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Gamification of Pharmaceutical Process Engineering: Undergraduate Academic Training for the Purification of Biologics Using Head-Mounted Virtual Reality

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ABSTRACT

Virtual reality (VR) provides the opportunity to deepen learning and experience learning situations in higher education that were previously inaccessible. Knowledge from theoretical classroom lectures is connected to scenarios from industrial practice and is thus experienced, consolidated, and anchored. VR allows students to immerse themselves in environments unattainable by university facilities, due to their temporal and spatial dimensions. The VR undergraduate academic training presented allows students to experience both an industrial scale and the regulations under which the production of biopharmaceutics is run, such as "Good Manufacturing Practice" (GMP) and safety regulations. A safety training on the virtual model of real laboratories—comprising six accident scenarios—continues in an environment based on reality with GMP-compliant dressing, a routine in the pharmaceutical industry usually not practised at universities. Main mental effort is afforded for the design of a purification process for one out of three biologics, using given parameter dependencies. After completion, students enter a large-scale downstream facility where they carry out their developed purification process. Students operate lifelike, large-scale devices rarely available at universities. Biologics are modern drugs, often produced in standardized so-called platform processes at large scale. Here, three classes of molecules, monoclonal antibody (mAb), fragment of an antibody (fab), and plasmid DNA (pDNA), are modeled. The task and challenge are to purify one of them according to product quality attributes such as yield, product concentration, and/or impurity levels. Calculations required for this run in the background of the program and are based on empirical experience and literature.

1 | Introduction

It is known from studies that a high degree of activation leads to very good amplification of learning effects and that learning content can be deepened in this way [1, 2]. Also, the provision of flexible learning methods that meet individual requirements is increasingly applied [3]. In the field of gamification in education, [4] one thrilling method revolutionizing education is Virtual Reality (VR), as it offers immersive and interactive learning experiences that enhance traditional teaching methods. Students can be immersed in spatio-temporal dimensions difficult to imagine. Processes that are very fast or slow can be adapted to experienceable time scales, and actual large-scale environments are often out of reach at university facilities. In higher education, VR has been successfully integrated in many fields [5, 6], such as arts and humanities [7]; medical and health education [8, 9]; science, technology, engineering [10]; and mathematics (STEM) education [11]; and is also increasingly

being used in vocational training and professional development [12, 13]. Gamification through head-mounted display virtual reality (HMD VR) enables truly interactive learning and helps to motivate and enthuse students to apply their theoretical knowledge from the traditional teaching concept in 'practical' experiences [14]. The associated emotional multisensory involvement will contribute to deeper learning [15, 16]. The head-mounted display-based (HMD) VR application presented in this paper contributes to the digitization of higher education. It was developed to train undergraduate students within a practical university course.

The main learning objective of the VR training presented is to transform and extend theoretical knowledge from classroom lectures into a 'practical' experience at the example of industrial-scale purification of biologics. Also, aspects of biotechnological production beyond the purification process itself are included in the training. The training is subdivided into three phases: Safety training, Whole process synthesis, and Large-scale processing.

a. Safety training.

   As safety has a major influence on product and production quality, part of the VR training course deals with safety regulations in practice. Safety ensures that employees can carry out their work safely and is a primary responsibility of employers [17]. The training of safety procedures with VR enables both participative and affective immersion [18] and in this way supports the internalization of procedures. Implemented in VR are, on the one hand, safety trainings on the virtual model of real laboratories that comprise six emergency scenarios. Here, students experience hazardous situations that cannot be easily practiced otherwise and play out what they have learned in a lecture on security under the stress of immersion. Correct safety procedures and behavior is practiced. On the other hand, students train a dressing routine in accordance with "Good Manufacturing Practice" (GMP) guidelines, as garment is the main barrier between the process/product and the operator, whereas its protective functionality works in both ways: product and its environment are protected from contamination and the operator is protected from the risks generated by the manufacturing in bioprocessing. Such rigorous dressing procedures are routine in the pharmaceutical industry but not practised at universities to this extent.

b. Whole process synthesis.

   While the lectures cover entire purification processes of biopharmaceuticals at a theoretical level, the standard practical courses at universities deal with single process steps one at a time. Due to time issues, internships allow for conducting, for example, one chromatography step of an overall purification procedure but never the Downstream Process as a whole. Therefore, the learning success is limited to one process step, and optimizations are made for a single process unit only. Executing this VR course, students experience the interdependencies of the single purification steps and obtain a deeper insight into the entire cleaning process.

c. Large-scale processing.

   The aforementioned downstream processes are being developed on a small scale. Lab-scale devices are available at universities, but technical-scale apparatuses are mostly inaccessible in higher education and are only taught in theoretical lectures. Large-scale devices often differ significantly from the usual university practical equipment. The VR training presented provides students with an insight into the design and scale of real technical systems and allows them to get active on these.

Using the presented HMD VR training, students experience three different settings and challenges. In phase A, the students learn safety regulations and are deliberately set under stress when performing the needed safety measures. In phase B, students need to apply the information provided during classroom lectures to synthesize a meaningful process. In phase C, students experience a large-scale industrial setting with realistic machinery and a noisy environment. Where appropriate, the various learning experiences (stress management, in-depth knowledge, industrial experience) are extended to all three phases (safety training, whole process synthesis, large-scale processing), Table 1.

2 | Story Board of the VR Training

Students are trained using HMD VR by consecutively passing five environments, see Figure 1 for a graphical storyboard and screenshots from the application. Throughout, the user is supported by a mobile digital wristband, which, depending on the scene, provides information on the current status, product properties, process flow, or measures to be taken. After an introduction of how to operate the VR device in the (0) Entrance Hall (Figure 1(0)) students enter a (1) Laboratory Wing (Figure 1(1)) where they are immersed in up to six hazardous situations in which they have to take safety measures. In the next scene, (2) Change Room (Figure 1(2)), students have to dress for a GMP-compliant production environment in a typical change room. Both trainings fall in phase A "Safety training", as described above. Following these scenes, students enter phase

TABLE 1 | Overview of different learning experiences and phases of the VR training.

Phase of training Learning experience	Phase A: safety training	Phase B: whole process synthesis	Phase C: large-scale processing
Stress management	×		
Skill deepening		×	
Industrial experience	×		×

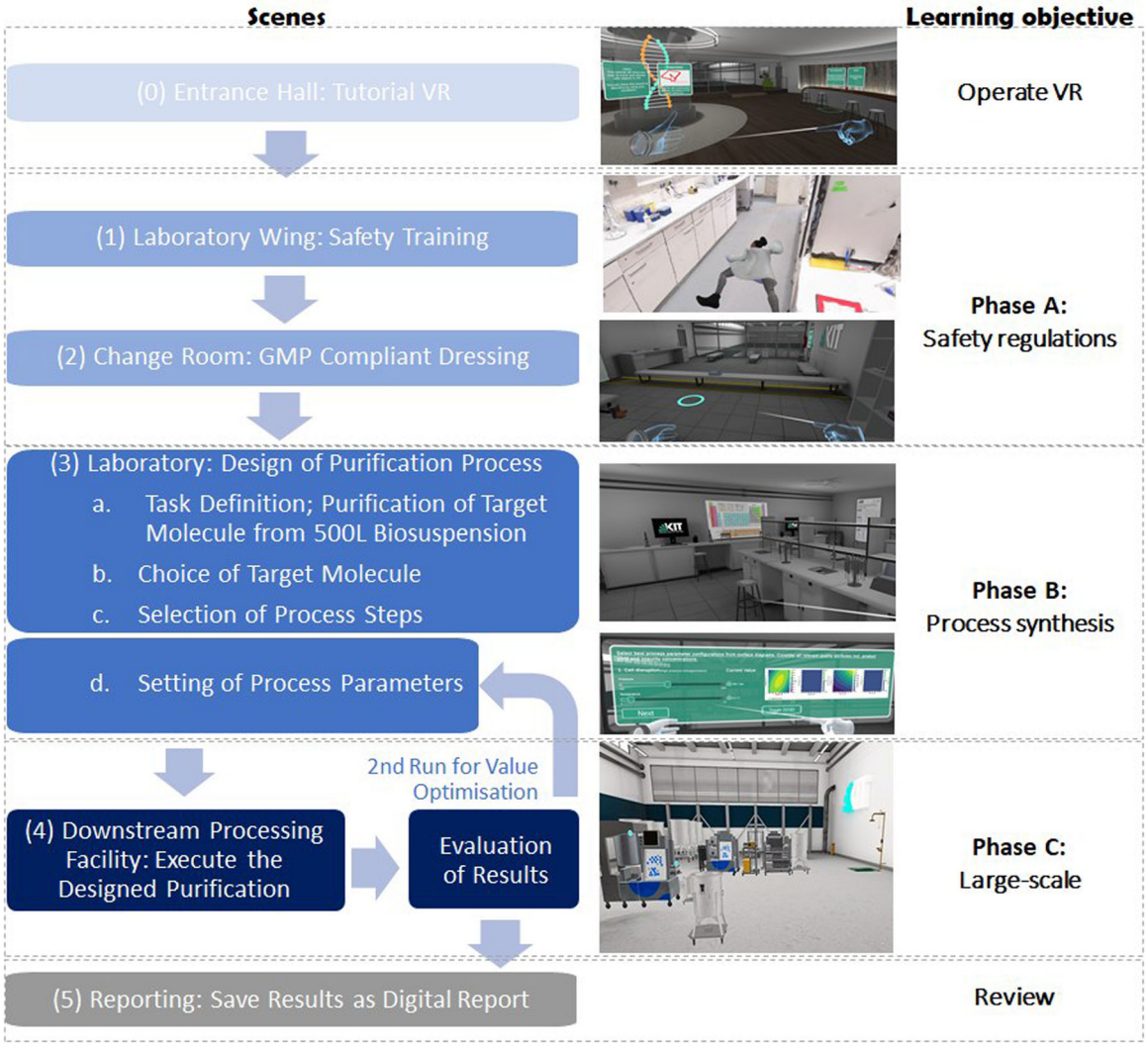

FIGURE 1 | Logic of the Story board of the undergraduate training 'Purification of biologics in industrial scale' in head mounted virtual reality (left) with screenshots (middle) of different sequential scenes: (0) entrance hall with tutorial; (1) laboratory wing with safety training; (2) change room with GMP compliant dressing; (3) laboratory with design of a purification process in four steps a–d; (4) downstream processing facility with DSP-Training in industrial scale; (5) reporting. Assignment of the different scenes to phases A–C and the learning objectives (right).

B, an area in which they pursue learning objective (b) "Whole process synthesis". This is carried out in the (3) Laboratory (Figure 1(3)). Students step into a laboratory where they design and configure a typical step-by-step process for one out of three possible biologics. Their task is to design a 500 L purification process for a biotechnological suspension. The challenge is to purify according to product quality attributes, such as yield, product concentration, and/or impurity levels. Finally, learning objective (c) "Large-scale processing" is addressed in phase C, the (4) Downstream Processing Facility (Figure 1(4)), which is based on real industrial equipment and allows the five previously developed process steps from scene (3) to be simulated at an industrial scale. To execute the purification, students slip into the role of a process technician who shifts vessels through the plant and operates five different large-scale devices. At the end of the process, the final product suspension is captured in a tank and stored in a cooling room. With this last action, a panel occurs, stating the properties of the final product suspension and thus evaluating students' performance. Now the application can be rerun starting at stage "Setting of Process Parameters" (Figure 1(3d)). This allows for either further optimizing the same purification task or tackling another one. Evaluation of the training is achieved through (5) Reporting (Figure 1(5)): All settings made in the VR experiment and the resulting outcomes are documented in a digital log file protocol. This automatically generated report contains all information on adjusted parameters and resulting values for the consecutive process steps and the overall purification regarding several quality attributes. As the digital report allows for further reflection and discussion of the designed purification process, the students receive it for their final protocol to be handed in after the experiment has been completed.

3 | Technical Background-Implementation-Logic

The program was developed as a stand-alone application for the HMD VR system "Pico 4 Enterprise". Implementation was carried out by an external company, "World of VR", Cologne, Germany, using the game engine "Unity". To make the

implementation simple and efficient, the visual scripting tool "PlayMaker Visual Scripting for Unity" by "Hutong Games LLC" was used. It allows the creation of finite state machines (FSM) to represent the logic of the Unity project.

The logic of the application comprises mainly linear sequences as well as one decision tree. The tutorial is following a linear logic sequence, and also scene (2) Change Room (Figure 1(2)), is predefined whereas several correct pathways exist: predefined garments (e.g., mask, gloves, overall etc.) have to be put on and only for some items the correct order must also be noted. If the procedure is carried out incorrectly, it can be repeated once. Scene (3) Laboratory (Figure 1(3)), includes an initial decision tree and further linear logic. Please compare "logic of the training" in Figure 2 for the following explanation: First, one out of three molecules (products) has to be chosen (decision tree) (Figure 2(1)), then the following steps have to be accomplished according to a predefined order. Second, for the molecule chosen that is contained in a biosuspension, five out of six essential process steps have to be selected and brought into the correct order (Figure 2(2)). Third, for each process step, the correct method for purification on a technical scale (Figure 2(3a)), important process parameters for each of these methods (Figure 2(3b)), and correct units for the respective process parameter (Figure 2(3c)) have to be picked. Finally, fourth, the values of two given process parameters are to be adjusted by means of a sliding controller (Figure 2(4)).

For deciding the best process parameter configuration, the operator considers relevant quality attributes such as production yield and impurity concentrations. Four relevant quality attributes are shown in surface diagrams (Figure 3), which can be toggled to heatmaps. Given are the dependencies of one respective quality attribute each, on the two abovementioned process parameters.

The large-scale production, storyboard to scene (4) Downstream Processing Facility (Figure 1(4)), follows the linear logic sequence, which was previously developed in scene (3) (Figure 1(3)). With the finishing scene (4) (Figure 1(4)) resulting values for each quality attribute are calculated by means of a stored calculation formula. These anticipated equations are based on both empirical experience and literature, and were also used to generate the above surface diagrams.

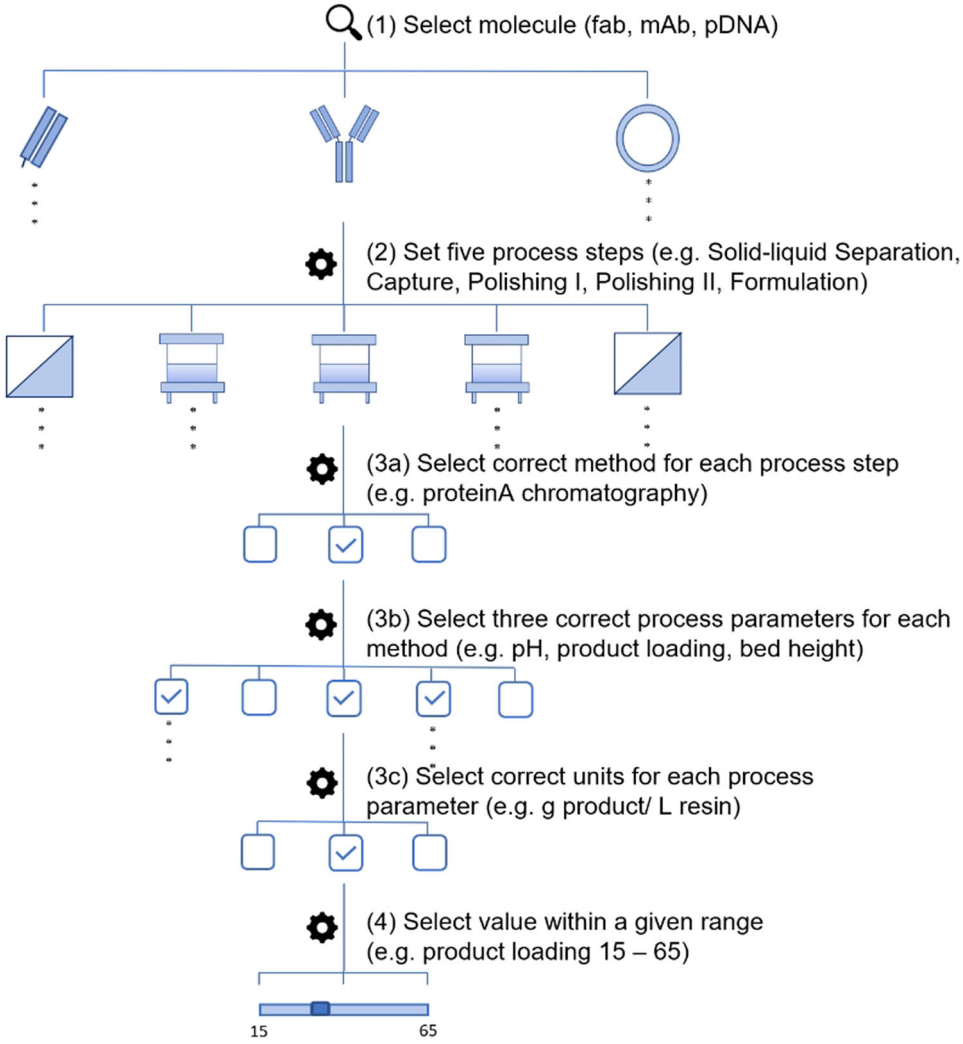

FIGURE 2 | Logic of the head-mounted virtual reality training using the example molecule mAb. (1) Selection of molecule. (2) Setting of process steps. (3a–c) Selection and further specification of purification methods. (4) Selection of values for process parameters.

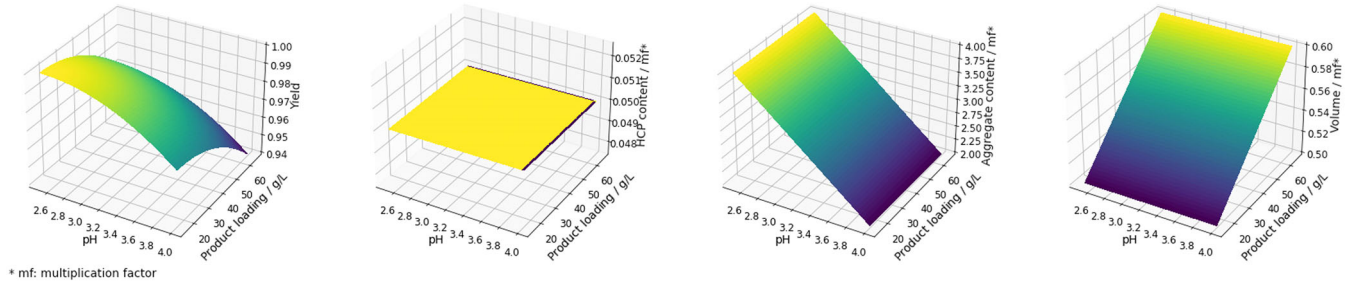

FIGURE 3 | Surface diagrams showing the dependence of one quality attribute (from left to right: yield, HCP content, aggregate content, volume) on the two process parameters for method two of the molecule mAb. Plotted values are fictitious and were calculated by anticipated equations based on empirical experience and literature.

3.1 | Communication Between VR and Real-World

For meaningful but simple communication between student and tutor/group partner, streaming and data transfer were established via a wireless connection between the HMD VR system and a computer.

The streaming function mirrors the VR user's view to an external computer, tablet, or screen and allows for collaboration with a group partner or a tutor.

Further, a companion-app is implemented, using the networking library, Mirror‘ of, Mirror Networking. This desktop application connects via WiFi to the stand-alone HMD VR application and shows the report file in real time. The report files are created on the HMD and contain all parameters the experimenter chooses. This allows a tutor to follow the actions and entries of the experimenter and also documents errors triggered by incorrect procedures. After finalizing the experiment actions, selected parameters as well as calculated values of all process steps are also saved in the report file and can be used further for discussion regarding the action or parameters and handed over to the student. The companion-app is also capable of downloading older report files stored on the HMD.

Most of the modeled rooms were designed based on industrial state of the art equipment. However, in the case of the Laboratory Wing, the model was created by stitching about 1–2000 photos per room, taken in real labs by the photogrammetry software “Reality Capture”. The resulting 3D model was smoothed using the software “Mudbox” and post-processed using the software “Maya”, both by Autodesk.

4 | Background and Teaching Content of the Training

This HMD VR training application addresses undergraduate students and is supposed to strengthen theory on “Downstream processing of biologics” presented during classroom lectures, but mostly covers topics, such as (a) safety training, (b) whole process synthesis, and (c) large-scale processing. Relevant topics within the downstream processing of biologics are covered in the following.

4.1 | Safety Issues During Processing

As mentioned in the learning objectives, the HMD VR application includes a safety training in the virtual model of real laboratories (Figure 1(1)) as part of phase A. Official recommendations for safety-compliant behavior [19] are incorporated for training the correct behavior in the following six scenarios: In the event of

- fire,
- accident with an injured person,
- electrical accident,
- spillage of liquids with physical contact,
- liquid splashes in the eye,
- disposal of spilled chemicals.

In this part of the training, participants are exposed to stressful emergency situations, have to react under time pressure, and experience multisensory impressions. The training can be practised several times until correct sequences are internalized.

Additionally, in phase A, aspects of GMP regulations are trained. For the manufacture of sterile pharmaceutical products, the risk of contamination with microorganisms, particles, and pyrogens must be minimized. Quality assurance is of particular importance, and production is carried out strictly in accordance with carefully defined and validated methods and procedures. These regulations are referred to as “GMP for medicinal products” and are laid down in national [20] and international regulations [21]. The special working precautions to be taken are illustrated in the HMD VR application using the example of a change room (Figure 1(2)) in which suitable clothing has to be put on in correct order.

4.2 | Safety Training Using the Example of “Training in Case of Fire”

The task in this “training in case of fire” is to take relevant actions in the correct order. These are (1) switch-off electricity, (2) activate the fire alarm, (3) activate the gas emergency stops, (4) make an emergency call, (5) warn people at risk and take them with oneself if necessary, (6) close doors and windows,

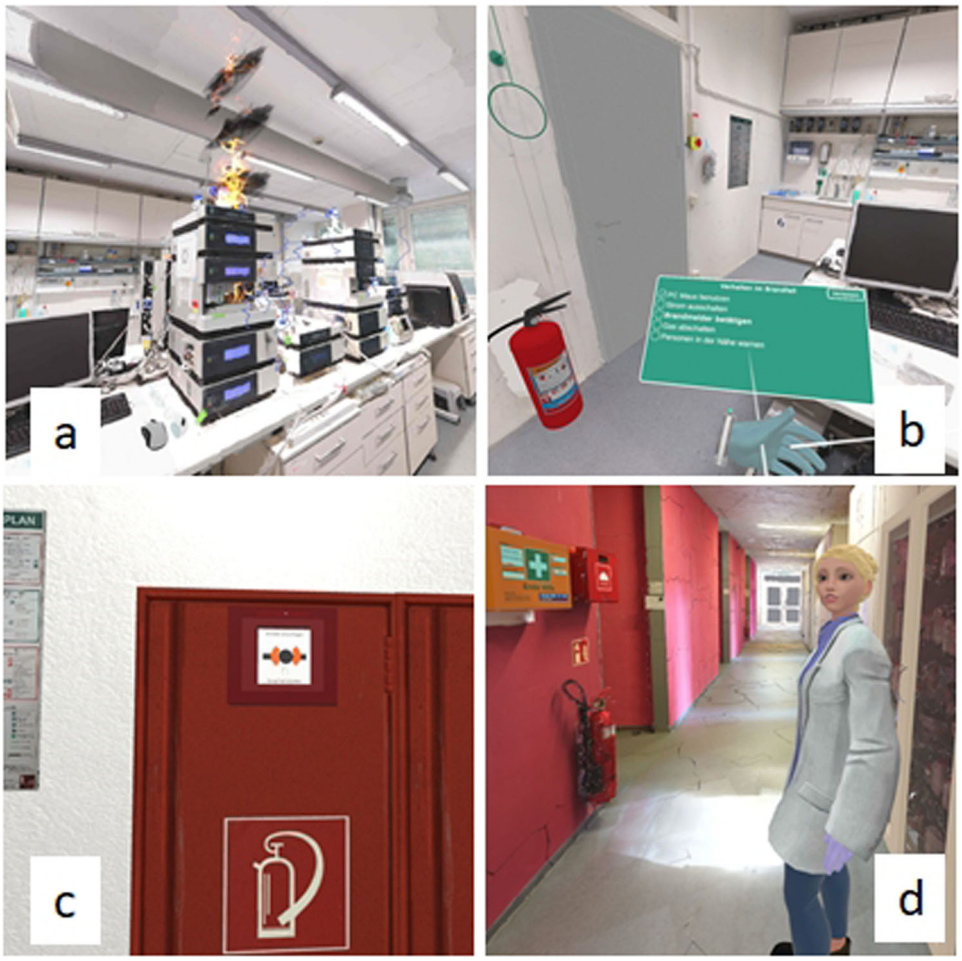

FIGURE 4 | Screenshots from head-mounted virtual reality application "safety training in case of fire": (a) incipient fire in the lab; (b) wristband with instructions in the correct order; (c) fire alarm box; (d) person to be alerted in the corridor.

(7) attempt to extinguish the fire, (8) leave rooms, follow escape routes, and take endangered persons with oneself.

Initially, the user finds himself at the control computer of a chromatography system. When moving the computer mouse, a flask with a liquid tips and spills into the electronics, provoking a fire. Over time, this initial fire enlarges and spreads to the chromatography system (Figure 4a). The first thing to be done is to cut off electricity by pushing the electrical emergency switch. In case the steps or the correct order cannot be recalled, the user can activate a sign panel at the wristband (Figure 4b) where the actions are listed. Next, the fire alarm has to be actuated. To somewhat of the surprise of most of our testers is the fact that in the real-life laboratories, the relevant buttons to actuate the fire alarm and stop the gas supply are outside the laboratory wing (Figure 4d). In both cases, the safety glass has to be smashed before the buttons can be pushed (Figure 4c). Returning to the burning lab, a person in the aisle has to be warned by touching her (Figure 4d). In the lab, a cell phone has to be found and an emergency call made by pressing a green button, confirming the correct real-life emergency number of the institution. Under stress, often our participants get nervous and drop the phone, losing time to pick it up again. After a trial to extinguish the fire with a hand-held fire extinguisher, the lab has to be left following the signage of the evacuation route. The training is finished when the last door (emergency exit) has been opened.

A timer is running as soon as the flask tips over. In this way, participants can complete the training several times and compare whether their times have improved or compete with others.

4.3 | Molecules

To meet challenges presented during lectures, three different molecules were selected:

4.3.1 | Monoclonal Antibodies

Monoclonal antibodies (mAbs), also known as immunoglobulins, are highly specific proteins that can bind to a single epitope of an antigen [22]. They are produced using a cell line specifically modified for a mAb. mAbs are used in research, diagnostics, and in particular, in the treatment of cancer [23] and autoimmune diseases.

In the pharmaceutical industry, extracellular production of mAbs in recombinant mammalian cells (e.g., Chinese Hamster Ovary) is favored to ensure correct posttranslational modification and easier purification. Subsequently, in the purification of mAbs, the capture method using protein A chromatography is

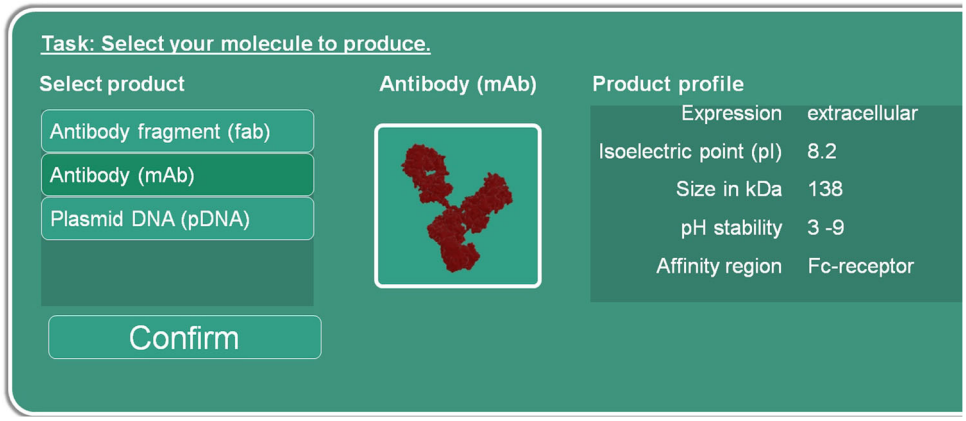

FIGURE 5 | Image detail from panel with task on molecule selection using the example of mAb from head-mounted virtual reality training on 'whole process synthesis' showing a 3D-model of the mAb molecule (middle) and product profile (right).

the most widely used, as the constant region (Fc) of antibodies can bind highly specifically to these ligands. The resulting surface net charge of the mAbs after elution with acidic pH can be used to decide on subsequent polishing chromatography steps [24]; mAbs have an average size of 150 kDa and are stable at pH values of 3–9, depending on their specificity. For most clinically relevant antibodies, the pI (isoelectric point) is found between pH 7 and pH 9.

In the HMD VR application, the product profile of the mAb to be purified is displayed with its respective specific properties on a panel on which the students can also grab, move, and look closely at a 3D model of the molecule, Figure 5. This also applies analogously to the other molecules.

4.3.2 | Fragment Antigen-Binding

Fragment antigen-binding (Fab) is obtained if an antigen-binding arm is separated from an antibody at the hinge region. A Fab thus consists of one variable and one constant domain, each from a light and a heavy amino acid chain. This reduced structure of functional components enables targeted and efficient binding to specific target structures. Due to this high specific antigen-binding capacity, Fabs are a key component in medical research, diagnostics, cancer, and immunotherapy [25, 26]. A single Fab fragment is usually around 50 kDa in size and, depending on specificity, stable at pH values of 3–9. For most clinically relevant insulins' the pI is found between pH 6 and pH 8.

Fabs can either be expressed directly or obtained by enzymatically digesting isolated antibodies. In HMD VR training, Fabs to be purified are his-tagged proteins, which were expressed intracellularly.

4.3.3 | Plasmid DNA

Plasmid DNAs (pDNAs) are ring-shaped DNA molecules that are frequently found in bacteria and serve as vectors for the transfer and expression of genes in cells. The field of application of pDNA is very diverse, including the production of viral vectors, mRNA production, in vivo gene therapy, and utilization for vaccines. pDNA is typically between 5 and 20 kbp in size and has a high negative charge and hydrophobic surface regions. pDNA only denatures at high basic pH values of around pH 12–12.5.

The technical production of pDNA takes place intracellularly in *Escherichia coli*, so that cell disruption is necessary after production [27, 28]. It should be noted that pDNA is very shear-sensitive and can form plasmid isoforms if subjected to excessive mechanical stress [29].

4.4 | Process Synthesis

Products to be purified in VR are three typical modern drugs, so-called biologics, which were selected according to their current and future importance in pharmaceutics: monoclonal antibody (mab), fragment of an antibody (fab), and plasmid DNA (pDNA) [30]. The specific products are fictitious molecules, adapted to the biochemical properties of real products.

For the three classes of molecules, standardized downstream processes are established in so-called platform processes. These are documented in the literature [25, 28, 31] and were adapted to the VR teaching application.

Platform processes are based on typical process steps and parameter ranges. They therefore offer an efficient approach for the production of biotechnological products. New products can be developed more quickly and transferred more easily to larger (production) scales, as optimized processes already exist. In addition, the good reproducibility of the process ensures consistent product quality [24, 31].

4.5 | Process Steps

Included in the HMD VR application are methods that have become established on a technical scale.

Cell disruption: If the target product is present intracellularly, the host cells must be disrupted. Depending on the sensitivity of

the cells and the product, cell disruption can be carried out enzymatically, chemically, physically, or mechanically. In VR, two methods are included that are available on a technical scale: (a) chemical breakdown by alkaline lysis and (b) mechanical disruption by high-pressure homogenization.

Liquid Chromatography (LC): Chromatographic methods are very potent and are used to solve a wide variety of separation problems. LC separation methods are one of the most frequently used methods for the purification of biomolecules, such as proteins, nucleic acids, or lipids [32]. The analytes in a mixture remain in the chromatography column for different lengths of time due to their different interactions with the stationary phase. Silica gel, resins, etc. are used as column material (resin). Within LC, a distinction is made according to the interaction between the analyte and the stationary phase, which is responsible for the separation. Interactions can include electrostatic, hydrophobic, or specific affinities. In VR, LC methods are included based on (a) ion exchange for anion exchange (AEX) and cation exchange (CEX), (b) affinity chromatography: immobilized metal ion affinity chromatography (IMAC) and protein A, as well as (c) hydrophobic interaction chromatography (HIC).

Filtration: Filtration steps play an important role throughout the entire purification process, whereby different filtration processes are used depending on the separation problem. Basically, filtration is a mechanical separation process of solid-liquid separation, in which particles or macromolecules from a fluid flow are retained on a filter medium through size exclusion, particle inertia, diffusion effects, electrostatics, or barrier effects.

In the processing of bioproducts, solid–liquid separation is used to separate particles, such as salt crystals, whole cells, or cell debris, after cell disruption and to separate high-molecular substances from low-molecular substances. Membrane processes are frequently used, the categorization of which depends on the size of the components to be separated, the so-called molecular size cut-off.

An effective method for formulating the product at the end of the purification process is ultrafiltration (UF) combined with diafiltration (DF) [33]. During ultrafiltration, the suspension is concentrated by retaining larger molecules and allowing smaller ones to pass through the membrane. Diafiltration is a special form of ultrafiltration in which additional volume is exchanged to remove salts and buffers from the previous process steps and/or to achieve a buffer change.

In HMD VR, dead-end filtration and dynamic (cross-flow filtration) filtration processes are used.

4.6 | Process Synthesis—"Purification of mAb"

Process synthesis (phase B) takes place in the logic described above (Figure 2) and is performed simply by using 2D panels (Figure 6a–c) for a selection of process steps and the associated process parameters. Characteristics of the starting material are defined in a product and batch profile and can be read off a wristband at any time at the touch of a button.

In the example mAb, the product profile states an isoelectric point (pI) of 8.2, a pH stability of 3–9, a size of 138 kDa, and an FC receptor as affinity region (Figure 5). Due to the batch profile, not shown, it is known that the mAb has been expressed extracellularly at a product concentration of 5 g/L in 500 L fermentation volume with 15×10^6 cells per mL. The level of the impurities is given at levels of 8 g/L for host cell protein (HCP), a DNA concentration of 1 mg/mL, and an aggregate content of 8%.

This starting material is to be purified into a final product that meets the initially stipulated quality attributes, for example, specified by a tutor. Reduction of impurities often leads to product loss, which also reduces the yield, and in most cases, is unfavorable. In any case, the interdependencies of single process steps should be reflected, and the individual aim has to be kept in mind throughout the process design.

The first task after choosing the molecule is to select five out of six process steps to be utilized in the purification process and bring them into the correct order, by using drag and drop (Figure 6a). Students will learn that for mAb, the correct order is solid–liquid separation, capture, polishing I, polishing II, and formulation. By pressing the confirmation button, the decision is stored in a log-file, reported to the tutor, and automatically evaluated. The selection procedure is repeated until the answer is correct. Only then can one move on to the next task. Here, for each of the aforementioned selected process steps, a method has to be selected that is suitable for large-scale. Correct methods would be depth filtration for the solid-liquid separation, ProteinA chromatography in the capture step due to the FC receptor of the molecule, for polishing I AEX-Chromatography in flow-through mode, for polishing II CEX-Chromatography in bind-elute mode, and UFDF for formulation. Again, the choices are to be confirmed (automatically saved) and possibly have to be corrected until they are correct.

The second task is the selection of three process parameters from five given, in which students prove their acquired capability to evaluate the importance of each process parameter. Shown here is the case of Protein A chromatography (Figure 6b), where the three most important process parameters are "pH", "bed height", and "product loading" above "flow rate" and "salt concentration". The latter two should, of course, be kept within reasonable limits in real life. Again, the selection is to be confirmed.

In the next design step, students recap their knowledge of the definitions of units for the given process parameters and demonstrate that they are capable of classifying certain value ranges. For instance, the process parameter "product loading" is given in a range of values from 15 to 65. Possible answers for the units are "g product/L resin", "mg product/L resin", and "g product/mL resin", from which only the first answer is reasonable in an established industrial process and to be confirmed.

Up to this point, the training is predetermined, which implies that after one or the other repetition, all students see the next panel (Figure 6c). This comprises four surface diagrams and two sliders, representing the two variables shown in the

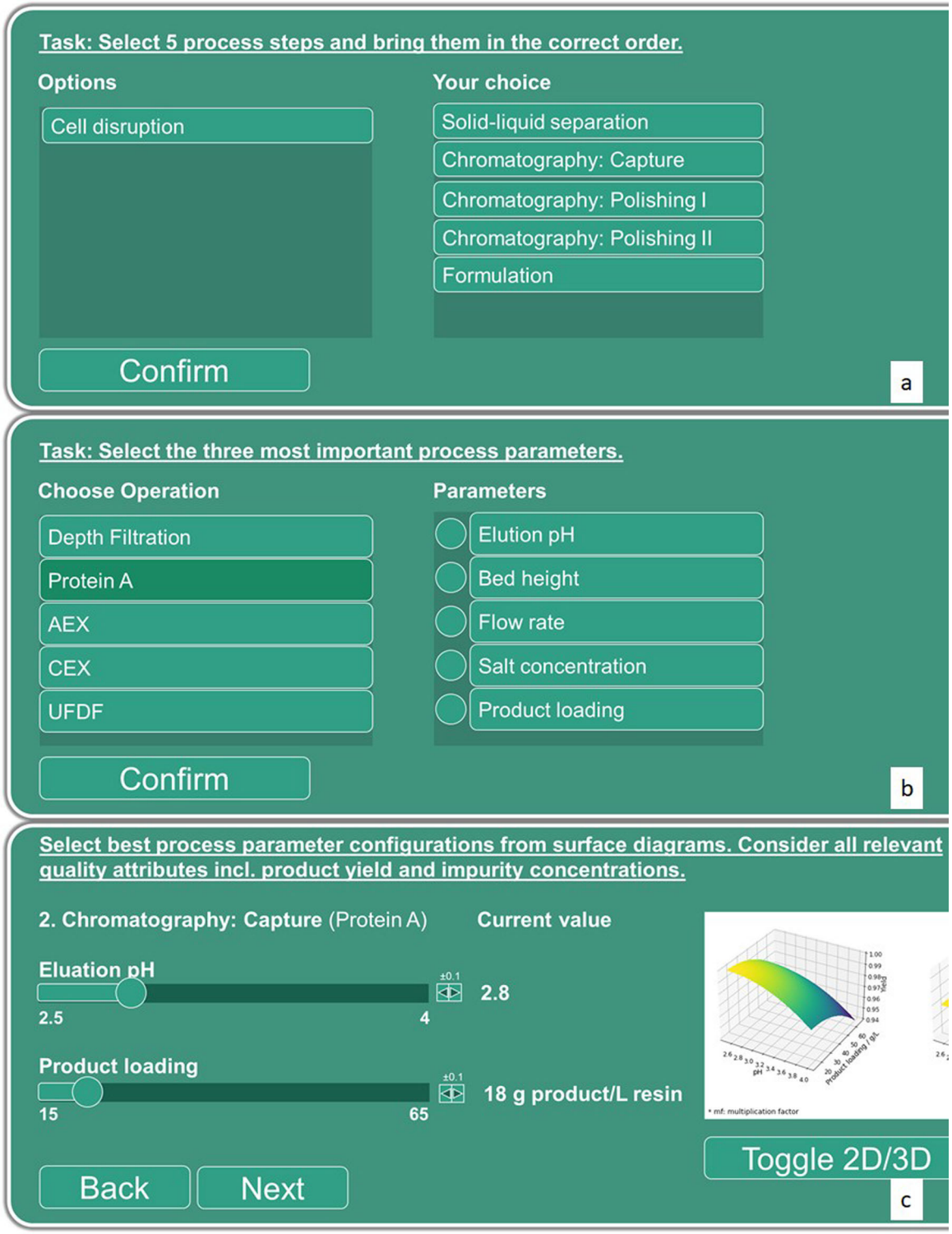

FIGURE 6 | Image details from panels using the example of mAb from head-mounted virtual reality training on "whole process synthesis": (a) task to select process steps; (b) task to select process parameters; c) task to configure process parameters.

diagrams. The diagrams can either be displayed as surface plots or toggled to heatmaps for better visualization. Charted are the dependencies of the four quality attributes yield, HCP concentration, aggregate content, and volume on the two process parameters given (Figure 3). One quality attribute is plotted per diagram. The easy-to-use task is to adjust the values of the two process parameters given. Intellectually, this is the most challenging task for the process design, since the aim is to select the best process parameter configurations considering all relevant quality attributes. It is important to know that not every single process step allows for the enrichment or depletion of impurities. In the example shown, the parameters pH and product loading can be adjusted. Here, a favorable high yield at low pH and product loading would come along with unfavorable high aggregate content (Figure 3). In this step, we train students on the one hand to take readings from surface

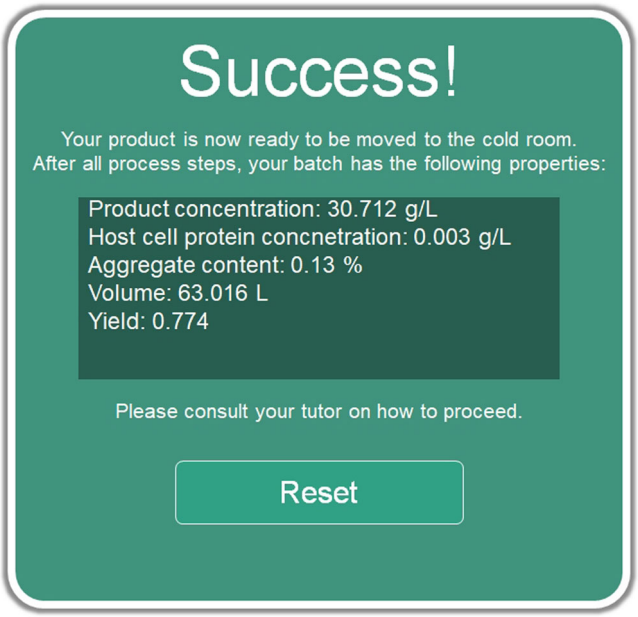

FIGURE 7 | Image of the final panel of the head-mounted virtual reality training showing the results after purification of the example molecule mAb.

diagrams and heatmaps, and on the other hand to consider complex interdependencies.

Depending on the abovementioned stipulated quality attributes, slider positions have to be set and confirmed. These values serve for the internal calculation of the final product concentration, HCP concentration, aggregate content, volume, and yield listed on a panel (Figure 7) after finalizing the application in the downstream processing facility (Figure 1(4)).

The design of the purification process is now finished and the training continues in the downstream processing facility. Due to the design sequence, the selection of equipment is predefined.

4.7 | Process Scale Up—"Purification of mAb"

In phase C, the student is relocated to the downstream processing facility (Figure 1(4)) and performs the previously selected process steps. In this part of the VR application, students learn about the dimensions, noise, and approximate handling of large devices, starting with a 500 L vessel of fermentation broth, which needs to be pushed to the first purification process step, the depth filtration in case of mAb. A timer runs, indicating the duration of the process step in reality, which in some cases can be hours. The intermediate product is then collected in a new vessel, which has to be transferred to the second, third, fourth, and fifth purification process steps, until the final product is then moved to a cold room for storage. With this, the training ends and the student receives the abovementioned calculated values on a panel (Figure 7). Optionally, a second (e.g., optimizing) run can be made, starting from Figures 1(3d).

5 | Learnings

The HMD VR application proved usability and functionality:

a. The application was tested throughout implementation and the final version was then used within our regular curriculum, a practical course, where no technical problems occurred.

b. The findings with an initial group of 30 students in a first round of a student internship include that students quickly found their way around the virtual world and had no problems with handling the controllers.

c. No physical problems occurred apart from slight dizziness or headache that disappeared by taking breaks. Depending on preparation using a script and the depth of the introductory oral colloquium, students could finish the required tasks quickly when well prepared.

d. Students considered the amount of work required to succeed in the course comparable to other parts of the annual practical course.

e. We received consistently positive feedback, especially the scenes (2) Change Room (Figure 1(2)) and (4) Downstream Processing Facility (Figure 1(4)) were repeatedly assessed as a meaningful and realistic experience.

f. Besides the abovementioned students from the practical course, the HMD VR training was performed by other students, scientists, and industrial experts working in the area of Downstream Processing. Excellent feedback was attested, especially mentioning the realistic environment and the need to act actively.

6 | Conclusion

This paper presents a practical course, which for the first time, aims to teach purification of biologics on the technical scale in virtual reality. The practical course is divided into three phases: "Safety training", "Whole process synthesis", and "Large-scale processing". The HMD VR application has been embedded in a practical course of the undergraduate degree program for bioengineers to intensify theoretical knowledge from face-to-face lectures. The course enables students to design and dimension complex downstream processes, with the challenge to go through interdependent subprocesses, that are out of reach in terms of scale/size and temporal dimensions at universities. The application promotes digitalization in academics and aims to improve the quality of education in bioengineering by increasing students' engagement. The modern playful method allows students to deepen knowledge and gain practical experience with all their senses in a technical environment that can otherwise only be taught theoretically.

7 | Outlook

This project has created the basis to add physical process models to each unit operation and to enable external control over process parameters. The long-term goal is to provide students with adaptive training, which is customized to the

individual learning level and abilities of the player, and to use external intervention during all unit operations, while multisensory stimuli will enhance the experience. For example, students would have to react to incidents during the execution of a virtual experiment or enter an unknown environment and have to realize what is happening and react appropriately. According to initial actions, the individual level of a learner can be picked up and supported. This could be implemented either externally by tutors with a mixing console or generated automatically possibly integrating Artificial Intelligence [34].

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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