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Review

Effects of moderately elevated pressure on gas fermentation processes

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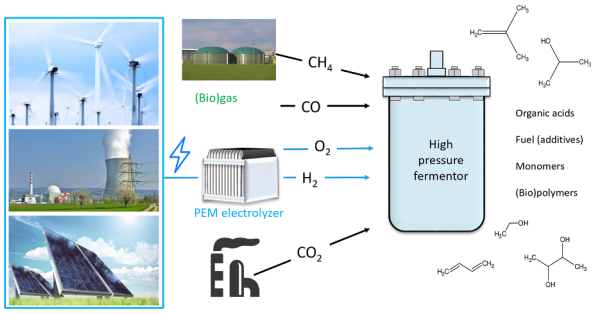
GRAPHICAL ABSTRACT



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ABSTRACT

Industrial biotechnology has a potential to tackle harmful CO_2 emissions and turn CO_2 into a valuable commodity. However, a major technical obstacle in gas fermentations is the limited gas mass transfer rate. Increasing system pressure is a way to increase the driving force for mass transfer. This review presents critical aspects of gas fermentation at elevated pressure, with a specific focus on results obtained at 5–10 bar. While a solid foundation for high pressure fermentations has already been laid in the past, mainly to enhance oxygen transfer rates, it can be concluded that fermentations at moderately elevated pressures using gases such as CO_2, CH_4, CO, H_2, O_2 are still underexplored. Microbial growth rates and product formation can be improved at higher pressures, but in general, titers and productivities need to be increased to allow a further industrialization. Hence, more systematic investigations and techno-economic assessments are required.

1. Introduction

Carbon emissions hit a record high of 11.3 ± 0.9 GtC in 2017 (Le Quéré et al., 2018). The most straightforward strategy to abate climate change is simply to burn less fossil fuels. CCS (carbon capture and storage) and CCU (carbon capture and utilization) constitute a second strategy in the effort to allow a sustainable low carbon future. Currently, a negligible amount of the emitted carbon is captured or utilized. Efforts are underway to develop these technologies to reach the goals set forward in the Paris Agreement [which is ratified up to date by 185 parties (https://unfccc.int/process/the-paris-agreement/status-of-ratification, Accessed on 19/04/2019)]. CCS offers a long-term geological sequestration while CCU has the potential to transform CO_2 into a variety of end products. Even though these technologies are still surrounded by uncertainties related to energy cost, type of (low-carbon) energy source (Winterbone and Turan, 2015) and effectiveness of CCU in mitigating climate change compared to CCS (Mac Dowell et al., 2017), CCU has the potential to create attractive business cases for production of fuels, chemicals and plastics. To illustrate this, Lanzatech is producing ethanol on a commercial scale in Caofeidian (Hebei

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Nomenclature

a,	Interfacial area between gas and liquid [$m^2.m^{-3}$]
ALR	Air lift reactor
$C_{i,L}$	Actual dissolved gas concentration in the liquid [$mol.m^{-3}$]
$C^{*}_{i,L}$	Saturation concentration of the dissolved gas [$mol.m^{-3}$]
$C^{in}_{O_2,G}$	Oxygen concentration in inlet fermentor [$mol.\ m^{-3}$]
$C^{out}_{O_2,G}$	Oxygen concentration in outlet fermentor [$mol.\ m^{-3}$]
CCS	Carbon capture and storage
CCU	Carbon capture and utilization
D_i	Diffusion coefficient for compound i in water [$m^2.s^{-1}$]
Da_{II}	Second Damköhler number or ratio of the chemical reaction rate to the mass transfer rate [–]
EROI	Energy return on investment
GtC	Gigatonne carbon
GTR	Gas transfer rate [$mol.m^{-3}.s^{-1}$]
GUR	Gas uptake rate [$mol.m^{-3}.s^{-1}$]
H_i	Henry's law constant of compound i [$mol.m^{-3}.Pa^{-1}$]
H_i^{REF}	Henry's law constant of compound I at reference temperature T^{REF} [$mol.m^{-3}.Pa^{-1}$]
ICI	Imperial Chemical Industries Limited
ISPR	In situ product recovery
K_L	Overall mass transfer coefficient based on liquid concentrations [$m.s^{-1}$]
K_La	Volumetric mass transfer coefficient [s^{-1}]
LOC	Limiting oxygen concentration
NRTL	Nationally Recognized Testing Laboratory
OSHA	Occupational Safety and Health Administration (agency of the united states department of labor)
OTR	Oxygen transfer rate [$mol.m^{-3}.s^{-1}$]
OUR	Oxygen uptake rate [$mol.m^{-3}.s^{-1}$]
P_1	Absolute pressure at compressor inlet [kPa]
P_2	Absolute pressure at compressor outlet [kPa]
P_{atm}	Atmospheric pressure [Pa]
P_{comp}	Power required in compressor [kW]
P_R	Pressure in reactor [Pa]
P_S	Stirred power input [kW]
P_{Stir}	Pressure at the stirrer [Pa]
PEM	Proton Exchange Membrane
Q_1	Volume rate of gas flow at compressor inlet conditions [$m^3.h^{-1}$]
Q	Gas flow rate [$m^3.s^{-1}$]
R	Gas constant [$J.mol^{-1}.K^{-1}$]
SCP	Single Cell Protein
STP	Standard Temperature (273 K) and Pressure (101.3 kPa)
STR	Stirred tank reactor
t	time [s]
T	Temperature [K]
T^{REF}	Reference temperature [298.15 K]
u_G	Superficial gas velocity [$m.s^{-1}$]
$\dot{V}_G$	gas flow rate under STP conditions [$m^3\ h^{-1}$]
V_L	Liquid volume [m^3]
y_i	Mole fraction of compound i [$mol.mol^{-1}$]
Δ	incremental change in a variable
$\Delta_{sol}H_i$	Molar enthalpy of dissolution of compound i [$J.mol^{-1}$]
α	Correlation parameter [–]
β	Correlation parameter [–]
γ	Correlation parameter [–]
$\varnothing$	Diameter of the vessel [m]

Province, China) based on fermentations using waste gases from steel mills. Additional commercial plants are planned or already built in Haryana (Indiana), Riverbank (California), Mpumalanga province (South Africa) and Ghent (Belgium). Sapphire Energy has conducted several pilot demonstrations since 2009 for the production of gasoline and jet fuel based on sunlight and CO_2 using algae grown in open ponds. Hence, diverse biotechnological CCU technologies are being reported and the range of CO/CO_2-derived products is expanding to e.g. jet fuel, butadiene, 2,3-butanediol, isopropanol and isobutylene (De Tissera et al., 2019). Hydrogen produced using decarbonized electricity (Glenk and Reichelstein, 2019) is expected to play a major role in the reduction of CO_2 in end-of-pipe installations. Although biological processes are usually slower than chemo-catalytic or thermochemical reactions, their main advantages are: (1) milder environmental conditions, (2) higher conversion efficiencies, (3) higher product specificity or selectivity, (4) lower sensitivity to variations in gas composition in comparison to e.g. Fischer-Tropsch synthesis (Griffin and Schultz, 2012), and (5) in general a higher tolerance to impurities that are toxic to inorganic catalysts (Liew et al., 2013; Kopyscinski et al., 2010). It should be mentioned that there are limits to the last advantage. As an example, HCN was reported as deleterious impurity in a semi-commercial facility in Vero Beach, FL commissioned by INEOS Bio for production of ethanol from syngas derived from municipal solid waste (De Tissera et al., 2019). Also nitric oxides (at high concentrations, e.g. generated in gasifiers) will result in inhibited microbial growth (Heijstra et al., 2017). Another major concern is the limited gas mass transfer leading to reasonably low productivities and potentially very large fermentors. High productivities are essential for the economic feasibility of gas utilizing fermentation processes and these strongly depend on achieving high mass transfer rates. Most research efforts have focused on increasing the K_La, e.g. by investigating gas liquid jets as dispersion devices (Weber et al., 2018) or by investigating microbubble formation leading to lower power-to-volume ratios (Bredwell and Worden, 1998; Hensirisak et al., 2002). Several review papers are available that summarize the current state-of-the-art on this topic, mostly in the context of syngas and CO fermentations (Daniell et al., 2016; Fernández-Naveira et al., 2017; Liew et al., 2013; Wainaina et al., 2018). In addition to the K_La, also the driving force for mass transfer can be increased, for instance by operating at increased pressure. This review aims to present the state-of-the-art, expected benefits and critical aspects of gas fermentation at elevated pressures, with a specific focus on results obtained in bioreactor tests at 5–10 bar.

2. Gas mass transfer for CO, H_2, CO_2, O_2 and CH_4

Sparingly soluble gases are required in most gas fermentation processes either as carbon and energy source (e.g. CO, H_2, CH_4) or as electron acceptor (e.g. O_2). Because micro-organisms can only take up gaseous substrates in their dissolved form, a series of mass transfer steps of the substrate from the gas bubble to the reaction site inside the cell has to take place. The gas-to-liquid mass transfer rate can be described by Eq. (1):

$$\frac{dC_{i,L}}{dt} = K_L a_i * (y_i * P_R * H_i - C_{i,L}) \quad (1)$$

K_L is the overall mass transfer coefficient (based on liquid concentrations) and is itself the resultant of resistances in the liquid phase boundary layer and the gas phase boundary layer (Munasinghe and Khanal, 2010; Phillips et al., 2017; Vega et al., 1989). Highly water soluble gases (e.g. ammonia) are gas-film controlled. Poorly water soluble gases (oxygen, hydrogen etc.) are liquid-film controlled (Raju, 2011). The interfacial area between gas and liquid is indicated by symbol a, the volumetric gas-to-liquid mass transfer coefficient $K_L a_i$ is a lumped parameter as it is hard to determine the interfacial area

between gas and liquid. P_R is the (absolute) reactor pressure, y_i the mole fraction of compound i in the gas phase and $C_{i,L}$ the dissolved gas concentration of compound i in the fermentor (Kim et al., 2017). H_i is Henry's law coefficient for component i which is variable with temperature (and also affected by salinity). Therefore, increasing the reactor pressure or the mole fraction in the gas phase are straightforward methods to increase the gas transfer rate.

The temperature dependency of Henry's law coefficient can be described by the van 't Hoff equation (Atkins et al., 2017):

$$H_i(T) = H_i^{REF} * exp\left(\frac{-\Delta_{sol}H_i}{R} * \left(\frac{1}{T} - \frac{1}{T^{REF}}\right)\right) \quad (2)$$

H_i^{REF} is Henry's law constant at reference temperature T^{REF} [298.15 K] and $-\Delta_{sol}H_i$ is the molar enthalpy of dissolution. The parameters H_i^{REF} and $\frac{-\Delta_{sol}H_i}{R}$ are listed for several compounds encountered in gas fermentations in Table 1.

Mass transfer does not only affect the availability of sparingly soluble gases in the liquid, but also affects the activity in microbial cells. Ideally, the mass transfer rate should continuously match the reaction rate [i.e. the second Damköhler number Da_{II} or the ratio of the (bio) chemical reaction rate to the mass transfer rate equals 1]. This is not straightforward in a system with an unsteady state behavior, due to e.g. increasing cell concentrations, potential substrate limitations or inhibitions as well as product inhibition. In practice, operation will therefore take place in diffusion-limited ($Da_{II} > 1$) or reaction-limited ($Da_{II} < 1$) regimes. In the former case, the gas mass transfer rate is insufficient to support the conversion process and liquid phase concentrations will drop and become limiting for microbial conversion. In the latter case, delivery of the gaseous substrate to the reaction system exceeds the consumption rate. Liquid phase concentrations and concentrations inside the cells will reach saturation, resulting in the absence of a driving force for further mass transfer and in case of inhibitory substrates, a negative effect on reaction kinetics (Yasin et al., 2015).

K_La determination for oxygen is routinely done in the fermentation industry. A common method is to sparge the vessel with nitrogen and then start aeration at a certain superficial flow velocity and stirring speed. The monitored experimental oxygen concentration as a function of time is fitted to the following equation:

$$C_{O_2,L,t} = C^*_{O_2,L} - (C^*_{O_2,L} - C_{O_2,L,t=0}) * e^{-K_L a_{O2} * t} \quad (3)$$

Eq. (3) results from the integration of Eq. (1), solved for O_2. $C^*_{O_2,L}$ is the saturated oxygen concentration in the vessel and is estimated along with $K_L a_{O2}$ using nonlinear regression techniques, also described in ASCE/EWRI 2-06 (ASCE/EWRI2-06, 2007). Eq. (3) can be used on the condition that the rate of dissolved oxygen concentration change is negligible compared to the probe response time. The measuring range of most, if not all dissolved oxygen sensors is relatively far from the saturated dissolved oxygen concentrations at 10 bar when using air [$C^*_{O_2,L}$ is around 82 ppm at 25 °C at 10 bar while maximum measuring range of oxygen sensors is ~40 ppm]. Therefore, oxygen depleted air containing e.g. 5% oxygen could be used to monitor the entire dissolved oxygen concentration profile as a function of time.

K_La determinations for other gases are less routinely performed, but several methods can be found in the literature to quantify the K_La of hydrogen, CO_2 and CO. The measurements are complicated as autoclavable sensors to monitor CO_2 and H_2 in the liquid have a shelf life limited to several months while sensors monitoring CO in the liquid are simply not available. Therefore, K_La determination for CO involves a myoglobin assay (Ungerman and Heindel, 2007). Myoglobin reacts with CO and forms carboxymyoglobin which is quantified by spectrophotometric analysis (Kundu et al., 2003; Riggs and Heindel, 2006). The $K_La_{CO_2}$ was quantified by monitoring the change in pH when applying CO_2 sparging. Overall volumetric mass transfer coefficients for carbon dioxide were correlated with temperature, stirring speed and gas flow (Hill, 2006). The dissolved carbon dioxide was also monitored directly as a function of time (Matsunaga et al., 2009) by using an in situ fiber optic chemical sensor (YSI BioVision 8500 from YSI Incorporated based on a fluorescent dye hydroxypyrenetrisulfonate) described in more detail by Pattison et al. (Pattison et al., 2000).

Dissolved CO_2 was measured using near-infrared Raman spectra (Berger et al., 1995). $K_La_{CO_2}$ was not determined based on near-infrared (Raman) spectroscopy, but this could be an interesting method, also for determining the K_La of other gases (if the quantification is precise enough). The price of the required equipment is a showstopper, but might be justified if the same equipment could be used for online monitoring and control of (dissolved) gases and products.

The $K_La_{H_2}$ was determined by monitoring the dissolved hydrogen concentration as a function of time from the moment hydrogen sparging was started (after all dissolved gases were removed by vacuum) (Kodama et al., 1976). The dissolved hydrogen concentration was measured by withdrawing liquid samples with a syringe, stripping the dissolved hydrogen with nitrogen and analyzing the hydrogen concentration with a GC. The sample-taking procedure has to be executed fast to ensure that no dissolved hydrogen is lost. Babcock and Radway (2002) have proposed that K_La_i values can be calculated as well based on the $K_La_{O_2}$ using the following formula:

$$K_L a_i = K_L a_{O2} * \left(\frac{D_i}{D_{O_2}}\right)^{\frac{1}{2}} \quad (4)$$

With D_i the diffusion coefficient for compound i in water. Eq. (4) was developed for CO_2 in tubular gas lift photobioreactors. If also valid for the other compounds of interest, it gives a practical and quick method for approximating mass transfer coefficients based on equipment available in every fermentation laboratory.

Oxygen transfer rates (OTR) can be determined during the fermentation by online off-gas analysis and by solving a (gas) oxygen mass balance on the bioreactor (Garcia-Ochoa et al., 2010). This system has its limitations in case differences between the incoming and outgoing oxygen concentrations are too small to distinguish for the detector. Oxygen uptake rates (OUR) can be determined by monitoring the dissolved oxygen concentration.

$$OTR = \frac{Q}{V_L} * (C^{in}_{O_2,G} - C^{out}_{O_2,G}) \quad (5)$$

$$OUR = OTR - accumulation = \frac{Q}{V_L} * (C^{in}_{O_2,G} - C^{out}_{O_2,G}) - \frac{\Delta C_{O_2,L}}{\Delta t} \quad (6)$$

In the case of aerating fermentors, most air is lost through the vents as air is readily available and only needs to be compressed to overcome

Table 1
Compilation of H_i^{REF}, $\frac{-\Delta_{sol}H_i}{R}$ and D_i (at 25 °C) for different gases.

i	H^{REF} [mol/m^3/Pa]	$\frac{-\Delta_{sol}H}{R}$ [K]	D_i [m^2.s^{-1}]	References
CO	$9.7 * 10^{-6}$	1300	$2.03 * 10^{-9}$	Warneck and Williams (2012)
H_2	$7.8 * 10^{-6}$	530	$1.92 * 10^{-9}$	Fernandez-Prini et al. (2003)
CO_2	$3.3 * 10^{-4}$	2400	$4.5 * 10^{-9}$	Sander et al. (2011)
O_2	$1.2 * 10^{-5}$	1700	$2.1 * 10^{-9}$	Warneck and Williams (2012)
CH_4	$1.4 * 10^{-5}$	1900	$1.49 * 10^{-9}$	Warneck and Williams (2012)

the hydrostatic pressure in the fermentor. Hence, there is no incentive to consume all oxygen in the incoming air. A fundamentally different situation arises in the case of fermentations based on e.g. CH_4, H_2, CO etc. Close to full conversion of these (gaseous) substrates is demanded to decrease substrate costs and avoid unwanted emissions of unconverted gases. To illustrate this, in the case of syngas to ethanol fermentations, unconverted syngas is sent to a burner to recover the energy. In such cases, designs involving gas recycling assist in improving substrate utilization (Winter and Hohman, 2018). Therefore, the mathematical approach for determining gas transfer rates (GTR) has to be redeveloped based on the particular reactor design. Furthermore, the determination of gas uptake rates (GUR) is complicated by lack of (robust) sensors measuring the dissolved gas concentrations. On-line gas analysis is deemed to be an indispensable asset not only to monitor the gas composition, but also to steer the composition of the headspace to avoid depletion or accumulation of a particular (substrate or product) gas.

3. Elevated pressure fermentation

The upper pressure limit that can be applied will evidently depend on the type of microorganism. Piezophilic strains which thrive at the bottom of the ocean where pressures of 100 bar and above are prevalent (Lemmer et al., 2017) are not within the scope of this review but rather microorganisms that are normally applied at atmospheric pressure. In industrial settings, bubble columns, airlift fermentors (with internal and external) draft tube, stirred tank reactors (van't Riet and Tramper, 1991) and hybrids between the airlift and the stirred tank reactor (Tervasmäki et al., 2016) (called stirred airlift reactors or stirred draft tube reactors) are used (see Fig. 1). Mechanical simplicity is often mentioned for bubble columns and airlift reactors as a benefit in comparison to stirred tank reactors, as engines and rotating parts are not required. Airlift reactors consist of three sections: a downcomer, a riser and a disengagement zone (Duan and Shi, 2014). When well designed and operated in proper regimes, the resulting liquid recirculation leads to improved hydrodynamics in comparison to simple bubble columns and hence translates to increased K_La's. Ratios of K_La to power input are important design factors in the commercialization of a product. Stirred tank reactors can achieve a higher power input per unit of volume in comparison to bubble columns and gas lift reactors and are favored in case high viscosity broths are obtained (van't Riet and Tramper, 1991). Stirred tank reactors seem interesting to use as (high pressure) pilot reactors for which characterization and interpretation of data might be more straightforward than for small-scale airlift or bubble columns. Computational fluid dynamics (CFD) can play a role as well in better understanding the factors that lead to a successful upscaling (Straathof et al., 2019).

The highest hydrostatic pressures industrially applied were in so-called ICI deep-shaft airlift fermentors applied for high-strength wastewaters (Sittig, 1982) using an in-ground vertical shaft between 90 and

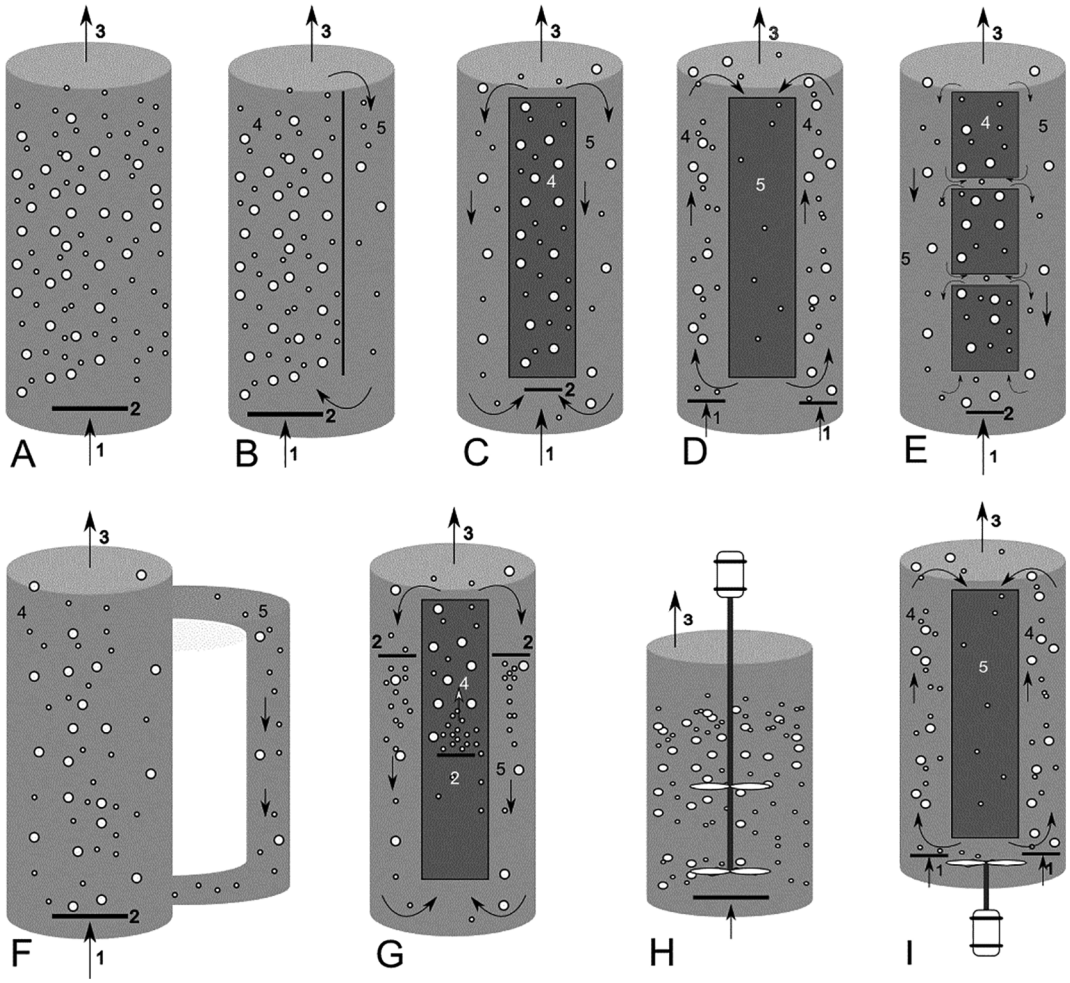

Fig. 1. Bioreactors for gas fermentation: A. bubble column; B. Split-cylinder internal-loop ALR; C. concentric draught-tube internal-loop ALR with centrally arranged riser; D. concentric draught-tube internal-loop ALR with centrally arranged downcomer; E. draught-tube internal-loop with vertically split draught-tube and centrally arranged riser; F. ALR with external draft tube; G. Deep-shaft airlift reactor with upward sparging in the riser and downward sparging in the downcomer; H. stirred tank reactor; I. Stirred airlift reactor. 1. gas inlet; 2. sparger; 3. gas exhaust; 4. riser; 5. downcomer.

Table 2
Overview of experiments with gaseous substrates, performed in bioreactors in 5–10 bar pressure range. T: temperature, P: pressure, B: batch, FB: fed-batch, C: continuous, OTR: Oxygen Transfer Rate, SCP: Single Cell Protein, SGV: superficial gas velocity. *incremental increase in pressure to match oxygen demand.

Gas substrate	Biocatalyst	T, pH, P	Reactor specifications	Liquid feed	Gas supply	Gas uptake	Product	Process performance	Ref.
O_2	Genetically modified *Escherichia coli K12 (W3110 and VH33)*	37 °C pH 7 1–11 bar	STR, 35 L, 3 × 6-blade Rushton turbines, baffles, 500 rpm	B, FB	Continuous*, SGV = 0,00179 m/s, OTR = 0,7–0,984 mol O_2/L.h at 9 bar	/	Biomass (and intracellular protein)	80 g biomass/L	Knabben et al. (2011))
O_2	Genetically modified *Escherichia coli K12 (W3110 and VH33)*	37 °C pH 7 1–4.8 bar	STR, 35 L, 3 × 6-blade Rushton turbines, baffles, 500 rpm	B, FB	Continuous*, K_La = 0,083/s, SGV = 0,00298/s, OTR = 450 mmol O_2/L.h	/	Biomass	Up to 4 bar: 48 g biomass/L Up to 4 bar: 2,1 g biomass/L.h (2– 3-fold increase vs. 1 bar)	Knabben et al. (2010))
O_2	Genetically modified *E. coli, Arxula adeninivorans, Saccharomyces cerevisiae, Corynebacterium glutamicum*	30–37 °C pH 4.5–7 1–11 bar	STR, 35 L, 3 × 6-blade Rushton turbines, baffles, 500 rpm	B, FB	Continuous*, OTR: 0,3 mol O_2/L.h at 4 bar (*S. cerevisiae*) till 0,9 mol O_2/L.h at 11 bar (*E. coli*) K_La = 0,2/s for O_2	/	Biomass (and intracellular product)	*E. coli*: 40 g biomass/L at 1 bar vs. 110 g biomass/L at elevated pressure *C. glutamicum*: 226 g biomass/L Max. productivity: 3 g lysine/L.h and 9,6 g biomass/L.h *A. adeninivorans*: 224 g biomass/L *S. cerevisiae*: 89 g biomass/L	Knoll et al. (2007)
O_2	*Yarrowia lipolytica W29*	27 °C pH 5.6 5–10 bar	STR, 0,6 L, 1 × 4-blade impeller, 400 rpm	B	/	/	Convert methyl ricinoleate to γ-decalactone	1 bar: approx. 300 mg γ-decalactone/L and 150 mg/L of downstream biotransformation product 3-hydroxy-γ-decalactone 5 bar: 75 mg γ-decalactone/L and 350 mg/L of 3-hydroxy-γ-decalactone	Aguedo et al. (2005)
air	*Yarrowia lipolytica W29*	27 °C 1–6 bar	STR, 0,6 L, 400 rpm	B			Lipase	6 bar: 5-fold increase in biomass production (30 g/L), 3.4-fold increase in specific growth rate (1 g cells/L.h) 5 bar: 3,7-fold increase in lipase productivity compared to 1 bar	Lopes et al. (2009))
CH_4/O_2	*Methylocystis GB25*	38 °C pH 5.7 1–5 bar	/	C	Continuous 5 bar: OTR = 15 g O_2/L.h	/	SCP – biomass	3 bar: 20–35 g biomass/L (2-fold increase compared to atmospheric pressure)	Wendlandt et al. (1993))
CO_2 (26,7%), H_2 (53,3%) in N_2	*Clostridium ljungdahlii DSM13528*	37 °C pH 5.9 1–7 bar	STR, 2,5 L, 2 Rushton turbines, baffles, sintered metal plate for gas supply	B	Continuous, 1 bar: K_La = 0,01/s for O_2 tests at constant volumetric amount of substance flow rate and at preset initial pressure	1 bar: 4,56 mmol H_2/min.g, 1 mmol CO_2/min.g − 0,3 mol H_2/L, 0,14 mol CO_2/L − 12% H_2, 11% CO_2	1 bar: mainly acetate 7 bar: mainly formate	1 bar: 4,3 g acetate/L, 0,4 g ethanol/L 4 bar: 1,9 g acetate/L, 0,2 g ethanol/L, 1,3 g formate/L 7 bar: 0,79 g acetate/L, 0,07 g ethanol/L, 3,2 g formate/L 1 bar: 0,05 g products/L.h 4 bar: 0,038 g products/L.h 7 bar: 0,045 g products/L.h	Oswald et al. (2018))
CO_2/H_2 (56%/44%)	Genetically modified *Escherichia coli K12,* tests with resting cells	37 °C pH > 6.8 2–10 bar	STR, 1,2 L, mechanically stirred	B	/	10 bar: approx. 100% CO_2 conversion	Formate	10 bar: max. 0,5 mol formate/L − 0,16 mmol formate/mg total cell protein (20-fold increase compared to atmospheric pressure)	Roger et al. (2018))
CO_2/H_2	Methanogenetic microorganisms	40 °C pH 6.5–7 1.5–9 bar	Trickle-bed reactor; 22.5 L	C	CONTINUOUS, 10.8 $L.h^{-1}$ hydrogen; 2.9 $L.h^{-1}$ CO_2;	10 bar: approx. 98% H_2 and 90% CO_2 conversion	Methane	Max. 4.28 ± 0.26 $m^3.m^{-3}.d^{-1}$	Ullrich et al. (2018))
CO (10–100%)	*Thermococcus onnurineus NA1 (KCTC10859) mutant 156T*	80 °C pH 6.5 1–10 bar	STR, 3 L, 1 × 6-blade Rushton turbines, microsparger, 600 rpm	B	Apply pressure when mass transfer limitation is apparent	Increased CO conversion at 4 bar (63%)	H_2	max. 360 mmol H_2/L.h upon pressure increase till 4 bar (3-fold enhancement compared to ambient pressure) but reduction at higher pressures	Kim et al. (2017))
CO	*Blautia (*previously *Peptostreptococcus) productus*	37 °C > 14.6 bar	STR, 0,65 L, 100 rpm	B	Direct or stepwise pressurization	CO consumption up to 14.6 bar	Acetate	Only CO consumption under stepwise pressurization because this avoids inhibition by too high dissolved CO	Ko et al. (1989))

(*continued on next page*)

Table 2 (*continued*)

Gas substrate	Biocatalyst	T, pH, P	Reactor specifications	Liquid feed	Gas supply	Gas uptake	Product	Process performance	Ref.
Syngas	*Clostridium ljungdahlii*	37 °C 1–10 bar	STR, 0,65 L, 200–500 rpm	C	Continuous	10 bar: 80% CO conversion, 55–60% H_2 conversion	Acetate, ethanol	10 bar: 4 g acetate/L and little ethanol, or 4,5 g ethanol/L in different runs	Fernandez-Prini et al. (2003)
Syngas	*Clostridium ljungdahlii*	30–40 °C 1–10 bar	Column with liquid recirculation, 1 L	C	Continuous	10 bar: higher CO consumption than at lower pressures	Acetate, ethanol	Reaction rate proportional to pressure	Anonymous (1993))
Syngas	*Clostridium ljungdahlii*	30–40 °C < 13 bar		B	Continuous		Acetate	Acetate production and biomass increase proportional to pressure	Gaddy (1997))

250 m in depth (Weston, 1982) and diameters up to 3 m. The concept was originally developed for single cell protein (SCP) production in England using methanol as feedstock requiring high oxygen uptake rates (Chen, 1990). To save energy in the compressors, the spargers do not necessarily need to be positioned at the bottom of the riser, but are reported to be located 20 m from the top of the fermentor. Air is sparged upward in the riser and downward in the downcomer. The liquid velocity (typically 0.9–1.5 $m.s^{-1}$) drags down gas bubbles to the bottom of the reactor where they (partially) dissolve before returning to the surface through the riser. Near complete oxygen consumption is reported in such fermentors with 2.7–5.4 kg oxygen transferred per kWh (Pollock, 1997).

Table 2 provides an overview of studies performed in bioreactors at moderately elevated process pressures of between 5 and 10 bar. Studies at pressures below 3 bar or in simple (serum) bottles were excluded from the table. Several patents on gas fermentation technology (Bell and Ko, 2017; Datta et al., 2016) or references to commercial processes (Calysta in Strong et al. (2016)) mention 5 to 10 bar operating pressures as well. Sublethal effects or a strong negative impact on the performance of the microorganisms are therefore not expected. Moreover, a 5- to 10-fold increase in system pressure results in a substantial improvement in gas solubility and a reduction in fermentor size (Anonymous, 1993) without the need for more expensive sensors and auxiliary equipment (Lemmer et al., 2017). Pressure devices in the European Union (excluding equipment with an allowable pressure lower than 0.5 barg) need to be compliant with the Pressure Equipment Directive (2014/68/EU).

3.1. Effects on mass transfer rates

An increase in pressure will affect the solubility of gases, but there is some debate as to whether it may also have an impact on the volumetric mass transfer coefficient. Several references summarized by Campani et al. (2015) report a pronounced effect on K_La in bubble column reactors. This was theoretically explained by the fact that larger bubbles will become unstable at a higher reactor pressure and collapse, leading to smaller average gas bubble diameters, a larger gas-liquid interfacial area, a lower terminal rise velocity of the gas bubbles and longer gas hold-up. However, in their own experiments, Campani et al. (2015) could not demonstrate a significant impact of air overpressures on K_La in the range of 1–4 bar. Also the results in stirred tank reactors (STR) are not consistent. Some authors assume that at a constant superficial gas velocity, K_La values are constant independent of the applied pressure (Knoll et al. (2005) and references therein). However, Lopes et al. (2013) observed that an air pressure increase up to 5 bar led to a slight decrease of the volumetric mass transfer coefficient. Applying a constant gas flow rate to the reactor, measured under standard conditions, actually results in a decrease in true gas flow rate with pressure, and consequently also in less gas bubbles and a lower gas holdup. The normalized gas flow rate should thus be increased with increasing pressure when the aim is to keep K_La constant (Knoll et al., 2007; Lopes et al., 2013).

Correlations (for STR) are firmly established between the volumetric mass transfer coefficient, the stirred power P_s and superficial gas velocity u_G as described in the seminal work of van't Riet and Tramper (1991). For aerated stirred tank reactors, the correlation (established for oxygen) is given in Eq. (7).

$$K_L a_i = \gamma * \left(\frac{P_s}{V_L}\right)^{\alpha} * \left(u_G * \frac{P_{atm}}{P_{Stir}}\right)^{\beta} \quad (7)$$

The superficial gas velocity u_G is a hypothetical velocity assuming gas is the only phase flowing through a certain cross-section. Under STP conditions, it can be calculated as:

$$u_G = \frac{\dot{V}_G}{\frac{\pi}{4} * \varnothing^2} \quad (8)$$

Therefore, when increasing the reactor pressure the concentration driving force increases [see Eq. (1)], but the pressure corrected superficial velocity term [see Eq. (7)] decreases (leading to a decreased $K_L a_i$). So increasing pressure does not increase the mass transfer rate linearly. Assuming the gas (compound i) is depleted in the reactor and P_{Stir} equals P_R (which is approximately the case in small scale pilot reactors with a negligible hydrostatic pressure) substitution of Eq. (7) in Eq. (1) results in:

$$\frac{dC_{i,L}}{dt} = \gamma * \left(\frac{P_s}{V_L}\right)^{\alpha} * (u_G * P_{atm})^{\beta} * y_i * H_i * P_R^{1-\beta} \quad (9)$$

Hence, in the best case, the gas transfer rate increases with the pressure to the power $(1-\beta)$ on the condition that other factors (superficial flow velocity u_G, stirred power P_s, fermentor volume) remain equal.

The pressure has implications on the choice of the compressor and its energy consumption. Knoll et al. (2005) state that for up to 10 bars of overpressure the same type of compressor can be used. The design will become more complex in the case where compressors are used to recirculate gas at the top of the fermentor to the bottom of the fermentor to increase the gas utilization (i.e. the ratio of generated product to supplied gas which tends to be lower than the ratio of the generated product to consumed gas).

A simple approximation of the power required in the compressor is given in the following formula if quasi isothermal conditions are reached (Boyce et al., 2007):

$$P_{comp}\,[\mathrm{kW}] = 2.78 * 10^{-4} * Q_1 * P_1 * ln\left(\frac{P_2}{P_1}\right) \quad (10)$$

with P_1 the absolute inlet pressure (kPa), P_2 the absolute discharge pressure [kPa] and Q_1 the volume rate of gas flow [m^3/h] at compressor inlet conditions.

Though Henry's law indicates that the solubility of gaseous compounds can be increased with reactor pressure, it only considers the dissolved gas, while the behavior of particularly CO_2 in solution is known to be complex, since it reacts with water to form carbonic acid, bicarbonate and carbonate in variable ratios depending on the initial pH range and presence of other (cat)ions. Obviously, an increase in CO_2 partial pressure will result in a more important pH drop and this may have a negative effect on the conversion process. For instance, resting cell assays with CO_2 and H_2 under a pressure of 10 bar, only resulted in optimal conversion to formate once proper pH control was applied to avoid the pH decrease of both CO_2 dissolution at the start of the test, and the production of formate at later stages (Roger et al., 2018).

3.2. Effects on microorganism growth and product formation

Although the use of elevated pressures has often been named as a means to increase gas-to-liquid mass transfer, only a few studies have investigated its effect in a fermentor set-up in the 5–10 bar range so far. Three references in Table 2 concern work of Büchs and colleagues in RWTH Aachen on O_2 supply in pressurized STRs. By incrementally increasing the headspace pressure when O_2 levels dropped below 20% or 30% of air saturation, O_2 limitations were avoided and 2–3 fold higher biomass densities and productivities could be reached compared to non-pressurized conditions (Knabben et al., 2010, 2011; Knoll et al., 2007). Likewise, an improved biomass production was measured for the strictly aerobic yeast *Yarrowia lipolytica* under elevated air pressure up to 6 bar (Aguedo et al., 2005; Lopes et al., 2009), for *Methylocystis* on CH_4/O_2 up to 3 bar (Wendlandt et al., 1993), for *Thermococcus onnurineus* on CO up to 4 bar (Kim et al., 2017) and for *Clostridium ljungdahlii* on syngas up to 13 bar (Gaddy, 1997). At higher pressures, growth of *Y. lipolytica* and *Thermococcus onnurineus* was inhibited (Aguedo et al., 2005; Kim et al., 2017) while for *Methylocystis* growth inhibition occurred when the produced CO_2 exceeded 150 mg/L or O_2 exceeded 1 mg/L (Wendlandt et al., 1993). In addition to earlier studies that showed inhibitory effects of CO partial pressures above 0.8 bar (Anonymous, 1993; Mohammadi et al., 2014), Oswald et al. (2018) now also observed a gradual decrease in *C. ljungdahlii* biomass formation on H_2/CO_2 gas mixtures with increasing pressure from 1 to 7 bar. The authors were not able to pinpoint whether this was caused by inhibitory effects of increased H_2 partial pressures and/or increased dissolved CO_2.

Increasing pressure may also have an impact on substrate consumption, extracellular product formation and product distribution. This was evaluated among others for *C. ljungdahlii* on different gaseous substrates. On syngas, either ethanol or acetate were found as the main product in different test runs, but there was no apparent link between product and applied pressure. CO consumption rates were higher at 10,4 bar than at lower pressures provided that a stepwise pressure increase was implemented (Anonymous, 1993). On CO_2/H_2, Oswald et al. (2018) noticed decreasing acetate and ethanol titers and increasing formate titers with increasing pressure. Although the product distribution shifted from acetate as predominant product at 1 bar to mainly formate at 7 bar, the overall product yield was not affected. Nevertheless, the observed titers (up to 3.2 $g.L^{-1}$ formate) do not allow an (energy-) efficient and economic downstream process of such compounds, especially given the fierce competition encountered for these (bulk) chemicals from alternative (and more efficient) production routes. Formate productivity increased as well at higher pressures, up to 0.045 $g.L^{-1}.h^{-1}$ at 7 bar, but too low to be considered for further industrialization (as a rule-of-thumb productivities exceeding 1 $g.L^{-1}.h^{-1}$ are demanded, especially for bulk chemicals). Also for other conversions, it can be observed that titers and productivities are too low to allow further industrialization. Gas-to-ethanol fermentations can be considered as a more mature conversion as 26 $g.L^{-1}$ ethanol and a productivity of 8.95–10 $g.L^{-1}.h^{-1}$ were reported by using cell recycling for a *Clostridium ljungdahlii* fermentation (Gaddy et al., 2014). To put this in perspective, 150 $g.L^{-1}$ ethanol can be easily reached in fermentations on carbohydrates (Pfromm et al., 2010). At the mentioned ethanol levels of 26 $g.L^{-1}$, the energy required to purify the ethanol is substantial in comparison to the lower heating value of ethanol (21.2 $MJ.L^{-1}$) (Huang and Percival Zhang, 2011; Luo et al., 2009). Therefore, higher titers are required to allow a reasonable energy return on investment (EROI) (Hall and Klitgaard, 2012). In case sufficiently high titers cannot be met, the reasons behind this should be elaborated to increase the understanding of the current limitations of such fermentations. If product inhibition is an issue, in situ product recovery (ISPR) technologies can be applied (Van Hecke et al., 2014), but these have their limitations as well. As the separation factors of such ISPR technologies are rather limited, a sufficient concentration in the fermentor is still demanded in most cases to end up with reasonable EROI's and allow competition with alternative production routes.

Interestingly, Roger et al. (2018) were able to reverse the reaction of formate hydrogenlyase in *Escherichia coli* by applying increased gas pressure and proper pH control. The enzyme which normally oxidizes formate to CO_2 coupled to the reduction of protons to H_2, was shown to rapidly convert 100% of gaseous CO_2 to formate at pressures up to 10 bar. Kim et al. (2017) investigated the effects of CO pressure on H_2 production by *T. onnurineus*. H_2 productivity was initially positively influenced by a higher CO partial pressure, but decreased drastically above 4 bar. This effect was mainly due to CO substrate inhibition because it did not occur to the same extent when CO partial pressure was kept constant at increasing system pressure. Two other studies focused on the effect of air pressure on product formation by *Yarrowia lipolytica*. Lopes et al. (2009) could not detect any oxidative stress to the cells up to 6 bar, and measured a 3,7-fold increase in extracellular lipase activity at 5 bar *versus* at 1 bar. The yeast is also capable of producing γ-

decalactone from precursors through β-oxidation. Although the use of pressure improved γ-decalactone production, it also increased the concentration of its oxidation compounds (Aguedo et al., 2005).

It can thus be concluded that a variable threshold, either as total pressure or as partial pressure of specific substrates, exists above which microbial growth and metabolism is affected. If one or more gaseous substrates are found to be inhibitory, their dissolved gas concentrations should be kept low by ensuring high uptake rates, either by employing pressurized fermentation only when the cell concentration has become sufficiently high or by stepwise increasing the pressure concomitant with cell concentrations (Mohammadi et al., 2014; Vega et al., 1989). Such gradual adaptation of biomass was found to be beneficial for CO consumption in *C. ljungdahlii* up to 10 bar (Anonymous, 1993), in *Blautia productus* (previously *Peptostreptococcus*) up to 15 bar (Ko et al., 1989), and in *T. onnurineus* up to 4 bar (Kim et al., 2017). In some cases, a preadaptation to elevated pressures was evaluated. For *Y. lipolytica*, pregrowth under 5 bar of air pressure did not improve subsequent lipase production (Lopes et al., 2009), while it did affect metabolite profiles in the β-oxidation pathway for production of decalactones (Aguedo et al., 2005).

3.3. Process operation and control

The use of higher gas flow rates is preferred. It has the benefit of increasing superficial velocity (and K_La), but may also result in a low conversion of the gaseous feedstock, unless the gas is recycled (Anonymous, 1993; Bredwell et al., 1999). Three studies executed with the same reactor set-up, applied a constant superficial O_2/air velocity (calculated at prevalent reactor pressures) by linearly increasing the normalized gas flow rate with the pressure (Knabben et al., 2010, 2011; Knoll et al., 2007). It is important to note that about half of the (few) reported elevated pressure tests concerned aerobic processes, in which O_2 is usually supplied in excess and only partially converted (Rittmann et al., 2015). This is not a feasible option for gaseous carbon substrates, for which a (close to) full conversion is desired to decrease feedstock costs. With one exception [(Roger et al., 2018) in Table 2], near full conversion efficiencies have not yet been demonstrated.

If reactors are continuously supplied with inhibitory substrates, any significant perturbation that temporarily affects the balance between the gas mass transfer rate and consumption may lead to process failure. Since micro-organisms sense the liquid concentration of a substance rather than the partial pressure in the gas phase (Häusler et al., 2016), feedback control of the dissolved gas concentration is desired to maintain reactor stability at elevated pressure (Bredwell et al., 1999). However, proper process monitoring as well as determination of kinetic parameters for gas transfer and uptake are complicated by the difficulty to measure liquid phase concentrations of sparingly soluble gases. Except for O_2 measurement, very few commercial dissolved gas sensors exist which are resistant to and accurate at broader pressure ranges. They are often specific for a certain application and expensive. Therefore, methods have been developed to determine mass transfer coefficients and calculate dissolved gas concentrations based on mass balances on the transfer rate to the liquid medium (Mohammadi et al., 2014). In case the end products of the bioconversion process are poorly soluble gases, attention should also be paid to potential supersaturation, occurring as a consequence of liquid-to-gas mass transfer limitations (Kraemer and Bagley, 2006). Supersaturation has been observed for H_2, CO_2 (Kraemer and Bagley, 2006) and CH_4 (Yeo et al., 2015) at ambient pressures. Certainly when the product is inhibitory, its concentration should be decreased, for instance by increasing the gas (recirculation) flow and/or implementing a product removal step.

Safety engineering is crucial in operating gas fermentors at high pressure. If oxygen is required in combination with e.g. CO_2, CO, H_2, (gaseous) products, potentially explosive conditions arise in which case the equipment has to comply with the ATEX directive [2014/34/EU] in the European Union. The employer needs to be compliant with ATEX directive [1999/92/EC] to ensure safety and health of his employees (Jespen, 2016). In the United States the equipment needs to be certified and marked by an OSHA-recognized NRTL. If the oxygen concentration in the gas mixture is lower than the limiting oxygen concentration (LOC), the gas mixture can be considered inert. Flammable minimum oxygen concentrations can be found in e.g. the Standard on Explosion Prevention Systems [NFPA 69, (NFPA69, 2019) (Zabetakis, 1965)].

The ability to test metabolically engineered strains that produce non-native chemicals based on C1 gaseous substrates in safe and well-designed high pressure fermentations is a luxury to most laboratories focusing on metabolic engineering, but in the same instance, a necessity to further advance this particular field and explore the full potential of these strains.

The principles of high pressure fermentation may be well understood, but in general not applied when investigating this interesting class of metabolically engineered strains. This might be due to several (financial and technical) hurdles that need to be overcome: 1. A high pressure reactor is not a readily obtained off-the-shelf piece of equipment as other general purpose bench or pilot scale fermentors. 2. Safety aspects related to the high pressure and to the (explosive) nature of the gas mixtures have to be well considered; 3. The price of such systems is quite high at any scale (due to the engineering costs, safety aspects and custom-made nature) in comparison to off-the-shelf bench or pilot scale fermentors. 4. Gas-to-gas and gas-to-liquid fermentations pose different constraints and challenges to the design of such installations (see Section 3.4).

3.4. Product recovery

While proof-of-concepts have been delivered for a range of (mainly bulk) chemicals, productivity and product titers (generally in the $mg.L^{-1}$ to several $g.L^{-1}$ scale) remain disappointingly low, stalling industrialization. Only when sufficient productivities and product titers can be reached, these technologies can be truly categorized as “carbon capture and utilization processes”. Product recovery is dependent on the type of product and determines the process configuration. A distinction can be made to products that are liquid and to products that are gaseous. Regarding the former, high concentrations need to be reached in the fermentation broth as to decrease downstream processing costs, eventhough the increased concentrations might introduce a certain degree of toxicity towards the fermenting organisms. In this case, a continuous (liquid) flow regime with cell retention seems a favorable mode of operation. In the latter case where gaseous fermentation products are obtained (such as isobutene and butadiene) a batch configuration (or continuous alternative allowing a small bleed for removal of dead cells) sounds more favorable as products cannot accumulate in the fermentation broth. The increased fermentation pressure might even lead to additional benefits as potentially volatile intermediates can have a higher utilization rate and as recovery of these gaseous compounds can be simplified by allowing condensation at high pressure and hence higher condensation temperatures. Such configurations require gas recycles and an elaborate online control system.

4. Conclusions and outlook

This review demonstrates that gas fermentation at moderately elevated pressures for autotrophic bacteria is an interesting field of research and of contemporary relevance given the challenges related to CO_2 abatement. In general, productivities are improved at higher pressures but titers and productivities need to be increased substantially to allow industrialization of this particular class of fermentations. Gas-to-ethanol fermentations are technically more advanced as can be judged as well from the number of pilot plant trials and (planned) commercial plants. More optimization work is needed and the range of tested microorganisms producing non-native chemicals based on C1 gases can be broadened.

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Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

Aguedo, M., Gomes, N., Garcia, E.E., Waché, Y., Mota, M., Teixeira, J.A., Belo, I., 2005. Decalactone production by *Yarrowia lipolytica* under increased O_2 transfer rates. Biotechnol. Lett. 27 (20), 1617–1621.

Anonymous, 1993. High Pressure Synthesis Gas Conversion. Final Report. University of Arkansas, Fayetteville, (USA), Department of Energy, National Energy Technology Laboratory (USA), Department of Energy, Office of Scientific Technical Information.

ASCE/EWRI2-06, 2007. Measurement of Oxygen Transfer in Clean Water.

Atkins, P., de Paula, J., Keeler, J., 2017. Physical Chemistry, 11th ed. Oxford University Press.

Babcock, R.W.M.J., Radway, J.C., 2002. Hydrodynamics and mass transfer in a tubular airlift photobioreactor. J. Appl. Phycol. 14, 169.

Bell, P.S., Ko, C.-w., 2017. Bioreactor for Syngas Fermentation. US 9,725,688 B2.

Berger, A.J., Wang, Y., Sammeth, D.M., Itzkan, I., Kneipp, K., Feld, M.S., 1995. Aqueous dissolved gas measurements using near-infrared raman spectroscopy. Appl. Spectrosc. 49 (8), 1164–1169.

Boyce, M.P., Edwards, V.H., Cowley, T.W., Fan, T., Kaiser, H.D., Geyer, W.B., Nadel, D., Skoda, L., Testone, S., Walter, K.L., 2007. Transport and storage of fluids. In: Green, D.W., Perry, R.H. (Eds.), Perry's Chemical Engineers' Handbook, second ed. McGrawHill.

Bredwell, M.D., Srivastava, P., Worden, R.M., 1999. Reactor design issues for synthesis-gas fermentations. Biotechnol. Prog. 15 (5), 834–844.

Bredwell, M.D., Worden, R.M., 1998. Mass-transfer properties of microbubbles. 1. Experimental studies. Biotechnol. Prog. 14 (1), 31–38.

Campani, G., Ribeiro, M.P.A., Horta, A.C.L., Giordano, R.C., Badino, A.C., Zangirolami, T.C., 2015. Oxygen transfer in a pressurized airlift bioreactor. Bioprocess Biosyst Eng 38 (8), 1559–1567.

Chen, N.Y., 1990. The design of airlift fermenters for use in biotechnology. Biotechnol. Genet. Eng. Rev. 8 (1), 379–396.

Daniell, J., Köpke, M., Simpson, S.D., 2012. Commercial biomass syngas fermentation. Energies 5 (12), 5372.

Daniell, J., Nagaraju, S., Burton, F., Köpke, M., Simpson, S.D., 2016. Low-carbon fuel and chemical production by anaerobic gas fermentation. In: Hatti-Kaul, R., Mamo, G., Mattiasson, B. (Eds.), Anaerobes in Biotechnology. Publishing. Cham, Springer International, pp. 293–321.

Datta, R., Calderone, S.G., Du, J., Hickey, R., Tobey, R.E., 2016. Processes and Control Systems for High Efficiency Anaerobic Conversion of Hydrogen and Carbon Oxides to Alcohols. US9528130B2.

De Tissera, S., Köpke, M., Simpson, S.D., Humphreys, C., Minton, N.P., Dürre, P., 2019. Syngas biorefinery and syngas utilization. In: Wagemann, K., Tippkötter, N. (Eds.), Biorefineries, first ed. Springer, Heidelberg, Germany.

Duan, Y., Shi, F., 2014. Chapter 2 – bioreactor design for algal growth as a sustainable energy source. In: Shi, F. (Ed.), Reactor and Process Design in Sustainable Energy Technology. Elsevier, Amsterdam, pp. 27–60.

Fernández-Naveira, Á., Abubackar, H.N., Veiga, M.C., Kennes, C., 2017. Production of chemicals from C1 gases (CO, CO_2) by *Clostridium carboxidivorans*. World J. Microbiol. Biotechnol. 33 (3), 43.

Fernandez-Prini, R., Alvarez, J.L., Harvey, A.H., 2003. Henry's constants and vapor-liquid distribution constants for gaseous solutes in H20 and D2O at high temperatures. J. Phys. Chem. Ref. Data 32, 903–916.

Gaddy, J.L., 1997. Clostridium Strain which Produces Acetic Acid from Waste Gases. 5593886.

Gaddy, J.L.F., Arora, D.K., Ko, C., Phillips, J.R., Basu, R., Wikstrom, C.V., Clausen, E.C., 2014. Methods for Increasing the Production of Ethanol from Microbial Fermentation. US8647851B2.

Garcia-Ochoa, F., Gomez, E., Santos, V.E., Merchuk, J.C., 2010. Oxygen uptake rate in microbial processes: an overview. Biochem. Eng. J. 49 (3), 289–307.

Glenk, G., Reichelstein, S., 2019. Economics of converting renewable power to hydrogen. Nat. Energy 4 (3), 216–222.

Griffin, D.W., Schultz, M.A., 2012. Fuel and chemical products from biomass syngas: a comparison of gas fermentation to thermochemical conversion routes. Environ. Prog. Sustain. Energy 31 (2), 219–224.

Hall, C.A.S., Klitgaard, K.A., 2012. The petroleum revolution. Energy and the Wealth of Nations. Springer, New York, NY.

Häusler, E.B.G., van der Wielen, L.A.M., Straathof, A.J.J., 2016. Evaluation of gas supply configurations for microbial product formation involving multiple gaseous substrates. Bioresour. Bioprocess. 3 (1), 18.

Heijstra, B.D., Leang, C., Juminaga, A., 2017. Gas fermentation: cellular engineering possibilities and scale up. Microb. Cell Fact. 16 (1) 60–60.

Hensirisak, P., Parsukulsatid, P., Agblevor, F.A., Cundiff, J.S., Velander, W.H., 2002. Scale-up of microbubble dispersion generator for aerobic fermentation. Appl. Biochem. Biotechnol. 101, 211.

Hill, G.A., 2006. Measurement of overall volumetric mass transfer coefficients for carbon dioxide in a well-mixed reactor using a pH probe. Ind. Eng. Chem. Res. 45 (16), 5796–5800.

https://unfccc.int/process/the-paris-agreement/status-of-ratification (accessed on 19/04/2019).

Huang, W.-D., Percival Zhang, Y.H., 2011. Analysis of biofuels production from sugar based on three criteria: thermodynamics, bioenergetics, and product separation. Energy Environ. Sci. 4 (3), 784–792.

Jespen, T., 2016. In: ATEX – Explosive Atmospheres Risk Assessment, Control and Compliance. Springer International Publishing, Switzerland. https://doi.org/10.1007/978-3-319-31367-2.

Kim, M.S., Fitriana, H.N., Kim, T.W., Kang, S.G., Jeon, S.G., Chung, S.H., Park, G.W., Na, J.G., 2017. Enhancement of the hydrogen productivity in microbial water gas shift reaction by *Thermococcus onnurineus* NA1 using a pressurized bioreactor. Int. J. Hydrogen Energy. 42 (45), 27593–27599.

Knabben, I., Regestein, L., Marquering, F., Steinbusch, S., Lara, A.R., Büchs, J., 2010. High cell-density processes in batch mode of a genetically engineered *Escherichia coli* strain with minimized overflow metabolism using a pressurized bioreactor. J. Biotechnol. 150 (1), 73–79.

Knabben, I., Regestein, L., Schauf, J., Steinbusch, S., Büchs, J., 2011. Linear correlation between online capacitance and offline biomass measurement up to high cell densities in *Escherichia coli* fermentations in a pilot-scale pressurized bioreactor. J. Microbiol. Biotechnol. 21 (2), 204–211.

Knoll, A., Bartsch, S., Husemann, B., Engel, P., Schroer, K., Ribeiro, B., Stöckmann, C., Seletzky, J., Büchs, J., 2007. High cell density cultivation of recombinant yeasts and bacteria under non-pressurized and pressurized conditions in stirred tank bioreactors. J. Biotechnol. 132 (2), 167–179.

Knoll, A., Maier, B., Tscherrig, H., Büchs, J., 2005. The oxygen mass transfer, carbon dioxide inhibition, heat removal, and the energy and cost efficiencies of high pressure fermentation. In: Kragl, U. (Ed.), Technology Transfer in Biotechnology: From lab to Industry to Production. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 77–99.

Ko, C.W., Vega, J.L., Clausen, E.C., Gaddy, J.L., 1989. Effect of high pressure on a co-culture for the production of methane from coal synthesis gas. Chem. Eng. Commun. 77 (1), 155–169.

Kodama, T., Goto, E., Minoda, Y., 1976. Determination of dissolved hydrogen concentration and $[K_La]_{H2}$ in submerged culture vessels. Agric. Biol. Chem. 40 (12), 2373–2377.

Kopyscinski, J., Schildhauer, T.J., Biollaz, S.M.A., 2010. Production of synthetic natural gas (SNG) from coal and dry biomass – a technology review from 1950 to 2009. Fuel 89 (8), 1763–1783.

Kraemer, J.T., Bagley, D.M., 2006. Supersaturation of dissolved H_2 and CO_2 during fermentative hydrogen production with N_2 sparging. Biotechnol. Lett. 28 (18), 1485–1491.

Kundu, S., Premer, S.A., Hoy, J.A., Trent, J.T., Hargrove, M.S., 2003. Direct measurement of equilibrium constants for high-affinity hemoglobins. Biophys. J. 84 (6), 3931–3940.

Le Quéré, C., Andrew, R.M., Friedlingstein, P., Sitch, S., Hauck, J., Pongratz, J., Pickers, P.A., Korsbakken, J.I., Peters, G.P., Canadell, J.G., Arneth, A., Arora, V.K., Barbero, L., Bastos, A., Bopp, L., Chevallier, F., Chini, L.P., Ciais, P., Doney, S.C., Gkritzalis, T., Goll, D.S., Harris, I., Haverd, V., Hoffman, F.M., Hoppema, M., Houghton, R.A., Hurtt, G., Ilyina, T., Jain, A.K., Johannessen, T., Jones, C.D., Kato, E., Keeling, R.F., Goldewijk, K.K., Landschützer, P., Lefèvre, N., Lienert, S., Liu, Z., Lombardozzi, D., Metzl, N., Munro, D.R., Nabel, J.E.M.S., Nakaoka, S.I., Neill, C., Olsen, A., Ono, T., Patra, P., Peregon, A., Peters, W., Peylin, P., Pfeil, B., Pierrot, D., Poulter, B., Rehder, G., Resplandy, L., Robertson, E., Rocher, M., Rödenbeck, C., Schuster, U., Schwinger, J., Séférian, R., Skjelvan, I., Steinhoff, T., Sutton, A., Tans, P.P., Tian, H., Tilbrook, B., Tubiello, F.N., van der Laan-Luijkx, I.T., van der Werf, G.R., Viovy, N., Walker, A.P., Wiltshire, A.J., Wright, R., Zaehle, S., Zheng, B., 2018. Global carbon budget 2018. Earth Syst. Sci. Data 10 (4), 2141–2194.

Lemmer, A., Merkle, W., Baer, K., Graf, F., 2017. Effects of high-pressure anaerobic digestion up to 30 bar on pH-value, production kinetics and specific methane yield. Energy 138, 659–667.

Liew, F.M., Köke, M., Simpson, S.D., 2013. Gas fermentation for commercial biofuels production. In: Fang, Z. (Ed.), Liquid, Gaseous and Solid Biofuels – Conversion Techniques. Intechopen.

Lopes, M., Gomes, N., Mota, M., Belo, I., 2009. *Yarrowia lipolytica* growth under increased air pressure: influence on enzyme production. Appl. Biochem. Biotechnol. 159 (1), 46–53.

Lopes, M., Mota, M., Belo, I., 2013. Oxygen mass transfer rate in a pressurized lab-scale stirred bioreactor. Chem. Eng. Technol. 36 (10), 1779–1784.

Luo, L., van der Voet, E., Huppes, G., 2009. An energy analysis of ethanol from cellulosic feedstock–corn stover. Renew. Sustain. Energy Rev. 13 (8), 2003–2011.

Mac Dowell, N., Fennell, P.S., Shah, N., Maitland, G.C., 2017. The role of CO_2 capture and utilization in mitigating climate change. Nat. Clim. Change 7, 243.

Matsunaga, N., Kano, K., Maki, Y., Dobashi, T., 2009. Culture scale-up studies as seen from the viewpoint of oxygen supply and dissolved carbon dioxide stripping. J. Biosci. Bioeng. 107 (4), 412–418.

Mohammadi, M., Mohamed, A.R., Najafpour, G.D., Younesi, H., Uzir, M.H., 2014. Kinetic studies on fermentative production of biofuel from synthesis gas using *Clostridium ljungdahlii*. Sci. World J. 2014, 8.

Munasinghe, P.C., Khanal, S.K., 2010. Biomass-derived syngas fermentation into biofuels: opportunities and challenges. Bioresour. Technol. 101 (13), 5013–5022.

NFPA69, 2019. Standard on Explosion Prevention Systems. National Fire Protection Association (NFPA).
Oswald, F., Stoll, I.K., Zwick, M., Herbig, S., Sauer, J., Boukis, N., Neumann, A., 2018. Formic acid formation by *Clostridium ljungdahlii* at elevated pressures of carbon dioxide and hydrogen. Front. Bioeng. Biotechnol. 6 6-6.
Pattison, R.N., Swamy, J., Mendenhall, B., Hwang, C., Frohlich, B.T., 2000. Measurement and control of dissolved carbon dioxide in mammalian cell culture processes using an in situ fiber optic chemical sensor. Biotechnol. Prog. 16 (5), 769–774.
Pfromm, P.H., Amanor-Boadu, V., Nelson, R., Vadlani, P., Madl, R., 2010. Bio-butanol vs. bio-ethanol: a technical and economic assessment for corn and switchgrass fermented by yeast or Clostridium acetobutylicum. Biomass Bioenergy 34 (4), 515–524.
Phillips, J.R., Huhnke, R.L., Atiyeh, H.K., 2017. Syngas fermentation: a microbial conversion process of gaseous substrates to various products. Fermentation 3 (2), 28.
Pollock, D.C., 1997. Aerobic Long Vertical Shaft Bioreactors. 5650070.
Raju, K.S., 2011. Fluid Mechanics, Heat Transfer, and Mass Transfer: Chemical Engineering Practice. John Wiley & Sons, Hoboken, New Jersey.
Riggs, S.S., Heindel, T.J., 2006. Measuring carbon monoxide gas—liquid mass transfer in a stirred tank reactor for syngas fermentation. Biotechnol. Prog. 22 (3), 903–906.
Rittmann, S., Seifert, A., Herwig, C., 2015. Essential prerequisites for successful bioprocess development of biological CH_4 production from CO_2 and H_2. Crit. Rev. Biotechnol. 35 (2), 141–151.
Roger, M., Brown, F., Gabrielli, W., Sargent, F., 2018. Efficient hydrogen-dependent carbon dioxide reduction by *Escherichia coli*. Curr. Biol. 28 (1), 140–145.
Sander, S.P., Abbatt, J., Barker, J.R., Burkholder, J.B., Friedl, R.R., Golden, D.M., Huie, R.E., Kolb, C.E., Kurylo, M.J., Moortgat, G.K., Orkin, V.L., Wine, P.H., 2011. Chemical Kinetics and Photochemical Data for Use in Atmospheric Studies, Evaluation No. 17, JPL Publication 10-6. available at:. Jet Propulsion Laboratory, Pasadena. http://jpldataeval.jpl.nasa.gov.
Sittig, W., 1982. The present state of fermentation reactors. J. Chem. Technol. Biotechnol. 32 (1), 47–58.
Straathof, A.J.J., Wahl, S.A., Benjamin, K.R., Takors, R., Wierckx, N., Noorman, H.J., 2019. Grand research challenges for sustainable industrial biotechnology. Trends Biotechnol.
Strong, P.J., Kalyuzhnaya, M., Silverman, J., Clarke, W.P., 2016. A methanotroph-based biorefinery: potential scenarios for generating multiple products from a single fermentation. Bioresour. Technol. 215, 314–323.
Tervasmäki, P., Latva-Kokko, M., Taskila, S., Tanskanen, J., 2016. Mass transfer, gas holdup and cell cultivation studies in a bottom agitated draft tube reactor and multiple impeller Rushton turbine configuration. Chem. Eng. Sci. 155, 83–98.
Ullrich, T., Lindner, J., Bär, K., Mörs, F., Graf, F., Lemmer, A., 2018. Influence of operating pressure on the biological hydrogen methanation in trickle-bed reactors. Bioresour. Technol. 247, 7–13.
Ungerman, A.J., Heindel, T.J., 2007. Carbon monoxide mass transfer for syngas fermentation in a stirred tank reactor with dual impeller configurations. Biotechnol. Prog. 23 (3), 613–620.
van 't Riet, K., Tramper, J., 1991. Basic Bioreactor Design. Marcel Dekker Inc, New York.
Van Hecke, W., Kaur, G., De Wever, H., 2014. Advances in in-situ product recovery (ISPR) in whole cell biotechnology during the last decade. Biotechnol. Adv. 32 (7), 1245–1255.
Vega, J.L., Clausen, E.C., Gaddy, J.L., 1989. Study of gaseous substrate fermentations: carbon monoxide conversion to acetate. 1. Batch culture. Biotechnol. Bioeng. 34 (6), 774–784.
Wainaina, S., Horváth, I.S., Taherzadeh, M.J., 2018. Biochemicals from food waste and recalcitrant biomass via syngas fermentation: a review. Bioresour. Technol. 248, 113–121.
Warneck, P., Williams, J., 2012. The Atmospheric Chemist's Companion: Numerical Data for Use in the Atmospheric Sciences. Springer Verlag.
Weber, S., Schaepe, S., Freyer, S., Kopf, M.-H., Dietzsch, C., 2018. Impact of nozzle operation on mass transfer in jet aerated loop reactors. Characterization and comparison to an aerated stirred tank reactor. Eng. Life Sci. 18 (8), 579–588.
Wendlandt, K.-D., Jechorek, M., Brühl, E., 1993. The influence of pressure on the growth of methanotrophic bacteria. Acta Biotechnol. 13 (2), 111–115.
Weston, R.F., 1982. Technology Assessment of the Deep Shaft Biological Reactor.
Winter, J.D., Hohman, J. 2018. Methods and Apparatus for Recycling Tail Gas in Syngas Fermentation to Ethanol. US20180141000 A1.
Winterbone, D.E., Turan, A., 2015. Chapter 10: Thermodynamics of combustion. Advanced Thermodynamics for Engineers, second ed. Butterworth-Heinemann, Oxford.
Yasin, M., Jeong, Y., Park, S., Jeong, J., Lee, E.Y., Lovitt, R.W., Kim, B.H., Lee, J., Chang, I.S., 2015. Microbial synthesis gas utilization and ways to resolve kinetic and mass-transfer limitations. Bioresour. Technol. 177, 361–374.
Yeo, H., An, J., Reid, R., Rittmann, B.E., Lee, H.-S., 2015. Contribution of liquid/gas mass-transfer limitations to dissolved methane oversaturation in anaerobic treatment of dilute wastewater. Environ. Sci. Technol. 49 (17), 10366–10372.
Zabetakis, M.G., 1965. Flammability characteristics of combustible gase sand vapors. B.o.M. Department of the Interior, Vol. Bulletin 626, pp. 121.