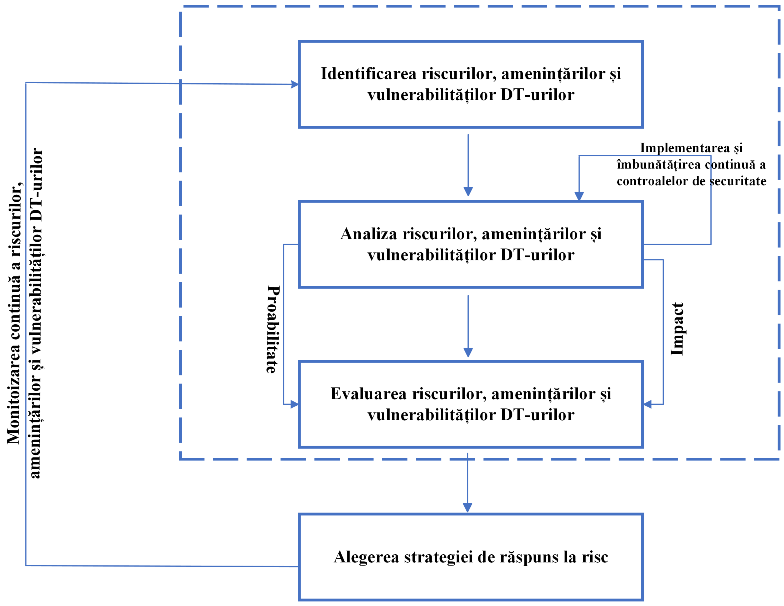


Figure 4.3. A risk response strategy

In this section, a risk analysis will be conducted, focusing on identifying risks at each layer of the "Digital Twin" modeling framework for e-health and personalized medicine systems. This will involve describing these risks and outlining risk response strategies, with examples drawn from the specialized literature.

Identified Risks at the Data Acquisition and Dissemination Layer

1. *Incorrect data capture from physical infrastructure, caused by exploiting vulnerabilities at the sensor level* [133]

   Malicious individuals may exploit vulnerabilities present in sensors or medical devices containing sensors. In this context, the collected data may be compromised, leading to the transmission of incorrect information to other layers of the modeling framework, thus affecting the accuracy and reliability of the digital representation. [133]

   It is recommended to use a real-time monitoring system to detect abnormal behaviors or suspicious activities at the sensor level, as well as to periodically test and simulate to assess the resilience of sensors and the system against cyberattacks. Another control measure is to implement a regular update plan for sensor programs and devices containing sensors, along with regular testing through security assessments to identify vulnerabilities and potential exploitation methods.

Risks Identified at the Layer of Implementing the Digital Twin System

1. *Insufficiency of data for model training* [133]

   The lack of a significant amount of data can lead to the creation of a Digital Twin that does not meet the initial requirements, affecting its functionalities and behavior. The total absence of data can cause significant errors in the creation of the digital representation associated with the patient or pathology. Consequently, the processes of pathology identification and personalized treatment design may lead to erroneous results. [133]

   It is recommended to communicate with various stakeholders to facilitate the accumulation of diverse and high-quality medical data based on different parameters (age, gender, race, presence of genetic factors that favor the onset of pathologies). Additionally, to avoid incomplete medical data, standards regarding data access, availability, and confidentiality must be adhered to.

2. *The accuracy of the results provided by the Digital Twin* [133]

   The accuracy of the results provided by the Digital Twin may be affected due to the data used for model training being incomplete or because it was not designed to take into account the patient's medical history, the presence of co-pathologies, or reactions to certain medications. [133]

   It is recommended to use reliable input data and set optimal parameters to achieve an accurate model. Applying model verification and validation techniques should be a priority, as well as comparing the obtained results with other sources of information (medical studies, suggestions from medical staff). This way, errors provided by the Digital Twin can be identified and corrected. Considering that changes in medical data may occur due to the evolution of patients' conditions caused by the emergence of co-pathologies or reactions to certain medications, regular model updates are recommended to improve accuracy. It is suggested to use in silico models to describe the range of adverse reactions that the administration of certain medications may generate in the body, so that the Digital Twin system can provide the optimal version of personalized treatment.

3. *Ethical risks* [133]

   The implementation of the Digital Twin system for pathology identification and proposing personalized treatment suggestions is carried out using patients' confidential data. These data can be used for illegitimate purposes, potentially making individuals targets of discrimination. The lack of transparency regarding the use of artificial intelligence algorithms can lead to data breaches and a loss of trust in medical personnel. Consequently, patients may become reluctant to provide complete and accurate information, which diminishes the accuracy of the results offered by the Digital Twin concerning diagnosis and personalized treatment suggestions. [133]

   It is recommended to ensure that the data acquired from patients comply with confidentiality, integrity, and availability standards and are protected by adhering to legislative regulations. Moreover, transparency is advised in terms of data usage and collection, as well as the algorithms used in pathology identification and simulation processes. The ethical risks that may arise in the Digital Twin system were discussed in [141], where Fuller et al. outlined several aspects related to the data used by artificial intelligence algorithms, as well as the continuous updating of regulations to ensure the protection of user data (compliance with GDPR). [133]

4.3.2 Ethical aspects related to the use of Digital Twin in e-health

In the medical field, ethical aspects have always been a challenge, and from this perspective, medicine has become one of the most scrutinized areas. For example, globally, ethical committees are responsible for evaluating research projects involving human subjects, ensuring that ethical guidelines are followed. This includes, for example, the collection and management of non-anonymized data, as well as patients' rights to access their own data. Additionally, the management of the patient data life cycle is regulated by laws such as GDPR in Europe. Security and safety in data management are also major concerns in e-health systems and personalized medicine, and the Digital Twin system collects significant amounts of data that must be stored and used with ethical considerations in mind. [149]

The United Nations Educational, Scientific and Cultural Organization (UNESCO) has proposed the creation of a global framework for the ethical use of artificial intelligence in medicine, addressing issues such as discrimination and stereotypes, combating misinformation, respecting patients' rights, and ensuring data confidentiality and security [151]. According to the WHO, to limit the risks associated with the use of artificial intelligence in medicine and to respect patients' rights, several principles have been presented, which are highlighted in figure 4.4. [149]

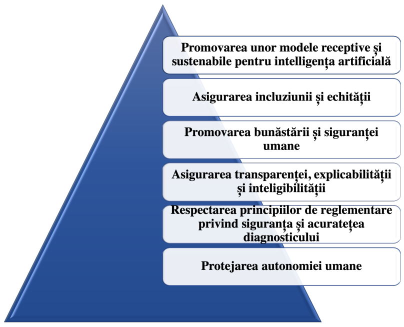


Figure 4.4. Fundamental principles of using artificial intelligence in medicine

A generic cyber-physical medical system (MCPS) representation can be discussed [152], in which the Digital Twin system should consider the roles of various stakeholders. It is essential to create a matrix of roles and responsibilities for the human resources involved in the decision-making process of reconfiguring the entire system based on the observations of medical specialists. Thus, each stakeholder contributes to the development of the transformation process of the entire medical system. Based on suggestions provided by the medical staff, the Digital Twin system will generate various decision scenarios, which will be adjusted by human operators responsible for parameterizing and verifying the results obtained. [149]

In regard to the models integrated into the medical Digital Twin system, several aspects are discussed, one of which concerns the relevance of the decisions made by decision-makers, who are currently the doctors. The objective of medical staff in the process of integrating models into the Digital Twin system is to assess whether the available data and personalized treatment suggestions correspond with real-world scenarios, contributing to parameter adjustments and decision-making that improve the entire system to optimize the decision-making process. However, a series of external, undetectable factors that influence parameter changes and shape a complex model must also be considered, so that these parameters are integrated not only into the decision-making process but also into the control process. [149]

Following a discussion with five medical specialists, each with different levels of experience, several ideas were extracted that highlight the advantages of using the Digital Twin system and artificial intelligence in medicine. Thus, the use of artificial intelligence contributes to increasing the speed and improving the accuracy of diagnosis, a process facilitated by the acquisition, processing, and modeling of data obtained from medical consultations and imaging investigations. These technologies provide the opportunity to create a 'digital fingerprint' of pathologies, enhancing the capacity for diagnosis and personalized treatment. [149]

Thus, several aspects have been presented that aim to outline an overall picture of the ethical challenges, starting from the awareness of these challenges, the role of ethics in engineering practices, and the implementation of a modeling framework to provide solutions to the ethical challenges of the contemporary world. In addition, the implementation of the Digital Twin system introduces challenges related to the loss of initiative by medical staff, which could lead to a decline in innovation and the adoption of standardized procedures. Furthermore, the improper use of medical data for administrative purposes by hospital management raises ethical concerns regarding consent and transparency. [149]

Addressing these ethical risks requires the active involvement of all stakeholders and adherence to legislative norms. Therefore, the design of the Digital Twin system must prioritize the integration of various scenarios, the accuracy of the results, and the respect for the roles and responsibilities of operators in the decision-making process. [149]

4.4 Conclusions

In this chapter, the focus was on developing a robust architectural framework for e-health systems and personalized medicine, aimed at identifying pathologies and suggesting optimal personalized treatment options.

The architectural framework was structured into five representation levels, with the first focusing on the acquisition of medical data from various sources such as anamnesis, medical consultations, wearable and invasive sensors, telemedicine, and systems medicine. At the second level, data storage and processing are performed, which will later be integrated into the construction of medical-predictive models.

Another objective was to conduct a detailed analysis of the risks that may arise at each level of the previously presented architectural framework. The risk analysis aimed to identify potential vulnerabilities that may occur within the system, as well as to assess the impact these risks have on the integrity and optimal functioning of the system.

Ethical aspects related to the use of the Digital Twin system in e-health were also discussed, integrating considerations regarding data confidentiality, patient rights, and the moral implications of using sensitive data. The development, implementation, and use of the Digital Twin system must be carried out in accordance with the observance of deontological norms and fundamental ethical principles, ensuring that ethical values are not compromised for either patients or medical staff.

5 | The architectural framework specific to ophthalmology for Digital Twin systems

5.1 Introduction

In the current medical context, according to a study conducted in recent years by the World Health Organization (WHO) [154], the number of people identified with visual impairments or blindness has significantly increased, reaching a global level of 2.2 billion, highlighting the fact that eye diseases represent a major challenge for the healthcare system. [114]

Based on the statistics presented in [154], one of the main causes of blindness is glaucoma, with over 76 million people diagnosed with this condition in recent years. Due to the fact that glaucoma is asymptomatic in its early stages and progresses very slowly, approximately half of those diagnosed were unaware of the existence of this condition in their eyes. Therefore, considering the rapid increase in the number of people identified with visual impairments and blindness, the WHO aims to conduct awareness and education campaigns for patients regarding the importance of eye care, increasing accessibility to healthcare services while also offering a patient-centered approach. [114]

5.2 The integration of information from systemic and personalized medicine into the Digital Twin with applicability in ophthalmology.

With the rapid evolution of technology, the world is in a continuous process of transformation and adaptation. By interconnecting the concepts of Digital Twin, systemic medicine, and personalized medicine, revolutionary medical approaches can be developed that prioritize patient health and safety. [114]

As mentioned in Section 2.3.1, the concept of Digital Twin [3] was first applied by Michael Grieves in 2003, in the context of product lifecycle management, during research conducted together with John Vickers [16]. [114]

Systemic medicine [155] represents an innovative approach to understanding both health and hereditary pathologies, offering personalized perspectives on the identification and diagnosis of diseases based on information stored at the DNA level. Starting from the molecular, cellular, and tissue levels, pathologies can be identified at the organ level, and subsequently at the level of the entire human body, viewed as a system of systems (SoS). Additionally, systemic medicine [156] provides a modern medical perspective that integrates information from diverse sources:

both from systems biology and bioinformatics (genomic, transcriptomic, proteomic, metabolic, and imaging data), as well as from physiological mathematical modeling for clinical applications. By using these integrative approaches, the functional and morphological structures of organs can be analyzed, beginning with DNA sequencing. Moreover, genetic pathologies that may occur within these organs are detected. [114]

Personalized medicine [160] involves the proactive identification of changes that may occur in a person's body, affecting their health. The most important feature of personalized medicine is that these changes can be detected before visible symptoms of the patient's health deterioration appear. [114]

A study conducted on the application of Digital Twin in medicine found that one of the promising research directions is ophthalmology. The novelty proposed in this paper consists of applying Digital Twin in ophthalmology, focusing on monitoring and diagnosing glaucoma. With the help of Digital Twin, personalized treatment plans can be developed based on the progression of the disease, or surgical interventions can be simulated. By using concepts from systemic medicine, gene mutations that influence predispositions to certain types of glaucoma can be detected, and their integration into the construction of the Digital Twin contributes to increasing the accuracy of diagnosis and the proposed treatment. [114]

Medically, glaucoma [161] is a progressive eye condition that, by damaging the optic nerve fibers, leads to irreversible vision loss. The risk factors that contribute to the onset of glaucoma include elevated intraocular pressure, the presence of ocular trauma, chronic diseases such as diabetes, prolonged corticosteroid treatments, myopia, hyperopia, and, not least, hereditary factors. [114]

The creation of the Digital Twin contributes to the monitoring of the patient's health and the implementation of a personalized treatment plan [165]. With the information from systemic and personalized medicine, the Digital Twin system will be enhanced, allowing the integration of complex interactions within the human body at various levels of organization [166]. Through DNA sequencing and the use of imaging protocols, biosensors, and health monitoring devices, the factors leading to hereditary pathologies can be identified. In this way, the risk of each patient developing such pathologies can be assessed [167]. By utilizing genetic sequencing procedures and genetic tests, patients have the opportunity to analyze their DNA and identify the presence of any genetic mutations, which can provide information for early diagnosis and the development of an optimal personalized treatment solution. [114]

A particular challenge in monitoring glaucoma progression is the lack of sensors capable of capturing real-time information from the patient, with monitoring only possible through medical personnel and equipment. In this context, monitoring is carried out during ophthalmological consultations, at well-defined intervals depending on the stage of the disease. Updating the Digital Twin with information regarding the patient's health status will be performed by medical personnel following the ophthalmological consultation. With the help of the Digital Twin, medical personnel benefit from an integrative approach to identifying predispositions to certain pathologies, early detection, treatment suggestions, visualization of progression stages, and the patient's response to the proposed medication. [114]

5.2.1 Considerations regarding the evolution of diagnostic and treatment techniques in ocular pathologies

Against the backdrop of advancements in diagnostic and treatment techniques for ocular pathologies, the representation of a Digital Twin can be adapted depending on the specific purpose and context in which it is used. Thus, a Digital Twin can be created at the level of an organ, serving as a detailed digital replica of a human organ. This model allows for monitoring, modeling, and simulating the behavior of the organ both in normal and pathological conditions. Another approach involves the development of a pathology-specific Digital Twin, which facilitates the identification of predispositions to a certain condition, the detection of its presence, and supports the modeling, monitoring, and simulation of various scenarios for the disease's progression and the effectiveness of the proposed personalized medication. The two approaches will be presented as follows: [168]

1. ***Digital Twin at the pathology level - Digital Twin for glaucoma***

   The creation of a Digital Twin for glaucoma starts with the characteristics of a healthy eye, both structurally and functionally. While many organs in the human body have characteristic values that vary across individuals, in the case of a healthy eye, the key elements are not subject to significant fluctuations [114].

   Within the Digital Twin, using artificial intelligence algorithms and patient data, simulations will be conducted to identify how increased intraocular pressure and changes in fluid flow (insufficient drainage of intraocular fluid and its accumulation) affect the functioning of the eye. Additionally, the Digital Twin system for glaucoma detection can simulate the deterioration of the optic nerve, and consequently, the progressive loss of vision. [168] [114]

   For the creation of the initial model, clinical databases will be used, with the model being automatically adjusted based on the integration of the specialist doctor's suggestions. Building a Digital Twin associated with glaucoma highlights the fusion of engineering and ophthalmology concepts, leading to the development of a highly accurate model that aids medical personnel in choosing the optimal treatment solution and contributes to improving the patient's quality of life. [168] [114]

2. ***Digital Twin at the organ level - Digital Twin for the eye*** [**168**]

   The creation of a Digital Twin of the eye can lead to an understanding of the eye's behavior from both structural and functional perspectives through the interaction of its components. The complexity level for constructing a Digital Twin of the eye is high, considering not only the main components of the eye (cornea, iris, lens, retina, optic nerve) but also its optical properties, focusing system, motor function, light sensitivity, vascularization, and fluid drainage. Modeling the eye highlights the simulation of the light refraction effect through the cornea and lens, as well as the adjustment of focus to produce a clear image on the retina. [168]

By utilizing the previously presented Digital Twin representation methods, the creation of digital models for e-health systems and personalized medicine is facilitated, significantly contributing to improved clinical outcomes, reduced risks, and lower costs associated with treatments. These models provide users with predictive scenarios for the evolution of pathologies through simulations, enhancing the ability to foresee and manage disease progression.

5.3 Modeling and integrating Digital Twin in the clinical field of ophthalmology

Modeling and integrating a Digital Twin in ophthalmology involves creating a digital model designed for monitoring, simulating, and analyzing clinical scenarios related to identifying predispositions to certain pathologies, as well as their presence or progression. This section will present the SysML diagram associated with a Digital Twin for diagnosing glaucoma and providing personalized treatment, alongside the SysML diagram for integrating Digital Twin into related fields such as cardiology.

5.3.1 The integration of the Digital Twin model in ophthalmology

To ensure the efficient integration of the Digital Twin model in the clinical field of ophthalmology, a SysML diagram has been created, highlighting the process of creating and managing a virtual patient within a medical system, following the integration of data from the physical patient, as shown in Fig. 5.1. This provides a systematic and detailed approach to all components within the system, and through the interactions between the diagram's blocks, the Digital Twin system for glaucoma diagnosis is created and updated.

The following sections will present a brief overview of the blocks involved in creating the Digital Twin system.

- *pacientFizic: @Pacient[1]* -This block is associated with the actual physical patient. It contains data from multiple sources that will be involved in the process of identifying pathologies. The data sources include: *istoricmedical : IstoricMedical [0..*]*, *anamnneza : Anamneza [0..*]*, *consultatieinitiala : ConsultatieInitiala [0..*]*, *consultatieperiodica : ConsultatiePeriodica [0..*]*, *medicinasistemica : MedicinaSistemica [0..*]*.

The following sections will present the blocks and their interactions that contribute to the development of the glaucoma diagnosis system and personalized treatment recommendations. Thus, the second part of the diagram in Fig. 5.1 illustrates the modeling of components and relationships within a medical system. Three categories of blocks are integrated, as follows: main blocks, component blocks, and state blocks. A presentation of these will follow. Each main block is associated with a component block, within which processes are carried out to model the medical system for the purpose of diagnosing the pathology and providing treatment.

1. *Main blocks* - these are digital blocks, entities responsible for managing and processing information, used to represent data and processes: *procesDiagnostic : @ProcesDiagnostic[*]* , *procesTratament : @ProcesTratament [*]*, *pacient : @Pacient [*]*, *feedback : @Feedback [*]*, *dispozitive : @Dispozitive [*]*, **sistem : @Sistem [*]*.

2. *Component blocks* - these are process blocks, entities used to describe sequences of actions, workflows, and interactions between system components that lead to achieving the objective: *procesDiagnostic : @ProcesDiagnostic[*]*, *procesTratament : @ProcesTratament [*]*, *procesDiagnostic : @ProcesDiagnostic[*]*. *pacient : @Pacient [*]*, *feedback : @Feedback [*]*, *dispozitive : @Dispozitive [*]*, *sistem : @Sistem [*]*,

3. *State blocks* - these blocks are designed for monitoring, evaluating, and representing both the current and potential states of system components or the entire system, providing information that facilitates decision-making, strategy adjustments for identifying glaucoma status, and optimizing performance.

- *statusGlaucomActual : StatusGlaucomActual [*]* - At the level of this *physical* block, the presence or absence of glaucoma status is identified, and in the event that the pathology is detected, the type of glaucoma and the current medication are noted.
- *statusGlaucomPotential : StatusGlaucomPotential [*]* - At the level of this *digital* block, predictions of the evolution of glaucoma status are provided.
  The *statusGlaucomPotential : StatusGlaucomPotential []* block utilizes the *statusGlaucomActual : StatusGlaucomActual []* block to determine potential evolutions with a high level of accuracy by integrating data from the patient and analyses performed within the system as a result of selecting the optimal treatment option.

As a result of integrating patient data into the Digital Twin system, glaucoma will not only be detected, but possible scenarios for the progression of this pathology will also be generated. Among the functionalities obtained, the following can be highlighted:

- *The creation of the digital patient based on the physical patient.*
- *The identification of glaucoma and the provision of personalized treatment.*
- *Making predictions for the progression of glaucoma.*

Another key element in the construction of a Digital Twin for glaucoma is the characteristics of the entire system. The main characteristics are as follows:

- *Data-driven management*
- *Multidimensionalitatea*
- *Multidimensionality*
- *Periodic updates*

Through the SysML diagram and the multidimensional approach to the data acquisition process, a detailed vision of the Digital Twin system for glaucoma identification and personalized treatment scenario suggestions has been outlined. To implement the representative functionalities of the system, the main blocks, component blocks, and state blocks have been represented, highlighting the role of each in the construction of the Digital Twin. Ensuring the accuracy and efficiency of the system is supported by the presence of the previously mentioned characteristics: data-driven management, multidimensionality, digital replication, and periodic updates.

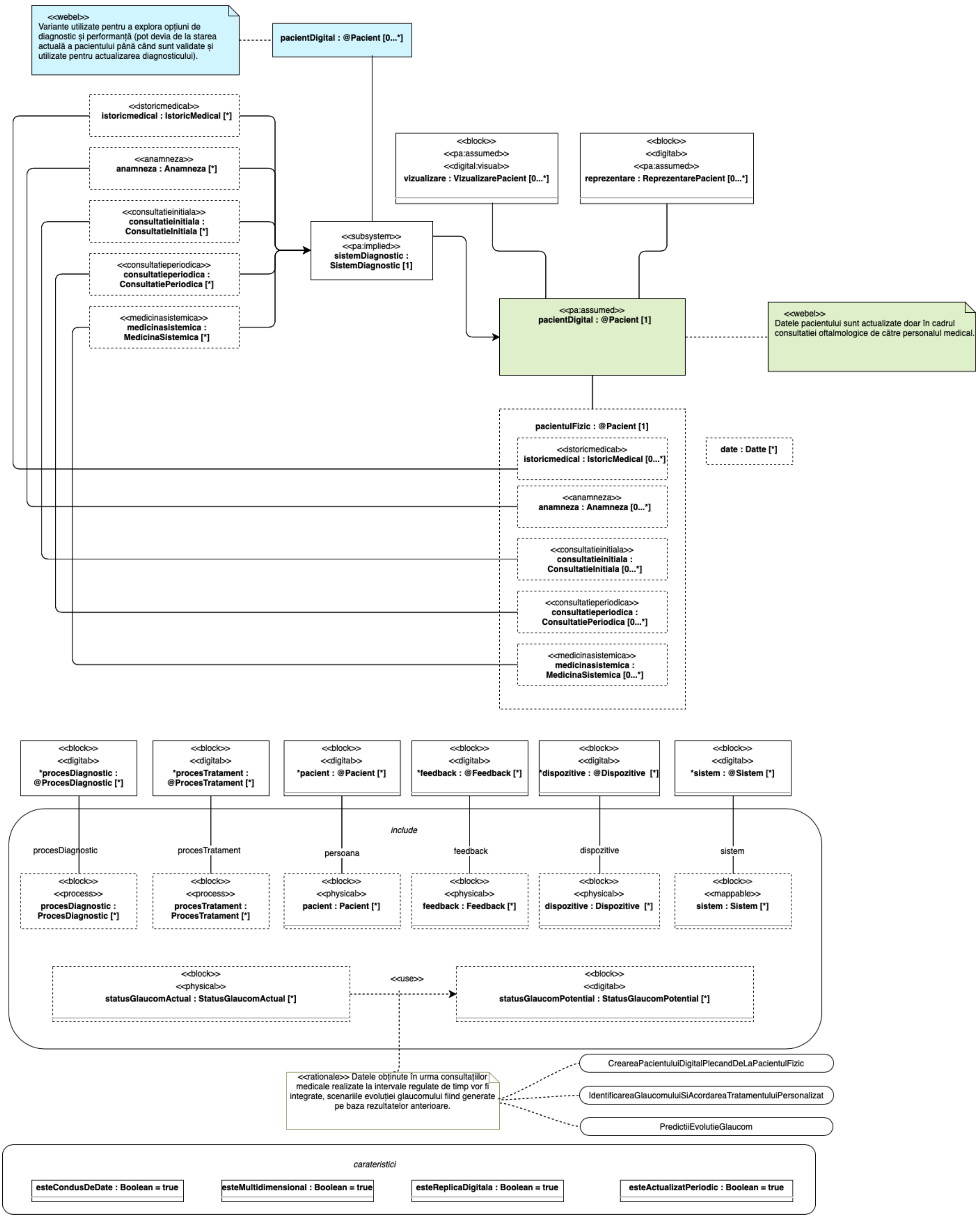


Figure 5.1. SysML diagram for glaucoma diagnosis

5.3.2 Integration with models from related medical fields

Since the clinical field of ophthalmology does not offer extensive opportunities for real-time data acquisition and patient health monitoring, in order to form a comprehensive vision of the medical system, the diagram previously presented in Fig. 5.1 has been adapted for the identification of cardiovascular pathologies.

Regarding data acquisition from *pacientulFizic : @Pacient[1]*, three blocks have been added: *analizemedicale : AnalizeMedicale [0...]*, *wearablesensors : WearableSensors [0...]*, and *senzoriinvazivi : SenzoriInvazivi [0...*]*.

In the process of diagnosing and monitoring pathologies, the following blocks have been added, enabling the modeling of the system:

1. *Main blocks*: *procesMonitorizare : @ProcesMonitorizare [*]*, *procesAlerta : @ProcesAlerta [*]*, *locatie : @Locatie [*]*.
2. *Component blocks*: *procesMonitorizare : @ProcesMonitorizare [*]*, *procesAlerta : @ProcesAlerta [*]*, *locatie : @Locatie [*]*.
3. *State blocks* - Within these blocks, no modifications have been made, as the scenarios for the progression of cardiovascular pathologies continue to be generated using the current data from the patient, based on their current health status.

Among the functionalities of the system for diagnosing, monitoring, and providing personalized treatment for cardiovascular pathologies, the following stand out:

- *The creation of pathological patterns and treatment suggestions*
- *The identification and monitoring of cardiovascular pathologies*
- *The creation of scenarios for the progression of cardiovascular pathologies*
- *The implementation of an alert system in exceptional situations*

At the level of the characteristics of the Digital Twin system in the clinical field of cardiology, compared to ophthalmology, there is one significant difference:

- The Digital Twin system is updated *in real time* through the integration of data obtained from sensors, allowing constant monitoring of the patient's health.
- The other characteristics—data-driven management, multidimensionality, and digital replication—maintain their role in ensuring the accuracy and efficiency of the diagnostic system and the provision of personalized treatment.

The previously presented SysML diagrams illustrate how the Digital Twin contributes to identifying predispositions to certain pathologies, detecting the presence of conditions, monitoring them, and shaping personalized treatment plans. The adaptation of the SysML diagram for identifying cardiovascular pathologies, starting from the diagram associated with glaucoma identification, emphasizes that real-time monitoring of patients' health can only be achieved through sensors. The Digital Twin system provides the possibility to develop complex functionalities that contribute to improving the quality of life for patients in contemporary society.

5.4 Adapting the Architectural Framework for the Clinical Field of Ophthalmology

The general objective of this section is to adapt the architectural framework detailed in section 4.2 to the clinical field of ophthalmology for glaucoma identification - see Fig. 5.2.

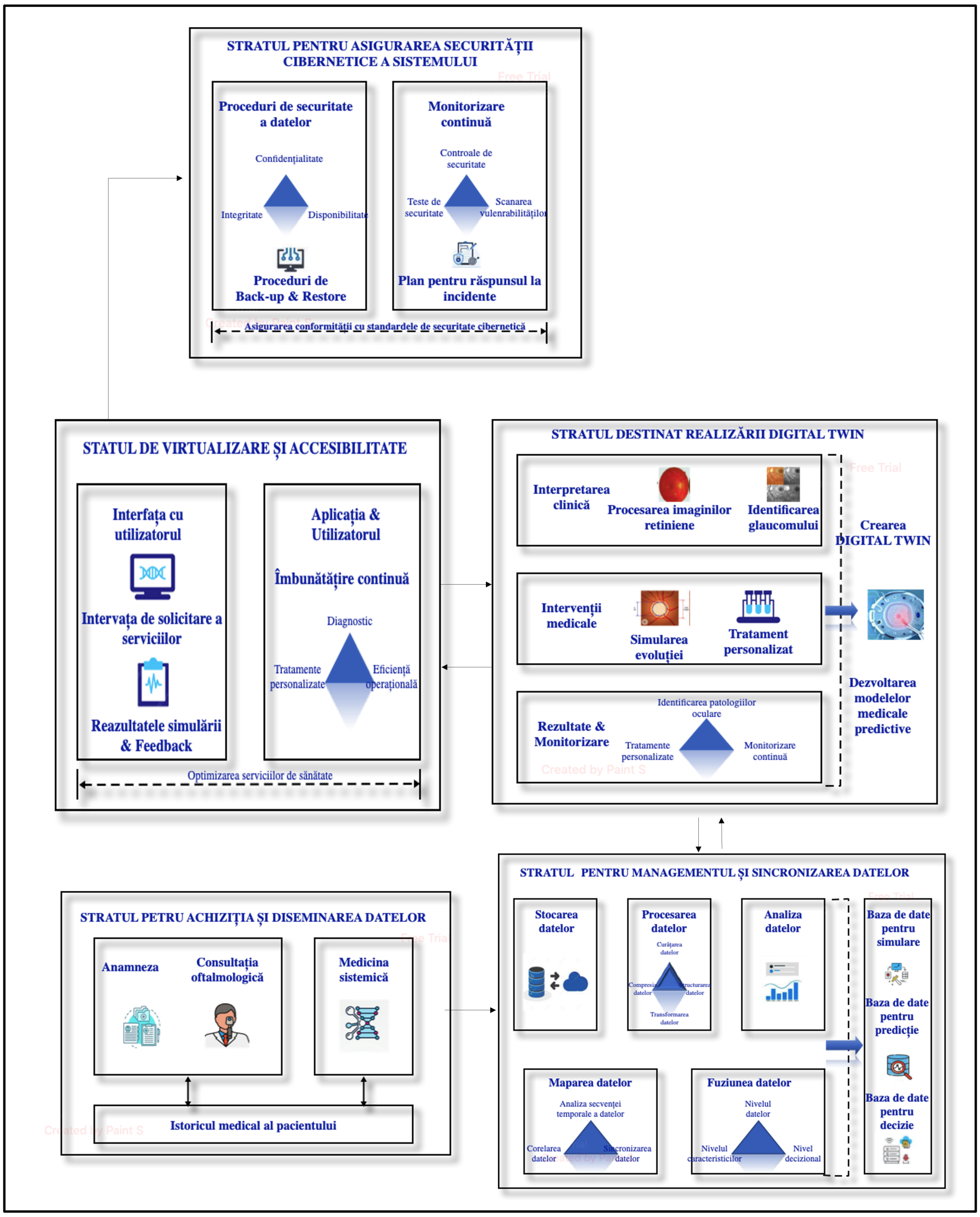


Figure 5.2. Adapting the General Architectural Framework to the Clinical Field of Ophthalmology for Glaucoma Identification

From a structural perspective, the architectural framework associated with the Digital Twin system for glaucoma identification and personalized treatment includes all layers from the general architectural framework for e-health and personalized medicine systems detailed in section 4.2. These layers are represented by data acquisition, management and synchronization, the creation of the Digital Twin system, the level of virtualization and accessibility, and ensuring the security of the entire system. [114]

Table 5.1. Data Used in the Construction of a Digital Twin for Glaucoma Identification

Stage	**Data Acquired from the Patient**
Patient Information	• Medical history • Information about co-morbidities • Current medication
Data Obtained from Ophthalmological Consultation	• Measurement of intraocular pressure • Visual acuity testing • Measurement of the irido-corneal angle • Determination of the cup-to-disc ratio • Measurement of corneal thickness • Detection of structural changes in the retinal nerve fibers • Electroretinography
Genetic Information	• Presence of mutations in genes that facilitate the onset of glaucoma

The first layer is represented by Data Acquisition and Dissemination. In this stage, the focus is on acquiring data from the patient's medical history, initial evaluation, information related to previous ocular conditions, co-existing pathologies, and current medication. Additionally, aspects related to the anatomy and physiology of the eye—such as the cornea, lens, retina, and optic nerve—will also be considered. [114]

The second stage involves acquiring data obtained from the ophthalmological consultation — Table 5.1.

For data acquisition from the patient, optical coherence tomography (OCT) is utilized to capture images of the retina and optic nerve and to measure the thickness of the retinal nerve fiber layer. To identify peripheral vision loss and monitor parameters for glaucoma detection, Goldman pachymetry is used. Goldman pachymetry assesses corneal thickness, as a thin cornea (less than 550 microns) is a risk factor for the progression of open-angle glaucoma.

Electroretinography (ERG) will be performed to measure the electrical response to light stimuli. In the process of identifying the presence of glaucomatous status, ERG helps in the early detection of retinal dysfunctions, functional evaluation of the retina, and monitoring the progression of the disease. ERG allows for the anticipation of changes in the electrical activity of the retina before these changes impact the progressive loss of the visual field or can be detected using medical imaging methods.

Another element to consider in the construction of a general Digital Twin is integration with other pathologies. The presence of ocular conditions such as myopia, uveitis, pseudoexfoliation syndrome, retinal vein occlusion, and ocular trauma can affect how glaucoma is identified and treated. [168]

The next step was selecting a database for storing and processing the data obtained from ophthalmic consultations. When choosing the database, non-functional requirements such as performance and scalability were considered. Since temporal sequence data, such as intraocular pressure values acquired at regular intervals, are used, InfluxDB was selected. The database contains tables for patients, doctors, examinations, OCT images, corneal thickness measurements, intraocular pressure, iridocorneal angle, treatment history, as well as tables for other clinical data such as medical history, current medication, and surgical interventions. Data processing at the database level involves removing redundant data, improving data quality, and transforming data into information. Methods used for data cleansing, compression, reduction, transformation, mapping, synchronization, and fusion are detailed in section 4.2 under the Data Management and Synchronization layer. [135]

At the level of the layer dedicated to the Creation of the Digital Twin System (Fig. 5.3), AI algorithms will use the information obtained from the previous processing stage to build medical-predictive models for identifying glaucomatous status and generating personalized treatment recommendations. [135]

After processing the data, it will be integrated into a pre-trained CNN model, which will be continuously adjusted. Due to its modular and scalable architecture, which aids in classifying complex medical images, the *Inception* model was used, and its training was performed using *TensorFlow* libraries. Additionally, to enhance the accuracy of glaucoma identification, artificial intelligence algorithms such as *Random Forests*, *GBM (Gradient Boosting Machines)*, and *SVM (Support Vector Machines)* were incorporated. The *Random Forests* algorithm contributed to obtaining a final prediction through features extracted from the *Inception* model, *GBM* was used to improve prediction performance through boosting techniques, and *SVM* was employed for binary classification of data extracted by the *Inception* model. These elements contributed to reducing overfitting and enhancing the overall system performance. [135]

Considering that electroretinogram is not a widely used clinical investigation, for this work, three electroretinograms were created in *MATLAB* corresponding to a healthy eye, early-stage glaucoma, and advanced-stage glaucoma. The construction of the electroretinograms was based on their components and characteristic medical information.

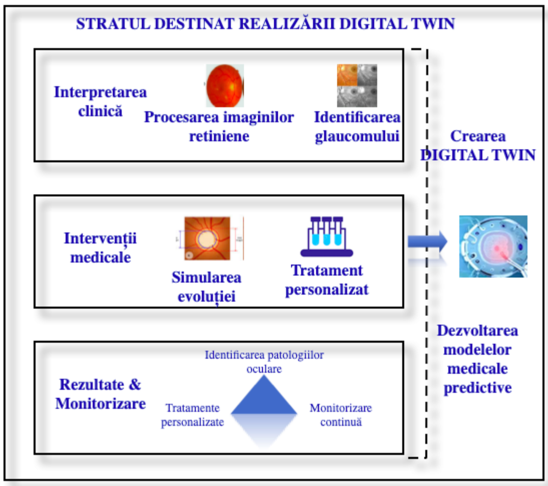


Figure 5.3. Layer for Implementing the "Digital Twin" System in Ophthalmology

Processing of retinal images will be performed using methods presented in [169]. As a result of processing these images, anatomical features such as the cup-to-disc ratio, retinal nerve fiber layer (RNFL), peripapillary atrophy (PPA), thinning of the neuroretinal rim, and blood vessel displacement are identified. This enables the detection of potential cases of glaucoma. The methods used to identify the optic disc and locate its center include: local color contrast enhancement, setting a threshold for pixels with maximum intensity, and shadow correction using morphology. By employing the *CLAHE (Contrast Limited Adaptive Histogram Equalization)* technique, the clarity of the boundary between the cup and disc is improved, facilitating their subsequent segmentation. Additionally, an intensity threshold can be set to differentiate high-intensity areas from low-intensity ones. In this case, the threshold adjustment isolates the cup from the rest of the optic disc, allowing the cup to be segmented as a distinct region and the disc to be identified separately. Undesired shadows in the retinal image are corrected using morphological operations of erosion and dilation, which enhances edge accuracy and improves segmentation reliability. [114]

Thus, continuous monitoring of the patient is necessary to adjust the treatment based on the progression of the pathology and its interaction with other conditions. Additionally, collaboration among physicians with various specialties is encouraged to ensure the ongoing improvement of the results provided by the Digital Twin. Administering treatment without considering all the pathologies for which the patient has been diagnosed affects not only the effectiveness of the treatment but also the occurrence of side effects. [168]

At the fourth layer of the architectural framework—*Visualization and Accessibility*—users access and view the results of simulations generated by the Digital Twin. Detailed reports are generated and stored in *.csv* format using Python, and notifications are sent to the specialist via SMTP services using the *smtplib* library in Python. Suggestions from the specialist are collected using Django. The Digital Twin system will be continuously improved by integrating feedback from the specialist to enhance result accuracy, and machine learning models will be retrained using libraries such as *TensorFlow* and *PyTorch*. [135]

At the *System Security Assurance* layer, security procedures are implemented for user authentication, data encryption, monitoring, and auditing, managing the entire lifecycle of information. Developing an incident response plan is a priority to ensure the continuity, security, and accuracy of the medical process, integrating both technical aspects and those related to the protection of users' sensitive data. [114]

The general architectural framework for e-health systems and personalized medicine has been adapted for the clinical field of ophthalmology, particularly for glaucoma identification and personalized treatment suggestions. Structurally, the five layers of the general model have been preserved, with adjustments made to each component to address the specific requirements and challenges in ophthalmology. Integrating digital techniques into the diagnostic process and personalized treatment of ocular pathologies not only improves patient quality of life but also enhances the relationship with medical staff. Through regular patient monitoring and continuous improvement of artificial intelligence algorithms and predictive models, the Digital Twin becomes a diagnostic tool for ocular pathologies that provides personalized treatment suggestions. [168]

5.4.1 Modeling the components of the architectural framework for ophthalmology

To provide a structured and detailed visualization of the interactions and interdependencies between the system components, a SysML block diagram was created, associated with the previously proposed architectural framework. This highlights the coherence between the functional, physical, and data levels of the model, contributing to the efficient integration and management of the entire system's complexity. The functionalities of each block will be presented in the descriptions for each layer of the architectural framework, explaining the contribution and role of each component in the overall system.

- ***The SysML block diagram associated with the Data Management and Synchronization Layer***

In Fig. 5.4, the SysML block diagram associated with the second layer of the proposed architectural framework for glaucoma detection through the integration of the Digital Twin is presented. In this context, the processes and data flows associated with the data processing are illustrated, which will be used by the Digital Twin in detecting the presence or absence of glaucoma status.

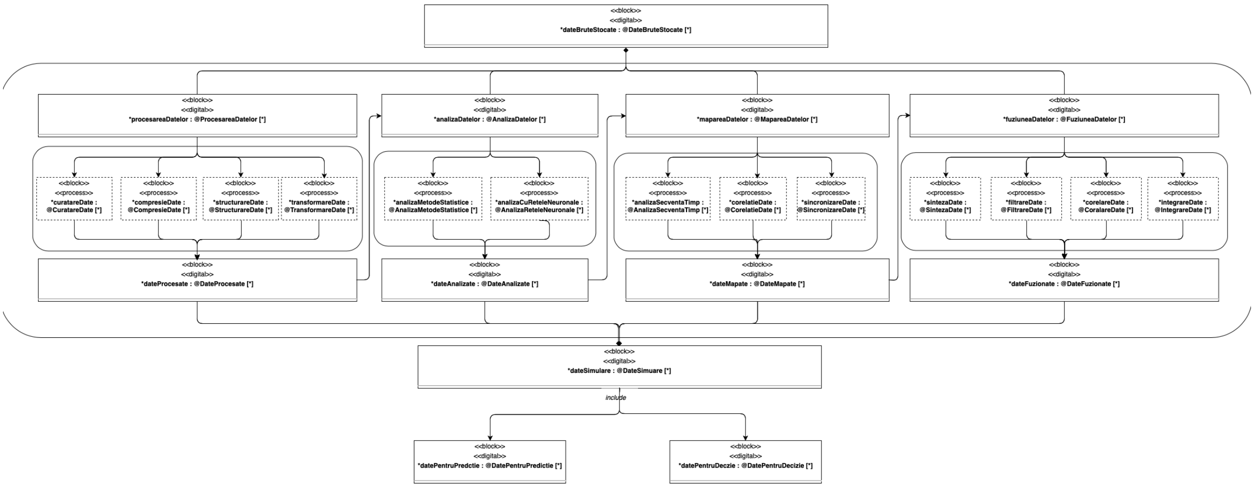


Figure 5.4. The SysML block diagram associated with the Data Management and Synchronization Layer

Thus, a comprehensive overview of the data processing procedures involved in the identification and monitoring of glaucoma status has been structured using the SysML diagram. Each main block and component block has a well-defined role, ensuring the integration of high-quality data into the prediction algorithms, which facilitate informed decision-making and optimize the diagnostic process.

- ***The SysML block diagram associated with the Digital Twin System Implementation Layer***

The SysML block diagram associated with the implementation level of the Digital Twin system is highlighted in Fig. 5.5. Each block integrated into the SysML diagram contributes to the identification of the pathology's presence and the development of personalized treatment plans. In the following sections, the main blocks and component blocks will be presented, which have shaped a personalized approach focused on improving the patient's quality of life.

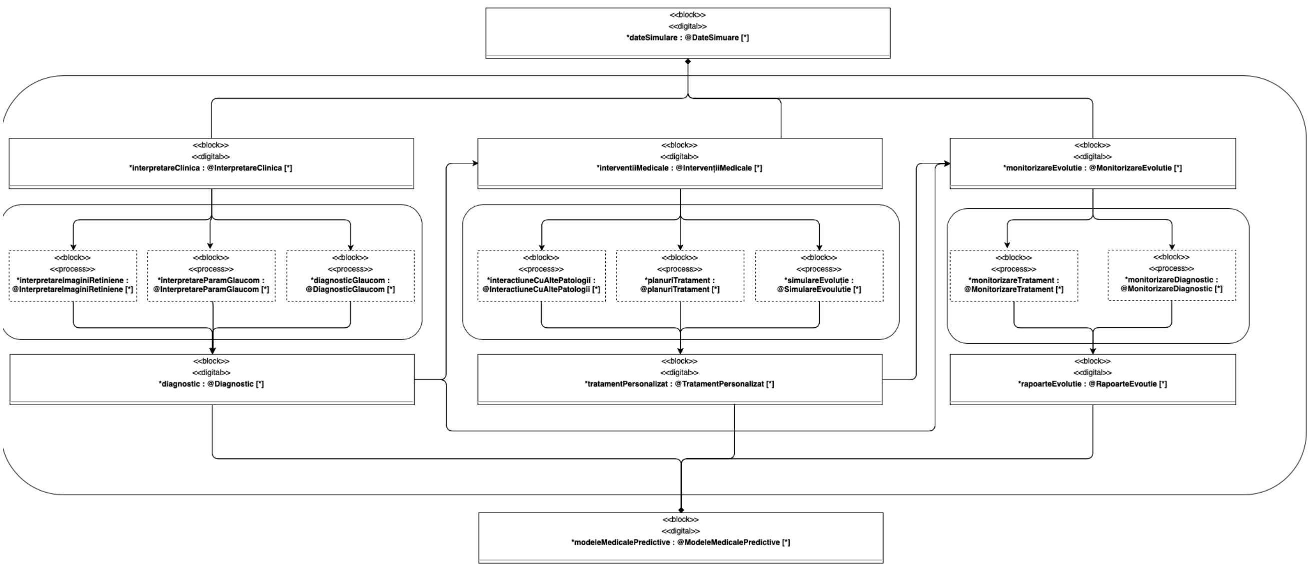


Figure 5.5. The SysML block diagram associated with the Digital Twin System Implementation Layer

As a result of creating the SysML diagram associated with the implementation of the "Digital

Twin" system, a structured system was developed, with its main components focused on clinical analysis for glaucoma diagnosis and treatment personalization. Through the interconnection of the blocks, a clear picture of the data flow involved in the diagnostic process is provided, contributing not only to the delivery of personalized treatment but also to the generation of pathology progression scenarios.

- ***The SysML block diagram associated with the Virtualization and Accessibility Layer***

In Fig. 5.6, the SysML block diagram associated with the Virtualization and Accessibility level of the "Digital Twin" system is presented. It is structured into three categories of blocks, as follows:

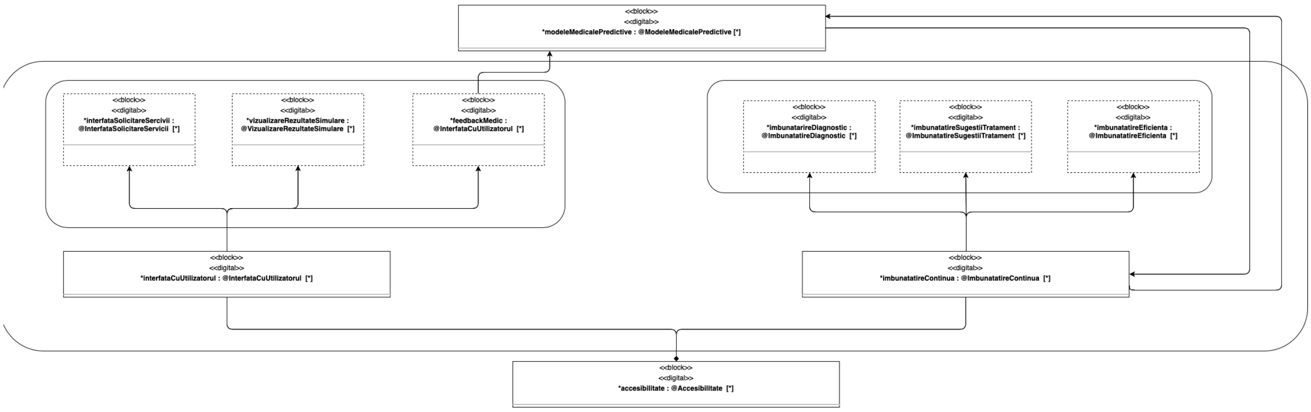


Figure 5.6. The SysML block diagram associated with the Virtualization and Accessibility Layer

he SysML diagram associated with the *Virtualization and Accessibility* level of the "Digital Twin" system highlights the importance of ensuring an efficient user experience for both patients and medical personnel, particularly in providing a highly accurate diagnosis. The three categories of blocks presented earlier contribute to the creation of a complex structure in the process of diagnosing and delivering personalized treatment for glaucoma.

- ***The SysML block diagram associated with the System Security Assurance Layer***

In Fig. 5.7, the SysML block diagram associated with the final layer of the "Digital Twin" system architectural framework is presented, with the objective of ensuring security across the entire system.

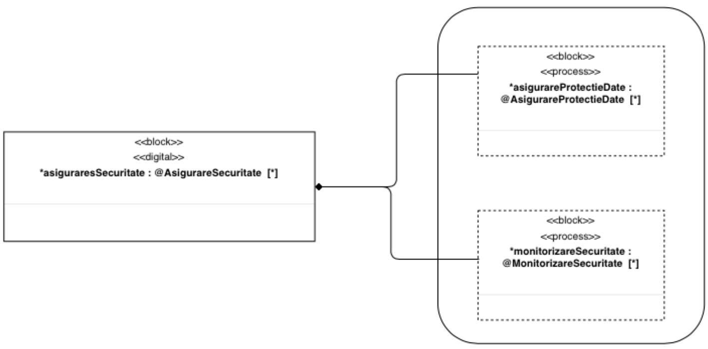


Figure 5.7. The SysML block diagram associated with the System Security Assurance Layer

Thus, all these components contribute to the implementation of security measures and the compliance with data protection standards, facilitating operational continuity and safeguarding sensitive user information.

The modeling of the architectural framework components associated with e-health systems and personalized medicine, with applicability in glaucoma identification and the generation of personalized treatment scenarios, highlights the efficiency of a systematic and detailed approach for modeling, monitoring, and simulating pathologies. The interactions between the diagram's blocks emphasize the relationships between the system's components, prioritizing diagnostic accuracy and the continuous improvement of the "Digital Twin" system through the integration of suggestions provided by the specialist doctor.

5.5 Ethical Aspects, Risk Management, and Challenges of Using Digital Twin in Ophthalmology

The use of the Digital Twin for glaucoma detection and the generation of personalized treatment suggestions may be associated with certain risks, which will be detailed in this subsection. As mentioned throughout this paper, in this context, the Digital Twin serves as a decision support tool for medical personnel by performing predictive analyses for glaucoma detection, simulating progression scenarios, and proposing personalized treatment plans. [114]

Thus, the use of the Digital Twin does not directly influence the patient's health. However, the decision-making process may be affected by errors during data collection from the patient, which are used to train the algorithm for detecting the presence of the pathology and providing treatment suggestions. These errors can also impact the relationship between the doctor and the patient. The implementation of a Digital Twin for pathology identification may be associated with numerous challenges that need to be addressed to ensure diagnostic accuracy. [114]

- ***Aspecte etice și de management al riscurilor în oftalmologie***

The risks associated with using Digital Twin in ophthalmology remain the same as those presented in section 4.3.1. However, in the process of identifying glaucoma and providing personalized treatment, the main risks include excessive reliance on technology, errors in data interpretation, and, in some cases, the loss of the medical staff's ability to make independent clinical decisions.

In conclusion, the use of Digital Twin in ophthalmology represents a significant technological advancement, where precision and trust in medical personnel are essential. The specialist's reliance on Digital Twin may lead to a decrease in patients' confidence, as they perceive the doctor to be relying more on technology than on their own knowledge and experience. To avoid the emergence of such risks, emphasis is placed on achieving a balance between the use of technology and the clinical skills of medical personnel. This requires making decisions in an ethical and responsible manner, along with maintaining effective communication with the patient. [114]

- ***Limitations of the Applicability of Digital Twin in Ophthalmology***

The implementation and use of Digital Twin in ophthalmology offer advanced diagnostic and personalized treatment possibilities but also come with challenges that impact the pathology identification process. These challenges are outlined in this subsection.

One significant challenge is the complexity and precision of the model [171]. Since glaucoma is influenced by multiple factors such as intraocular pressure, corneal thickness, the cup-to-disc ratio, and fundus images, accurately modeling the interactions between these parameters requires the implementation of complex algorithms and the availability of comprehensive data. This data must be correctly processed and integrated into the Digital Twin [172]. The integration of heterogeneous data, which may vary in format and structure depending on the source, necessitates advanced preprocessing and normalization techniques.

The approach to addressing the challenges previously detailed supports technological advancement and collaboration among specialists from various fields, facilitating the development of effective solutions for identifying ocular pathologies. The advancement of retinal image processing techniques and the continuous training of predictive algorithms, along with collaboration with medical specialists, enhance the accuracy of the results provided by Digital Twin.

5.6 Conclusions

As a result of researching the applicability of Digital Twin in e-health and personalized medicine, it has been noted that one of the promising research directions is ophthalmology, the clinical field selected for this work. This chapter has focused on integrating information from systemic and personalized medicine into the Digital Twin, aiming to develop innovative medical approaches with the goal of prioritizing patient health and safety.

Depending on the purpose and context established with the advancement of diagnostic and personalized treatment techniques in ocular pathologies, two modalities of representing a Digital Twin have been presented:

- Digital Twin at the organ level - Digital Twin for the eye: This approach allows for the monitoring, modeling, and simulation of the organ's behavior under both normal and pathological conditions.
- Digital Twin at the pathology level - Digital Twin for glaucoma: This approach facilitates identifying predispositions to a specific condition, detecting its presence, simulating progression scenarios, and monitoring treatment effectiveness.

Additionally, efforts were made to integrate with models from related medical fields such as cardiology. The SysML diagram for glaucoma detection was adapted for identifying cardiovascular pathologies, emphasizing real-time updates of the Digital Twin system through continuous integration of sensor data, which facilitates rapid intervention by medical personnel in critical situations.

Significant attention was given to adapting the architectural framework for e-health and personalized medicine systems, detailed in section 4.2, for detecting the presence of glaucoma and developing personalized treatment plans. The modeling of system components was also carried out, where the interactions between the diagram blocks highlight the component-level interactions to ensure diagnostic accuracy and the continuous improvement of the Digital Twin system.

Ethical and risk management aspects, along with the challenges of using the Digital Twin in ophthalmology, were discussed, with a focus on using technology in medical practice in an ethical and responsible manner.

6 | Implementation of Process Block Components of the Digital Twin Representation System and Model Validationi

6.1 Introduction

The development of a Digital Twin for glaucoma identification and the provision of personalized treatment requires the integration of advanced materials and methods for creating medical-predictive models, following the construction approach outlined in the proposed architectural framework in Section 5.4. This involves leveraging patient-specific data, predictive algorithms, and decision-making processes that align with the overall structure and objectives of the Digital Twin system for personalized ophthalmological care.

In creating the medical-predictive models within the Digital Twin system, attention was focused on implementing blocks from the SysML diagrams associated with the *Data Management and Synchronization* layer and the layer associated with the *Realization of the Digital Twin*.

These blocks ensure efficient data management and synchronization across various system components, enabling real-time predictive analysis and personalized treatment planning within the Digital Twin framework.

To form a detailed perspective on glaucoma identification, electroretinogram (ERG) processing will be carried out in MATLAB, and by applying the Fourier Transform and Discrete Wavelet Transform, characteristics suggesting the presence of the pathology will be extracted.

The implementation of methods for outlining treatment plans will be achieved by using the treatment algorithm for primary open-angle glaucoma and integrating the specific characteristics of each patient. The goal of selecting the optimal treatment method for glaucoma will be to reach a target intraocular pressure value through simulations carried out over the next 5 years.

In this chapter, the process blocks mentioned earlier will be implemented to facilitate glaucoma identification and the selection of the optimal personalized treatment solution, using Digital Twin representations.

6.2 Materials and methods used in the implementation of a Digital Twin for glaucoma

6.2.1 The dataset *Harvard Glaucoma Fairness*

One of the datasets used for this study is the *Harvard Glaucoma Fairness with 3300 records (Harvard-GF3300)* [175, 176]. The data categories contained in this dataset include information from medical imaging—RNFLT OCT (Optical Coherence Tomography of Retinal Nerve Fiber Layers) with a size of 200 × 200, glaucoma status, mean deviation value of the visual field, 52 values of visual field deviation, age, gender, race, marital status, ethnicity, and the language spoken by the patient [114].

6.2.1.1 Statistics on the occurrence of glaucoma based on demographic factors

The construction of a Digital Twin for the diagnosis of glaucoma and the provision of personalized treatment can begin with the development and interpretation of statistics based on demographic parameters such as gender, age, and race. Based on the results obtained from these statistics, possible correlations between the aforementioned parameters are identified, and the probability of developing this condition is calculated. All these contribute to forming a holistic view of the factors that favor the occurrence of the pathology, as well as identifying patient groups predisposed to glaucoma. [114]

As mentioned in Section 6.2, the dataset used for the statistical analysis was the *Harvard Glaucoma Fairness dataset with 3,300 records (Harvard-GF3300)* [175, 176], the details of which are also provided in this section. [114]

As a result of the previously presented analysis, the dataset could serve as a starting point for constructing a Digital Twin aimed at identifying glaucoma. To ensure that the Digital Twin system provides highly accurate predictions, the dataset should be enhanced by incorporating information obtained from ophthalmological consultations, as well as environmental factors that may influence the patient's health and contribute to the development of glaucoma. All the information contained in the dataset can be integrated to build predictive models for glaucoma diagnosis. [114]

Based on the results obtained from the interpretation of previous statistics, correlations were identified concerning demographic parameters, which assist in both segmenting patients into relevant categories and proposing personalized treatments. Thus, the highest number of glaucoma cases occurs in patients over 50 years old and those of Black or African American race, while gender or marital status are not primary determining factors. Due to the factors indicating an increased risk of glaucoma, measures can be taken to improve the effectiveness of personalized treatment and the quality of life for patients. Based on these correlations, "Digital Twin" systems can be built to diagnose glaucoma from its early stages, simulating personalized treatment options and patient responses. [114]

6.2.1.2 The architecture of the convolutional neural network

In this section, the neural network used to identify the presence of glaucoma will be presented. The model was trained on the *Harvard Glaucoma Detection (Harvard-GD500)* dataset [178, 179], which contains 500 records from 500 patients for glaucoma detection. The records in the dataset consist of grayscale images from medical imaging (RNFLT OCT) of the retinal nerve fiber layer (RNFL), each with a resolution of 225 × 225 pixels, accompanied by the mean deviation of the visual field and a label indicating whether the patient was diagnosed with glaucoma or not. [114]

After normalizing the dataset, it was split as follows: [114]

- *Training* - 80% of the dataset was used to train the network.
- *Validation* - 10% of the dataset was used to adjust the model's hyperparameters and prevent overfitting during the training phase. This helps evaluate the model's performance on unseen data during training. Since the dataset contains only 500 records, to avoid underfitting, only 10% was allocated for validation.
- *Testing* - 10% of the dataset was used for model testing. This serves as an independent dataset, unused during training and validation, and is exclusively used after model training to evaluate its prediction performance on unseen data.

6.2.1.3 The results of training the neural network for glaucoma detection

Using as input data the medical imaging data—RNFLT, the corresponding mean deviation of the visual field (MD), and labels containing information about the presence or absence of glaucoma, a mixed data network with multiple inputs was constructed. The model was trained using the *Harvard Glaucoma Detection dataset with 500 records (Harvard-GD500)* [178, 179]. [114]

As a result of processing the information obtained through optical coherence tomography, which measured the thickness of the retinal nerve fiber layer (RNFL), Fig. 6.1 highlights the presence of glaucoma, while Fig. 6.2 illustrates the absence of glaucomatous status. [114]

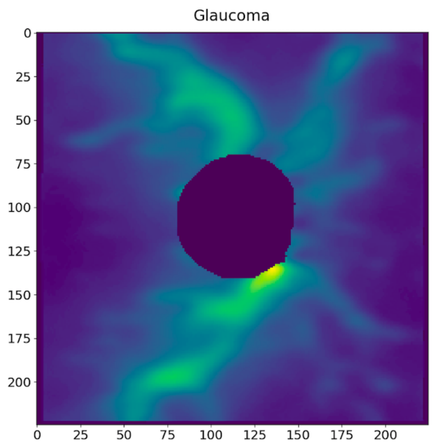


Figure 6.1. The presence of glaucoma

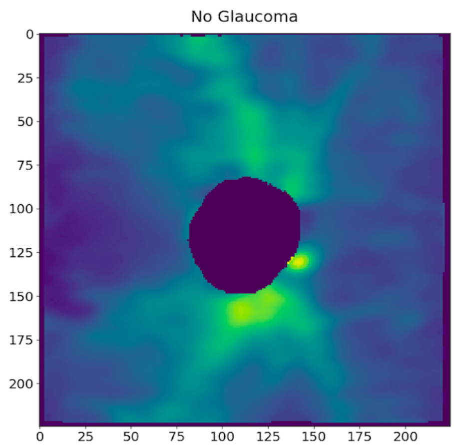


Figure 6.2. The absence of glaucoma

After training the model, a 5x5 image was created, where each subgraph represents an image from the dataset—Fig. 6.3. Labels were added to identify the presence of the pathology: 1 indicates that the patient was diagnosed with glaucoma, while 0 indicates that the patient does not have glaucoma. [114]

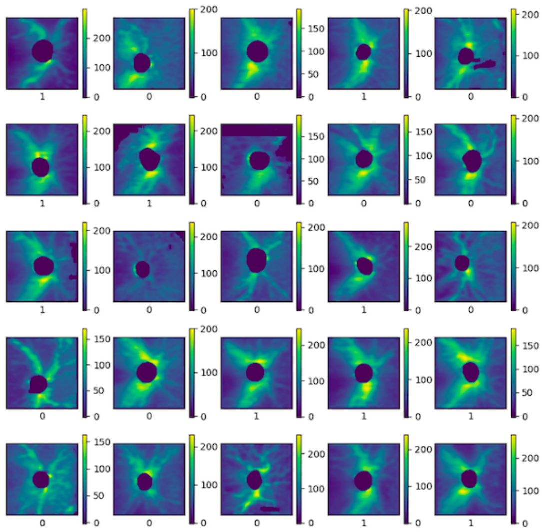


Figure 6.3. The presence/ the absence of glaucoma - 5x5

After loading the trained model, its performance was evaluated on a testing dataset using the 10% of the data allocated for this purpose. After loading and normalizing the data, the trained model was applied to the testing dataset to make predictions. Subsequently, the accuracy of these predictions was calculated. [114]

The final step focused on creating graphs to visualize the loss evolution and to calculate the model's accuracy during training. The loss function graph was generated using data from both the training set and the testing set—Fig. 6.4. Similarly, the accuracy calculation graph utilized data from both sets—Fig. 6.5. Consequently, an accuracy of 84% was achieved on the testing data. [114]

Figure 6.4. The graph associated with the loss function

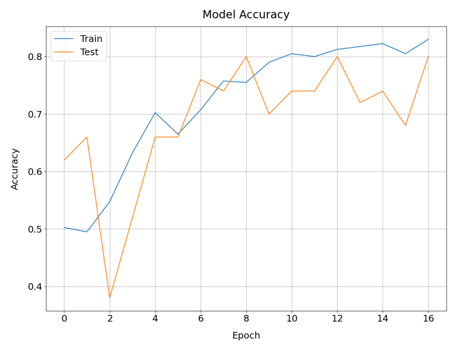


Figure 6.5. The graph associated with the model's accuracy

As a result of the findings, it is observed that the achieved accuracy does not fully meet expectations, which leads to the need for adjustments in the methods used. To improve the results, considerations will be made for optimizing the neural network architecture, adjusting parameters, and employing new techniques. As mentioned earlier, the dataset needs to be enhanced to include a diverse range of demographic data from patients, as well as measurements obtained during ophthalmological consultations, in order to build a "Digital Twin" for glaucoma detection. Additionally, another improvement method could involve implementing a functionality that adjusts the model based on the integration of suggestions from a specialist doctor. [114]

6.2.2 The *GRAPE dataset*

The second dataset used for glaucoma identification comes from the *Ophthalmology Center of the Second Affiliated Hospital of Zhejiang University (ZJU)* and is known as the *"GRAPE Dataset"* [181]. [168]

The dataset contains information from 144 patients diagnosed with open-angle glaucoma, aged between 18 and 80 years. The associated images have dimensions of 1556×1556 pixels and 2136×2136 pixels and were acquired using TRC-NW8 Fundus and CR-2 PLUS AF Digital Retinal cameras. [168]

For the development of this model, specific glaucoma parameters considered were: *visual field (VF)*, *initial intraocular pressure (IOP)* with values ranging from 8-55 mmHg, *central corneal thickness (CCT)* with values between 424-610 micrometers, and the *measurement of the iridocorneal angle*. [168]

6.2.2.1 The architecture of the convolutional neural network

Regarding the model construction, since the dataset contains both images and numerical feature values (mixed data), a convolutional neural network (CNN) with multiple inputs was used, similar to the example presented earlier. This architecture facilitates the proper handling of each type of data, allowing the network to process both the visual features from the images and the numerical characteristics, such as intraocular pressure or corneal thickness, in parallel for more accurate glaucoma detection.. [168]

For each follow-up measurement, the time interval between the initial check-up and the respective measurement became a characteristic element for the pathology's progression, used in labeling the region of interest (ROI). The time interval was then removed from the follow-up values, with the subsequent analysis relying solely on the use of the labels. [168]

After this process, a dataset with 1115 elements was obtained, as follows: [168]

- 67 features: time interval, age, gender, IOP, CCT, glaucoma category, and 61 VF values.
- 62 labels: IOP and 61 VF values.

6.2.2.2 The results of training the neural network for glaucoma detection

For each element in the initial dataset, regions of interest (ROI) were cropped from the associated fundus images, then converted to grayscale and resized to 256 x 256 pixels. Following this, normalization and standardization processes were applied. For categorical features such as gender and glaucoma type, label encoding techniques were used. [168]

For time interval, age, intraocular pressure (IOP), corneal thickness, and visual field (VF) characteristics, Min-Max scaling was applied. The minimum and maximum values for each characteristic type were stored to convert the model's predictions into readable data. The values were then normalized to the range [0, 1]. Visual field (VF) values may include -1, which, according to the authors of the GRAPE dataset, represent blind spots. Therefore, these values were kept as -1, and normalization was applied only to the positive values, resulting in visual field (VF) values ranging from [-1, 1]. After normalization, the data was split into training (90%) and testing (10%) subsets. The network was trained for 15 epochs using a batch size of 16. [168]

The loss function used was the mean squared error (MSE) — as shown in Fig. 6.6. Additionally, the mean absolute error (MAE) was employed to facilitate the interpretation of the results — as shown in Fig. 6.7. As we can observe, both MSE and MAE converge in a similar manner. [168]

In [186], the results were obtained by training a convolutional neural network (CNN) for 50

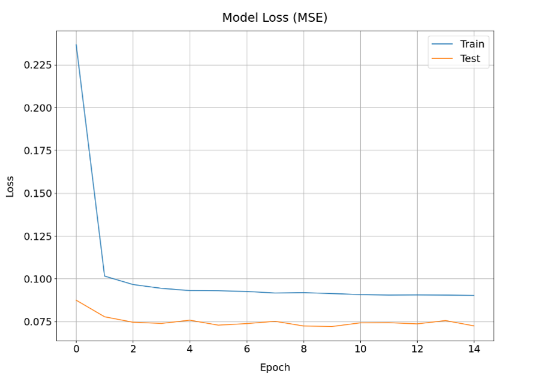


Figure 6.6. The graph associated with the mean squared error (MSE)

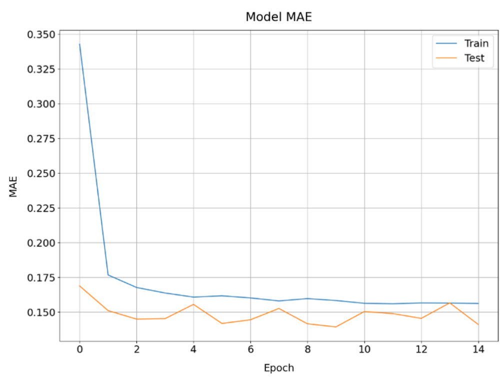


Figure 6.7. The graph associated with the mean absolute error (MAE)

epochs, whereas in the present work, 15 epochs were used, with a batch size of 16. To evaluate the effectiveness of the model in predicting the evolution of the visual field (VF) and intraocular pressure, an analysis of the network's sensitivity and specificity is required, which will be conducted in future research. The results obtained using MSE and MAE indicate consistency between the two metrics, implying stable and reliable model performance. [168]

6.2.3 The integration of electroretinography into Digital Twin

Since the goal is to obtain a detailed view of the process of identifying the presence of glaucomatous status, this section will include the processing of electroretinography, a clinical investigation that contributes to the identification and monitoring of glaucoma. Given that electroretinography is not widely used in clinical practice and there are limitations in data collection, an electroretinogram will be constructed and processed using simulation environments based on its components and their significance.

Similar to the results obtained for the healthy eye and the early stage of glaucoma, the analysis of the 500 frequency components obtained through the application of FFT (Fast Fourier Transform) led to the following conclusions:

- *The largest amplitudes are associated with the frequencies at the beginning of the spectrum*, which supports the fact that the ERG signal has dominant components at low frequencies.
- It is observed that *as the frequency increases, the amplitude decreases considerably*, with high-frequency components being less significant.
- *The phases change gradually as the frequencies increase, without rapid shifts*, indicating a relative coherence of the frequency components.

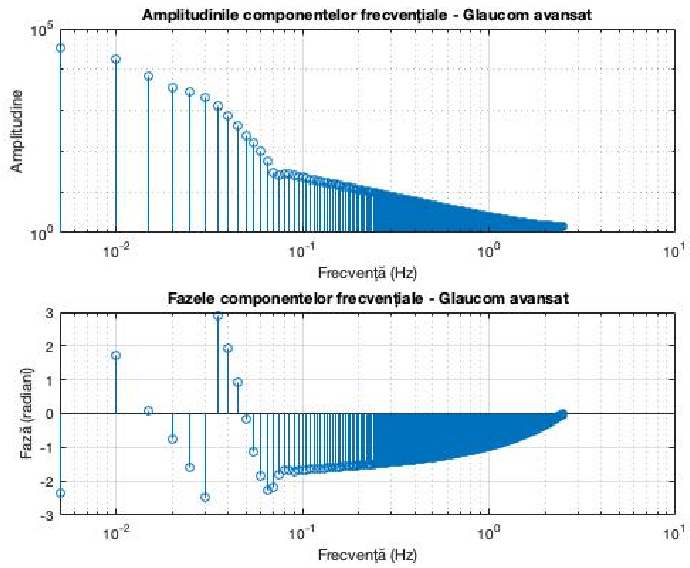


Figure 6.8. The amplitudes of the frequency components and their phases - Advanced glaucoma

Additionally, a comparison was made between the amplitudes and phases obtained for advanced glaucoma and early-stage glaucoma. Thus, depending on the different frequency ranges, the following observations will be presented regarding:

- *Amplitudes at:*
  - *Low frequencies [0.00 Hz - 0.05 Hz]* - Generally, in this frequency range, the amplitudes obtained in advanced glaucoma tend to be lower than the amplitudes associated with early-stage glaucoma.
  - *Medium frequencies [0.06 Hz - 0.20 Hz]* - The amplitudes for advanced glaucoma are generally higher than the amplitudes for early-stage glaucoma.
  - *Frequencies higher than 0.20 Hz* - The amplitudes associated with advanced glaucoma are larger compared to the amplitudes of early-stage glaucoma.
- *Phases at:*

  - *Low frequencies [0.00 Hz - 0.05 Hz]* - The phases associated with advanced glaucoma tend to be generally higher than the phases associated with early-stage glaucoma.
  - *Medium frequencies [0.06 Hz - 0.20 Hz]* - In this frequency range, the phases associated with advanced glaucoma are lower than the phases associated with early-stage glaucoma.
  - *Frequencies higher than 0.20 Hz* - In this frequency range, for 47% of the frequency vector components (459 components), the phases associated with advanced glaucoma are lower than those associated with early-stage glaucoma. Therefore, in the remaining 53% of cases, the phases associated with early-stage glaucoma are lower than those of advanced glaucoma.

From the analysis of the amplitudes in all three cases, it is observed that the ERG signal varies depending on the stage of the pathology and the frequency band. Thus:

- *Amplitudes at:*
  - *Low frequencies [0.00 Hz - 0.05 Hz]* - In this frequency range, the amplitude of a healthy eye is higher compared to the amplitude associated with the early-stage and advanced glaucoma. Thus, the decrease in amplitude highlights the overall decline in retinal activity and the progressive degradation as the pathology advances.
  - *Medium frequencies [0.06 Hz - 0.20 Hz]* - In this frequency range, the amplitude associated with advanced glaucoma is higher than the amplitude in early-stage glaucoma, and also higher than that of a healthy eye. The increase in amplitudes at medium frequencies as the pathology progresses suggests an intensification of retinal activity, likely seen as a compensatory mechanism.
  - *Frequencies higher than 0.20 Hz* - At high frequencies, the amplitudes decrease in early-stage glaucoma compared to a healthy eye, indicating a loss of signal energy. However, they increase in advanced glaucoma, suggesting either residual retinal response or a specific pathological manifestation of the advanced stage of the disease.
- *Phases at:*
  - *Low frequencies [0.00 Hz - 0.05 Hz]* - In this frequency range, the phases associated with advanced glaucoma are larger than those associated with early-stage glaucoma, and also larger than those of a healthy eye, which equates to an increasing delay in retinal response as glaucoma progresses.
  - *Medium frequencies [0.06 Hz - 0.20 Hz]* - In this frequency range, the phases associated with advanced glaucoma are smaller than those associated with early-stage glaucoma, and also smaller than those of a healthy eye. This may indicate a change in the temporal processing of the retinal signal as the disease advances.
  - *Frequencies higher than 0.20 Hz* - In this frequency range, phase variability has been observed, indicating that the pathology may influence the retinal response in non-linear or unpredictable ways, which may require further investigation to fully understand the impact on retinal function.

Thus, monitoring the amplitudes and phases within these frequency bands, and integrating the results of the analyses into the Digital Twin system, can be considered key features that influence the process of glaucoma diagnosis and the evaluation of personalized treatment effects.

In conclusion, integrating the electroretinogram into the Digital Twin system for glaucoma detection not only facilitates the identification of this pathology but also aids in recognizing existing predispositions. Collecting and processing electroretinograms from patients with various stages of glaucoma within the Digital Twin can enable automatic classification based on their frequency and temporal characteristics, improving the existing pathological patterns. Although this comparison represents only a starting point for identifying parameter differences through the processing of electroretinograms associated with different stages of glaucoma, the results presented in this work are not sufficient to create well-defined pathological patterns. By training a convolutional neural network on a set of electroretinograms classified according to the identified level of glaucoma, the Digital Twin could detect early symptoms of the pathology with a high level of accuracy, thus facilitating personalized interventions.

6.3 Creating Personalized Treatment Plans for Glaucoma Through Digital Twin

In this section, a use case diagram was created to illustrate the interactions between the two actors of the system: the ophthalmologist and the "Digital Twin" system. The diagram highlights how these two actors interact to select the optimal treatment solution for glaucoma. It presents a systematic view of the information flow and the roles each actor plays within the system. [188]

The following section will present the treatment algorithm for primary open-angle glaucoma with elevated intraocular pressure. [188]

Monotherapy is initiated with first-line antiglaucoma medications, and the goal is to achieve an effective reduction in intraocular pressure to the level prescribed by the specialist. [188]

1. If monotherapy is well-tolerated, a progressive reduction in intraocular pressure will be observed.
   - If the desired intraocular pressure is reached, regular monitoring of intraocular pressure and visual field will be conducted.
   - If the desired intraocular pressure is not reached, monotherapy can be adjusted, with laser therapy or the addition of a second medication being considered.
     – If the desired intraocular pressure is achieved after adding the second medication, regular monitoring of intraocular pressure and visual field will be conducted.
     – If not, the second medication can be replaced to assess its efficacy, or other treatment options such as surgery or laser therapy may be suggested.
   - Additionally, after choosing the surgical or laser treatment option, monotherapy with first-line antiglaucoma medications will continue, aiming to achieve and maintain the desired intraocular pressure.

2. If monotherapy is not well-tolerated, meaning no effective reduction in intraocular pressure is observed, monotherapy will be adjusted until it is well-tolerated, considering laser therapy as well. [172]

In Fig. 6.9, the activity diagram illustrating the implementation of the treatment algorithm for primary open-angle glaucoma with elevated intraocular pressure is presented. [188]

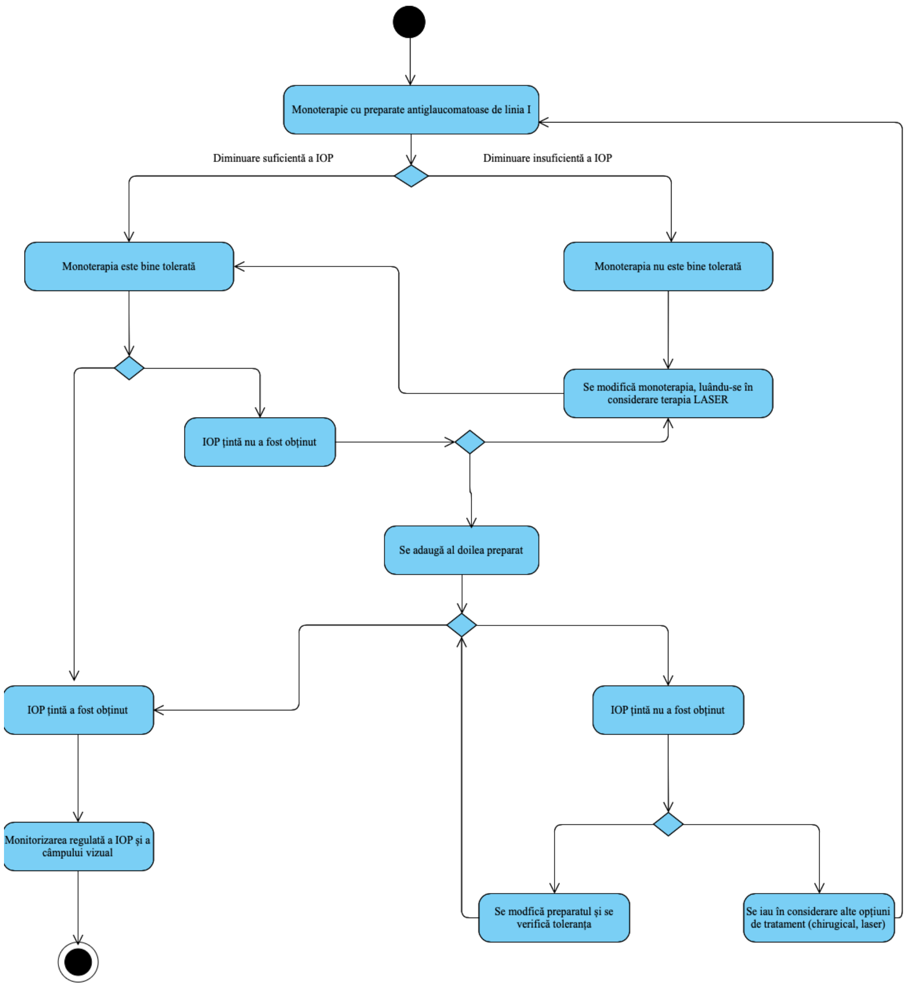


Figure 6.9. The Treatment Algorithm for Primary Open-Angle Glaucoma with Elevated Intraocular Pressure

According to the dataset [181] on which the neural network aimed at glaucoma identification was trained, a 22-year-old male patient was selected for this case study. The initial measurements obtained from the ophthalmological consultation are presented in Fig. 6.10, leading to the diagnosis of glaucoma for the patient. [188]

IOP [mmHg]		CCT [μ]		Grosimea stratului de fibre nervoase retiniene măsurată prin OCT									
OD	OS	OD	OS	Ochiul drept (OD)					Ochiul stâng (OS)				
				M	S	N	I	T	M	S	N	I	T
23	22,5	602	600	92	93	87	116	70	93	122	88	98	63

Figure 6.10. Initial measurements obtained from the ophthalmological consultation

As a result of the glaucoma treatment algorithm presented in Fig. 6.9, the goal is to reduce intraocular pressure according to the guidelines provided by the specialist. Once the desired value is reached, the patient will be monitored at regular intervals to assess the evolution of the aforementioned parameters. [188]

In Fig. 6.11, the CFP images associated with the patient's right eye over a span of 6 years are presented. It can be observed that during the first two years, intraocular pressure remained constant, and after the third year, it began to decrease. However, the need to change the treatment may be justified by the fact that in the fifth year, intraocular pressure showed a tendency to increase compared to the previous year. [188]

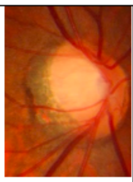
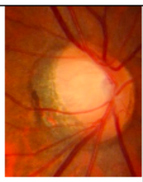
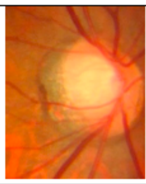
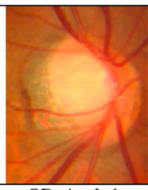
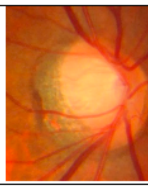
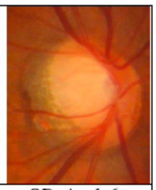
CFP						
	OD_Anul_1	OD_Anul_2	OD_Anul_3	OD_Anul_4	OD_Anul_5	OD_Anul_6
IOP	23 mmHg	23 mmHg	22,7 mmHg	19 mmHg	19,7 mmHg	19,5 mmHg

Figure 6.11. The CFP images associated with the patient's right eye

Using linear regression, the relationship between the year of observation and intraocular pressure values will be modeled. Based on this model, which uses the intraocular pressure values from the first 6 years as initial data and follows the guidelines and constraints provided by the specialist, the intraocular pressure over the next 5 years was calculated, as shown in Fig. 6.12. It can be observed that intraocular pressure gradually decreases, with the lower limit of 14.5 mmHg being reached in year 11. [188]

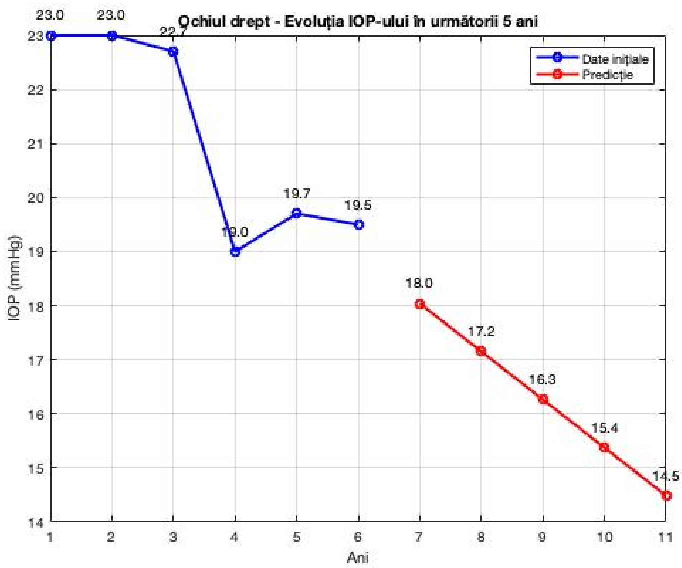


Figure 6.12. Predictions of Intraocular Pressure Values Over the Next 5 Years - Right Eye

6.4 Conclusions

The development of a *Digital Twin* for identifying glaucoma and shaping personalized treatment plans was carried out using two datasets: *Harvard Glaucoma Detection (Harvard-GD500)* and *"GRAPE Dataset"*.

The first stage involved identifying pathological patterns that favor the onset of glaucoma based on various factors such as age, gender, race, and marital status. In this context, statistics were conducted using the *Harvard Glaucoma Fairness dataset with 3300 records (Harvard-GF3300)*, identifying correlations at the parameter level. The factors that favor the onset of glaucoma are age and race: this pathology peaks in the number of cases after the age of 50 and is more common among individuals of Black or African-American descent. These two factors suggest that glaucoma is primarily caused by the aging process, which promotes both structural and functional changes in the eye. Furthermore, it can be stated that the onset of glaucoma is not directly associated with gender or marital status.

In the process of glaucoma identification, where the neural network was trained on the *Harvard Glaucoma Detection (Harvard-GD500)* dataset, the second dataset — *"GRAPE Dataset"* — was used for training the neural network over 15 epochs. The values obtained for MAE and MSE highlighted significant convergence between the training and testing datasets. Thus, this dataset can serve as a starting point for developing a Digital Twin aimed at improving the accuracy in glaucoma identification and providing personalized treatment.

In this section, electroretinograms associated with a healthy eye, early-stage glaucoma, and advanced glaucoma were constructed and processed. Integrating the electroretinograms into the Digital Twin enhances diagnostic accuracy by classifying them based on their temporal and frequency characteristics, contributing to the formation of pathological patterns. The classification of these characteristics and the use of artificial intelligence algorithms aid in detecting predispositions to glaucoma, thereby facilitating the management of the condition.

Additionally, the method for providing personalized treatment in glaucoma was presented, based on a treatment algorithm constructed using information from the medical literature. The goal of the algorithm is to achieve a target intraocular pressure, with therapeutic options tailored to the stage of the pathology and the individual characteristics of the patient.

7 | Conclusions and Future Work

7.1 Conclusions

In this thesis, the general objective of developing an architectural framework for Digital Twin type digital representation systems for e-health and personalized medicine, aimed at facilitating the representation and aggregation of patient data in a virtual environment and structuring and correlating this data within diagnostic and treatment models, has been successfully achieved.

The adopted research methodology highlighted the need for a rigorous approach, which significantly contributed to achieving the established objectives. By meeting these objectives, an overall view of the thesis was obtained, emphasizing how each stage of the research contributed to the design, development, testing, and validation of the proposed model.

The creation of the electroretinogram was carried out in MATLAB, and it was processed using the Fourier Transform and Discrete Wavelet Transform. The results of this processing will be integrated into the Digital Twin and considered reference points for glaucoma identification. Although the electroretinogram is not a clinical investigation frequently performed during medical consultations, its integration into the Digital Twin provides a detailed view for glaucoma diagnosis.

During the PhD studies, the focus was on acquiring knowledge, conducting comparative studies, proposing architectural frameworks, identifying interdependencies, and expanding interdisciplinary integration, which contributed to the development of a comprehensive vision of the research process. This process was characterized by rigor in activities and constant involvement. Among the lessons learned, the following stand out:

1. ***The importance of a solid theoretical foundation and the continuous evolution of knowledge***
2. ***Flexibility and adaptability in modeling***
3. ***The quality and quantity of data used***
4. ***Interdisciplinary collaboration***
5. ***Participation in scientific conferences and presenting papers to the academic community***

In conclusion, this thesis proposed an architectural framework for e-health and personalized medicine systems, based on the Digital Twin concept. Through an in-depth study, adaptation, and implementation of the model in ophthalmology, particularly in the identification of glaucoma and the provision of personalized treatment, the potential of Digital Twin systems to contribute to the diagnosis of ocular pathologies and the development of personalized treatment plans was highlighted. Additionally, aspects such as the importance of interdisciplinary collaboration and data quality were discussed, emphasizing the need for an ethical approach and risk analysis in the use of Digital Twin digital representations in e-health and personalized medicine systems.

7.2 Personal Contributions

In this section, the contributions that have underpinned the development of this thesis will be presented, starting from the questions formulated in Section 1.3. In the context of developing this digital model for e-health and personalized medicine systems, the following contributions stand out:

1. ***Synthesis and analysis of information from the specialized literature on the Digital Twin concept***
2. ***Conceptual development of an architectural framework for e-health and personalized medicine systems***
3. ***Adaptation of the architectural framework for e-health and personalized medicine systems to the clinical field of ophthalmology***
4. ***Development of a model for Digital Twin systems in ophthalmology***
5. ***Extension of the developed model to correlate diagnosis and treatment with other medical fields***
6. ***Conducting a risk analysis and addressing ethical challenges in the medical field***
7. ***Implementation of components of the Digital Twin system for ophthalmology and validation of the model***

The contributions presented above support the integration of the Digital Twin concept into e-health and personalized medicine systems. The development and adaptation of an architectural framework to various clinical fields highlight the potential of Digital Twin systems to optimize diagnosis and personalize treatment plans.

7.3 Future Research Directions

Although the objective of the thesis has been achieved, considering that there are always opportunities for further research, several potential directions for exploration are presented:

- One of the priority research directions is the creation of a Digital Twin capable of integrating and interacting with multiple pathologies, thus forming a system that analyzes in real-time the interdependencies between conditions and their impact on personalized treatment plans. By expanding interdisciplinary integration, this system could provide a holistic view of the patient's health, and the personalization of multi-pathological treatment could optimize medical interventions and maximize their effectiveness.
- The second research direction focuses on clinical validation and implementation in medical practice. Clinical studies could be developed to evaluate the effectiveness of a multi-pathological Digital Twin through prototype testing in medical clinics, with continuous adaptation based on feedback from specialists in various clinical fields. This approach would ensure the system's relevance and efficiency in real-world medical environments, ultimately facilitating its integration into routine clinical practice.

7.4 List of Publications

The research activity during the doctoral studies, particularly for the realization of this thesis, included the publication and presentation of the results obtained at national and international conferences, as well as in specialized journals. Additionally, this section will mention papers that have been accepted and are scheduled to be presented.

1. ***Journals***
   - ***Iliuţă, M. E.***, Moisescu, M. A., Pop, E., Ionita, A. D., Caramihai, S. I., & Mitulescu, T. C. (2024). Digital Twin—A Review of the Evolution from Concept to Technology and Its Analytical Perspectives on Applications in Various Fields. Applied Sciences, 14(13), 5454.
   - ***Iliuţă, M. E.***, Moisescu, M. A., Caramihai, S. I., Cernian, A., Pop, E., Chiş, D. I., & Mitulescu, T. C. (2024). Digital Twin Models for Personalised and Predictive Medicine in Ophthalmology. Technologies, 12(4), 55.

2. ***Conferences***
   (a) ***National Conferences***
   - ***Iliuţă, M. E.***, Pop, E., Moisescu, M. A., Caramihai, S. I., & Tiganoaia, B. (2023, May). A Digital Twin Based Approach in Healthcare. In 2023 24th International Conference on Control Systems and Computer Science (CSCS) (pp. 356-362). IEEE.
   - ***Iliuță, M. E.***, Moisescu, M. A., Pop, E., & Mitulescu, T. C. Integration of Digital Twin models with Systems Medicine for Eye Diseases.
   - ***Iliuță, M. E.***, Pop, E., Moisescu, M. A., & Mitulescu, T. C. (2024, May). A Digital Twin Framework for Applications in Ophthalmology. In 2024 IEEE International Conference on Automation, Quality and Testing, Robotics (AQTR) (pp. 1-5). IEEE.
   - ***Iliuță, M. E.***, Moisescu, M. A., Pop, E., & Mitulescu, T. C. (2024, June). Insights into Risk Management: Leveraging Digital Twins for Ophthalmic Diagnosis. In 2024 16th International Conference on Electronics, Computers and Artificial Intelligence (ECAI) (pp. 1-6). IEEE.

   (b) ***International Conferences***
   - ***Iliuţă, M.E.***, Pop, E., Caramihai, S. I., & Moisescu, M. A. (2022, September). A digital twin generic architecture for data-driven cyber-physical production systems. In International Workshop on Service Orientation in Holonic and Multi-Agent Manufacturing (pp. 71-82). Cham: Springer International Publishing.
   - ***Iliuță, M. E.***, Moisescu, M. A., Pop, E., & Mitulescu, T. C. (2023, September). Risk Assessment for Digital Twins Applied in Systems Medicine. In International Workshop on Service Orientation in Holonic and Multi-Agent Manufacturing (pp. 89-101). Cham: Springer Nature Switzerland.
   - ***Iliuță, M. E.***, Moisescu, M. A., Pop, E., & Mitulescu, T. C. (24 June 2024, Madeira). Personalized Diagnosis and Treatment Using Digital Twins in Ophthalmology. In International Conference on Engineering, Technology, and Innovation.

3. ***Accepted Papers, Pending Presentation***

   (a) ***Journals***

   - ***Iliuță, M.E.***, Moisescu, M.A, Caramihai, S.I., Pop, E., Anghel, A.M. & Mitulescu T.C., Integration of Digital Twin in glaucoma identification an monitoring - An advanced perspective in ophthalmologic diagnosis, Buletinul Științific UPB. Series C, Electrical engineering.

   (b) ***International Conferences***

   - ***Iliuță, M. E.***, Trentesaux, D., Moisescu, & Mitulescu, T. C. (26 September 2024). Ethical Implications of Digital Twins in Ophthalmology. In International Workshop on Service Orientation in Holonic and Multi-Agent Manufacturing.

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