PROPOSING 3D SIMULATION OF IMMUNE SYSTEM CELL MICRO-LEVEL RESPONSES IN VIRTUAL AND MIXED REALITY ENVIRONMENTS: A COMPARATIVE ANALYSIS

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ABSTRACT

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When working in any informatics field, it is necessary to understand the core mechanisms of the domain. This is also true in the field of bioinformatics. At least a basic understanding of the biological subject to be studied is required. However, understanding biological phenomena is not always easy. Sometimes the biological complexity of the events and the difficulty of visualizing the events cause difficulties in understanding the subject. This is particularly important in the field of education. For educational purposes, various biological events are described in writing or illustrated. In some cases, newer technologies such as Virtual (VR) and Mixed Reality (MR) are used to make training more effective. In this study, an interactive simulation of the response of white blood cells, one of the elements of the body's defense system, against bacteria in the blood vessel was prepared in a 3D environment. This interactive demonstration was evaluated and evaluated by the participants. The application was evaluated in PC, VR, and MR environments and participants were asked to fill out various questionnaires. With the questions asked, answers were sought to the questions of whether the participants found such an application effective and which platform they found most effective for such an application. As a result of the studies conducted on 27 volunteers, it was determined that the users found such an interactive learning process effective, and they preferred the VR platform the most for such content.

Keywords: Simulation, Virtual Reality, Multimedia Applications, Immune System, Comparative Analysis

ÖZ

BAĞIŞIKLIK SİSTEMİ HÜCRELERİNİN MİKRO SEVİYEDEKİ TEPKİLERİNİN SANAL VE KARMA GERÇEKLİK ORTAMLARINDA 3 BOYUTLU SİMÜLASYONU: KARŞILAŞTIRMALI BİR ANALİZ

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Herhangi bir bilişim alanında çalışırken, alanın temel mekanizmalarını anlamak büyük önem taşımaktadır. Bu, biyoinformatik alanında da geçerlidir. Çalışılacak biyolojik konu üzerinde rahat çalışılabilmesi için çalışılacak konunun temel bir düzeyde anlaşılmış olması gerekmektedir. Ancak, biyolojik olayları anlamak her zaman kolay olmamaktadır. Bazen olayların biyolojik karmaşıklığı ve olayların görselleştirilmesinin zor olması konunun anlaşılmasında zorluklara neden olmaktadır. Bu durum özellikle eğitim alanında önem taşımaktadır. Eğitim amacıyla çeşitli biyolojik olaylar yazılı olarak anlatılmakta veya bazı durumlarda resimli olarak tasvir edilmektedir. Bazı durumlarda ise eğitimi daha etkili hale getirmek için Sanal Gerçeklik (SG) ve Karma Gerçeklik (KG) gibi daha yeni teknolojiler kullanılmaktadır. Bu çalışmada vücudun savunma sistemi unsurlarından biri olan beyaz kan hücrelerinin kan damarındaki bakterilere karşı verdikleri tepkinin etkileşimli simülasyonu 3 boyutlu ortamda hazırlanmıştır. Beyaz kan hücrelerin tepkilerine dair etkileşimli bu gösterim, katılımcılar tarafından test edilmiş ve değerlendirilmiştir. Uygulama bilgisayar, SG ve KG ortamlarında test edilmiş ve katılımcılardan çeşitli anketleri doldurulması istenmiştir. Sorulan sorular ile katılımcıların bu tarz bir uygulamayı anlamlı bulup bulmadığı ve bu tarz bir uygulama için hangi platformu en etkili buldukları sorularına cevap aranmıştır. Yirmi yedi gönüllü üzerinde yapılan çalışmalar sonucunda, kullanıcıların böyle bir etkileşimli öğrenme sürecini etkili buldukları ve bu tür içerikler için en çok Sanal Gerçeklik platformunu tercih ettikleri belirlenmiştir.

Anahtar Sözcükler: Simülasyon, Sanal Gerçeklik, Çokluortam Uygulamaları, Bağışıklık Sistemi, Karşılaştırmalı Analiz

To My Family

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

WBC	White Blood Cell
MR	Mixed Reality
VR	Virtual Reality
PC	Personal Computer (Flat display)
TAM	Technology Acceptance Model
PQ	Presence Questionnaire
ITQ	Immersive Tendency Questionnaire
SUS	System Usability Scale

CHAPTER 1

INTRODUCTION

1.1 Definition of the Research Problem

In any field, a solid grasp of the foundational concepts is crucial for successful work. This is particularly prominent in the field of informatics, where the analysis and interpretation of data necessitate a thorough understanding of the underlying processes. Without comprehensive knowledge of the process under consideration and the ability to evaluate known values within this context, there is the risk of incorrect evaluation. This also applies to the field of bioinformatics. It is necessary to understand the biological process under consideration and to be able to make sense of the obtained values. However, sometimes it is not easy to understand biological processes. Some biological processes contain overly complex structures and are almost impossible to examine visually. In this case, delays in understanding and misconceptions regarding these biological phenomena arise. This makes it difficult to work in this field and this difficulty prolongs the working processes. Not having visualizations and resources on a topic may cause difficulties in comprehending the concepts of the topic at hand. Especially with a focus on training and education, biological processes are sometimes explained by narrowing the focus. In this way, it is aimed to make the understanding of the biological process easier. Sometimes, subject comprehension can be made more efficient through visualization. These techniques allow the users to gain a better understanding of the complex interactions of biological phenomena and to explore how these interactions affect system functions. This is particularly important in training and education, where visualization can facilitate better comprehension of complex phenomena.

Different technologies are used in this direction, and educators attempt to use the most effective methods for the users. Different studies have been done on the visualization of biological processes for this purpose[1], and there is evidence showing that these studies have positive effects on users. Technologies such as Virtual Reality (VR), Mixed Reality (MR), and Personal Computers (PC) which directly interact with the user and where the users can directly observe the results of their actions in the environment, provide a new experience to the users in this regard. With these technologies, studies have been conducted to show and simulate various biological phenomena. Our study aims to interactively simulate the defense mechanism of phagocytes, which are one of the important aspects of the body's defense against bacteria and other pathogens.

The main question of the study is "Can a biological process be made easier for users to understand by providing the users with different interaction methods on different platforms? If it can be facilitated, which platform would be the best platform for this kind of experience?" has been in the form.

By addressing these research questions, this study aims to contribute to the understanding of how different interaction methods and platforms can facilitate the comprehension of biological processes, ultimately helping researchers in developing more effective and engaging learning experiences in the field of biology and bioinformatics.

1.2 Aim of the Research

The main purpose of the study is for users to experience the defense of white blood cells, which is one of the body's defense mechanisms, in an interactive simulation environment. In this way, it was desired to evaluate what the users thought about the subject and whether the interactive simulation was effective. The aim is to evaluate users' perceptions and the effectiveness of the interactive simulation. At the same time, users will experience the interactions on three different platforms, VR, MR, and PC, and it will be decided which platform is more effective for such an interactive simulation. Thus, it will be possible to reach conclusions about whether the users find such an interactive experience effective.

The objectives of this thesis can be listed under the headings as follows:

- To provide users with a simulation environment where they can interactively experience the defense of white blood cells, one of the body's immune mechanisms, in the vein.

[1] Medialab. (n.d.). Simulator: White Blood Cell. Retrieved from https://www.medialab.com/case-simulator-wbc.

- To enable users to experience interactive simulation on PC, VR, and MR. Each platform offers unique capabilities and interaction methods.

- Determining whether the application is effective or not for users in terms of learning white blood cells' behaviors in the immune system.

- Investigate the impact of platform preferences on the outcomes of the interactive simulation. By comparing the user feedback and performance across the different platforms, we aim to identify the platform that provides the most immersive and effective learning experience for understanding the defense mechanism of white blood cells.

By trying to achieve these objectives, this research aims to enhance our understanding of the effectiveness of interactive simulations in the context of immune system defense mechanisms. The findings will contribute to the field of educational simulations.

1.3 Research Method

In this study, we simulated the dynamics and behavior of white blood cells in a three-dimensional (3D) environment to provide users with an effective understanding of their dynamics and role in the immune system. Our interactive simulation allows users to observe the basics of white blood cell defense in a simulated blood vessel (capillary), interact with the system, and directly observe the effects of various factors. The simulation was presented on three different platforms: Personal Computer (PC), Virtual Reality (VR), and Mixed Reality (MR). By offering the simulation on multiple platforms, we aimed to determine which platform would be more effective and usable for users in such a study. With different platforms, we aimed to make the subject more clear and more permanent for users.

For this purpose, a 3D capillary environment was created. To create the 3D capillary environment, we utilized the Unity 3D engine[2]. We implemented a customized version of Unity's experimental Spline package to enable the simulation of unidirectional laminar blood flow within the vein. The movement of bacteria and white blood cells in the simulation follows the flow in the vein, but white blood cells also have the ability to target and migrate toward bacteria in an attempt to destroy them. This behavior is developed using a density factor, which determines the movement of white blood cells when they encounter a bacterial area. If the density value is higher than a certain limit, the white blood cell starts migrating toward the source to eliminate the bacteria.

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[2] Unity Technologies. (n.d.). Unity - Game Development Platform. Retrieved from https://unity.com/.

Furthermore, users can create different scenarios within the simulation and observe the outcomes of these trials. With these interactions, they can establish a persistent bacterial field and simulate a basic disease scenario, observing that white blood cells are vulnerable to new threats in a situation where they are on active defense. Users can also introduce additional bacteria into the environment, allowing them to observe changes and interactions in real-time. They can interact with the world and see the results of these interactions in real-time. These interactive features improve user engagement and provide a more immersive learning experience.

To gather data and assess the user experience, we conducted a survey with 27 volunteers who interacted with the simulation. Participants filled out several questionnaires, including the Technology Acceptance Model, the System Usability Scale, Immersive Tendency, and the Presence Questionnaires. These questionnaires allowed us to measure users' preferences for such an application, their criteria, and considerations.

The results of the survey showed that users found the application useful on all platforms, and their priority platform preference was VR. The positive feedback suggests that VR and MR technology holds significant potential for bioinformatics training and biological visualization. Overall, our study demonstrates the effectiveness of VR and MR technologies in enhancing the understanding and visualization of biological processes.

By employing this research method, we aimed to provide valuable insights into the interactive simulation of white blood cell activity and evaluate the usability and effectiveness of different platforms in delivering such interactive simulations. The results from this study contribute to the field of bioinformatics training and highlight the potential of VR and MR technologies in visualization experiences.

1.4 Thesis Outline

The rest of the thesis is outlined as follows: Chapter 2 presents the literature review of the importance of visualization of biological processes, existing biological simulation and research, usage of interactive platforms like VR and MR in training and their possibilities, and research on evaluations of interactive applications and simulations. In Chapter 3, the materials and methods that have been used to develop the simulation are introduced. Chapter 4 presents the results we obtained from the questionnaires filled out by participants who interacted with the simulation.; Chapter 5 presents a detailed discussion and interpretation of the questionnaire results. Chapter 6 presents the summary of the key findings of the study and presents the conclusions drawn from the research. It is also presenting possible improvements for future works.

CHAPTER 2

LITERATURE REVIEW

2.1 Visualization in Training

The basic building blocks are essential for learning in almost any field, and this is even more prominent in the field of informatics. Because the data at hand must be analyzed and interpreted, while doing this, it is necessary to have knowledge about the process under consideration and to evaluate the proposed solution, procedure, or outcome from this perspective. Otherwise, it is possible to evaluate the values incorrectly and reach a wrong conclusion. This also applies to the field of bioinformatics, and it is necessary to understand the biological process under consideration and to make sense of the acquired values. However, sometimes it takes effort to understand biological processes as some biological processes contain overly complex structures and are almost impossible to examine visually. In this case, delays in understanding and misconceptions regarding these biological phenomena may arise.

With a focus on training, biological processes can sometimes be explained by narrowing down the focus, or subject comprehension can be made more efficient by visualization. Pigozzo et al. [2] made computational modeling for the innate immune system and stated that this kind of computational model will contribute to a better understanding of the relationship between complex phenomena and immune response and this kind of computational model will support the development of new research.

The visualization and modeling carried out during the Covid-19 period helped research on this topic to gain momentum. Harb et al. [3] made a three-dimensional model for the viruses for helping researchers and stated that in vitro culture model systems, such as three-dimensional (3D) cultures, are emerging as a desirable approach to better understand the virus-host interactions and to identify novel therapeutic agents. Also, they mentioned that the need for new tools to study the pathogenesis of respiratory viruses as well as to test for new antiviral drugs and vaccines is urgent.

Modeling the structures of proteins in 3D and experiencing them interactively has accelerated the work in this field. In this way, it has been possible to understand protein structures and to develop structures suitable for the shapes of proteins. Cassidy et al.

[8] developed VR-based web applications for molecule-based protein structure visualizations. Also, they stated that properly understanding the three-dimensional structures of these machines—as well as the small molecules that interact with them—can advance scientific fields ranging from basic molecular biology to drug discovery. Virtual reality (VR) is a powerful tool for studying protein structures. Also, molecular structures within 3D environments give useful biological context and allow users to situate themselves in 3D space.

Different studies have been performed on the visualization of biological processes for this purpose, and there is evidence showing that these studies have positive effects on users [8].

2.2 Biological Simulations

Simulations are used to understand a biological phenomenon clearly and comfortably. In this respect, many subjects in biology have been subject to simulation and presented to users. In this way, users can know about the biological phenomenon by experiencing the environmental parameters and variables.

There are currently many different biological simulations that can be used for different purposes. In most of these simulations, users can set simulation parameters and get simulation outputs. These printouts are sometimes just text, and sometimes they can be in the form of various images. Some applications and simulations show the images of real experiments and studies for this purpose. However, many existing simulations remain at a high level and have a structure that can be used by people with knowledge in the field and can include steep learning processes. Therefore, it is not very suitable for the beginner level, it is difficult for people to understand at first sight. In addition, most of the existing simulations are static and do not contain real-time interaction and movement. This makes it very difficult for users to examine the cause-and-effect relationship in real-time. In addition to these, the existing biological simulations are mostly in 2D but simulations in 3D virtual environments are still a very new field and do not have a widespread prevalence. New studies and simulations are being developed in this regard and there is lots of research on these topics.

Andrews et al. [31] developed detailed simulations of cell biology. They developed algorithms to simulate the diffusion, membrane interactions, and reactions of individual molecules and implemented these in the Smoldyn[3] program. With this tool, they can make various biological simulations easily. It is aimed to use by researchers.

[3] Smoldyn. (n.d.). Home - Smoldyn. Retrieved from https://www.smoldyn.org/.

Ghaffarizadeh et al. [32] developed an open-source agent-based simulator called PhysiCell[4] and they stated that it provides the stage to the players for studying many interacting cells in dynamic tissue microenvironments. It can be simulating emergent tissue-scale effects of cell-scale hypotheses on several examples arising from cancer biology and synthetic multicellular systems bioengineering.

Such simulations and programs contribute to learning and research processes by facilitating studies and experiments in the digital environment. It can be used to perform an operation that is sometimes dangerous to do, and sometimes to have quick information and results about processes that take a very long time. In some cases, learning with methods such as simulation and interaction can be more effective and faster.

Macklin et al. [35] made research on tumors and emphasized that cancer should be investigated as an adaptive, multicellular system in a dynamic microenvironment. Computational modeling offers the potential to detangle this complex system. Such a platform should leverage high-throughput experimental data while using open data standards for reproducibility.

2.3 Virtual Reality and Mixed Reality Applications in Training

With the development of VR and MR technologies, the use of these technologies in the field of training is frequently encountered. VR and MR, which enable direct interaction with the users where the users can observe the results of their actions in the environment, provide a new experience to the users in this regard. For this reason, a lot of research has been done on this subject. Different technologies are used in this direction, and educators attempt to use the most effective methods for the users. There is lots of research on the effectiveness of this kind of technology.

Zhang et al. [5] developed a platform for virtual reality-assisted biological data integration and visualization that shows protein structure in 3D using a VR-based platform and they stated that this kind of application makes things obvious to the users and makes it easier to understand complex structures in biology.

There are some benefits and new opportunities in the training and education field with these recent technologies and there is much research on this topic. Bower et al. [7] stated that Augmented Reality has the potential to supplant the Internet in terms of size and application. This kind of technology and applications can engage thinking skills

[4] MathCancer. (n.d.). PhysiCell. GitHub Repository. Retrieved from https://github.com/MathCancer/PhysiCell.

and can be useful for mental exercise, overemphasis upon lower order thinking in the curriculum constrains the amount of time that can be dedicated to having students think critically and utilize knowledge in creative and meaningful ways. They stated that this kind of technology has new potential learning methods with new challenges in the education field and methodology.

Such technologies can be used anywhere, regardless of age and field. Lee et al. [18] stated that VR is especially useful for providing several opportunities: increasing student engagement; providing constructivist, authentic experiences to impact student identity; allowing for new perspective taking and empathy; and supporting creativity and the ability to visualize difficult models. Also, VR can offer the potential to expose students to environments and people that are normally inaccessible.

There is a concept called ‘Serious Games’ for training and educational purposes. The concept of serious games involves the use of games for purposes beyond entertainment. Serious games are designed with specific educational, training, informational, or persuasive objectives in mind. These games leverage the engaging and interactive nature of games to create immersive experiences that facilitate learning, skill development, behavior change, or problem-solving. Serious games offer a unique approach to engaging users in a meaningful and enjoyable way, making learning or other serious activities more engaging, interactive, and effective.

Roozeboom et al. [20] made a study about the effectiveness of serious games compared to traditional classroom instruction on learning features and learning outcomes. They made three empirical studies to test the learning outcome. They measured learning outcomes by self-report and knowledge tests. And they stated that their outcomes show that serious gaming is more effective on self-reported learning outcomes than traditional classroom instruction.

Murad et al. [21] performed a study about an application in virtual reality for educational purposes for students in the field of engineering. In this application, students will be able to perform experiments, attend online live 360° lectures, watch pre-recorded lectures, have a campus tour, and visit informative labs virtually. And they stated that this kind of application develops the way of learning in a way that helps students to practice dangerous experiments safely and deliver the information easily and it also supports gaining and learning the information in an interesting way. Also, the application can help the disabled to perform experiments easily.

2.4 Evaluating the Interactive Applications and Simulations

Designing and developing applications or tools requires rigorous assessments of their usability. They should be checked for if they can serve their purposes or not. Many studies and research methods have been developed for this purpose.

Evaluating interactive applications and simulations is essential for improving the user experience for almost all applications. With feedback gathering and systematic methods, developers can identify areas for improvement. This direct feedback from users helps address usability issues, interface design flaws, and user preferences, leading to iterative improvements that enhance user engagement and satisfaction. By measuring learning outcomes, and skill development, evaluations determine the impact of these applications on users' understanding.

Petri et al. [36] made research on how to evaluate educational games' effectiveness. They performed a systematic literature review of a sample of 3617 articles from which 12 relevant articles have been identified, describing 117 studies on the evaluation of games for computing education. And many of them used questionnaires as the main evaluation method. And they state that they can confirm that most evaluations use a simple research design in which, typically, the game is used, and afterward subjective feedback is collected via questionnaires from the learners.

2.4.1 Technology Acceptance Model Questionnaire

It is important and necessary to test the acceptability of the studies and developments in the technological field by the users. There are different studies and research on this subject. Davis et al. [14] suggested a model named the Technology Acceptance Model (TAM), which is a questionnaire focused on the perceived usefulness of the users and perceived ease of use. Today TAM is widely used to evaluate the acceptance of users in lots of different fields.

The Technology Acceptance Model holds significant importance in understanding and evaluating the acceptance and adoption of new technologies and applications. This model helps predict and explain user acceptance of technology by examining factors such as perceived usefulness and perceived ease of use. It provides valuable feedback about users' attitudes and intentions toward adopting and using a particular technology. The TAM also guides technology design and development processes. By considering the factors that influence user acceptance, developers can develop technologies that meet users' needs and expectations. Incorporating TAM principles into the design and development process helps create user-friendly and effective technologies that are more likely to be accepted by users. The Technology Acceptance Model plays a crucial role in understanding and predicting user acceptance of technology. It guides technology design and helps identify areas for user experience improvement. By considering the TAM's factors, developers can create user-centric technologies that are more likely to be accepted, adopted, and embraced by users.

2.4.2 System Usability Scale Questionnaire

Usability is one of the most important aspects when it comes to the evaluation of any application or in this case interactive simulations. The users need to find applications that are assessed as usable to reach their purposes. For this thesis, the System Usability Scale (SUS), which was introduced by Brooke [15] was used to measure the usability of the project. Evaluation of usability has been tested with SUS in many different areas and systems, such as applications, games, and more.

The System Usability Scale (SUS) is a widely used tool for evaluating the usability of interactive systems and technologies. It consists of a questionnaire designed to measure users' subjective assessments of the usability of a system. The SUS provides valuable insights into the overall usability and user experience of a technology. One key importance of the SUS is its ability to provide a standardized and quantifiable measure of usability. By using a standardized questionnaire, the SUS allows for consistent and comparable usability evaluations across different systems and user groups. This standardization enables researchers and practitioners to collect data that can be analyzed and compared. The SUS also offers a practical approach to evaluating usability. It is a relatively simple and straightforward questionnaire that can be administered quickly to gather feedback from users. Also, the SUS can capture the user's perspective on usability. It focuses on users' subjective assessments of their experience with the system, considering factors such as ease of use, learnability, efficiency, and satisfaction. This user-centered approach provides valuable insights into the system's overall usability and user satisfaction. Overall, the System Usability Scale is an important tool for evaluating the usability of interactive systems. Its standardized approach, cost-effectiveness, ability to identify areas for improvement, and focus on the user perspective make it valuable for research.

2.4.3 Immersive Tendency Questionnaire

It is particularly important to understand how impressive a developed project or application is found by users. There are many studies and methods to do this. Immersiveness is critical, especially in studies conducted in digital environments. One of the most used immersiveness evaluations is Immersive Tendency Questionnaire from Jerome et al. [17]. This methodology is widely used in many different areas and research.

The Immersive Tendency Questionnaire is a tool used to measure an individual's tendency to engage and feel immersed in virtual and mixed-reality environments. It assesses subjective experiences of presence, immersion, and engagement within these immersive technologies. The questionnaire provides valuable insights into users' tendencies and preferences for immersive experiences. One key importance of the Immersive Tendency Questionnaire is its ability to capture individual differences in immersive tendencies. The immersion feeling for people can vary in virtual environments. By utilizing this questionnaire, researchers can identify individuals with higher immersive tendencies. This customization enhances the overall user experience and increases the potential for user immersiveness. The questionnaire also helps evaluate the effectiveness and impact of immersive technologies. This assessment is crucial in understanding how effectively the technology can transport users into a virtual environment and create a sense of presence in the environment. Additionally, the Immersive Tendency Questionnaire assists in identifying potential barriers or challenges to user immersion. It helps to create more seamless and immersive user interactions. The information gathered from Immersive Tendency Questionnaire assists in developing immersive experiences, refining technology design, and optimizing user engagement and satisfaction in virtual and mixed-reality environments.

2.4.4 Presence Questionnaire

Evaluating presence in a virtual environment is one of the most important aspects of the application or project. Singer et al. [17] described presence as an awareness phenomenon that requires directed attention and is based on the interaction between sensory stimulation, environmental factors that encourage involvement and enable immersion, and internal tendencies to become involved. They made questionnaires to evaluate relationships among reported presence and other research variables in virtual environments, and they stated that presence questionnaires (PQ) are highly reliable when it comes to evaluation.

The Presence Questionnaire is a tool used to measure an individual's subjective sense of presence in virtual and mixed-reality environments. It assesses the degree to which users feel as if they are "present" in a virtual environment, experiencing a sense of being there. The questionnaire provides valuable insights into the level of immersion and engagement users experience within these virtual worlds. It helps in understanding the effectiveness and impact of their immersive applications. The Presence Questionnaire aids in understanding the factors that contribute to the sense of presence in virtual environments. This knowledge helps in improving the design and development of immersive applications, focusing on aspects that create a more immersive and engaging experience for users. The questionnaire assists in exploring the relationship between presence and user outcomes.

CHAPTER 3

MATERIALS AND METHODS

During the development process of the simulation, preliminary preparations were made, and development studies continued in this direction. Answering the questions of the cell types in the area, the behavior of the cells, how the cell environment should look, and how the users would interact with the environment constituted a large part of the preparation phase.

After the preliminary preparation, the development studies started, first, algorithms that determine the cell behavior were developed, then 3D models and the environment were created, and then preparations and changes were made for different platforms.

3.1 White Blood Cell Targeting Mechanism

White blood cells play a crucial role in targeting and eliminating bacteria and viruses in the body. There are several mechanisms by which white blood cells accomplish this task.

One mechanism involves the recognition of pathogens by white blood cells through the activation of specific receptors. Toll-like receptors (TLRs) are a type of receptor that can recognize pathogen-associated molecular patterns (PAMPs) present on the surface of bacteria and viruses. When a white blood cell encounters a pathogen, TLRs on its surface bind to the PAMPs, triggering a signaling cascade that leads to the activation of the immune response [43].

Chemotaxis is another important process by which white blood cells target bacteria and viruses. Chemotaxis refers to the ability of white blood cells to move towards a concentration gradient of chemical signals released by pathogens or damaged tissues. This allows white blood cells to migrate toward the site of infection and directly engage with the pathogens. Phagocytosis is a key mechanism used by white blood cells to engulf and destroy bacteria and viruses. During phagocytosis, white blood cells extend pseudopods to surround and engulf the pathogens, forming a phagosome. The phagosome then fuses with lysosomes, forming a phagolysosome, where the pathogens are degraded by enzymes and reactive oxygen species [42].

In addition to these mechanisms, white blood cells can also produce antibodies that specifically target and neutralize bacteria and viruses. Antibodies are proteins produced by B cells in response to the presence of pathogens. They can bind to specific antigens on the surface of bacteria or viruses, marking them for destruction by other components of the immune system [44].

In summary, white blood cells employ various mechanisms, including receptor recognition, chemotaxis, phagocytosis, and antibody production, to target and eliminate bacteria and viruses in the body. These processes work together to mount an effective immune response and protect the host from infectious diseases. In our study, we carried out our study based on the fact that white blood cells go toward the center of the chemical signals (Chemotaxis) and try to destroy the source of it.

3.2 Selection of Unity3D as the Simulation Environment

After determining the main lines of the simulation, answers were sought to the questions of which tools and methods to develop the simulation. First, it was focused on which tool the simulation would be developed and Unity 3D real-time game engine was chosen as the main platform. The fact that Unity 3D supports the easy release of applications to different platforms and facilitates the transition between VR and MR has been very effective in making this choice. In addition, C#, the coding language used by Unity 3D, and familiarity with the tools included in it were also a factor in the choice. After the development platform was chosen, the prototyping work was started, and the development work continued. Prototypes were made using the basic models and materials available in Unity 3D and algorithms were tested to make experiments at the initial stage. In this direction, the spheres represented the cells. Red spheres represent bacteria, green spheres represent chemical trail intensity around bacteria, and white and blue spheres represent white blood cells (Figure 1).

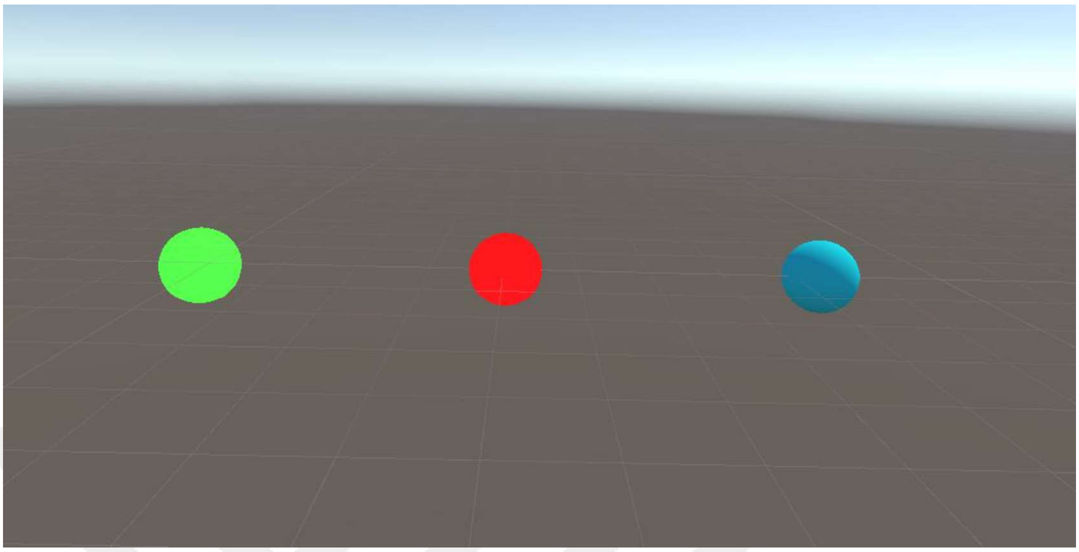

Figure 1: Cell representation at the beginning of the study.

3.3 Algorithms

3.3.1 Movement Algorithm

The first work to be done at the beginning was to determine how the cells would move in the simulation environment. Because the cells will move in a blood vein environment and will try to perform their movements in the vascular environment. Therefore, it is necessary to create a similar movement of both white blood cells and bacteria in the vessel. In this context, studies and research were carried out. As a result of the studies, it has been determined that the cells in the environment should be able to perform the following movements:

White Blood Cells:

- They will move in laminar flow under the flow (This path will be calculated and created to be different and unique for each cell when the cell is created).
- They will head to random points within certain limits in the flow.
- When a cell enters a bacteria area, it will be able to follow and destroy the bacteria depending on the current situation and calculations.
- When the bacteria are targeted and destroyed, white blood cells will continue their movement in the environment.

Bacterium:

- It will move in laminar flow under the flow (This path will be calculated and created to be different and unique for each cell when the cell is created).
- It will head to random points within certain limits in the flow.

The cells in the environment should move in laminar flow and target a cell when it is needed and continue its movement accordingly. After deciding on the movements of the cells in the environment, the coding process was started. The studies carried out are mentioned below, respectively.

The cells are in a flow movement within the vessel. Therefore, this movement must be created in the simulation environment. Within the scope of the objectives of the study, it was decided that the laminar flow movement would be the most accurate movement type and the studies continued with this flow type. In addition, the capillary environment was chosen as the target environment in order not to create the turbulence created by the heartbeats in the vessel and the speed change movements of the flow. In this way, it is aimed that the flow algorithm to be developed will be simpler and the environment will offer a more easily understandable movement structure by the users. So, the flow speed is the same for all the cells in the environment in this way. Different attempts have been made to develop this flow type of movement for the cells.

In the first stage, it is developed that the cells move from one point to another within the given time parameter. However, this type of movement is not preferred because the movements are direct between two points, and it is extra difficult to create inclined movements. Because the cells move directly to the target point in a straight direction and their movements do not have a realistic appearance (Figure 2).

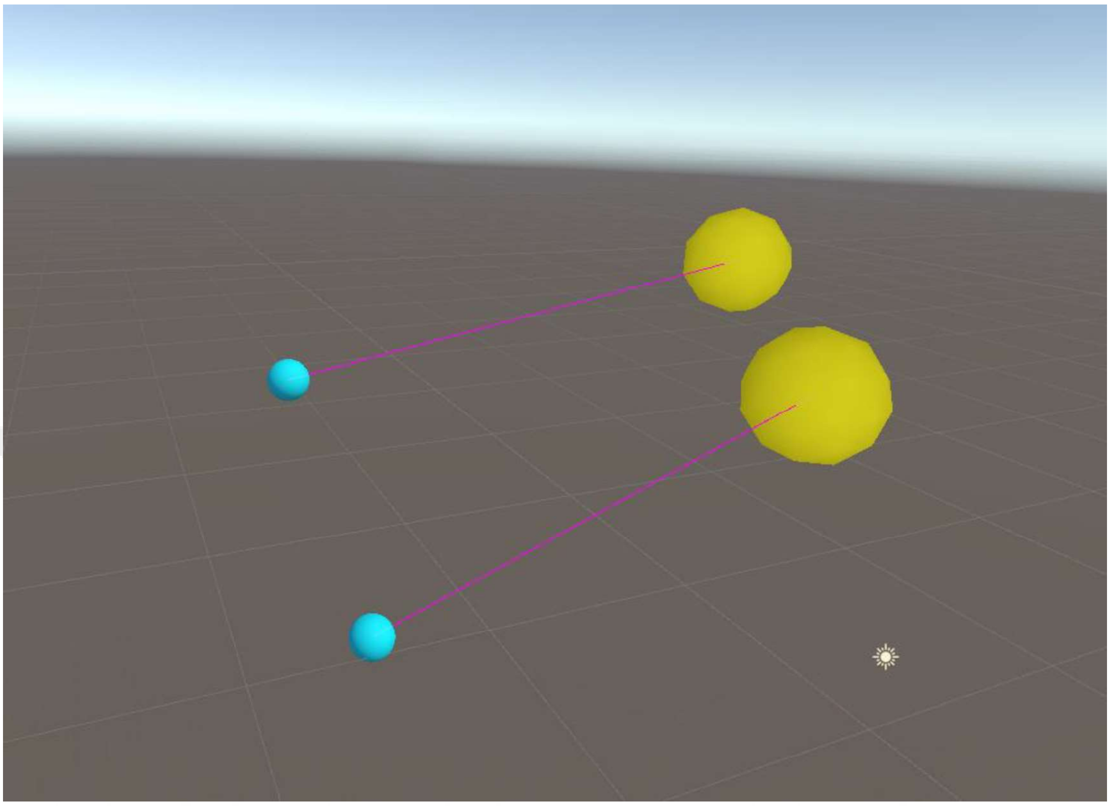

Figure 2: Targeting path for the white blood cells.

After the first algorithm was developed, it was understood that the objects should have the ability to move on a determined path and to move to new points on this path depending on the surrounding factors. In this direction, the subject of how this type of movement could be started to be investigated. First, it is focused on how to achieve a realistic movement in a predetermined path. It has been determined that the best way to achieve this goal is to move the object (cells) on a Spline, which can both create a sense of flow motion and create it dynamically in a comfortable way. Different spline packages have been tried and in addition to these (Figure 3), a fully customized spline function has been written from scratch. Advantages and disadvantages against each other are evaluated.

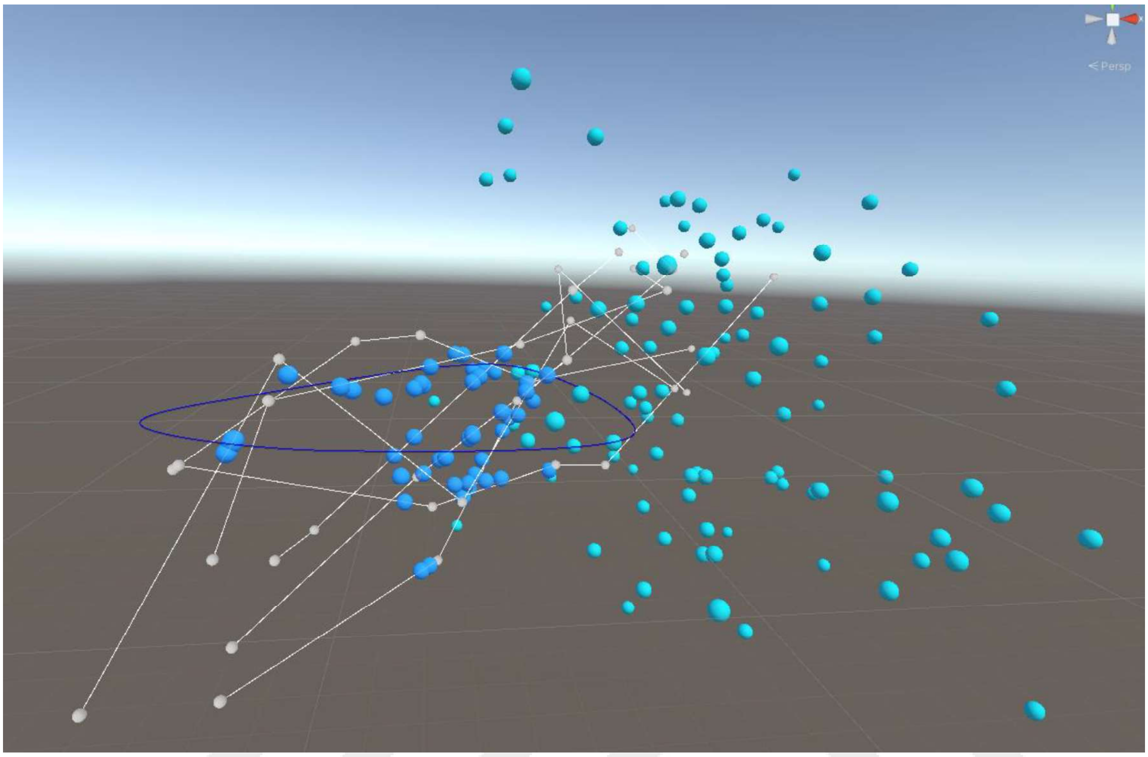

Figure 3: Different spline algorithms representations.

At the beginning of the development work, the use of the official Spline package[5] of Unity version 2.1.0 was also tested experimentally. It has been determined that this package is preferable because it is directly from Unity and has the direct support of the engine. However, since the package is experimental yet, it could not meet all the needs of the project in the version used. A customized structure was created by writing manual functions at points not included in the package. The spline package in question does not support dynamic spline formation in the version used and does not allow the points that make up the spline to be edited in runtime. Therefore, with this tool, a solution to meet these needs was developed and used in the project. Figure 4 shows the final version of the spline drawn by the custom spline tool developed for the project.

[5] Unity Technologies. (n.d.). Unity Spline Package Documentation. Retrieved from https://docs.unity3d.com/Packages/com.unity.splines@2.1/manual/index.html.

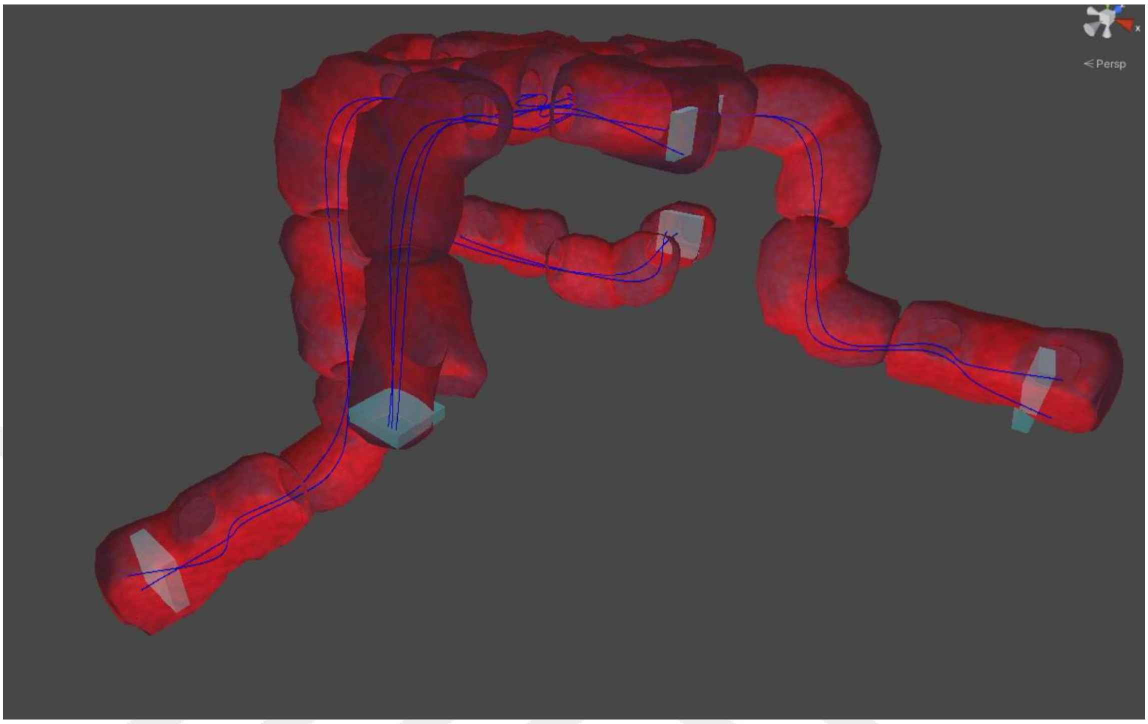

Figure 4: Final spline representations.

3.3.2 Bacterial Density - Chemical Trail Area Controls

In order to create the chemical trace area around the bacteria, a new object was created in the center of the bacterium object and this object was controlled over time. The maximum size at which the chemical trace area can grow is fixed, and this value differs for each bacterium with a small offset (Figure 6). This created object was enlarged step by step over time to reach its maximum size (Figure 5). The growth rate and duration of the field growth show slight differences for each bacterium. In this way, it is aimed to provide diversity in the environment (Figure 7). The IsTrigger feature of the field is activated, and a specific tag is given to each field. In this way, it is ensured that the objects in the environment pass through the chemical trace area without any problems, the white blood cells understand that they are in this area, and they can target the bacteria.

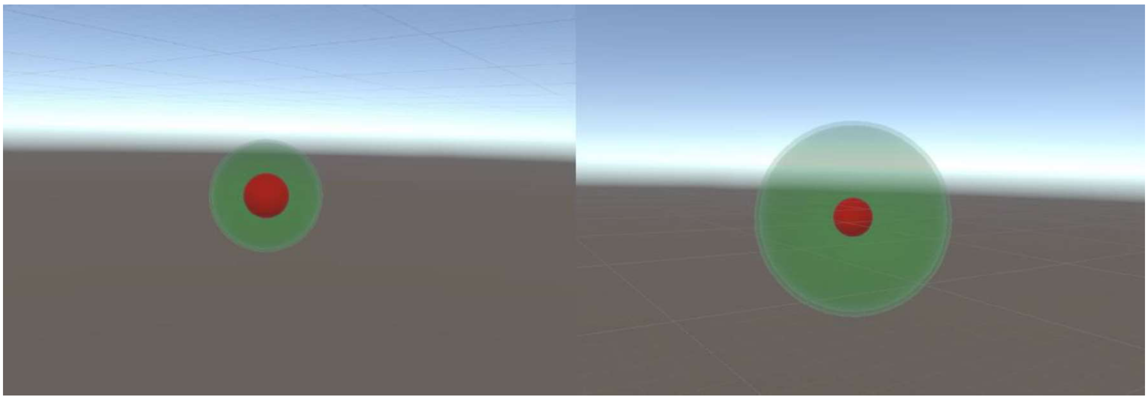

Figure 5: Bacteria with chemical trail area, the chemical density area growing over time.

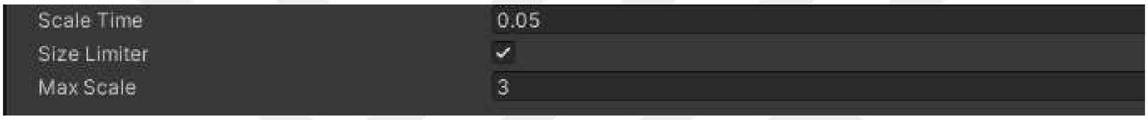

Figure 6: Bacteria Chemical Trail Variables.

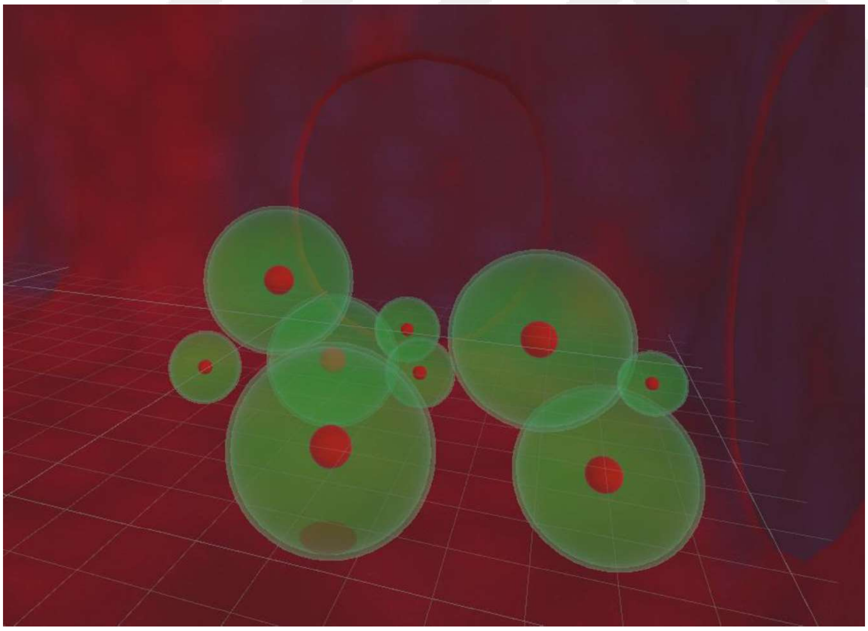

Figure 7: Each chemical trail area's properties slightly differ from bacteria to bacteria.

3.3.3 Targeting Algorithm

After the cell's movement systems were developed, we developed the targeting and migration algorithm that the white blood cells will use to follow the bacteria. The default trigger structures in Unity were used up to this point, and each cell was set to activate directly when it interacted with a target cell. However, we aim to design a simulation that can better reflect reality. For this purpose, the responses and movements of white blood cells were studied. As a result of this research, it was seen that white blood cells detect the chemical trails of bacteria (e.g., endotoxins secreted by these bacteria) in the environment through their receptors. When an offending cell is detected, it migrates toward the pathogen and tries to destroy it by engulfing and digesting it, i.e., by phagocytosis [12,13]. To show this structure in the virtual environment, the following structure has been developed: As soon as white blood cells enter the chemical trail of any bacteria (in other words, when its receptors detect a bacterium in the area), a density factor is calculated depending on the distance from the center of that area. Depending on the value of this density factor, a decision is made as to whether it will follow the bacterium (Figure 8). For the calculation of the density factor, the exponential fog formula from the Microsoft DirectX library was taken as a basis, and the values were updated according to the number scale in the environment. Figure 9 represents the logic behind the white blood cell targeting algorithm.

$$f = 1/e^{d*density} \qquad (1)$$

```
private bool ChaseCell(Transform transform)
      {
       float fogFactor =(1 / Mathf.Exp(transform.localScale.x)) * 2.58f;

       float randomF =((1 / Mathf.Exp(Random.Range(1.00f, 10.00f))) * 2.58f);

       if (fogFactor > randomF)
       {
            return true;
       }
            return false;
      }
```

Figure 8: White blood cell bacteria chasing calculation, true means it will chase and try to destroy triggering bacteria.

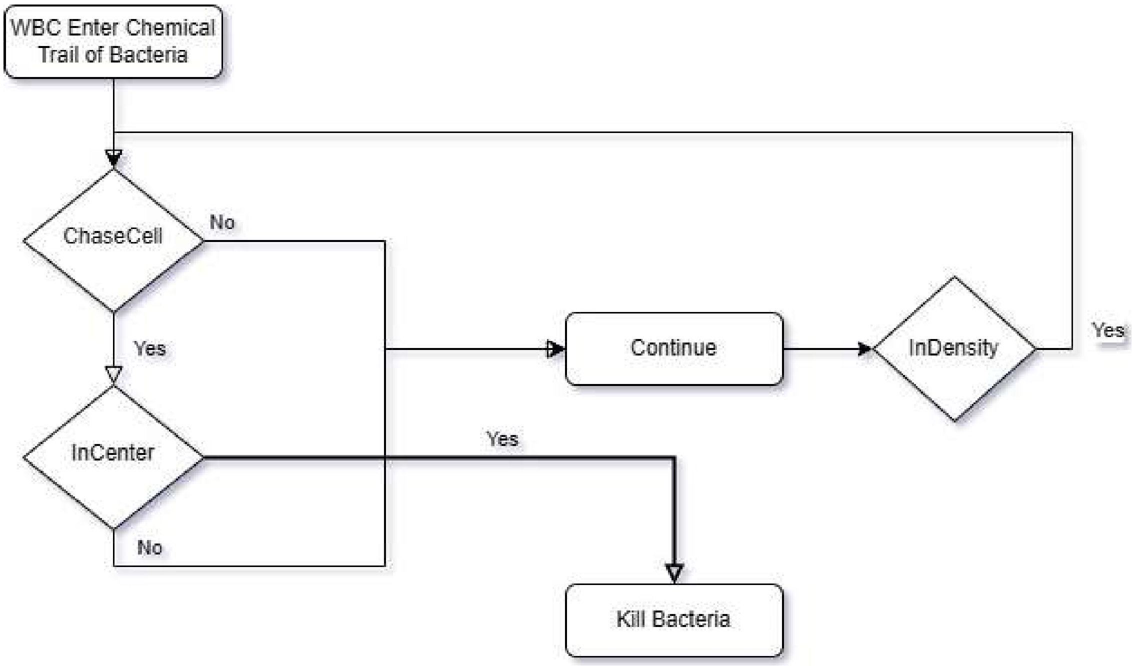

Figure 9: Cell Chasing Logic Diagram.

The higher the calculated value, the higher the probability of following and destroying the bacterium involved. The value is directly related to the distance from the point where it enters the area to the bacterium in the center of that area. While moving toward the center of the area, if it encounters another bacterial area and the targeting score calculated at that point in this area is higher than the one it is currently following, the probability of following the newly encountered bacteria will also increase. In this way, we aimed to develop a dynamic cell tracking system within the field. If the white blood cell stays within the chemical field of a bacterium, the probability of destroying that bacterium increases. White blood cells will target the bacteria they touch during their movement and will destroy them in turn. When a target cell is destroyed, all white blood cells migrating to the cell return to the path, they follow in normally and continue their movement in the flow. Figure 10 shows the white blood cells bacteria targeting trials in the scene with lots of cells. The green ray-line between bacteria and white blood cells means that there is active chasing.

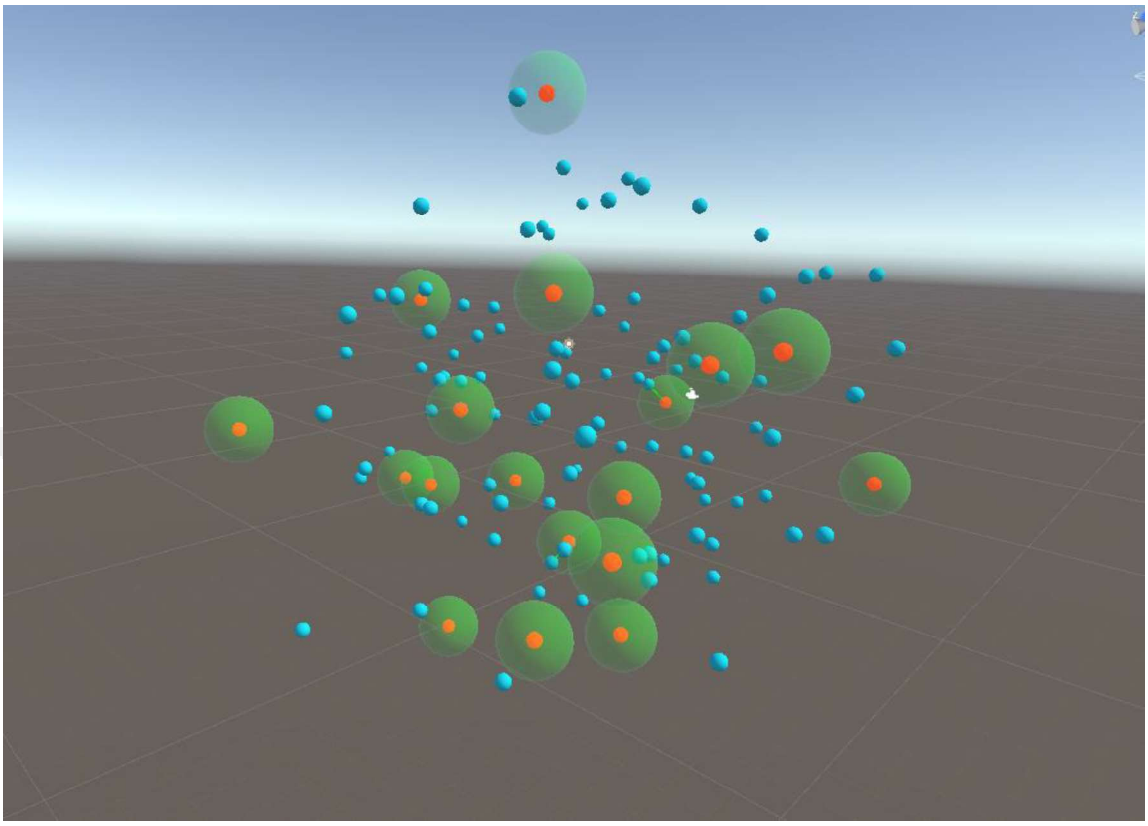

Figure 10: Targeting algorithm trials.

3.3.4 Scene Logic

Regardless of the platform, the logic in the simulation scenes proceeds in the same way. At the beginning of the stage, bacteria and white blood cells are created. Their number is constant and set by the scene manager. While creating these cells, new splines are created for each of them by looking over the main splines. This makes the laminar flow look more dynamic. The newly created splines are created by looking at the offset threshold values on the XYZ axis. When the cells are first created, the white blood cells start their action immediately, while the bacteria start their movement with a delay. In the meantime, the bacteria are in a waiting state and in a disabled way. White blood cells begin to move in the flow, and during this time it is possible to see white blood cells traveling at different points in the vascular structure. Then the bacteria are activated, and the movement of the bacteria starts in the environment. Every cell that visits the last part of the scene is teleported back to one of the starting points and continues its movement in the vessel. If a bacterium is destroyed, all data of that object is destroyed and cleared from memory. If the endless bacteria creation mode is active in the scene, when each bacterium is destroyed, a new bacterium is created in the scene after some random time with a threshold, thus ensuring that the simulation continues continuously. However, this mod is not open to users, it is only used in development work. After a certain time in the environment, the bacteria end, and only white blood cells remain. In the meantime, if any unnecessary objects are remaining after the event it will remove in the first garbage collection to reduce memory usage and optimize performance. Figure 11 shows the overall logic in diagram form.

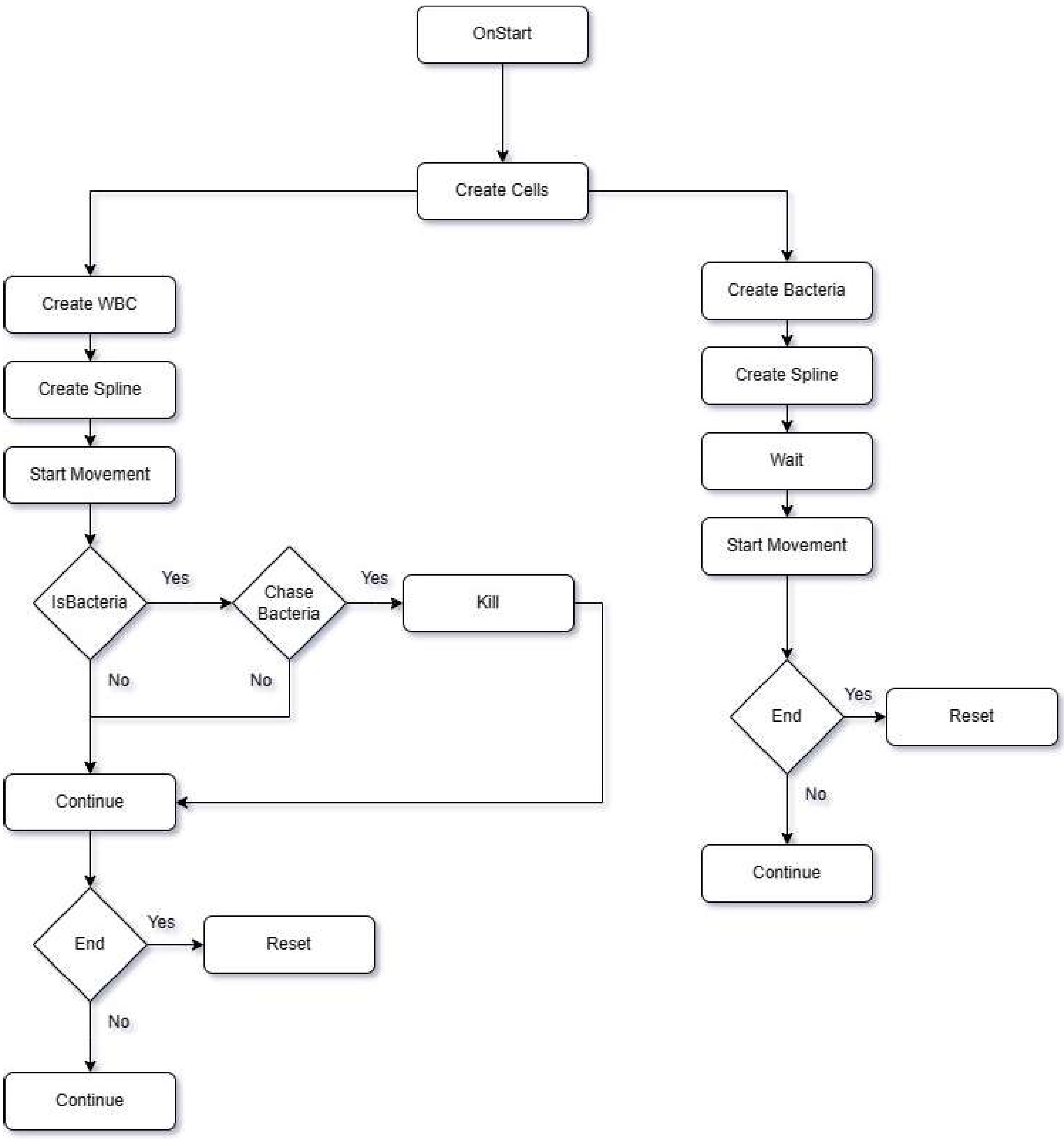

Figure: 11 Scene Logic Diagram.

3.4 3D Modelling and Environment

Initially, hollow cylindrical objects were used to represent the veins, and experiments were made on these models. However, because these models do not support the distance taken from the inside of the model (because of the rendering type and calculation of the model surface normal type) and the rendering type used on Unity (the engine contains more than one rendering method), the two-sided material display is not supported, various problems have been experienced during the trials. In order to show the chemical trace areas of the bacteria and to ensure that the targeting-movement algorithms work correctly, wireframe cubes were used for control around the bacteria (Figure 12).

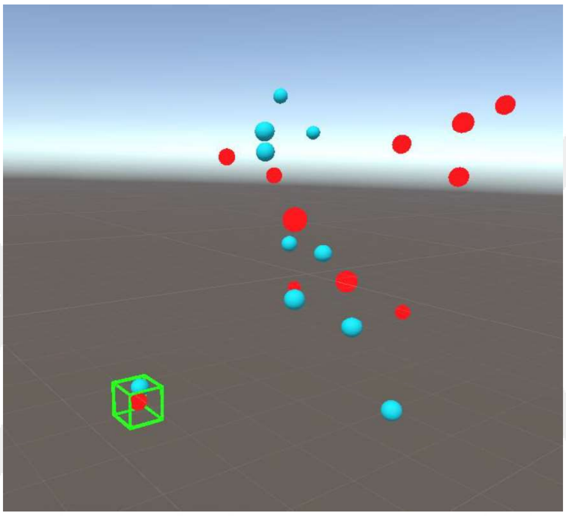

Figure 12: Wireframe cube used for the representation of bacteria chemical area and the active targeting between bacteria and white blood cell.

Therefore, different models have been sought and studies have been carried out on this subject. Since the simulation will take place inside the vessel, we decided to use modular models that can represent the vessel's interior and simultaneously allow the creation of different environments quickly. To speed up the development, ready-made and free-to-use packages were prioritized. We determined that the environment models in Unity's official Creator - FPS Kit[6] were suitable. Because this kit contains a vein-like shaped game-level model for prototyping. This package contains various tools and models for learning how to make a game in First Person mode in an environment set in Unity. The vessel models included in it were examined and it was decided that they could be used with minor changes in the simulation environment both in terms of model and appearance. After the environment models were taken from the package, changes were made to the custom shader to suit the desired environmental background texture (i.e., the interior of a blood capillary), and the work progressed on these models. First, different vascular environments were created (Figure 13). It was then planned that the vessel structure should present a unidirectional laminar flow

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[6] Unity Technologies. (n.d.). Creator Kit FPS. Unity Asset Store. Retrieved from https://assetstore.unity.com/packages/templates/tutorials/creator-kit-fps-149310.

environment. In addition, this environment should be easy to understand for users. In this direction, a three-channel vascular structure was created in the final and the studies continued in this vascular environment (Figure 14).

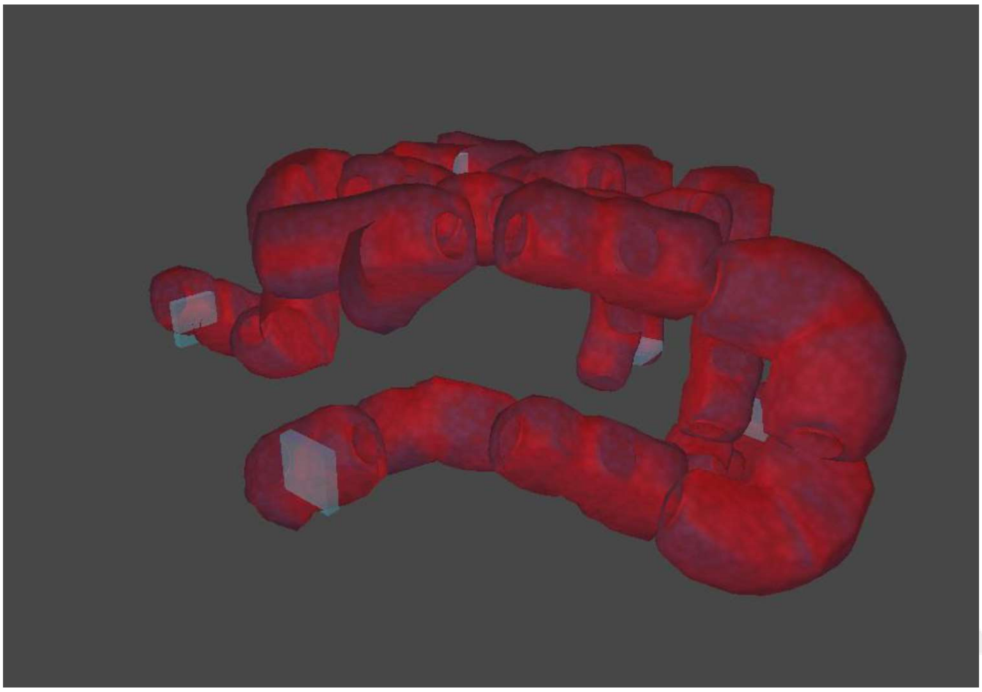

Figure 13: Vessel environment layout trials.

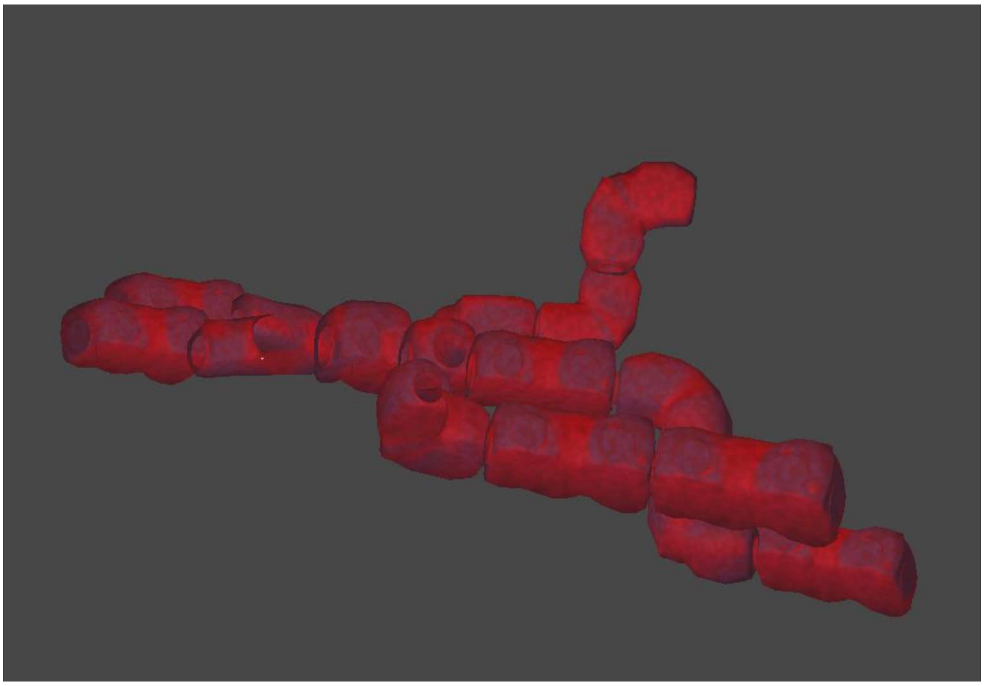

Figure 14: Final vein environment layout and shape.

3.5 Platform Customizations

When the development studies reached the level that could be tested, preparations for the VR and MR versions of the application were also started. Since the application will be run on the Oculus Quest 2 device, we primarily aimed to develop an infrastructure compatible with this device.

We integrated the official input libraries developed for Oculus into the project and ensured that these systems work within the application. For the application, a control structure was created based on the control chart of the Oculus device, and their implementation was done. To make the use easier and more practical, the controls that users use to interact with the environment are provided through only one controller. In this way, users do not need to use two controllers at the same time. VR and MR platforms were enabled to work with the same control scheme, so we aimed to enable users to easily switch between the two platforms.

After all this control chart development work, the building part started to load the project on the device. At this stage, various changes were made in the project settings to be able to build for the device. The vast majority of these were built to comply with the limitations set by Oculus. Most of the changes made were details about rendering settings and lighting. After the build was taken and it was determined that it was working on the device, improvements were made to the working conditions and structures of the control schemes, and the development of the control structures on the Oculus device was completed. Then, the control scheme was customized for keyboard use on the PC and the application was enabled to switch between these control schemes according to the platform on which it is running. In addition, to minimize cross-platform differences, the cameras used for VR-MR were also used in the PC version of the application, and users were able to see the environment through this camera. For this, some features of the VR-MR camera are provided to work with mouse input on the PC.

3.6 User Interactions

We developed the simulation to work on three different platforms so that the differences between these modalities could be evaluated by the users. The platforms are Personal Computer (PC), Virtual Reality (VR), and Mixed Reality (MR) platforms. Although each platform has a different control scheme, there are also different user inputs. We aimed to investigate whether these features make a difference in the experience of the users. User inputs for PC are taken directly from the keyboard and mouse. The OVRInput package[7] was used to get user inputs for the VR and MR platforms.

User entries on the platforms are as follows:

1. Bacteria Creation: The user can create bacteria for observation while in various positions and monitor their interaction with white blood cells. The number of bacteria that can be created in the environment is limited to maintain a minimum viable frame rate. These created bacteria are created in the areas where bacteria are normally created and continue their natural movements within the simulation.

2. Creating a Permanent Bacterial Chemical Trail Area: The user can experience a small-scale infection simulation by creating a permanent bacterial field. The white blood cells that start to follow this area will remain closed to the created area and will not be able to interact with other bacteria, which will show the effect of weakening the defense system at the time of illness. Users will be able to destroy this area at any time. The position of the created bacterial chemical trace area is randomly selected from predetermined positions and created at the selected position. These positions were chosen at the points where the white blood cells pass collectively so that the interactions between bacteria and white blood cells can be observed directly and clearly. Figure 15 presents the positions for the permanent bacteria creation points in the environment.

[7] https://developer.oculus.com/documentation/unity/unity-ovrinput/Oculus. (n.d.). Unity OVRInput Documentation. Retrieved from https://developer.oculus.com/documentation/unity/unity-ovrinput/.

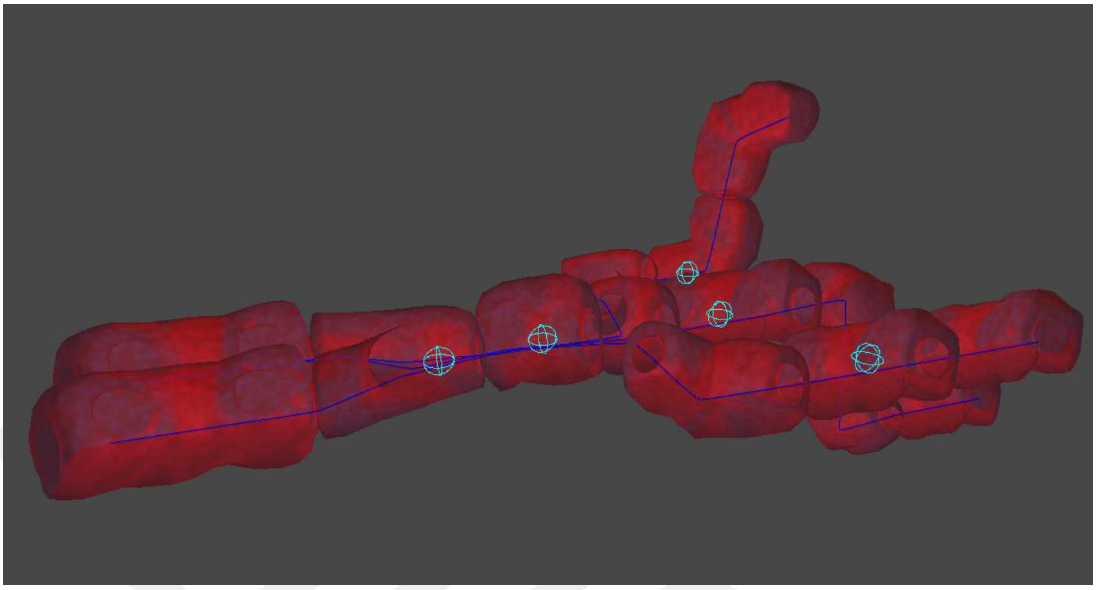

Figure 15: Bacteria chemical density area possible positions presented as light blue colored spheres.

3. Becoming Bacteria: In the first-person camera mode, users will be able to become bacteria if they want and observe the white blood cells targeting them. While in this mode, white blood cells will not be able to destroy the bacterium assigned to the user.

4. Camera Mode Switching: Users will be able to switch between first-person and third-person camera modes on supported platforms and experience the environment from different perspectives. The camera positions that users can pass through are predetermined and listed. The positions were chosen from the points that are important for the examination, such as the junction of the vessels and the birth points of the cells in the simulation environment. Users can switch between these positions in turn and view the simulation from various positions.

5. Third-Party Camera Mode Position Changing: Users will be able to try the simulation environment from different positions and observe the results of interacting with the environment by changing the positions they are in while in the third-person mode on the supported platforms. Figure 16 shows the positions of camera points in the environment.

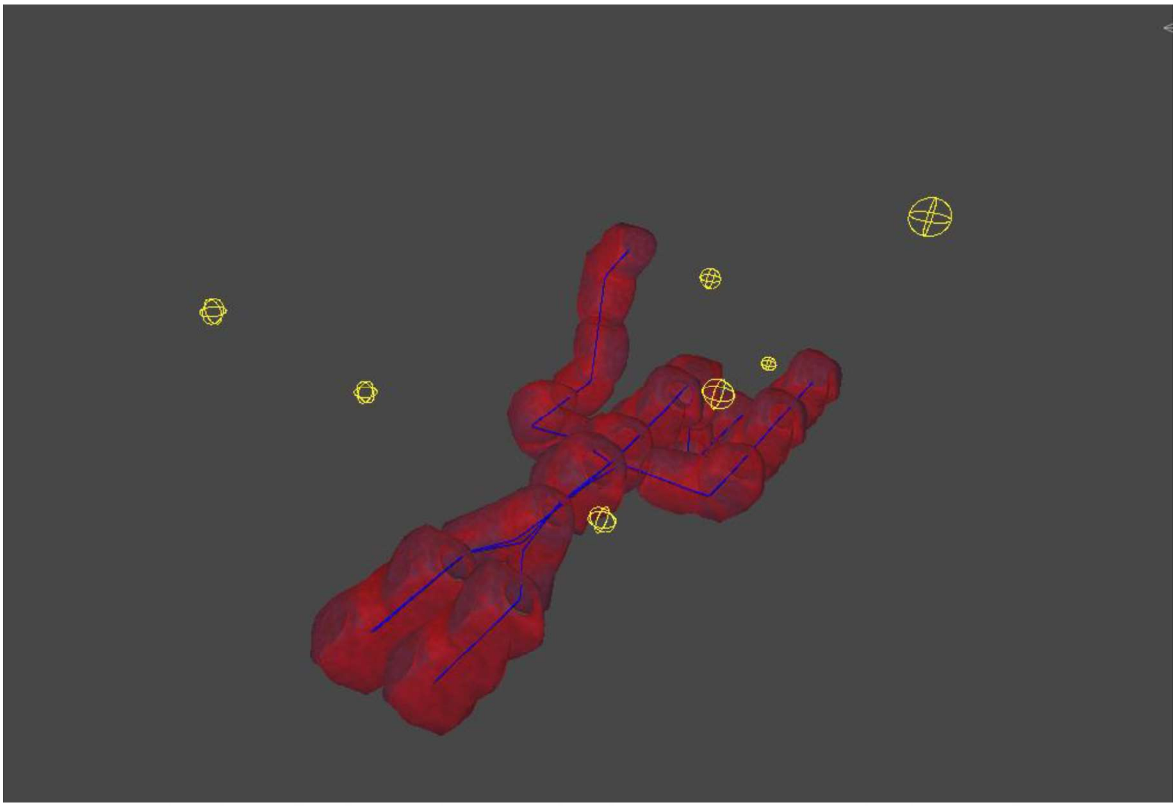

Figure 16: Different camera positions are presented as yellow-colored spheres.

The environment, the number of cells, and the behavior of the cells are common to all platforms, and the platforms are differentiated in terms of user inputs and the hardware they work with. The user inputs for each of the platforms are listed below:

- **PC:** This is the default environment for the simulation and includes both a primary and a third-person camera viewpoint. It has the features of creating new cells with keyboard inputs, creating a permanent bacteria area, becoming bacteria, and switching between camera modes-positions. There is no frame rate limit.

- **Virtual Reality (VR):** Has all the user inputs in the PC environment. However, the speed of the player bacteria area can be controlled and is directly proportional to the time of holding the trigger. The frame rate is limited to 60 frames per second.

- **Mixed Reality (MR):** Unlike the other two versions, this version only has a third-person perspective. In this way, simulations can be made and observed on the real-world image taken from the cameras. Other user inputs were used in the same way as VR. The frame rate is limited to 60 frames per second.

3.7 Optimization

3.7.1 Cell Number Optimizations

At the beginning of the study, it was aimed to have thousands of cells in the environment and to simulate them in a flow. The first simulations were performed using 5000 cells. However, it has been noticed that performing a simulation with this number of cells causes various performance problems. In simulations made with 5000 cells, the performance sometimes drops to around 10 fps and cannot provide a meaningful experience. To overcome this performance problem, optimization studies have been carried out. First, it was tried to increase the performance by changing the method of creation of the cells, the materials they use in the environment, and the lighting values. However, these changes did not provide sufficient performance increase. After these results, different methods were started to be investigated. At this stage, it was decided to test Unity's DOTS[8] system. DOTS is a new development infrastructure and can be defined as a system that aims to increase performance by using all the multiple cores in the processors. Due to the parallelism of operations using DOTS, a very serious performance increase is observed compared to operations performed in a single core. However, the problems in parallel programming can be seen here as well, since it is parallel, and the written codes should be written with these problems in mind. Otherwise, there is a possibility that all systems and the application will crash. The codes written in the use of DOTS are completely different from the codes used classically in Unity, so the learning time takes longer than the traditional use. At this stage of the development work, Unity DOTS is still an experimental package, and version 0.1.9 is used. With the DOTS infrastructure, the creation of cells, the realization of their movements, and the rewriting of targeting systems in the code were carried out. The performance obtained as a result of these processes has been at very serious levels. While the simulation was difficult to give 30 fps in the previous system, in the number of 1000 cells, in the new system developed with DOTS, ~35 fps could be obtained in the simulation made with approximately 100 thousand cells. This performance difference is very promising. However, in addition to this performance increase, it has been observed that the use of DOTS causes deficiencies in the simulation. Because the DOTS version used does not support all the objects and elements in Unity, and therefore not all the systems developed so far work. Especially the collider and targeting structure used in the flow and cell targeting parts in laminar flow cannot work with DOTS in a stable way and some unexpected movements are observed in cell movements. In addition to all of these, the DOTS package is still in an experimental state, and the infrastructures and naming used in each update have changed, so there have been problems with the working of the written codes. During the development process, an updated version of DOTS was released, and the codes

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[8] Unity Technologies. (n.d.). Unity DOTS (Data-Oriented Technology Stack). Retrieved from https://unity.com/dots.

had to be updated and rewritten more than once to work properly with this update. As a result of these situations, it was decided that the use of DOTS might cause problems in the development process of the study, and it was decided not to continue with the use of DOTS. After this stage, the optimization studies moved in a different direction and the optimization was tried to be improved by changing the number and properties of the cells.

3.7.2 Lighting Optimizations

At the beginning of the project, the lighting values, and properties of the objects in the environment were left as default and used as such. The scene lighting has also been set to have both real-time and baked lighting together by default. During the optimization studies, both the lighting method used by the scene and the lighting properties of the objects were changed. Scene lighting was completely switched to the static lighting method and when the scene was finalized, it was baked for lighting. In this way, light data was created for the scene and the colors of the lighting in the scene were displayed by reading this data. In this way, no processing power is consumed for scene lighting. It is ensured that the objects in the environment use Unlit material directly and are not included in any calculations related to lighting. In this way, while the simulation is running in the environment, no calculations are made regarding the lighting, and no processing power is used for the lighting. In addition, all materials using a two-sided rendering structure have been translated into a one-way rendering structure and unnecessary calculations have been tried to be prevented. Figure 17 shows the lightning settings for the environment in Unity 3D.

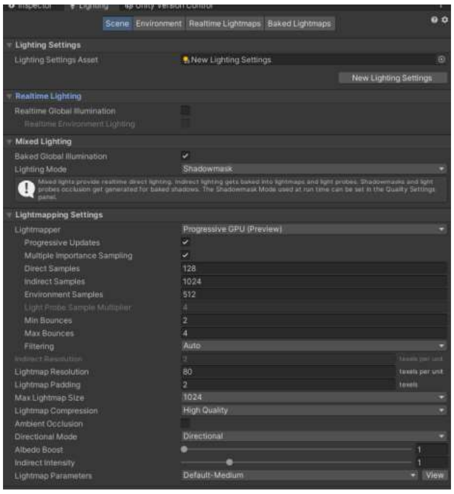

Figure 17: Lighting settings.

3.7.3 Cell Movement Optimizations

At the beginning of the stage, a spline is created for each cell that outlines the path that the cell will follow in the vessel. However, we found that sometimes cells cross the vessel walls during movement. To prevent this, different methodologies have been developed. A support vector calculation algorithm has been developed that prevents the cell from staying in the laminar flow inside the vessel and from leaving the vessel walls. This algorithm sends rays at certain intervals in the X, Y, and Z axes, and if the ray hits the vessel wall, it calculates the distance of that point from the cell center (Figure 18).

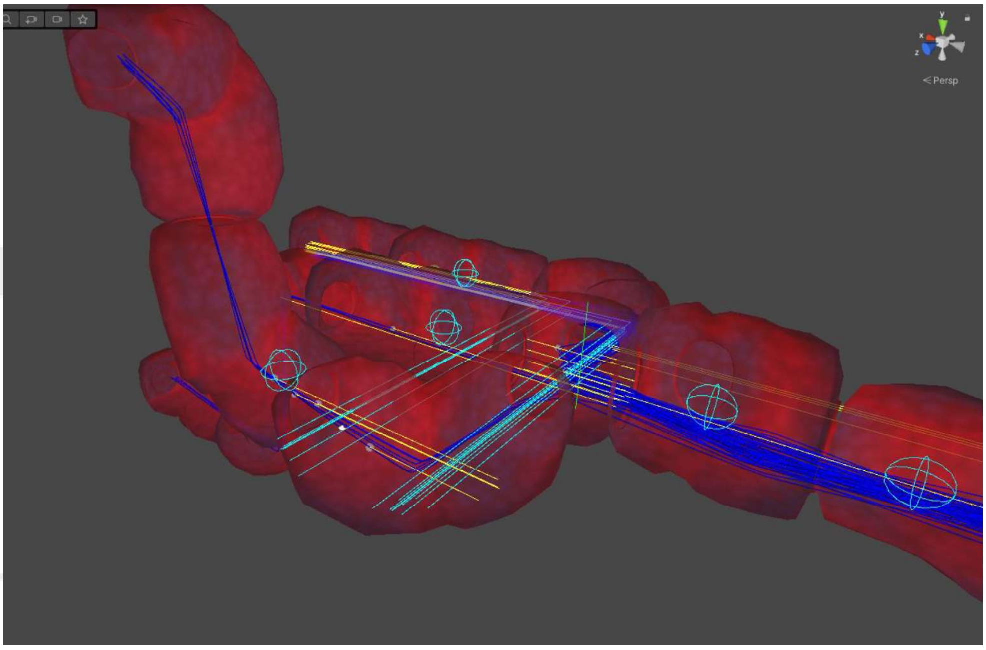

Figure 18: WBC Vessel wall controls.

If the calculated distance is below a certain limit, it is understood that the cell approaches the vessel wall in that direction. In this case, a support vector is added to the motion vector in the laminar flow of the cell to prevent the cell from going out of the vessel. In this way, it is ensured that the cells stay within the borders of the vessel during laminar flow. Figure 19 shows the support vector control rays in the vessel environment.

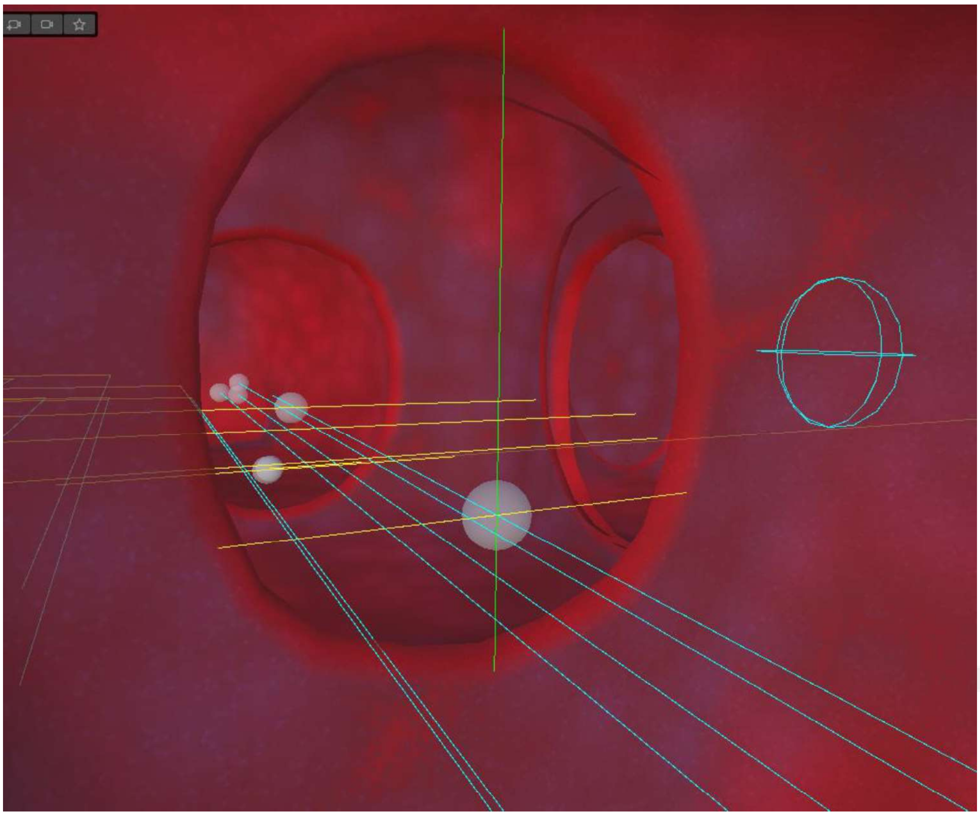

Figure 19: WBC wall support vector controls.

While the WBC continues to move in the laminar flow, if the WBC encounters a chemical trace area, there is a possibility to target and destroy that bacterium. At the beginning of the study, when a WBC targeted the bacterium, the point it should have been on its spline path continued to be calculated, but instead of moving in that direction, the WBC kept moving toward the target bacteria. In the later stages of the study, we determined that the knowledge of where to be on the calculated spline in this case causes performance loss due to the costly computation. In order to solve this situation, when any WBC target a bacterium, any information about the spline is stopped from calculating, and if the targeted bacterium is destroyed, then the information about the spline is started to be calculated again. Since this process is done for all WBCs in the simulation environment, performance increases have been observed.

3.7.4 Model Shape Optimizations

The default sphere in the Unity engine was used for the trials and initial studies in the development process, but the performance was found to be very low in the trials with the VR system (on Oculus Quest 2). After it was determined that the performance was not satisfactory, optimizations were made in the models used. Namely, to represent cells, an IcoSphere with 32 segments was created on the open-source program Blender[9], and this was used in place of a sphere. In addition, the compression methods and formats of these objects have also been changed. In addition, surface normal values were calculated in Unity and the values on the model were overridden. Following this substitution, the performance increased significantly and reached a satisfactory level. Figure 20 and Figure 21 represent the final shapes of the cell and trail area model without lightning and shading in Unity 3D.

Figure 20: Optimized 3D model for bacteria with density area.

Figure 21: Optimized 3D model for white blood cell.

3.8 Evaluation

After the development processes of the simulation, working versions for three different platforms, PC, VR, and MR, were implemented using the Oculus Quest 2 device. This

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[9] Blender Foundation. (n.d.). Blender - Home. Retrieved from https://www.blender.org/.

device allowed for quick trials and supports testing in both VR and MR environments. This provided the opportunity to quickly try two different versions of the application on the same device. It was decided to test the application with the participants in order to try and get results. For this, the necessary permissions were obtained from the ethics committee to conduct experiments with the participants, after submitting appropriate documents to the ethics committee. Then, studies were carried out to make experiments with the participants. To ensure a comprehensive evaluation, an open space designed as a workshop was arranged at the Middle East Technical University campus, where participants had the opportunity to experience the application on each platform in a controlled setting (see Figure 22). Participants first experienced the VR version of the application, then the MR version, and finally the PC version, respectively. The age range of the participants is average between 20-32 and all the participants have at least a bachelor's degree. In addition, the male-female ratio among the participants was approximately 50%. Most of the participants are graduates of different engineering disciplines, but there are also graduates of architecture, sound design, animation design, and bioinformatics departments. Some participants are both knowledgeable in the field of biology, at least in general, and do not have any knowledge about the subject. A wide range of participant experiences were carried out.

Figure 22: User Experience Tests with Oculus Quest 2 for VR and MR Simulations.

To gather data on user experiences with each platform, a combination of standard questionnaires was filled out after each trial by participants. The questionnaires used are the Technology Acceptance Model (TAM) [14], the System Usability Scale (SUS) [15], the Presence Questionnaire [16], and the Immersive Tendency Questionnaire [17]. These questionnaires are well-established and widely used in evaluating user experiences and perceptions in interactive environments. All questionnaires were conducted in English as the questionnaires were and were answered in English by the participants. The Technology Acceptance Model questionnaire was employed to measure the participant's acceptance of the technology. It consisted of questions focused on participants' perceptions of the system's usefulness and ease of use. This questionnaire provided insights into participants' attitudes and intentions regarding the adoption and usage of the simulated system. The System Usability Scale questionnaire was utilized to assess the overall usability of the system. This standardized questionnaire helped to understand participants' subjective evaluations of the system's ease of use, efficiency, learnability, and user satisfaction. The Presence Questionnaire was employed to measure participants' sense of being present in the simulation environment. This questionnaire aimed to capture participants' subjective experiences of presence, immersion, and engagement within virtual and mixed reality environments. The Immersive Tendency Questionnaire was utilized to measure the degree to which participants were immersed in the simulation. This questionnaire helped identify individual differences in participants' tendencies to engage and feel immersed in virtual and mixed reality environments.

After the completion of the experiments and the collection of questionnaire responses, the gathered data were subjected to thorough analysis. Statistical techniques were employed to examine and interpret the data, allowing for meaningful insights and conclusions to be drawn from the evaluation process of the application.

CHAPTER 4

RESULTS

The application was evaluated by 27 participants in PC, VR, and MR platforms. The participants filled out questionnaires after they test the applications. The results, based on 27 participants' responses to the Technology Acceptance Model, System Usability Scale, Presence Questionnaire, and Immersive Tendency Questionnaire, are shown in Table 1. The table contains the means and standard deviations of the user feedback.

Table 1: Mean and Standard Deviation Values of Presence, Technology Acceptance, Immersive Tendency, and System Usability Questionnaires.

	Presence (Out of 7)	**Technology Acceptance Model (Out of 10)**	**Immersive Tendency (Out of 7)**	**System Usability Scale (Out of 5)**
Personal Computer (PC)	4.74±1.21	7.19±1.55	4.78±0.77	2.87±0.25
Virtual Reality (VR)	5.20 ±0.96	7.02±1.86	4.55±1.03	2.92±0.18
Mixed Reality (MR)	4.89 ±1.46	6.83±1.91	5.14±1.11	2.86±0.26

A two-tailed t-test was conducted on the TAM questionnaire results. The test results are shown in Table 2. According to these results, there were significant differences between the PC-VR and VR-MR values, but no such difference could be observed between the PC-MR values.

Table 2: Two-tailed t-test results for the Technology Acceptance Model Questionnaire.

	PC-VR	PC-MR	VR-MR
n	27	27	27
t	2.21	0.88	2.71
p	0.038	0.39	0.013
df	26	26	26
Std. Error	0.15	0.16	0.07

A two-tailed t-test was conducted on the SUS questionnaire results. The test results are shown in Table 3.

Table 3: Two-tailed t-test results for the System Usability Scale Questionnaire.

	PC-VR	PC-MR	VR-MR
n	27	27	27
t	1.64	0.32	1.87
p	0.130	0.752	0.088
df	11	11	11
Std. Error	5.99	3.22	5.78

A two-tailed t-test was conducted on the ITQ questionnaire results. The test results are shown in Table 4. The standard deviation value for all three platforms is so close to each other in this table.

Table 4: Two-tailed t-test results for the Immersive Tendency Questionnaire.

	PC-VR	PC-MR	VR-MR
n	27	27	27
t	1.52	3.77	2.76
p	0.143	0.001	0.012
df	26	26	26
Std. Error	0.15	0.17	0.15

Table 5 shows the two-tailed t-test results of the participants' answers to the Presence questionnaire.

Table 5: Two-tailed t-test results for the Presence Questionnaire.

	PC-VR	PC-MR	VR-MR
n	27	27	27
t	3.64	0.61	2.57
p	0.002	0.55	0.02
df	26	26	26
Std. Error	0.144	0.188	0.16

The distributions of the feedback given by the users to the System Usability Questionnaire are given in Figure 23 in the form of a Boxplot representation. The data in the figure shows that the scores of the 3 platforms are not far from each other.

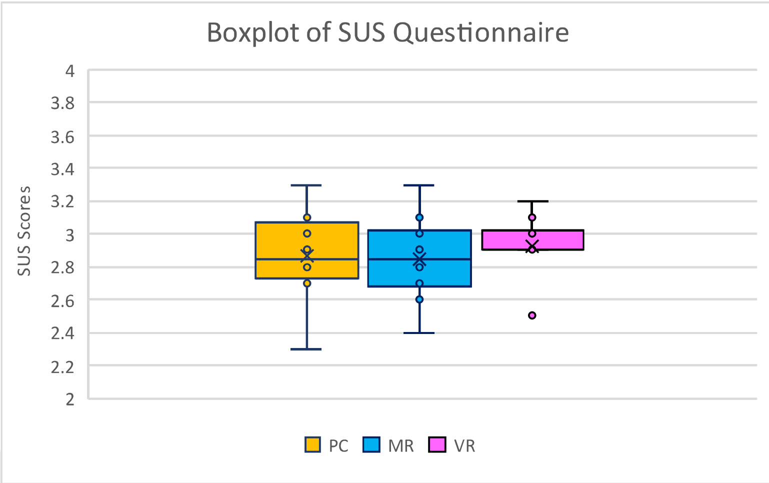

Figure 23: Boxplot Visualization of System Usability Scale Questionnaire responses given by participants to each platform shows the distribution of the calculated SUS Scores.

The distributions of the feedback given by the users to the Technology Acceptance Model Questionnaire are given in Figure 24 in the form of a Boxplot representation. It is also the same as SUS scores in this one, data in the figure shows that the scores of the 3 platforms are not far from each other.

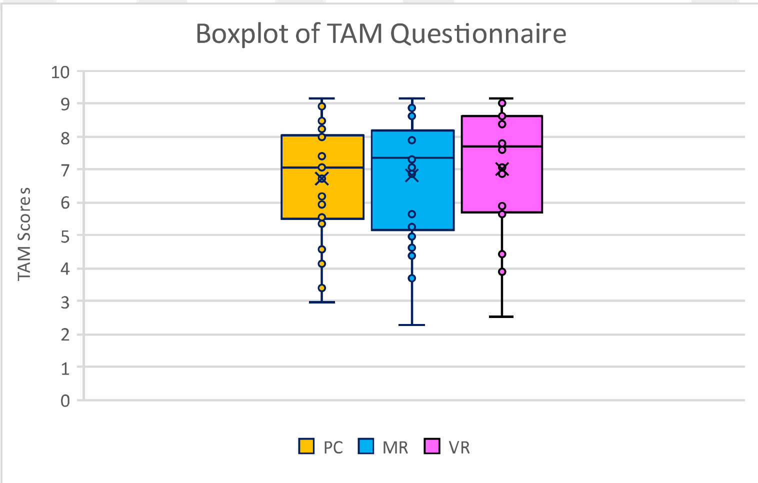

Figure 24: Boxplot Visualization of Technology Acceptance Model Questionnaire responses given by participants to each platform shows the distribution of the calculated TAM Scores.

The distributions of the feedback given by the users to the Immersive Tendency Questionnaire are given in Figure 25 in the form of a Boxplot representation.

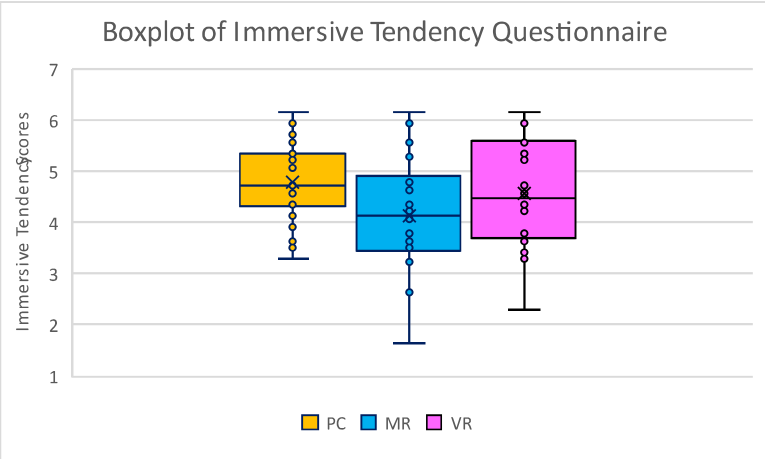

Figure 25: Boxplot Visualization of Immersive Tendency Questionnaire responses given by participants to each platform that shows the distribution of the calculated Immersive Technology Scores.

The distributions of the feedback given by the users to the Presence Questionnaire are given in Figure 26 in the form of a Boxplot representation.

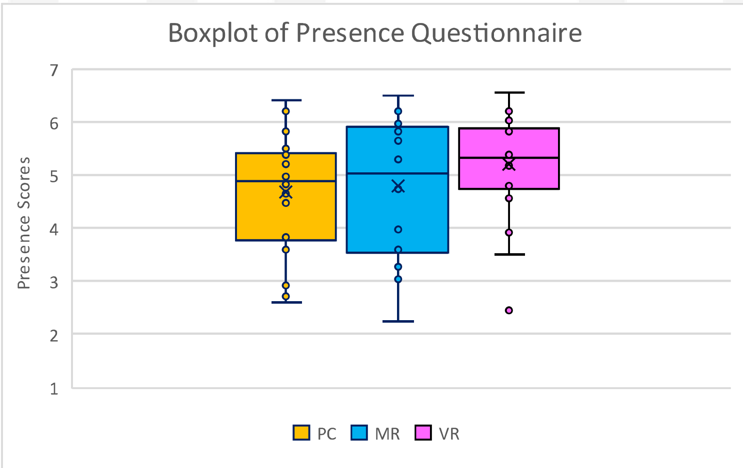

Figure 26: Boxplot Visualization of Presence Questionnaire responses given by participants to each platform that shows the distribution of the calculated Presence Scores.

CHAPTER 5

DISCUSSION

In this study, a 3D simulation environment of immune system cell micro-level responses has been developed. The response of white blood cells, when they detect bacteria, is simulated interactively in PC, VR, and MR platforms. After the application was developed, the volunteering participants were allowed to try the application on different platforms, respectively. Then the participants were asked to fill in certain questionnaires. The survey results were evaluated and the impressions of the application on the users were evaluated. The participants stated that the usability study was effective and that they would be interested in experiencing different biological processes in this way. It was also among the comments that an interactive training method could be easier to keep with such an application.

The infection simulation, done by creating a permanent bacterial density area, was stated to be the most effective interaction method by the volunteers. Participants often stated that they thought it was an effective demonstration of white blood cells targeting that area and being vulnerable to other bacteria because of the fixed bacterial area.

A frequent request received was that there should be more interaction in this kind of direct environment, where the effect can be seen. Many participants stated that the available interactivity currently for such an application is less, and more of it would be much more effective. In addition, users also stated that their first choice was the VR platform, and they would try it if there were a more interactive and advanced MR version. This is also seen in our results. Many users stated that the current version of the MR version of the application has deficiencies and remains at a very basic level. They stated that they would like to try a more advanced version of MR and that they thought it could be very effective. Users who experienced problems such as motion sickness with virtual glasses stated that they preferred the PC version more.

Based on the t-test on the System Usability scale, results revealed that the usability of the system is high among the users. For the System Usability Scale results for the VR platform, the median value was 2.84, the standard deviation was 0.25, and IQR was 0.35. In addition, system usability scores for the platforms were found to be 76.0 for PC, 78.0 for VR, and 75.25 for MR, respectively, showing that the application was found usable by the users based on the System Usability Scale. Considering the scores, it is seen that in general, users find the VR platform more usable than the other two platforms with a slight difference. This strengthens the opinion that users find the VR platform more effective, considering the results of other tests and the verbal feedback given by the participants. Another point seen in the system usability score results is that the PC platform score is slightly ahead of the MR platform. This value is consistent with the verbal feedback given by the users, especially about the MR platform. Users frequently stated that it was interesting to use the MR platform, but they preferred the PC platform because the interaction in the environment was insufficient as it is.

The distributions of the feedback given by the users to the system usability questionnaire are given in Figure 24. It is seen that the answers given to the VR platform had less variance stability. More interactive platforms such as VR and MR can offer more options in terms of user experience. However, the differences and preferences between the platforms based on Technology Acceptance Model scores are analyzed, and no significant difference was detected. The VR platform is slightly ahead of the other two platforms, as shown in the results.

A two-tailed t-test was conducted on the TAM questionnaire results. The test results are shown in Figure 25. According to these results, there were significant differences between the PC-VR and VR-MR values, but no such difference could be observed between the PC-MR values. These values also match with the verbal feedback of the users and strengthen the result that the users primarily find the VR platform effective. In addition, these results show that the acceptance levels of the participants between the PC and MR platforms are not very different from each other in the current situation of the platforms.

The calculated TAM scores were 6.86 for PC, 7.02 for VR, and 6.84 for MR; thus, it can be concluded that the participants found all platforms usable. Parallel to the other results, the TAM score results also show that the participants found the VR platform the most effective. Again, PC and MR platforms are close to each other.

When the overall survey results are evaluated in general, it is seen that the VR platform is found most effective by the participants, followed by PC and MR. Participants stated that such an application is effective, and they would prefer it to be used for training purposes. Some users, on the other hand, stated that they learned information about white blood cells that they did not really know and that they would remember it easily because they learned it by experience. Therefore, they said that more training and education content of this kind would be an effective learning method for them.

Participants (denoted by P, followed by participant number) gave verbal and written feedback in addition to the survey questions.

P1: “MR version is very different and exciting to see compared to the other platforms, but currently it does not have enough interactions for the simulation.”

Based on verbal feedback from participants, there is also the possibility that the enhanced MR version may have an impact on the results, as it is possible that an MR simulation allowing users to interact using real-world objects, without the need for any controller, has been a positive experience.

P2: "I wish I can control the number of bacteria and the white blood cells because it is very fun to see bacteria creation."

P3: "We want more cell types."

Participants stated that they could not especially choose the number of cells in the simulation among the negative feedback they gave verbally. Therefore, they stated that they could not see the large-scale movements as they wanted to do, and in some cases, they would want to see the bacteria winning and the situations where the white blood cells were insufficient, so they thought it would be a more comprehensive simulation.

P4: "I think the existing camera angles are not enough, I would like to see more camera angles."

P5: "It was really fun watching white blood cells attacking me and watching bacteria getting spawned. But I wish I can move myself to dodge bacteria."

Some participants also stated that it would be more effective to have more camera angles in various positions. In addition, some users stated that they wanted to be able to move, especially in the first-person camera mode. They wanted to avoid white blood cells when the bacteria mode was enabled, so they thought this modality would be more effective.

P6: "In-game inputs need to be shown. A button can toggle that interface."

P7: "I would like to toggle for the user interface (UI) system because I want to see information about the current status of the simulation."

Some participants stated that there should be an informative UI system, that they want to change the variables in the simulation environment, and that they want to follow the results through this interface.

P8: "Maybe a laser pointer can be used to select where to create new bacteria or select existing bacteria for control."

P9: "It was fun, but I would like to have more control over the cells."

Another frequently spoken improvement suggestion was that users want to control the bacteria they want specifically; they want to move the bacteria with the controllers and see the results of their movements. With this, the white blood cells can follow the path created by the users in the vessel (while chasing the bacteria), and they will be able to experience the results.

P10: "More visual effects and feedback are needed."

P11: "Sound would make things easier and more immersive."

P12: "Sound effects for actions would make it much better."

P13: "The lack of sound impacted my feedback."

In addition to these, it was also among the feedback that it would be nice to have sound and visual effects to increase impressiveness. The positive and negative verbal feedback given by the participants for the application is included in Figure 27 and Figure 28 as a word cloud so that it can be understood more easily. Topics on which users gave feedback regularly are shown in a larger format. Since these keywords are from the feedback regarding the simulation, they can be of utter importance to guide and indicate areas for development in future studies.

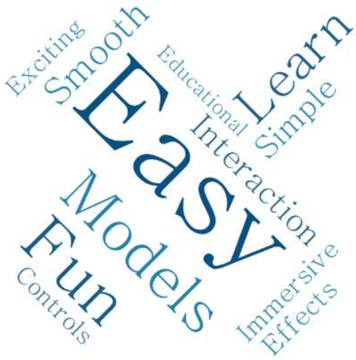

Figure 27:Word cloud of participants' positive verbal feedback.

Figure 28: Word cloud of participants' negative verbal feedback.

CHAPTER 6

CONCLUSION AND FUTURE WORK

It is not always easy to explain and show biological processes in the field of visualization. Therefore, different methods are tried to facilitate this process. In this way, it is aimed to facilitate the demonstration of such biological processes with real-time interaction and accelerate the studies. While doing this, the use of new technologies such as VR and MR is frequently seen. Technologies such as VR and MR offer completely different experiences and offer new methods and possibilities in the training process. Therefore, studies using such technologies are increasing rapidly. While carrying out such studies, the platform preferences of the users are also examined, and new control schemes are developed. In this way, it is aimed to find the platform and control structure where users will feel most comfortable. Thus, the most suitable and comfortable structure will be found for the users.

This study shows a 3D interactive environment created for the PC, VR, and MR platforms that demonstrates the defense mechanism of white blood cells against pathogen cells. In this way, it is aimed to accelerate this learning process by allowing users to see the reactions of white blood cells and interact with them. The use of such an interactive simulation shows the potential in enhancing the understanding of biological phenomena. A 3D vessel structure was developed for interactive experiments, allowing cells to move in laminar flow and interact with each other within that vessel. At the same time, the application was developed for PC, VR, and MR platforms, and user preferences between these platforms were investigated. In this area, we have seen that there are few such simulations that can work in 3D and on different platforms with real-time interactions, and because of the questionnaires and evaluations, we have determined that users want more such applications. Users want to see the environment and environment variables quickly at a more basic level. In this way, it has been seen that the simulation is easily understandable by the users. Unlike the existing simulations, it has been seen that the interaction and display at the basic level have a positive effect on the users.

The study was evaluated on 27 volunteer participants and Technology Acceptance Model, System Usability Scale, Immersive Tendency, and Presence questionnaires were filled in by the participants. The Technology Acceptance Model measures the acceptance of the application by the users, The System Usability Scale measures the ease of use of the application for the users, Immersive Tendency is used the measuring the immersive feeling of the users in the application, and the Presence questionnaire measured the feeling of presence in the environment for the participants. As a result, it has been seen that such an interactive simulation can become a promising visualization framework.

As a result of the evaluation of the survey results, it was concluded that the participants found the use of such an application for visualization purposes logical and effective. They stated that an interactive learning method is effective, and they easily understand certain behaviors of white blood cells. Participants stated that they found the VR platform the most effective, followed by the PC and MR platforms, respectively. Also, it was seen that participants expected more different scenarios and interactions with the environment, there is still an opportunity for advancement in terms of enhancing the interactions of the simulation and establishing additional real-world interactions. Seeing the simulations of many different cells and structures passing through the vessel in the same environment can increase the immersiveness and also the user experience. Adding many elements in the body to simulation, such as interactions of white blood cells with viruses other than bacteria, interactions with other cells in the vessel, structures in which more vessels are together, and experiencing them both together and separately, can create different scenarios. In this way, it will be possible to simulate many different biological processes. Participants found all platforms effective and usable. And for all of them, they stated that they would like to see a more advanced and more content full version in the future. However, the participants shared that they especially wanted to see MR develop more in the future. Because users intensely stated that it was enjoyable to try the MR platform, but the existing interactions were insufficient, and they also stated that they would want to try it if there was much more interaction. They stated that it was exciting to see the real world directly and to see it by placing objects in the real world. In the future, many improvements can be made, such as interacting with the environment directly using hands without controllers, creating a dynamic vein system directly on physical objects in desired places, and more.

Our findings add to the corpus of knowledge about the effectiveness of employing 3D interactive environments to visualize biological activities. Overall, this study represents a promising step toward the utilization of 3D interactive settings for biological visualization and research. With sustained work and further development, interactive simulations will most certainly become crucial tools in improving knowledge of complex biological phenomena. We hope that this study will help and lead to the development of more such interactive simulations and applications in the biology field.

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APPENDICES

APPENDIX A

Additional Simulation Visuals from Different Phases

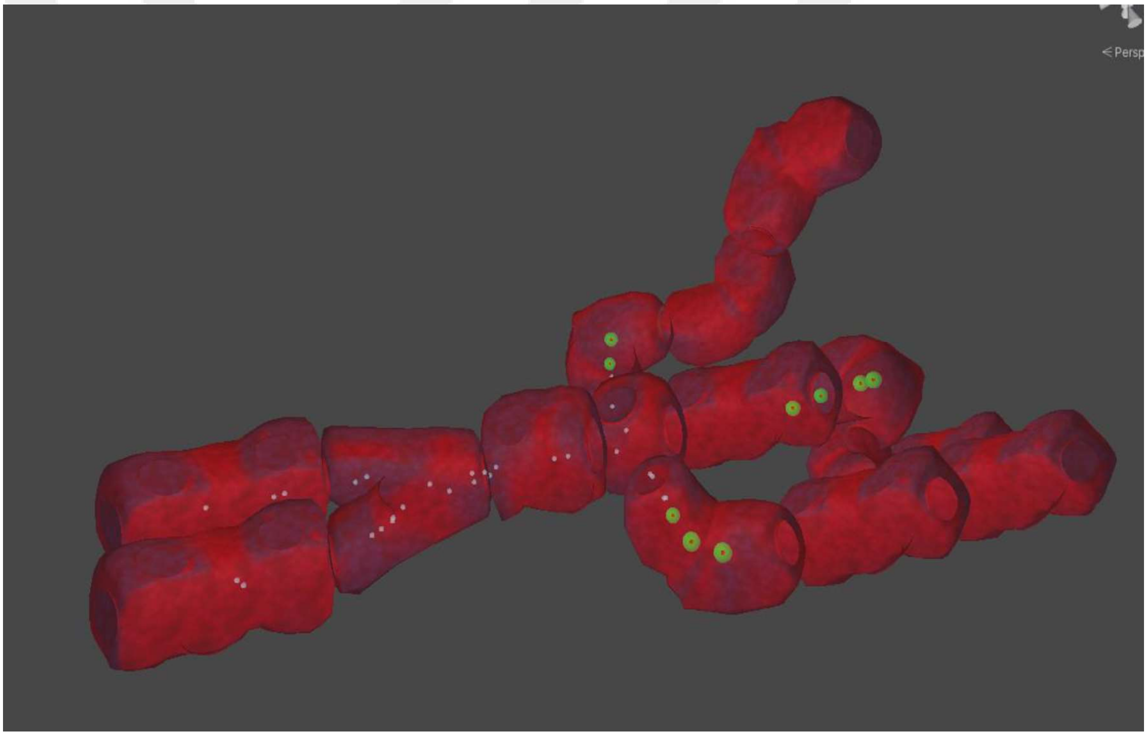

Figure 29: Simulation run time visuals.

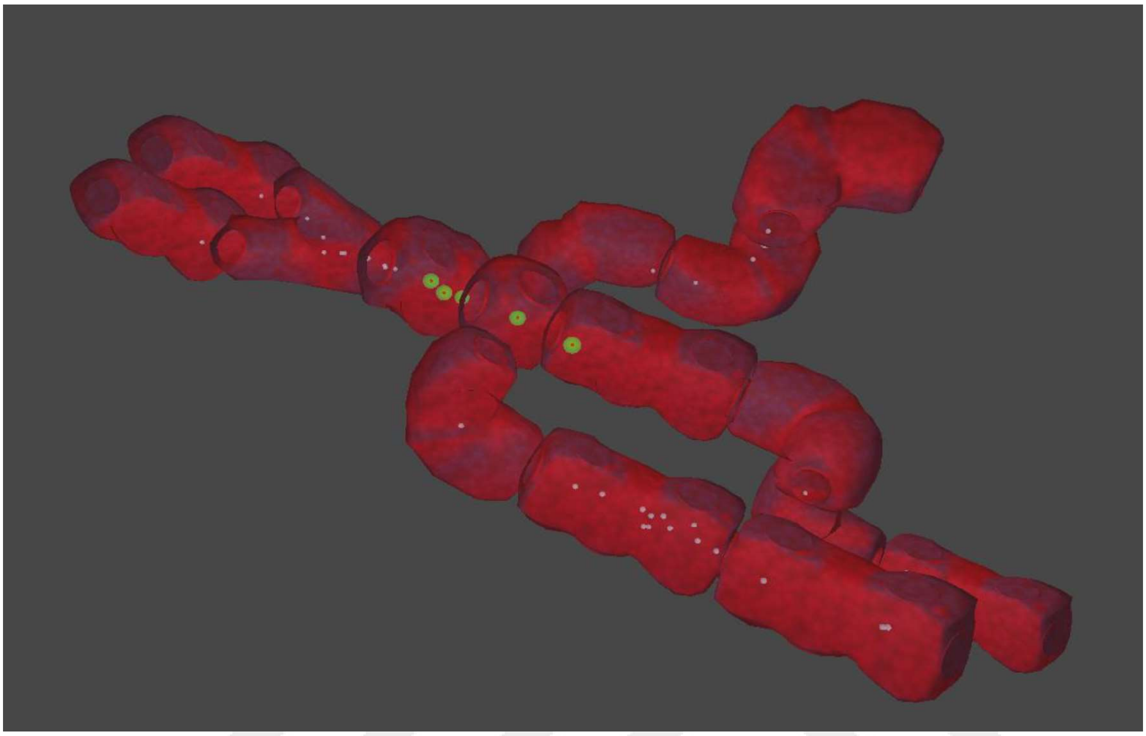

Figure 30: Simulation runtime visuals.

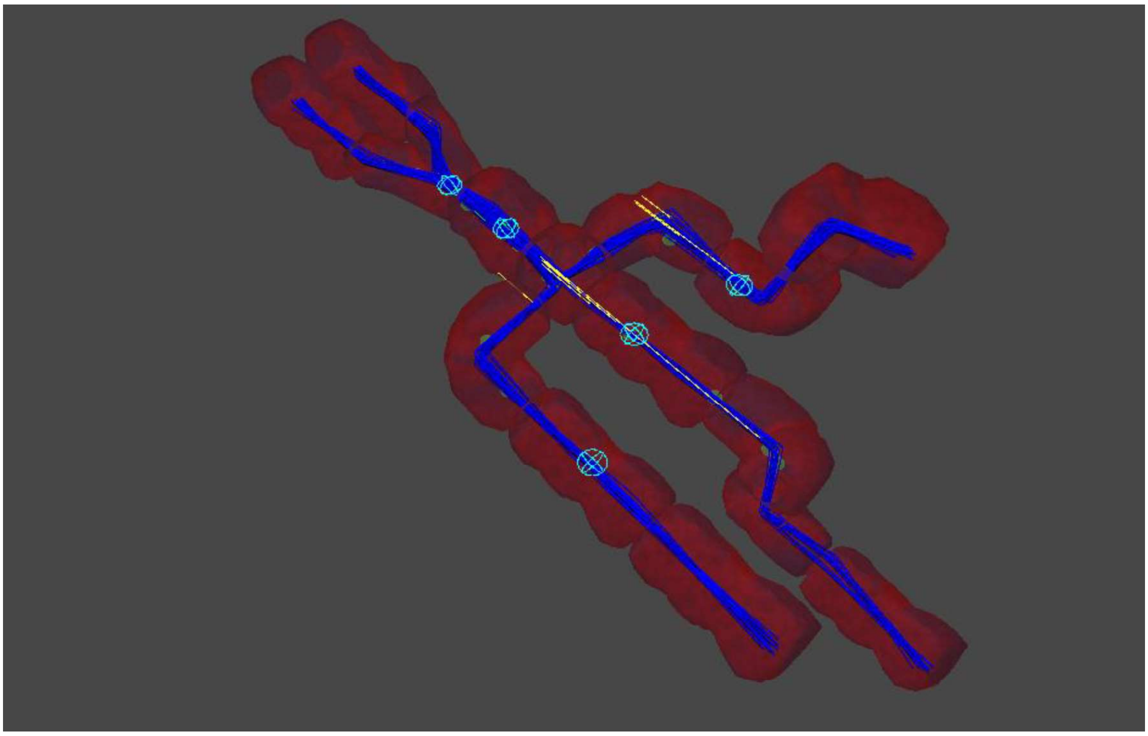

Figure 31: Cell spline paths and possible permanent bacteria creation points in the runtime.

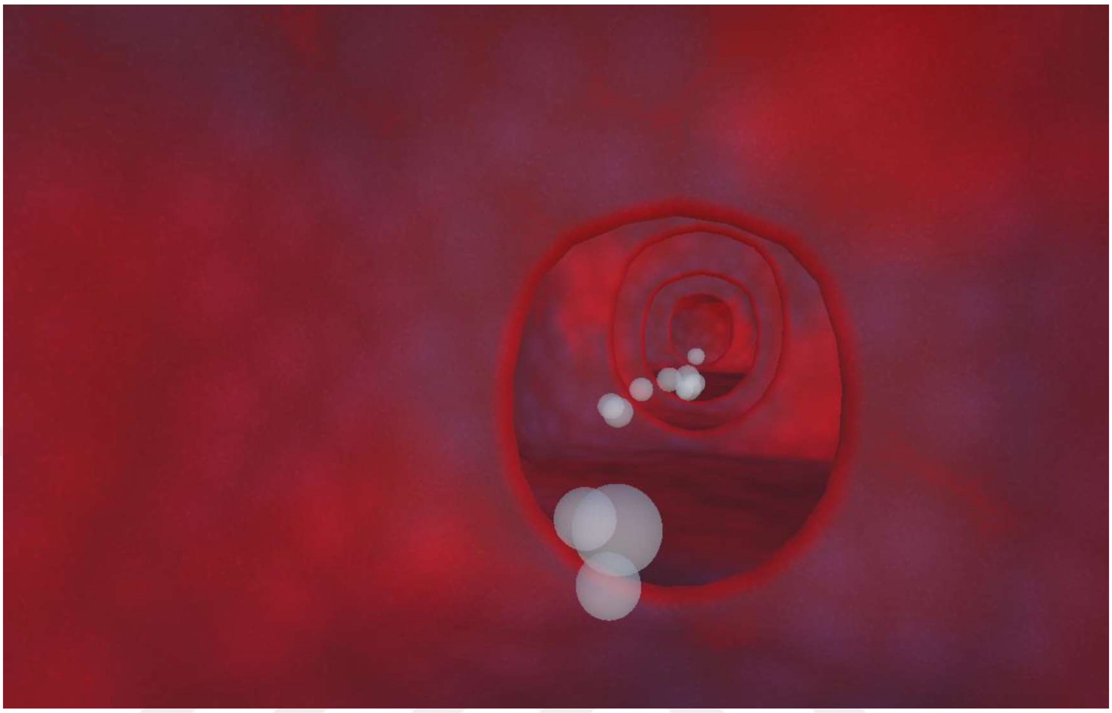

Figure 32: WBCs moving in the vessel.

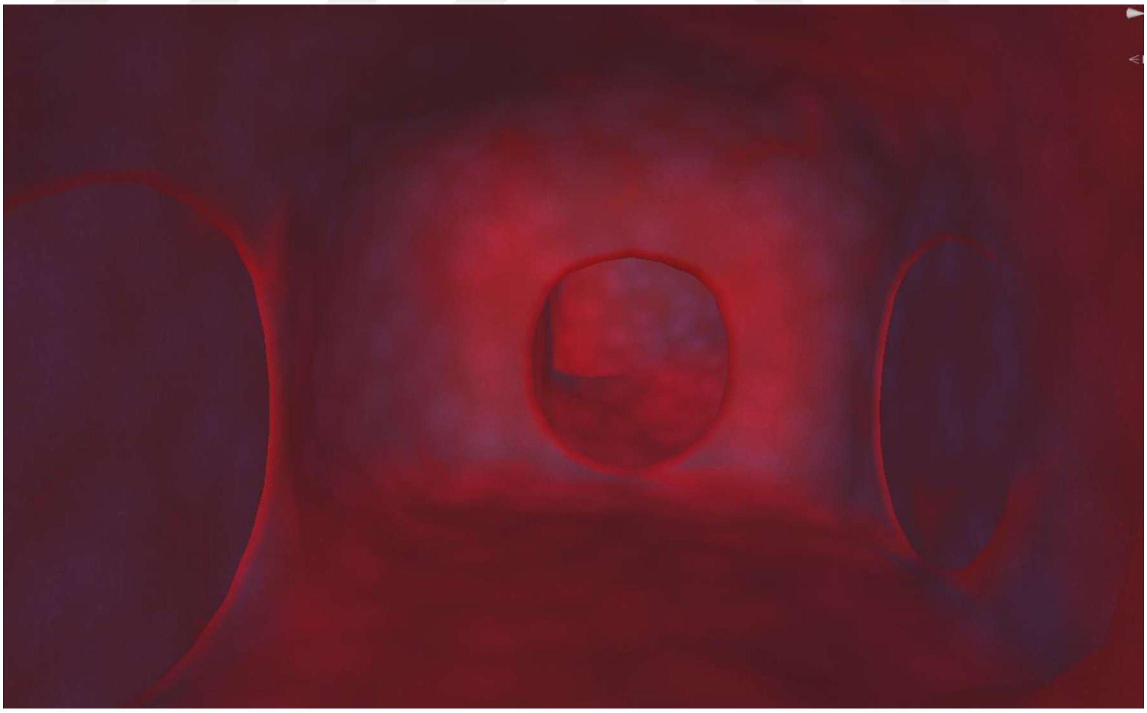

Figure 33: Empty vessel representation.

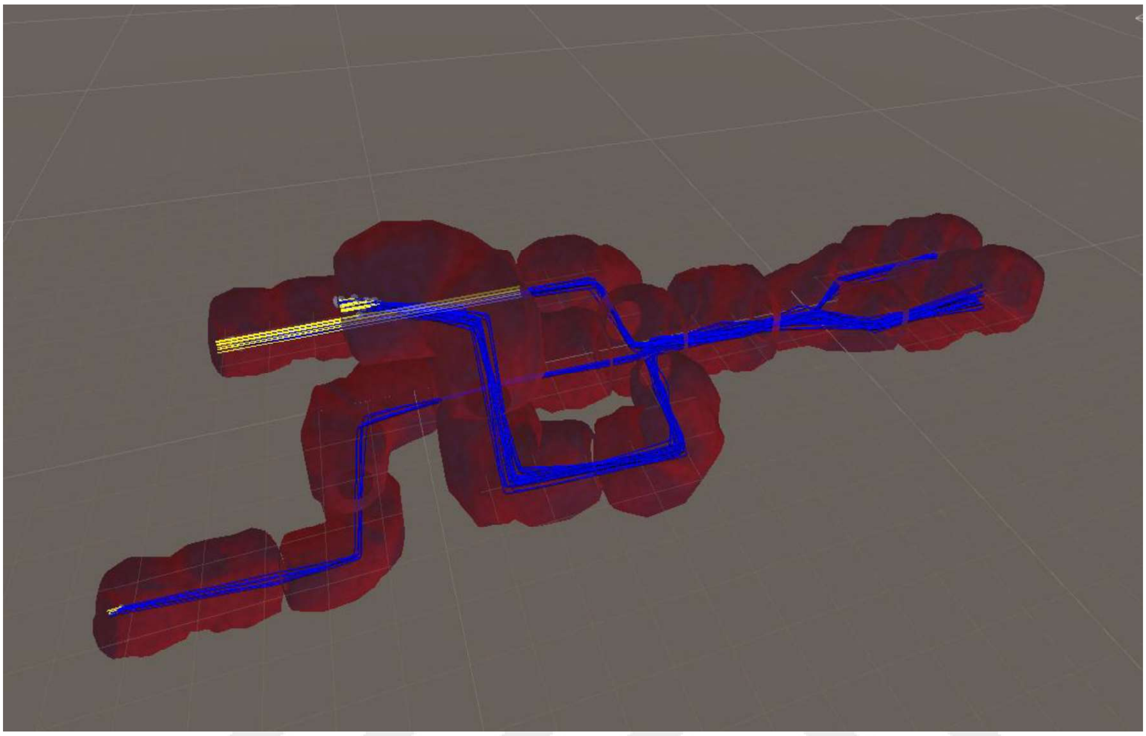

Figure 34: Cell spline paths and control vector rays.

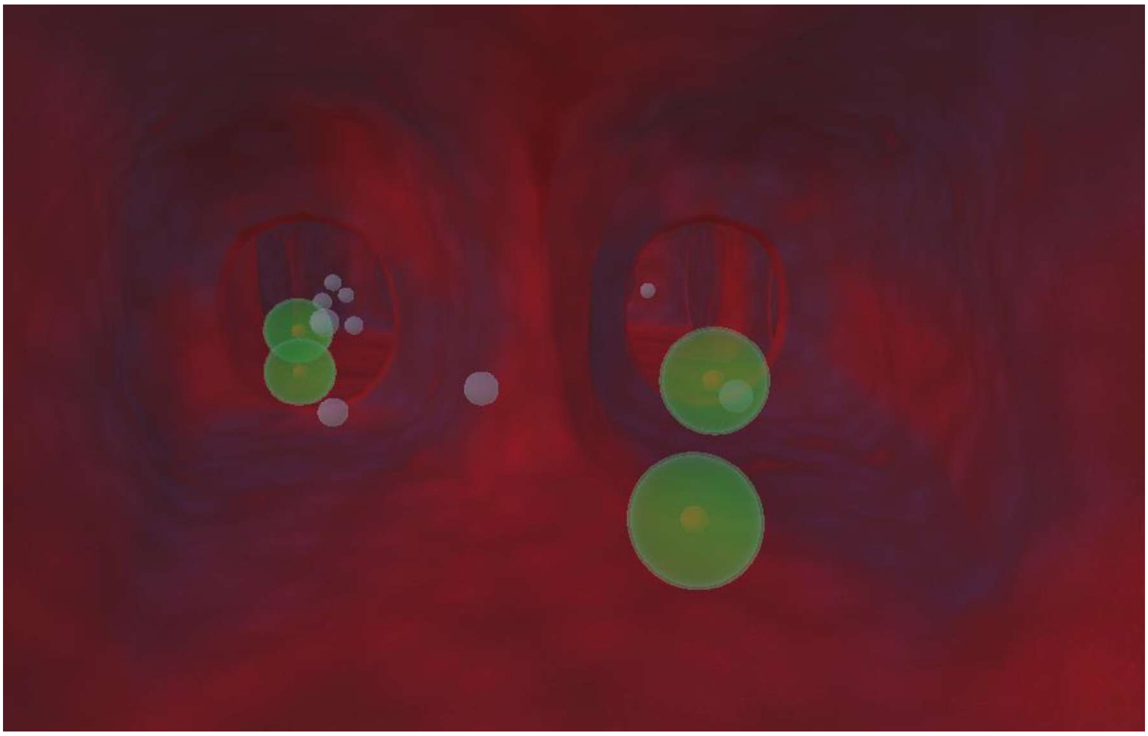

Figure 35: Runtime representation of WBCs and bacteria together.

APPENDIX B

Platform Selection Menu in the Immersive Environments

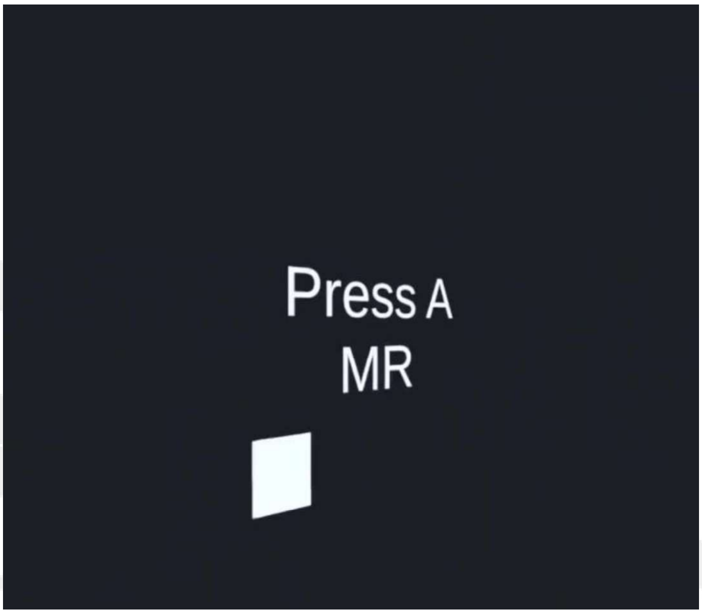

Figure 36: Platform selection menu in an immersive environment.

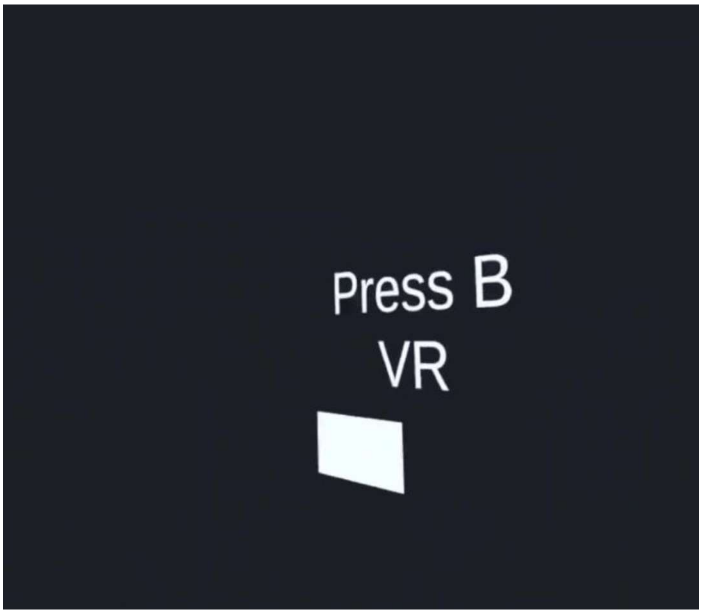

Figure 37: Platform selection menu in an immersive environment.