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Learning metabolism with virtual reality to optimize biochemistry education in the Spanish-speaking region

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ABSTRACT

Learning science is undoubtedly a challenge, considering that new generations have plenty external stimuli to overcome. Students are surrounded by digital experiences such as video games, animation and videos, etc., therefore, their way of learning has evolved to be more attached to visual and dynamic resources rather than to plain texts. Hence, the objective of this study was to design, implement, and evaluate a virtual reality environment as a microteaching mechanism for human metabolism, including the electron transport chain and oxidative phosphorylation. This was a pilot study used to evaluate the learning experience of a platform designed at our institution. The study included the design of Virtual Reality experience, the organization of activities and instructional design, and the evaluation of the knowledge acquired, as well as the students' perception of its usefulness. Nine groups of students from our institution's health entry programs, from different academic periods, were taught the electron transport chain and oxidative phosphorylation using Virtual Reality by different instructors. Their learning through Virtual Reality was compared to what they would have learned through 2D activities. The results showed that the level of knowledge increased significantly associated with the use of Virtual Reality compared to their traditional system ($p<0.00001$). A high percentage of students (>90%) found it beneficial to use Virtual Reality. The implementation of a Virtual Reality strategy for learning complex topics in metabolism provides a learning facilitator that students enjoy, promoting engagement, as it allows them to be transported to virtual scenarios in the actual "digital world."

1. Background

In education, a constant challenge is ensuring that students achieve meaningful learning during self-study, as most strategies involve guided reading or tasks in 2D systems. However, when it comes to basic sciences, the situation becomes even more complicated, as learning and assimilating different concepts often requires students to rapidly use or develop their capacity for abstraction and imagination of these complex processes, which often seem unreal because they are obviously beyond the reach of a human scale to easily imagine. The latter is the case with metabolism, where it is crucial to obtain the core of basic knowledge to be used in the following stages of the student́s training according to their professional area [1–3].

The implementation of virtual reality in learning has proven to be a revolutionary tool in education. One gap is that learning complex processes that require a high degree of imagination become topics classified as extremely difficult and require modifications in the teaching strategy. Therefore, the importance of our results, which agree with what has been observed regarding the implementation of VR in other contexts for the active learning process, is that it allows students to immerse

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themselves in digital environments, allowing them to explore and manipulate concepts that could not be achieved otherwise due to being expensive, dangerous, or difficult to implement in real life [4,5].

The fact that the implementation of VR improves learning in metabolic processes opens the possibility of generating more resources that allow students to access the cellular sites where the processes occur and where the human scale could not have access, thus allowing experiential activities and therefore facilitating assimilation and, we believe, long-term retention [6,7].

The use of virtual reality (VR) in medical education, especially in basic sciences such as biochemistry, offers several significant advantages. One of the main ones is the ability to provide immersive and realistic experiences that allow students to interact with three-dimensional models of biological structures, facilitating a deeper and more detailed understanding of biochemical concepts [8]. This is especially useful in teaching anatomy and physiology, where 3D visualization can help students better understand how biological systems work [9,10].

Another important advantage of using VR in medical education is its ability to simulate clinical situations without risk to real patients. This allows students to practice medical procedures and diagnoses in a safe and controlled environment, reducing errors and improving confidence in their skills [11,12]. Furthermore, VR can be customized to each student's individual needs, allowing for more flexible and efficient learning.

Virtual reality also makes it possible to explore complex biochemical concepts in a more accessible way. 3D visualization of biological molecules and processes can help students better understand how biochemical systems work, which is essential for the biological sciences [13,14]. Furthermore, the ability to interact with these virtual models allows students to experiment and learn hands-on [10,13].

Biochemistry, and metabolism in particular, is an important and necessary basic science for understanding many of the biological phenomena in different areas of health [15–17]. This science allows us to understand the processes involving the degradation and synthesis of biological molecules that are important for obtaining or using cellular energy, and thus, life [1,17]. Many of these reactions are particularly important for understanding cellular development, signaling, cell division processes for growth, and even cell death [15] . However, for these processes to occur, there are energy requirements that must be met. When this is not the case, the cells inevitably die. However, during the students' learning journey, several questions emerge, such as how are the processes for generating ATP carried out? And what mitochondrial systems are involved in? Furthermore, teachers often One central question: how can students understand and internalize this knowledge more easily?

Because metabolic processes can be highly complex, learning them is challenging and requires a high level of abstraction. Moreover, since these processes occur in cellular sites on such a tiny scale it is often not possible to materialize them [4,18,19].

A neurocognitive framework for understanding the learning process suggests that educational effectiveness is maximized when instructional strategies promote either cognitive or procedural development—or ideally, a synthesis of both. This is best achieved through experiential learning environments that encourage the dynamic interplay between these domains (Perception, Instinct, Intuition and Reflection) agile method for a non-rigid structure in teaching and learning. Such integration is particularly significant within structured academic contexts, where the alignment of learning experiences with neurocognitive principles can enhance both retention and application of knowledge until reaching the level of creation on Bloom's Taxonomy [20,21]. Consequently, designing educational interventions that reflect this dual focus not only supports deeper learning but also aligns with contemporary pedagogical models grounded in cognitive science [18].

Many authors believe that it is possible to implement various digital resources to facilitate learning. This is even more evident considering that today's students are exposed to a handful of distractions and are frequently stimulated by technology [4].

Moreover, it is important to consider that technological tools have facilitated the educational process [22]. Today, virtual reality (VR) solutions allow people to access sites in an immersive digital format that provides 360-degree sensations [23,24] and fosters the development of creativity and imagination [25].

The advantage of immersive learning with technologies typical of virtual worlds comes in the achievement of a deeper understanding of the concepts, allowing students to be the protagonists of the immersion while also being the promoters of their own learning [19,26]. Furthermore, virtual environment are ideal platforms that allow for micro-learning of relevant concepts or situations in short, experiential situations designed to achieve a specific objective and with an orientation that matches the user's learning needs [27,28].

The use of VR has emerged as an educational strategy that improves learning. However, most applications designed for health sciences education have focused on training in situations, on a human scale, for difficult and dangerous scenarios, where emphasis is placed on the development of necessary attitudes and skills [29–32], or on safety and training in the chemical laboratory [33,34].

Some digital platforms for teaching biochemistry and metabolism have allowed us to evaluate knowledge retention for long periods through changes in the neurocognitive processes of the student by improving the learning environments [33,35,36]. Other digital systems such as augmented reality [37], or VR with Scape-room modality have been implemented on biochemistry [4,38], allowing students to understand the processes that occur from the molecular point of view. For instance, users are able to experience the processes of enzymatic biotransformation by the manipulation of organic molecules or the learning of enzymatic catalysis and molecular dynamics in order to understand the importance of stereochemistry, the transition states during metabolic reactions [8,39].

Under these circumstances, the possibility of supporting learning through digital technologies is evident. Therefore, this study investigates the pedagogical impact of integrating a virtual reality (VR) activity focused on the electron transport chain (ETC/OXPHOS) within standard coursework. Specifically, it evaluates whether this immersive approach yields greater immediate learning gains and higher levels of student acceptance compared to traditional instructional methods, which typically involve lectures, assigned readings, collaborative activities and quizzes.

2. Material and methods

2.1. Participants

Subjects were undergraduate students enrolled in metabolism course this course is integrated by biochemistry and focuses on developing collaborative and disciplinary competences. The biochemistry course is taught in the first semester of first year. It is a 4-hour per week course that is a course designed to provide basic foundations in biochemistry.

Demographic characteristics of gender, teaching instructor, period, score for pre and post VR activity and score for another metabolic topic were collected.

2.2. Materials

The complete methodology included the creation of a VR system, planning the logistics of the activities in our VR zone (institutional physical space), designing the instructional moments, implementing the activity with students, assessing pre- and post-implementation knowledge, and assessing students' perceptions of the usefulness of VR activity. For the purposes of this description, these steps will be grouped into three stages: 1) Design and development of VR experience, 2) logistics and implementation of the activity, and 3) assessment of knowledge and students' perceptions of its usefulness.

2.2.1. Design and development of VR experience

The proposed topic was the electron transport chain and oxidative phosphorylation. To this end, a VR environment for the metabolic processes in question was designed within the system so that the student could be fully immersed in the experience. A virtual design was developed, how it was suggested in a *van Dinter* mode and used by some authors to construct VR experiences [24]. The experience begins by welcoming the student and providing a brief overview of the importance of the process in the biological context.

Prior to implementation, we questioned the possibility that some students might not want to participate in VR activity for various reasons. Therefore, an alternative platform World Wide Web was created that could be accessed from a computer and, during the COVID-19 pandemic, allowed other students to continue the experience outside the VR platform (The www link is available and can be sent upon request and non-evaluated its impact today).

Once the user press starts, the experience virtually takes you to the intermembrane space of the mitochondria, where these metabolic processes take place (Fig. 1. Panels A-D).

Once in the intermembrane space, the VR experience begins. For this experience, the platform was installed on a computer and additional screens, where the student wearing the VR headset completes the project in real time in the virtual space for their classmates to view and integrate the information. Oculus Quest 2® headsets and controllers are required. The controllers allow participants to move freely through the virtual space in a simple, natural, and intuitive way, just as they would in a video game.

To avoid discomfort for participants, usage time was restricted to a maximum of 10 min, or less if the student reported any discomfort (they were continuously questioned about their physical condition). Once the time was up, participants were switched, and VR headset and manual controls were cleaned before switching.

As mentioned, the experience takes place between the mitochondrial membranes. This is where the different I-V complexes are located, along with the rest of the elements necessary for the process (NADH/NAD, H^+, FAD/FADH2, electrons, protons, ubiquinone, cytochrome c, oxygen, water, etc.) so that participants can recognize and locate them. Along with the VR experience, students are able to reflect on the following question regarding the different components participating in the metabolic process: What's happening? Where does it happen? Ultimately, what are the results? (Fig. 2. Panels A-D).

Additionally, during the tour, participants can access small areas where they can receive an audio explanation of what is happening at that stage of the process, further enhancing their immersive experience and learning.

2.2.2. Logistics for the implementation of VR activity

For the implementation of the activity, the logistics for teaching and learning moments of the VR platform were designed.

The available physical space (VR room) is shown in Fig. 3. It shows the computer equipment and monitors in the center, where the interaction of the user with the virtual environment is projected in real time.

In this setting, in the corners, there are spaces identified with different colors, where the different teams (1–4) were assigned to carry out the activity. The colored area corresponds to their team location in the room. This was not for waiting, but rather for collaborative work. While one team member was in the virtual space and carried out VR activity, the rest of their teammates had to complete (with their help and that of the rest of the team) a diagram of the metabolic processes in the different complexes. They would question or provide feedback to the team members in VR and capture their findings about what was happening in their diagram. In this way, everyone was actively involved in the implementation.

For student health protection and to prevent accidents, the exposition to VR activity was limited to 10 min per participant.

The learning activity consisted of incorporating the use of VR into the theoretical module for learning the topics "the electron transport chain and oxidative phosphorylation" in the theoretical sessions of Metabolism and Energy. For this activity, students were asked to collaboratively create a diagram locating what was indicated in the instructional design (Table 1) (also developing the collaborative work competency).

Because the activity was developed collaboratively, no additional materials were allowed to complete the activity deliverable. Additionally, learning assessment tools were administered at the beginning and end of the session, and at the end, assessments were conducted to rate the perceived usefulness of VR activity as a learning tool.

2.2.3. The VR instructional design consisted of the following instructional moments

Moment 1. In the classroom, students learned that glycolysis ends

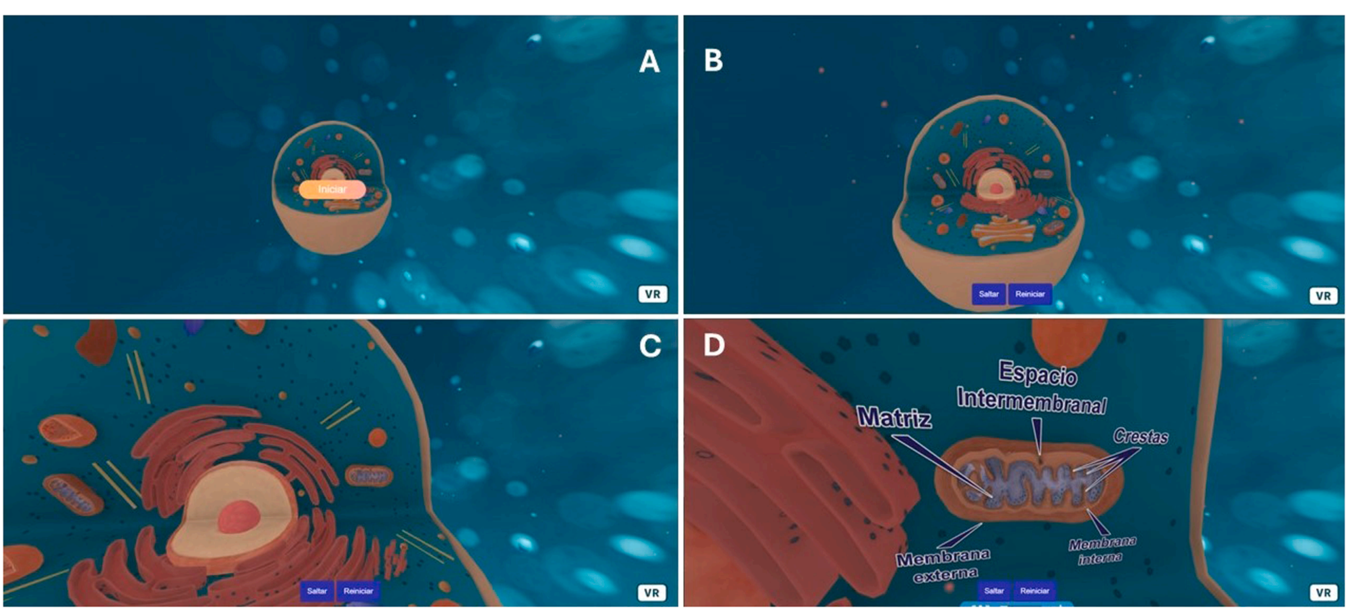


Fig. 1. Entering VR platform for the electron transport chain and oxidative phosphorylation.

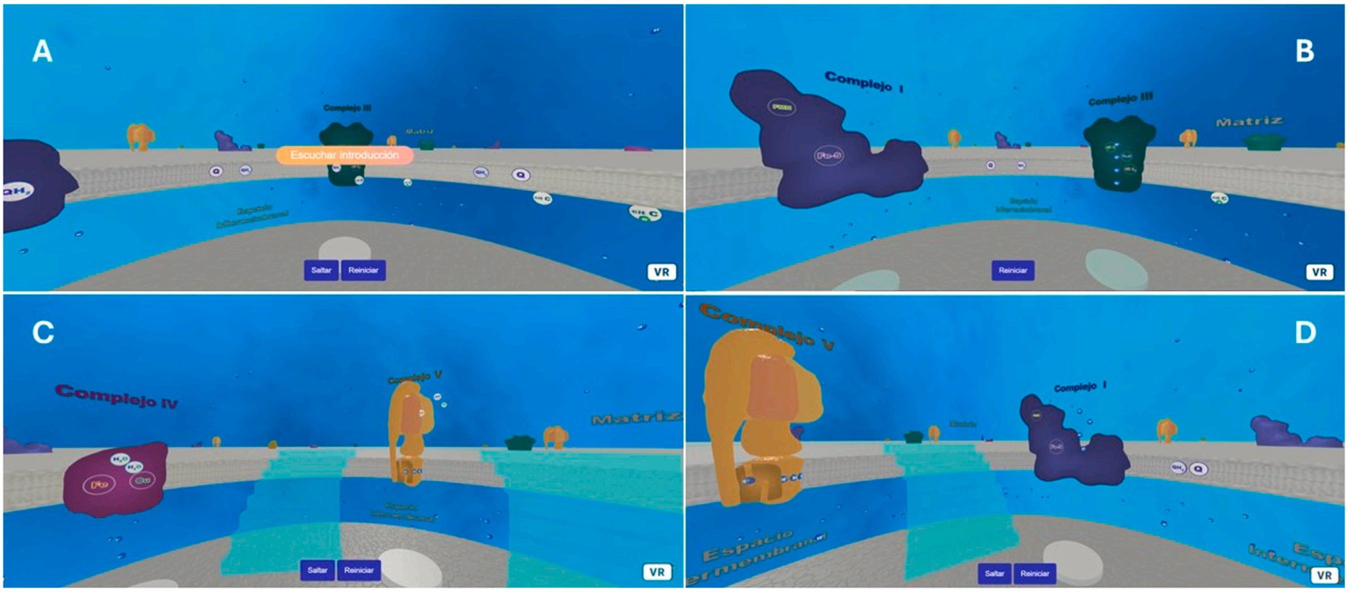


Fig. 2. ETC and OXPHOX on VR platform shows the mitochondrial complexes.

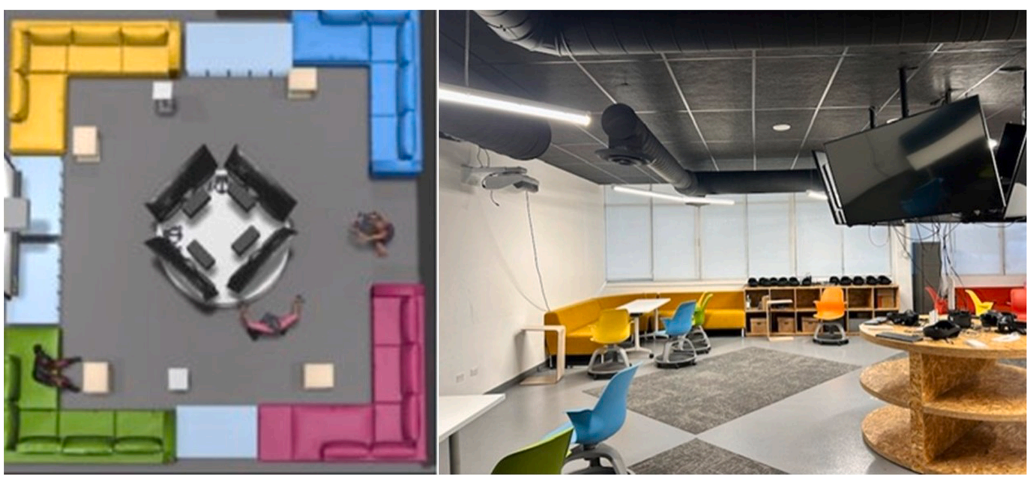


Fig. 3. Space and layout of our institutional VR room.

with the production of pyruvates, which must be transferred into the mitochondria for further metabolism through the Krebs cycle. In this mitochondrial process, reduced cofactors are produced from pyruvate, and these electrons will be transferred and used in the ETC and ultimately in OXPHOX for ATP synthesis.

Moment 2. Apply the Pre-Activity diagnostic tool.

Moment 3. Explain that the group will move to VR space to conduct immersive activity on the ETC and OXPHOX processes and that we will return to the classroom upon completion.

Moment 4. Provide instructions on the distribution assigned to each team, the equipment they will use, and instructions on the activity that they must complete as their evidence, as well as the time limit for completing the VR activity. Students should be free to report any discomfort or problems with the implementation at any time.

Moment 5. Start the activity, address team questions upon request, and monitor the physical status of those participating in VR activity.

Moment 6. End the activity, administer the post-activity evaluation and VR usefulness perception survey.

Moment 7. Close the session.

The knowledge assessments (pre- and post-tests VR activity) were completed individually within a 10-min time limit.

2.2.4. Glycolysis or lipolysis sessions

During these two weeks, students received instruction on the topics (glycolysis or lipolysis, one per week). They were assigned a task equivalent to the ETC and OXPHOX-VR activity, with references to the bibliography for reference. All students receive a theoretical session, followed by collaborative reinforcement in the construction of a metabolic map (physical or virtual), which must include the session topic and its interrelationships with other metabolic pathways. Consequently, they include not only the disciplinary content but also collaborative work and imagination process (Design of instructional methods compared are shown in Table 2).

2.3. Knowledge assessment

To assess the effectiveness of the VR platform introduced in Week 2, students' ability to independently and collaboratively learn additional metabolism topics, specifically glycolysis and lipolysis, which are less complex than electron transport chain (ETC) and oxidative phosphorylation (OXPHOS), was evaluated during Weeks 1 and 3.

In weeks 1 or 3, at the end of the session, lecture, and collaborative activity (metabolic map), an assessment on glycolysis and lipolysis was

Table 1
Instructional design for VR activity.

Stage	Description
Activity Name	Energy (ATP) and the mitochondria
Topic/Subtopics	Theorical concepts of Metabolism and Energy Topic: Krebs Cycle and Oxidative Phosphorylation Subtopic: Electron Transport Chain and Oxidative Phosphorylation
Learning Objective	Upon completion of this activity, the student will understand the electron transport chain and oxidative phosphorylation processes.
Estimated Time	20 min before the activity, in the classroom.55 min during the activity, 10 min per student, and 10 min for review.20 min afterward, for group discussion.10 min in the classroom.10 min for post-activity evaluation.
Instruccions	Before: Instructions are given about the activity, and a diagnostic test is administered on the topic. During: After the diagnostic test, go to the VR room accompanied by your team members (3–4 people total). Two teams will be placed per squad; odd-numbered teams will use headsets with screens, while even-numbered teams will use headsets only. Each student will take a turn for approximately 10 min, during which time they will explore the different complexes, their components, and how they work. At the end, they will share the experience with their teammates and make a concept map or simple drawing of what they observed during the activity. Each team will receive a blank sheet of paper to capture their agreed-upon version. As a team, they will discuss where electrons come from, how they were obtained, and so on. Then they will return to the classroom where they will again complete the post-activity knowledge assessment. Finally, as a group, they will integrate the reviewed topic with the previous topics discussed in the course.
Participation Rules	Expected student attitudes during the activity. Students are expected to be respectful of their classmates and laboratory equipment, to refrain from playing games or engaging in unrelated activities, and to collaborate with the team for their learning.
Working Evidence	The participation evidence is the diagram or schematic representation created by the team and posted on the educational platform. This diagram should include and detail the ETC and OXPHOS processes in mitochondria, the entry of reduced cofactors, the movement of electrons, protons, etc. The post-activity test will be administered, along with their perception of the experience using VR.
Material resources	VR ETC/ OXPHOS platform.

Activities	Evaluation	
Checklist	yes / no	%
Is respectful of the materials and their classmates. Does not wander around, use the phone, chat, or perform tasks other than those assigned.		10
Complete VR activity.		10
Collaborate with classmates.		10
Content of the ETC and OXPHOS mind map or diagram. Introduce the ETC complexes, map, or diagram.		20
In the evidence, it shows the electron donors in complexes I and II. Includes the electron transporters between complexes. Introduces the final electron acceptor.		20
Represents or diagrams the proton pumping.		10
Represents or diagrams the ATP formation		20
TOTAL		100
Notes to the teacher:		

Table 2
Description of the two instructional methods compared.

Week	Week 1	Week 2	Week 3
Scheduled Topic	Glycolysis	(ETC/ OXPHOS)	Lipolysis
Teaching Activity	Lecture	None	Lecture
VR Assessment	None	Pre-VR Assessment	None
Active-learning Student's activity	Glycolysis pathway metabolic map construction (collaborative)	VR activity (collaborative)	Lipolysis pathway metabolic map construction (collaborative)
VR Assessment	None	Post-VR Assessment	None
Teaching Activity	None	Lecture	None
Course evaluation	Assessment	Assessment	Assessment

Pre and Post-VR Assessment results were not considered for the official course evaluation.

conducted. The structure was similar to that used in the VR intervention. The resolution time and length (10-question and 10 min quick quiz) using the digital platform to assess their learning. Unfortunately, we did not have the opportunity to measure the resolution time of the evaluation instruments to have greater clarity and richness in the analysis of the results as suggested by Kadri et al. [40,41].

In the second week (VR week), participants were instructed to go to the institution's virtual reality room to experience the immersive topic (unlike the previous weeks, this one did not require prior self-study) and a quick pre-activity test was administered. Instructions for the activity were provided

This allows for different comparisons for the same participants, their 2D vs. VR learning ability, and baseline knowledge pre- and post-VR activity.

To avoid recall bias, the assessment instruments, ETC and OXPHOS, which consisted of 10 multiple-choice questions labeled pre- and post-VR, had different content but were similar in structure and duration.

The transferability of experience among teachers was also assessed through the implementation of the activity by three teachers. They applied the same teaching strategy in the three periods in different groups.

Additionally, we evaluated whether student learning was influenced by the academic periods (P1, P2, and P3) in which the class was taken, both using the traditional strategy and the implementation of VR, both by groups/period and overall.

2.4. Perception of VR's usefulness

Finally, to comprehensively evaluate the intervention, both objective and subjective outcomes are measured. Objective outcomes, such as knowledge gain, provide quantifiable evidence of learning, while subjective measures—like perceived usefulness—capture students' attitudes and engagement. Interpreting these jointly allows us to assess not only whether learning occurred, but also whether learners found the experience valuable and relevant, offering a more holistic understanding of impact. By doing so, we obtained and analyzed student feedback on the usefulness of the experience for their learning and how it could be used as an improvement strategy for future implementations through an open-ended question in which students could freely express their perception of the use of this strategy in their training. All surveys and evaluations (including the open-ended one) were completed online anonymously and had no impact on their course results.

At the conclusion of the instructional session, participants were administered a post-activity assessment utilizing virtual reality (VR), along with a brief, blinded survey designed to evaluate their perceptions of learning effectiveness within both the traditional educational model and the VR-based approach.

2.5. Statistical analysis

Results are presented as median and interquartile range (IQR) and were analyzed using Minitab® 21.4.3 with an institutional license. Differences between groups were carried out through statistical analysis using the Mann-Whitney U, Kruskal-Wallis test adjusted with the Bonferroni correction test depending on the type of variables and their outcomes. Statistical significance was established at a p value of 0.05 or lower with a 95 % CI. Additionally, responses regarding the perception of VR experience versus learning outcomes are presented using heat maps separated by variables. Similarly, a multivariate analysis was conducted to assess the individual and combined effects of the evaluated variables on the scores obtained by participants following the virtual reality (VR) activity.

3. Results

Learning activity was designed and implemented using virtual reality as part of the learning strategies for topics in Metabolism and Energy for first-semester university students in the health program at the School of Medicine and Health Sciences. A virtual reality learning activity was implemented as part of the regular curriculum, without prior ethics board approval or formal consent. For publication, the study was reviewed by the institutional ethics education committee (CEI). Sociodemographic characteristics of participants are shown in Table 3. 289 students were invited to participate. There were no repercussions for not participating in VR activity Therefore, their participation did not affect their final grade for the course. CONSORT Flow diagram is included. Data collection (weeks 1, 2, and 3) was conducted over three academic periods of 5 weeks each one, with the participation of three different instructors based on the assignment of the teaching groups (A, B, and C). 284 students agreed to participate 95 in period 1, 92 in period 2 and 79 in period 3.

The student learning score was determined based on the results obtained in the quick quizzes (Fig. 4) administered after the readings and collaborative activity (weeks 1 and 3) versus the quiz administered after VR collaborative experience (week 3). Those who did not agree to participate in VR phase of the study (for any reason) were given the option of using the system through web access from their computer so they could have an equivalent learning experience in addition to providing the conventional educational strategy. Some students, after using this "web" version, were motivated to participate in the VR experience; others, using the "lecture and assessment" strategy, requested VR experience, convinced that it could benefit their learning. In both cases, the results obtained from these students were not included in the final analysis of the study.

The overall outcomes of the VR intervention (week 2) were compared with those obtained through the conventional strategy of lectures, readings, metabolic map construction and evaluation in two different topics (glycolysis in week 1 and lipolysis in week 3) and a greater number of correct answers was observed in the topics reviewed through VR compared to the topics reviewed through class and reading of bibliography strategy ($p < 0.00001$) vs week 1 and ($p < 0.00001$) for VR vs reading week 3 (Fig. 4, panel A). Although the overall performance was improved after the implementation of the VR strategy, individual outcomes varied. Notably, some students who had demonstrated strong performance during the non-VR weeks experienced a decline in scores when using VR. Fortunately, this effect was limited to a small subset of participants, suggesting that while the strategy is broadly effective, individual differences may influence their impact (Fig. 4, panel B).

To assess whether VR implementation can be transferred to another teacher, the outcomes obtained from the implementation of VR activity by three teachers who used the same instructional design to teach this topic were analyzed. It was observed that the implementation of the activity significantly increased topic learning compared to the beginning of the corresponding session and that this improvement in learning was independent of the instructor teaching the topic when using VR.

The findings indicate that there were no statistically significant differences in post-implementation scores across instructors (with a maximum variation of one correct response), and that these outcomes were consistent regardless of the period during which the VR experience was conducted, reaching a median of 80 % correct answers ($p = 0.136$).

The differences observed between groups could be linked to the students assigned to each group during course registration, before the implementation of VR, there were already differences between the groups, perhaps caused by their prior study habits (reading and preparation of the topic previously to topic schedule). The results are shown in Fig. 5.

Consistently, in the groups in which VR activity was implemented, it was observed that at the beginning of the activity, students had a low level of knowledge on the subject (median of 30–40 % on a scale of 100) and that as a result of the implementation and completion of VR activity, their knowledge increased to scores to 80–90 % (median) suggesting that VR activity improves learning. This increase was highly significant ($p < 0.0001$) compared to the initial knowledge in each of the groups (Fig. 6 panels A-C) and in all of them (Fig. 6 panel D). As previously mentioned, the VR strategy does not produce positive results in all students, and a subgroup (few of them) had a reduction in their performance compared to the results obtained by the traditional methodology.

Different multiple linear regression analysis was carried out to estimate the relationship among the values of Post VR activity result as a function of dependent variables such as Pre VR, instructor, gender, academic period, performance in other topics in metabolism (glycolysis, weeks 1 and lipolysis week) and acceptance rate. The results are shown in Table 4.

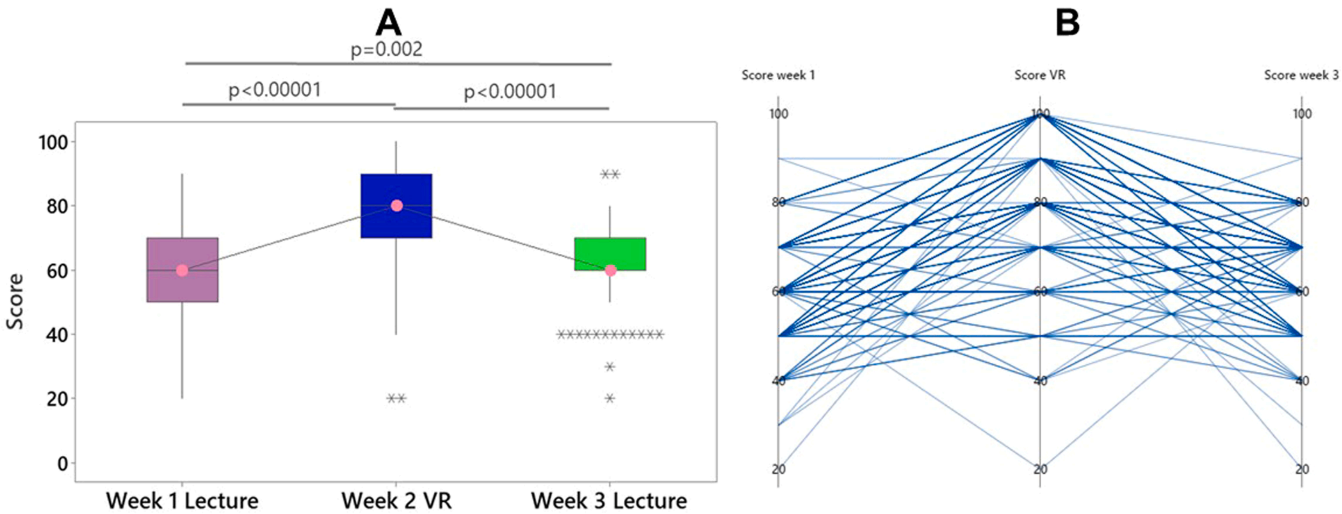
Four linear regression models were generated, ranging from an untransformed and natural logarithm transformed data into a forward and backward analysis. Although the maximum R squared value was 31.66 %. The variables Pre-VR score, week 1 score, and academic period together contributed to the model's explanation ($p < 0.001$).

Consistently across all multivariate models, whether employing forward or backward selection and applied to both transformed and untransformed datasets, the same variables demonstrated the highest explanatory power regarding the impact on learning outcomes. This suggests the involvement of additional, undocumented factors such as reading and study habits, prior experience with video games, and other individual characteristics that may influence learning efficacy.

Thus, the evolution in knowledge shows that students demonstrated improvement in 97.8 % of the student population with different levels, while in the student's perception regarding whether the strategy was useful for learning, 92 % of students gave positive comments about VR activity. As previously noted, the improvement in outcomes was not

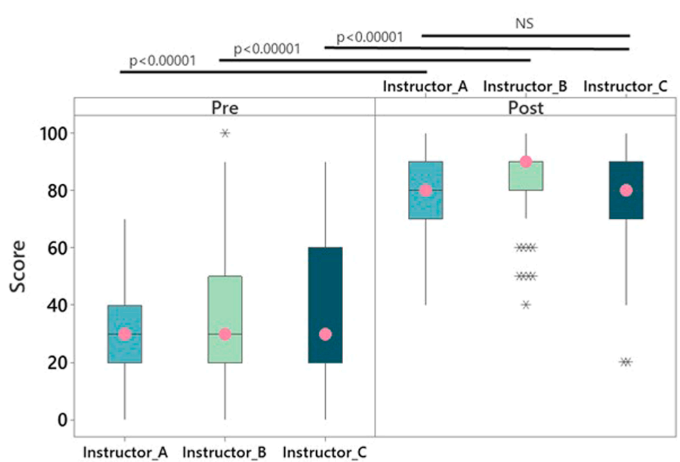
Table 3
Sociodemographic characteristics of participants.

Characteristic	Value
Gender n (%)	203 (70.2)
Female	86 (19.8)
Male	
Major	289 (100)
Common Core Health Sciences	
This includes the following areas:	
Medicine,	
Biosciences,	
Dentistry,	
Nutrition,	
Psychology	



Kruskal Wallis: All Pairwise comparisons	N	Score median	gl	p	Groups
Week 1 Lecture	244	60	2	0.0000	1 vs 2
Week 2 VR activity	244	80	2	0.0000	2 vs 3
Week 3 Lecture	244	60	2	0.0026	3 vs 1

Fig. 4. Assessment results obtained from reading (weeks 1 and 3) vs. VR (week 2). Median [IQR]. High level of statistical significance was observed among the groups VR vs. week 1 activity, Kruskal-Wallis test p value was <0.0001, followed by Bonferroni test for multiple comparations VR vs. reading week 1 $p < 0.00001$, VR vs. reading week 3 $p < 0.00001$. $N = 244$ paired data. Unpaired data were excluded from statistical analysis. Central pink points depict the median value for each group. Box depicts the interquartile range (IQR).



Kruskal Wallis: All Pairwise comparisons	N= 220	Score median	gl	p	Groups
Pre-VR instructor 1	110	40	5		
Pre-VR instructor 2	84	30	5		
Pre-VR instructor 3	26	45	5		
Post-VR instructor 1	110	85	5	0.0000	Pre vs Post inst 1
Post-VR instructor 2	84	80	5	0.0000	Pre vs Post inst 2
Post-VR instructor 3	26	90	5	0.0000	Pre vs Post inst 3

Fig. 5. Pre- and post-VR evaluation grades obtained by groups with different instructors. Median [IQR]. Statistically significant differences were observed, Kruskal-Wallis test p value was <0.0001, followed by Bonferroni test for multiple comparations among the groups Pre-VR Instructor A vs. Post-VR Instructor A ($p < 0.00001$), Pre-VR Instructor B vs. Post-VR Instructor B ($p < 0.00001$), Pre-VR Instructor C vs. Post-VR Instructor C ($p < 0.00001$). No statistical significance difference was observed among the learning obtained from the VR activity implemented by the different instructors, Post-VR Instructor A vs. Post-VR Instructor B ($p < 0.13$), Post-VR Instructor B vs. Post-VR Instructor C ($p < 0.091$), and Post-VR Instructor A vs. Post-VR Instructor C ($p < 0.43$). $N = 220$ paired pre- y post VR activity, $n = 110$ instructor A, $n = 84$ instructor B, $n = 26$ instructor C. Unpaired data were excluded from statistical analysis. Central pink points depict the median value for each group. Boxes depict the interquartile range (IQR).

universal. In fact, a subset of high-performing students exhibited a decline in their results following the implementation of the VR strategy, indicating that the intervention may not benefit all learners equally.

A heat map comparing students' acceptance of the activity with their evaluation outcomes reveals a notable alignment, suggesting a potential relationship between perceived usefulness and performance. This correspondence indicates that students who rated the activity more positively tended to achieve higher results following its implementation (Fig. 7 and Table 5).

Most students had a positive perception of the use of VR platform for learning, finding it enriching for their learning. However, there were suggestions for improvements for future implementation. These included reports of physical discomfort among students (1.12 %), connectivity issues (2.25 %), and, in some cases, confusion about concepts

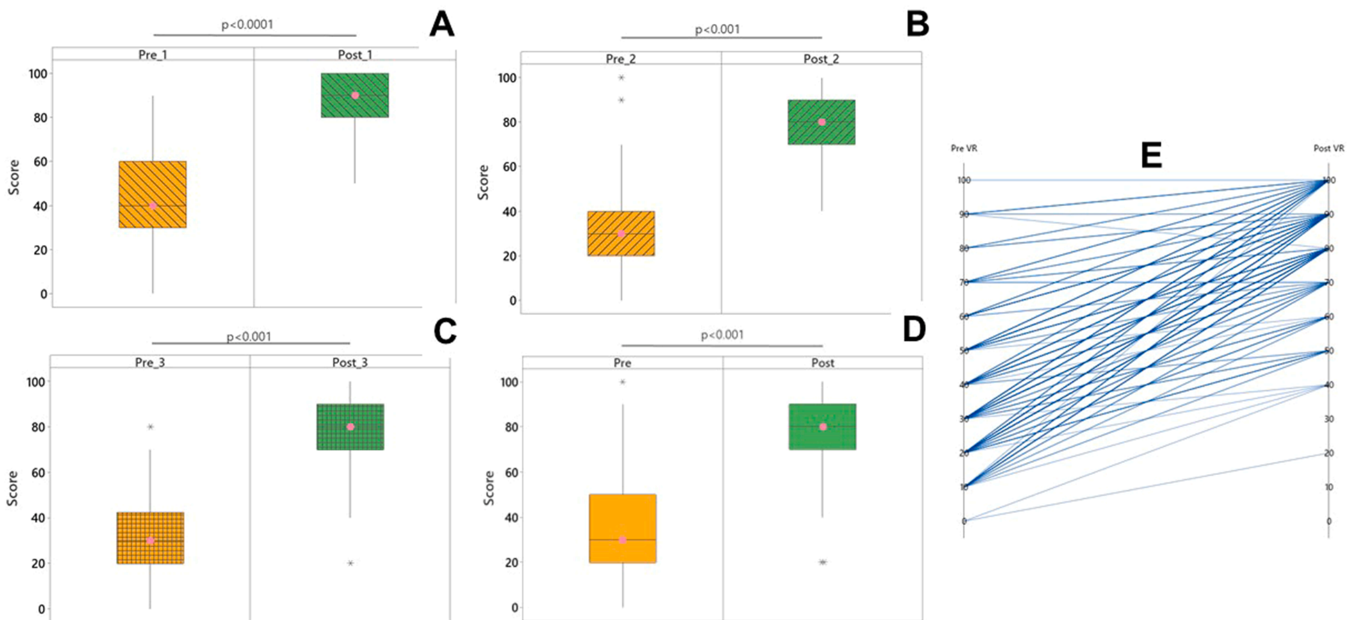


Fig. 6. Score obtained from VR implementation in groups during different academic periods. Panel A (Period 1 vs 2), panel B (Period 2 vs 3), panel C (Period 1 vs 3), panel D (Overall results). Median [IQR]. Kruskal-Wallis test p value was <0.0001, followed by Bonferroni test for multiple comparations. Pre (yellow) vs. Post VR implementation (green) ($p < 0.0001$). Panel E depicts student paired changes in score results. $N = 220$ paired data, $n = 83$ period 1, $n = 67$ period 2, $n = 70$ period 3. Data unpaired were excluded. Central pink points depict the median value for each group Box depicts the interquartile range (IQR).

due to the movement of the molecules involved in the biochemical process (0.37 %) (real simulation of the process). They also proposed the possibility of having a button to pause the auditory description of the process to improve the assimilation of the information described. The most representative open-ended responses, both positive and negative, are presented in Table 5.

4. Discussion

A challenge facing science learning in the health field, as in many other areas, is developing strategies that facilitate knowledge assimilation, are easy to implement, and are accepted by teachers and students. This is undoubtedly a challenge considering that new generations have many external stimuli (distractors) to overcome. Students are surrounded by digital experiences in video games, videos, etc., so their learning style has evolved to be more tied to visual and dynamic resources than simply reading texts.

Seeking to address this issue, in this study, we developed, implemented, and evaluated a VR platform to improve the learning of ETC and OXPHOX. These are highly complex biochemical processes due to the number of protein components, intermediaries, and their biological importance.

At our institution, according to the entrance program to basic health sciences for the different careers (psychology, dentistry, biosciences, medicine, nutrition and biomedical engineering), it is very important to acquire deep and significant knowledge of the basic subjects in which biochemistry and metabolism are immersed so that, by developing the competencies, they can apply them to solve the challenges of our educational model and in their professional life in the future [16,42]. The findings of this study suggest that the integration of virtual reality (VR) resources is positively associated with enhanced learning outcomes in students studying complex cellular processes. Nonetheless, the effectiveness of educational interventions is multifactorial, influenced by elements such as instructional strategies, curriculum design, and learner motivation [43]. The relevance of these results lies in the fact that the VR-based approach facilitates learning across diverse professional orientations, thereby supporting broader educational applicability [16,42].

Our findings reveal at least two distinct behavioral patterns: one, more prevalent, indicates that students tend to perform better when learning is supported by technological tools compared to traditional methods such as lectures and classroom instruction. The second pattern suggests that some students do not benefit from digital activities; in fact, their performance appears to decline relative to outcomes achieved through conventional learning approaches. One possible explanation is that they are the result of a generational change, not of these students (they had almost the same age) but of their parents or siblings who still influence their study habits [44], thus shaping their academic results thus shaping their academic results an influence that is still common, although in small proportion [45].

A growing evidence supports the notion that technology-enhanced learning environments, however it is nether “not for all nor not forever” or “one size fits all” if new educational technologies can significantly improve student performance, particularly when these platforms are designed to promote engagement, flexibility, and personalized learning other learning strategies should be provided so

Table 4
multivariable regression model for explanatory variables.

Model	Variable	Coef.	Std. error of the estimate	R square	CI 95 %	*p*-value
1	Constant	86.29	1.68	29.00	(82.97, 89.62)	0.000
	Pre-VR	3.83	1.10		(1.65, 6.01)	0.001
	Score week 1	3.62	1.14		(1.37, 5.87)	0.002
	Period 3	−9.75	2.67		(−15.05, −4.46)	0.000
2	Constant	87.31	2.05	31.66	(83.25, 91.38)	0.000
	Pre-VR	3.31	1.11		(1.10, 5.51)	0.004
	Score week 1	3.76	1.16		(1.46, 6.06)	0.002
	Period 3	−9.16	2.72		(−14.54, −3.78)	0.001
3	Constant	4.4407	0.0237	25.30	(4.3937, 4.4876)	0.000
	Pre-VR	0.0511	0.0155		(0.0204, 0.0819)	0.001
	Score week 1	0.0475	0.0161		(0.0157, 0.0792)	0.004
	Period 3	−0.1209	0.0377		(−0.1956, −0.0462)	0.002
4	Constant	4.4407	0.0237	25.30	(4.3937, 4.4876)	0.000
	Pre-VR	0.0511	0.0155		(0.0204, 0.0819)	0.001
	Score week 1	0.0475	0.0161		(0.0157, 0.0792)	0.004
	Period 3	−0.1209	0.0377		(−0.1956, −0.0462)	0.002

ANOVA

Model	Variable	Sum of squares	Contrib %	df	Mean square adj	F	*p-value*
1	Regression	7298.5	29.00	4	7298.5	13.17	0.000
	Pre-VR	3079.8	12.24	1	1670.3	22.24	0.000
	Score week 1	2223.1	8.83	1	1404.3	16.05	0.000
	Period	1995.6	7.93	2	1995.6	7.20	0.001
	Error	17,866.4	71.00	129	17,866.4	1.18	0.439
	No-adj	16,916.4	67.22	121	16,916.4		
	Pure error	950.0	3.78	8	950.0		
	Total	25,164.9	100.00	133			
2[a]	Regression	7967.4	31.66	6	7967.4	9.81	0.000
	Pre-VR	3079.8	12.24	1	1192.4	22.74	0.000
	Score week 1	2223.1	8.83	1	1417.5	16.42	0.000
	Period	1995.6	7.93	2	1711.0	7.37	0.001
	Error	17,197.5	68.34	127	17,197.5	1.15	0.456
	No-adj	16,247.5	64.56	119	16,247.5		
	Pure error	950.0	3.87	8	950.0		
	Total	25,164.9	100.00	133			
3	Regression	1.2050	25.30	4	0.3012	10.92	0.000
	Pre-VR	0.5250	11.02	1	0.2987	10.81	0.001
	Score week 1	0.3575	7.51	1	0.2413	8.75	0.004
	Period 3	0.3225	6.77	2	0.1612	5.85	0.004
	Error	3.5582	74.70	129	0.0275	1.22	0.413
	No-adj	3.3753	70.86	121	0.0279		
	Pure error	0.1829	3.84	8	0.0228		
	Total	4.7631	100	133			
4	Regression	1.2050	25.30	4	0.3012	10.92	0.000
	Pre-VR	0.5250	11.02	1	0.2987	10.81	0.001
	Score week 1	0.3575	7.51	1	0.2413	8.75	0.004
	Period 3	0.3225	6.77	2	0.1612	5.85	0.004
	Error	3.5582	74.70	129	0.0275	1.22	0.413
	No-adj	3.3753	70.86	121	0.0279		
	Pure error	0.1829	3.84	8	0.0228		
	Total	4.7631	100	133			

[a] variable Instructor 2, *p value* 0.089 df 2, all models were obtained with an alpha: 0.05 and beta 0.95

Model 1 FORWARD NON-TRANSFORMED

Period

3	Post VR	=	50.29 + 0.1815 Pre VR + 0.324 Score week 1

(*continued on next page*)

Table 4 (*continued*)

Model	Variable	Coef.	Std. error of the estimate	R square	CI 95 %	*p*-value
Model 2 BACKWARD NON-TRANSFORMED						
Period	**Instructor**					
3	2	Post VR	=	47.91 + 0.1569 Pre VR + 0.336 Score week 1		
Model 3 FORWARD ln-TRANSFORMED						
Period						
3	ln(Post VR)	=	3.9739 + 0.002425 Pre VR + 0.00424 Score week 1			
Model 4 BACKWARD ln-TRANSFORMED						
Period						
3	ln(Post VR)	=	3.9739 + 0.002425 Pre VR + 0.00424 Score week 1			

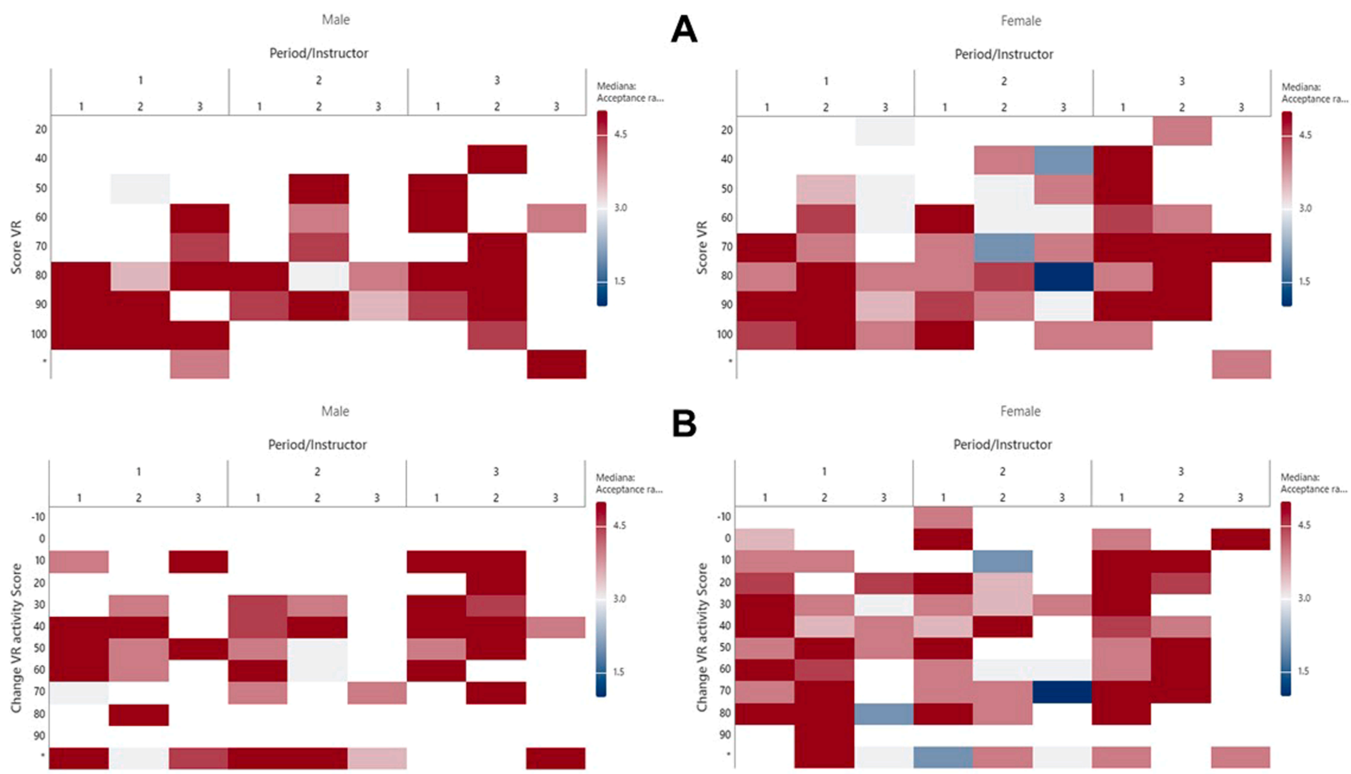


Fig. 7. Clustered heatmap, each panel depicts a pattern among Score obtained during VR Panel A) implementation and the perceived usefulness by different students (or Change in VR score, Panel B). Results were clustered by gender, period and instructor. $n = 220$ paired data.

that students can improve their learning and performance [46]. For example, Yu et al., conducted a meta-analysis showing that students in online or blended learning environments often outperform those in traditional classrooms, especially when interactive elements such as discussion boards and collaborative tools are included [47]. The flexibility of digital platforms allows learners to study at their own pace and revisit complex concepts, which is particularly beneficial for non-traditional students balancing academic and personal responsibilities [48]. Additionally, adaptive learning systems and multimedia resources have been shown to increase motivation and deepen understanding, contributing to better academic outcomes [49].

Challenges faced by Students in Digital Learning Environments. Despite the advantages, not all students benefit equally from digital learning tools. Some learners experience reduced performance in technology-mediated environments due to factors such as lack of self-regulation, limited interaction, and feelings of isolation. Akpen et al.

Table 5
Fallouts of the perception evaluation (translation).

Question	Open response
What did you think of VR experience?	Over 90 % positive feedback. "It was a better way to learn; however, it makes you a little dizzy." "I could barely get into it and it kept getting stuck." "All the movement confused me." "I think it was a good experience; I would only change the lack of pauses." "Honestly, I didn't think it would be as interesting as it was. You learn very differently when you visualize what you're learning. Now I feel like I know a lot more about the subject than when I entered the virtual reality room." "It helped me a lot since I'm a person who learns best visually. I was able to better understand the processes and how complex things work." "I feel that since we were able to see the motion and how each electron and proton moved, it made it very easy to understand because it was very visual." "I think it was a very enriching and interactive way to learn the concepts, and I liked breaking away from the traditional classroom format." "Very good, it's more practical and easier to understand when viewed in 3D" "I thought it was a very good learning resource since I was able to see and understand the topic better by having a more visual perspective than textbooks." "It was super fun and educational." "It was very useful to view it in three dimensions." "Very interesting. The animations helped me understand processes more quickly, and I feel like I retain more information." "Incredible, because these concepts are somewhat complicated to digest even with illustrated images in textbooks; therefore, explicitly visualizing the ETC process was a great help"

[50] found that students in online courses often report lower engagement and participation compared to those in face-to-face settings or by modifying their behavior to prepare for the session in advance [50]. The absence of immediate feedback and peer interaction can hinder motivation and comprehension, especially for students who thrive in socially interactive and structured environments [50,51]. Moreover, digital learning requires a high degree of autonomy and time management, which not all students possess. These challenges underscore the importance of considering individual learning preferences and support mechanisms when implementing educational technologies.

It is interesting that the multivariate model determined that academic period also improves the model, suggesting that motivation for new teaching and learning strategies results in changes in the educational psyche and therefore in the assimilation of knowledge towards an individualized learning model even personal maturity as you advance in university life [52,53] .

Given the diversity in student responses to digital learning, a blended approach that integrates both technological and traditional pedagogical elements may offer the most inclusive and effective solution. Blended learning combines the flexibility and resource richness of online platforms with the interpersonal engagement and structure of conventional classrooms. Research by Muller [54], suggests that blended models can enhance student motivation, satisfaction, and performance by catering to varied learning styles and needs. This approach allows educators to leverage the strengths of both modalities while mitigating their respective limitations. As higher education continues to evolve, institutions must prioritize pedagogical adaptability and student-centered design to ensure equitable learning outcomes across diverse populations [54]

According to our results, virtual reality also promotes active and motivated learning. Students are more engaged in the learning process when presented with interactive and challenging scenarios, which improve their knowledge retention, team-collaboration and problem-solving skills [55]. In the context of biochemistry, this includes simulating chemical reactions or visualizing metabolic processes in a virtual environment at the cellular level, with a high level of acceptance in strategy and academic outcomes [2,33]. Moreover, VR can be an invaluable tool for distance education, especially in times of social restrictions such as those imposed by the COVID-19 pandemic. It allows students to access high-quality educational experiences without needing to be physically present in the classroom, which has been crucial for maintaining educational interest [56].

In biochemistry education, VR can be used to simulate laboratory experiments, reducing the costs and risks associated with handling hazardous chemicals. This allows students to practice laboratory techniques in a safe and controlled environment, improving their ability to design and conduct experiments [8,57]. Furthermore, with instructional design, our VR activity is relatively easy to transfer experience to colleagues at other institutions, allowing instructors to easily implement it and potentially obtain similar results. However, a significant limitation is its implementation in remote locations with difficult access to internet connections. Therefore, loading VR into the devices' memory could possibly help resolve this issue. Longitudinal VR studies indicate that initial gains can persist when measured with delayed post-tests; future work should include retention testing following protocols like C-IVAL [58]

Inclusivity is another significant advantage of using VR in health sciences education. Students with disabilities can access educational experiences like those of their peers, promoting equal learning opportunities [59]. Furthermore, VR is accessible due to its compatibility with common mobile devices, which reduces implementation costs. In the context of biochemistry, this could mean that students with visual impairments can explore molecular structures in a virtual environment that adapts to their needs [60,61].

Instant feedback is another advantage of using VR in biomedical education. Students can receive immediate feedback on their performance in virtual simulations or experiments, allowing them to identify areas for improvement and effectively adjust their learning [62,63], what happened in our implementation that probably improved their attention and willingness to learn.

Furthermore, VR can be integrated with other emerging technologies, such as augmented reality (AR) and artificial intelligence (AI), to create even more advanced educational experiences. For example, AR can be used to overlay additional information on real-time anatomical models or technical procedures, while AI can help personalize learning to each student's individual needs [64].

Finally, the use of VR in biomedical education has the potential to transform the way basic biological sciences are taught. By providing immersive, hands-on experiences, VR can significantly improve the understanding and retention of biochemical knowledge, which is essential for success in a health science career [65]. Furthermore, its ability to adapt to each student's individual needs and promote active and motivated learning makes it an invaluable tool for the future of health education.

Due to the partial confounding of instructional modalities and content topics across deployment periods, this study primarily assesses feasibility, student receptivity, and short-term learning outcomes. Robust causal inferences regarding modality effects would require controlled experimental designs or within-subject replications adding more variables that allow to further enrich the analysis of the phenomenon

A key strength of this study is its educational deployment, characterized by integration into routine coursework and a large sample size as it enhances methodological validity and supports the generalizability of the findings to real-world instructional settings.

Another strength was the transfer among instructors was established, since there was no difference between the results obtained by the implementation even though the instructors did not receive extensive training to achieve comparable implementation fidelity, thereby reinforcing the robustness and scalability of the intervention, our results demonstrate that implementation can easily be transferred to other professors without significantly affecting its academic usefulness. Our mixed-methods approach allows us to establish an intervention focused on increasing learning and performance as well as convergence of results and acceptance and learning change strategies.

The main limitation is that the results come only from our school, with our infrastructure and control of activities. We believe it could be implemented in other schools so they can experience the VR environment and verify our results in their own implementations.

One important weakness of the study is that the results presented correspond to implementation in different groups with different professors, all at our institution and in short-term measurement. Therefore, we propose that other universities contact us soon so that we can transfer the educational experience (with the necessary adjustments) so that it can be implemented and evaluated at their institutions, thereby verifying its usefulness in learning.

This study employed a non-randomized, quasi-experimental period design, wherein different instructional modalities were implemented across distinct time periods. As a result, the content topics covered during each period were inherently linked to the instructional modality used, introducing a potential confound between topic and period. This design choice, while reflective of authentic educational settings, limits the ability to isolate the effects of the instructional modality from those of the specific content. Consequently, observed differences in outcomes may be partially attributable to variations in topic difficulty or student familiarity, rather than the modality alone. This limitation underscores the need for cautious interpretation of causal claims and highlights the importance of future studies employing randomized or within-subject designs to disentangle these factors.

The interpretation of results must consider the possibility of a novelty effect, wherein the initial exposure to the VR intervention may have temporarily enhanced engagement or performance due to its perceived innovativeness rather than its instructional efficacy. Additionally, cross-period cohort differences, such as variations in recruitment procedures, attendance rates, or baseline characteristics, may have influenced outcomes independently of the intervention. These factors introduce potential biases that could confound comparisons across periods, underscoring the importance of cautious interpretation and the need for future studies to control for cohort variability and isolate the sustained impact of the intervention.

Another limitation/opportunity is that, for now, the platform is available in Spanish, so we see this as an opportunity for Spanish-speaking schools to adopt it because most platforms are English-language. Although English language proficiency should certainly be promoted in Latin America, some schools or students could be left behind due to this lack of language proficiency. The VR experience is delivered via WebXR, allowing users to access it through a compatible web browser without the need for additional downloads or equipment (the impact has not been assessed). The link is available and can be provided upon request. We will later develop an English version so that it can be used, if appropriate, in English-speaking institutions.

Another limitation is the cost-effectiveness of virtual reality applications compared to traditional methods, especially in the context of developing countries.

Future work (AI/adaptive guidance): An additional direction is adaptive in-game guidance (contextual hints / conversational agents) which recent GenAI+VR prototypes suggest can improve efficiency and scaffold complex tasks [66]; testing whether adaptive support reduces cognitive load is recommended.

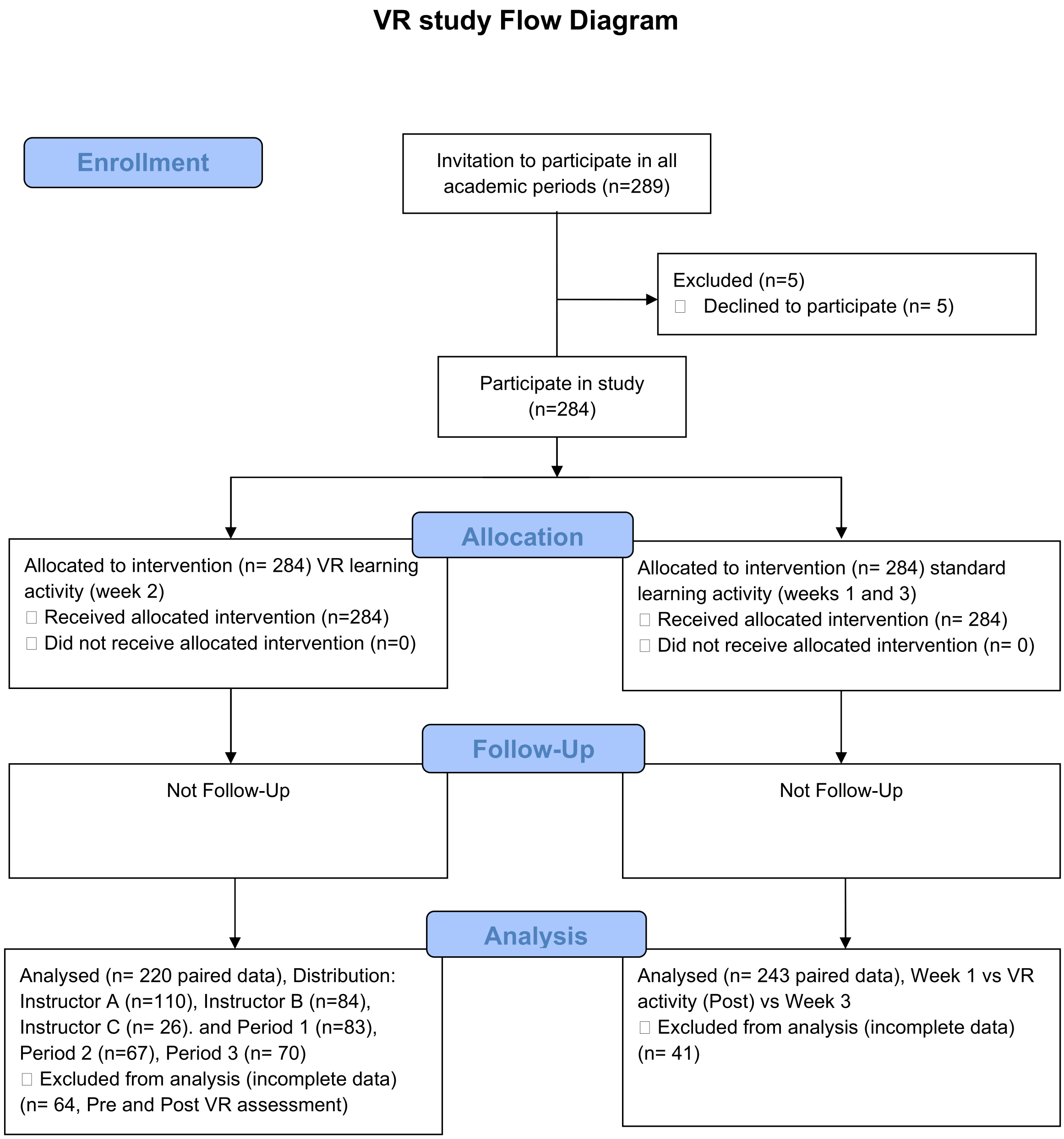
5. Conclusions

The use of VR as an educational aid allows students to access complex processes and places, where they would otherwise be unable to access on a human scale without developing their imagination. In this case, our VR platform developed at the institution also made it possible to optimize the learning of highly abstract and complex concepts in a short period of time.

We believe that the platform designed and implemented for learning ETC and OXPHOS in health sciences meets its objective, as it facilitates its implementation by professors and was well accepted by students and faculty. Therefore, we believe it can be easily adapted to other higher education institutions in the biosciences branch.

List of abbreviations

ETC:	Electron Transport Chain
OXPHOS:	Oxidative Phosphorylation
VR:	Virtual Reality
ATP:	Adenosine triphosphate
ADP:	Adenosine diphosphate
NADH/NAD:	Nicotinamide adenine dinucleotide, reduced/oxidated
H^+:	Proton
FADH2/FAD:	Flavin Adenine Dinucleotide reduced / oxidated



CONSORT-VR Flow-Diagram.

Data availability

Anonymized participant data (pre/post item responses), and other variables could be shared upon request.

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CRediT authorship contribution statement

Rosa C. Lopez-Sanchez: Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Ana G. Rodriguez-Mendoza:** Writing – review & editing, Software, Project administration, Funding acquisition, Formal analysis, Conceptualization. **Juan P. Nigenda-Alvarez:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Data curation. **Lizette S. Hernandez-Cardenas:** Writing – review & editing, Software, Investigation, Conceptualization. **Luis M. Villela-Martinez:** Writing – review & editing, Software, Methodology, Data curation. **Jose A. Hernandez-Hernandez:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare no competing interests.

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