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Development of a Platform for Storage, Simulation and Remote and Virtual Experimentation of Physiological Processes

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Development of a Platform for Storage, Simulation and Remote and Virtual Experimentation of Physiological Processes

Dissertação apresentada à Universidade de Coimbra para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Engenharia Biomédica

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This work was developed in collaboration with:

Centre for Informatics and Systems of the University of Coimbra

Centre for Informatics and Systems of the University of Coimbra

Abstract

Biological processes are the outcome of complex interactions between several elements in scales of time and space that are impractical, for the human eye, to understand. In Biomedical Engineering, a field of study that applies the concepts of exact sciences to medical problems, there is the need to understand, in detail, the physiological phenomena of human beings. With the amount of concepts to integrate, comes the inevitability of exploring educational tools out of the traditional setting. In recent years, there has been an increasing number of multimedia-based instructions, such as videos, computer modeling tools and digital laboratory scenarios, and many of its advantages are already known. The online sharing of these resources has been an important mean of knowledge dissemination, since it is possible to access it at any time, from anywhere.

In this work, we sought to develop a platform that, based on scientific papers about modelling of physiological processes, introduces a theoretical approach about its concepts, through text or digital media, provides mathematical simulation contexts and shares remote and/or virtual laboratories related to the presented subject. This platform must allow the sharing and acquisition of knowledge and resources from and to the users, store all the data and be easy to operate.

The result of this work, an online platform available on *physio.dei.uc.pt*, complies with the initial idealized requirements and its first test and validation was already made. Future work comprises the testing of the platform in an actual school subject context, in the first semester of the school year of 2016/2017, in order to evaluate its effectiveness near the students.

Resumo

Os processos biológicos resultam de interações complexas entre diversos intervenientes, em escalas temporais e espaciais impraticáveis de observar ao olho humano. Em Engenharia Biomédica, área que aplica os conceitos das ciências exatas aos problemas da medicina, existe a necessidade de compreender, em detalhe, os fenómenos fisiológicos dos seres vivos. Com tantos conteúdos a integrar, surge, com frequência, a necessidade de ferramentas de ensino fora do cenário tradicional. Nos últimos anos, tem-se observado um aumento crescente de instruções multimédia no ensino, como vídeos, ferramentas de modelação computacional e cenários de experimentação prática digitais, sendo já conhecidas muitas das suas vantagens. A partilha destes recursos em meios online tem sido uma via importante de disseminação de conhecimento, dado ser possível o seu acesso, em qualquer altura, a partir de qualquer lugar.

Neste trabalho, pretendeu-se desenvolver uma plataforma que, partindo de artigos científicos sobre modelação de processos fisiológicos, introduzisse uma abordagem teórica aos seus conceitos, através de texto e conteúdo digital, fornecesse contextos de simulação matemática e partilhasse laboratórios remotos e/ou virtuais relacionados com o assunto apresentado. Esta plataforma deveria permitir a partilha e aquisição de conhecimentos e recursos por parte dos utilizadores, guardar todos os dados e ser de fácil utilização.

A plataforma resultante deste trabalho, disponível em *physio.dei.uc.pt*, cumpre com os requisitos inicialmente idealizados e a sua primeira fase de teste e validação já foi efetuada. No futuro a plataforma será testada em ambiente escolar real, durante o primeiro semestre do ano letivo de 2016/2017, de forma a avaliar a sua eficácia junto aos estudantes.

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"If it works, it's out of date."

David Bowie

Contents

Abbreviations

AIDS   Acquired Immunodeficiency Syndrome

CMPP   Computer Models of Physiological Processes

CMS   Content Management System

DNA   Deoxyribonucleic Acid

FLC   Free Light Chain

HIV   Human Immunodeficiency Virus

HSC   Hematopoietic Stem Cells

HTTP   Hypertext Transfer Protocol

HTTPS   Hypertext Transfer Protocol Secure

Ig   Immunoglobulin

ODE   Ordinary Differential Equation

OPG   Osteoprotegerin

PTC   Proximal Tubule Cell

RANK   Receptor Activator of Nuclear Factor κ-B

RANKL   Receptor Activator of Nuclear Factor κ-B Ligand

RNA   Ribonucleic Acid

RT   Reverse Transcriptase

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Chapter 1

Introduction

This project was developed in the Department of Informatics Engineering (DEI) of the Faculty of Sciences and Technology of the University of Coimbra, within the Biomedical Engineering Master's program, and in collaboration with the Centre for Informatics and Systems of the University of Coimbra.

In this chapter, a brief overview of the developed work was made. Initially, the contextualization and motivation of this work are discussed. Then, the work plan is analyzed, by comparing the initial schedule and the real schedule. Furthermore, the structure of the thesis is presented with a short summary of what each chapter contains. Finally, the scientific contribution of this project is indicated.

1.1. Contextualization and Motivation

In physiological phenomena, what is noteworthy is usually a set of complex interactions between different elements, which can happen in extreme temporal and spatial scales, being impossible to observe in real-time events [1] [2] [3]. Thus, physiological processes cannot be truly apprehended without the understanding of biological functions in a macroscopic way, acknowledging the connections of its constituent parts, and in a microscopic way, knowing, in detail, its components [3].

Biomedical engineering focuses on the analysis and problem solving in biological and medical contexts, by applying concepts of engineering and exact sciences. Consequently, there is, in this field, the need of a thorough comprehension of the physiological processes

of living beings. Even though the living systems are more complex than any highly advanced machine, multiple conceptions used in its development can be applied to mimic biological structures [4], existing a growing tendency to formulate analogies between physiological processes and fluidic, mechanical, electric and electromechanical models [5]. Given the massive amount of different areas and contexts to integrate in biomedical engineering, there is the need of educational methods out of the conventional settings.

Furthermore, the rising number of students registered in biomedical courses requires the rationalization of teaching processes [6]. Even with the existence of tangible laboratory tools, there may not be time for each student to interact, freely, with them. Thus, multimedia resources can be a solution, both to overcome these difficulties, both to enhance the understanding of physiological processes in their different time and space scales [7].

Computer modeling has also gained recognition as a tool in the perception of life sciences, given the complementarity between the mathematical power of abstraction and simplification and the realism of computational simulations [2] [3].

The Internet has unquestionably changed the way we absorb and share information. Decades ago, the access to educational resources was restricted to schools and libraries, which caused time and displacement limitations. Currently, the Internet provides information in real time, at any hour and from any location with a connection. Consequently, e-learning platforms have become, through time, a more widely used approach to spread knowledge. Teachers and students both agree that e-learning improves the instruction and the learning processes [8].

Recently, there has been an emergent use of mobile technologies and many people see them as their first selection for connectivity [9]. Consequently, the use of tablets and smartphones may have an important role in e-learning, enabling learners to have their lessons anywhere, even in their dead times [10].

1.2. Objectives

In our work, we intended to create an e-learning platform to share and acquire knowledge about physiological processes. This platform shall provide biological/medical phenomena analysis and, based on scientific papers about modelling of physiological processes, allow: the allocation of theoretical approaches about its concepts, the support of computational simulations and the sharing of online experiments.

In order to amplify the platform's lifecycle and utility, it is desirable that it offers the possibility to upload content by users and, consequently, empower the enlargement of the scientific papers' analysis' repository.

With the aim of making the platform accessible at any time, from anywhere, it must be available online and its access shall be conceivable from any device (*e.g.,* personal computers, tablets and smartphones).

The platform to be developed must also be built in a way that it can be used in Computer Models of Physiological Processes (CMPP), a subject of the Integrated Masters in Biomedical Engineering of the University of Coimbra. In this course, there is a semester project where the students analyze a scientific paper on mathematical modeling of physiological processes, simulating its computational model and discussing its theoretical foundations.

1.3. Planning

In this section, a comparison between the initial planned work time for each task, the actual consumed time to perform each task and the unexpected tasks that emerged and were not initially considered in the scheduling is presented (Figure 1.1).

TASK	Sep 2015	Oct 2015	Nov 2015	Dec 2015	Jan 2016	Feb 2016	Mar 2016	Apr 2016	May 2016	Jun 2016	Jul 2016	Aug 2016	Sep 2016
Definition of the work to be developed	■												
Analysis of the state of the art covering online platforms		■	■										
Analysis of the state of the art covering digital representation of physiological processes		■	■										
Identification of the characteristics to be implemented in the platform			■	■									
Identification of the characteristics of physiological models to be analyzed			■	■									
Design of the Platform					■	■							
Learning about web development tools							■	■					
Development of the Platform							■	■	■	■	■		
Selection and analysis of the study cases										■	■	■	
Writing of a Scientific Paper											■		
Test and Validation of the platform												■	
Writing of the final report										■	■	■	■

■ initial plan   ■ actual event   ■ unexpected task

Figure 1.1.: Initial scheduled vs. real scheduled.

As seen in the Figure 1.1., the real scheduled work was composed by 12 tasks:

- **Definition of the work to be developed**: At the beginning of the project, it was necessary to delineate goals, methods and formulate a work strategy;

- **Analysis of the state of the art covering online platforms**: With the purpose of developing an online platform to act as a mean of knowledge spread, a detailed

exploration of e-learning platforms was required. This task was essentially the analysis of platforms focused on similar objectives;

- **Analysis of the state of the art covering digital representation of physiological processes**: In order to create and share computer-based learning tools, an analysis of the current digital representation of physiological processes was crucial.

- **Identification of the characteristics to be implemented in the platform**: Preceding the development of the platform, we identified the main general features to be implemented;

- **Identification of the characteristics of physiological models to be analyzed**: At this phase, the key characteristics to approach in the exploration of the physiological processes' models were identified;

- **Design of the platform**: After all the core features were determined, the platform's functioning requirements were pointed out and a prototype was built;

- **Learning about web development tools:** For the purpose of building the platform, it was necessary to learn some web development concepts, in order to deal with technologies that I had never worked with before. This was a task that was not counted in the initial schedule, but that was decisive to proceed with the project. In this period, for example, I took part in an online course about "Responsive Website Basics: Code with HTML, CSS, and JavaScript" developed by the University of London, Goldsmiths, through COURSERA INC. [11];

- **Development of the platform:** At this stage, the platform was built, taking into account the desired features in the previously designed prototype;

- **Selection and analysis of the study cases:** Some physiological processes' models, as educational, illustrative and useful examples, were selected, explored and then shared in the platform;

- **Writing of a scientific paper:** The time spent on writing a scientific paper, later accepted, was also not taken into account in the first work planning. This task included the time of idealizing and writing the scientific paper;

- **Test and validation of the platform:** This task consisted in putting the platform to be used by real users and in the collection of their opinions;

- **Writing of the final report:** At the end, the final report of the project was written.

There were some differences between the original schedule and the real work strategy. The greatest challenge to solve, but also the personally most pleasant achievement, was the need to deal with tools and technologies that I had never used before. However, the initial objective was achieved and the platform was developed as planned.

1.4. Document Structure

The structure of the document is organized as follows: in Chapter 2, it is investigated the state of the art and the educational contribution of computer-based representations of physiological processes; in Chapter 3, an approach about e-learning is made, and some online platforms with focus on life sciences are explored; in Chapter 4, it is formulated the design of the platform to be built; in Chapter 5, it is described the development of the platform; in Chapter 6, the study cases to be inserted in the platform are chosen and studied; Chapter 7, reports the results of the test and validation of the platform; as a final point, in Chapter 8, the final results and the proposals for future work are presented.

1.5 Scientific Contribution

The work entitled "Development of an E-learning Platform for Storage, Simulation and Online Experimentation of Models of Physiological Processes", elaborated in the scope of this project, was accepted in the special session "Talking About Teaching 2016" of the "International Conference on Interactive Collaborating Learning 2016", which will take place in Belfast, United Kingdom, in September 2016.

Chapter 2

From Physiology to Computational Representation

2.1 Physiological Processes: An Overview

Physiology, a subdivision of biology, focuses on the quantitative understanding of the multifaceted behavior of living beings [12] [13]. It covers a range of topics that comprises biological compounds, cells, tissues and organs, and how they connect to make life conceivable [14].

2.1.1 Complexity of the Analysis of Biological Systems

In biological contexts, what is important is usually a set of relations between elements of a system. Given the enormous complexity of living organisms, compounded by the presence of external agents in very short of very large contexts of time and space, the human capacity to understand these processes is very limited [1] [2] [3]. – e.g., for the human body, temporal scales can range from 1 μs (ion channel gating) to 10^9 s (human's lifetime) and spatial scales can range from 1 nm (protein) to 1 m (whole body), which means 16 and 10 orders of difference between magnitudes, respectively [3].

Physiology cannot be understood without the perception of biological phenomena neither in a macroscopic way nor in a microscopic way. To recognize how the living systems work, a clear comprehension of all interactions of the evolved components is needed, and, at the same time, a precise conception of their constituent parts [5].

Thus, a proper knowledge of the biological functions arises only if we are able to combine all the information in all points of organization [3]. For example, in the case of the ingestion of a drug, it is not only important its effects on the target, but all its course and interactions. Without this awareness, the drug could potentially lead to dangerous side effect that would not be acknowledged [1] [3]. In the case of tumor formation, in addition to understand its growing, it is crucial to realize several processes that occur at the same time and that may play a central role on wound healing, for example [15].

2.1.2 Use of Modeling in Physiology

According to [16], a model can be described as a "construct invented as an aid to understand a specific system under study, and possibly the relationships of that system with other systems".

In all sciences, models are used to represent in a simplified way a more complex reality, embodying the essential and interesting aspects of the reality. These are very important as learning tools, once they make the subject more familiar and accessible and ease the formulation of intuitive descriptions. Any abstraction of a biological event can be considered a model [2].

A mathematical model is an abstract model that is defined by a set of equations and expresses the behavior of a system [16] [17]. The formulation of mathematical models that describe biological processes of great complexity and dynamism are very important to understand physiological functions, mainly because this models can take into account the multiple spatial and temporal contexts in which the processes occur. Such extreme scales lead to the need of a joined hierarchy of models for the perception of those systems [3]. For the study of large systems, the most known and reliable mathematical technique is the use of differential equations [18].

2.2 Computational Simulation of Physiological Processes

Generally, the mathematical models resulting from the analysis of biological processes are so complex that they can only be solved computationally, which increases the importance of computer simulations [3].

A computer simulation can be defined as a "program that is run on a computer and that uses step-by-step methods to explore the approximate behavior of a mathematical model" [19]. Widely, computer simulations can be seen as simpler approaches to understand processes, which includes: the choice of a model, the decision of how to implement it on a computer, the calculation of the algorithms' output and the analysis of the results [19].

In general, dynamic interactions in biological systems take place in temporal and spatial scales that are impossible to observe. One of the only feasible approaches to understand complex connections between physiological processes is through the performance of computational simulations based on previously developed mathematical models [3]. Generally, a computational model replicates the behavior of a system, overcoming the length scales concerns and incorporating multiple concepts [20].

Biomedical sciences have been experiencing an enormous revolution, with increasingly more discovered data and explored materials, and, therefore, more information to integrate [3]. Thus, the current amount of collected information is beyond the capability of any human to analyze. To understand and explore these data, modelling simulations are essential [2].

Moreover, computational simulations can be performed in real-time and allow the analysis of different contexts and the changing of parameters, getting results faster than using any other approach [2].

2.3 Remote and Virtual Experiments in Biomedicine

Students in biology fields are constantly filled with new information, theories, techniques and vocabularies, which are essential to learn and discuss the mechanisms of biological phenomena. Still, the unsophisticated act of learning by rote is progressively becoming outdated and there is a growing tendency to absorb knowledge through exercise, particularly through the use of practical experiences that demonstrate biological principles. These scenarios create a learning environment that stimulate students to critical thinking [21].

Science teachers claim, since the 19th century, that practical activities are an important mean of instruction [22]. Through the use of laboratories, students can be encouraged to inquire and investigate, improving their sense about certain concepts and understanding how science is made and how the facts are discovered [22].

At the present, even with the existence of physical laboratory spaces, the opportunity for each student to interact freely with it might not exist. Beyond this, the use of these laboratories is only accessible to students usually once, in short periods of time (as the time of a single class lecture). Besides, there are still many isolated locations without any or poor access to laboratory equipment. In those cases, there is a great need for alternatives that compensate that lack.

Remote experiments can be termed as structures based on real equipment that allows students to execute practical work through a computer remotely linked with it, (*e.g.,* through an internet connection) [23]. Many of their advantages are: these practical experiments can be accessed 24 hours per seven days, without any supervision and, through the use of automated management systems, users can be assigned to time limits during busy periods, ensuring that everyone has a chance to execute the experience [24]; given that a public access and an actual physical interaction with the experiment are not needed, the equipment is less likely to be damaged, vandalized or stolen [24]; although the remote experiments are handled by computer, they retain the characteristics of a real-time physical experiences, returning real experimental results.

A virtual experiment can be defined as a virtual studying and learning environment in which is possible to conduct an experiment [25] [26]. Many of the benefits of the remote experiments can be applied to virtual experiments. In virtual environments, although we are not dealing with a real physical context and real experimental outputs, there are other advantages, such as the possibility to represent scenarios in non-real scales, in order to facilitate the understanding. Moreover, these scenarios can be accessed by several users at the same time. With the power of technology, it is now possible to create great user interaction and a plausible manipulation of objects and parameters [27]. Furthermore, studies show that the use of virtual experiments increases students' learning levels [28].

In this way, remote and virtual experimental scenarios can play a fundamental role in the learning of concepts in the field of biology.

2.4 Summary

In this chapter, some of the current difficulties in the analysis of physiological processes (and how they may be overcoming) were discussed. It approaches the role of modeling and mathematical modeling in the study of biological phenomena and in what manner computer simulations can be a key element in the understanding of these concepts.

The importance of experimental scenarios in the field of biology was also reviewed. Given the limitations of physical access to this type of equipment, remote and virtual experiments can be considered as a solution.

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Chapter 3

E-learning in Modern Education

In this chapter will discuss the advantages and the challenges of e-learning, as well as its blend with traditional education. We will also explore some selected e-learning platforms and analyze their features of interest.

3.1 E-learning: definition

E-learning can be defined as the usage of electronic technologies to access educational resources [29]. Traditionally, it has been considered two types of e-learning: distance learning, which is the use of technologies to provide lessons in remote locations, and computer-based learning, which is the use of computers to support multimedia learning. Nowadays, with the popularity of the Internet, these two definitions became integrated inside the characterization of e-learning [8].

In recent years, education delivery has been under a tremendous revolution [30]. Blogs, wikis, virtual environments and social networks have been gaining an increased use in higher education [31]. Wikis are termed as server software that allows users to collaborate on the forming of websites (*e.g.,* accept the insertion of content) [32].

The benefits and adversities of e-learning have been widely discussed and investigated. Its effectiveness has also been tested when combined with traditional teaching settings.

3.1.1 Advantages

Computer-based teaching empowers learning to be more individualized (adaptive learning) and, at the same time, stimulates learners' connections with others (collaborative learning), placing apprentices in control of their own tuition. Through e-learning, there is generally an increased accessibility for the user to find what he requires, at any time. This appears to be crucial, once learning is often an unexpected practice [8].

It is usually easier to renew digital media than on paper material, which facilitates and accelerates the sharing of updated knowledge. [8] [33]. In addition, Internet offers a faster and expanded spread of information, allowing the discovery of subjects beyond the limits of a book [8] [31]

Students tend to learn more through e-learning than with traditional teaching settings, presenting higher retention rates and greater acquirement of knowledge [8] [34]. Interactivity acts as a major part in this occurrence, leading to more intellectual commitment. In computer-based instruction, it is possible to stop, repeat and reflect, consenting the user to focus on his own doubts [34]. Web-based technologies offer a massive learning flexibility. In this environment, learners can move at their own pace and control their learning sequence [8] [33]. These can be some of the reasons why, when faced with computer-based tuition, students learn often in less time than with other learning approaches. This one-to-one involvement removes, for example, the time waiting for other colleagues' doubts to be answered, as in a classroom, allowing the learner to concentrate only in his own questions. Time saved can vary from 30% to 60% [34].

This self-control can also contribute as a motivating element. If the learner has the option to decide when and how to learn, learning might be more substantial. Furthermore, the absorbed knowledge is more significant when the student is in the mood to study [34].

One of the most obvious advantages of e-learning is that it defeats physical distances, reaching the most isolated places [33]. This can be very helpful, for example, to share online experimental scenarios that may not be available in those locations. Besides, even with the existence of tangible laboratories, online experiments may still be useful, once they allow an individualize contact and the possibility of repetitions [6] [7].

Smartphones and tablets have become increasingly more popular [9]. Given its easiness of use and the fact that people are usually carrying one, e-learning is an amazing opportunity to spread knowledge, allowing the delivery of information at any time, even during other activity breaks or waiting times (dead times) [10].

3.1.2 Challenges

Although digital technology apparently facilitates the learning process, it is still difficult to truly understand its effectiveness and accurately assure that an appropriate learning is achieved [31]. Moreover, the elaboration of effective online laboratories can be very expensive and, regardless of the best plans, technical problems are always inevitable [33].

Despite the evidences that show that an individualized study can be an advantage, this can lead to social isolation. Even with the involvement on discussion forums, it still is a different kind of community integration, compared with face-to-face debates [33]. Nowadays, the learning process is still very much linked to personal communication: eye contact, tone of voice and body language are essential, once the brain requests and expects these channels of interaction [30].

3.1.3 E-learning Combined with Traditional Education

A relatively recent new term in the education field is blended learning [8]. According to [30], blended learning can be described as "the combination of face-to-face instruction with online platforms". In this context, teachers will no longer act primarily as providers of content, but will become more focused on facilitating the learning process and behave as evaluators of competency [8]. Students do not see e-learning as a replacer of traditional educational methods, but a supplement [8] and an "expected and integral part of the learning process" [35]. Through the use of computer-based instruction, teachers can focus on the support, motivation and help of the students, instead of delivering "repetitive stand-up training" [34].

Over the past decades, institutes of higher education have been embracing blended learning, merging the greatest characteristics of real and virtual environments [35]. With blended learning it is possible to experience the benefits of e-learning and overcome quite

a few of its disadvantages. Summing up, with blended learning it is possible to combine "the potentials of web-based training with those of classroom techniques" [30].

Both benefits of face-to-face communication and the power of e-learning are incontestable. Their complementarity can generate an extremely solid learning method [30].

3.2 Biomedical E-learning Platforms

In the last few years, e-learning platforms have amplified its attractiveness, arising several alternatives, appearing several options, such as theoretical approaches based on digital media, computational modeling tools and online laboratories.

In the subsequent topics, we will explore some e-learning platforms with a focus on the life sciences.

3.2.1 hhmi|Biointeractive

hhmi|Biointeractive [36] is an online platform developed by the Howard Hughes Medical Institute. The main goals of this platform are to provide free and up-to-date education resources to the teachers and to stimulate students to be curious and passionate about science [37]. Some of the resources we can find at hhmi|Biointeractive are short films, virtual laboratories, interactive tutorials, classroom resources and teacher guides [38]. For the common use of the platform, there is no need to register. However, there is the possibility of ordering materials and, in that context, registration is required.

In the platform's homepage (Figure 3.1), we are able to do a free search, a search by topics, a search by resource types (*e.g.*, video, interactive media, short courses) and a search by collections; we can also observe the team suggestions and the most popular and newest content [36].
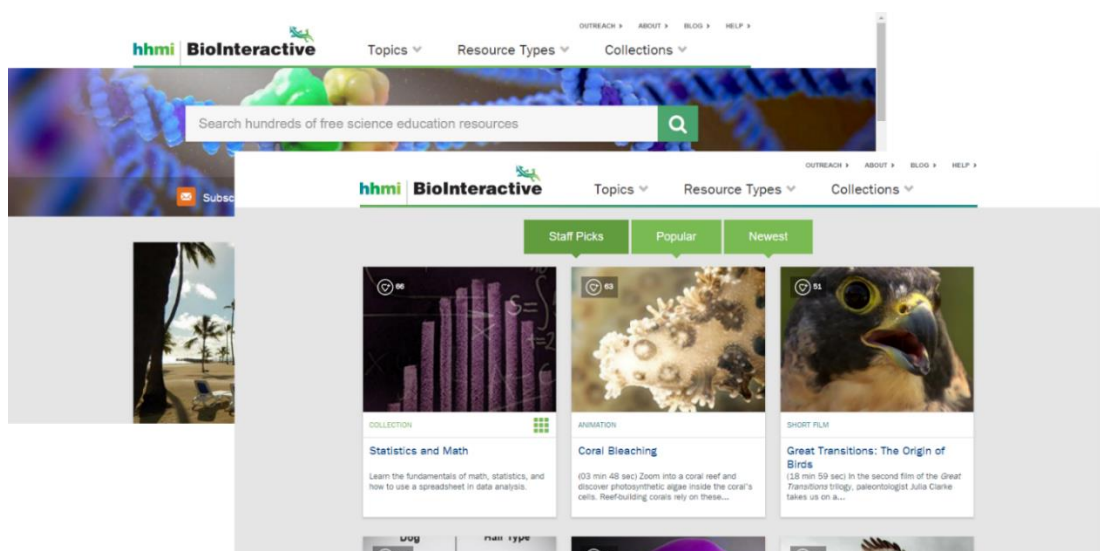
Figure 3.1: hhmi|Biointeractive homepage [36].

When we select a resource (*e.g*., Figure 3.2), there is a brief overview of the subject. In many cases, it is possible to download materials such as worksheets, theoretical explanations, videos, among others. Some of the materials are available as applications for smartphones.
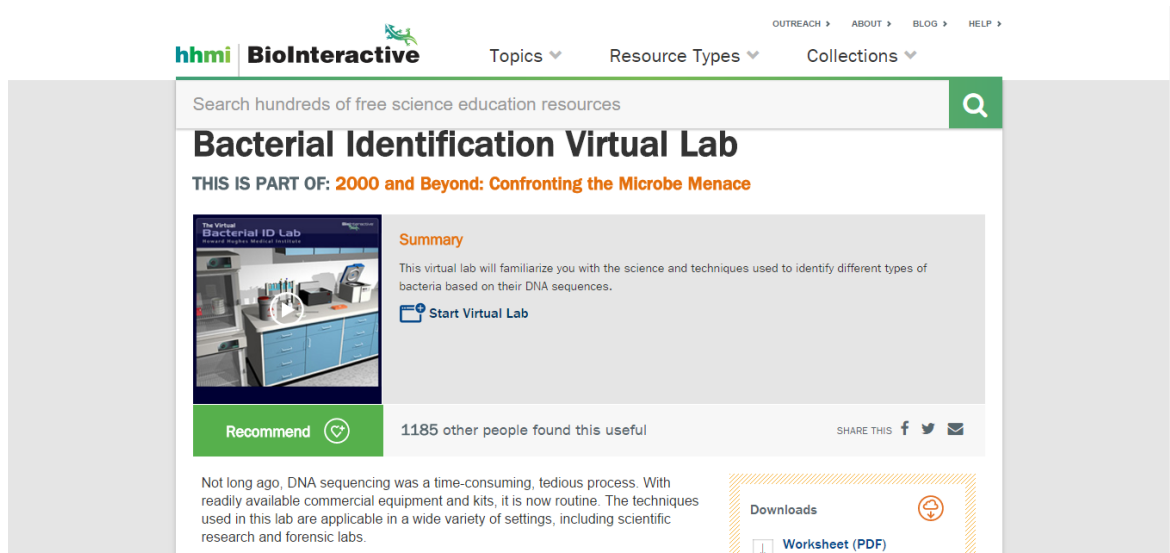
Figure 3.2: Example of a resource of hhmi|Biointeractive [39].

3.2.2 Virtual Labs

Virtual Labs [40], an initiative of the Ministry of Human Resource Development of the government of India under the national mission on education through information and communications technologies, offers numerous virtual/remote laboratories and simulation environments, among others, in multiple areas of science and technology. This project aims to create online experimentation environments that can overcome the difficulties of geographical and equipment constraints, as well as sharing an assortment of learning tools, in a way that can create enthusiasm and interest in the students.

The Virtual Labs initiative has several participating institutes. When we choose a scientific/technology field to explore (*e.g.*, Biotechnology and Biomedical Engineering) and the concrete resource to be investigated, we are redirected to the institution that is hosting the experiment environment. In this context, for a total access of the materials, depending on the host platform, it may be necessary to create an account.

Depending on the selected subject, the presented type of resources (*e.g.*, video, animations, simulations, virtual and/or remote laboratories) varies; sometimes, there is the possibility of downloading materials and, if the context suits, it is possible to export the data obtained.
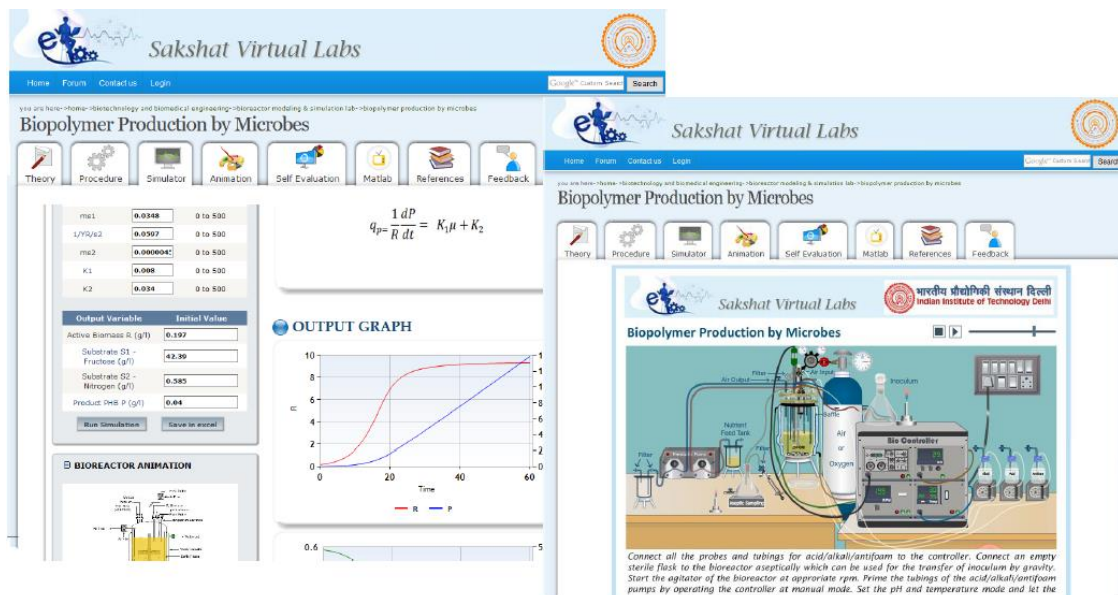
Figure 3.3: Example of a resource of Virtual Labs [41] [42].

In the example showed above (Figure 3.3) there is a mathematical simulator [41], an animation with a virtual laboratory [42] and the possibility to download MATLAB files [43]. Although some aspects change depending on the selected subject, there are, in all the areas I searched, a theoretical approach and a self-evaluation task.

3.2.3 The Biology Corner

The Biology Corner [44] is an online platform created by Shannan Muskopf, a teacher at Granite City High School, with a Bachelor's degree in Biology and a Master's degree in Educational Technology [45].

In the homepage (Figure 3.4), there is the possibility to choose the content by its topic and resource type, as well as to observe the most popular and newest lessons [44].
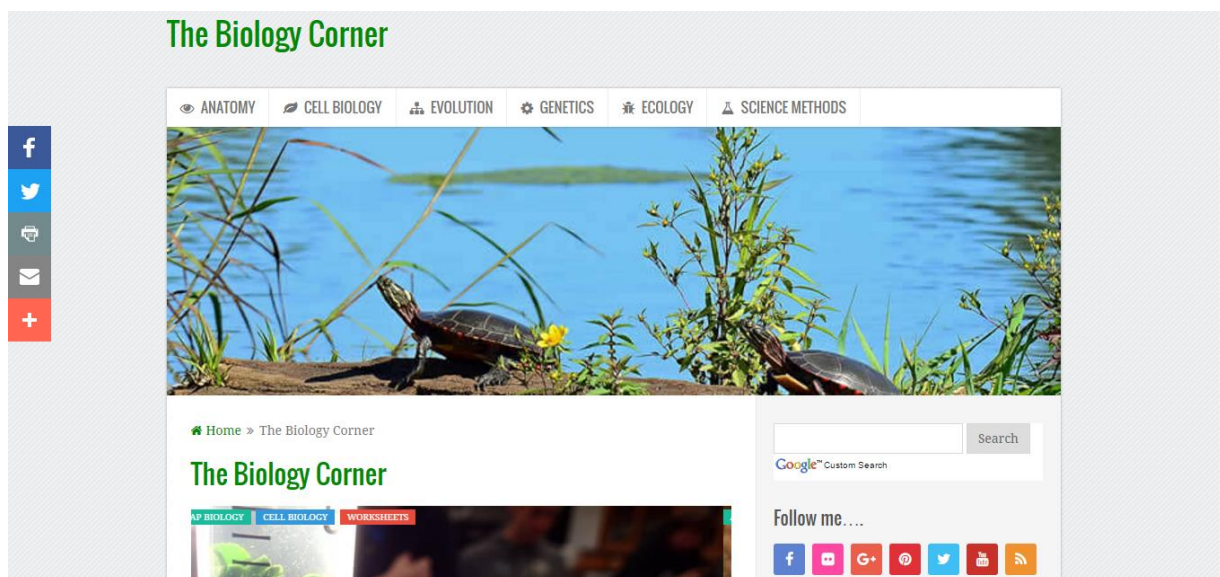
Figure 3.4: The Biology Corner homepage [44].

The platform contains several lessons (as Figure 3.5), quizzes, online laboratories, webquests and theoretical information on a variety of topics.

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Figure 3.5.: Example of a lesson of The Biology Corner [46].

Some of the resources that are presented are not hosted in The Biology Corner and, when we select them, we are redirected to the host webpage; however, in those cases, this platform gives us a detailed explanation of how they will work (Figure 3.6).

Figure 3.6: Example of an explanation of a resource hosted in another web platform [47].

At The Biology Corner, there is no option for creating an account, being the navigation completely free.

3.2.4 PhET Colorado Interactive Simulations

PhET Colorado Interactive Simulations [48], a project at the University of Colorado Boulder, was founded by Nobel Laureate Carl Wieman. This platform shares interactive math and science simulations, based on extensive education research, with the purpose of stimulating students through a learning environment of exploration and discovery. Those simulations are written in Java, Flash and HTML5 and can be ran online or downloaded for free [49].
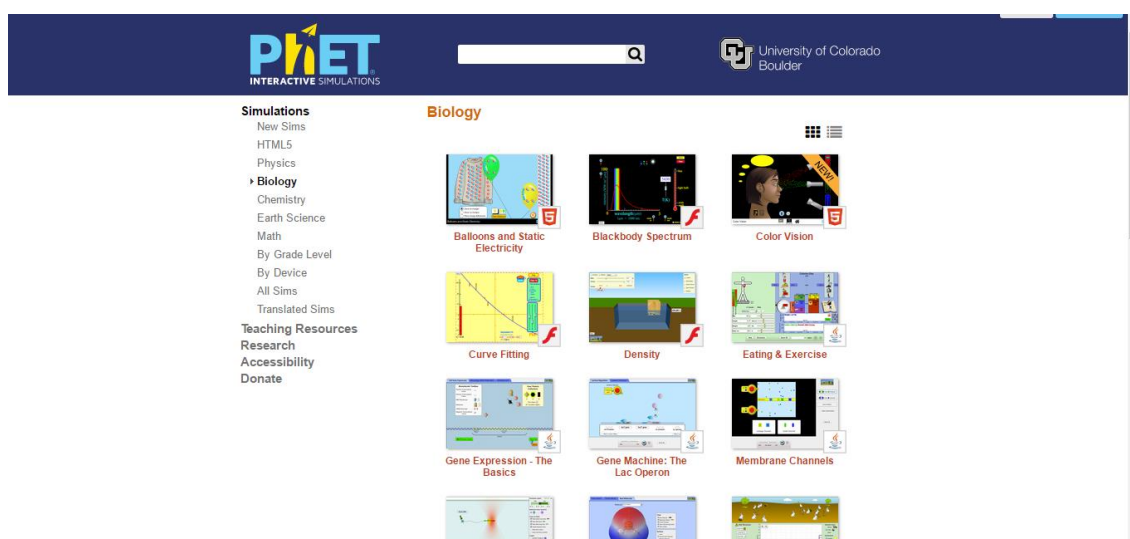
Figure 3.7: PhET Interactive Simulations' Biology Separator [50].

When we opt for an area to explore, the platform shows the simulators related to that field and the language in which they were written. Clicking in a specific simulator (Figure 3.8), we are allowed to download it, as well as embed it in our own website, and read some information about the content, software requirements and credits.
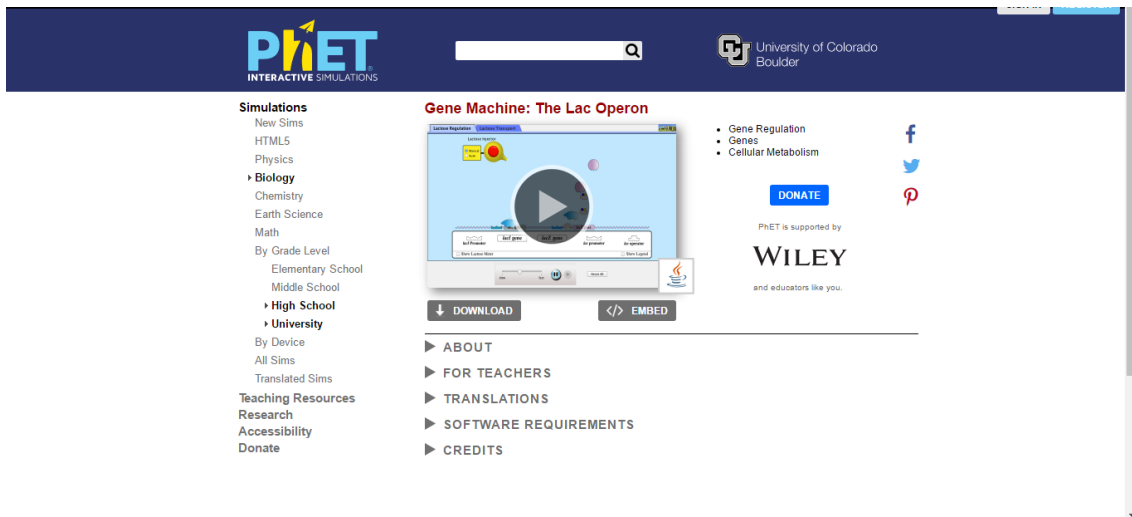
Figure 3.8: Example of a simulator at PhET Colorado Interactive Simulations [51].

In addition to the simulations, resources target to educators are also available. In this context, it is possible to share teaching activities, which requires a previously registration in the platform.

3.2.5 Wisc-Online

Wisc-Online [52] is an online platform created by sixteen colleges in the Wisconsin Technical College System and it is maintained by the Fox Valley Technical College [53]. Its purpose is to offer free quality education materials that condense the information into small segments easy to understand, giving users the possibility to choose what to learn, at their own step.

Selecting the field of Life Sciences [54] (Figure 3.9) we can choose to observe the content by its rating, name, views and updated date. The resources types vary among videos, animations and educational games and others.

When we pick a specific learning object [55] (Figure 3.10), in addition to have access to the material, we can download a copy of it. Also, we can leave a question, start a discussion and see related resources.

Figure 3.9: Wisc-Online Life Sciences' main page [54].

Figure 3.10: Example of a Wisc-Online learning content [55].

It is also possible the creation of our own educational game [56] (Figure 3.11) which can be played in any device. For the general access to the contents, a registration is not needed; however, to download and update materials, it is necessary an account or a log in through social media.
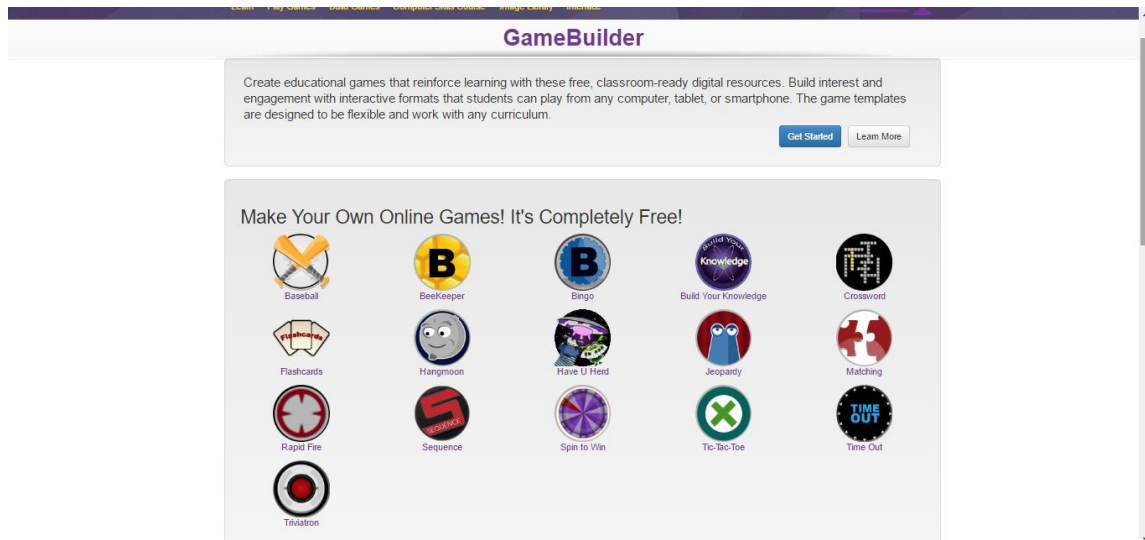
Figure 3.11: Wisc-Online game builder [56].

3.2.6 Features' Analysis

After a detailed exploration of the platforms described in 3.2.1, 3.2.2, 3.2.3, 3.2.4 and 3.2.5, we summarized and evaluate the existence of a set of features, described below. The remaining references in this document to those features will be made in accordance to the concepts described below (with the assigned definitions).

- **Computational Simulations (1):** real-time computer simulations of mathematical models, displayed as graphics or tables;
    - o **Interactive (1.a):** when there is the possibility of varying initial conditions or other parameters;
    - o **Non-Interactive (1.b):** when all the parameters are fixed;
- **Virtual Experiments (2):** multimedia contexts that implement a practical experiment or display an animated physiological perspective;
    - o **Interactive (2.a):** when there is the possibility of changing parameters or interact with the experiment;
    - o **Non-Interactive (2.b):** when all the parameters are fixed and no interaction is available;
- **Remote Experiments (3):** physical remote laboratories that implement a practical experiment;

- o **Interactive (3.a):** same as 2.a;
- o **Non-Interactive (3.b):** same as 2.b;
- **Registration (4):** creation of a user account;
  - o **Optional (4.a):** when the registration is optional and it is possible to use most of the features of the platform without it;
    - **Free (4.a.i):** when the registration is free;
    - **Paid (4.a.i.i):** when the registration is paid;
  - o **Required (4.b):** when it is not possible to interact with core functionalities without an account;
    - **Free (4.b.i):** same as 4.a.i.;
    - **Paid (4.b.ii):** same as 4.a.ii;
  - o **Depending on external entities (4.c):** when the necessity of an account depends on external entities;
- **Content Upload (5):** option to upload content;
- **Content Download (6):** option to download content;
  - o **Theoretical Material (6.a):** (*e.g.*, theoretical reading files);
  - o **Practical Material (6.b):** (*e.g.*, simulation files, virtual experiments);
  - o **Multimedia Files (6.c):** (*e.g.*, audio, videos, images);
  - o **Export of generated data (6.d):** (*e.g.*, graphics or tables generated in simulations or experiments);
- **Mobile Devices (7):** possibility of access content through a mobile device;
  - o **In the form of an app (7.a):** when the content is available as an application for download for mobile devices;
  - o **Optimized to mobile devices (7.b):** when the platform is responsive and can be accessed with quality from a mobile device;
- **Content's Approach (8):** address a review of the offered content;
  - o **Theoretical Lectures (8.a):** theoretical elucidations of the presented topic;
    - **Text Documents (8.a.i):** when it is presented in the format of a text;
    - **Multimedia Files (8.a.ii):** when it is presented in a digital format (*e.g.*, audio, videos, images);

- o **Critical Analysis of the References (8.b):** critical inquiry of the matter of the references;

- o **Evaluation Activities (8.c):** tasks and quizzes to evaluate the knowledge of the user in the subject;

- o **Critical Reviews and Debate (8.d):** possibility to introduce questions, reviews and/or start a debate;

    - ▪ **User's Feedback (8.d.i):** possibility to rate an existing content or leave an opinion;

    - ▪ **Discussion Forums (8.d.ii):** existence of debate forums where is possible to start a conversation;

Table 3.1 presents an analysis of the existence of the previously defined features in the explored platforms; the last column represents the features that arouse more interest and are more appealing to include in the platform to be developed.

Table 3.1.: Analysis of the described platforms and the selection of the features of greater interest.

	hhmi|Biointera-ctive	Virtual Labs	The Biology Corner	PhET Colorado Interactive Simulations	Wisc--Online	Features of greater interest
Computational Simulations		1.a, 1.b				1.a, 1.b
Virtual Experiments	2.a, 2.b	2.a, 2.b	2.a, 2.b	2.a, 2.b	2.a	2.a, 2.b
Remote Experiments		3.a, 3.b				3.a, 3.b
Registration	4.a.i	4.c		4.a.i	4.a.i	4.a.i
Content Upload				5	5	5
Content Download	6.a, 6.c	6.b, 6.d	6.a	6.a, 6.b, 6.c	6.a, 6.b, 6.c	6.a, 6.b, 6.c, 6.d
Mobile Devices	7.a, 7.c		7.b		7.b	7.b
Content's Approach	8.a.i, 8.a.ii, 8.c, 8.d.i	8.a.i, 8.a.ii, 8.c, 8.d.i	8.a.i, 8.a.ii, 8.c, 8.d.ii	8.a.i, 8.a.ii, 8.c	8.a.i, 8.a.ii, 8.c, 8.d.i, 8.d.ii	8.a.i, 8.a.ii, 8.b, 8.d.i, 8.d.ii

It is important to refer that the previous analysis of the explored platforms considers what was found in the quest and, once the platforms have not been observed in the absolute

totality of its content, given its breadth, there is the possibility of them to contain characteristics not recognized in Table 3.1.

3.3 Summary

Through this chapter, we realize that e-learning is gaining popularity and, despite its current challenges, many of its advantages are already recognized. In addition, blended learning, a learning strategy that combines traditional education scenarios with e-learning, is also increasing its attractiveness, by merging the benefits of both methods.

Furthermore, we analyzed some e-learning relevant platforms and explored its main features and characteristics of interest.

Chapter 4

Platform Design

In this chapter will be discussed the characteristics and desired features to be included in the platform of this project. We will also develop a prototype of its navigation structure and its general appearance. It will also be discussed tools that may facilitate the construction of the system.

4.1 Overview

The solution to be developed is an e-learning platform that supports the sharing and the acquiring of knowledge in the physiological field. This platform, having scientific articles as reference, shall allow the introduction of theoretical analysis about the subject, the share of multimedia materials, the performing of computer simulations and the allocation of available online laboratories. To increase the platform's longevity, it shall be possible to upload examinations and resources. In this way, to ensure the significance and the constraints of the shared materials, there shall be different levels of users, including a top level, that must moderate the inserted content. However, not all the introduced material needs to be completely precise and proven; consequently, it is crucial to provide feedback and discussion means, allowing critical debates from other users. The platform shall be completely free and available on any device.

4.2 Requirements' Analysis

The Requirements Analysis can be described as the identification of the features and the functionalities that shall be presented in a system [57], which can be divided into functional and non-functional requirements [58]. Functional requirements define what the system shall offer to the users. Non-functional requirements focus on matters such as constraints, targets and/or control mechanisms (*e.g*., different user levels) [59]. The MoSCoW Method was used to classify the priority of each requirement. This method ranks queries in four levels [60]:

- **MUST (M):** Must have this requirement to the success of the system;
- **SHOULD (S):** Should have this requirement, but the success of the system does not depend on it;
- **COULD (C):** Could have this requirement, if it does not harm other parameters in the project;
- **WOULD (W):** Would like to have this requirement, but it is considered as future work.

In the subsequent sections, the functional and non-functional requirements of the platform are listed, grouped by their context, and classified according to the MoSCoW method. In order to ease the future references to the requisites, an ID was assigned to each requirement.

4.2.1 Functional Requirements

To allow an effortless and simples use of the platform, search engines that return articles (and articles' analysis) from the database must be available.

Table 4.1: Search Requirements.

ID	Search	Category
S.1	The website allows the user to search through default topics.	M
S.2	The website allows the user to search through natural language, returning content that match the inserted words.	S
S.3	The website's homepage suggests some articles (*e.g.,* the most viewed).	C

Authentication is a key point in the system, since it ensures the privacy of content and the protection of data. Each account is associated with credentials that are described below.

Table 4.2: Authentication Requirements.

ID	Authentication	Category
A.1	Each user has a name, username (unique identifier), password and e-mail address (unique identifier).	M
A.2	A logged-out user has to enter his credentials in order to access his account.	M
A.3	A registered user is able to remain logged-in into the website.	C

The platform must allow the insertion and handling of content through easy-to-use management tools.

Table 4.3: Management of Articles Requirements.

ID	Management of Articles	Category
MA.1	Creation/edition/deletion of an article's analysis and its content.	M
MA.2	Approval of submitted analyses.	M
MA.3	In each article's analysis, the website is prepared to accommodate text, multimedia files and web development languages (HTML, JavaScript and PHP), as well as embed other websites' pages/contents.	M
MA.4	For each article's analysis, the user has total freedom to insert any sections, in the form of tabs (e.g., theoretical approaches, computational simulations, practical experiments, download options).	S
MA.5	Observation of own submitted articles (approved/ unapproved).	S
MA.6	There is, at least, one entity responsible for the control and management of all article's analyses, being able to edit all their parameters.	M

The platform must allow the insertion and handling of users and their parameters through easy-to-use management tools.

Table 4.4: Management of Users Requirements.

ID	Management of Users	Category
MU.1	Creation of a new account.	M
MU.2	Any account is associated with a name, username (unique identifier), password and e-mail address (unique identifier).	M
MU.3	A new account becomes activated after an e-mail confirmation (the e-mail is automatically sent by the website).	S
MU.4	All the account parameters can be edited, except username and status.	S
MU.5	There is, at least, one entity responsible for the control and management of all users, being able to edit all their parameters.	M

The system must provide discussion forums and the possibility for users to give feedback.

Table 4.5: Feedback and Discussion Requirements.

ID	Feedback and Discussion	Category
FD.1	The website includes a discussion forum.	M
FD.2	The reading of the discussion forum is possible.	M
FD.3	The start of new topics of discussion in the forum and the participation in a previously created one are possible.	M
FD.4	A rating system, in every inserted article's analysis, is available and the mean of the given responses is showed.	S

4.2.2 Non-Functional Requirements

The platform must be responsive and capable of being displayed in the most used browsers.

Table 4.6: Browser and Responsiveness Requirements.

ID	Browser and Responsiveness	Category
BR.1	The website is available in the most popular browsers (Chrome, Internet Explorer, Firefox and Safari) [61].	M
BR.2	The website is responsive.	M

All the actions available in the system must be accessible through the front-end, in an organized and orderly way.

Table 4.7: Interface Requirements.

ID	Interface	Category
I.1	The website has a user-friendly interface.	M
I.2	All the features are available through the front-end.	M
I.3	The content is organized in a hierarchical way.	M
I.4	The names of the sections are clear.	M
I.5	The aspect of the website is consistent and clean.	S

A help section should be available, containing documentation guides. After the performing of an important action, a notice message shall be displayed.

Table 4.8: Help Requirements.

ID	Help Section	Category
I.1	A documentation guide, including a detailed explanation about how to operate the functionalities of the website, is available.	M
I.2	A proper message is displayed, when any creation/edition/deletion action is performed.	S

4.2.2.1 User Levels

The platform must have three levels of users: guests, authors and super users. Guests are public users that are not registered into the website; on the other hand, authors and super users are both registered users. When a new account is created, the user's group is, by default, defined as an author.

Only some of the functional requirements, discussed in Section 4.1, must be reachable to all the users. In Table 4.9 and Table 4.10 the functional requisites with special access that must be accessible only to registered users and super users, respectively, is approached in more detail.

Table 4.9: Registered Users Special Accesses.

ID	Category	Functional Requirement
MA.1	M	Registered users are able to create an article's analysis, and edit/delete it.
MA.4	S	Registered users have total autonomy in the choice of the sections (tabs) to be inserted/examined in an article's analysis.
MA.5	S	Registered users can observe their own submitted articles – both approved and unapproved.
MU.4	S	Registered users are allowed to edit all their account parameters, except their username and status.
FD.3	M	Registered users can start a new discussion topic in the forum. They can also participate in an existent one.

Table 4.10: Super Users Special Accesses.

ID	Category	Functional Requirement
MA.2	M	An analysis stays pendent until a super user's approval.
MA.6	M	Super users have full control in all the inserted content, being able to edit/delete it and change their publishing state.
MU.5	M	Super users are able to see all the user's parameters, except for their passwords, and edit his data, including their user group.

Super users must, in addition, be allowed to see some statistics of the website, such as its number of visitors.

4.3 Conception of a layout

A layout can be defined as the initial design of a project and shall be used as a reference in its development. It must include all the major details to be incorporated in the final version [62].

In the following section, the website's structure and wireframes will be elaborated.

4.3.1 Structure Diagram

A structure diagram is a scheme model used to document the different elements of a system and how they connect. It is a useful guide tool in the design of a project, given that it helps to understand how the elements of a system must interact and to ensure the relationship of all the parts [63].

The platform to be built must have three different levels of users, with different accesses. The structure diagram (Figure 4.1) takes into account the permission of each user.
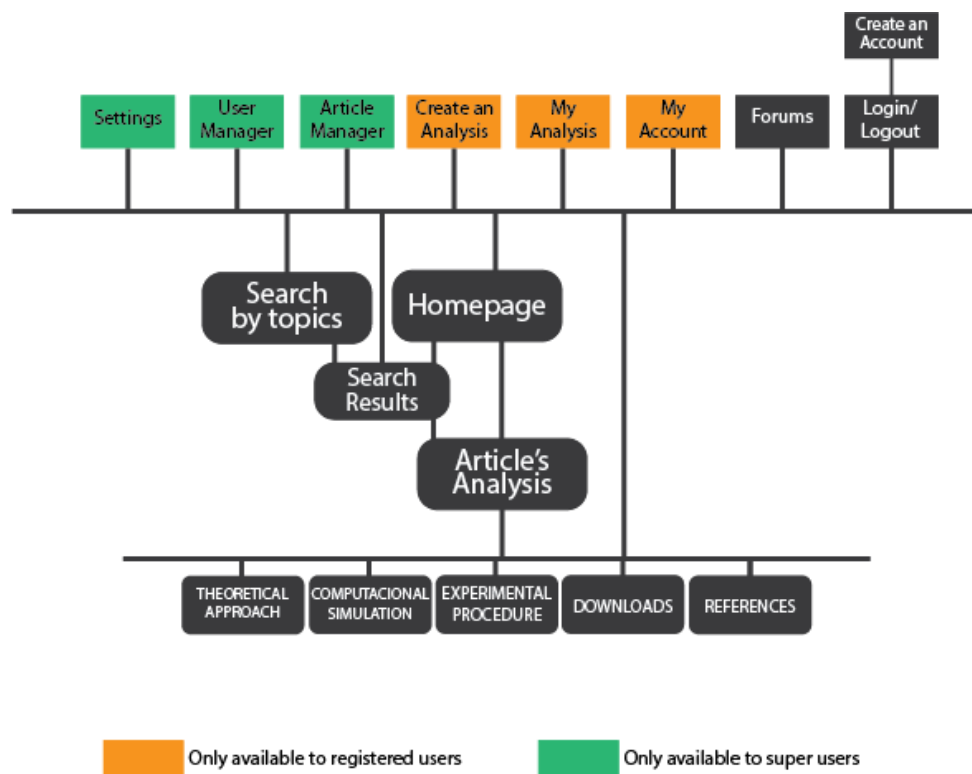
Figure 4.1: Navigation diagram of the platform.

The platform to be developed shall contain a hidden menu, accessible from any page, that allow: the contact with the forum, the personal account, the creation of an analysis, the management of own submissions, the user manager, the article manager and the settings options, taking into account that the visibility of those actions follows the diagram above. It shall also have a sticky header, present on every page, giving access to the homepage and the search for topics.

The homepage must provide access to: a natural language search engine, a search by topics and a window of suggested articles' analyses (presenting the most recent and the most popular ones), enabling the navigation through all the platforms' contents. After performing a search, we are conducted to a page with the search results. Selecting one of the results, we are sent to its content, which may vary. Examples of the analyses' topics may be theoretical approaches, computer simulations and online experimental laboratories.

4.3.2 Wireframes

The drawing of wireframes is a very important step in the development of websites, because they display the skeleton of the pages, through two-dimensional visual representations of the website's interface [64] [65] [66].

Using MockFlow [67], a few wireframes were created, which are shown below.

As aforementioned, on the homepage (Figure 4.2) there shall be a free search engine and suggestions of analyses to read, such as the most viewed and the newest.
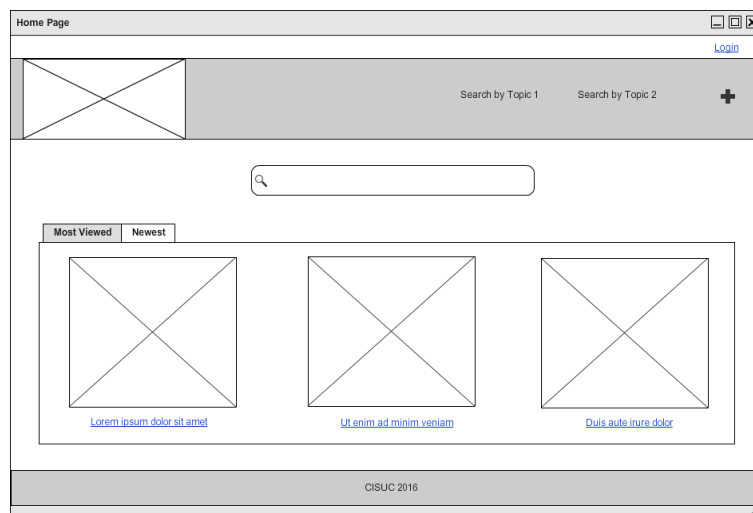
Figure 4.2: Homepage's prototype.

As referred, there must be a hidden menu available through any page (Figure 4.3), containing essential links. This menu will allow the reaching of important features, such

as the management of users and inserted analyses, as well as main website settings. It shall also be possible to introduce an article's analysis, visualize own submissions and consult/edit account parameters. The access to the discussion forum must also be achievable. What appears in the hidden menu must be in accordance to what was defined in Figure 4.1.
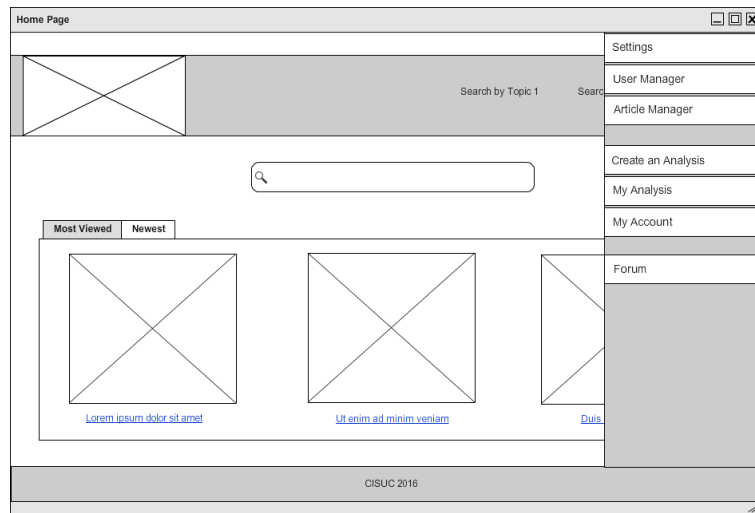
Figure 4.3: Example of the hidden menu, viewed from a super user, available from any page.

A login option must also be present in all pages. Through this link, it is possible to create a new account.
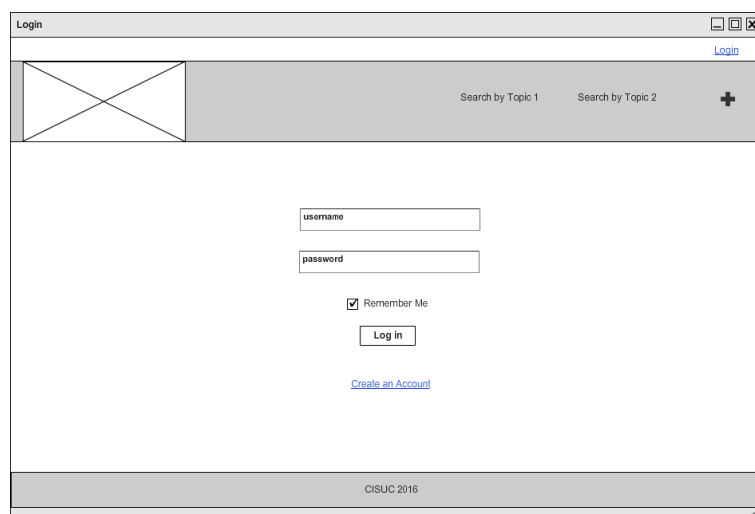
Figure 4.4: Login's prototype. Through this page, it is also possible to create an account.

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After a search by topics, the results that meet the requested field shall appear. It shall also come into view a side menu, with the subtopics of the researched theme.
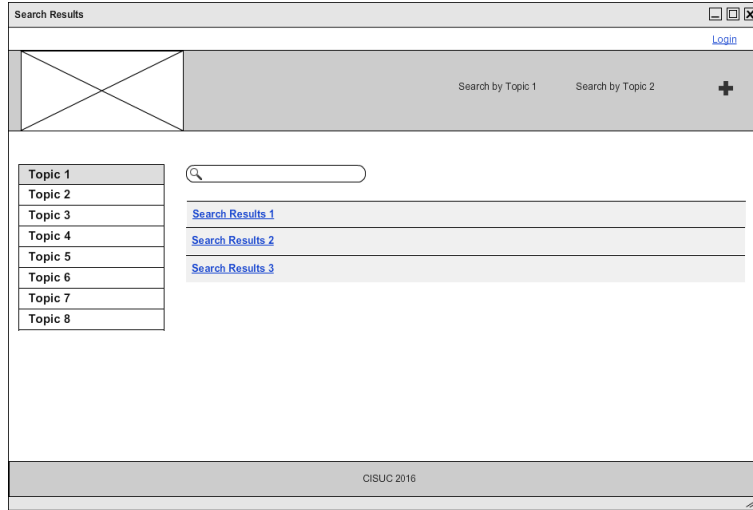
Figure 4.5: After a search by topic, the results must be shown and the subtopics of the main topic must appear in a side menu.

Super users must have access to a special page where they can view all the submitted analyses and approve, edit and delete them.
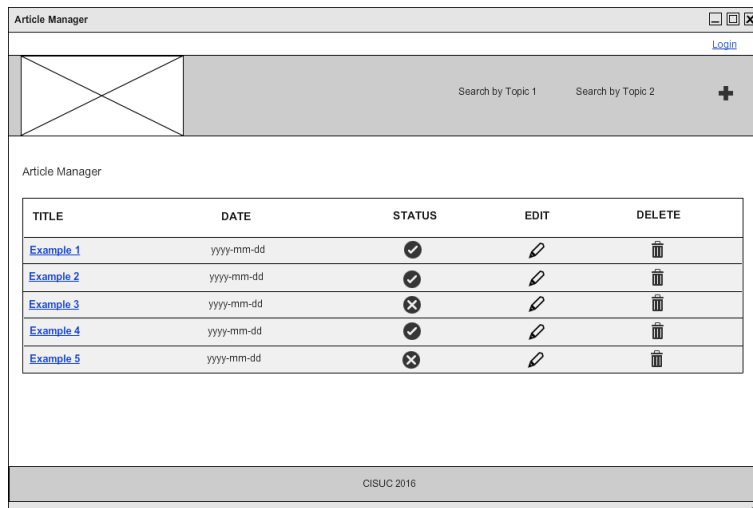
Figure 4.6: Prototype of the "Article Manager".

The contents of the analyses may vary, depending on the intents of its creator. For example, it can integrate theoretical approaches, computer simulations and practical experiments.
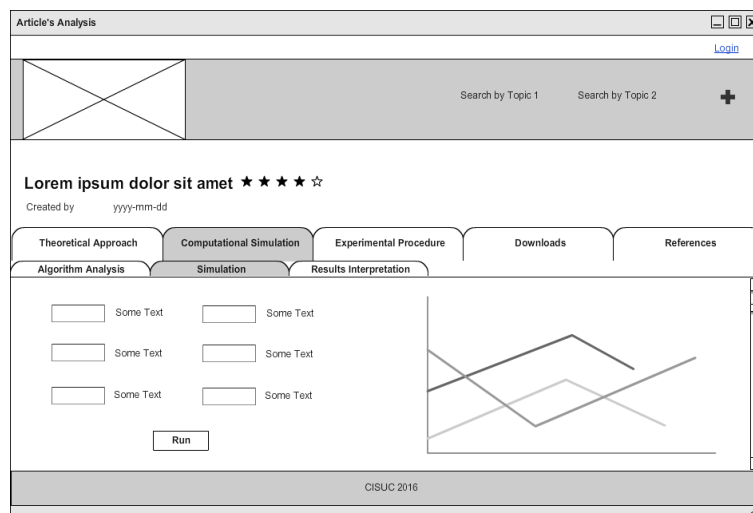
Figure 4.7: Example of an article's analysis. A computational simulation can be seen as an example.

4.4 Development Tools

In order to ease the construction of the platform, several tools were considered. Given the defined requirements and characteristics to build, we decided that a Content Management System (CMS) would be a good solution.

The following subsections are to discuss and chose which CMS would be better to construct the project.

4.4.1 Content Management System

A CMS can be defined as a software application that is used to create and control digital content [68].

The three more popular and free CMS are WordPress, Drupal and Joomla!, offering many features and strong security [69]. All the three are written primarily in PHP, support MySQL and use themes and extensions to lengthen their features [70].

WordPress is the most popular CMS in the world and, for beginners, it may be the best choice. Drupal is one of the most powerful open source options available, which comes with an increase in the complexity of use. Joomla! can be considered a compromise between WordPress and Drupal [69] In table 4.11, it is made a brief analysis and comparison between these three CMS.

Table 4.11: Brief analysis and comparison between WordPress, Drupal and Joomla!.

	WordPress	Drupal	Joomla!
Ease-of-Use	It does not require technical experience and is very intuitive and simple to use [71] [72].	It requires significant technical experience [71].	An intermediate knowledge in web development languages is needed. It is less complex than Drupal, but more than WordPress [71] [72].
Advantages	Wide support community (plus, the larger amount of users leads to more online questions and answers) [69]; it is very easy to use in the building of a simple website [71] [72]; it has an extensive collection of themes and extensions [69] [71].	It has a powerful capability for the organization of complex content [71]; it is capable of producing advanced websites [71]; it is massively scalable [73].	It is easy to export and import backups from/to the server to/from the localhost [72]; it supports e-commerce and social networking [71]; it has a good structural and code organization [72].
Disadvantages	It is difficult to adapt complex designs in the platform [72]; it is not very scalable and it is difficult to add content once the site is complete [74].	It is not very user-friendly [75]; it has some compatibility issues [76].	Of the three, it is the one who contains less additional plugins [74]; there are some extensions that are free on the others CMS, but paid in Joomla! [77].
Best used for	Simples websites and blogs [71].	Complex and advanced websites [71].	Community platforms [69] [71].

It can be considered that Joomla! combines the ease-of-use of WordPress with the power and flexibility of Drupal [69]. Thus, it is the best of the three when it comes to create

social networks [69] [71] [74], which may be useful in the construction of our platform. Therefore, it seems to be the best choice for the development of our platform.

4.4.2 Choice of CMS

After a meticulous research and a detailed analysis, we concluded that the most appropriate tool for the development of our project would be the CMS Joomla!.

4.5 Summary

In this Chapter, we described the main platform requirements and developed a prototype to serve as future reference. It was also decided that we would use Joomla! to simplify the development of the platform.

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Chapter 5

Platform Development

In this chapter, the techniques, tools and solutions used in the construction of the platform, taking into account the characteristics previously defined, will be presented. Regarding the development of the platform, the version 3.4.8 of Joomla! [78] was used and installed on the servers of the Department of Informatics Engineering of the University of Coimbra. The version 1.2 of Helix3 Template Framework [79], developed by JoomShaper.com, was applied.

5.1 Implementation of Features

In the subsequent sections, the current appearance and characteristics of the platform will be presented and the extensions and tools used in its construction will be described. A more detailed explanation of the platform construction methods can be consulted in Appendix A.

In the building of the desired features, margins and paddings were established so that the global appearance was considered aesthetically pleasant. In addition, harmonious and matching colors were picked; blue was chosen to be the predominant color, since it has a calming effect, is related to intellect and can be associated with health [80].

For an easier handling of the platform modules, a free version of Advanced Module Manager [81] was installed (consult Table A.1).

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5.1.1 Search Systems

In the platform, three major search systems are available: a search by topics (by anatomical system or physiological context), a search by natural language and a reference to the most read/newest contents.
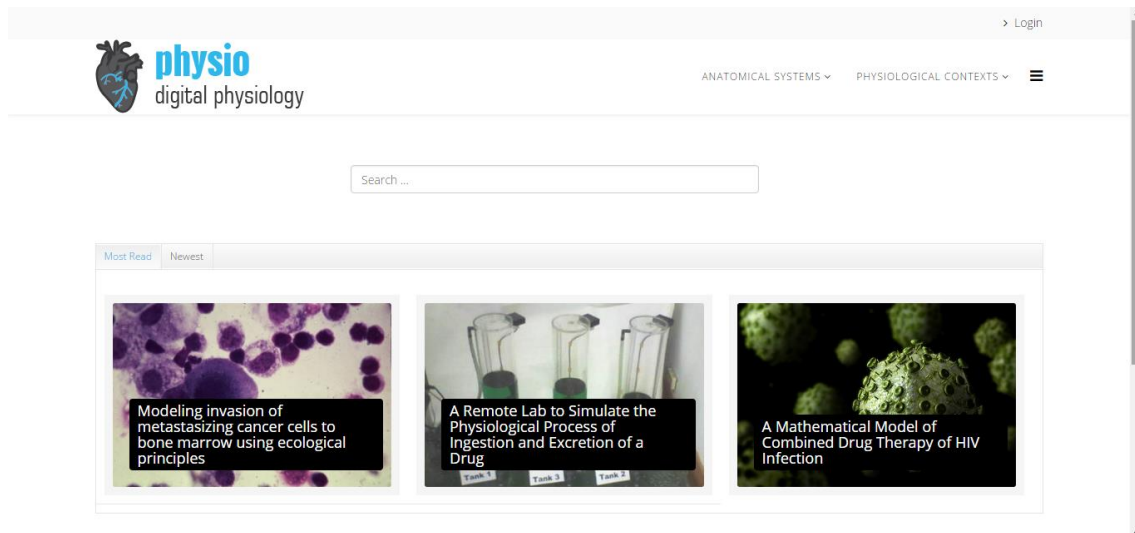
Figure 5.1: Homepage.

To enable the search by topics, it is possible to assign one or more defaulted tags to each inserted article's analysis (since an analysis of a scientific paper can address to more than one of the defined topics); on the other hand, each topic is associated with a single tag. Thus, when we choose a topic (which is associated with a particular tag), all the inserted content, associated with that tag, is shown.

After choosing a topic of one of the two possible fields (anatomical systems or physiological context), we are directed to a search results page (Figure 5.2) that has a fixed menu, created using Accordeon Menu CK [82], with the possible topics within that field. For a more detailed explanation, consult Table A.2.
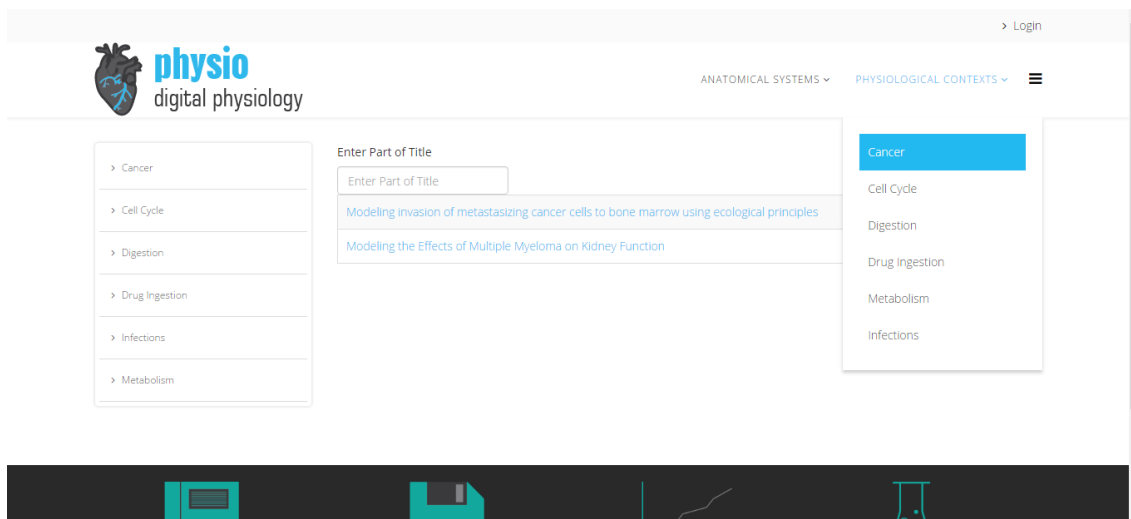
Figure 5.2: Search by topics.

To elaborate a search by natural language, a core feature of Joomla!, called Smart Search, was used (consult Table A.3). In this area, it is possible to perform a free search, which results are shown if the inserted terms are contained in the submitted analysis.
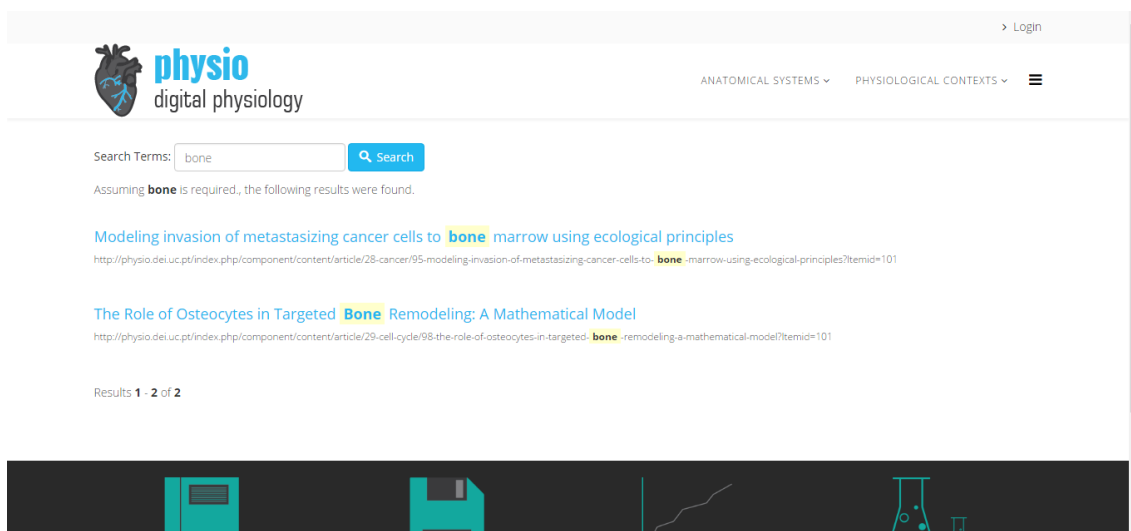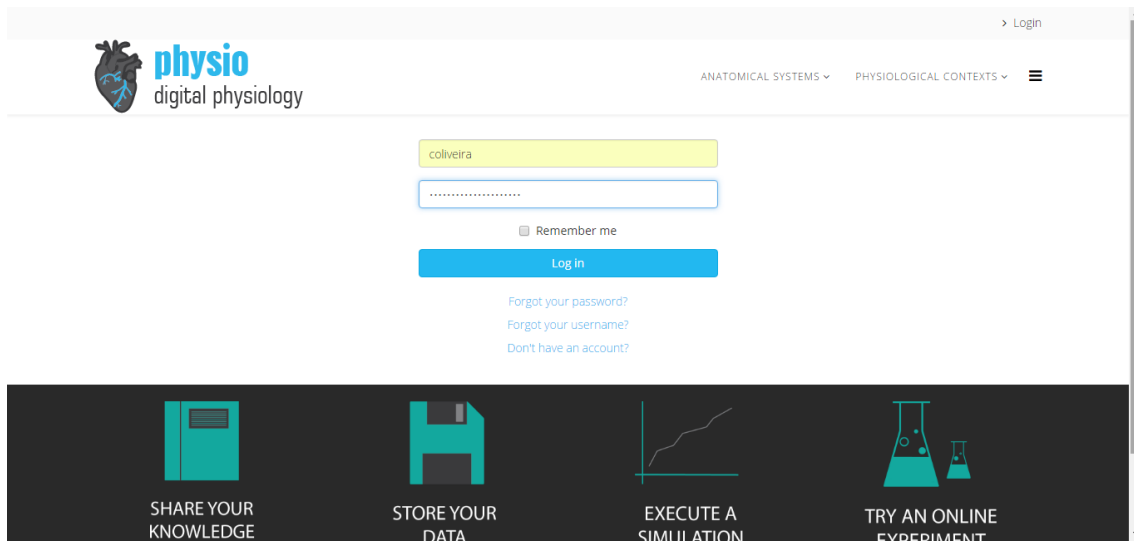
Figure 5.3: Free search results.

Using the SP Portfolio [83] and the SP Tab [84] extensions, the most viewed and the newest inserted contents were displayed in the homepage, as shown in Figure 5.1 (consult Table A.4).
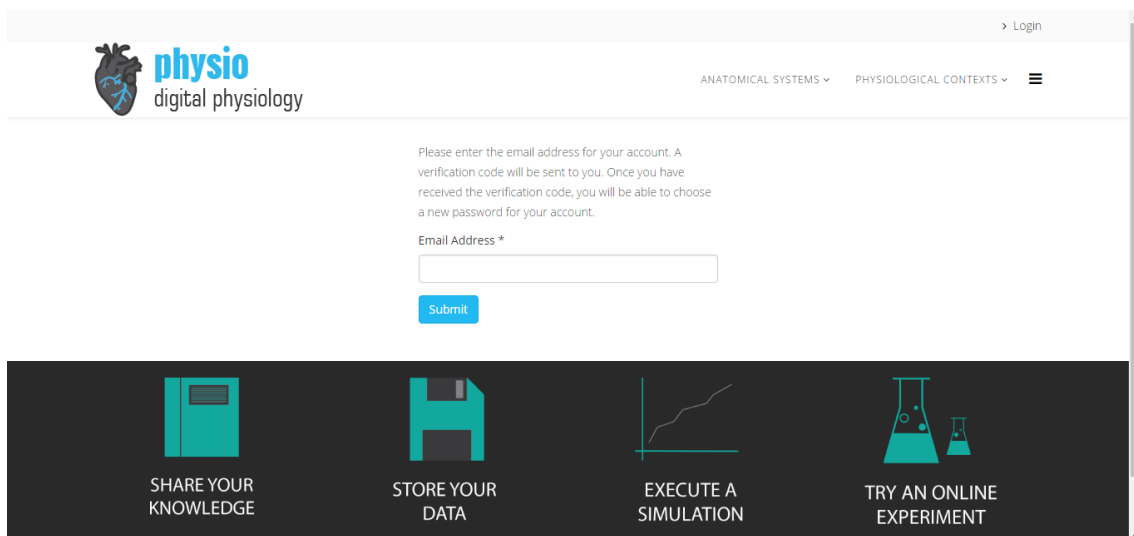
5.1.2 Authentication

For the login and the logout processes, the Joomla!'s login form and the Quick Logout [85] extension were used, respectively. The link to login and logout is available at the top of every page of the website. However, the login and logout menu is only displayed, correspondingly, to guest users and to registered users.

Figure 5.4: Authentication page.

Figure 5.5: Form for password recovery.

At the authentication page, in the case of forgetfulness regarding the password (Figure 5.5) or username, the user is allowed to complete a questionnaire to recover them.

More information can be obtained in Table A.5.

5.1.3 User Features

As seen in the authentication page (Figure 5.4), there is the possibility of creating a new account; the new account becomes activated after an e-mail confirmation – the e-mail is automatically sent, after the saving of the account. After a user logs in, he is directed to his account page, where he has the option to edit his data. There are three levels of users: guests, authors and super users. Guests are public users that are not registered into the website, while authors and super users are both registered users. When a new account is created, that user is considered, by default, an author.

Super users have special access to a users' management page, where they are able to look at general information of all the users, except for their password. They can also edit other users' data – such as changing their user group – and delete them from the system. These functionalities were built using SEBLOD [86] extension.

Figure 5.6: User manager.

For convenience, a link to this resource (and others forwardly approached) was added to an off-canvas menu (the hidden menu previously mentioned), in accordance to the restrictions found in Figure 4.1.
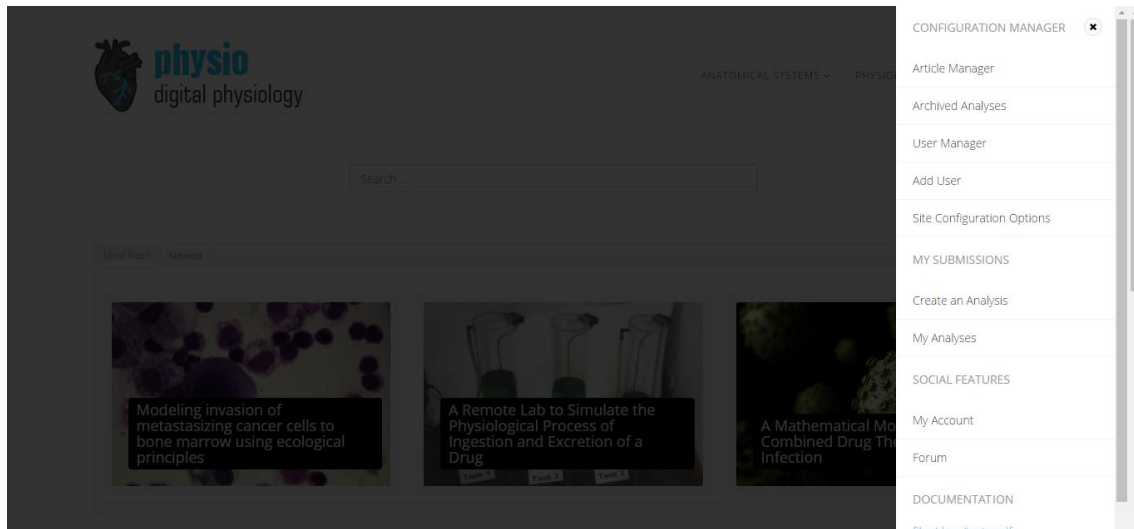
Figure 5.7: Super users' off-canvas menu.

To view more details, verify Table A.6.

5.1.4 Content Features

For the creation and the management of content, several Joomla! extensions were used: SEBLOD [86] and the free versions of Ark Editor [87], Ark Media Manager [88], Tabs [89] and Sourcerer [90] (See Table A.7).

All the registered users have the option to submit their analyses about scientific papers related to physiological processes' modeling. Pressing "Create an Analysis" in the off-canvas menu, they are led to a page (Figure 5.8) where it is possible to insert content.
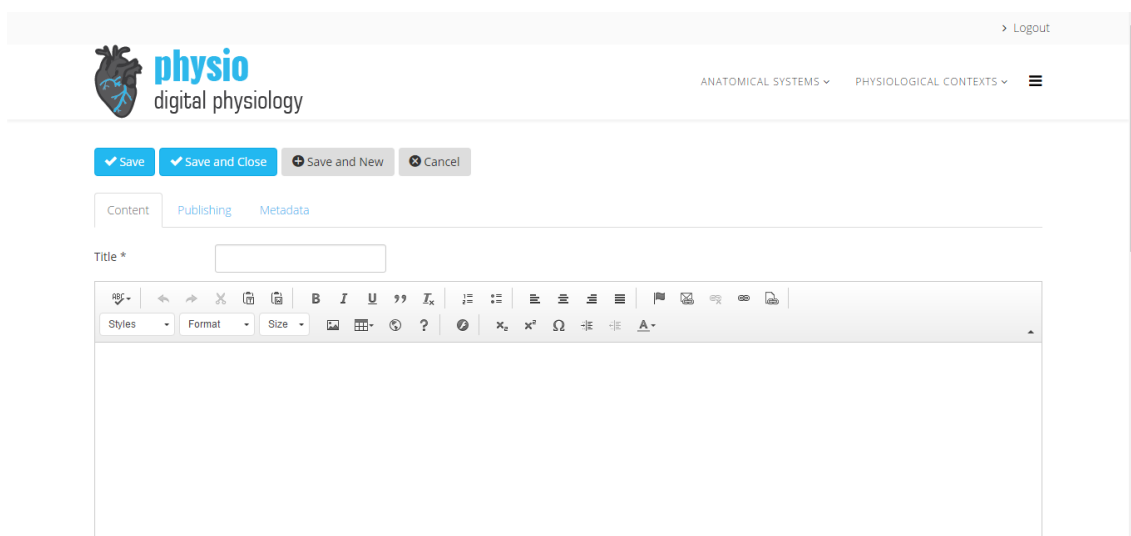
Figure 5.8: Insertion of an analysis.

Here, users are able to choose the parameters they want to analyze about the article, as well as to create different sections to explore it, using Tabs [89] plugin. An example of an analysis can be seen in Figure 5.9.
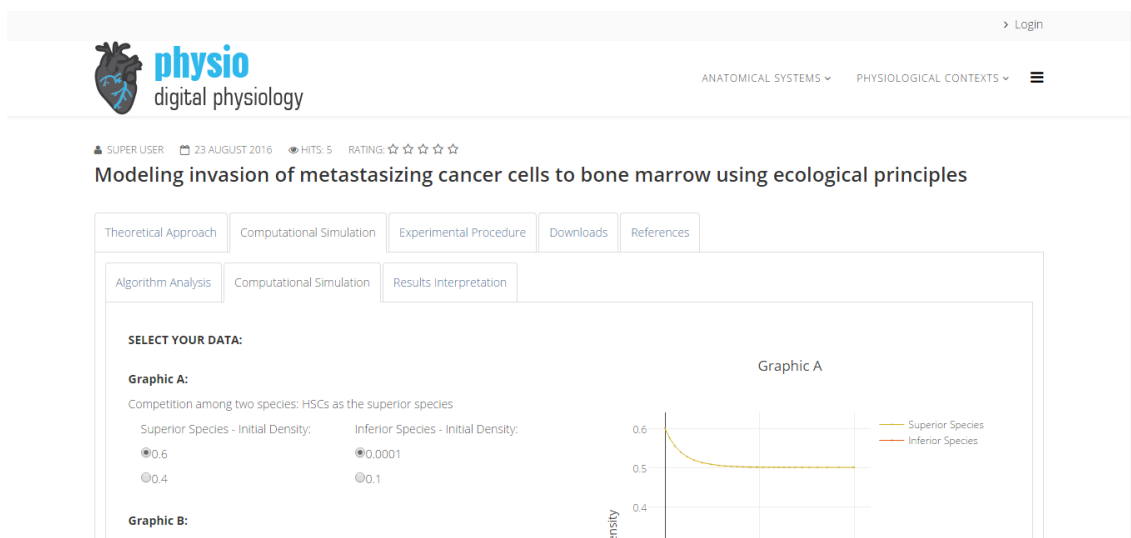
Figure 5.9: Example of an article's analysis.

It is possible to insert code written in HTML, JavaScript and PHP; through Sourcerer [90] (Figure 5.10).
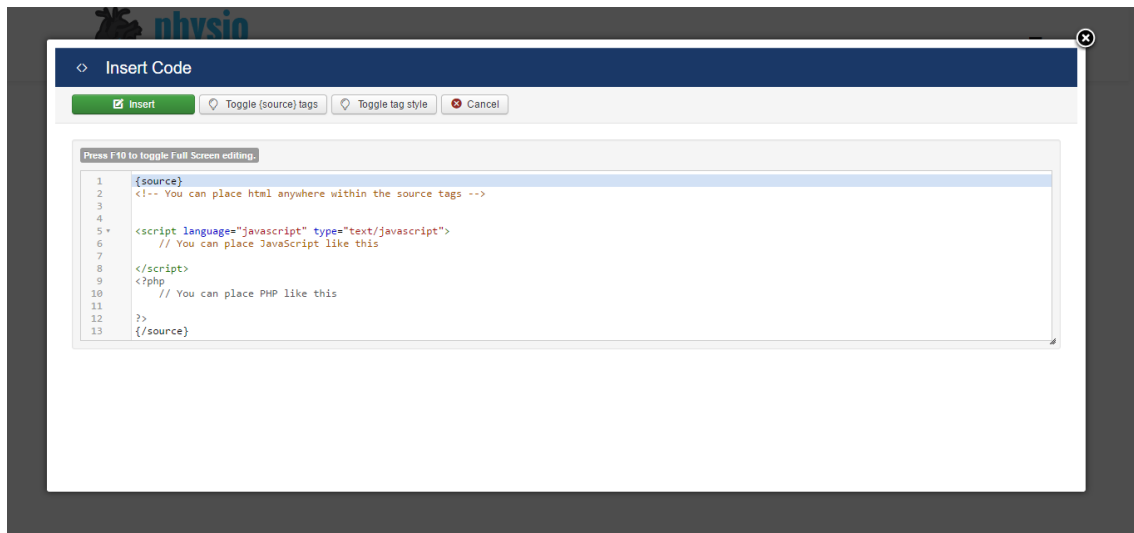
Figure 5.10: Inserting code in an analysis, using Sourcerer [90] plugin.

In order to perform mathematical calculus and to draw graphical displays of the results (as seen in Figure 5.9), two JavaScript libraries may be used: numeric.js [91] and plotly.js [92]. To solve ordinary differential equations (ODE), the variable-step numerical method of Dormand-Prince can be used, through a numeric.js method.

To share online content, an iframe can be used. Using Ark Media Manager [88], users can insert multimedia content from their devices, such as images (in .jpg, .png, .gif, .bmp, .svg, .ico and .tiff format) and files (in .swf, .txt, .rtf, .zip, .pdf, .swf, .fla, .doc, .xls, .ppt, .odp, .odt, .html, .xhtml., .xml, .ttf, .woff, .otf, and .eot format).

Each user has his own personal folder, where they store their files (Figure 5.11). Super users can edit and delete all the users' folders (Figure 5.12). For more information, consult Table A.8.
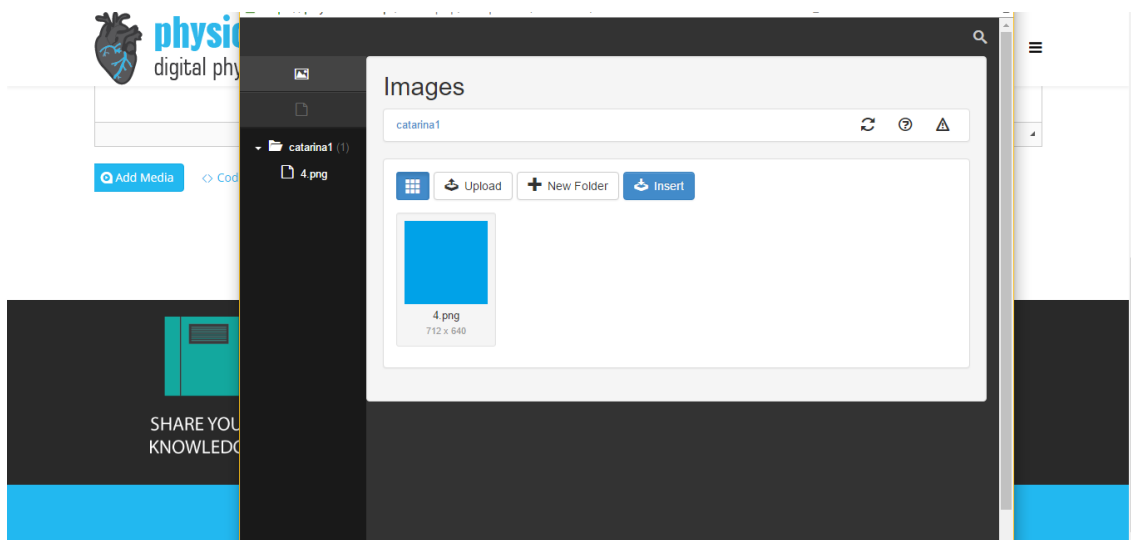
Figure 5.11: Example of an author's personal folder.
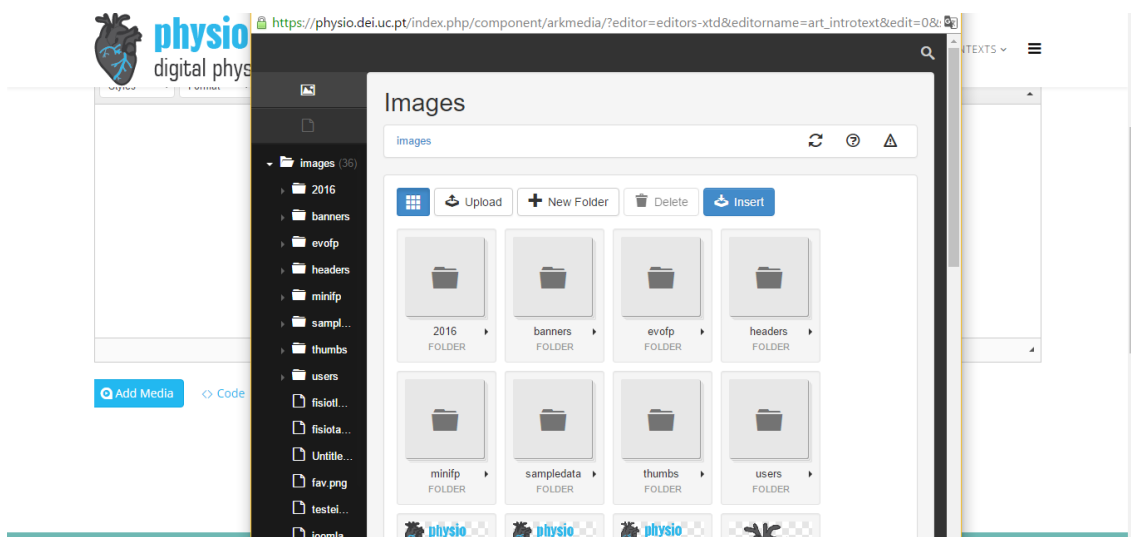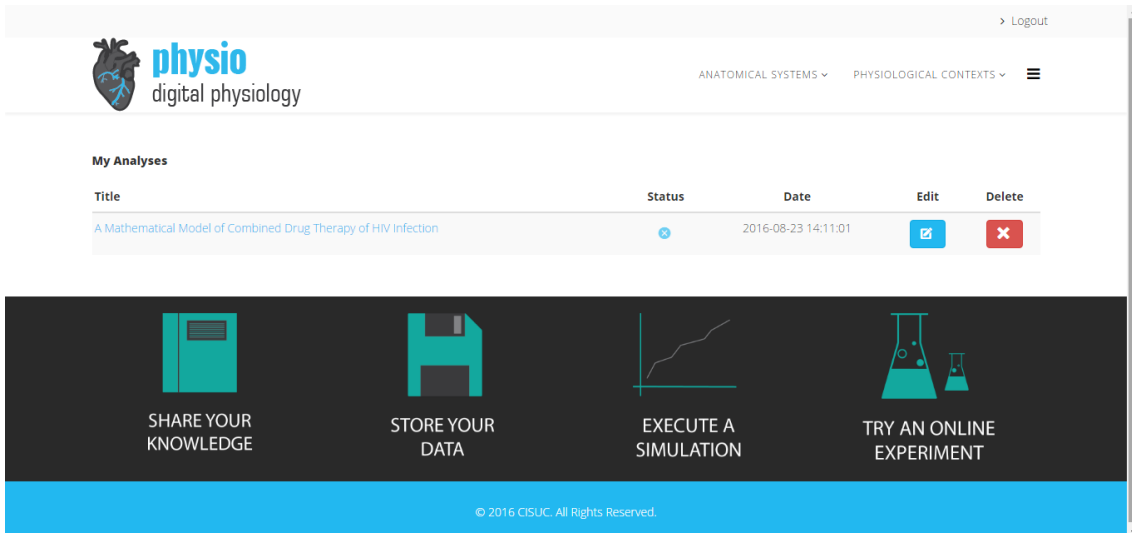
Figure 5.12: Example of a super user's media view.

Since the insertion of articles' analyses is unrestricted and can be made by any registered user, to ensure its quality, all the analyses stay unpublished until a super users' approval. However, authors can edit and delete their own content, at any publishing state (see Figure 5.13). Consult Table A.9.
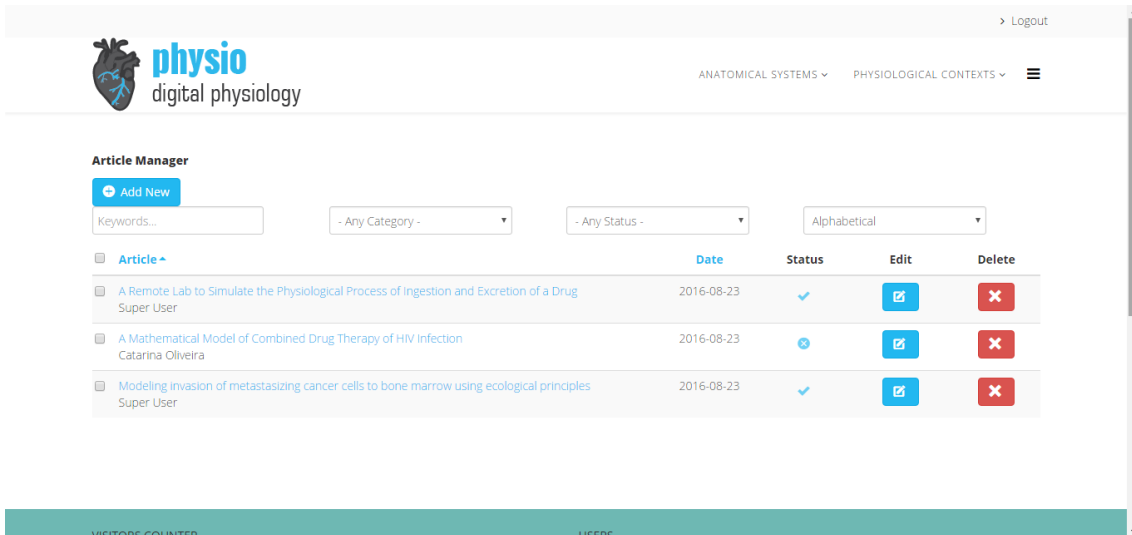
Figure 5.13: Example of the view of a "My Analyses" area. Each user can see his own submissions. In this case, there is only one submission, which is unpublished.

Super users have a special access page in which they can view the inserted content in order to evaluate it, with the most recent appearing at the top (Figure 5.14). These features were created using SEBLOD [86]. They can also visualize the aspect of the content before they approve it (Figure 5.15).

Figure 5.14: Article manager.

Figure 5.15: Example of an unpublished analysis.

Super users can, moreover, change an analysis' status to archived. In this case, the analyses are not in a published or unpublished state, staying stored.

For more information, see Table A.10.

5.1.5 Feedback and Discussion

Any user can rate every inserted article, from one to five stars. When the analysis is opened, the mean of the rates is displayed.

There is also available a discussion forum, created using Kunena [93] (Figure 5.16). Non-registered users are only able to read the existing topics. Registered users are able to create new topics, as well as comment or subscribe other ones. In both cases, if other users comment that topic, an e-mail with that information is sent. When creating or commenting a topic, there is the possibility to attach an image or a file. Moreover, when a new topic was not yet consulted by a user, an indication is shown.

For more details, consult Table A.11.
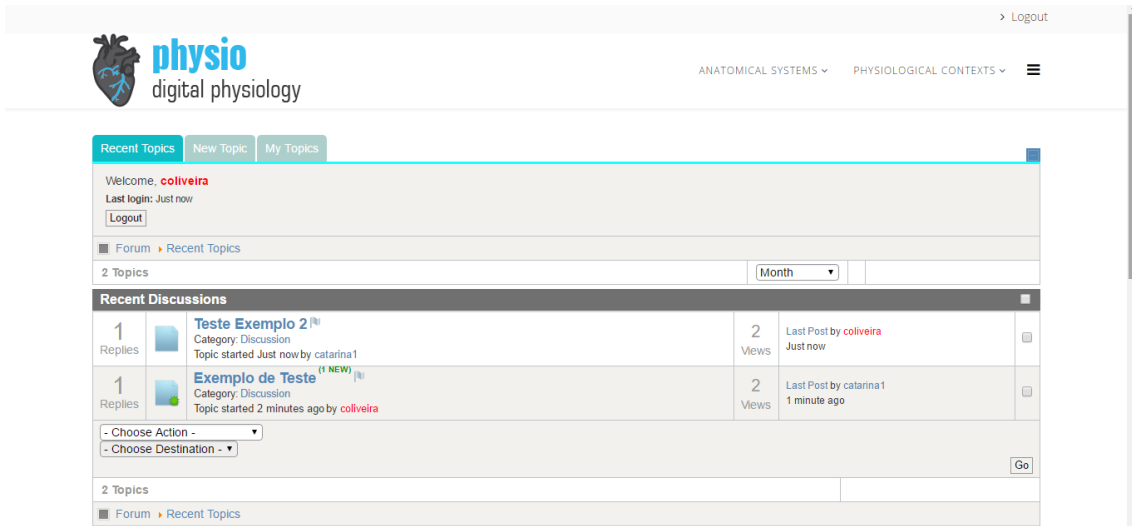
Figure 5.16: Forum's "Recent Topics" example.

5.1.6 Front-end Settings

Super users are allowed to configure some website options through the front-end, such as putting the site offline and changing Search Engine Optimization settings (Figure 5.17). For more information, consult Table A.12.
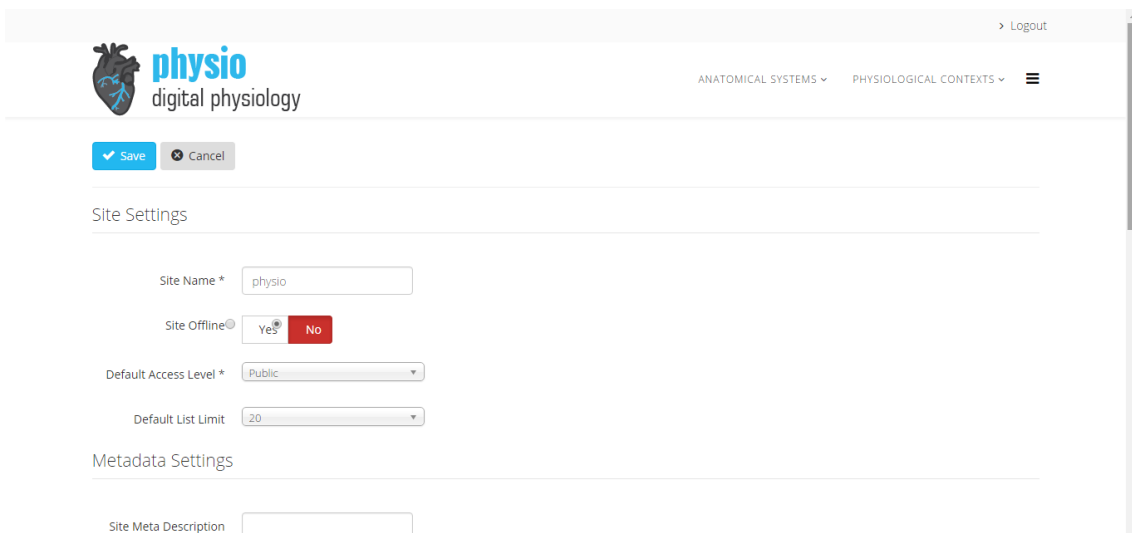
Figure 5.17: Super users' website settings.

5.1.7 Statistical Analysis

When a super user logs in, a bar appears at the bottom of the pages, showing some real-time statistics (using Visitors Counter [94]), such as the website's visitors number and the logged-in users, online guests and registered users (Figure 5.18). Consult Table A.13.
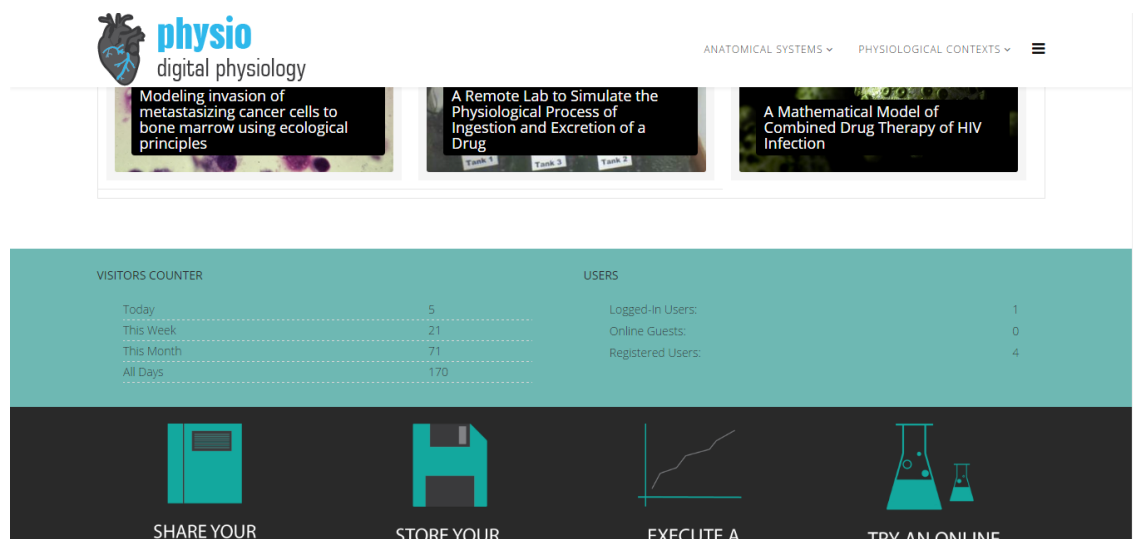
Figure 5.18: Statistical analysis.

5.1.8 Help Documentation

To ease the understanding of the features of the platform, a user's guide is available for downloading in the website. The guide is different for authors and super users, being the second an extended version. The documentation available for super users can be found in Appendix B.

When operating the platform, if a major action is performed a suitable message is exhibited.

5.2 Security

Joomla! CMS offers a strong security [69] [95]. Besides, the construction of the menus and the modules was very careful, with special attention to the users' permissions settings and user groups' accesses.

Hypertext Transfer Protocol Secure (HTTPS) can be defined as the secure version of Hypertext Transfer Protocol (HTTP), a set of rules for transferring files through the World Wide Web. In HTTPS, all the communications between the website and the browser are encrypted. This protocol is used to safeguard extremely confidential online transactions, such as online banking [96] [97].

The pages of the website that require additional security, (*e.g.,* authentication, inserting content, editing personal data, managing users) are accessed exclusively over HTTPS. However, as the integration of content from other websites is expected – and they can use either HTTP Protocol or HTTPS Protocol – it is necessary that the pages where this content is displayed – for example, an article's analysis – are accessed over HTTP (to allow the incorporation of HTTP and HTTPS pages). This change from HTTP-pages to secure HTTPS-pages (and vice-versa) was doable using Yireo SSL Redirection [98] extension. More information can be found in Table B.14.

5.3 Responsiveness

When selecting the template to apply on the platform, one of the main criteria for the selection was its responsiveness. A responsive web design is an approach that generates dynamic modifications in the website, depending on the screen size of the device used to access it [99].

Helix Framework Template [79] has a responsive layout and uses Bootstrap 3.2. Bootstrap is a free front-end framework that eases web development, such as the design of responsive layouts [100]. On the introduction of some content, this tool was used.

We were cautious in the structuration of the platform. For example, when dealing with small devices, such as smartphones, the search system through natural language no longer appears in the homepage (it is presented in the off-canvas menu) and the search by topics disappears. The display of the most viewed and newest analyses also changes to smaller screens – more information, consult Table B.15.

Some examples of the platform on different screen sizes can be seen in Figure 5.19.a and Figure 5.19.b.
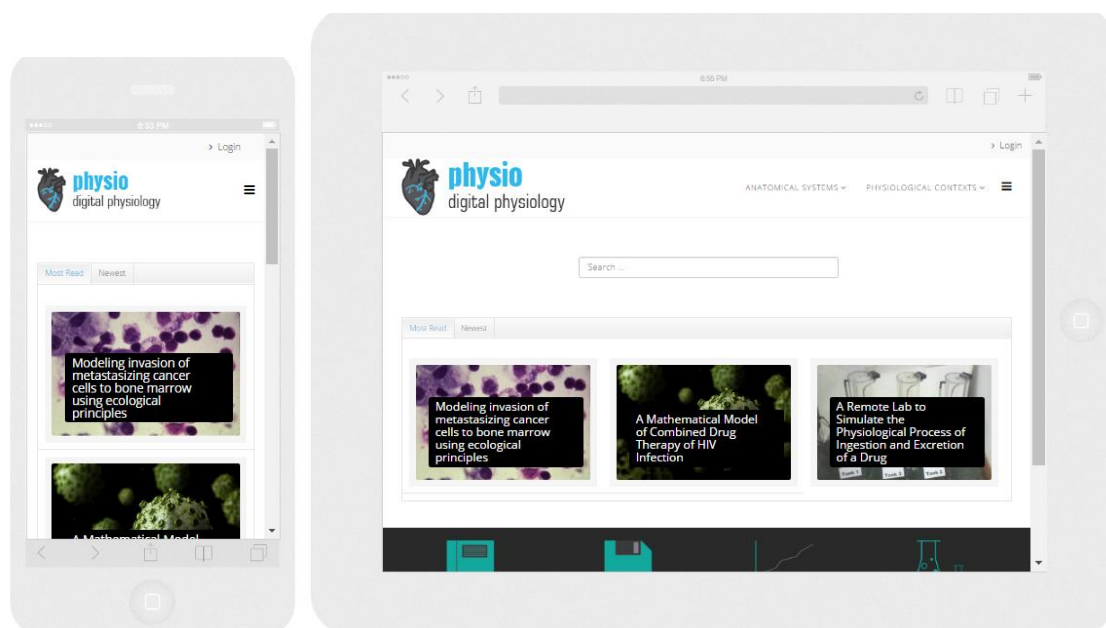
Figure 5.19.a: iPhone 6 portrait (width: 375px); Figure 5.19.b: iPad landscape (width: 1024px) [101].

The images above were taken using Responsinator [101], a website that checks if an online platform is responsive. The Google's mobile-friendly test (a test to evaluate the compatibility of a website with mobile devices) [102] was also performed, achieving the result "Impressive! This page is compatible with mobile devices.".

5.4 Summary

In this section, the platform functions and key steps of its development were, globally, described. We believe that the requirements stated in the previous section were followed and the structure of the website and wireframes were respected.

Chapter 6

Study Cases

In this chapter, some examples of content that can be introduced in the platform will be presented and studied. Thus, we will analyze some scientific papers about physiological modeling and add it to the platform, exemplifying some supported features.

6.1 Scientific Papers about Physiological Modeling

Five scientific papers were selected and analyzed in order to illustrate the platform's features: two are based on works done in CMPP; one is based on a scientific paper that explores the features of an online experiment located in the Laboratory of Industrial Informatics and Systems of the University of Coimbra; the others are based on scientific papers about physiological modeling that seemed interesting to include.

Many physiological models are built with some complex mathematical operations, such as ODEs. After some research, a JavaScript library capable of performing such operations was found. As mentioned in Chapter 5.1.4, this library is called Numeric JavaScript [91] and provides a lot of useful mathematical operations, listed in [103].

The ODE solver included in this library implements the Dormand-Prince-Runge-Kutta integrator with adaptive time stepping [103] [104] and it was a very important tool in the simulation of the different ODE systems analyzed.

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For the graphics display, it was used a JavaScript library called plotly [92]. This library also allows the download of the graphics as .png, among other features (*e.g.,* zooming, select suitable windows)..

6.1.1 *Modeling invasion of metastasizing cancer cells to bone marrow using ecological principles*
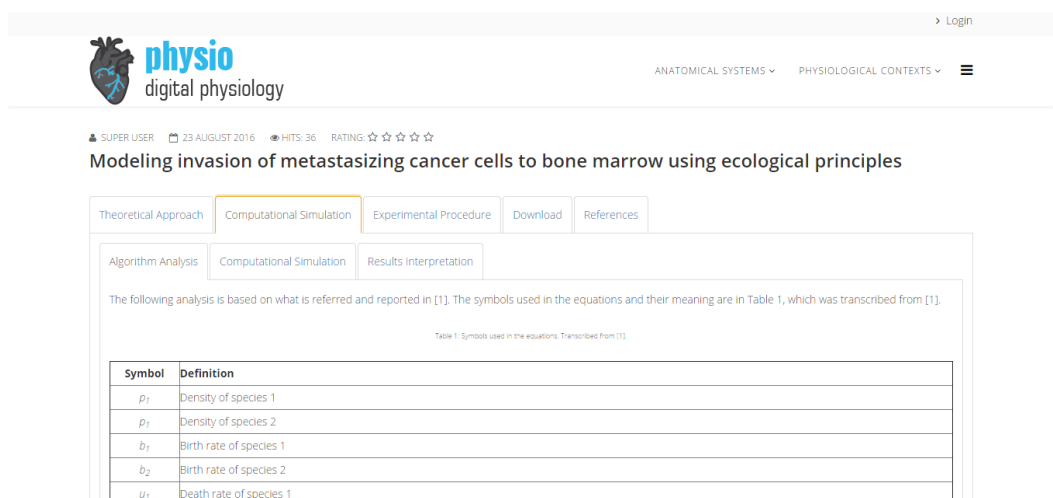
This analysis was based on the scientific paper "Modeling invasion of metastasizing cancer cells to bone marrow using ecological principles" by Kun-Wan Chen and Kenneth J. Pienta [105] and in an exploration work of the same, done by Catarina Sá Silva and Tiago Curado [106] in CMPP.

For this revision, it was included a glossary of important concepts and explored the biological fundamentals of the subject (Figure 6.1).

Figure 6.1: Theoretical review of the analysis of [105].

The mathematical equations presented in [105] were analyzed (Figure 6.2), simulated and its results were interpreted.
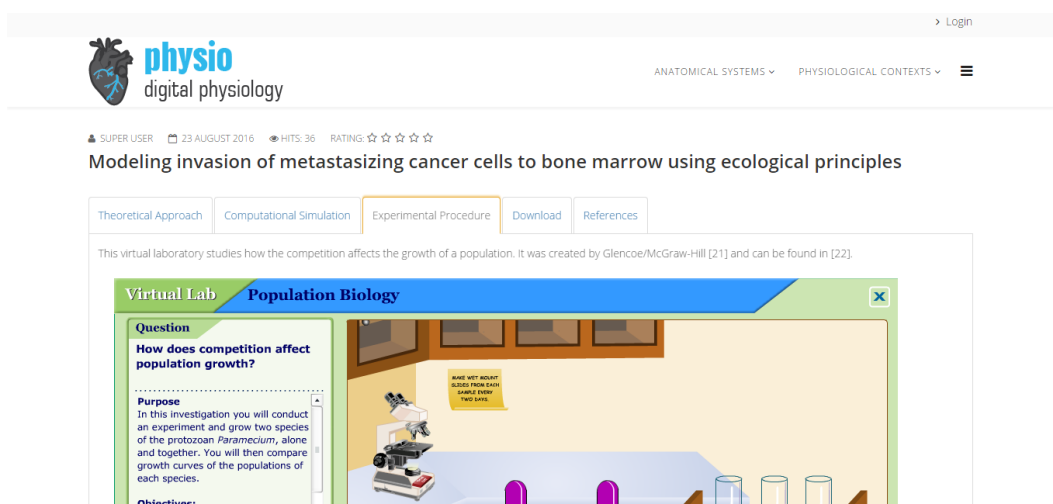
Figure 6.2: Exploration of the algorithm presented in the analyzed scientific paper [105].

A virtual laboratory that involves one of the discussed topics was also shared (Figure 6.3), It was developed by Glencoe/McGraw-Hill [107] and found in [108].

Figure 6.3: Virtual laboratory, developed by Glencoe/McGraw-Hill [107] and found in [108], shared in the platform, in the analyzed article.

Finally, the work of Catarina Sá Silva and Tiago Curado [106] was released for download. The references of the analysis are also available (Figure 6.4).

The majority of the introduced content can be found in Appendix C.1.

Figure 6.4: References of the analysis made about the scientific paper ""Modeling invasion of metastasizing cancer cells to bone marrow using ecological principles" by Kun-Wan Chen and Kenneth J. Pienta [105].

6.1.2 *Modeling for the drug therapy for HIV infection*

This analysis was based on the scientific paper "Modeling for the drug therapy for HIV infection" by P. K. Srivastava, M. Benerjee and Peeyush Chandra [109] and in a work grounded on it, done by Baptiste Enes and Joana Rita Santos [110] in CMPP.

A theoretical analysis of the content was introduced in the platform, including a glossary (Figure 6.5) and a review of concepts.

Figure 6.5: Glossary of important concepts approached in the analysis of [109].

The mathematical model presented in [109] was analyzed, simulated (Figure 6.6) and its results were interpreted. It is possible to download the calculated values of the simulation in a .csv file.
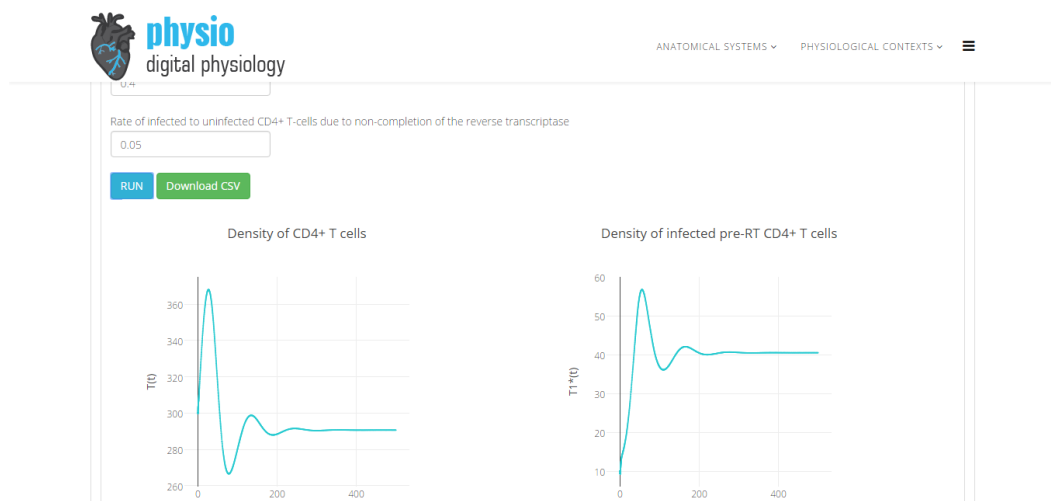
Figure 6.6: Simulation of the mathematical model of the analyzed scientific paper [109].

The work of Baptiste Enes and Joana Rita Santos [110] is available for downloading and the references of the inserted analysis are shown.

The majority of the introduced content can be found in Appendix C.2.

6.1.3 *A Remote Lab to Simulate the Physiological Process of Ingestion and Excretion of a Drug*

This analysis was based on the scientific paper "A Remote Lab to Simulate the Physiological Process of Ingestion and Excretion of a Drug" by A. Cardoso, D. Osório, J. Leitão, V. Sousa and C. Teixeira [7], which explores the features of an online experiment located in Laboratory of Industrial Informatics of the University of Coimbra.

A review of the literature, the remote laboratory (Figure 6.7) and the references of the analysis were introduced in the platform.
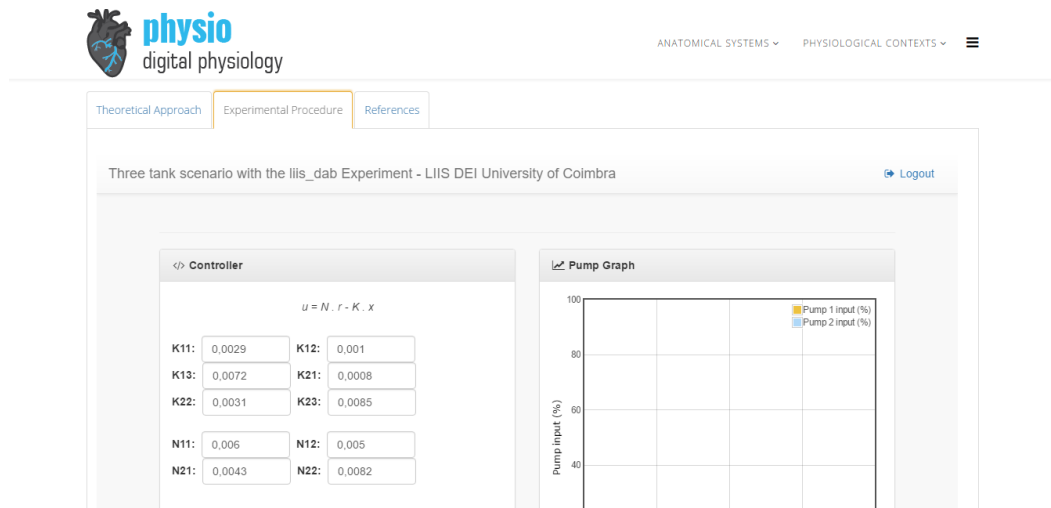
Figure 6.7: Remote laboratory embedded in the platform, simulating the physiological process of ingestion and excretion of a drug. This laboratory is located in Laboratory of Industrial Informatics and Systems of the University of Coimbra.

The majority of the introduced content can be found in Appendix C.3.

6.1.4 *The Role of Osteocytes in Targeted Bone Remodeling: A Mathematical Model*

This analysis was based on the scientific paper "The Role of Osteocytes in Targeted Bone Remodeling: A Mathematical Model" by Jason M. Graham, Bruce P. Ayati, Sarah A. Holstein and James A. Martin [111].

In the theoretical exploration of this scientific paper, a glossary with important concepts was introduced, as well as a review of the content. A video, hosted in YouTube and created by Amgen [112], was also shared.

The model algorithm was reviewed, simulated (Figure 6.8) and its results were examined. It is possible to export a .csv file of the obtained values. Moreover, in the first graphical display, it is allowed to select and unselect the data to show (through their labels).
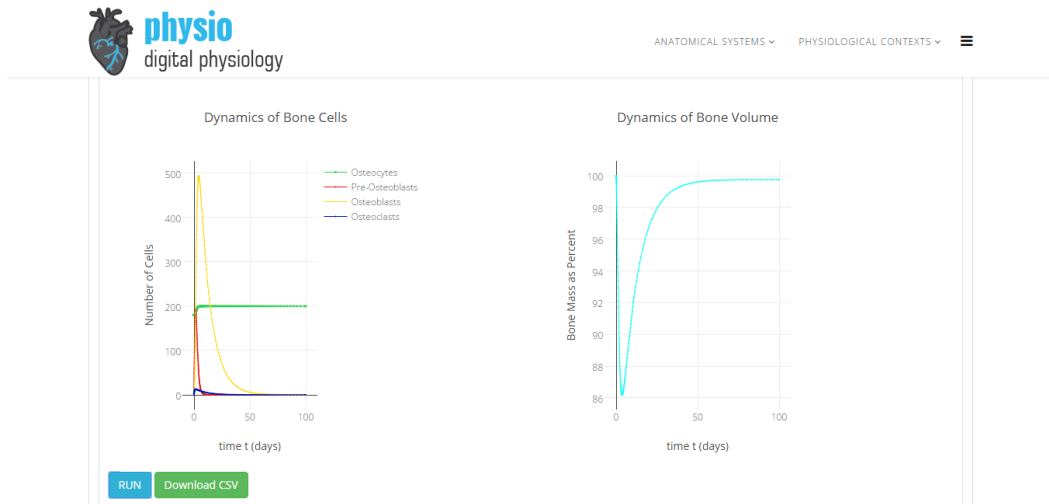
Figure 6.8: Simulation of the mathematical model presented in the analyzed scientific paper [111].

A virtual experiment (Figure 6.9), developed by Susan Ott and found in [113], was allocated in the platform. Furthermore, the references of the inserted analysis were also exposed.
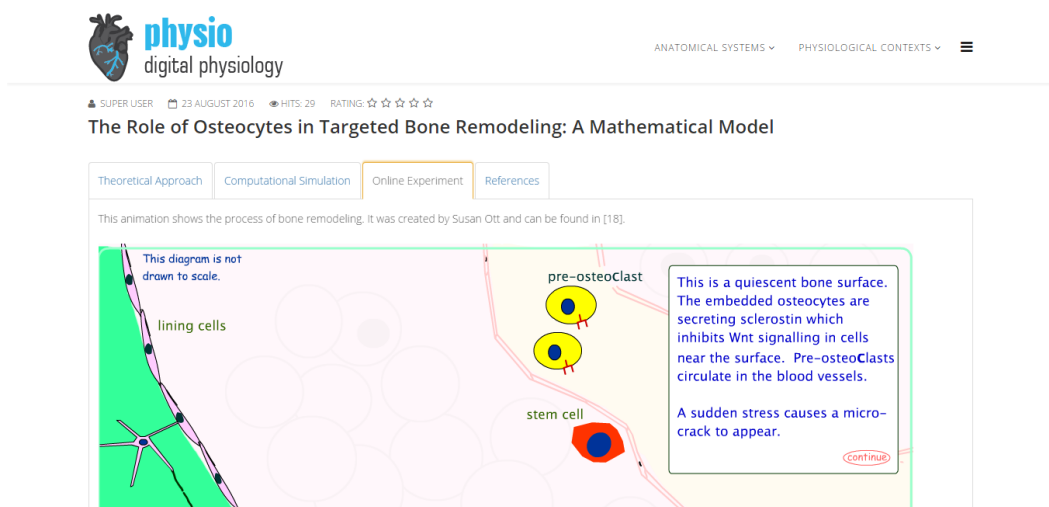
Figure 6.9: Virtual experiment related to the content of the analyzed article [111]. It was created by Susan Ott and found in [113].

The majority of the introduced content can be found in Appendix C.4.

6.1.5 *Modeling the Effects of Multiple Myeloma on Kidney Function*

This analysis was based on the scientific paper "Modeling the Effects of Multiple Myeloma on Kidney Function" by Julia C. Walk, Bruce P. Ayati and Sara A. Holstein [114].

The theoretical fundamentals of the scientific paper were analyzed. For this, it was introduced: a glossary with important concepts, a review of its fundaments and a video, hosted in YouTube and created and shared by Armando Hasudungan [115] (Figure 6.10).

Figure 6.10: Video shared in the platform. It is hosted on YouTube and created by Armando Hasudungan [115].

The mathematical model presented in the scientific paper [114] was studied, simulated (Figure 6.11) and its results were interpreted. The download of a .csv file with the values obtained in the simulation is allowed. The consulted references were also exposed.
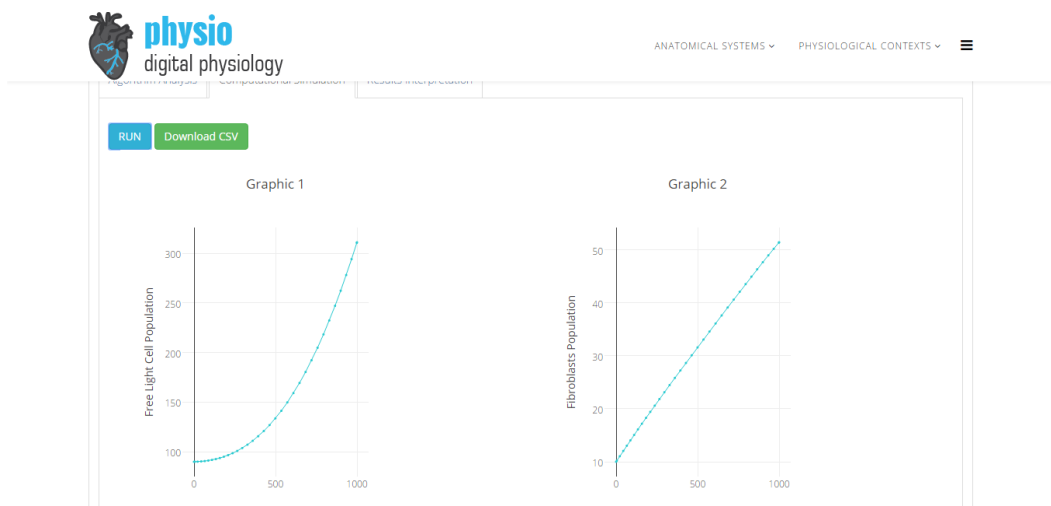
Figure 6.11: Simulation of the mathematical model presented in the analyzed article [114].

The majority of the introduced content can be found in Appendix C.5.

6.2 Summary

This chapter was focused on the display of some case studies that show the different features that can be incorporated in the platform.

Each case study is based on a published scientific paper and its selection followed three criteria: the paper is freely accessible online, it is of an interesting physiological subject and its theme is substantially different from the others. In this way, it was possible to demonstrate the several characteristics of the website.

As it can be seen, to perform a paper's analysis, an author has as many options as he wants, being able to: choose the content's organization (for example, which tabs he wants to use), insert multimedia sources, upload files and embed code. However, the quality and legitimacy of the content is ensured, since all the insertions have to be approved by an administrator, before being openly published.

Summing up, this section showed, through examples, the potential technical interest that this platform has, proving its educational use both to people that publish works here, both to people that just read the articles.

Chapter 7

Test and Validation

This chapter presents a survey regarding the functionality and usefulness of the platform to its target users. Furthermore, the obtained results are explored.

7.1 Overview

A questionnaire was answered by 58 anonymous students of the Integrated Master in Biomedical Engineering of the University of Coimbra, in order to analyze the significance of the developed platform.

The designed survey contains two groups of questions. The first group focuses on understanding if the students use to consult digital media as an auxiliary form of study and as a mean to overcome their difficulties of learning through traditional teaching and studying methods. The second group centers on a practical appraisal of the platform, in order to evaluate its helpfulness within the target users and the role that it may have in CMPP.

Given that all the inquired students spoke Portuguese natively, the survey was written in that language. Nevertheless, in this chapter, it is presented in English.

7.2 Questions and Answers

In the first group of the evaluation, the users were asked if they have the habit to use the Internet to overcome queries and doubts about learning concepts and if they used mobile devices to do so. It was also explored if there was a tendency to use digital media to understand biomedical subjects and if the questioned targets used to identify struggles in practical experimental scenarios that blocked the advantages of learning through them. Both the usage of online discussion forums and the utility of a forum within the Biomedical Engineering course were also questioned. The questions and answers of the inquiry are described below:

Table 7.1: First question of the first group of queries and respective answers.

When you have doubts in school contents, do you use to surf on the Internet?		
Answers		
Yes	100%	58
No	0%	0
Total		58

Table 7.2: Second question of the first group of queries and respective answers.

If so, have you ever used you phone or tablet to do so?		
Answers		
Yes	100%	58
No	0%	0
Total		58

Table 7.3: Third question of the first group of queries and respective answers.

Have you ever consulted online websites in order to clarify doubts that you failed to understand in school environment?		
Answers		
Yes	98.3%	57
No	1.7%	1
Total		58

Table 7.4: Fourth question of the first group of queries and respective answers.

Have you ever used digital contents to better understand certain biological processes or other matters related to biomedicine?		
Answers		
Yes	100%	58
No	0%	0
Total		58

Table 7.5: Fifth question of the first group of queries and respective answers.

Have you ever felt, in practical laboratory environments, that you did not have the opportunity to get the best out of the practice, for example, because the high number of students or because you could not contact directly with the experience?		
Answers		
Yes	86.2%	50
No	13.8%	8
Total		58

Table 7.6: Sixth question of the first group of queries and respective answers.

Have you ever used online discussion forums to look for answers to your questions in academic subjects?		
Answers		
Yes	34.5%	20
No	65.5%	38
Total		58

Table 7.7: Seventh question of the first group of queries and respective answers.

If so, do you think that a forum dedicated to questions within Biomedical Engineering subjects would be useful?		
Answers		
Yes	95%	19
No	5%	1
Total		20

In the second group of questions, after exploring the platform, target users were asked to evaluate its features and functionalities. The students that had already attended CMPP were inquired, in the context of the course, about its usefulness. The questions and answers are shown below.

Table 7.8: First question of the second group of queries and respective answers.

Do you think the platform is easy to use?		
Answers		
Yes	93.1%	54
No	6.9%	4
Total		58

Table 7.9: Second question of the second group of queries and respective answers.

Do you find its overall aspect pleasant?		
Answers		
Yes	98.3%	57
No	1.7%	1
Total		58

Table 7.10: Third question of the second group of queries and respective answers.

Do you consider that the functionalities of the platform are adequate?		
Answers		
Yes	96.6%	56
No	3.4%	2
Total		58

Table 7.11: Fourth question of the second group of queries and respective answers.

Do you consider that the fundament of the platform could help to overcome the problems identified in the previous group?		
Answers		
Yes	98.3%	57
No	1.7%	1
Total		58

Table 7.12: Fifth question of the second group of queries and respective answers.

From 1 to 5, how do you classify the usefulness of the platform (1 for low usefulness and 5 for high usefulness)?		
Answers		
1	0	0
2	0	0
3	12.0%	7
4	55.2%	32
5	32.8%	19
Total		58

Table 7.13: Sixth question of the second group of queries and respective answers.

Would you use the platform in the future?		
Answers		
Yes	93.1%	54
No	6.9%	4
Total		58

Table 7.14: Seventh question of the second group of queries and respective answers.

Have you already attended Computer Models of Physiological Processes?		
Answers		
Yes	82.8%	48
No	17.2%	10
Total		58

Table 7.15: Eighth question of the second group of queries and respective answers.

If so, do you think the platform would help you to better understand the purpose of the six-monthly project of the course?		
Answers		
Yes	95.8%	46
No	4.2%	2
Total		48

Table 7.16: Ninth question of the second group of queries and respective answers.

If so, do you think that the introduction of those projects in the platform would make sense?		
Answers		
Yes	89.6%	43
No	10.4%	5
Total		48

7.3 Results' Analysis

The answers obtained in the questionnaire show that the examined students have the habit of consulting Internet in order to consult educational content (100%), including to overcome doubts that arise in the classroom environment (98.3%). Moreover, all the questioned students admitted to use smartphones and/or tablets as a mean to accessing this information, which is in accordance to what was expected, given that, as referred in[9], people see them as their first choice for connectivity.

In the last years, driven by the fast development of digital media, there has been a massive intensification of the use of multimedia resources in biomedical education [116]. In our survey, 100% of the respondents admitted that they have been using digital means to better understand biological processes and other contents related to biomedicine.

86.2% of the questioned students claimed to have experienced difficulties in taking advantage of laboratory experimental practices, due to external factors. In this context, remote and virtual experiments can be, as discussed in Chapter 2.3, a solution.

Only 34.5% of the respondents stated that they had used discussion forums to to get answers about academic questions. This percentage may be low because it is possible to visit forums without asking questions. In fact, the aim of this question was to find out how many people consulted forums, considering the ones who make questions and the ones that only read other people's dialogues. In our opinion, not all the interviewed students understood our intentions. If this was clear, we believe that the rate of "Yes" would be much greater, since the finding of an answer in a public forum does not imply

that a question was explicitly made (the subject may simply read others' doubts). However, 95% of the students that admitted to use discussion forums stated that would be useful to have a discussion forum within biomedical engineering.

After an exploration of the platform, 93.1% of the respondents said that the platform was easy to handle, 98.3% think that its appearance is satisfying and 96.6% stated that the features of the platform are adequate. When asked to evaluate the usefulness of the platform from 1 to 5 (minimum and maximum, respectively), 32.8% of the respondents rated it as 5 and 55.2% rate is as 4. 93.1% of the questioned students stated that they see themselves using the platform in the future.

Within the sample of examined students, 82.8% had already attended the course of CMPP. 95.8% believe that the platform would have helped to better understand the purpose of the six-monthly work. Moreover, 89.6% agree that those works shall be inserted in the platform.

To get a better understanding of respondents' opinion, we analyzed the association between different answers.

We analyzed the answers regarding the usefulness of the platform (from 1 to 5) from who admitted to have experienced struggles in laboratory experiment (Figure 7.1) – 50/58 subjects.
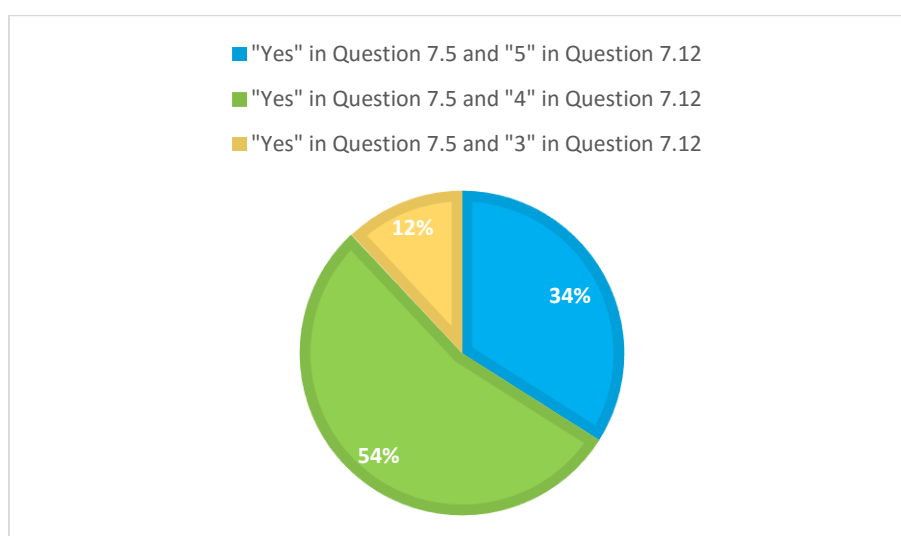
Figure 7.1: Answers regarding the usefulness of the platform (from 1 to 5), among the ones who admitted to have experienced struggles in laboratory experiments.

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Though, the trend of the responses is similar to that shown for the entire sample, with the "4" being the most chosen value (fulfilling more than a half of the opinions) and the "5" being the following one (chosen almost three times more than the mark "3").

100% of the respondents that agreed that a discussion forum within biomedical engineering would be useful, considered that the functionalities of the platform are adequate (Figure 7.2).
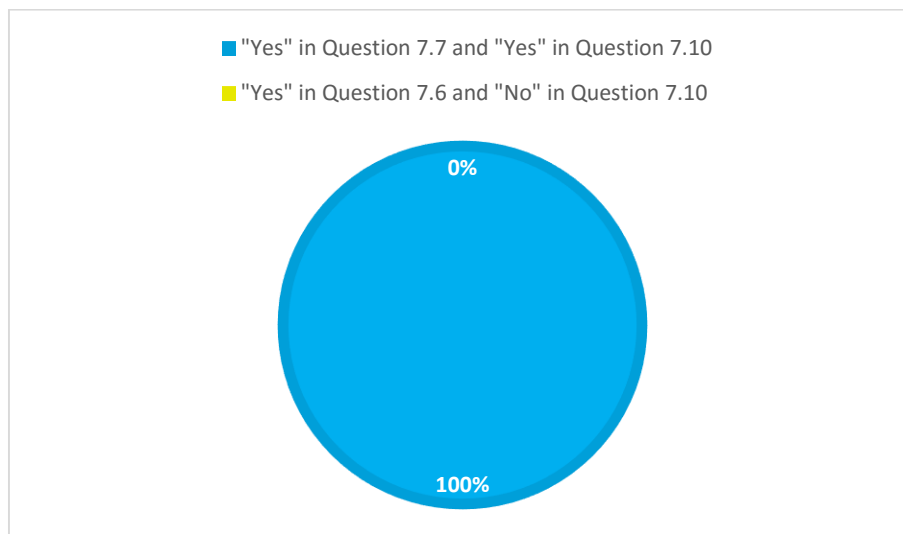
Figure 7.2: Opinion about the adequacy of the platform's functionalities within the respondents that agreed that a discussion forum within biomedical engineering would be useful.

Within the group of respondents who attended CMPP – 48/58 students – 96% indicated that the features of the platform are appropriate (Figure 7.3). Again, this value is identical to the one obtained in the responses of the entire sample.

Given that the platform is only in its first version, built from scratch, this is a very positive sign for us, validating both our requisites' analysis and the construction of the product.
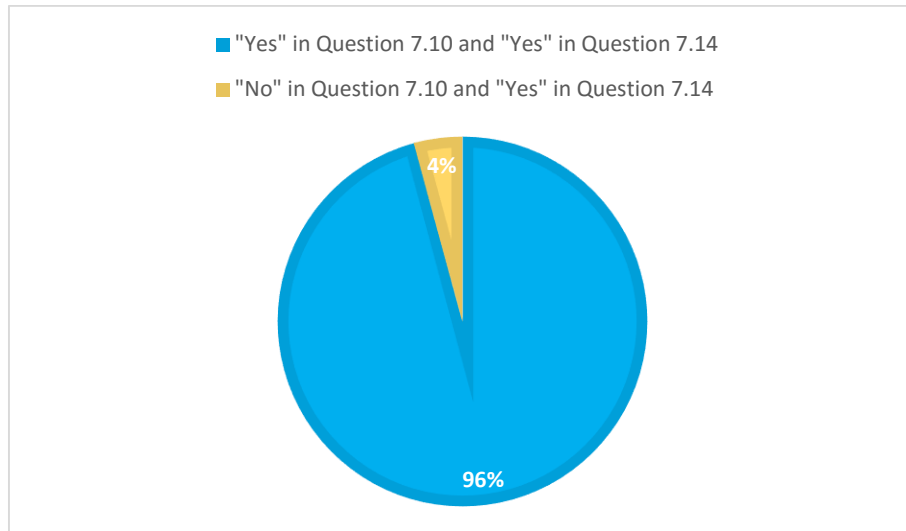
Figure 7.3: Opinion on the adequacy of the platform, within the group of respondents who attended CMPP.

Among the group of people who claimed that the platform would have helped them to understand the aim of the CMPP's project – 46/48 subjects –, 93% indicated that those works should be placed on the platform. Despite the fact that this is a higher rate than the one obtained within the total amount of answers, we find it peculiar that there are users that confess the utility of the platform on the perception of CMPP's work, but believe that those should not be inserted in the platform.
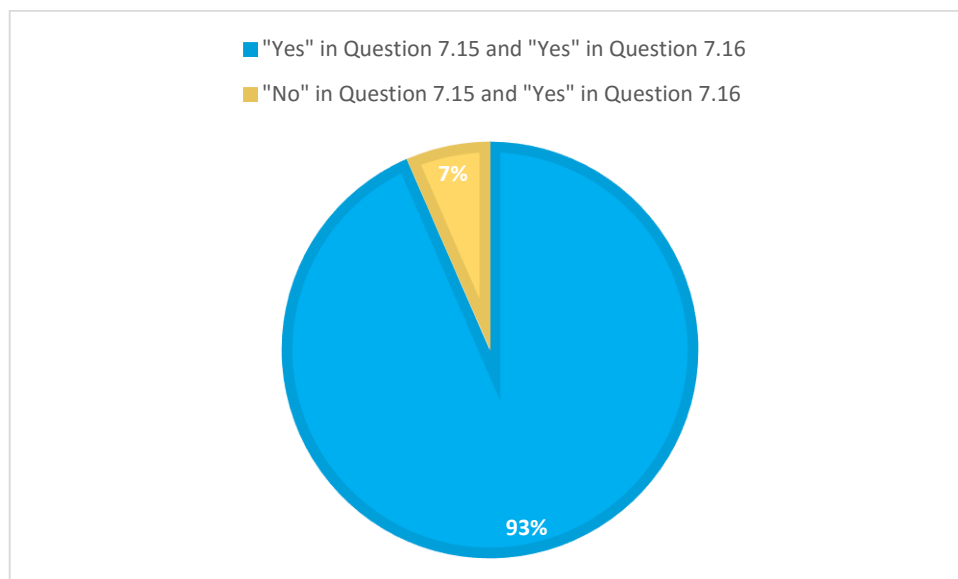
Figure 7.4: Opinions about the insertion of CMPP's projects on the website, among the group of people who claimed that the platform would help them to understand the goal of the course.

In general, we believe that the opinions of the target users about the platform were very positive, particularly because it is an early version and it already had much acceptance. However, in the future, the platform shall be extensively testes, namely is real school environment, in order to detect gaps and add other important features.

7.4 Summary

In this chapter, a survey was analyzed to understand some study trends of the students of the Integrated Master in Biomedical Engineering of the University of Coimbra. These included their use to consult the Internet for educational purposes, their struggles in traditional teaching methods and their opinion about the developed platform.

Most of the inquired students use the Internet to overcome their difficulties, particularly through their mobile devices. Furthermore, most of them had already consulted multimedia resources to achieve a better comprehension of biological processes and admitted to have problems in the achievement of knowledge in laboratory experiments due to external agents. Only less than half of the inquired students claimed to use discussion forums to clear doubts about educational subjects. Among them, most of all agreed that it would be useful to have a forum within the biomedical engineering field.

On the evaluation of the platform, the majority of the respondents believe that the platform is easy to handle, has a nice appearance and has appropriate features. Almost all the respondents consider that such a platform could help them overcoming some of the difficulties approached in the first group of questions.

Almost all the students who attended CMPP consider that the platform would ease the perception of the course and that the semestral projects should be introduced in the website.

Chapter 8

Conclusion

This chapter focuses on a consideration about the project's final result and in an analysis about the future work to execute.

8.1 Final Result

The main goal of this project was the development of a platform that allowed the storage of content based on scientific papers about modeling of physiological processes, supported real-time modeling simulations and admitted the sharing of experimental scenarios regarding related subjects.

This project started with a detailed analysis in order to find out which features should the platform include and how should them be presented, taking into account the need it was facing. Based on this, the design of the platform was planned and all the predictably important instruments to its development were studied and analyzed.

The construction of the platform, from scratch, was the next step, the most challenging and the longest one, including the identification of some needed tools, their operation, their embedding in the platform and the integration of everything in one single product. The creation of a parallel platform in a localhost was an important move here, allowing the early testing of many applications and their effects when incorporated in the website. The biggest challenges happened, as mentioned, in this stage and concerned, most of all, problems related to the integration of the used tools with each other, as well as related to

the small amount of completely free extensions available on Joomla!, as discussed in Chapter 4.4.1, which eventually hindered the work.

Fortunately, we did not have to let go any of our pretenses, and all the difficulties were overcome.

After developing the platform, it was filled with some study cases, illustrating its functionalities.

As a final assignment, a survey was delivered to some target users, in order to validate the use of the platform.

All these milestones of the project were planned and all of them were fulfilled.

We believe that, in the available time, a worthy first version of the platform was created and we consider that it reached the desired characteristics. This thesis also reveals that it is possible to create a platform with complex functionalities (as our e-learning platform), completely free, using CMS Joomla!.

One of the major advantages of this platform is the possibility of introducing content through the front-end, by any registered user, which is a key point to ease its implementation in academic means. Besides, this allows the increasing of the repository of scientific papers' analysis and, consequently, enhances the platform's lifetime.

In fact, all the operations on the platform are available through its front-end, including not only the ones related to authors' actions, but also the ones that concern the management of users and all the platform's content (tasks reserved to super users).

Moreover, given that the platform is responsive and can be used in any mobile device, this may lead to a bigger interest of the users and to amplify the contexts in which it may be used.

Although this project was, undoubtedly, the biggest challenge of my entire academic route, it was also the most rewarding. Throughout this year, I had contact with technologies that I had never used before and with which I had to deal in order to complete this project. I believe that this truly increased my perseverance and work persistence, and I am very thankful for that.

8.2 Future Work

In the future, the platform will be tested and validated in a real educational context, in the CMPP subject. The benefits and the advantages of blended learning shall also be tested, by combining the developed platform with the course traditional teaching methods. Subsequently, the writing of a scientific paper that reports these results is planned. This step is encouraged by the results of our validity survey, which show that students usually value the existence of such technological options in the Biomedical Engineering field.

The range of features of the platform can also be increased, making it more user-friendly and expanding its functionalities. Namely, the platform can be further lengthened to other scientific areas, since its structure already allows it.

Appendices

Appendix A

Platform Development Guide

Table A.1: Installation of the Advanced Module Manager [81] extension.

Extension/ Version	Advanced Module Manager/version 6.1.3
Type	Component/Plugin
Author	Regular Labs (Peter van Westen)
Implementation	Extensions -> Manage -> Select a File -> Upload and Install

Table A.2: Main steps of the development of a search by topics.

First step: creating the desired tags	
Implementation	Components -> Tags -> New; (as an example) Title: "drug ingestion" -> Save
Second step: creating the topic menus	
Implementation	Menus -> Manage -> Main Menu -> New; (as an example) Details -> Menu Title: "Physiological Context"; Menu Item Type -> Tags -> Compact list of tagged items; Tag: [insert all tags related to physiological contexts]; -> Save and New; (as an example) Details -> Menu Title: "Drug Ingestion"; Menu Item Type -> Tags -> Compact list of tagged items; Tag: "drug ingestion"; Parent Item -> Physiological Contexts -> Save
Third step: creating a side menu to appear on the results page, using Accordeon Menu CK [82]	
Extension/ Version	Menu Accordeon CK/version 2.0.19
Type	Module
Author	JoomlaCK (Cédric KEIFLIN)
Implementation	Extensions -> Manage -> Select a File -> Upload and Install; Extensions -> Modules -> New -> Accordeon Menu CK (as an example) Module ->Select Menu: "Anatomical Systems"; Position: left; Assignments -> Menu Items -> Include -> "Anatomical Systems"; -> Save

Table A.3: Main steps of the development of the search system by natural language.

First step: adding a module position in Helix 3 Framework Template [79] layout to show the search system	

Implementation	Extensions -> Templates -> Helix 3 Framework Template -> Layout;
	 (as an example) Main Body -> Add Row;
	     Settings -> Section Title: "Search";
	     Add Columns -> Custom Layout: 3,9,3;
	     Select the middle section -> Module Position -> search -> Save

Second step: changing some default settings in Smart Search extensions	

Implementation	Extensions -> Manage -> Manage -> Search for "Smart Search";
	     Disable "Smart Search – Categories", "Smart Search – Contacts" and "Smart Search – News Feeds";
	     Enable "Content Smart Search" -> Save

Third step: changing some default settings in Smart Search Global Configurations	

Implementation	System -> Global Configurations -> Smart Search;
	     Results Description: Hide; Query Explanation: Hide; Advanced Tips: Hide
	     -> Save

Fourth step: creating a page to display the Search Results	

Implementation	Menus -> Manage -> New;
	     (as an example) Title: "Search Results"; -> Save;
	 Menus -> Manage -> Search Results -> New;
	     (as an example) Details -> Menu Title: "Search Results"; Menu Item Type -> Smart Search -> Search -> Save

Fifth step: creating the Smart Search module	
Implementation	Extensions -> Modules -> New -> Smart Search (as an example) Module -> Title: "Initial Search"; Show Title: Hide; Position: search; Search Field Label: Hide; Set Item ID: Search Results; Assignments -> Menu Items -> Include -> Home -> Save

Table A.4: Main steps of the development of the most read/ newest analysis display in homepage.

First step: creating the most read and the newest analysis modules, using SP Portfolio [83]	
Extension/ Version	SP Portfolio/ version 1.4
Type	Module
Author	JoomShaper.com
Implementation	Extensions -> Manage -> Select a File -> Upload and Install; Extensions -> Modules -> New -> SP Portfolio Module -> Title: "Most Read"; Show Title: Hide; Options -> Count:3; Column: 3; Ordering: HITS; -> Save Extensions -> Modules -> New -> SP Portfolio Module -> Title: "Newest"; Show Title: Hide; Options -> Count:3; Column: 3; Ordering: Created Date; -> Save
Second Step: adding a module position in Helix 3 Framework Template [79] layout to show the suggested analysis.	
Implementation	Extensions -> Templates -> Helix 3 Framework Template -> Layout; (as an example) Search -> Add Row; Settings -> Section Title: "Suggested Analysis"; Add Columns -> Custom Layout: 12; Select the section -> Module Position -> position2 -> Save
Third step: creating the tabs using SP Tab [84]	
Extension/ Version	SP Tab/version 2.0
Type	Module
Author	JoomShaper.com
Implementation	Extensions -> Manage -> Select a File -> Upload and Install; Extensions -> Modules -> New -> Tab (as an example) Module ->Title: "Suggested Analysis"; Show Title: Hide; Position: position2; Assignments -> Menu Items -> Include -> Home -> Save

Table A.5 Main steps of the development of the authentication system.

First step: installation of Quick Logout [85] Extension.	
Extension/ Version	Quick Logout/version 1.9.3
Type	Component
Author	John Muehleisen
Implementation	Extensions -> Manage -> Select a File -> Upload and Install
Second Step: creating a menu for login and logout.	
Implementation	Menus -> Manage -> New; (as an example) Title: "Authentication"; -> Save; Menus -> Manage -> Authentication -> New; (as an example) Details -> Menu Title: "Login"; Menu Item Type -> Users -> Login Form; Access: Guests; -> Save; Menus -> Manage -> Authentication -> New; (as an example) Details -> Menu Title: "Logout"; Menu Item Type -> Quick Logout -> Quick Logout; Access: Registered; -> Save;
Third step: editing a module position in Helix 3 Framework Template [79] layout to display an authentication menu module	
Implementation	Extensions -> Templates -> Helix 3 Framework Template; (as an example) Basic -> Contact Information: No; (as an example) Layout -> Top Bar -> Settings -> Custom Layout: 11,1;-> Save
Fourth step: creating a menu module to display the authentication menu	
Implementation	Extensions -> Modules -> New -> Menu; (as an example) Module -> Title: "Authentication"; Select Menu: Authentication; Show Title: Hide; Position: top2; Assignments -> Menu Items -> Include -> Select All-> Save

Table A.6: Main steps of the development of the users' functionalities.

First Step: changing users' global configurations	

Implementation	System -> Global Configuration -> Users -> Component; Allow User Registration:
	     Yes; New User Registration Group: Authors; Frontend User
	     Parameters: Hide; -> Save

Second step: installing SEBLOD [86]**extension.**	
Extension/ Version	SEBLOD/version 3.8.3
Type	Component, Module, Plugin
Author	Octopoos
Implementation	Extensions -> Manage -> Select a File -> Upload and Install
Third Step: changing SEBLOD's [86] **global configurations**	
Implementation	System -> Global Configuration -> SEBLOD -> Permissions -> Author -> Delete Own: Allowed; -> Save
Forth Step: changing SEBLOD's [86] **"User" from Form & Content Types**	

Implementation	Construction -> Form & Content Types -> User -> Site Form -> Add "User Groups
	     (JForm – User Groups)" -> Button 4 -> User Groups (JForm –
	     User Groups) – Acess: Super Users; -> Save

Forth Step: changing SEBLOD's [86] **"User Manager" from List & Search Types**	
Implementation	Construction -> List and Search Types -> User Manager -> List -> Add "User Groups (JForm – User Groups)" to Column-C -> Save
Fifth Step: creating menus to access this resources in the off-canvas menu	

Implementation	Menus -> Manage -> New;
	     (as an example) Title: "Social Features"; -> Save;
	Menus -> Manage -> Social Features -> New;
	     (as an example) Details -> Menu Title: "My Account"; Menu Item
	     Type -> Users -> User Profile; -> Save;
	Menus -> Manage -> New;
	     (as an example) Title: "Configuration Manager"; -> Save;
	Menus -> Manage -> Configuration Manager -> New;
	     (as an example) Details -> Menu Title: "Add User"; Menu Item Type
	     -> SEBLOD-> Form; Content Type: User; Access: Super Users;
	     -> Save;
	Menus -> Manage -> Configuration Manager -> New;
	     (as an example) Details -> Menu Title: "User Manager"; Menu Item
	     Type -> SEBLOD -> List & Search; Search Type: User Manager;
	     Access: Super Users; -> Save;

Sixth step: creating a menu module to display the previously created menus	

Implementation	Extensions -> Modules -> New -> Menu;
	     (as an example) Module -> Title: "Social Features"; Select Menu:
	     Social Feature; Position: off-canvas; Assignments -> Menu
	     Items -> Include -> Select All-> Save
	Extensions -> Modules -> New -> Menu;
	     (as an example) Module -> Title: "Configuration Manager"; Select
	     Menu: Configuration manager; Position: off-canvas; Access:
	     Super Users; Assignments -> Menu Items -> Include -> Select
	     All-> Save

Table A.7: Installing the extensions used in the content features.

Installing Ark Editor [87]	
Extension/ Version	Ark Editor/version 1.8.5.
Type	Component, Plugin
Author	Webx Solution Ltd
Implementation	Extensions -> Manage -> Select a File -> Upload and Install
Installing Ark Media Manager [88]	
Extension/ Version	Ark Media Manager/version 1.11.0
Type	Component, Plugin
Author	Webx Solution Lt
Implementation	Extensions -> Manage -> Select a File -> Upload and Install
Installing Sourcerer [90]	
Extension/ Version	Sourcerer/version 6.1.3
Type	Plugin
Author	Webx Solution Lt
Implementation	Extensions -> Manage -> Select a File -> Upload and Install
Installing Tabs [89]	
Extension/ Version	Tabs/version 6.0.8
Type	Plugin
Author	Webx Solution Lt
Implementation	Extensions -> Manage -> Select a File -> Upload and Install

Table A.8: Main steps of the development of the content insertion.

First Step: changing some Ark Editor [87] global configurations	
Implementation	System -> Global Configuration -> Ark Editor -> Inline; Enable Inline Editing: No; Enable Autosave: No;
Second Step: changing SEBLOD's [86] "Article" from Form & Content Types	
Implementation	Construction -> Form & Content Types -> Article -> Site Form -> Article State -> edit ->Default Value: "0"; Add "Article Tags (JForm – Tag); -> Save
Third Step: creating menus to access the creation of an analysis in the off-canvas menu	
Implementation	Menus -> Manage -> New; (as an example) Title: "My Articles"; -> Save; Menus -> Manage -> My Articles -> New; (as an example) Details -> Menu Title: "Create an Article"; Menu Item Type -> SEBLOD-> Form; Content Type: Article; Access: Registered -> Save;
Fourth step: creating a menu module to display the previously created menus	
Implementation	Extensions -> Modules -> New -> Menu; (as an example) Module -> Title: "My Submissions"; Select Menu: My Articles; Position: off-canvas; Access: Registered; Assignments -> Menu Items -> Include -> Select All-> Save

Table A.9: Main steps of the development of the super users' article manager.

First Step: Creating menus to access the Article Manager from the off-canvas menu	
Implementation	Menus -> Manage -> Configuration Manager -> New; (as an example) Details -> Menu Title: "Article Manager"; Menu Item Type -> SEBLOD -> List & Search; Search Type: Article Manager; Access: Super Users -> Save;
Second Step: Changing SEBLOD's [86] CCK Storage Location - Joomla! Article	
Implementation	Extensions -> Plugins -> CCK Storage Location - Joomla! Article -> Default Status: Unpublished -> Save

Table A.10: Main steps of the development of the users' submission content.

First Step: changing some SEBLOD [86] global configurations	
Implementation	System -> Global Configuration -> SEBLOD -> Permissions -> Author: Delete Own: Allowed;
Second Step: creating a SEBLOD's [86] new "List & Search Types" field	
Implementation	Construction -> List & Search Types -> New -> (as an example) Title: "User Submissions"; App Folder: Articles; -> Search Form -> Add "Article Created By (JForm-User) -> Variation: Hidden; -> Button 2; Live: User; Live Value -> Configure -> Properties -> "id"; Add "Article State (Select - Simple); Live Value: "0,1,2"; List ->Template: "Table – seb_table"; List -> Fields -> (s an example) Add "Article Title (text); Add "Article Created (Calendar); Add "Article State"; Add "Icon Edit"; Add "Icon Delete; -> Save
Third Step: creating menus to access the creation of an analysis in the off-canvas menu	
Implementation	Menus -> Manage -> My Articles -> New; (as an example) Details -> Menu Title: "My Submissions"; Menu Item Type -> SEBLOD-> List & Search Types; Content Type: User Submissions; Access: Registered -> Save;

Table A.11: Main steps of the development of the forum.

First step: installation of Kunena [93]Extension.	
Extension/ Version	Kunena/version 4.0.11
Type	Component, Module, Plugin
Author	Kunena Team
Implementation	Extensions -> Manage -> Select a File -> Upload and Install
Second Step: changing some Kunena's [93] configurations	
Implementation	Components -> Kunena Forum -> Configurations -> (as an example) General; Enable RSS Feeds: No; -> Show Announcements: No; Show Moderators in Category Index: No; -> Users; Show Users Statistics: No; Show Karma Indicator: No; -> Avatars: Allow Avatar Upload: No; -> Ranking; Ranking: No; -> BBCode; Disable Emoticons: Yes; -> Save
Third step: changing "Kunena – Kunena Integration" [93] plugin	
Implementation	Extensions -> Plugins -> Kunena – Kunena Integration; Enable Kunena Avatars: No; Enable Kunena Profiles: No; -> Save
Fourth step: disabling some Kunena's [93] Menu Items	
Implementation	Menus -> Manage -> Kunena Menu; Disable "Index", "No Replies", "Profile", "Help" and "Search -> Save
Fourth step: creating a menu to access the forum	
Implementation	Menus -> Manage -> Social Features -> New; (as an example) Details -> Menu Title: "Forum"; Menu Item Type -> Kunena Forum -> Home Page; Default Menu Item: Recent Topics -> Save;

Table A.12: Main steps of the insertion of front-end settings.

First Step: Creating menus to access the Configuration Manager from the off-canvas menu	
Implementation	Menus -> Manage -> Configuration Manager -> New; (as an example) Details -> Menu Title: "Configuration Manager"; Menu Item Type -> Site Configuration Options -> Configuration Manager; Access: Super Users -> Save;

Table A.13: Main steps of the development of the statistical analysis.

First step: installation of Visitors Counter [94] Extension.	
Extension/ Version	Visitors Counter/version 2.0.4
Type	Module
Author	Majunke Michael
Implementation	Extensions -> Manage -> Select a File -> Upload and Install
Second step: editing a module position in Helix 3 Framework Template [79] layout to display the statistical modules	
Implementation	Extensions -> Templates -> Helix 3 Framework Template -> Layout; (as an example) Bottom ->Add Columns -> Custom Layout: 6,6;-> Save
Third step: adding and editing a Visitors Counter [94] module	
Implementation	Extensions -> Modules -> Add ->Visitors Counter -> Module -> (as an example) Show Yesterday: No; Show Digit Counter: No; Position: bottom1; Access: Super Users -> Save
Fourth step: adding and editing a new Visitors Counter [94] module	
Implementation	Extensions -> Modules -> Add -> Visitors Counter -> Module -> (as an example) Show Today: No; Show Yesterday: No; Show Week: No; Show Month: No; Show All Days: No; Show Digit Counter: No; Show Logged in Users: Yes; Show Guests; Yes; Show Registered Users; Yes; Position: bottom2; Access: Super Users -> Save

Table A.14: Using Yireo SSL Redirection [98] extension.

First step: installation of Yireo SSL Redirection [98] Extension.	
Extension/ Version	Yireo SSL Redirection/version 0.11.3
Type	Plugin
Author	YIREO
Implementation	Extensions -> Manage -> Select a File -> Upload and Install
Second Step: changing some Yireo SSL Redirection [98] configurations	
Implementation	Extensions -> Plugins -> System – SSL Redirect -> SSL Pages -> SSL Menu Items: "Add User", "Create an Article", "My Account", "Login", "Logout", "Site Configuration Options", "User Manager"; SSL Components: "com_admin", "com_login", "com_quicklogout"; -> Save

Table A.15: Main changes to improve the Platform Responsiveness.

First Step: adding and editing Helix 3 Framework Template [79] layout (examples)	
Implementation	Extensions -> Templates -> Helix 3 Framework Template -> Layout; Top Bar -> top1 -> Settings -> Tablet Layout: col-sm-10; Mobile Layout: col-xs-8; -> top2 -> Settings -> Tablet Layout: col-sm-2; Mobile Layout: col-xs-4; Extensions -> Templates -> Helix 3 Framework Template -> Layout; Search -> Settings -> Hide on Mobile; Extensions -> Templates -> Helix 3 Framework Template -> Layout; (as an example) Suggested Analysis -> Add Row; Settings -> Section Title: "Phone Suggested Analysis"; Add Columns -> Custom Layout: 12; Select the section -> Module Position -> position5 -> Save
Second Step: adding a free search system on the off-canvas menu	
Implementation	Extensions -> Modules -> New -> Smart Search (as an example) Module -> Title: "Phone Search"; Show Title: Hide; Position: off-canvas; Search Field Label: Hide; -> Save
Third step: creating the most read and the newest analyses modules, using SP Portfolio [83]	
Implementation	Extensions -> Modules -> New -> SP Portfolio Module -> Title: "Most Read"; Show Title: Hide; Options -> Count:3; Column: 1; Ordering: HITS; -> Save Extensions -> Modules -> New -> SP Portfolio Module -> Title: "Newest"; Show Title: Hide; Options -> Count:3; Column: 1; Ordering: Created Date; -> Save
Fourth step: creating the tabs using SP Tab [84]	
Implementation	Extensions -> Modules -> New -> Tab (as an example) Module ->Title: "Suggested Analysis Phone"; Show Title: Hide; Position: position5; Assignments -> Menu Items -> Include -> Home -> Save

Appendix B

User Guide

IT IS EXTREMELY IMPORTANT THAT YOU READ THIS DOCUMENT BEFORE THE INSERTION OF CONTENT IN THE PLATFORM.

This platform is based on the sharing of analysis of scientific papers about physiological modeling. After the insertion of an analysis, it stays pendent until the approval of a platform's administrator.

ARTICLE'S ANALYSIS

To insert an analysis, click on:

Off-canvas menu (☰) -> Create an Analysis.

1.1 How do I insert images and files?

To insert media in an article's analysis, click on "Add Media".

You can choose to insert/upload images or documents. The allowed formats for images are: .jpg, .png, .gif, .bmp, .svg, .ico and .tiff. The allowed formats for documents are: .swf, .txt, .rtf, .zip, .pdf, .swf, .fla, .doc, .xls, .ppt, .odp, .odt, .html, .xhtml., .xml, .ttf, .woff, .otf, and .eot.

You can also create folders to organize your data, by clicking on "New Folder".

After the selection of the media you want to share in your analysis, click on "Insert". Here, for example, in the case of an image, you can set is alignment in the "Align"

option and change its size by clicking on "Styles", "width" and defining its proportions. When you are done, click on "Insert into content".

1.2 How do I insert the tabs I want to display?

For the insertion of tabs, you only need to enter the following brackets, as in the example:

{tab Title 1}

Your text

{tab Title 2}

Your text

{/tabs}

To insert more than one level of tabs, as in the following example, you can write:
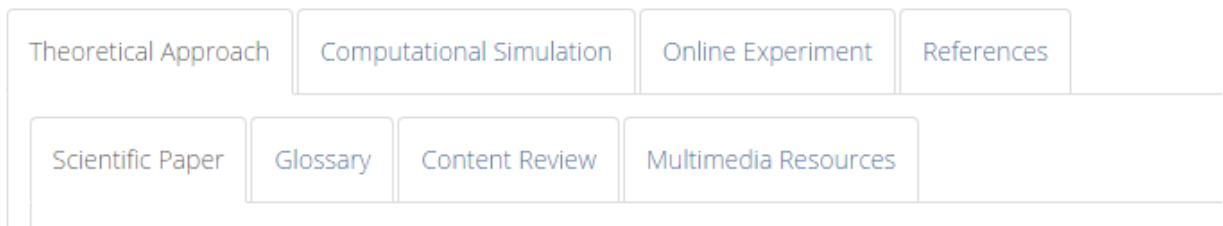
{tab Theoretical Approach}

    {tab-ex Scientific Paper}

    Your text

    {tab-ex Glossary}

    Your text

    {tab-ex Content Review}

    Your text

    {tab-ex Multimedia Resources}

    Your text

    {/tabs-ex}

{tab Computational Simulation}

{tab Online Experiment}

{tab References}

{/tabs}

The indentation above was just for clarity and you do not need to do that in your text. To create different levels of tabs, as tabs inside other tabs, you just need, an in the example above, to give the tab an extra name. It is absolute necessary that you close the group of tabs, as shown above. For a detailed information, consult *https://www.regularlabs.com/extensions/tabs#nested-tabs*.

1.3 How do I insert code?

To insert code in an article's analysis, click on "Code", copy-paste it and click on "Insert". You can also directly insert your code into your analysis, inside the brackets *{source}* your code *{/source}*.

1.3.1 What libraries may I use to perform computational simulations?

You can use any library. However, we suggest that you use the Numeric JavaScript library, in order to perform the simulation of the models you study. The library performs a lot of useful operations, including the solving of ODE systems. This library is available in: *http://www.numericjs.com/*.

You can read its documentation in: *http://www.numericjs.com/documentation.html*.

To use it in your code, you can add

```
<script
src="https://cdnjs.cloudflare.com/ajax/libs/numeric/1.2.6/numeric.min.js"></script>
```

into your HTML head.

One example using this library can be found at the end of this document.

More information on the ODE solver:

The ODE solver included in this library implements the Dormand-Prince-Runge-Kutta integrator with adaptive time stepping. This solver is called through the instruction "numeric.dopri", assigning a Dopri object to the specified JavaScript variable. This object contains the independent (x) and dependent (y) series of the calculated solution, in addition to some other attributes that inform about some details of the operation, such as the number of performed iterations and the mean value of the dependent variable, in each interval.

It must be noted that the instruction enables the calculation of several equations in the same iteration (in an ODE system), returning all the dependent series' values in an array (Ar1) of arrays (Ar2) – for each equation solved, Ar1 will include one more Ar2 (and each Ar2 contains the calculated values of one equation).

The mandatory input arguments of the instruction must be in this order: first value of the independent variable, last value of the independent variable, initial value for each dependent variable (if there are several equations, this argument must be indicated as an array) and, at last, the JavaScript function that maps all the equations to be calculated. Besides the mandatory inputs of the instruction, a few more can be optionally added, following the first ones and introduced in this order: tolerance of the method, maximum number of iterations and an event function. The event function follows the same implementation rules as the ODE-defining function, and it stops the integration process when its values pass from negative to positive. When some optional input argument is not to be set, but the next one needs some specification, the first can be declared as "undefined".

You can consult the documentation to read about this information.

One example of a Dopri object called "sol" could be:

```
var sol = numeric.dopri(0,1000,[400, 90, 1, 10],f,
undefined, 2000);
```

The JavaScript function that expresses the ODE to be solved must be implemented with the declaration of two input arguments that define the dependent variable and the independent variable(s) – which can be an array of arrays, as mentioned above –, in this order (see example above). However, when this function is called as an input for

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the "numeric.dopri" instruction, its implemented inputs are not to be explicitly replaced by values in the instruction (as in the example above), since the library will do this part.

The example below shows a function expressing an ODE system:

```
f = function(x,vec) {
  //definition of constants
  var gamal = 0.005;
  var ul = 0.0005;
  var gamat = 0.005;
  var gamaf = 0.004;
  var bp = 0.004;
  var Ls = 400;
  var Lt = 100;
  var up = 0.0035;
  var ul = 0.0005;
  var uf = 0.0004;
  var g1 = 1;
  var g2 = 1;
  var g3 = 0.3;
  var g4 = 0.2;
  var g5 = 0.5;
  var g6 = 0.5;


  //definition of the differential equations
  var P = vec[0];
  var L = vec[1];
  var T = vec[2];
  var F = vec[3];

  var    dP    =    bp*Math.pow(l,g1)*Math.pow(P,    g2)-up*P-
gamaf*Math.pow(L, g3)*Math.pow(P, g4);
  var dL = gamal*Math.pow(T, g5)*Math.pow(L, g6)-ul*L;
  var dT = gamat*T*Math.log10(Lt/T);
  var dF = gamaf*Math.pow(L, g3)*Math.pow(P,g4)-uf*F;


  return [dP, dL, dT, dF];
}
```

As shown above, in the implementation of the equations, it must be explicitly demonstrated what are the input arguments related to each ODE, since the library will go through this function in every iteration performed by the method. Thus, this function "f" (or any similar one) is expected to return the new values of each equation

in the same order that will receive them in the next iteration, as inputs (to perform new calculations). Note that the independent variable shall not be returned.

1.3.2 What libraries may I use to display graphics?

Again, you can use any library. However, we suggest you to use plotly.js, available in: *https://plot.ly/javascript/*.

You can go through many examples in: *https://plot.ly/javascript/line-charts/*.

To use it in your code, you can add

```
<script src=" https://cdn.plot.ly/plotly-
latest.min.js"></script>
```

into your HTML head.

One example using this library can be found at the end of this document.

1.3.3 How should I embed content?

To embed content, you can write:

```
<html>
<div>
<object data="your url" width="1200" height="1000">
<embed src="your url" width="1200" height="1000"> </embed>
Error: Embedded data could not be displayed.
</object>
</div>
</html>
```

You can set the width and the height that fits the most.

Before the embedding of any content, it is important to ensure that the owners allow its sharing.

IMPORTANT:

- It is essential that you test the code before inserting it in the platform. For this, you will need a special text editor, such as Sublime Text (available in *https://www.sublimetext.com/3*), save the code in .html format and open it in your browser;

- If you use Bootstrap, do not call its CDN in the final code you want to embed in the platform, since it is already integrated in the platform.

1.4 How do I select the tags and the category of my analysis?

In the insertion of an analysis, click on the "Publishing" tab.

Choose all the tags that are related to your inserted content. The available tags are: **digestive**, **cardiovascular**, **endocrine**, **integumentary**, **immune**, **muscular**, **nervous**, **reproductive**, **respiratory**, **skeletal**, **urinary**, **cancer**, **drugingestion**, **digestion**, **cellcycle**, **metabolism** and **infections**.

Chose one category that is the most related to your inserted content. The available categories are: **Cancer**, **Cell Cycle**, **Digestion**, **Drug Ingestion**, **Metabolism** and **Infections**.

1.5 How do I insert an intro image?

In the insertion of an analysis, click on the "Publishing" tab.

Select an Intro Image. Here, you can use one of the available images or upload your own. The inserted image shall be 500x330px.

1.6 How can edit my submitted analysis?

Click on: Off-canvas menu -> My Analysis.

1.7 How do I approve users' submissions? (Reserved for super users)

Click on: Off-canvas menu -> Article Manager -> Select the analysis you want to approve -> Edit -> Status -> "Published".

You can preview the final shape of the inserted analysis by clicking on the link that appears in the "Article Manager".

It is also possible to change the status of the analysis to "archived". To view the archived analysis, click on: Off-canvas menu -> Archived Analysis.

USERS' ACCOUNTS

2.1 How do I edit my account parameters?

Click on "My Account", on the Off-canvas menu. Press "Edit Profile".

2.2 How do I edit other users' account parameters? (Reserved for super users)

Click on: Off-canvas menu -> User Manager.

DISCUSSIOM FORUM

2.1 How do I insert a new topic?

Click on: Off-canvas menu -> Forum -> New Topic.

2.2 How do I see the recent topics?

Click on: Off-canvas menu -> Forum -> Recent Topics.

2.3 How do I see my own topics?

Click on: Off-canvas menu -> Forum -> My Topics.

EXAMPLE OF A COMPUTATIONAL SIMULATION:

The example of this computational simulation was based on the scientific paper "Modeling the Effects of Multiple Myeloma on Kidney Function" by Julia C. Walk, Bruce P. Ayati and Sara A. Holstein.

```html
<!DOCTYPE html>
<html lang="en">
<head>
<meta charset="utf-8">
<script
src="https://cdnjs.cloudflare.com/ajax/libs/numeric/1.2.6/n
umeric.min.js"></script>
<script src="https://cdn.plot.ly/plotly-
latest.min.js"></script>
</head>

<body>

<button onclick="calculo()" type="button" class="btn btn-
info">RUN</button>

<script>
window.onload = function(){
  grafico1([], []);
  grafico2([], []);
  grafico3([], []);
  grafico4([], []);
}

calculo = function() {
    var sol = numeric.dopri(0,1000,[400, 90, 1, 10],f,
undefined, 2000);
    var vector1=[];
    var vector2=[];
    var vector3=[];
    var vector4=[];

    for (var i = 0; i < sol.y.length; i++) {

      vector1[i] = sol.y[i][0];
      vector2[i] = sol.y[i][1];
      vector3[i] = sol.y[i][2];
      vector4[i] = sol.y[i][3];
    }
    solucao = [sol.x, vector1, vector2, vector3, vector4];

    grafico1(solucao[0], solucao[2]);
```

```javascript
      grafico2(solucao[0], solucao[4]);
      grafico3(solucao[0], solucao[3]);
      grafico4(solucao[0], solucao[1]);
   }

f = function(x,vec) {
  //definition of constants
  var gamal = 0.005;
  var ul = 0.0005;
  var gamat = 0.005;
  var gamaf = 0.004;
  var bp = 0.004;
  var Ls = 400;
  var Lt = 100;
  var up = 0.0035;
  var ul = 0.0005;
  var uf = 0.0004;
  var g1 = 1;
  var g2 = 1;
  var g3 = 0.3;
  var g4 = 0.2;
  var g5 = 0.5;
  var g6 = 0.5;


  //definition of the differential equations
  var P = vec[0];
  var L = vec[1];
  var T = vec[2];
  var F = vec[3];

  var    dP    =    bp*Math.pow(l,g1)*Math.pow(P,    g2)-up*P-
gamaf*Math.pow(L, g3)*Math.pow(P, g4);
  var dL = gamal*Math.pow(T, g5)*Math.pow(L, g6)-ul*L;
  var dT = gamat*T*Math.log10(Lt/T);
  var dF = gamaf*Math.pow(L, g3)*Math.pow(P,g4)-uf*F;


  return [dP, dL, dT, dF];
}
</script>

<div class="container-fluid">
  <div class="row">
    <!--  FIRST COLUMN -->
    <div class="col-sm-6">
     <div id="myDiv1" style="width: 50%; height: 50%;"><!--
Plotly chart will be drawn inside this DIV --></div>
        <script>
            grafico1 = function(a, b) {
```

```
                                fazerPlot1(a,b,'Graphic 1','time t
(days)','Free Light Cell Population', 'myDiv1');
                    }
            </script>
      </div>

<!--  SECOND COLUMN -->
    <div class="col-sm-6">
      <div id="myDiv2" style="width: 50%; height: 50%;"><!--
Plotly chart will be drawn inside this DIV --></div>
          <script>
                grafico2 = function(a, b) {
                        fazerPlot1(a,b,'Graphic 2','time t
(days)','Fibroblasts Population', 'myDiv2');
                    }
            </script>
      </div>

<!--  THIRD COLUMN -->
    <div class="col-sm-6">
      <div id="myDiv3" style="width: 50%; height: 50%;"><!--
Plotly chart will be drawn inside this DIV --></div>
          <script>
                grafico3 = function(a, b) {
                        fazerPlot1(a,b,'Graphic 3','time t
(days)','Tumor Cells Population', 'myDiv3');
                    }
            </script>
      </div>

<!--  FOURTH COLUMN -->
    <div class="col-sm-6">
      <div id="myDiv4" style="width: 50%; height: 50%;"><!--
Plotly chart will be drawn inside this DIV --></div>
          <script>
                grafico4 = function(a, b) {
                        fazerPlot1(a,b,'Graphic 4','time t
(days)','Proximal Tubules Cell Population', 'myDiv4');
                    }
            </script>
      </div>
   </div>
</div>

<script>
function fazerPlot1(a,b,titleGraph,titleX,titleY, janela){
    var trace = {
        x: a,
        y: b,
        mode: 'lines+markers',
        marker: {
```

```
                color: 'rgb(41, 203, 209)',
            size: 3
        },
        line: {
                color: 'rgb(41, 203, 209)',
            width: 1
        }
    };
    var data = [trace];
    var layout = {
        title:titleGraph,
        xaxis: {
            title: titleX
        },
        yaxis: {
            title: titleY
        },
        height: 500,
        width: 400
        };
          Plotly.newPlot(janela, data, layout);
    }
  </script>
 </body>
</html>
```

Appendix C

Case Studies: Analyses

C.1 Analysis of "Modeling invasion of metastasizing cancer cells to bone marrow utilizing ecological principles" [105]

C.1.1 Theoretical Approach

C.1.1.1 Glossary

Ecosystem: This describes a system of interconnected elements within a bounded area, and the dynamics that are created among them. In biological terms, it includes a biological community of living beings (the biotic component) and all the non-living (physical and chemical) elements that are presented in their surrounding environment (the abiotic component) [117] [118]. The network of interactions that exists between the several parts of these components (dynamic over space and time) is the one that establishes the "system". The boundaries of an ecosystem are specified simply for practical reasons. The

study of an ecosystem is mainly focused on the study of the mentioned processes, which usually comprise energy transformations and biogeochemical cycles [118].

Population biology: It covers the study of populations of organisms and the existing relationships, both among themselves and between them and the environment. This concerns the tracking of population changes (related, for example, to population size, historical events, diseases, overcrowding, extinction, etc.) and the underlying processes that lead to that [119], dealing with genetic, physiological, demographic and age heterogeneities [120].

Ecological niche: This describes the position of a population in its environment or habitat, showing the way it responds to external factors, as well as the way it is affected by them. These factors may be abiotic components, food and shelter resources, competitors or predators, for example [121] [122]. This leads to the evolution of the population in the niche, since all these factors affect the survival and reproduction of the individuals [121].

Intraspecific competition: The individuals of a population have similar needs in terms of survival, growth and reproduction, which may lead to demands for resources that exceed the existing supplies. In this case, the individuals of the same species will compete for the resources among them (intraspecific competition). This scenario may influence innumerous events, such as: decreased rates of resource intake per individual, decreased rates of individual growth or development, decreases in the amounts of stored reserves, increased risks of predation, decreases in survivorship and decreases in fecundity [123].

Interspecific competition: It may cause, in a population, the same fecundity, growth and survivorship consequences of the last concept, but, in this case, the resource exploitation or interference is made by individuals of other species. As seen, this phenomenon affects the populations' dynamics, and the dynamics, in their turn, can influence, over time, the species' distributions and their evolution in the environment [124].

Hematopoietic stem cell niche: Hematopoietic stem cells are a subpopulation of hematopoietic cells capable of differentiating to all blood cell lineages. Their characteristic of having a long-lived self-renewal ensures the generation of blood cells throughout life. These stem cells are mostly located in the bone marrow, surrounded by a specific microenvironment, called the hematopoietic stem cell niche. This niche provides protection and plays a role in signaling the start of the stem cells' differentiation [125].

Bone marrow: Located in the hollow spaces inside bones, bone marrow is a soft, spongy and gelatinous tissue that consists of the two main types of stem (undifferentiated) cells, supported by a fibrous tissue called stroma. The bone marrow may, then, be red or yellow, depending on whether it consists of mainly red-colored hematopoietic tissue or yellow-colored fatty tissue. The first one is involved in producing blood cells, whereas the other is involved in producing stromal cells [126].

Metastasis: Cancer cells from a metastatic cancer have the ability of breaking away from a tumor in the primary site and spreading to other parts of the body, both by moving into nearby normal tissues and by moving through the bloodstream and lymph system to more distant sites [127] [128]. When some of these cells are able to settle in the new location and to grow and form new tumors, it is said that a metastasis occurred [88].

C.1.1.2 Content Review

A niche can be considered a space occupied by an organism in an ecological community. Similar species tend to reside in similar niches [129]. When the niches of two different species overlap, an interspecific competition occurs, which is a competition of two species for the same resources [130] [131].

An invasive species can be defined as an organism that causes ecological damage in an ecosystem where it is not native [132]. The invasive species can either die or settle in, starting to propagate and creating impact on the new environment, causing consequences to the native species [105].

It is possible to make an analogy between invasive species and cancer metastasis, once cancer cells grow in a place, escape and survive until they reach a new tissue (*i.e.,* new environment) [105]. Thus, in this context, the following analogy may be made:
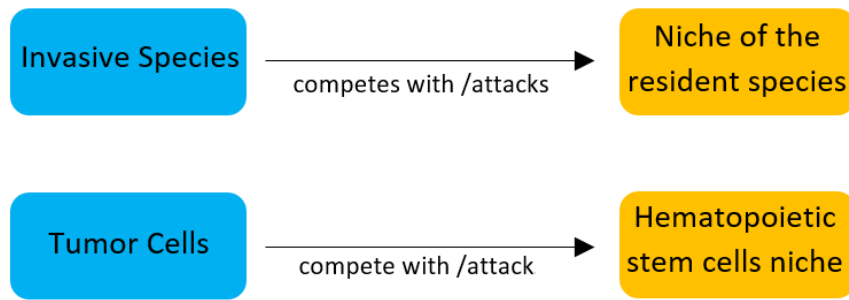
Figure C.1: Analogy between invasive species and metastasizing cancer, grounded on Tilman's model. Adapted from [105] [106].

C.1.2 Computational Simulation

C.1.2.1 Algorithm Analysis

The following analysis is based on what is referred and reported in [105]. The symbols used in the equations and their meaning are in Table D.1, which was transcribed from [105].

Table C.1: Symbols used in the equations of [105]. Transcribed from [105].

Symbol	Definition
ρ_1	Density of species 1
ρ_2	Density of species 2
β_1	Birth rate of species 1
β_2	Birth rate of species 2
μ_1	Death rate of species 1
μ_2	Death rate of species 2
k	The ability (proportion) that species 1 can displace species 2 by the growth (birth) of species 1
v	The ability (proportion) that species 2 can displace species 1 by the growth (birth) of species 1
t	Time

In Tilman's model [133], a superior species can occupy the niche of an inferior species. However, an inferior species can only colonize an environment that is not occupied neither by itself nor by the superior species [105] [106].

$$\frac{\partial \rho_1}{\partial t} = \beta_1 \rho_1 (1 - \rho_1) - \mu_1 \rho_1 \quad (1)$$

$$\frac{\partial \rho_2}{\partial t} = \beta_2 \rho_2 (1 - \rho_1 - \rho_2) - \mu_2 \rho_2 - \beta_1 \rho_1 \rho_2 \quad (2)$$

In the Equation 1, it is seen that the proliferation of the superior species (species 1) depends only on its birth and death rate. Observing the Equation 2, it is seen that the birth and death rates of the inferior species (species 2) are dependent on the competitive interactions between the two species [105] [106].

Kun-Wan Chen and Kenneth J. Pienta adapted the Tilman's model of invasion dynamics, considering that the invaders are the tumor cells and that the hematopoietic stem cells (HSC) are already in the bone marrow [105] [106]. As seen in Tilman's unmodified model, the superior species is not affected by the inferior species. However, when modeling the real dynamics between HSC and tumor cells, it is difficult to understand which is the superior and inferior species and it shall be taken into account that they both have the capability to displace each other [105] [106].

$$\frac{\partial \rho_1}{\partial t} = \beta_1 \rho_1 [1 - \rho_1 - (1 - k)\rho_2] - \mu_1 \rho_1 - \beta_2 \rho_2 \rho_1 v \quad (3)$$

$$\frac{\partial \rho_2}{\partial t} = \beta_2 \rho_2 [1 - (1 - v)\rho_1 - \rho_2] - \mu_2 \rho_2 - \beta_1 \rho_1 \rho_2 k \quad (4)$$

It was considered that $k = 0.9$ and $v = 0.1$, which indicates that the tumor cells displace 90% of the HSCs and the HSCs displaces 10% of the tumor cells [105]. In the simulations performed in the platform, it was considered the following values for the graphic 1, graphic 2 and graphic 3, according to what was simulated in [105]: $\beta_1 = 0.2$, $\beta_2 = 0.8$, $\mu_1 = 0.1$ time^{-1}, $\mu_2 = 0.1$ time^{-1}. The initial values may be changed in the simulation.

C.1.2.2 Simulation

A computational simulation was performed and displayed in the platform, taking into account the previously discussed equations.

C.1.2.3 Results Interpretation

The graphics obtained are identical to those presented in [105].

The first graphic analyzes the Tilman's unmodified equations, to the dynamics between tumor cells and HSCs. HSCs are considered to be the superior species. As expected, the colonization of the superior species (HSCs) is completely independent of the behavior of the inferior species (tumor cells). After the local density of the HSCs stabilizes, the density of the tumor cells also tends to a constant value. The lower is the initial local density of HSCs, the sooner will the local density of tumor cells tend to stabilization. In this case, the initial values for local density were always higher for HSCs and near zero to tumor cells.

The second graphic presents the Tilman's unmodified equations, to the dynamics between tumor cells and HSCs, in which tumor cells are considered the superior species. Again, the behavior of the superior species (tumor cells) is independent of the inferior species (HSCs). The local densities of both species tend to stabilize. Although the initial values for local density are higher for HSCs (inferior species) and nearby zero to tumor cells (superior species), the stability values for the local density are higher to tumor cells than to HSCs cells.

In the third graphic, the Kun-Wan Chen and Kenneth J. Pienta adapted Tilman's model of invasion dynamics is analyzed. In this case, it is taken into account that both species have influence on each other. Tumor cells are considered to be the superior species. In this perspective, as expected, the graphical behavior of one influences the other's behavior. Although tumor cells are still the superior species and the initial values are identical, unlike the previous case, the local density of tumor cells does not surpass the density of HSCs, although the density of the superior species increases and the inferior species decreases. Again, the densities tend to stabilize.

C.1.3 Experimental Procedure

A virtual laboratory, studying how the competition affects the growth of a population, was shared in the platform. The reference to the laboratory was found in The Biology Corner [134]. It was created by Glencoe/McGraw-Hill [107] and can be found in [108].

C.2 Analysis of "Modeling for the drug therapy for HIV infection" [109]

C.2.1 Theoretical Approach

C.2.1.1 Glossary

Human Immunodeficiency Virus (HIV): A lentivirus – a subgroup of retrovirus – composed by two single chains of Ribonucleic Acid (RNA) and envelope proteins. HIV attacks, gradually, the immune system, destroying a type of white blood cells, CD4 $^+$ T cells, by making copies of itself inside them [135] [136] [137] [138].

Immune System: The immune system is a collection of cells, tissues and organs that protect the body against diseases and infections. When functioning properly, it detects threats – as viruses, bacteria and parasites, distinguishing them from the body's tissue, and fights these pathogen agents [139].

Acquired Immunodeficiency Syndrome (AIDS): It is a syndrome caused by HIV virus, when a person's immune system is too weak to fight and the organism becomes vulnerable to many diseases and infections. When the number of CD4 $^+$ T cells drops below 200 cells per millimeter of blood, they are said to have AIDS [135].

CD4+ T Cells: CD4$^+$ T cells are a type of white blood cells that are vital to human immune responses as they coordinate the activity of other T-cells subsets, B-cells and innate immune responses. CD4$^+$ T cells have specific membrane receptors; after they recognize pathogen agents, bound to macrophages, dendritic cells or B cells, they stimulate the activity, differentiation and expansion of other immune cells, through the production and release of chemical compounds [110] [138] [140] [141].

Reverse Transcriptase (RT) – Enzyme encoded in retroviruses that catalyzes the transcription of the retrovirus' RNA into deoxyribonucleic acid (DNA). This is the reverse process of what occurs in cellular transcription, in which DNA is transcribed into RNA [142].

C.2.1.2 Content Review

Immunity can be defined as our body's way to protect us from infections and diseases. When our body is infected with pathogen agents, such as viruses and bacteria, the immune system fights those organisms and substances [110] [143]. As a consequence, the following time our body meets the same organism, we will be immune to that infection, which means that we will be less likely to get that disease or, if we do, it will be less intense [144].

CD4$^+$ T cells, also known as T-helper cells, are possibly the most important cells in adaptive immunity, once they are required for all immune responses [145]. This type of white blood cells plays a major role in protecting our body, by sending signals to activate our body's immune system when invaders are detected, controlling other T-cell subsets, B-cells and innate immune response [141] [146]. Consequently, our CD4$^+$ T cells count – number of CD4$^+$ T cells per cubic millimeter of blood – provides an indication of the health of our immune system [147] [148]. A normal CD4+ T cells count range from 500 to 1600 cells per cubic millimeter of blood [146].

HIV attacks the immune system, especially the CD4+ T cells. AIDS is the final stage of HIV infection, when the immune system becomes badly vulnerable. When the number of CD4+ T cells drops below 200 cells per cubic millimeter of blood, a person is considered to have AIDS [149]. There is still no definitive cure for HIV, but there are ways to control it, such as antiretroviral therapy [149].

Once HIV is inside the cells, the virus releases its RNA and RT turns the virus' RNA into DNA, becoming this DNA into the cell [150].

Fig. 3 | *HIV replication cycle. RT: reverse transcriptase; dsDNA: double strand DNA.*
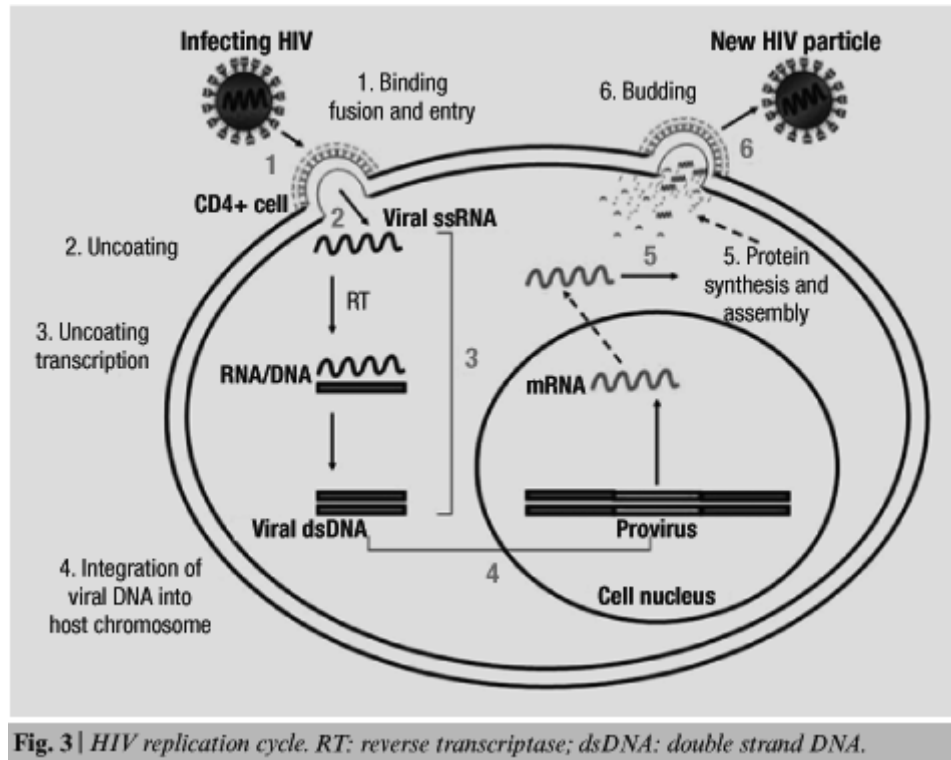
Figure C.2: HIV replication cycle. Taken from [151].

RT can be blocked by RT inhibitors [152]. Thus, drugs such as RT inhibitors have been used to control HIV, given that they can prevent the reverse transcription of the virus [153].

C.2.2 Computational Simulation

C.2.2.1 Algorithm Analysis

The following analysis is based on what is referred and reported in [109] and explored in [110]. The symbols used in the equations, their meaning and their value are in Table 1, which was transcribed from [109].

Table C.2: List of parameters used in the simulation of [109]. Transcribed from [109].

Parameter	Definition	Value
s	Inflow rate of CD4$^+$ T cells	10 mm^{-3} days^{-1}
k	Interaction-infection rate of CD4$^+$ T cells	0.000024 mm^3 days^{-1}
μ	CD4$^+$ T cells natural death	0.01 days^{-1}
η	Effectiveness of reverse transcriptase inhibitor	0.6
α	Transition rate from pre-RT infected CD4$^+$ T cells class to productively infected class (post-RT)	0.4 days^{-1}
b	Reverting rate of infected cells to uninfected class due to non-completion of reverse transcriptase	0.05 days^{-1}
μ_1	Death rate of infected cells	0.015 days^{-1}
δ	Death rate of actively infected cells	0.26 days^{-1}
N	Total number of viral particles produced by an infected cell	1000
c	Clearance rate of virus	2.4 days^{-1}

This mathematical model corresponds to the dynamics of HIV on the effect of RT inhibitor. The equations to be simulated are [109]:

$$\frac{dT}{dt} = s - kVT - \mu T + (\eta\alpha + b)T_1^* \quad (\mathbf{1})$$

$$\frac{dT_1^*}{dt} = kVT - (\mu_1 + \alpha + b)T_1^* \quad (\mathbf{2})$$

$$\frac{dT^*}{dt} = (1 - \eta)\alpha T_1^* - \delta T^* \quad (\mathbf{3})$$

$$\frac{dV}{dt} = N\delta T^* - cV \quad (\mathbf{4})$$

There are three types of CD4+ T-cells populations: Equation 1 represents the susceptive CD4+ T-cells; Equation 2 represents the infected CD4+ T-cells, before reverse transcriptase – pre-RT cells; Equation 3 represents the infected CD4+ T-cells, after reverse transcriptase – post-RT cells, and that are able to produce the virus; and Equation 4 represents the virus density [109] [110].

The initial conditions presented in the scientific paper for the mathematical model, and used in the simulation, are: $T(0) = 300$ mm^{-3}, $T_1^*(0) = 10$ mm^{-3}, $T^*(0) = 10$ mm^{-3} and $V(0) = 10$ mm^{-3}. Some of the constants can be changed in the simulation, according to what was performed in the article.

C.2.2.2 Computational Simulation

A computational simulation of the mathematical model presented in [109] was simulated, according to the previously approached conditions.

C.2.2.3 Results Interpretation

The graphics obtained are identical to those presented in [109].

Through the simulation, we see that the greater is the effectiveness of RT inhibitor (η), more pre-RT infected cells become uninfected and less pre-RT cells become post-RT cells. Consequently, the greater η is, the more effective is the treatment [109] [110].

The lower is the transition rate between pre-RT and post-RT CD4$^+$ T cells (α), less pre-RT cells become post-RT cells. Consequently, the lower α is, the more effective is the treatment [109] [110].

When the rate of infected to uninfected CD4+ T-cells due to non-completion of the reverse transcriptase (b) is zero, no cell is converted from infected to uninfected. However, the greater b is, more infected cells become uninfected. Consequently, the greater b is, the more effective is the treatment [109] [110].

C.3 Analysis of "A Remote Lab to Simulate the Physiological Process of Ingestion and Excretion of a Drug" [7]

C.3.1 Theoretical Approach

C.3.1.1 Literature Review

The scientific paper focus on the explanation of a remote experimental system presented in the Laboratory of Industrial Informatics and Systems of the University of Coimbra, constituted by the Amira's DTS200 three-tank system [154].

The simulation consists of a fluidic system and the liquid (supposed drug) that flows within the device is water. The need for three interconnected tanks comes from the fact that each of them mimics one anatomical structure, in the following order: intestines (tank 1), bloodstream (tank 2) and bladder (tank 3). The links between the tanks represent the interactions between the organs (including the kidneys, which are considered as transition elements). Furthermore, the input of the system is the drug intake that flows to tank 1, and its concentration in each tank is then variable through time, depending on different conditions that may be defined by the user [7] [155] [156].

Figure 1, taken from [7], is a scheme of the division of the three-tank system.
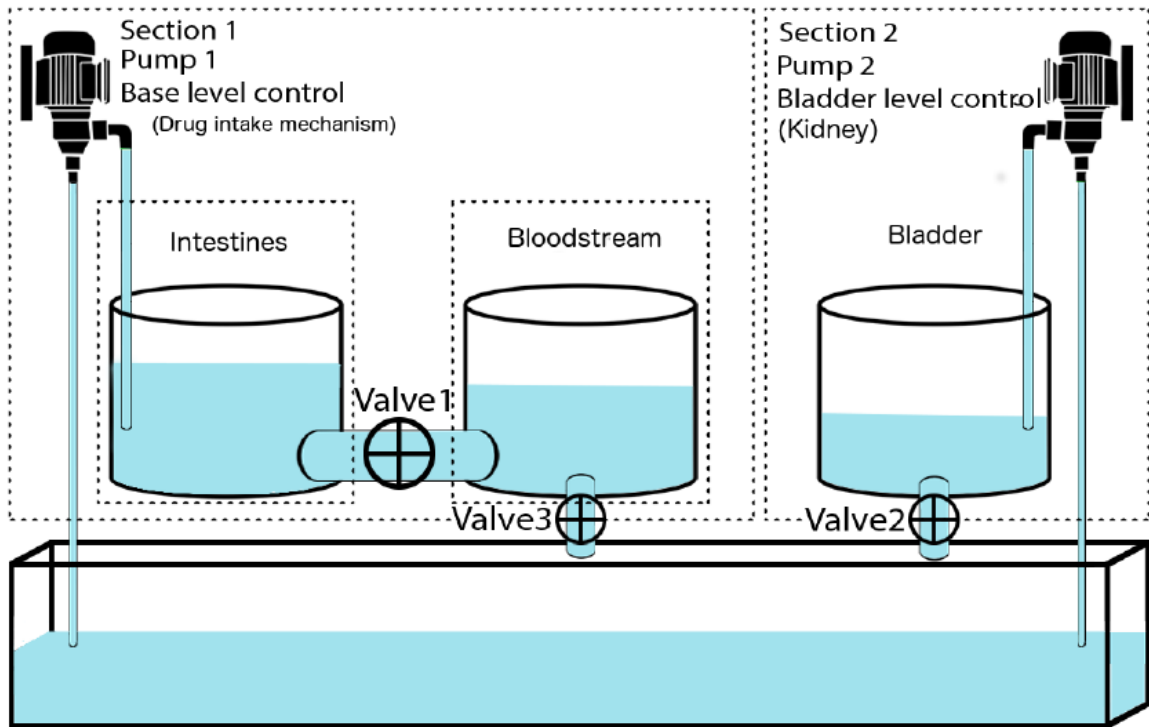
Figure C.3: Scheme for the division of the three-tank system. Taken from [7].

C.3.2 Experimental Procedure

The remote laboratory, regarding the three-tank system located in the Laboratory of Industrial Informatics and Systems of the University of Coimbra that simulates the physiological process of ingestion and excretion of a drug, was shared in the platform.

C.4 Analysis of "The Role of Osteocytes in Targeted Bone Remodeling: A Mathematical Model"

C.4.1 Theoretical Approach

C.4.1.1 Glossary

Osteocytes: Most abundant bone cells, inserted in the bone [157]. They produce type I collagen and other substances to form the extracellular matrix [158].

Pre-Osteoblasts: Mesenchymal cells that develop into osteoblasts [159]. They secrete osteoid, an organic non-mineralized part of the bone matrix that is produced before the maturation of the bone [160].

Osteoblasts: Large bone cells, found in the surface of bones, responsible for the synthesis and mineralization of bone formation and bone remodeling. They can differentiate into osteocytes [158] [161].

Osteoclasts: Large multinucleated bone cells, descendent from stem cells, responsible for the bone resorption. They occupy small depressions on the surface of the bone [158] [162].

Bone Remodeling: Regulated process of resorption by osteoclasts followed by replacement of new bone by osteoblasts [163] [164].

Bone Resorption: Stage of the bone remodeling process where the old bone is broken down and absorbed [165].

Sclerostin: Formed primarily by osteocytes, it inhibits the bone formation and stimulates apoptosis of osteoblasts [166].

Receptor Activator of Nuclear Factor κ-B Ligand (RANKL): It binds to the Receptor Activator of Nuclear Factor κ-B (RANK) on osteoclast precursors and leads to the maturation of osteoclasts. It is secreted by osteoblasts [167].

Osteoprotegerin (OPG): Receptor secreted by osteoblasts and sequesters RANKL, inhibiting osteoclast [167]. It is produced by differentiated osteoblastic cells [111].

Wnt/β-catenin pathway: A signaling pathway that stimulates pre-osteoblasts' replication and osteoblastogenesis and inhibits osteocytes and osteoblasts' apoptosis [168].

C.4.1.2 Content Review

Bone remodeling, a process that undergoes continuously through life, involves the removal of old bone by osteoclasts followed by the formation of bone matrix through the osteoblasts [164] [169] [170]. Thus, it can be defined as an active process that balances the bone resorption and the bone formation [167].

Bone resorption is assured by active osteoclasts, which are, in normal conditions, stimulated by RANKL. On the other hand, bone formation is achieved by inhibiting osteoclasts, through OPG, and stimulating osteoblasts [167].
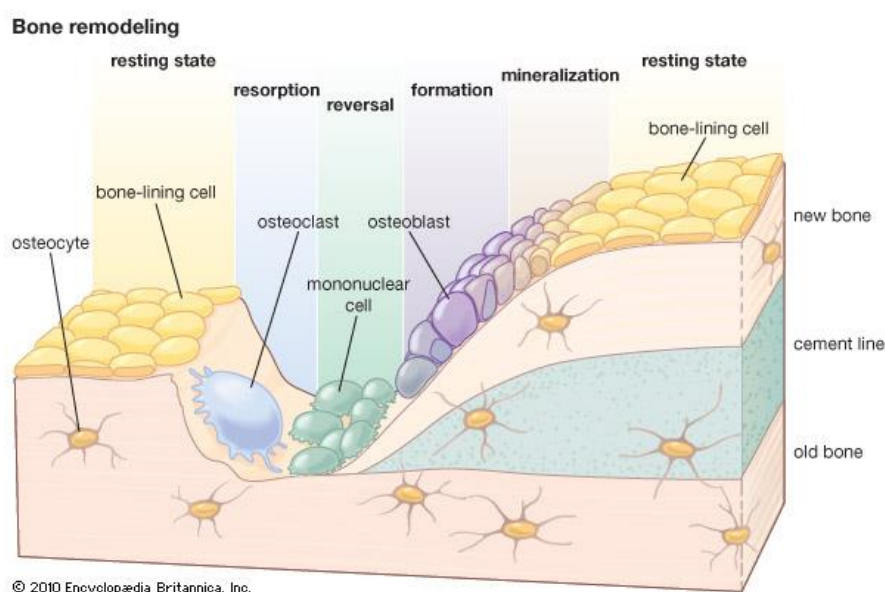
Figure C.4: Bone remodeling. Taken from [170].

Until recently, not much attention was given to the role of osteocytes in bone remodeling. However, as discussed in [111], there is increasing evidence that it has a fundamental role secreting sclerostin and being also a source of RANKL [111].

It has been suggested that sclerostin is a major mediator in bone remodeling, through two opposite mechanisms: high sclerostin levels can lead to an antagonization of Wnt/β-catenin signaling pathway and direct to bone resorption; low sclerostin levels can activate Wnt/β-catenin signaling pathway and lead to bone formation [171].

C.4.1.3 Multimedia Resources

It was inserted in the platform a video that explains the process of bone remodeling. The video is hosted on YouTube and was created and shared by Amgen [112].

C.4.2 Computational Simulation

C.4.2.1 Algorithm Analysis

The following analysis is based on what is referred and reported in [111]. The symbols used in the equations, their definition and their values are in Table 1, which were transcribed from [111]. We will focus our analysis, and following simulation, on the baseline case presented in [111].

Table C.3. The parameters used in the equations and their definition and values [111]. Transcribed from [111]

Parameter	Definition	Value
α_1	Osteoblast embedding rate	0.5 per day
α_2	Differentiation rate of pre-osteoblast precursors	0.1 per day
α_3	Pre-osteoblasts proliferation rate	0.1 per day
β_1	Differentiation rate of pre-osteoblasts	0.1 per day
δ	Apoptosis of pre-osteoblasts	0.1 per day
β_2	Osteoblast apoptosis	0.1 per day
α_4	Differentiation rate of osteoclasts precursors	0.1 per day
K_S	Critical value of osteocyte population	200 cells
k_1	Bone resorption rate	0.7 % volume per day
k_2	Bone formation rate	0.015445 % volume per day
g_{31}	Effectiveness of osteoblast autocrine signaling	1 (dimensionless)
g_{21}	Effectiveness of osteocyte paracrine signaling of osteoblasts	2 (dimensionless)
g_{22}	Effectiveness of sclerostin regulation of osteoblastogenesis	1 (dimensionless)
g_{32}	Effectiveness of pre-osteoblasts autocrine signaling	1 (dimensionless)
g_{41}	Effectiveness of osteocyte paracrine signaling of osteoclasts	1 (dimensionless)
g_{42}	Effectiveness of sclerostin regulation of osteoclastogenesis	1 (dimensionless)
g_{43}	Effectiveness of osteoblast paracrine signaling of osteoclasts	-1 (dimensionless)
g_{44}	Effectiveness of sclerostin regulation of osteoclastogenesis	1 (dimensionless)
f_{12}	Effectiveness of pre-osteoblast paracrine signaling of osteoblasts	1 (dimensionless)
f_{14}	Effectiveness of osteoclasts paracrine signaling of osteoblasts	1 (dimensionless)
f_{23}	Effectiveness of osteoblasts autocrine signaling for apoptosis	1 (dimensionless)
f_{34}	Effectiveness of osteoclasts autocrine signaling for apoptosis	1 (dimensionless)

Jason M. Graham, Bruce P. Ayati, Sarah A. Holstein and James A. Martin established a cell population model for osteocyte-induced targeted bone remodeling. This resides in an osteocyte, a pre-osteoblast, an osteoblast and an osteoclast cell population, the interactions of these cells and the relation of the autocrine and paracrine signaling among these cells [111].

$$\frac{dS}{dt} = \alpha_1 B^{g_{31}} \left(1 - \frac{S}{K_S}\right)_+ \quad (\mathbf{1})$$

$$\frac{dP}{dt} = \alpha_2 S^{g_{21}} \left(1 - \frac{S}{K_S}\right)_+^{g_{22}} + \alpha_3 P^{g_{32}} \left(1 - \frac{S}{K_S}\right)_+ - \beta_1 P^{f_{12}} C^{f_{14}} - \delta P \quad (\mathbf{2})$$

$$\frac{dB}{dt} = \beta_1 P^{f_{12}} C^{f_{14}} - \beta_2 B^{f_{23}} - \alpha_1 B^{g_{31}} \left(1 - \frac{S}{K_S}\right)_+ \quad (\mathbf{3})$$

$$\frac{dC}{dt} = \alpha_4 S^{g_{41}} P^{g_{42}} (\varepsilon + B)^{g_{43}} \left(1 - \frac{S}{K_S}\right)_+^{g_{44}} - \beta_3 C^{f_{34}} \quad (\mathbf{4})$$

$$\frac{dz}{dt} = -k_1 C + k_2 B \quad (\mathbf{5})$$

Equation 1, Equation 2, Equation 3 and Equation 4 describe the dynamics, respectively, of the osteocyte, pre-osteoblast, osteoblast and osteoclast cell population at a time t. Equation 5 defines the bone mass at a given time t [111].

The initial conditions presented in the scientific paper for the mathematical model, and used in the simulation, are: $S(0) = K_S - \rho$, where $\rho > 0$ is a constant that denotes the osteocytes apoptosis, $P(0) = B(0) = C(0)$ and $z(0) = 200$ [111].

C.4.2.2 Computational Simulation

A computational simulation of the baseline case, approached in [111], was implemented and demonstrated in the platform, according to the parameters previously mentioned.

C.4.2.3 Results Interpretation

The simulations presented in [111] were replicated for the baseline case and the graphics obtained are identical to those displayed in the scientific paper.

The graphics show the simulation results for bone cell populations and the dynamics of bone volume during a complete bone remodeling that occurs over a period of one hundred days, in which the bone resorption is equal to the bone formation [111].

Graphic 1 shows the dynamics of all cell populations. The level of osteocytes is initially low, representing the cells' apoptosis and the subsequent decreasing in local sclerostin levels, which leads to the proliferation and differentiation of pre-osteoblasts. The differentiation of these pre-osteoblasts leads to the increasing of the number of osteoblasts. This goes along with the differentiation of osteoclast precursors to mature osteoclasts. Once the bone remodeling finishes, all the cell population go back to their initial values, except for osteocytes, which remain in their steady state value [111].

Graphic 2 represents the dynamics of bone volume, illustrating the resorption and formation of bone. As it can be seen, and because of the aforementioned, the old bone resorption is equal to the new bone formation, at the end of the process [111].

C.4.3 Online Experiment

An animation, showing the process of bone remodeling, was inserted in the platform as an online experiment. It was created by Susan Ott and can be found in [113].

C.5 Analysis of "Modeling the Effects of Multiple Myeloma on Kidney Function"

C.5.1 Theoretical Approach

C.5.1.1 Glossary

Multiple Myeloma: Cancer formed in plasma cells, a type of white blood cells [172] [173].

Monoclonal Free Light Chains: The earliest biomarkers in malignant plasma cell-proliferative disorders [174] [175].

Tubulointerstitial fibrosis: Process initiated by the interaction of free light chains (FLCs) and tubule cells, causing inflammation on the kidneys [114]. Regular end-stage for renal diseases [176].

Fibroblasts: Active cells of connective tissue, responsible for synthetizing collagen and extracellular matrix [177] [178].

Proteinuria: High concentrations of protein in the urine [179]. The overflow of proteinuria can be related with an enlarged production of light chains in multiple myeloma [180].

C.5.1.2 Content Review

Multiple myeloma is a form of cancer that affects the plasma cells, a type of white blood cells located in bone marrow. When cells become malignant, they overproduce a protein that grows and takes over the bone marrow, blocking the action of healthy cells [181].
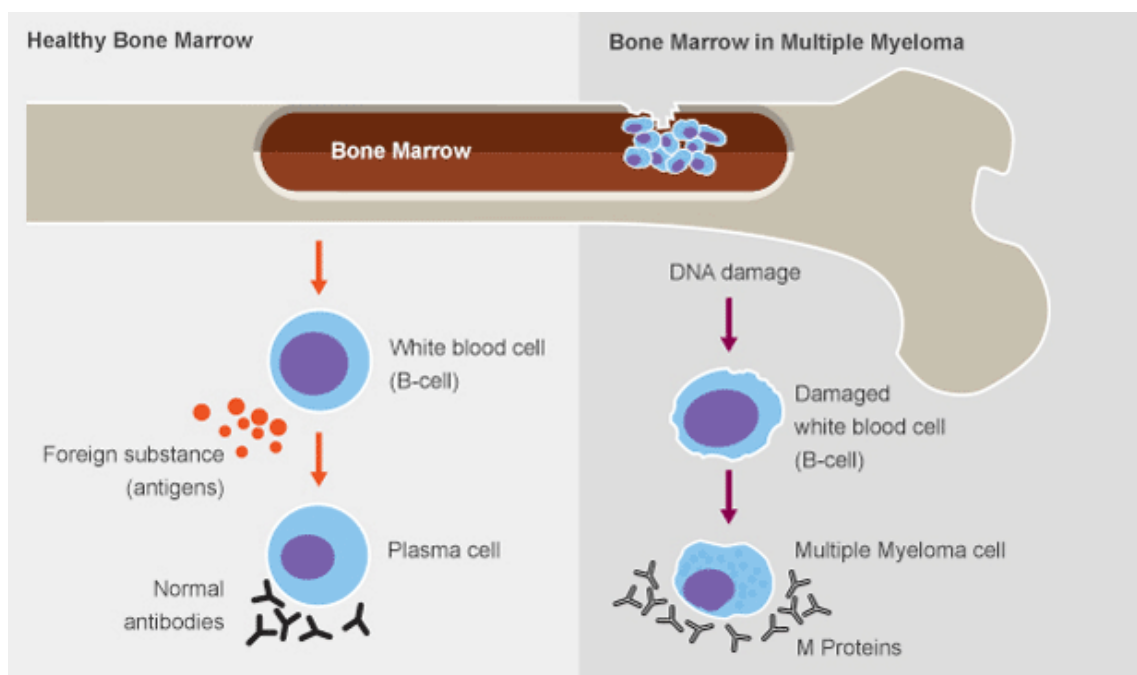
Figure C.5: Healthy bone marrow and bone marrow in multiple myeloma. Taken from [182].

Although it has been given more attention to how multiple myeloma affects the bone, it is also important to examine how it affects the kidneys [114]. Fast evolution of tumor cells inhibits the bone rebuilding and they begin to degenerate, which can cause proteinuria, once it is released high amounts of calcium and proteins to the bloodstream, instigating kidneys to overwork and consequent failure [181].

The protein that leads to this damage is called monoclonal immunoglobulin (Ig) light chain (also named M protein). It is a subunit of the antibodies, which are produced to combat infections. Tumor plasma cells overproduce this protein, leading to the most common cause of severe renal failure, tubulointerstitial pathology, resulting from the high concentration of Ig light chains. However, not all the FLCs are toxic to the kidneys, appearing this to be related to its structure or protein folder [114].

FLCs can be noxious to proximal tube cells (PTCs) by activating tubulointerstitial fibrosis, an inflammation that causes the excess accumulation of extracellular matrix, which may be replaced for scar tissue – which is largely irreversible. This process leads to the damage of proximal tubule cells and end stage renal disease [114]

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C.5.1.3 Multimedia Resources

A video that describes multiple myeloma was embed in the platform. The video is hosted on YouTube and was created and shared by Armando Hasudungan [115].

C.5.2 Computational Simulation

C.5.2.1 Algorithm Analysis

The following analysis is based on what is referred and reported in [114]. The following table, transcribed from [114], shows the list of parameters used in the simulation, as well as its meanings and values.

Table C.4: List of parameters used in the simulation [114]. Transcribed from [114].

Parameter	Definition	Value
γ_L	FLC growth constant	0.005 cells^{-1} days^{-1}
γ_T	Tumor growth constant	0.05 days^{-1}
γ_F	Fibroblast growth constant	0.004 dL/(mg days)
β_P	PTC proliferation constant	0.004 days^{-1}
L_S	FLC saturation constant	400 mg/dL
L_T	Maximum tumor size	100 (maximum percentage)
μ_P	PTC natural apoptosis rate	0.0035 days^{-1}
μ_L	Natural FLC apoptosis rate	0.0005 days^{-1}
μ_F	Natural fibroblast apoptosis rate	0.0004 days^{-1}
g_1	Strength of inhibited FLC on PTC growth	1 (dimensionless)
g_2	Strength of PTC on its own growth	1 (dimensionless)
g_3	Strength of FLCs on PTC growth	0.3 (dimensionless)
g_4	Strength of PTC on its own death	0.2 (dimensionless)
$g5$	Strength of tumor on FLC growth	0.5 (dimensionless)
g_6	Strength of FLC on its own growth	0.5 (dimensionless)

The authors chose to use Gompertz model to model the evolution of multiple myeloma [114].

$$\frac{dP}{dt} = \beta_P \left(1 - \frac{L}{L_S}\right)_+^{g_1} P^{g_2} - \mu_P P - \gamma_F L^{g_3} P^{g_4} \quad (1)$$

$$\frac{dL}{dt} = \gamma_L T^{g_5} L^{g_6} - \mu_L L \quad (2)$$

$$\frac{dT}{dt} = \gamma_T T \log\left(\frac{L_T}{T}\right) \quad (3)$$

$$\frac{dF}{dt} = \gamma_F L^{g_3} P^{g_4} - \mu_F F \quad (4)$$

Equation 1, Equation 2, Equation 3 and Equation 4 describe, respectively, the population of proximal tubule cells, the amount of free light chains, the tumor density and the populations of fibroblasts, at time *t* [114].

The initial conditions presented in the scientific paper for the mathematical model, and used in the simulation, are: P(0) = 400, L(0) = 90, T(0) = 1 and F(0) = 10 [114].

C.5.2.2 Computational Simulation

A computational simulation was performed and displayed in the platform, taking into account the previously discussed equations.

C.5.2.3 Results Interpretation

In this simulation, the forms of our graphics follow the ones showed in the paper [114]. However, there is a difference in the evolution through time of the graphics, since, in our simulation, a little greater time interval is needed to reach the same values as in [114]. The behavior of the graphics is consistent to what was expected. As the density of the tumor cells increases, the FLCs amount and fibroblasts population rises and the population of proximal tubule cells falls [114].

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