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Review

A brief review on recent development of multidisciplinary engineering in fermentation of *Saccharomyces cerevisiae*

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ABSTRACT

Fermentation technology has unprecedented potential to upgrade state-of-art biotechnology and refine the processes used in existing ones, taking into account of complex technical, economic and environmental factors. Given the economic importance and ongoing challenges of biotech sector, multidisciplinary engineering technologies is poised to become an increasingly important tool along with the emergence of modern technology and innovation. This article reviews recent technology advancement in the field of fermentation using *Saccharomyces cerevisiae*. Interesting research progress has been made by leveraging multiple engineering fields such as electrical engineering, information engineering, electrochemical engineering and new material development, leading to recent development of novel real-time probes (electronic nose technology, analysis of yeast morphology and metabolites, timely control of glucose feed), improved understanding of electro-fermentation (enhanced electronic transfer provision), as well as application of cost-effective and sustainable materials (bioreactor vessel manufactured from textile, and yeast immobilisation support matrix made from abundant natural biomass). To the best of our knowledge, the subject is reviewed for the first time in recent years. Furthermore, this review also constitutes a futuristic *S. cerevisiae* fermentation process based on the recent advancement discussed.

1. Introduction

Fermentation technology plays a key role in upstream process development and associated scale-up, leading to microbial cell factories (Rangel et al., 2020), bioenergy (Amoah et al., 2019), by-product or waste utilisation (Dhanya et al., 2020), sustainable food production (Marti-Quijal et al., 2020; Shiferaw Terefe and Augustin, 2019) and pharmaceuticals (Mapelli-Brahm et al., 2020). Together, fermentation is a key enabler of circular bioeconomy (Archer and Bustard, 2020; Ubando et al., 2020) in the global industrial biotechnology market, which was valued at USD 417 billion in 2018 and anticipated to be worth > USD 729 billion by 2025 (Ugalmugle and Swain, 2019) (note the value can be affected by global coronavirus pandemic). In particular, the European biotechnology market demand is expected to grow at a rate of 8.5 % per annum, owing to increasing demand of bio-based products and services (Ugalmugle and Swain, 2019). For example, as of 2019 the Scottish industrial biotechnology sector has grown significantly to over £747 million representing an increase of over 270 % compared to 2012 (data source: Industrial Biotechnology Innovation Centre, Scotland). Furthermore, the biotech sector is still confronted with three major challenges in 2021, including maximizing cost-effectiveness, hiring and holding onto the biotech talent, as well as keeping up with regulatory standards (web reference: Velocityglobal.com). In particular, low R&D efficiency, and intense market competition remain an obstacle especially when trying to develop and roll out products onto the market. To this end, industrial fermentation technologies must be capable of resolving essential engineering problems, but also providing creative solutions such as novel multidisciplinary technologies and bringing in added-values to customers.

Saccharomyces cerevisiae is the most useful species in yeast that has been widely used for industrial fermentation and research demonstration. This is primarily due to its well-known genetic and physiological background, as well as the compatibility of high-density and large-scale fermentation (Nandy and Srivastava, 2018; Parapouli et al., 2020). The yeast has been used for commercial production of a wide variety of products, and also for studying new fermentation technologies. Hence research development in the field of *S. cerevisiae* fermentation has usually served as an exemplar of wider application in multiple species.

It is well acknowledged that industrial biotechnology is a multidisciplinary field and fermentation technology as an important branch is of

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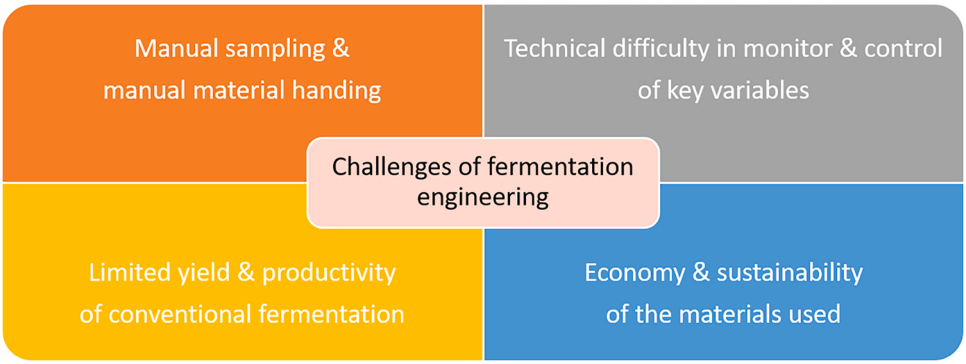

Fig. 1. Ongoing challenges of fermentation engineering.

great relevance. The multidisciplinary fields include microbiology, chemical engineering, cell engineering, mechanical engineering, computer engineering, and synthetic biology etc. Today industrial fermentation of *S. cerevisiae* has been dominated by Stirred Tank Bioreactors (STBR), where well-mixed phases are obtained mainly by designated internal configuration and agitation (Garcia-Ochoa et al., 2011). The bioreactor is usually equipped with online thermometer, pH and dissolved oxygen probes for real-time monitoring and control of the biotechnological progress. Quantification of the exhaust gas has also been developed by integrated gas analysers or external gas chromatography. Although these exiting technologies could be the best solution for current fermentation process, leading to useful biological products for humans such as alcoholic beverages (e.g. beers, wines) and drugs (e.g. insulin, penicillin), there are still ongoing challenges to fermentation engineering (Fig. 1): (i) there is a core requirement for more advanced real-time analytics involving process analytical technology (PAT), to ensure timely measurement of performance and consistent product quality (Maruthamuthu et al., 2020; Wasalathanthri et al., 2020). During a typical manufacturing process, in-process samples are taken by operators and transported to the laboratory for offline analysis, such as biomass density, cell morphology, consumption of key ingredients (e.g. glucose). The procedure involves manual handling and material handling, potentially resulting in cross-contamination risk (e.g. during transportation), process inefficiency (e.g. delayed analytical result), data repeatability and reproductivity issues (e.g. different operators). In contract, establishing of PAT-based analytics would benefit from a faster, safer, and more accurate process for the manufacturing; (ii) much attention has been attracted into better understanding and better utilisation of electro-fermentation, that merges traditional fermentation with electrochemistry. The emerging technology has shown significant enhancements to fermentation performance, leading to a very promising technology as an alternative operational mode (Moscoviz et al., 2016). Previous research has suggested that such electro-chemical control not only has significant effects on microbial fermentative metabolism and cellular regulation, but also introduced interspecies interactions and selection of bacterial populations in mixed microbial cultures. Nevertheless, some shortages such as reactor design and manufacturing scale-up, as well as selection of electrode materials have limited its industrial application (Bhagchandanii et al., 2020); (iii) there is still a demand to development new materials associated with fermentation progress, to address economy and sustainability requirements. Over years a variety of bioreactors are manufactured from borosilicate glass, stainless steel, and plastic etc; however, challenges have still existed such as high construction costs, time-consuming to install, ease of operation. Because of these aforementioned reasons, textile fermenter has been emerging as one of alternative bioreactor vessels for biofuel production via fermentation of *S. cerevisiae*, and research progress has made to improve its economic efficiency and practicality.

To tackle these challenges, it becomes an increasing trend for fermentation engineering to be further merged with multiple engineering fields, in particular, electrical and information engineering, electrochemistry engineering, as well as material engineering (Fig. 2). Taken together, the purpose of this article is to give a brief review of recent multidisciplinary development in the field of fermentation of *S. cerevisiae*, and to provide a hint to future perspectives on these advancements. It should be noted that the system and control engineering such as soft-sensing modelling method (Zhu et al., 2020) is not covered in this review.

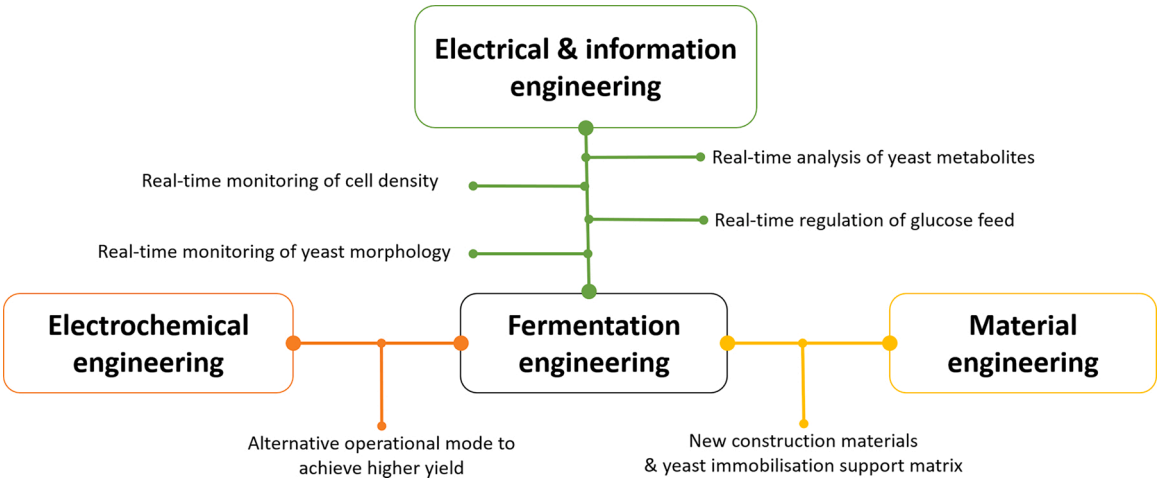

Fig. 2. Recent development of multidisciplinary fermentation engineering.

Table 1
Summary of commercial probes used for online monitoring of biomass concentration during microbial fermentation.

Company	Product description	Technology	Applications	Reference
Total cell density				
Infors HT	Cell Growth Quatifier (CGQ)	Backscattered lighting technology	Shake flasks	https://www.infors-ht.com/en/shakers/shaker-accessories/cgq/
PreSens	SFR vario BM	Backscattered lighting technology	Shake flasks	https://www.presens.de/products/detail/sfr-vario-bm
Applikon Biotech	BugLab optimal biomass measurement	Backscattered lighting technology	Shake flasks & bioreactors	https://www.applikon-biotechnology.com/en/products/process-analytics/optical-biomass-measurement/
Mettler Toledo	In-line turbidity sensor	Backscattered lighting technology	Bioreactors	https://www.mt.com/gb/en/home/products/Process-Analytics/turbidity-meter/turbidity-sensor.html
Infors HT	Optek turbidity sensor	Backscattered lighting technology	Bioreactors	https://www.infors-ht.com/en/bioreactors/bioreactor-accessories/optek-turbidity-sensor/
Hamilton	Dencytee total cell density sensor	Backscattered lighting technology	Bioreactors	https://www.hamiltoncompany.com/process-analytics/sensors/cell-density-sensors/total-cell-density-sensors-dencytee#how-does-it-work
H.E.L Group	BioVIS total cell density and biomass monitor probe	Not mentioned	Bioreactors	https://helgroup.com/products/bioreactors/biovis/
Exner Process equipment	EXcell 231 NIR Biomass Sensor	Backscattered lighting technology	Bioreactors	https://www.bioprocess-eng.co.uk/product/exner-excell-231-nir-biomass-sensor/
Solida Biotech	On-line biomass sensor	Backscattered lighting technology	Bioreactors	https://solidabiotech.com/product/biomass-sensors/
Viable cell density				
Hamilton	Incyte viable cell density sensor	Capacitance measurement	Bioreactors	https://www.hamiltoncompany.com/process-analytics/sensors/cell-density-sensors/viable-cell-density-sensors
Sartorius Stedim Biotech	BioPAT® ViaMass automatic biomass measurement	Capacitance measurement	Bioreactors	https://www.sartorius.com/shop/ww/en/gbp/products-bioprocess-process-analysers/biopatviamass/p/BIOPATVIAMASS
Aber Instruments	Futura online viable cell density measurement	Capacitance measurement	Bioreactors	https://aberinstruments.com/biotech/biotech-product-range/#gref

2. Merging electrical and information engineering with fermentation of *S. cerevisiae*

One pronounced advancement merges electrical engineering and information technology with fermentation, leading to the development of novel probes for automated online motoring and control. Recent development focus on cell density, yeast morphology, metabolic profiling and regulation of glucose feed.

2.1. Real-time monitoring of cell density

Online measurement of biomass concentration has received continuous interest, which has led to commercialisation of a series of online probes over years (Table 1). There are a few sensors commercially available for total cell density measurement based on backscattered near-infrared (NIR) lighting technology (Bruder et al., 2016), developed for both shake flasks and bioreactors applications. In addition, viable cell density monitoring is also available in the market based on capacitance analysis, where viable cells behave like small capacitors and can be measure by the sensors. It is noticed that these sensors are widely suitable for microbial cell cultures, as stated. In addition, several advanced sensors have been reported for online monitoring of biomass concentration in yeast fermentation process (Table 2), including UKF (unscented Kalman filter) derived algorithm (Yousefi-Darani et al., 2021), Raman spectroscopy (Jiang et al., 2020), colorimetric assay derived algorithm (Jiang et al., 2019; Xu et al., 2019), and magnetic induction spectroscopy (Zhang et al., 2019).

In particular, colorimetric sensor assay technique is an emerging analytical tool in monitoring cell concentrations, on the basis of strong chemical interactions between sensor materials and analytes, such as acid-base, dipolar and hydrogen bonding (Askim et al., 2013). The technique has developed rapidly in recent years due to strong specificity, high sensitivity and broad spectrum of colour sensitive materials (Jiang et al., 2019). The method has been successfully used for recognising changes of volatile components in vinegar during fermentation (Chen et al., 2014), key aroma development in coffees with different roast degree (Kim et al., 2018) and identification of rice wine with various marked age (Ouyang et al., 2013). Recently, a novel colour sensor was developed to quantitatively monitor cell concentration during the fermentation process of *S. cerevisiae* (Jiang et al., 2019). In this study, 11 colour sensitive materials and 1 pH indicator were selected to build a colour sensor assay, which was then used to visualize odour information of yeast culture and extract corresponding colour features. Subsequently the data was optimised and a back propagation neural network (BPNN) model was further constructed to monitor yeast cell concentration in real-time. The authors showed that the overall result can meet the needs of accuracy and stability of the yeast cell concentration monitoring, potentially useful for industrial applications.

The research provides a positive starting point to utilise the so-called 'electronic nose technology' in quantify yeast culture concentration. This is interesting and encouraging, given the change of odour information derived from volatile organic compounds is one of the important characteristics during the growth of *S. cerevisiae*. It is realised that the pattern of odour is affected by the change of the substrate components

Table 2
Advanced sensors for online monitoring of biomass concentration in yeast fermentation process.

Description	Technology	Reference
UKF (Unscented Kalman Filter) algorithm	The measurement was achieved by a gas sensor array and an algorithm derived from unscented Kalman filter (UKF), based on infrequent ethanol measurement	Yousefi-Darani et al., 2021
Raman spectroscopy	The determination was based on Raman spectroscopy integrated with chemometric approaches	Jiang et al., 2020
Colour sensor	It was developed based on a colorimetric assay, and optimised using the ant colony optimisation (ACO) algorithm.	Jiang et al., 2019
Olfactory visualization sensor system	It was developed based on a colorimetric assay, and integrated with three pattern recognition algorithms.	Xu et al., 2019
Magnetic Induction Spectroscopy	It measured the impedance spectrum (commonly known as the conductivity spectrum)	Zhang et al., 2019

and the intermediate or end metabolites produced; however, the study indicated that a quantitative model between odour information, colour features and cell concentration can be established to help 'visualise' odour change during a specific yeast culturing process. From technical point of view, it is expected the technology not only could be used for monitoring cell concentration, but also can be helpful as a quality control tool to identify contamination in the bioprocess.

2.2. Real-time monitoring of yeast morphology

The morphology of yeast is an important indicator for diagnosis and control of the process. It affects fermentation time and efficiency as well as downstream processing, such as centrifugation system (Ceccato-Antonini, 2008). Recently, an automated online monitoring system for yeast morphology was present for the first time (Belini et al., 2020), which was used for *in situ* monitoring of an industrial *S. cerevisiae* during sugarcane fermentation. In this work, an *in situ* microscopic system (Wiedemann et al., 2011) including a transmitted light microscopy and a video camera were integrated into a fermenter and used to capture microscopic images of the cell suspension directly. In particular, the sampling channel allows the suspension to flow freely through an observation zone, compared to a decelerated flow in other *in situ* microscopes. This feature helps to eliminate velocity gradients that can cause changes in cell concentration. After image acquisition, the image data was processed and implemented using MATLAB in the order of image pre-processing, object segmentation, and yeast classification. The authors demonstrated the technique by using it to monitor single cells, budding cells, and psedohyphae-forming cells during sugarcane molasses fermentation. Furthermore, cell morphological change due to thermal stress was also present as an example of the *in-situ* microscopy. Consequently, the data indicates the technique can be a useful online tool in examination of yeast morphology and help in early detection of atypical morphological change, enabling an automated warning and corrective action accordingly.

Indeed, the switch from a round or ovoid cell form to filamentous form of *S. cerevisiae* not only indicates nutritional status and environmental stresses, but also signifies the presence of fusel alcohols which are derived from amino acid catabolism due to nutrient limitation (Ceccato-Antonini, 2008). Whilst current monitoring techniques of yeast morphology are offline in most cases, it is expected that an online microscope would become a standard analytical tool, as a useful addition into the existing bioprocess control system for a systematic diagnosis of yeast morphology in real-time.

2.3. Real-time analysis of yeast metabolites

Metabolites are small molecules that provide direct read-out of the cellular state and phenotype during metabolic process of an organism (Patti et al., 2012). In recent years, real-time metabolomics profiling of the metabolites has become a powerful tool in clinical diagnosis (Blackburn et al., 2020) and in understanding cellular responses of living microorganisms (Ibáneza et al., 2013; Khomenko et al., 2017; Link et al., 2015; Tejero Rioseras et al., 2017). In particular, increasing attention has been drawn on real-time monitoring of yeast volatilome, a subset of the metabolites. A non-invasive real-time method was reported for assessment of volatilome of *S. cerevisiae* strains growing on standard solid media (Khomenko et al., 2017). The yeast cultures have been monitored online by Proton Transfer Reaction-Time-of-Flight-Mass Spectrometry (PTR-ToF-MS), leading to extraction of more than 300 peaks with 3640 measurements. Analysis of data matrix revealed the strain-specific characteristics and volatilome evolution of the yeast strains. The authors concluded that the novel method has great potential for phenotyping of yeast strains, identification of new metabolic pathway and investigation of bioprocessing. Similarly, a real-time analysis of the yeast volatilome was demonstrated on standard liquid media (Tejero Rioseras et al., 2017). It utilised secondary electrospray ionization-high resolution mass spectrometry (SESI-HRMS), resulting in detection of approx. 300 metabolites. Interestingly, data indicated that a large number of the metabolites produced neither are reported in the literatures nor are their biochemical deciphered. Consequently, it was anticipated that such comprehensive metabolic coverage could potentially leading to tune industrial processes where yeast fermentation is involved.

Table 3
Summary of major commercial sensors for rapid quantification of glucose.

Company, Country	Product description	Applications	Reference
Jobst Technologies (an IST AG company), Germany	Glucose biosensor platform	On-line measurement	https://www.jobst-technologies.com/products/biosensors/
Yellow Springs Instruments (YSI), US	Biochemical Analyzer	Off-line measurement	https://www.ysi.com/ysi-2950-biochemistry-analyzer
Roche Diagnostics GmbH, Germany	The Cedex Bio analyzer	Off-line measurement	https://custombiotech.roche.com/home/Product_Details/INS_2895.product-classes%5CCedexAnalyzers%5Ccedex-bio-analyzer.html
Nova biomedical, US	BioProfile Flex Analyser	Off-line measurement	https://www.novabiomedical.com/bioprofile-flex/
Sunostik Medical, P.R. China	Biochemical analyzer	Off-line measurement	http://www.sunostik.com/cpxx.php?id=16
Trace Analytics C2 Glucose Lactate, Germany	Trace C2 Glucose Lactate	On-line measurement	https://pro-analytics.net/lactate-glucose-analyzer-fermentation/
C-CIT Sensors AG, Switzerland	CITSens MeMo	On-line measurement	https://www.b3cnewswire.com/20180820181 6/c-cit-sensors-single-use-cell-culture-in-situ-technologies-for-the-simultaneous-automated-and-continuous-monitoring-of-glucose-and-lactate-in-cell-cultures.html

Table 4
Advanced sensors for glucose determination in yeast fermentation process.

Description	Technology	Reference
Non-enzymatic screen printed sensor	Screen-printed carbon electrodes (SPCE) have been modified by casting the synthesized cuprous oxide nanocubes (Cu_2O-NC). The fabricated Cu_2O-NC-SPCE sensor prepared at 25 °C provided the best sensing performance toward glucose.	Espro et al., 2020
UKF (Unscented Kalman Filter) algorithm	A gas sensor array and an algorithm derived from unscented Kalman filter (UKF), based on infrequent ethanol measurement	Yousefi-Darani et al., 2021
Non-invasive Raman spectroscopy	It was achieved by noninvasive Raman measurements with the aid of spectral pretreatment and multivariate data analysis.	Hirsch et al., 2019
Electrochemical biosensor	The determination is based on the measurement of enzymatically generated NADH that occurs at a potential.	Acevedo-Restrepo et al., 2019
Bienzymatic biosensor	The biosensor was based on glucose oxidase (GOx) and alcohol dehydrogenase (ADH) chemisorbed on core shell Fe_3O_4@Au nanoparticles.	Samphao et al., 2018

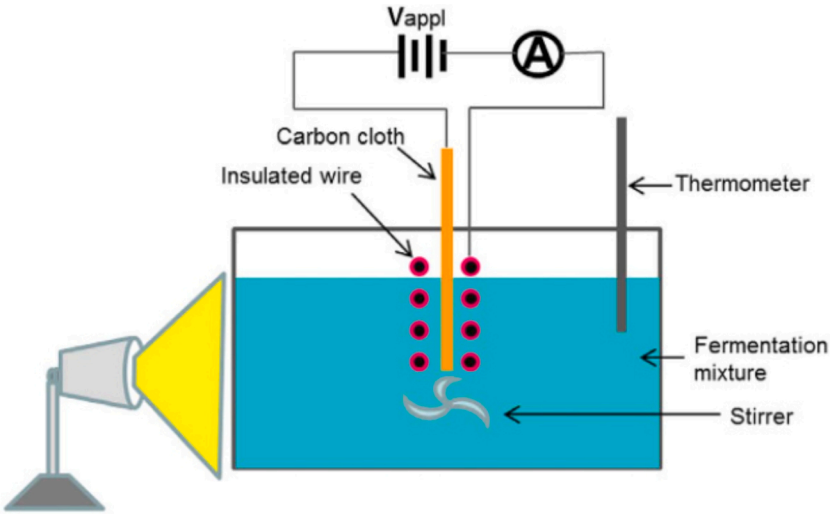

Fig. 3. Schematic diagram of an electrostatic fermentation used for high gravity and very high gravity fermentation (Osadolor et al., 2014).

2.4. Real-time regulation of glucose feed

It is known that glucose concentration plays a vital role in regulating yeast metabolism between oxidative and oxidoreductive growth. When the glucose concentration is above a critical value (i.e. above 150 mg/L) in an aerobic fermentation, it results in oxidoreductive metabolism and ethanol is produced, known as the Crabtree effect (Boulton and Quain, 2001). Therefore, in a fed-batch fermentation of *S. cerevisiae* it is necessary to control glucose concentration and eliminate ethanol production in order to achieve high biomass yield. However, whilst there are a series of glucose measurement tools available in the market (Table 3) and in the research laboratories (Acevedo-Restrepo et al., 2019; Espro et al., 2020; Hirsch et al., 2019; Samphao et al., 2018; Yousefi-Darani et al., 2021; see Table 4), it remains a critical challenge to regulate glucose concentration precisely at this low level in real time. To address this, a closed-loop control of glucose feed rate was reported on the basis of NADH fluorescence intensity (Assawajaruwan et al., 2018), whereby a yield coefficient of approx. 0.49 was achieved, indicating pure oxidative growth of the yeast. In this experiment, various metabolic fluorophores including NADH, tryptophan, flavins and pyridoxine were monitored in different states of oxidative compared to oxidoreductive metabolism, resulting in identification of NADH intensity as a key metabolic switch between the two metabolisms. Subsequently, the NADH derived value was used as a single signal to regulate the feed rate of glucose in a fed-batch process using a 2.5 L stainless steel tank bioreactor, leading to a fine control of glucose concentration in the media, which ensured a high conversion rate from glucose to yeast biomass. Compared to direct glucose measurement offline, the NADH-based measurement provides a feedback control in a timely manner and eliminate certain errors at the low level of glucose. It should be noted that there is still a challenge to transfer the bench scale to larger scale cultivation primarily due to the changing environmental conditions, which could affect metabolic activities in the cells, and hence the NADH derived signal. Nevertheless, the authors concluded that the method shows great potential in detecting yeast metabolic change in real time and providing process monitor and control of yeast fermentation.

More recently, an online refractive index sensor was used to measure relative fermentation rate in yeast fermentation for the first time (Knudsen and Rønnow, 2020). The authors developed a standard curve to directly correlate a refractive index (RI) to total sugar concentration in an aqueous sugar solution, and in complex media the RI value gives a proportional measure of the sugar concentration, as the reading can be affected salts, acids and fermentation products such as glycerol and ethanol. Using an online sampling system, the RI reading can thus be used to monitor relative sugar conversation rate of a fermentation. The authors demonstrated the online monitoring system in a 1 L batch fermentation and applied it to run a regular fed-batch fermentation. The technique was further used to guide a new feeding strategy whereby overflowing culture broth of the primary fermenter was collected into hold tanks to allow extended fermentation, leading to increased ethanol yield and process economy. Consequently, the online RI sensor provides a new and promising tool for fermentation monitor and control, which has potential to improve ethanol industrial and wider spread biotechnology application areas.

Whilst most of the existing technologies focus on offline direct measurement of glucose, the above two research demonstrated that, establishment of real-time indirect measurement was effective in the regulation of fed-batch glucose fermentation using *S. cerevisiae*. It provides an alternative way to monitor and control glucose concentration that is very hard to measure in a typical yeast biomass manufacturing. For the future advancement in the field of fermentation, it can be estimated that more research and development effort would be put to develop such indirect measurements in combination with data driven soft-sensing technology (Krämer and King, 2019; Zhu et al., 2020), with outstanding performance and robustness on the basis of industrial compatibility.

3. Merging electrochemistry engineering with fermentation of *S. cerevisiae*

In recent years, electro-fermentation technology has emerged to tackle some limitations of conventional fermentation (Bhagchandanii et al., 2020; Moscoviz et al., 2016). It is expected to control microbial fermentative metabolism with electrodes, which not only act as electron sinks or sources in an unbalanced fermentation, but also change the redox balance in the media to increase specificity of the metabolic routes (Mathew et al., 2015). The technology has been reviewed extensively (Bhagchandanii et al., 2020). The benefits are that the process: (i) produces target biochemical with improved selectivity; (ii) increases sugar/carbon utilisation efficiency and hence higher production of a specific product, e.g. ethanol (iii) mitigates the use of additives for redox balance or pH control; (iv) enhance cell growth and (v) in some cases enhance product recovery.

In terms of application for *S. cerevisiae* fermentation, an enhanced ethanol production via an electrostatic fermentation system (Fig. 3) was initially reported (Mathew et al., 2015), where a voltage source (a series assembly of 1.5 V batteries connected to a variable resistor) was applied

Table 5
Comparison of major commercial bioreactors built with different types of materials.

Materials	Advantages	Limitations
Borosilicate Glass Stainless steel 304	• Transparent (good see-through property) • Inert to chemicals • Resistant to high temperature, pressure and corrosive agents (acid/base) • Long lifespan • Available in many sizes • Fast to install	• Fragile • Limited scale (usually used at bench and lab scales) • High construction costs • Process flexibility (e.g. convention stirred tank are not suitable for shear-sensitive organisms)
Concrete	• More cost-effective than steel-based bioreactor	• Time-consuming to install • Contamination risk
Plastic	• Reduced process down time (e.g. vessel cleaning and sterilisation are not required) • Reduced validation load (i.e wave bag comes pre-validated by the manufacturer) • Potential for Shear-sensitive cells e.g. mammalian and plant cell cultures	• Limited scales of up to 2000 L • Not easily adaptable for continuous production • Easy to damage • Increased risk of leachables and extractables due to chemical additives of the construction materials
Textile	• Inexpensive materials • Light-weight and foldable • Low storage and transportation costs • long-lasting and resistant to high temperatures, UV radiation and process residue.	• Limited scales • Not easily adaptable for continuous production

to a fermentation broth in a sealed glass container. The novelty of the system lies in the fact that it does not consume external energy due to its electrostatic nature, which was an advancement over previous electrochemical bioreactors where an electric current was introduced (Shin et al., 2002). The method has been demonstrated at 1 L batch fermentation containing 200 g/L glucose (High Gravity range) and using dry yeast *S. cerevisiae* without pre-culture. When voltage was increased from 0 V to 15 V, a progressively faster fermentation progress was observed within 24 h' fermentation, and consequent application of a 15 V voltage led to ethanol yield of 12.3 % (v/v) compared to 4.8 % (v/v) by applying 0 V. Similarly, the technology has also been used to accelerate 1 L batch fermentation containing 250 g/L of glucose (Very High Gravity Range) and dry yeast *S. cerevisiae* with pre-culture, resulting in ethanol yield of 14 % (v/v) within 20 h and corresponding glucose consumption rate of 98 %. The authors also provided evidence that the applied voltage increased the cell growth of *S. cerevisiae*; however, main mechanisms of the enhanced ethanol yield remains to be explored.

Furthermore, (Joshi et al., 2019) reported an enhanced ethanol production in electrochemical cells by *S. cerevisiae* CDB7 and *Wickerhamomyces anomalus* CDBT2 (a xylose utilising yeast). On introduction of external voltage of 4 V, *S. cerevisiae* showed the highest ethanol production in the anodic chamber, whereas *W. anomalus* was the most efficient in the cathodic chamber, resulting in an enhancement of 19.8 ± 0.50 % and 23.7 ± 0.51 %, respectively. Further substantial enhancement of ethanol production (average increase of 52.8 ± 0.44 %) was observed when fine platinum nanoparticles coated on the platinum anode, and neutral red was deposited on graphite cathode. The above experiments were demonstrated using defined media with 5% glucose, and lignocellulosic biomass hydrolysate with 3.3 % of reducing sugar. Working volume of the cathodic and anodic compartments were approx. 300 mL each. The author concluded that the yeast strains were capable of producing ethanol effectively and efficiently in the electrochemical

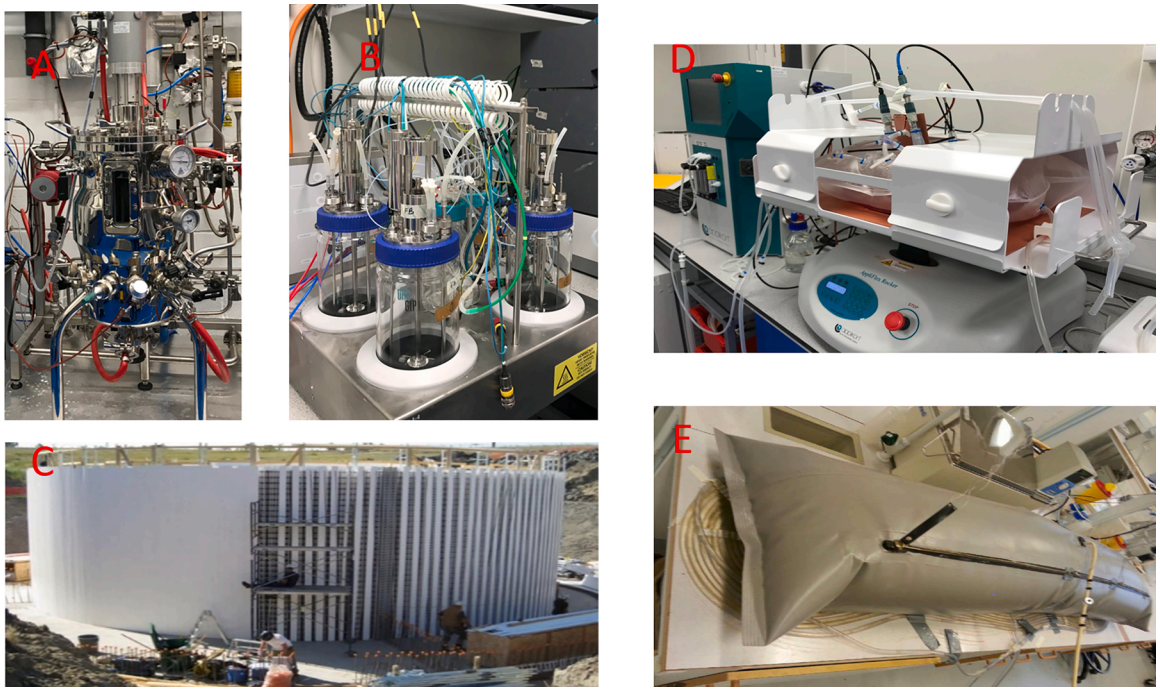

Fig. 4. Examples of bioreactors manufactured from stainless steel (A), glass (B), concrete (C), plastic (D) and textile (E).

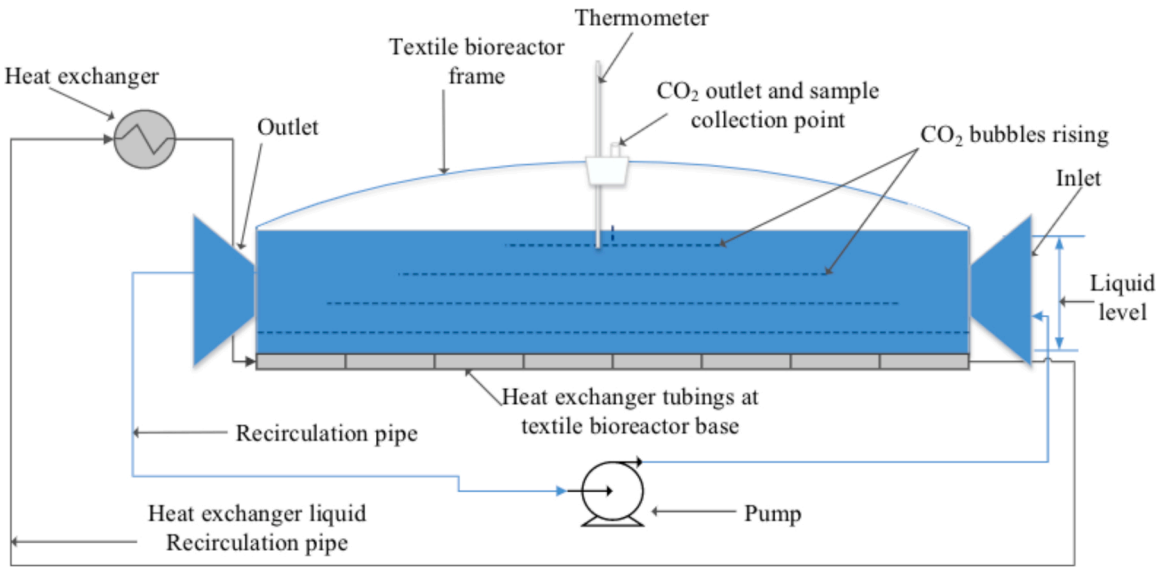

Fig. 5. Schematic diagram of the textile bioreactor used for ethanol fermentation (Osadolor et al., 2014).

cells, in particular, with better electron transport provision when the cathode/anode coated and next phase study of scale-up is in progress.

Despite of the achievements as described above, the technology is not fully clarified and has not been up scaled yet (Bhagchandanii et al., 2020). Some shortages have limited its industrial application: (i) the electron transfer mechanisms and its impact on the metabolism of the organism of interest remain to be clarified; (ii) a gap of large scale fermenter designs incorporating electrodes remains to be filled; (iii) feasibility and economic assessment is required to build such novel fermenter for manufacturing; (iv) More research efforts are required to understand the stability of electrode materials and energy efficiency in long term operation, particularly when in contact with complex media/cultures. Nevertheless, it can be estimated a bright future in this field, and a wide application such as electricity generation, treatment of waste effluents in waste water, bioremediation, and manufacturing of added-value products.

4. Merging new materials engineering with fermentation of *S. cerevisiae*

4.1. Alternative materials for bioreactor construction

Over time bioreactors have been built using a variety of construction materials, including borosilicate glass, stainless steel 304, concrete, plastic and coated textile (Table 5 and Fig. 4). Among these, while only stainless steel 304 and carbon steel bioreactors are used for bioethanol production via *S. cerevisiae* fermentation, coated textile bioreactor is a horizon vessel for this purpose. A schematic diagram of the textile bioreactor (Fig. 5) was firstly reported (Osadolor et al., 2014), with a total volume of 30 L and working volume of 25 L. The bioreactor was constructed with a textile backbone coating with several protection layers which make it resistant to sterilization (121 °C for 20 min), diverse environmental conditions (pH 3–12), and airtight. Due to the high tensile strength of the material used, the bioreactor was easy to assemble and disassemble. Using the novel bioreactor, the authors showed an optimal ethanol yield of 0.48 ± 0.01 g/g (corresponding to 88 % of theoretical value) within 15 h at 30 °C with mixing via recirculation.

More recently, the same research group reported an enhanced mixing system used for flocculating yeast in producing ethanol under anaerobic conditions (Alex Osadolor, 2018). Briefly, at the bottom of the 30 L textile bioreactor, holes of 0.42 mm diameter at 1 cm intervals was made through the internal, and therefore an upward flow of liquid stream was created to help in re-suspending settling flocs. It was observed that the developed mixing system resulted in effective substrate utilisation and thus enhanced fermentation rate in comparison with other experimental conditions. Consequently, the report estimated that a 37 % fermentation cost-saving could be realised, by using the developed textile bioreactor in replacement of conventional bioreactor in a 100,000 m^3/year ethanol production facility. In addition, (Jabbari, 2020) improved the thermal insulation of the textile bioreactor by utilising all-polyamide composite coated textiles (APCT), leading to enhanced energy efficiency of the process in the textile bioreactor. In addition, the new material is not only mechanically stronger and lighter than the existing Polyvinyl chloride coated polyester textile (PVCT), but also fully recyclable as it is made of a single recyclable component.

These findings increased the cost-efficiency and feasibility of bioethanol production using the novel textile fermenter. Given the feature of the textile fermenter, it is especially useful in developing countries or in remote villages, where local biofuel production can be installed at 'small scale'.

4.2. New materials for yeast immobilisation

Another development of new material is used for the immobilisation of yeast cells, which has been applied extensively in ethanol fermentation owing to its high cell density, high substrate tolerance and ease of separation (Zhu et al., 2018). The support material for immobilisation determines the activity of the immobilised cells and an ideal material would be conductive to cell viability, easy to use, renewable, biodegradable and naturally available in abundance (Singh et al., 2013). To this end, natural biomass materials have shown great advantages of being free of toxic components compared to inorganic and synthetic support materials and hence yeast immobilisation technology has been developed using a variety of natural biomass materials such as sugarcane bagasse (Saeed and Iqbal, 2013), loofa sponges (Baldikova et al., 2017) and bacterial cellulose (Zhu et al., 2018).

Recently, a new support matrix, polyethyleneimine grafted collagen fibre (CF-PEI), was developed for immobilisation of yeast cells (Archer and Bustard, 2020). The CF is an abundant natural biomass and the obtained CF-PEI was a biocompatible, non-toxic support material. It exhibited highest cell loading capacity and highest cell viability over 4 weeks' storage period, compared to other support matrix including cellular glass, porous ceramic and activated carbon. The authors

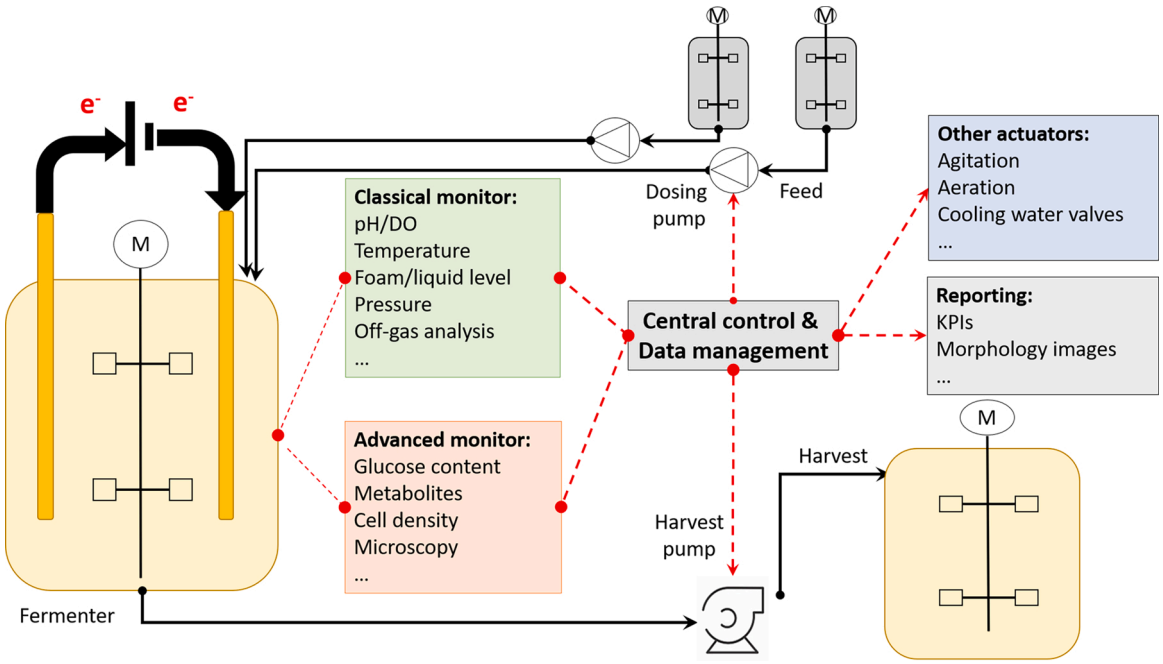

Fig. 6. Futuristic *S. cerevisiae* fermentation process based on the recent advancement discussed.

compared fermentation kinetics of immobilised *S. cerevisiae* cells and free cells during ethanol production in a repeated batch process (250 mL Erlenmeyer flask containing 120 mL synthetic media), whereby CF-PEI immobilised cells displayed highest average ethanol production (45.04 g/L) with ethanol yield of 0.46 g/g and glucose conversion efficiency of 90.4 %, compared with cellular glass immobilised and porous ceramic immobilised cells, as well as free cells. In addition, CF-PEI immobilised cells also showed a more stable ethanol production over 10 cycles of batch fermentation, indicating the CF-PEI exhibited highest stability over other supporting counterparts. In this paper, continuous fermentation was also conducted in a down-flow trickling bed reactor charged with CF-PEI immobilised cells for a total of 2 months. The author reported stable continuous operation at a dilution rate of 0.16 h^{-1}, with ethanol concentration of 44.90 g/L and glucose conversion rate of 88.94 %. Further scanning electron microscopy results showed that the there was a dramatic increase of yeast cell numbers after the continuous fermentation, confirming high cell density in the entire network of the material. The authors concluded that the CF-PEI is a highly potential material as a biocompatible support for *S. cerevisiae* immobilisation.

5. Conclusion and future perspective

To the best of our knowledge, for the first time the review presented multidiscipline engineering in the field of *S. cerevisiae* fermentation. A few interesting research progresses have been made over past 4 years. First of all, with the integration of process equipment, analytical instrumentation and computer communication, the development of novel probes enabled the improvement of in-process monitor or control including cell density via electronic nose technology, yeast morphology via online microscopy, metabolite profiling and control of glucose feed via indirect sensors. Secondly, with the further engagement of electrochemical engineering and conventional fermentation, better electron transport has been demonstrated when the cathode/anode was coated, leading to higher bioethanol yield and ongoing scale-up study. Last but not the least, new materials have been demonstrated in construction of textile bioreactor and yeast immobilisation support matrix, driving towards cost-effective and sustainable solutions. It is worth noting that we focus on *S. cerevisiae* as it is a widely-used microorganism for industrial fermentation and for research demonstration; however, our thoughts would be applicable to multiple species.

As industrial biotechnology aims progressively more-robust and lower-cost processes, it is anticipated that multidiscipline engineering would appear to be an increasingly important paradigm and mind-set from a R&D perspective. However, Bridging the gap between from R&D to manufacturing is often a difficulty for companies (Noorman and Heijnen, 2017; Welss Steve, 2016). This is acknowledged in that (i) one cannot simply enlarge lab-scale equipment and duplicate lab-scale conditions at large-scale (Crater and Lievense, 2018); (ii) there can be strict regulatory legislations and process compatibility, especially in food and pharmaceutical industry; (iii) the uncertainty of translating the engineered novel functionality from the laboratory to the real world, may result in a potential risk in disturbing routine manufacturing. Taken together, it is critical to 'begin with the end in mind' (Mathew et al., 2015), by using skilled engineering resources at large-scale to provide guidance to R&D and to overcome technical and economic barriers when scaling-up.

Provided that the current economic and technical barriers are solved, these multidiscipline technologies can be an effective solution for improved manufacturing of bio-products such as bioethanol. As shown in Fig. 6, it is anticipated that electrochemical fermentation would be fully merged with conventional stirred tank bioreactor, equipped with a series of novel probes to allow real-time regulation of feed or harvest at large scale. In addition, it is expected that novel textile would be utilised more often for small scale yeast fermentation, where the local infrastructure is limited or not guaranteed.

Declaration of Competing Interest

The authors report no declarations of interest.

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