3D Simulation and Comparative Analysis of Immune System Cell Micro-Level Responses in Virtual Reality and Mixed Reality Environments

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Abstract. When working on any informatics topic, it is critical to understand the primary mechanism of the domain. This is no different in bioinformatics, which necessitates a fundamental grasp of the biological phenomena under consideration. Understanding biological phenomena, on the other hand, is not always easy since the intricacy of the events and the difficulty in picturing the events can often lead to difficulties in gaining insight, which is especially important in education. For teaching purposes, many biological processes are shown in written and visual form. New technologies such as virtual reality (VR) and mixed reality (MR) are occasionally used to increase the efficacy and ease of use of the training. In this study, a 3D interactive simulation of white blood cells, one of the body's defense system components, battling bacteria in a blood artery, was used. Twenty-two participants tested the interactive demonstration of how these cells function in Personal Computer (PC), VR, and MR settings, and an answer to which platform was favored for this sort of visualization was sought. The findings highlight the potential of such interactive experiences, in which participants effectively evaluate usability, immersion, and presence.

Keywords: Virtual Reality · Mixed Reality · Multimedia Applications · Biological Applications · System Usability Scale

1 Introduction

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

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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 very 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 education, biological processes can sometimes be explained by narrowing down the focus, or subject comprehension can be made more efficient by visualization [1–3]. These techniques allow the learners to better understand the complex interactions of biological phenomena and explore how these interactions affect system functions [4]. This is particularly important in education, where visualizations 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 [5–7]. Different studies have been performed on the visualization of biological processes for this purpose[1], and there is evidence showing that these studies have positive effects on users [8]. Technologies like Virtual Reality (VR) and Mixed Reality (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. With these technologies, studies have been carried out to show and simulate various biological phenomena [9–11].

There are currently many different biological simulations that can be used for different purposes. Andrews et al. [18] 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[2] program. Ghaffarizadeh et al. [19] developed an open-source agent-based simulator called PhysiCell and they stated that it provides the stage to the players for studying many interacting cells in dynamic tissue microenvironments. In most of these simulations, users can set simulation parameters and get simulation outputs. Some simulations show the images of real experiments 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 too. 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. Also, 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.

This 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 activity of these cells in a 3D environment is simulated so that users can effectively understand the dynamics of these white blood cells. Users can see the basics of the defense of white blood cells in the vessel, interact with this system, and directly

[1] White Blood Cell Differential Simulator, https://www.medialab.com/case-simulator-wbc, Last accessed: 2023–04-30.

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

observe the effects of different factors. This interactive experience provides a simple explanation of the activity of these white blood cells in a blood vessel (a capillary). The interactive simulation was presented for three different platforms, and one of the research questions was to determine which platform would be more effective and usable for users. The three platforms, PC (Flat Display), VR, and MR, have been used so that a comparison regarding the clarity of the proposed simulation is possible. For this purpose, a 3D capillary environment was created in the Unity 3D engine[3], and a one-way laminar blood flow was simulated in this vein. A customized version of Unity's experimental Spline package was used to enable unidirectional laminar flow. Although the movements of the bacteria and white blood cells in the vein follow the flow, it is also possible for the white blood cells to target and migrate toward the bacteria and to try to destroy them in the simulation. A density factor is used to model this movement. When a white blood cell enters a bacterial area, it calculates this value. If the calculated value is above a certain limit, it begins migrating toward the source and tries to destroy that bacterium. In addition, users can create different situations and observe the effects of these trials. With these interactions, users can create a permanent bacterial field and perform a basic disease simulation, observing that white blood cells are vulnerable to new threats in a situation where they are on active defense. In addition to that, users can follow the changes and interactions in the environment by creating more bacteria in the environment. They can interact with the world and see the results of these interactions in real-time. We surveyed 22 participants who interacted with the simulation and filled out standard questionnaires such as Technology Acceptance Model, System Usability Scale, Immersion Tendency Questionnaire, and Presence. The results show that users found the application useful and that their priority platform preference was VR. Overall, this study demonstrates the potential of VR and MR technologies in bioinformatics education and highlights the potential use of these technologies in the bioinformatics domain.

2 Materials and Methods

2.1 Development Process

During the development of the simulation, the Unity3D game engine has been used since the Unity3D game engine can easily be adapted to different platforms in a fast and efficient way. Initially, prototypes of the interactions between bacteria and white blood cells have been visualized. White spheres are used to represent white blood cells in the simulation, red spheres to represent bacteria, and green areas around the bacteria to represent their chemical trail intensity (i.e., the "odor" that the white blood cells use for chemotaxis). Initial implementation starts with an empty development environment and spheres representing bacteria and cells.

2.2 Movement Algorithm

At the beginning of the study, white blood cells were instantiated in random positions in an environment with defined borders and moved using random walks. Then, bacterial

[3] Unity Real-Time Development Platform, https://unity.com, Last accessed: 2023–04-30.

cells were created at random points in the environment. The OnTrigger function in the Unity3D library was used to target bacteria. First, the bacterial cells were directly targeted, and the white blood cells were allowed to follow them until they reached the center of the bacterial cells. However, it has been observed that this movement is unnatural, and the method is insufficient to perform this movement in case of a flow in the environment. Therefore, an alternative movement algorithm has been developed to give a sense of movement in a natural flow structure and support flow vectors in different directions. In this way, both the flow in the vessel is represented, as well as the movements of the targeted cells are shown more naturally. Spline structures are used to represent the flow within the vessel so that the main paths to be followed by the cells over the predetermined main routes and to generate different random deviations over these routes are determined. Different ready-made Spline packages and a manual Spline algorithm have been developed and tested for the creation of paths. Manual additions were made to satisfy the project requirements by using the experimental version of Unity3D's official Spline package (v2.1.0.)[4]. The working logic of the movement system of the cells is as follows: The main waypoints that the white blood cells will travel through the vessel were determined manually, and different paths were produced for each cell centered around these main waypoints. Each cell thus moves on one of these pathways. If the cell encounters any chemical signal during the movement and decides to follow it, it leaves this path and starts to follow its target. If the target cell is destroyed, it returns to its original spline path and continues that path (Fig. 1).

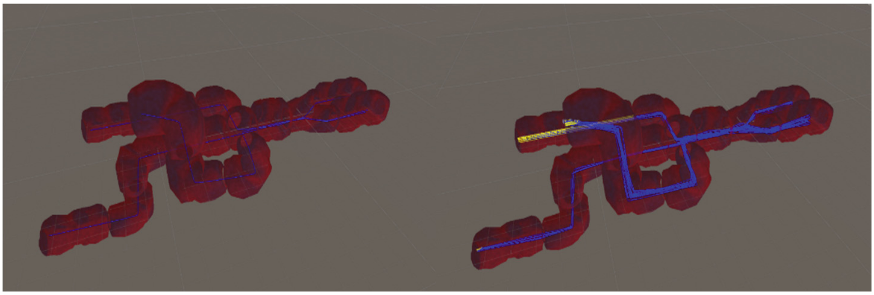

Fig. 1. Main spline paths (left panel), each cell creating its path in the veins (right panel)

2.3 Environment Models

Since the simulation takes place inside the vessel, modular models that can represent the vessel's interior and simultaneously allow the creation of different environments quickly are used. To speed up the development, ready-made and free-to-use packages (i.e., Unity3D's official Creator - FPS Kit[5]) were selected. FPS Kit has a vein-like shaped

[4] About Splines, https://docs.unity3d.com/Packages/com.unity.splines@2.0/manual/index.html, Last accessed: 2023–04-30.

[5] Creator Kit: FPS, https://assetstore.unity.com/packages/templates/tutorials/creator-kit-fps-149310, Last accessed: 2023–04-30.

game level model for prototyping while containing various tools and models to teach how to make a game in the first-person camera mode in an environment set in Unity3D. The vessel models included in the package 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 extracted 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).

2.4 Targeting Algorithm

After the cell's movement systems were developed, the targeting and migration algorithm that the white blood cells will use to follow the bacteria was developed. The default trigger structures in Unity3D were used up to this point, and each cell was set to be activated directly during an interaction with a target cell. However, in this study, realism has been an important design parameter while creating the simulation environment. For this purpose, the responses and movements of white blood cells were studied, and it was seen that white blood cells detect the chemical trails of bacteria (e.g., through 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. For the calculation of the density factor, the exponential fog formula (Eq. 1) from the Microsoft DirectX library was taken as a basis, and the values were updated according to the number scale in the environment.

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

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 center of the bacterial 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, a dynamic cell tracking system within the field is developed. White blood cells target the bacteria they touch during their movement and destroy them in turn. When a target cell is destroyed, all white blood cells migrating to the cell return to the path, they continue their movement in the flow.

2.5 Environment and Units

White Blood Cell. White blood cells represent the main defense cells in the vein, and they are modeled as white spheres in the environment (Fig. 2). They move in the direction of flow in the vein, and if they encounter the chemical trail of a bacterium, they may migrate toward the target and kill it, with probability based on the calculated density value. When the target is destroyed, a white blood cell continues its movement in the flow from where it leaves off. The velocity of each white blood cell in the flow is calculated randomly and thus differs from one another. When the cell is created, a new path of its own is created in the flow over the main turning points, and the cell follows this path.

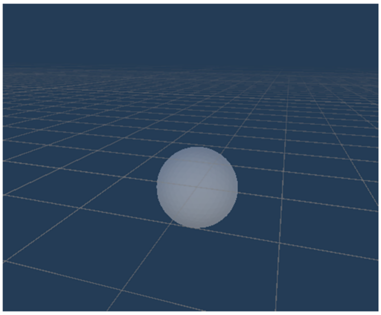

Fig. 2. White Blood Cell Visualization

Bacteria. Bacteria represent the harmful elements in the vein (e.g., bacteria or dead cells). The red sphere in the middle represents the bacterium, and the green sphere around it represents the chemical field of the bacterium (Fig. 3). The chemical field volume grows over time. The duration and limit of this growth vary from cell to cell, so the probability of targeting each bacterium is different. The speed of each bacterium is different in the flow, thus increasing the randomness in the environment. When the cell is created in the environment, a new path specific to each cell is created by using the main turning points, and the cells follow this path. In addition to this movement in bacteria, there is also the possibility of turning to different points on the path at random time intervals.

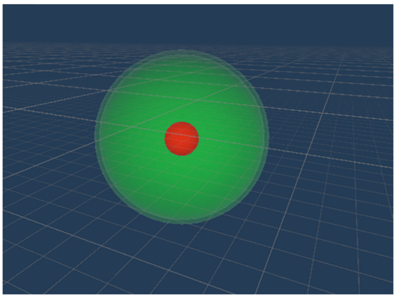

Fig. 3. Bacteria Visualization

Vessel Walls. Vessel walls serve as the limiting elements of the space in the environment. Cells, both white blood cells, and bacteria, are limited to moving in the volume enclosed by the vessel walls—migrating into tissue is not simulated. The material of the vessel wall model has been made so that the interior of the model can be seen from the outside (Fig. 4). In addition, the shader on the model offers a lively look and contributes to the feeling of the environment. Vessel walls are used when the movement path-related variables like spline shape, creation points, and flow direction parameters are set within the limits of the environment.

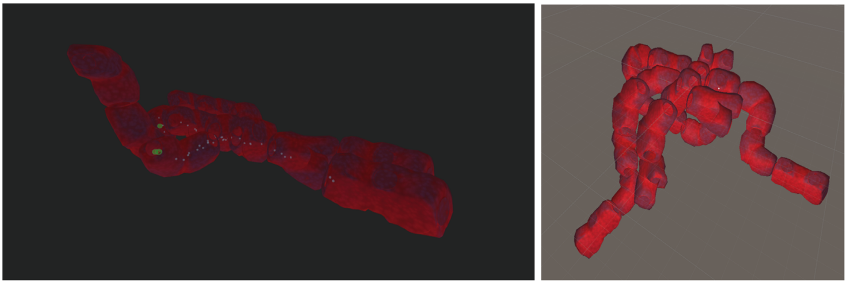

Fig. 4. Vessel Walls Representations

2.6 User Interactions

The 3D simulation is developed for three different platforms (Personal Computer (PC), Virtual Reality (VR), and Mixed Reality (MR)) so that a thorough comparison based on the differences between these modalities could be made by the users. Given that each platform has a different control scheme and there are different user inputs, the impact of these features on the user experience is investigated. User inputs for PC are taken directly from the keyboard and mouse, and the OVRInput package[6] is used to get user inputs for VR and MR platforms. Initially, 50 WBCs and 20 bacteria are created in the environment. As soon as the user enters the scene, these cells are present in the environment and they interact with each other. After a while, all the bacteria die, and WBCs continue their actions. The user can create changes in this process with various inputs. However, the WBC number is constant, and the total bacteria count cannot exceed 45 in the run-time because of visual understandability and optimization perspectives.

User entries. 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 interactions with white blood cells. There is an upper limit on the number of bacteria that can be created in the environment to maintain a minimum viable frame rate.
2. **Creating a Permanent Bacterial Field:** The user can experience a small-scale infection simulation by creating a permanent bacterial field. The white blood cells that start

[6] Map Controllers | Oculus Developers, https://developer.oculus.com/documentation/unity/unity-ovrinput/, Last accessed: 2023–04-30.

to follow this area remain closed to the area created and are not able to interact with other bacteria, which shows the effect of weakening the defense system at the time of illness. Users can destroy this area at any time.

3. **Interacting as Bacteria:** In the first-person camera mode, users can interact as bacteria and observe the white blood cells targeting them. While in this mode, white blood cells are not able to destroy the bacterium assigned to the user.
4. **Camera Mode Switching:** Users can switch between first-person and third-person camera modes on supported platforms and experience the environment from different perspectives.
5. **Third-Party Camera Mode Position Changing:** Users can try the simulation environment from different positions and observe the results of interacting with the environment by changing their positions in the third-person mode (Fig. 5).

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 it includes both a primary and a third-person camera viewpoint. The PC version has the features of creating new cells with keyboard inputs, creating a permanent bacteria area, interacting as bacteria, and switching between camera modes and positions. There is no frame rate limit.

Virtual Reality (VR): VR has all the user inputs as in the PC environment, but the speed of the simulation 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, the MR version only has a third-person perspective. In this way, simulations can be made and observed on the real-world images taken from the cameras. Other user inputs were used in the same way as the VR. The frame rate is limited to 60 frames per second.

Optimizations. Sphere Shapes. The default sphere in the Unity3D game 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[7], and this optimization was used in place of a sphere. Following this substitution, the performance increased significantly and reached a satisfactory level.

Environment Modeling. Environment models were used from Unity3D's official FPS kit asset, and changes were made to them. The custom environment shader included in the package was customized for two-sided rendering and lighting. However, no changes were made to the motion and animation parts in the shader.

Lighting. Ambient lighting is used as bake lighting considering performance. There is no dynamic lighting in the environment. While developing the ambient lighting, care was taken to ensure that the cells and vessel walls were clear and not obstructing the

[7] Blender.org | Home of the Blender project, https://www.blender.org/, Last accessed: 2023–04-30.

users' line of sight. After adjusting the colors and powers of the lights in the scene, they were baked, and the light data were applied to the scene.

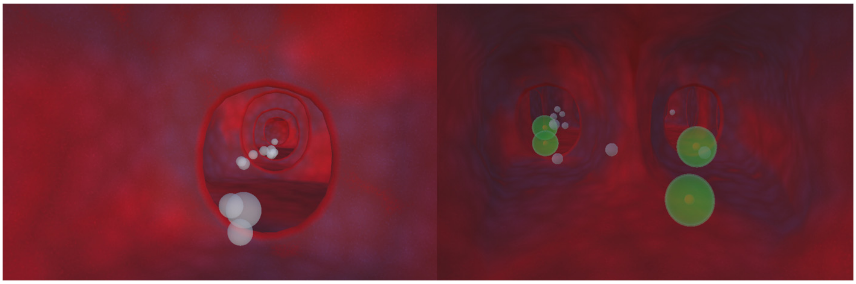

Fig. 5. User View in The Scene

2.7 Evaluation

After the development of the simulation, working versions for three different platforms were implemented: PC, VR, and MR using the Oculus Quest 2 device. An open space was arranged like a workshop where users could experience the application on each platform in turn (Fig. 6). To gather data on user experiences with each platform, the participants were asked to fill out several standard questionnaires after each trial. The questionnaires used are the Technology Acceptance Model (TAM) [14], System Usability Scale (SUS) [15], Presence Questionnaire [16], and Immersive Tendency Questionnaire [17]. The TAM questionnaire was used to measure the participants' acceptance of the technology and it includes questions about the perceived usefulness and ease of use of the system. The SUS questionnaire was used to measure the overall usability of the system. The Presence questionnaire was used to measure the users' sense of being present in the simulation environment. Finally, the Immersive Tendency Questionnaire was used to

Fig. 6. User Experience Tests with Oculus Quest 2 for VR and MR Simulations

measure the degree to which users were immersed in the simulation. After completing the experiments and filling out the questionnaires, the collected data were analyzed.

3 Results and Discussion

In this study, a 3D simulation environment of immune system cell micro-level responses has been developed and tested by 22 participants. The age range of the participants is 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. The results, based on 22 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. The participants stated that the educational 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 learning method could be easier to retain.

The infection simulation, done by creating a permanent bacterial density area, was stated to be the most effective interaction method by the volunteers. A frequent request received was that there should be more interaction in this kind of direct environment, where the effect can be seen. The participants also stated that being able to interact with more features in the environment and seeing their results would be 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. Users who experienced problems such as motion sickness with virtual glasses stated that they preferred the PC version more.

When we applied the t-test on the System Usability scale, results revealed that the usability of the system was 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 the 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 Fig. 7. Considering these distributions, 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 Fig. 8.

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. These values also match with the verbal feedback of the users and strengthen the result that the users primarily find the VR platform effective. 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. Table 2, Table 3, Table 4, and Table 5 show the t-test results of the participants given to the Technology Acceptance Model, System Usability Scale, Immersive Tendency, and Presence questionnaires, respectively. Figure 7, Fig. 8, Fig. 9, and Fig. 10 show the answers given to the System Usability Scale, Technology Acceptance Model, Immersive Tendency, and Presence questionnaires as boxplots, respectively. 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.

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)
Personal Computer (PC)	4.74 ± 1.21	7.19 ± 1.55	4.78 ± 0.77
Virtual Reality (VR)	5.20 ± 0.96	7.02 ± 1.86	4.55 ± 1.03
Mixed Reality (MR)	4.89 ± 1.46	6.83 ± 1.91	5.14 ± 1.11

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

	PC-VR	PC-MR	VR-MR
n	22	22	22
t	2.210	0.881	2.708
p	0.038	0.389	0.013
df	21	21	21
Std. Error	0.15	0.16	0.07

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."

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

	PC-VR	PC-MR	VR-MR
n	22	22	22
t	1.636	0.324	1.873
p	0.130	0.752	0.088
df	11	11	11
Std. Error	5.99	0.75	1.87

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

	PC-VR	PC-MR	VR-MR
n	22	22	22
t	1.521	3.768	2.761
p	0.143	0.001	0.012
df	21	21	21
Std. Error	0.15	0.17	0.15

Table 5. Two-tailed t-test results for the Presence Q uestionnaire

	PC-VR	PC-MR	VR-MR
n	22	22	22
t	0.016	0.546	1.479
p	0.016	0.546	0.154
df	21	21	21
Std. Error	0.02	0.55	1.48

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 could 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.

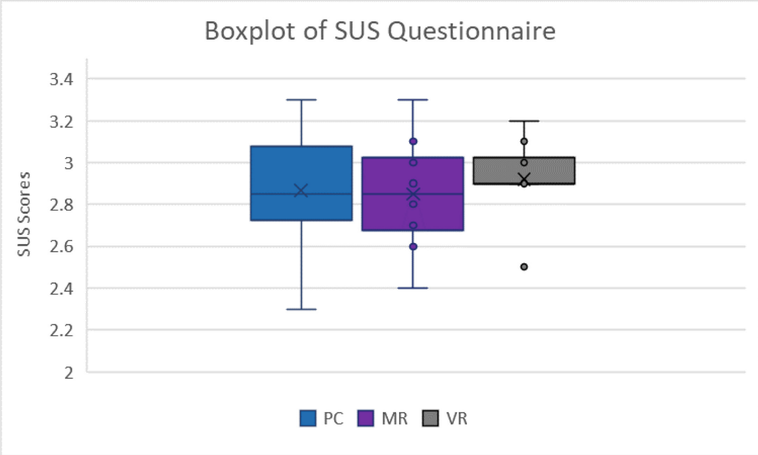

Fig. 7. Boxplot Visualization of System Usability Scale Questionnaire responses given by participants to each platform that shows the distribution of the calculated SUS Scores

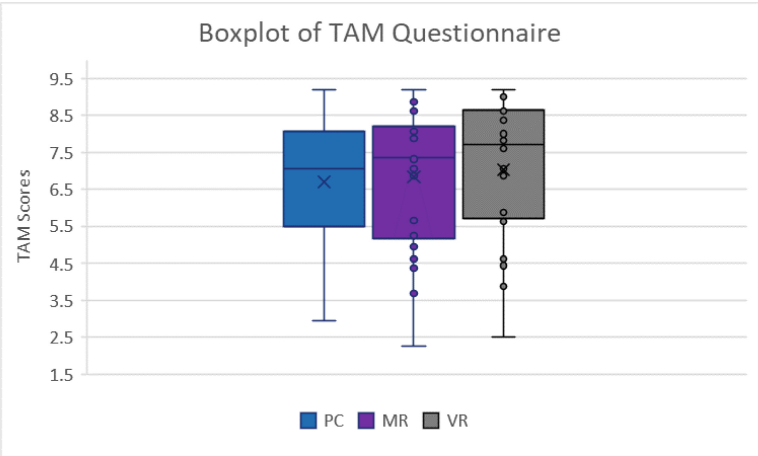

Fig. 8. Boxplot Visualization of Technology Acceptance Model Questionnaire responses given by participants to each platform that shows the distribution of the calculated TAM Scores

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 could move myself to dodge bacteria."

Some participants also stated that it would be more effective to have more camera angles in different 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.

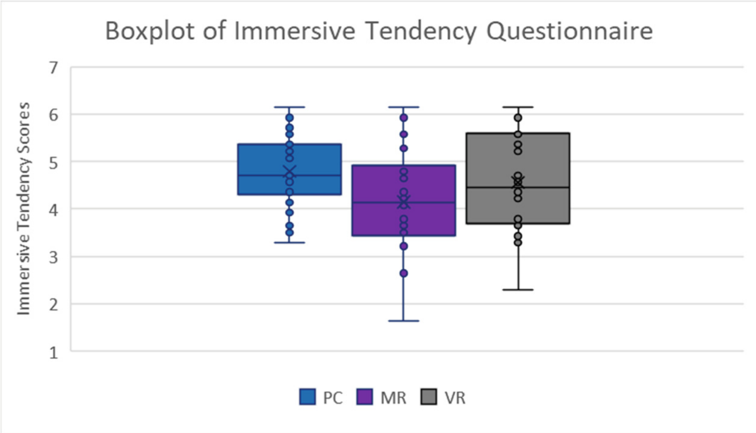

Fig. 9. Boxplot Visualization of Immersive Tendency Questionnaire responses given by participants to each platform that shows the distribution of the calculated Immersive Technology Scores

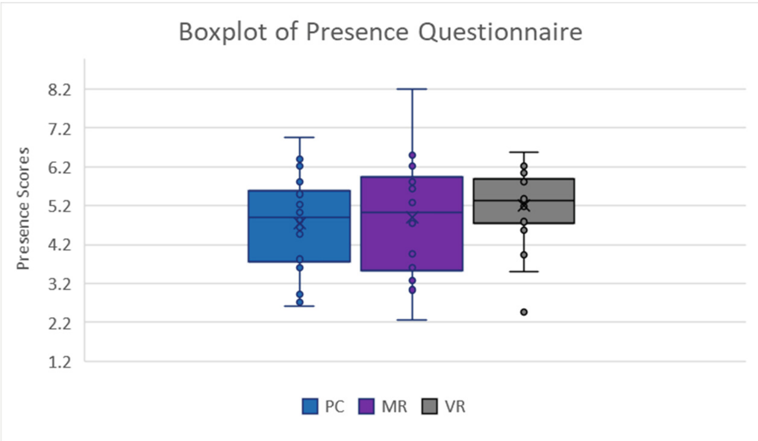

Fig. 10. Boxplot Visualization of Presence Questionnaire responses given by participants to each platform that shows the distribution of the calculated Presence Scores

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 Fig. 11 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.

(a) **(b)**

Fig. 11. (a) Word cloud of participants' positive verbal feedback, and **(b)** Word cloud of participants' negative verbal feedback

4 Conclusion

This study shows a 3D interactive environment created for the PC, VR, and MR settings that demonstrates the defense mechanism of white blood cells against pathogen cells. The use of such an interactive simulation shows the potential to enhance 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. As a result of the study conducted with 22 participants, it has been seen that such an interactive simulation can become a promising visualization framework. Following the user experiments, it was seen that participants expected more interaction with the environment, and they found the VR platform to be the most effective of the evaluated platforms, whilst the MR platform provided insufficient interaction. However, there is still an opportunity for advancement in terms of enhancing the interactions of the simulation and establishing additional real-world interactions, particularly for MR. 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.

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