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Original article

Virtual reality-based bioreactor digital twin for operator training

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ABSTRACT

The use of immersive technologies and digital twins can enhance training and learning outcomes in various domains. These technologies can reduce the cost and risk of training and improve the retention and transfer of knowledge by providing feedback in real-time. In this paper, a novel virtual reality (VR) based Bioreactor simulation is developed that covers the set-up and operation of the process. It allows the trainee operator to experience infrequent events, and reports on the effectiveness of their response. An embedded complex simulation of the bioreaction effectively replicates the impact of operator decisions to mimic the real-world experience. The need to train and assess the skills acquired aligns with the requirements of manufacturing in a validated environment, where proof of operator capability is a prerequisite. It has been deployed at UK's National Horizons Center(NHC) to train the trainees in biosciences.

1. Introduction

Due to the surge in the availability of consumer-grade affordable hardware, the remarkable development of the technology and the predicted boom of industry in the post-pandemic era, immersive technologies such as Virtual Reality (VR) have observed unprecedented popularity. Their application spectrum ranges across various domains, for example, construction training (Carozza et al., 2015; Wang et al., 2018), industrial education (Palmas et al., 2019; Hassan et al., 2019), occupational health and safety training (Nakai et al., 2014; Sacks et al., 2013), health care management (Yiannakopoulou et al., 2015; Siu et al., 2016), transport simulation (Xue et al., 2018; Defence et al., 2018), exergaming (Norouzi-Gheidari et al., 2020; Ringgenberg et al., 2022), etc.

A digital twin is a virtual replica of a physical process or system that can collect data through sensors and then use analytics and modelling techniques to simulate its behaviour, performance, and characteristics in a digital environment. The concept of digital twins has become very popular in the industry for several reasons. From predictive maintenance through monitoring and identifying potential issues at early stages to reduce costs and increase operational efficiency. Also, digital twins create innovation by simulating different scenarios and testing before implementing them in the physical world, which can save time and resources.

Particularly in training, the effectiveness of VR is significant. It reduces the training cost and risk and at the same time, diverse real-world training scenarios can be simulated (Fisher et al., 2019).

It also helps to retain tacit knowledge and aids in near and far knowledge transfer (Vasenev et al., 2013). Above all, it lets the trainees engage in an active learning process where they learn by carrying out actions themselves (self-affordance) (Widiaty et al., 2022). According to Arnold et al. (2023), VR is an example of constructive learning that supports the trainee to learn through role play and acquire collaborative skills. According to the Cognitive load theory (Bloom's Taxonomy) (Randeniya et al., 2019; Iqbal, 2022), VR training is substantially effective in cognitive and psychomotor learning (Randeniya et al., 2019; Mulders et al., 2022) in both hierarchical (i.e., take cognitive decisions- tactical flight navigation) (Lele, 2013) and procedural tasks (i.e., tasks in the process industry) (Cibulka et al., 2016; Gavish et al., 2015) which makes this form of training an ideal candidate for vocational education (Plotzky et al., 2021). VR training reduces the challenges of limited equipment availability, complicated lab preparation, long cycle time, and high costs that can be associated with vocational training (Fisher et al., 2019). Moreover, it supports the trainees in improving their skills by letting them practice repeatedly, flexibly and dynamically on a particular module of study. One of the advantages of this mode of learning is that the trainees are allowed to make mistakes.

Recent research in the field of empirical psychology (human factor) outlines how trainees retain information more effectively if they are allowed to make mistakes during the training sessions and the mistakes are later highlighted to them (Zhao et al., 2018; Keith and Frese, 2008). Thus, the incorporation of 'error management' as opposed to

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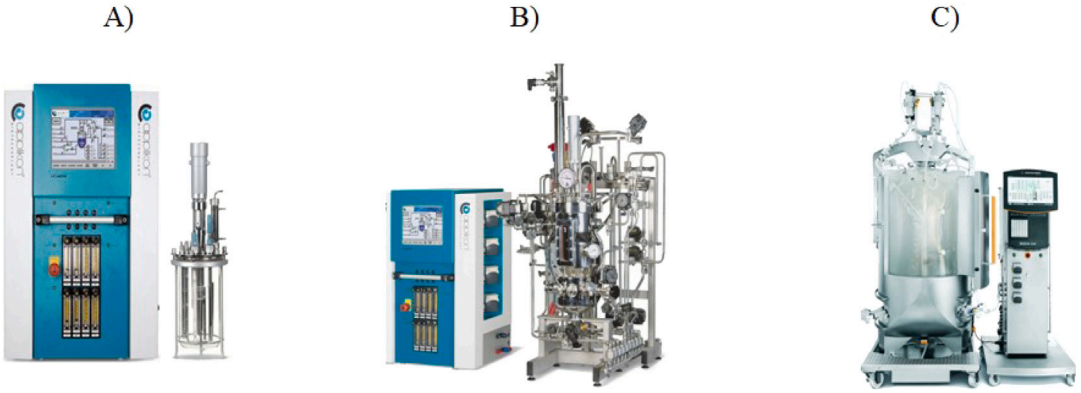

Fig. 1. (A) Autoclavable glass bioreactor (B) Stainless steel (Steam In Place- 20L) bioreactor (C) Single-use bioreactor.

'error avoidance' in training is becoming popular (Keith and Frese, 2008). In the bio-manufacturing/bioprocessing field, in particular, the application of VR-based training would be beneficial (Fisher et al., 2019; Zhang et al., 2019). Bio-manufacturing is a multidisciplinary field that is currently undergoing a severe labour shortage. According to Langer et al. (2017), a shortage in expertise is causing bottlenecks in the bio-manufacturing space, with around half of the drug makers struggling to fill process positions. Training in bioprocessing is a complicated procedure as it is complex, time-consuming and involves hands-on training (Broeze, 2006). It also has the challenge of smooth knowledge transfer (training critical decision-making for anomalous scenarios which occur rarely). According to a survey, people in the biopharmaceutical manufacturing industry think that the principal cause of operational errors in the bioprocess industry is 'human error (71.4 %)' (Filtration, 2023). VR-based operator training has the potential to reduce this and could contribute in a significant manner to the broad challenges facing the bio-manufacturing industry. The upstream process is an important component of the overall bio-manufacturing process in which the bioreactor/fermenter is the heart. A bioreactor is a closed system that is used to culture cells in a controlled manner to produce biopharmaceuticals (i.e., vaccines, therapeutics, gene therapies and cell therapies). Bioreactors can be of different types (i.e., microbial, cell culture, single-use etc.) and range in size e.g., an autoclavable glass bioreactor at a few litres working volume to an industrial scale bioreactor of thousands of litres working volume. In Fig. 1 a selection of types of bioreactor is shown.

Training the operators 'hands-on' (in the laboratory environment) for bioreactor setup, pre-processing, operation and monitoring is a considerable challenge (Fisher et al., 2019). It is largely because of the complexity of the bioreactor system but also due to the high cost of the equipment and materials, long training cycle, shortage of instructors etc. Moreover, different processes require a different configuration of the bioreactor and some rare industrial manufacturing emergencies cannot be recreated easily in the laboratory setting (Xiao et al., 2004). There are physical training modules available both in academia and in various vocational institutes but they all face the preceding challenges. There have been efforts to introduce Operator Training Simulators (OTS) (Gerlach et al., 2016; Peroni et al., 2005), which are primarily desktop-based mathematical simulation models for different processes, for bioreactor operator training in process monitoring. However, they lack the attributes of procedural interactive training (i.e., what mechanical valve to open or close if the internal vessel pressure of a bioreactor deviates beyond a threshold value etc.). Furthermore, they lack immersiveness and fail to create a sense of presence for the trainees (Haar et al., 2021), which directly correlates with performance in the real world. There are a few ongoing developments that propose VR as a medium to train the procedural tasks related to the bioreactor (i.e., sterilisation training of a Steam In Place (SIP) bioreactor Fisher et al., 2019) but they too are limited by providing training for the offline tasks only (while the bioreactor is not running any processes). Therefore, there is a gap for a training tool that can serve the purpose of both offline setup and online operation. In this paper, we propose a novel gamified VR-based 3D bioreactor (20-litre SIP stainless steel bioreactor) simulation training (serious game) experience with an integrated penicillin production simulation based on mathematical models parameterised by industrial batch data. The learning objectives to be facilitated by the VR tool are to allow an operator to be trained not only on the offline mode of the bioreactor (setting up the reactor for the process, sterilise it etc.) but on the online operational mode (monitoring the progress of the process) while the bioreactor is running. The game simulates a penicillin production process and various faults are added at different steps of penicillin production (for example, the pH decreasing and the control system not being able to compensate). The trainee must investigate different parameters, detect the nature of the fault and take appropriate corrective actions. The results of the actions taken by the trainee can also be observed instantly (i.e., the pH levels return to the optimum level). To the best of our knowledge, this is the only VR-based bioreactor training simulator that encompasses the training features that allow for both setup and online operational experience. Moreover, we have developed different practical scenarios in VR that are associated with bioreactor setup such as (a) Standard Operating Procedure (SOP) for sterilisation of the bioreactor (b) pH probe calibration module (c) Orientation module of the bioreactor (introducing the different components of the bioreactor) (d) Gamified emergency training (i.e. excessive pressure inside the bioreactor). In addition to the SIP bioreactor, we replicated the equipment setup considerations and applied them to a glass lab-scale bioreactor for those progressing through the early stages of training. Here, we established a quiz to identify component parts and incorporated errors in setup to test fault-finding ability. Finally, another novel contribution of our proposed VR bioreactor training simulation is, while the trainee is performing the tasks in the VR, there is an automated back-end AI module that records all the activities of the trainees (i.e., the completion time of a step, the number of errors they make, what type of errors they are making etc.) and logs them into a dashboard like 'Learning management system tool'.

2. Related work

2.1. Virtual reality as a tool for training

As discussed in the previous section, VR has been gaining considerable popularity as a training tool in various domains in the last few years. A aimed to evaluate the level of improved self-confidence through VR surgical training for maxillofacial surgery (Pulijala et al., 2018). This form of surgery is particularly challenging to be trained in as the trainee's field of view is often occluded by the surgeon. The assessment of confidence level (which correlates with performance)

of the trainees were assessed through a 'Likert-scaled' questionnaire and the situation awareness, skill level and efficiency were evaluated manually by experienced surgeons. VR training has helped to reduce the overall learning time of orthopaedic surgical education (Lohre et al., 2020). VR-based surgical training simulation has shown more positive impact on novice (non-independently operating surgeons) and surgeons having performed fewer than 75 cataract surgeries in comparison to the more experienced cataract surgeons (Thomsen et al., 2017).

In the field of industrial education, for instance, maintenance training, a VR-based training paradigm is popular. To find the effectiveness of VR training in the rail industry, 'Cognitive and Psychomotor Index (CPSI)' proposed which is a numerical rating that allows assessment of workers over various tasks and it can also be used as an indicator of the competencies of the trainees (Arnold et al., 2023). The key assessment matrices for CPSI scores are task completion time, accuracy, the diagnostical approach of the problem and the general quality of the solution strategy selection. A research identified the key factors that can affect VR-based automotive maintenance training (Manca et al., 2013). Factors such as people skills, previous experience, cyber-sickness, presence and engagement, usability and satisfaction were raised as critical for conducting an effective VR training session. The effectiveness of VR-based training was compared with desktop-based training in industrial maintenance in Bailey et al. (2017) where their results show that though desktop-based training is faster, it leads to more decremental errors if proper/rigid instructions are not given during the real-world case. Another research describes the importance of self-embodiment to improve presence and immersion levels in the VR world and subsequently to improve industrial VR training (Hassan et al., 2019). Flight navigation and disaster management training through virtual reality has been available for a considerable period. VR is an effective support measure to reduce training cost and risk and a variety of severe environments can be simulated. Another research proposed an effective analytical network process (ANP) and fuzzy comprehensive evaluation model based on 'helicopter emergency relief training' in VR (Xue et al., 2018). VR is also extensively used in safety training (Nakai et al., 2014) and hazard anticipation (Agrawal et al., 2018). The effectiveness of VR-based safety training is measured against the effectiveness of PowerPoint-based safety training (Leder et al., 2019). The results demonstrated that VR outperforms the PowerPoint-based methods in risk perception, risk learning and decision-making. Additionally, It proved that VR can improve young drivers' latent hazard anticipation and also can improve their mitigation skills (Agrawal et al., 2018).

2.2. Virtual reality training in the process industry

Due to the high level of physical and psychological strain experienced by field operators working in real-world process plants, training them can be a considerable challenge. VR-based training is currently proving effective as a training medium in this domain due to its ability of engagement, interactiveness and immersiveness. Furthermore, VR can be used to recreate real-world complex and anomalous situations in which the operators can be trained not only for procedural tasks but also for highly demanding decision-making skills. A research investigated currently available VR simulators for chemical plants and proposed a set of novel features to assess the physiological and psychological condition of the trainees (Cibulka et al., 2016). They proposed measuring some of the physiological features that elevate during the VR training process such as body temperature, heart rate, respiration rate, eye movement, EMG, pulse oximeter etc. They also suggested that realistic graphics and wearing protective gear while VR training increased the training effectiveness greatly. The goal of the research is to improve operator readiness (Manca et al., 2013), i.e., operators' potential to perform satisfactorily under ordinary plant conditions as well as more challenging phases (i.e., start-ups, shutdowns, turnarounds) and more stressful conditions in case of an accident. An investigation about the use of automatically collected metrics in a 3D Virtual Learning Environment (VLE) for the process industry along with metrics related to the learning process derived from established assessment criteria for higher-order skills such as critical thinking, communication, and collaboration (Nowlan et al., 2018). The VR training effectiveness for mitigating severe accidents in chemical plant results show that VR training increases the capabilities of young engineers to take instant decisions at a critical time (Nakai et al., 2014). A research focused on identifying adequate design principles for a virtual reality training environment for the chemical industry, including the features that enhance the effectiveness of VR training such as game-based learning elements, learning analytics, and assessment methods (Fracaro et al., 2021). An online VR-based system was developed (Schofield, 2012) which is designed for use by undergraduate chemical engineers and simulates the configuration and operation of a polymerisation plant. Simulated desktop-based operator training modules (OTS) are commonly used to train bioreactor operators with a focus on the fermentation production data simulation and prediction but the proposed VR-based interactable bioreactor is novel (Zhang et al., 2019). In this paper, the authors have proposed a VR (3D interactable) based 30 Litre SIP bioreactor orientation and sterilisation modules. Training operators for SIP sterilisation of bioreactors is challenging due to its complex structure (Fisher et al., 2019), limited equipment availability, long cycle time etc. and the VR-based bioreactor proposed in Fisher et al. (2019) and Zhang et al. (2019), was partially successful in overcoming the challenges. Another virtual fermenter (2D desktop-based) was developed (Xiao et al., 2004), which not only allows students to explore the inner workings of the fermentation tank but also to be able to simulate the fermentation process so they can test-run the virtual fermenter by varying the operating parameters and observe the results instantly.

Fig. 2. Example of a 20L SIP bioreactor from Applikon Biotechnology.

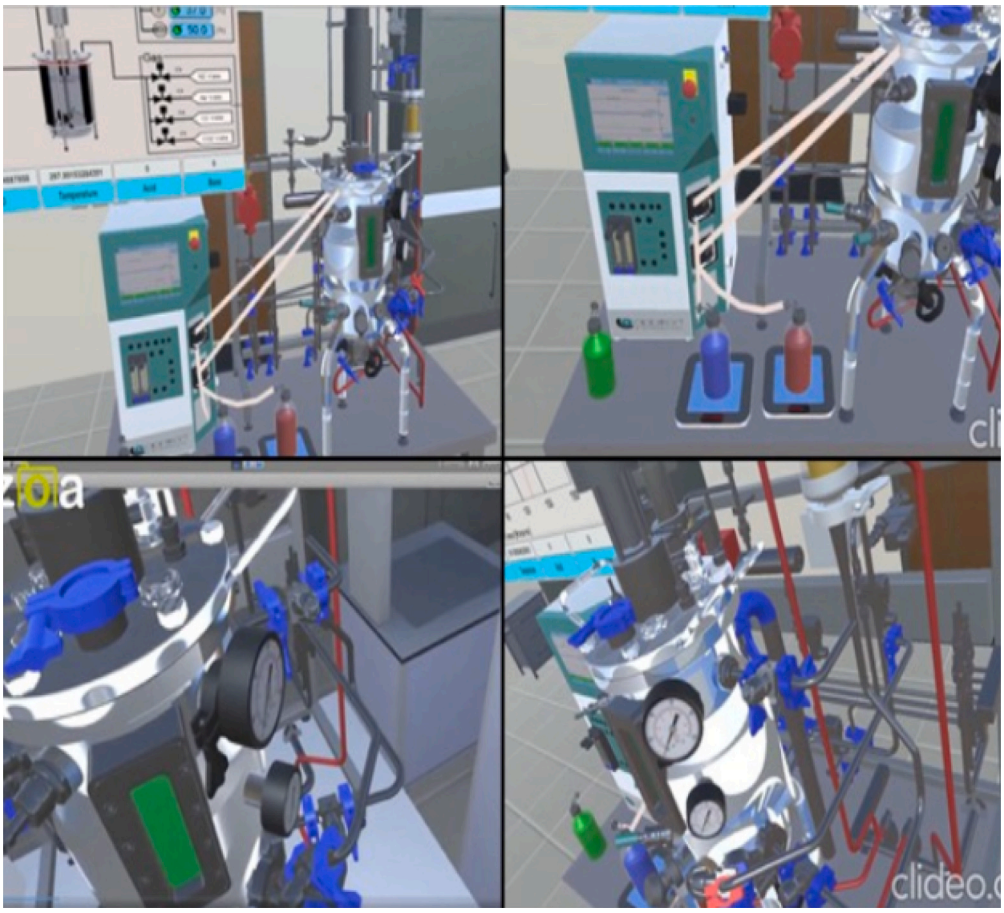

Fig. 3. Our developed VR Bioreactor (from different perspectives).

3. Methodology

In this section, we have discussed the VR bioreactor and its functionalities in greater detail. The following subsections will cover (1) the design and development of the core SIP VR bioreactor (2) procedural tasks that can be trained on with the VR bioreactor, (3) a description of our integrated penicillin production mathematical simulation, (4) the AI-based Learning management system proposed for effective trainees' performance assessment and (5) a proposed gamified VR simulation in which randomly generate errors can be simulated on a lab-scale glass bioreactor setup, with the user required to identify if any errors are present. A quiz-like structure guides the user through the training experience.

3.1. VR bioreactor

The VR Bioreactor which was developed replicates the 20L SIP stainless steel bioreactor from 3D drawings provided by Applikon Biotechnology. The VR bioreactor is fully interactable (i.e., all the valves, pipes, and probes are interactable). The VR bioreactor is a replica and identically scaled to the actual bioreactor to facilitate effective training. In Fig. 2 the actual 20L SIP bioreactor is shown. In addition to the bioreactor, a fully interactable controller panel was developed. The control system display can be used to input different process parameters, as well as display various graphs and values related to the process.

The virtual scenarios are developed for Head Mounted Display (HMD) based VR and in Fig. 3 the VR bioreactor is shown from different perspectives. Currently, the VR bioreactor can be experienced with Oculus 'Quest 2' and 'Rift S' HMDs. Unity3D was the game engine in which the game was developed and for interaction, the Virtual Reality Tool Kit (VRTK) asset was used. The VR scenes can be experienced with the Oculus Touch controllers (one for each hand), which are studded with a constellation of LEDs that are invisible to the naked eye. These LEDs allow Oculus VR constellation sensors to track the position of each controller, which lets the player move their hands around and rotate them through a full range of motion. The game also can be played with Oculus's new improved hand tracking system (in the Quest2 setup only), where the player's bare hands are being tracked by the inside-out cameras of the Oculus HMD (Quest2) (Iqbal and Campbell, 2023).

3.2. Procedural functionalities of the VR bioreactor

3.2.1. The VR bioreactor orientation module

Bioreactors are complex equipment with many parts and components. Identification and learning about each component is a challenging task. To address this issue, we have developed a VR bioreactor orientation module, where 'Text Labels' pop up from various components of the VR bioreactor. The trainees can walk around the VR space and learn about each component. They can also touch different parts of the VR reactor with their virtual hands (and instantly text labels with the component name pop-ups) and learn about the components by their labels. Furthermore, when they virtually touch any component, details about that component are displayed on a canvas inside the VR scene (this setting can be toggled on or off). There are in total 34 bioreactor components that can be touched and be learned from the VR bioreactor orientation module, some examples of which are water inlet, air filter, sparger, condenser, Rushton turbine, pH probe, DO probe, acid pump, rotameter etc. In Fig. 4, example images from the VR Bioreactor orientation module are shown.

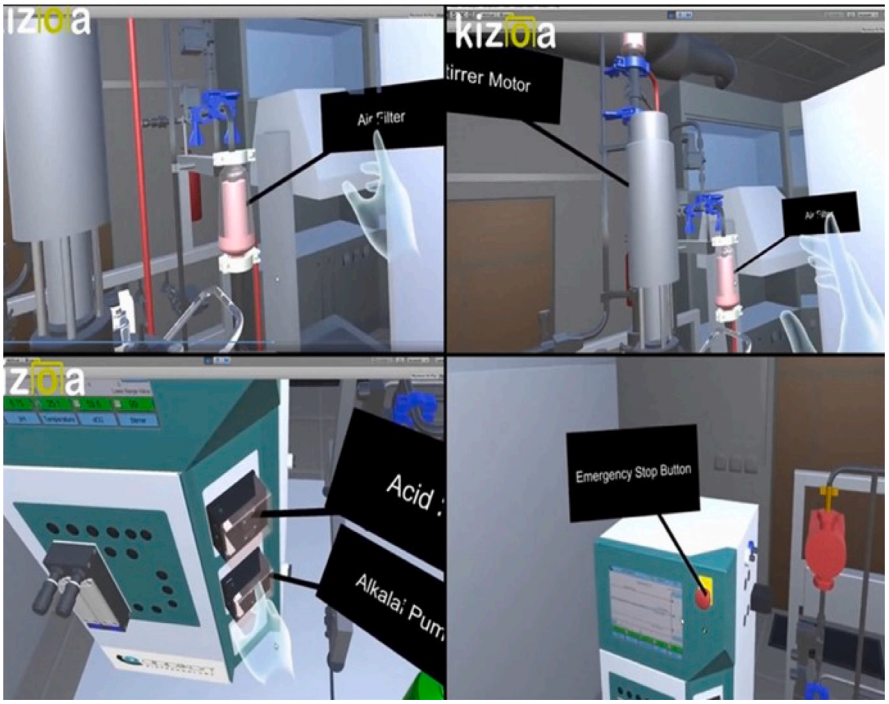

Fig. 4. Example images from the VR Bioreactor orientation module.

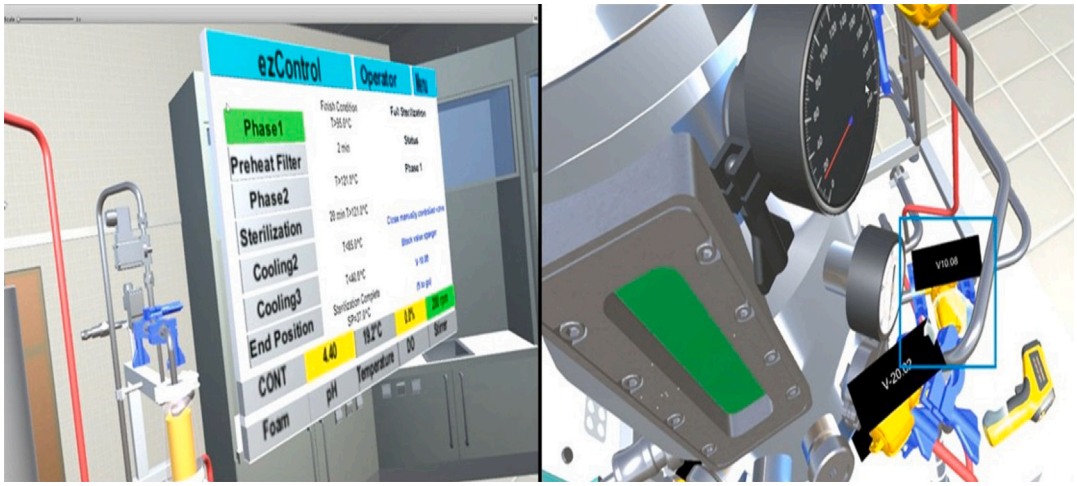

Fig. 5. Images of the virtual SOP and sterilisation function.

3.2.2. The VR bioreactor sterilisation module

The SIP bioreactor unlike an autoclavable bioreactor uses pressurised steam to sterilise the vessel prior to operation. The process is moderately complex from a procedural perspective and very important as incomplete/faulty sterilisation may lead to contamination issues. We have developed a VR module where the trainees are given instructions from a virtual Standard Operating Procedure (SOP) inside the VR environment and they need to perform a series of steps and maintain conditions for specified periods (i.e., close/open certain valves of the bioreactor) to complete the sterilisation process. The task is eased by all the components of the VR bioreactors being labelled. The virtual SOP and a labelled valve associated with the sterilisation process are displayed in Fig. 5.

3.2.3. The pH probe offline calibration module

Prior to bioreactor operation, it is necessary to calibrate measurement equipment such as pH and dissolved oxygen probes. We have developed a VR experience where the trainees can perform the whole pH probe calibration process, starting from mixing the buffer pH liquid (pH4 and pH7) to setting the pH points in the calibration. Different stages during the pH calibration process in the VR simulation are shown in Fig. 6.

3.2.4. The anomalous event training module

To provide in-depth bioreactor operator training, multiple virtual scenarios have been developed that encompass different abnormal events, i.e., emergency events that occur rarely in the real world and it would be undesirable to force them to occur (i.e., very high vessel head pressure). As an example, during the sterilisation process of the bioreactor, the vessel/tank pressure may increase and in rare cases, it can go beyond a threshold value. In these circumstances, the bottom valve of the reactor has an associated bursting disc which without action will burst to release the pressure. Clearly, such an event is highly undesirable. The trainees are encouraged to take action before such events occur to avoid the consequences seen in Fig. 7.

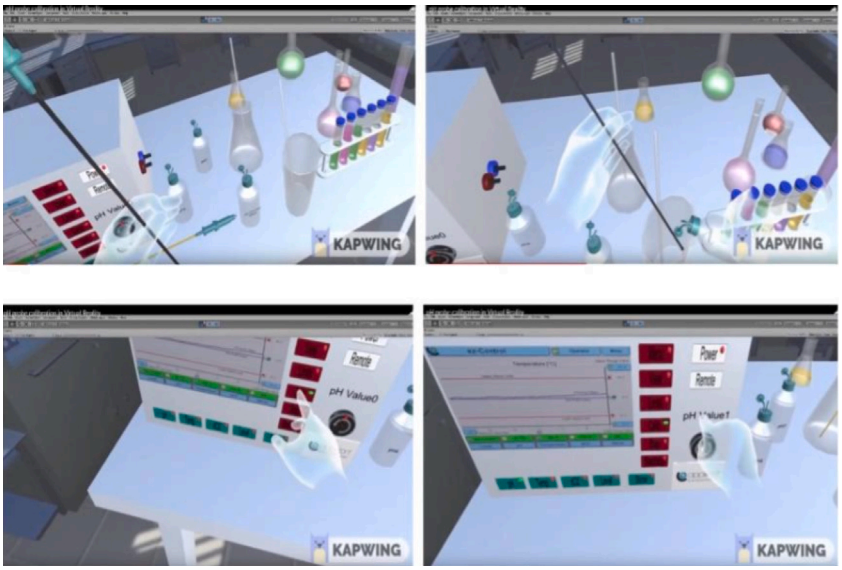

Fig. 6. Example screen grabs showing different phases of the pH probe calibration.

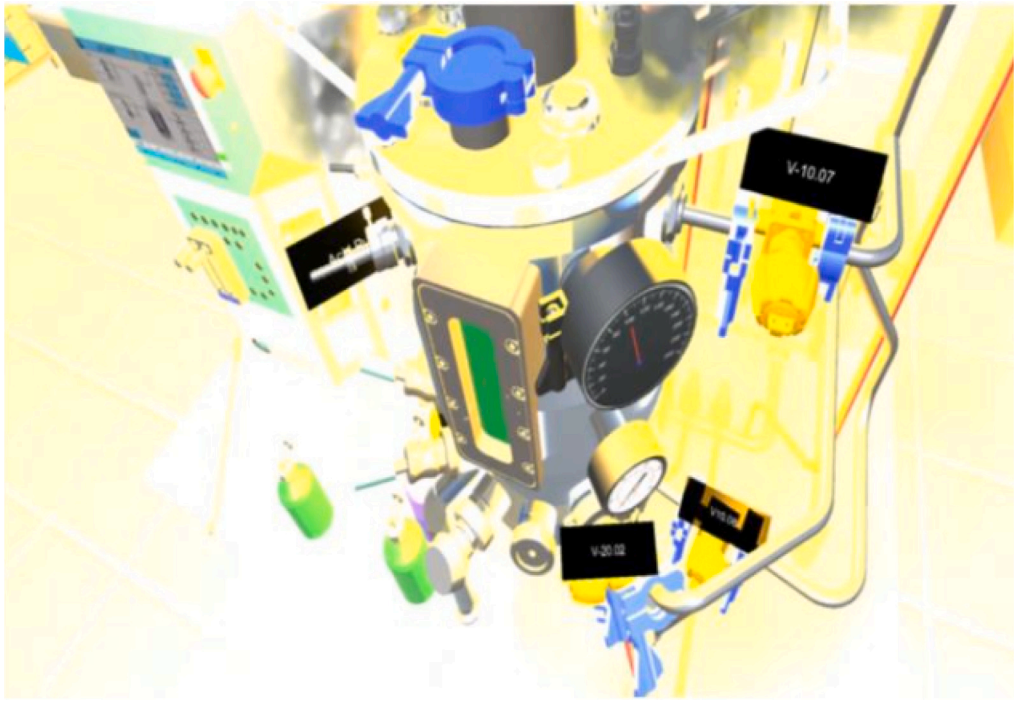

Fig. 7. A bursting disc activation occurring within the VR bioreactor in the 'emergency event training scene'.

3.3. Integration of an industrial-scale fed-batch fermentation (mathematical) simulation with the VR bioreactor

The proposed VR bioreactor training application introduces a distinctive feature by seamlessly integrating an existing penicillin production simulation (Birol et al., 2002), which relies on mathematical models and real batch data, with the 3D VR bioreactor model. This integration extends the foundational simulation to incorporate the impact of fault scenarios, allowing operators to train not only on offline tasks like setting up the bioreactor but also on operational tasks such as monitoring process parameters during bioreactor operation.

The graphical user interface (GUI) of the virtual controller unit in the VR bioreactor displays process parameter and input parameter values. This GUI, depicted in Fig. 8, features interactive buttons to control input values, constraint values, and other process parameters. The mathematical simulation employs a set of ordinary differential equations (ODEs) to simulate system states, as detailed in Birol et al. (2002), and additional equations to model the behaviour of PID-based local controllers. Displayed on the controller's GUI as graphs, the system's process parameters include substrate concentration, dissolved oxygen, biomass concentration, penicillin concentration, fermenter volume, carbon dioxide evolution rate, oxygen uptake rate, pH, fermenter temperature, and heat generated. However, substrate and penicillin concentrations, available only through offline sample analysis, are updated every four simulation hours. Initial parameter values are sourced from recommendations by Birol et al. (2002). The GUI allows operators to adjust input parameters such as aeration rate, agitator motor power, feed substrate concentration, feed flow rate, temperature set point,

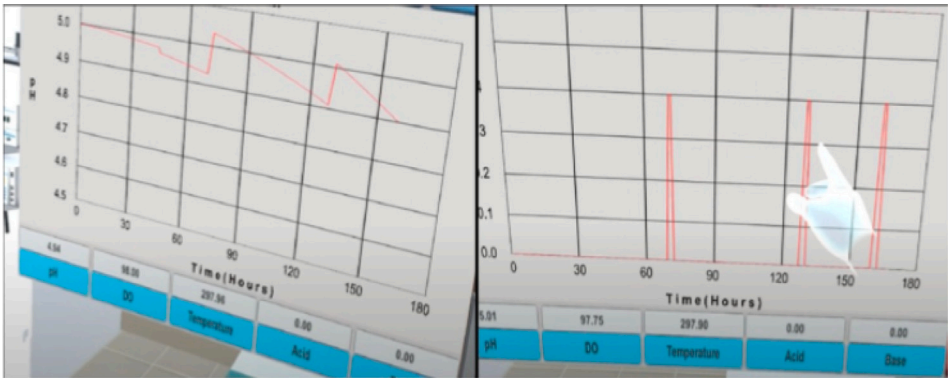

Fig. 8. The mathematical simulation running in VR Since the simulation is for a PID controller, the corresponding Alkaline pump spike can be observed for decreased pH level.

and pH set point. Additionally, the system simulates PID controllers to regulate pH and temperature levels. Variables for pH control include Acid controller gain, Acid integral time, Acid derivative time, Base controller gain, Base integral time, Base derivative time, and set point gap. For temperature control, variables include Cooling controller gain, cooling integral time, Cooling derivative time, Heating controller gain, Heating integral time, and Heating derivative time. To simulate the ordinary differential equations within the .NET framework (for integration with Unity 3D game engine), the 'Math.NET Numerics' plugin is utilised. This plugin provides methods and algorithms for numerical computations across various domains, including special functions, linear algebra, probability models, random numbers, interpolation, integration, regression, optimisation problems, and more.

The game further simulates various faults at different stages of the penicillin manufacturing process batch (i.e. the pH of the system decreasing at an unusually high rate and the controller failing to act). The trainees need to consider possible fault scenarios and investigate whether they are likely from the information available to them. They then have the opportunity to consider corrective action if it is possible. For example, the alkaline bottle for pH control is empty and alkaline could not be pumped into the bioreactor-refilling the bottle is a possible solution. The results of the actions taken by the trainees can also be observed in the game instantly. The game also can be used as a learning tool to train operators about the optimum settings of the bioreactor. Given that the operator can modify the feed rates and environmental conditions, it is possible for them to consider making changes that would lead to more efficient production. While this is a possible use, it is not the prime motivation for developing the VR simulation. Firstly, such optimisation could effectively be carried out without resorting to VR simulation and furthermore, for validated processes such flexibility in operation is uncommon.

3.4. AI-based training performance assessment

Another important feature that the proposed VR bioreactor possesses is an 'AI' module that records, logs and analyses all the interactions of the trainees while they are in the virtual world and completing any SOP-based procedural tasks. In the back-end of the game, there is a process (AI) that runs and collects performance data such as how much time a trainee is taking to complete a particular task, and is tracking if the trainee is making errors in the process. To use this information, a learning management system (LMS) dashboard was developed (shown in Fig. 9) that displays all these performance data and metadata associated with the training session. This performance dashboard helps to rate the trainee's current attempt in comparison to their previous attempts and also with the attempts of other trainees.

3.5. Autoclavable glass bioreactor error finding game

Smaller bioreactors of around 5L in the working volume are far more common than SIP reactors and are used by bioscientists who are less familiar with larger-scale bioreactor operational practices. In addition to the SIP 20L VR bioreactor, another gamified VR simulation game was developed to help teach users about a laboratory-scale autoclavable bioreactor and its components. The simulation was developed to teach users on the functionality of the equipment and to aid them in fault finding in equipment setup. Users can answer a quiz which will first give them some information about a component on the bioreactor and then ask if they can see any errors with the setup. At the end of the quiz the user can then review their answers, if incorrect they can then see what the correct answer was and then look back at the reactor to see the error. Some frames from the autoclavable bioreactor VR game are shown in Fig. 10.

4. Evaluation

The VR trainer is appropriate for both engineering students wishing to learn the principles of bioreactor design and operation and for bioscientists who are more focused on equipment setup and operation. Recent training sessions for undergraduate 2nd-year chemical engineers were in support of a bioprocessing module and for MSc-level bioscientists in a module on bioprocessing. Around 40 students were introduced to the VR trainer in sessions lasting approximately 90 min. The majority of students were not familiar with VR prior to the training and therefore, a learning phase occupied the first 15 min or so of each session. The students were split into groups of two to undertake the training to provide individual activities of around 15 min, swapping between the two as activities were completed. This was found to be more comfortable than one long session per student. During the initial training introduction, interaction with the trainer is frequently required to learn the functionality. Therefore, the number of student groups per trainer was limited to two or three. This has been a constraint on the size of class groups using the VR facility. It is also worthy of note that of the 40 students, only one found the VR experience too unnerving visually and could not undertake the training.

5. Future work

The VR-based bioreactor trainer has proven to be a useful tool for supporting the training of operators and laboratory-based scientists. Its current use is to provide 'practical' training following lecture-based delivery of the fundamental science and engineering aspects of bioreactor design and operation. This is likely to continue as a means of

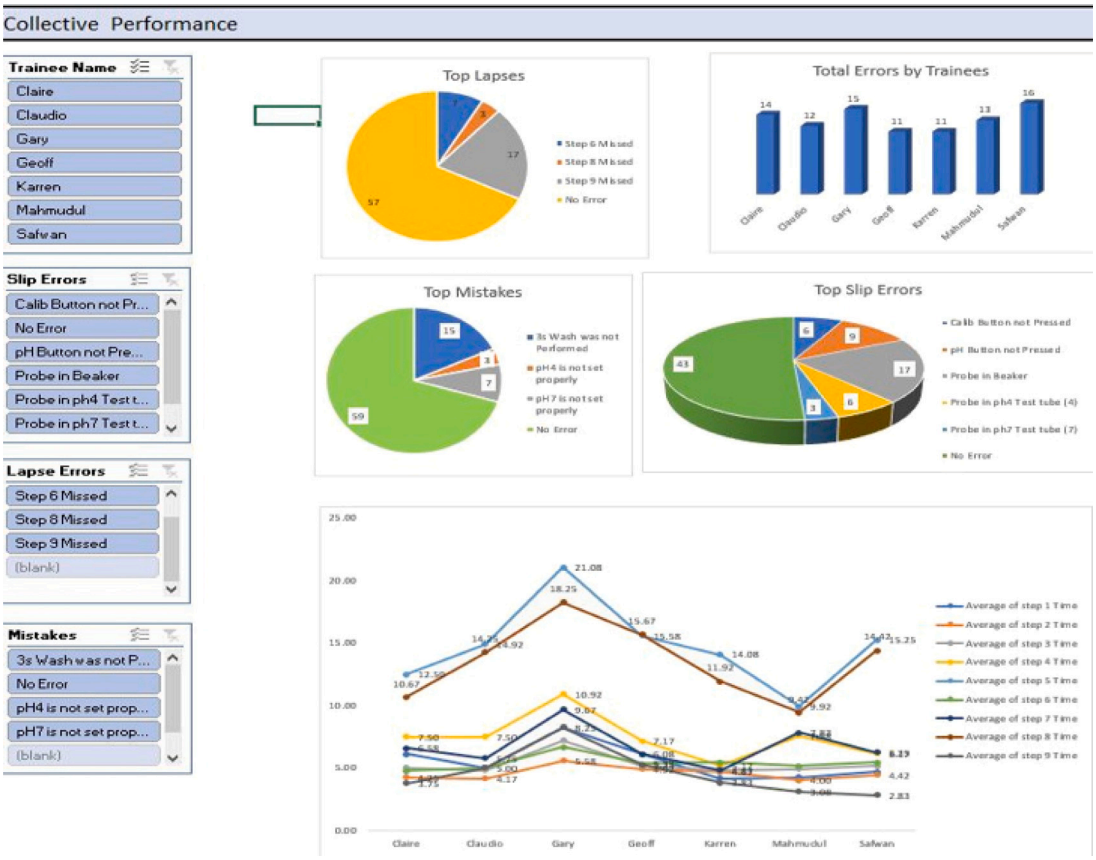

Fig. 9. The performance assessment dashboard.

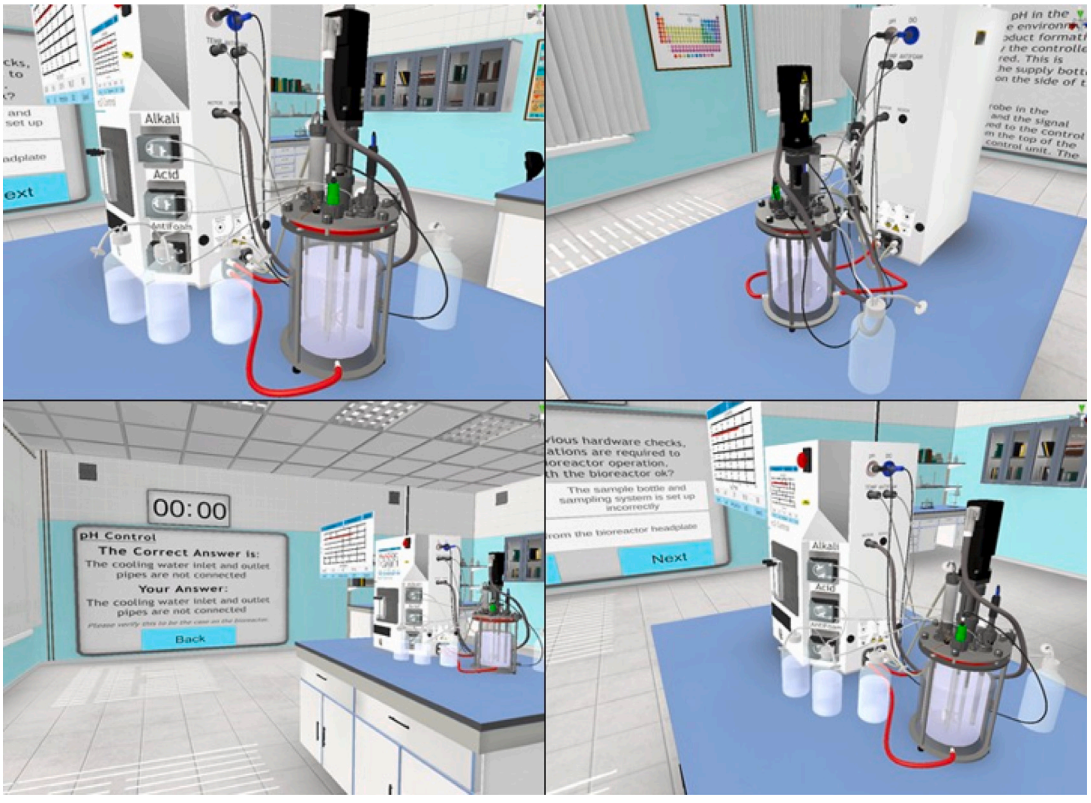

Fig. 10. Some frames from the autoclavable glass bioreactor error-finding game.

VR exploitation. However, there are a number of aspects that need to be addressed if the VR bioreactor is to play its full role in training support. Firstly, there are different types bioreactor designs and single-use plastic bioreactors are increasingly the norm. Broadening the VR experience to encompass the other designs is underway and is not excessively challenging given the core routines developed for the initial bioreactor simulation. A significant finding from the developments discussed is that the developers perception of what is required and the trainees requirements are difficult to align. The misplaced tendency to consider aspects as obvious from a developer's perspective was clearly apparent in the VR bioreactor creation. Considerable modifications followed trials of the VR system with perspective industrial users attending upstream continuing professional development short courses. Importantly, with the modifications suggested by the end-users, subsequent use of the VR simulation within short course modules has been uniformly praised in post-course questionnaires. Replicating this frequent development feedback strategy to guide alignment with need will be crucial as further equipment virtualisation is undertaken. Looking to the future, a challenge is the modification of the numerical simulation that sits behind the VR bioreactor. A broad range of new drug modalities leads to increasingly diverse bioreactor operation policies and experiences. The core operational requirements are broadly similar and training on a limited number of standard bioreactor configurations would suffice. It is the more specific operational characteristics where operator intervention impacts on bioreaction progression where product-specific characteristics are needed. Modelling complex bioreactions is notoriously difficult to achieve with high accuracy. However, whereas such accuracy would be required for the optimisation of performance, it is likely that lower model accuracy thresholds can be accepted for training purposes. Thus, the prospect for broad use is feasible. The research question remaining is that the models need to be more than qualitatively correct, but from a quantitative perspective, what is required for effective training is uncertain.

Acronyms

VR Virtual Reality
OTS Operator Training modules
GUI Graphical User Interface
SOP Standard Operating Procedure
HMDs Head Mounted Displays

Statements on open data and ethics

All included studies have been appropriately cited, and the data sources are listed in the References section. All included studies were assessed for compliance with relevant ethical guidelines, and only studies that reported ethical approval and informed consent were considered for inclusion.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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