| **Title** | The dairy biorefinery: Integrating treatment processes for cheese whey valorisation |
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| **Author(s)** | Asunis, Fabiano; De Gioannis, Giorgia; Dessì, Paolo; Isipato, Marco; Lens, Piet N.L; Muntoni, Aldo; Polettini, Alessandra; Pomi, Raffaella; Rossi, Andreina; Spiga, Daniela |
| **Publication Date** | 2020-08-28 |
| **Publication Information** | Asunis, Fabiano, De Gioannis, Giorgia, Dessì, Paolo, Isipato, Marco, Lens, Piet N. L., Muntoni, Aldo, Polettini, Alessandra, Pomi, Raffaella, Rossi, Andreina, Spiga, Daniela. (2020). The dairy biorefinery: Integrating treatment processes for cheese whey valorisation. Journal of Environmental Management, 276, 111240. doi:https://doi.org/10.1016/j.jenvman.2020.111240 |
| **Publisher** | Elsevier |
| **Link to publisher's version** | https://doi.org/10.1016/j.jenvman.2020.111240 |
| **Item record** | http://hdl.handle.net/10379/16461 |
| **DOI** | http://dx.doi.org/10.1016/j.jenvman.2020.111240 |

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The dairy biorefinery: Integrating treatment processes for cheese whey valorisation

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Abstract

With an estimated worldwide production of 190 billion kg per year, and due to its high organic load, cheese whey represents a huge opportunity for bioenergy and biochemicals production. Several physical, chemical and biological processes have been proposed to valorise cheese whey by producing biofuels (methane, hydrogen, and ethanol), electric energy, and/or chemical commodities (carboxylic acids, proteins, and biopolymers). A biorefinery concept, in which several value-added products are obtained from cheese whey through a cascade of biotechnological processes, is an opportunity for increasing the product spectrum of dairy industries while allowing for a sustainable management of the residual streams and reducing disposal costs for the final residues. This review critically analyses the different treatment options available for energy and materials recovery from cheese whey, their combinations and perspectives for implementation. Thus, instead of focusing on a specific valorisation platform, in the present review the most relevant aspects of each strategy are analysed to support the integration of different routes, in order to identify the most appropriate treatment train.

Keywords: Anaerobic digestion; Bioplastic; Circular economy; Dairy industry; Fermentation; Microbial electrochemical technology

Highlights

• Cheese whey is an outstanding feedstock for bioenergy and biochemical production
• Integrating treatment processes is key for cheese whey managing and valorisation
• Dark fermentation will be the core of the future dairy biorefineries
• VFA production and extraction will benefit of favourable market conditions
• Bioelectrochemical systems can be applied for tertiary treatment and CO₂ recycling
| Abbreviation | Full Form |
|--------------|-----------|
| AD           | Anaerobic digestion |
| AFBR         | Anaerobic fluidized bed reactors |
| AS           | Activated sludge |
| ASTBR        | Anaerobic structured-bed reactor |
| BMP          | Biomethane potential |
| BOD          | Biological oxygen demand |
| CE           | Coulombic efficiency |
| COD          | Chemical oxygen demand |
| CSTR         | Continuous stirred tank reactor |
| CW           | Cheese whey |
| DF           | Dark fermentation |
| FBR          | Fluidized bed reactor |
| FCW          | Fermented cheese whey |
| GDL          | Gas diffusion layer |
| HAc          | Acetic acid |
| HBu          | Butyric acid |
| HCa          | Caproic acid |
| HPr          | Propionic acid |
| HRT          | Hydraulic retention time |
| MEC          | Microbial electrolysis cell |
| MET          | Microbial electrochemical technology |
| MFC          | Microbial fuel cell |
| MMC          | Mixed microbial cultures |
| OLR          | Organic loading rate |
| PABR         | Periodic anaerobic baffled reactor |
| PBR          | Packed bed reactor |
| PEM          | Proton exchange membrane |
| PHA          | Polyhydroxyalkanoates |
| PHB          | Polyhydroxybutyrate |
| PHV          | Polyhydroxyvalerate |
| PLA          | Polylactic acid |
| PTFE         | Polytetrafluoroethylene |
| SBR          | Sequence batch reactor |
| TOC          | Total organic carbon |
| TRL          | Technology readiness level |
| UASB         | Upflow anaerobic sludge blanket |
| UFAF         | Up-flow anaerobic filter |
| VFAs         | Volatile fatty acids |
| VS           | Volatile solids |
| VSS          | Volatile suspended solids |
1. Introduction

Fossil fuels, which include coal, oil and natural gas, supply about 80% of the world total energy (International Energy Agency, 2017). These non-renewable sources provide electricity, heat, and transportation fuels, as well as supply raw materials and platform chemicals for the manufacturing of a wide range of products. Fossil fuels and industrial processes, on the other hand, account for 65% of the global greenhouse emissions to the atmosphere (IPCC, 2014). In 2015, the increased awareness of climate change issues led to the Paris agreement, in which 195 countries committed themselves to reducing their greenhouse gases emissions by 40% by 2030. Achieving such ambitious target requires a shift from fossil fuels to renewable sources for energy and chemicals production. Among renewable resources, biodegradable waste streams are a promising source of green energy and (bio)-chemicals.

Recently, the awareness of the unexploited potential of waste has increasingly driven the industrial sector to implement integrated systems, the so-called biorefineries, to produce not only biofuels, but also a wide spectrum of bio-based chemicals from organic by-products and waste streams (Cherubini, 2010; Mohan et al., 2016; Moscoviz et al., 2018). Such a transition is fully in line with the efforts the EU is making towards a circular bioeconomy (European Commission, 2018) as well as its commitment to becoming the first climate-neutral area in the world by 2050 (European Commission, 2020).

Among the business areas producing waste and wastewater potentially suitable for biorefineries, the dairy sector plays a significant role in the EU economy and many dairy companies are making tremendous efforts to meet the European environmental protection measures and targets (European Dairy Association, 2019). In the EU, a total of 170 billion kg of milk was produced in 2017, 93% of which was converted into dairy products including cheese (37%), butter (30%), cream (13%), fresh milk (11%), acidified milk (4%), milk powder (2%), and other minor products (Eurostat, 2018). Dairy industries produce an average of 2.5 L of wastewater per L of processed milk, as well as about 9–10 L of cheese whey (CW) per kg of cheese produced, resulting in approximately 400 billion L of wastewater per year (Eurostat, 2018). Dairy effluents, and CW in particular, are characterized by a high organic load representing, at the same time, a severe hazard for the environment and a huge opportunity for bioenergy and biochemicals production (Ahmad et al., 2019).

Currently, a large share of dairy effluents, including about 50% of the CW produced worldwide, is discharged into the environment without any treatment (Bosco et al., 2018; Slavov, 2017). Among the available treatment options, traditional activated sludge processing is economically not sustainable due to the high organic load of dairy effluents, and the consequent huge quantities of both oxygen required for aeration and excess sludge produced. Activated sludge treatment consumes an average of 900 kWh(e) d⁻¹, including 100 kWh(e) d⁻¹ for dewatering (using a filter press) and 800 kWh(e) d⁻¹ for aerobic stabilization, accounting for 30% of the total energy required for aerobic treatment of dairy effluents (Dąbrowski et al., 2017). Thermo-catalytic treatment has been also proposed for CW valorisation (Remón et al., 2016), but the high temperature required (450-600°C) and the production of solids make such a process expensive.

Bioprocesses such as anaerobic digestion or fermentation, as well as biological production of polymers and bioelectrochemical systems, have the advantage of coupling the treatment of dairy effluents with the production of bioenergy and/or chemical commodities at mild temperature conditions, typically within the range 20-55°C. Though promising, none of the mentioned options alone represents the ultimate solution for CW treatment, since the energy/chemicals production rates are too small for an economically sustainable scale-up. The implementation of an integrated process, including a combination of physical, chemical and biological processes, is therefore the key for a cost-effective and efficient valorisation of dairy effluents. The aim of this review is to summarize and critically discuss the progress made towards the implementation of biorefineries for energy and...
chemicals recovery in dairy industries, with a specific focus on CW. This review provides an insight into the most promising biorefinery models for resource recovery from CW, based on critical considerations on the potentials, prospects and limitation of the available options, to support the creation of an innovative and scalable industrial chain.

2. Cheese whey characterisation
Cheese production usually generates three different waste streams, including CW and secondary CW (from cheese and ricotta/cottage cheese production, respectively), and dairy wastewater (from washing of tanks and equipment) (Fig. 1).

![Cheese production process and effluents generated.](image)

CW is a green-yellow by-product of cheese and casein powder production, with an estimated worldwide production of about 190 billion kg year⁻¹. Due to its high organic and volumetric load, CW is considered the main polluting waste stream in dairy industries (Ryan and Walsh, 2016; Slavov, 2017). The CW composition depends on the cheese production process, on the milk source (sheep, goat, cow or buffalo), as well as on the quantity of water, detergents and sanitizing agents used (Demirel et al., 2005; Shete and Shinkar, 2013). In general, CW accounts for 85–95% of the milk volume, retains 55% of milk nutrients (vitamins and minerals) and 20% of milk proteins, and is characterized by COD and BOD concentrations of 50–102 and 27–60 g L⁻¹, respectively, more than 90% of which is made up of lactose (Carvalho et al., 2013; Ryan and Walsh, 2016). CW also contains sodium, potassium and calcium salts (0.46–10%), and has a pH of 3.8–6.5 depending on the whey type (acidic or sweet) and a low alkalinity (Prazeres et al., 2012). More details can be found in the comprehensive review by Carvalho et al. (2013).

CW can be processed to obtain cottage, curd or ricotta cheese, generating secondary CW as a by-product. Secondary CW retains about 60% of the dry matter contained in CW, and is characterised by a lower protein concentration and a higher salinity because of the second flocculation step and addition of salts in the manufacturing process (Carvalho et al., 2013). Dairy wastewater contains similar compounds as CW, but at lower concentrations. Another waste stream, whey permeate, can be obtained as a by-product of protein recovery from CW by ultrafiltration. CW permeate retains about 80% of the lactose contained in the original CW, has a high salinity and low concentration of proteins and fats, depending on the efficiency of the ultrafiltration process (Bosco et al., 2018).
3. Biotechnologies for bioenergy and biochemicals production from cheese whey

3.1 Anaerobic digestion

Anaerobic digestion (AD) is a well-established process to exploit the energy content of CW (De Gioannis et al., 2017; Traversi et al., 2013). However, due to the high organic load and low alkalinity of CW, AD may result in the accumulation of volatile fatty acids (VFAs). This leads to acidification and inhibition of the methanogenic activity, adversely affecting the CH₄ yield and process stability (De Gioannis et al., 2014; Escalante-Hernández et al., 2017; Hagen et al., 2014; Prazeres et al., 2012; Traversi et al., 2013). As a consequence, relatively low biomethane potentials (BMPs) ranging from 270 to 600 L CH₄ kg⁻¹ VS have been reported for AD of CW under mesophilic conditions (35–37 °C) (Escalante et al., 2018; Labatut et al., 2011; Vivekanand et al., 2018), implying that long HRT values (> 5 days) are required in continuously operated AD systems to prevent process instability (Table 1).

In AD, alkali addition or dilution is generally required to mitigate acidification, but both strategies increase the operational costs, and/or the volumes to be treated. A more economic option is co-digesting CW with substrates characterised by a high buffering capacity, such as sewage sludge (Carrieri et al., 1993), dairy manure (Kavacik and Topaloglu, 2010; Rico et al., 2015; Vivekanand et al., 2018), poultry manure (Gelegenis et al., 2007), cattle slurry (Comino et al., 2012), or fish ensilage (Vivekanand et al., 2018), although literature results are controversial. Furthermore, when digesting CW in combination with pathogenic waste streams, health and safety issues may hamper the use of the digestate as a fertilizer. Labatut et al. (2011) reported that co-digestion of CW with dairy manure, at 10:90 or 25:75 ratios, resulted in a lower CH₄ yield (238–252 L kg⁻¹ VS) than with raw CW (424 L kg⁻¹ VS). Vivekanand et al. (2018) also reported a decreased CH₄ yield when blending CW with cattle manure, fish ensilage, or both. On the other hand, Comino et al. (2012) obtained the highest CH₄ yield of 343 L CH₄ kg⁻¹ VS co-digesting 50% CW and 50% cattle slurry at 35°C and 42 d HRT. Hublin and Zelić (2013) reported a maximum CH₄ yield of 15.7 L L⁻¹ reactor by co-digestion of CW and cow manure at 55°C, with an optimum mixing ratio of 10:90, and addition of 5 g NaHCO₃ L⁻¹ for alkalinity control.

In co-digestion, not only the maximum CH₄ yield, but also the process stability, may be affected by the mixing ratio of substrates. When co-digesting CW and diluted poultry manure in a continuous-flow stirred tank reactor (CSTR), Gelegenis et al. (2007) reported an increasing CH₄ yield for mixtures with CW concentrations up to 35%, but the process became unstable when the CW fraction exceeded 50% (based on VS). In contrast, when co-digesting CW and the screened liquid fraction of dairy manure, Rico et al. (2015) reported an increase in the CH₄ yield from 161 to 187 L CH₂ kg⁻¹ COD when increasing the CW proportion from 15 to 85% at 35°C and 15.6 d HRT, with no instability concerns.

A two-stage process, where hydrolysis-acetogenesis and methanogenesis are carried out in two separate reactors, is another strategy to avoid process instability (Fernández et al., 2015) and enhance COD removal and CH₄ production (Bertin et al., 2013; Yazar et al., 2016), although with increased capital and operational costs. Another advantage of two-stage AD is the possibility of operating the methanogenic reactor at lower HRTs (< 5 d) compared to the single-stage process. More innovative systems involve a two-step process in which H₂ is recovered in the acidogenic reactor (see Section 3.2), which can be used as a fuel, either alone or in combination with CH₄ (hytane). Yilmazer and Yenigün (1999) and Saddoud et al. (2007) reported a biogas yield of 550 and 300 L kg⁻¹ COD_removed, respectively, with COD removal efficiencies above 90%, in a two-stage AD process with 4 d HRT in the methanogenic reactor. With a HRT of 4.4 d, Antonopoulou et al. (2008) obtained a CH₄ yield of 75.6 L CH₄ d⁻¹ (or 383 L CH₄ kg⁻¹ COD_removed), notably higher than that obtained by Venetsanoeas et al. (2009) with a CSTR at 20 d HRT (1 L CH₄ d⁻¹ or 134 L CH₄ kg⁻¹ COD_removed). Fernández et al. (2015) compared single- and two-stage AD of CW under thermophilic conditions (55 °C), reporting for the former a maximum yield of 349 L CH₄ kg⁻¹ COD_removed at 8.3 d HRT, whereas for the latter an inhibition
effect at a HRT < 12.5 d. This suggests that two-stage processes may not be optimal for thermophilic AD.
| Process | Substrate | Inoculum | Reactor* | T (°C) | pH     | HRT (d) | Methane production | COD removal (%) | Reference |
|---------|-----------|----------|----------|--------|--------|---------|--------------------|-----------------|-----------|
| One-stage | 50% CW 50% cattle slurry (v/v) | None | CSTR | 35 | 6.9–8.7 | 42 | 187 L CH₄ kg⁻¹ COD<sub>feed</sub> | 82 | Comino et al. (2012) |
| CW | Granular anaerobic cultures | UASB | 35 | n.a. c | 2–4.95 | 424 L CH₄ kg⁻¹ COD<sub>feed</sub> | 95–97 | Erguder et al. (2001) |
| 2 L CW + 1 kg Dairy manure + 1 L water | None | CSTR | 34 | 6.5–7.5 | 5 | 0.9 L CH₄ L⁻¹ d⁻¹ | n.a. c | Kavacik and Topaloglu (2010) |
| 85% CW 15% liquid fraction of dairy manure (v/v) | None | CSTR | 35 | 6.4–7.1 | 15.6 | 392 L CH₄ kg⁻¹ VS<sub>feed</sub> | n.a. c | Rico et al. (2015) |
| Two-stage | CW | None | PABR | 35 | 8.0 | 4.4 | 383 L CH₄ kg⁻¹ COD<sub>removed</sub><sup>b</sup> | 94 | Antonopoulou et al. (2008) |
| CW | None | SBR | 55 | n.a. c | 25 | 349 L CH₄ kg⁻¹ COD<sub>feed</sub><sup>b</sup> | n.a. c | Fernández et al. (2015) |
| Diluted CW | Anaerobic sludge | CSTR | 37 | 7.3–8.5 | 4 | 300 L biogas kg⁻¹ COD<sub>removed</sub><sup>b</sup> | 99 | (Saddoud et al., 2007) |
| CW | Anaerobic sludge | CSTR | 35 | 7.7 | 20 | 134 L CH₄ kg⁻¹ COD<sub>feed</sub><sup>b</sup> | 95 | Venetsaneas et al. (2009) |
| CW | Anaerobic sludge | UFAF | n.a. c | n.a. c | 4 | 550 L biogas kg⁻¹ COD<sub>removed</sub><sup>b</sup> | 90 | Yilmazer and Yenigün (1999) |

*a CSTR, continuously stirred tank reactor; PABR, periodic anaerobic baffled reactor; SBR, sequence batch reactor; UASB, upflow anaerobic sludge blanket; UFAF, up-flow anaerobic filter. b For two-stage processes, it refers to the COD of the acidogenic effluent rather than the initial substrate. c Not available.
3.2 Fermentative processes
3.2.1 Dark fermentation
Dark fermentation (DF) is a promising option for CW valorisation due to its high carbohydrate content, which can be converted to biohydrogen and VFAs (Akhlaghi et al., 2019; Asunis et al., 2019; De Gioannis et al., 2014). In the absence of CW pre-treatments and external inoculum, DF of CW mainly involves three steps, including (i) lactose hydrolysis into glucose and galactose, (ii) conversion of monomeric sugars into lactate by homolactic microorganisms, such as Lactobacillus, and (iii) conversion of lactate into H₂ and VFAs by fermentative microorganisms, such as Clostridium (Fig. 2).

Figure 2. Most common lactose fermentation pathways from CW indigenous microorganisms.

A theoretical maximum yield of 8 mol H₂ mol⁻¹ lactose can be obtained by DF, if acetate is the only soluble reaction product. However, DF is sensitive to substrate composition, organic loading rate, inoculum type and pre-treatment, reactor type and operation regime, temperature, pH, hydraulic and cell residence time (Akhlaghi et al., 2017). This results in actual H₂ yields between 1 and 4 mol H₂ mol⁻¹ lactose, accompanied by the production of a mixture of VFAs, mainly acetic, propionic, and butyric acid (Table 2).

Inocula of different origin, including pure cultures, anaerobic sludge, activated sludge, and compost, with or without pre-treatment, have been used in DF of CW (Table 2). However, some studies relied exclusively on the indigenous biomass of CW (Akhlaghi et al., 2017; Antonopoulou et al., 2008; De Gioannis et al., 2014; Montecchio et al., 2018; Venetsaneas et al., 2009), reporting H₂ yields as high as those obtained using external inocula. De Gioannis et al. (2014) compared batch DF of CW with pre-treated activated sludge and without an external inoculum, obtaining similar yields of 160–170 L H₂ kg⁻¹ TOC at pH 6–6.5. To achieve a faster start-up, pre-fermented CW can be used as the inoculum in large-scale plants in place of methanogenic inocula that require chemical or thermal pre-treatment to inhibit methanogenesis. However, Perna et al. (2013) obtained a yield of only 0.7 mol H₂ mol⁻¹ lactose (40 L H₂ kg⁻¹ COD_lactose) when using fermented CW as the inoculum in a packed bed reactor (PBR), with a relatively high production of acetate (10 g L⁻¹), which suggests the onset of H₂-consuming homoacetogenic pathways. Among pure cultures, both Clostridium saccharoperbutyacetonicum (Ferchichi et al., 2005) and Escherichia coli (Rosales-Colunga et al.,
Various CW-based substrates have been used for DF. Raw CW is easily degraded by indigenous bacteria, even at 4 °C, making storage difficult (Tribst et al., 2019). Thus, many studies used rehydrated CW powder (Table 2), adjusting the water content to restore the original content of raw CW. Addition of bicarbonate was proposed to prevent acidification (Perna et al., 2013), although codigestion with an alkaline substrate, such as manure can also be done (Ghimire et al., 2017). Dilution of CW can prevent acidification of the fermentation broth, thus increasing the H2 yields, but also drastically increasing the already huge amount of wastewater to be treated. Furthermore, dilution of CW would reduce the concentration of micro and macro nutrients available to the microorganisms. Yields above 3 mol H2 mol⁻¹ lactose, and acetate and isobutyrate concentrations above 5 g L⁻¹ were obtained by supplementing CW with micronutrients such as calcium (Azbar et al., 2009a), whereas yields below 2 mol H2 mol⁻¹ lactose (117 L H2 kg⁻¹ CODlactose), as well as low VFA concentrations were obtained from deproteinated or ultrafiltered CW (Fernández et al., 2015; Montecchio et al., 2018). Since this was likely due to the lack of nitrogen to support microbial growth, excessive diluting or including a protein recovery step before DF of CW is not recommended.

Bioreactors with high biomass retention, such as fluidized bed reactors (FBR) (Ferreira Rosa et al., 2014a, 2014b; Ottaviano et al., 2017), or sequencing batch reactors (SBR) (Fernández et al., 2015) can be advantageous for DF of CW, compared to CSTRs, as much lower HRTs can be applied (Table 2). However, too low HRTs, below 4 h, may decrease the H2 yield (Ferreira Rosa et al., 2014a). Among the operating parameters, pH has the strongest impact on both H2 yield and VFA production. An optimum pH between 5.5 and 6.5 for H2 production from CW under mesophilic conditions was identified in several studies (Asunis et al., 2019; Azbar et al., 2009b; Davila-Vazquez et al., 2008; De Gioannis et al., 2014; Ferchichi et al., 2005). However, an optimum pH of 4.5 was reported under thermophilic conditions by Azbar et al. (2009b). Ottaviano et al. (2017) obtained a remarkable yield of 3.67 mol H2 mol⁻¹ lactose (214 L H2 kg⁻¹ CODlactose) from diluted CW in a thermophilic (55 °C) FBR operated at pH 4–4.5 and HRT of 4 h.

Besides H2 production, the pH affects the yield and spectrum of VFAs, so that the operating conditions of DF reactors can be adjusted to target specific VFAs (or a mixture of them), in combination or as an alternative to H2. The production of butyrate and acetate from CW occurs at pH 5–6 (Table 2), whereas propionate production prevails over the butyrate pathway at pH 7–7.5 (Asunis et al., 2019). Generally, a total of 0.5–0.6 g VFA g⁻¹ CW is obtained in the pH range 5–7 (Asunis et al., 2019; Colombo et al., 2016; Duque et al., 2014; Gouveia et al., 2017). CW fermentation at pH < 5 can promote the accumulation of lactic acid (Asunis et al., 2019; Gouveia et al., 2017). Interestingly, in continuous reactors, the type and concentration of VFAs produced at a given pH appear to be the same irrespective of the starting conditions (Gouveia et al., 2017). This suggests that the fermentation pH may be adjusted during continuous operation to target specific metabolic products. In-line VFA extraction can be implemented during DF of CW to improve process stability and allow a continuous recovery of VFAs (Dessì et al., 2020).
| Substrate                  | Inoculum                      | Reactor  | T (°C) | pH     | OLR       | HRT (h) | H2 yield          | VFA<sup>b</sup> production | Reference                  |
|----------------------------|-------------------------------|----------|--------|--------|-----------|---------|------------------|----------------------------|----------------------------|
| Cheese whey                | None                          | CSTR     | 35     | 5.2    | (at steady state) | 24      | 41 L H₂ kg⁻¹ COD | HAc: 9.4 g L⁻¹ HBu 7.2 g L⁻¹ | Antonopoulou et al. (2008) |
| Cheese whey powder         | Pre-fermented cheese whey     | ASTBR    | 25     | 5.13   | (average) | 24      | 82 L H₂ kg⁻¹ COD<sub>lactose</sub> | HAc: 5.0 g L⁻¹ HBu: 3.0 g L⁻¹ | Blanco et al. (2019)      |
| Cheese whey                | Acidogenic sludge             | UASB     | 30     | 5      | (average) | 10–20 g<sub>COD</sub> L⁻¹ d⁻¹ | 24–12 | 122 mL H₂ L⁻¹ d⁻¹ | n.a.                       | Castelló et al. (2009)    |
| Cheese whey                | Kitchen waste compost         | CSTR     | 30     | 5.5    | (controlled) | 24      | 52 L H₂ kg⁻¹ COD<sub>lactose</sub> | HAc: 3.0 g L⁻¹ HBu: 1.6 g L⁻¹ | (Castelló et al., 2018)   |
| Cheese whey powder         | Pretreated anaerobic granular sludge | CSTR     | 37     | 5.9    | (controlled) | 92.4–184.4 g<sub>COD</sub> L⁻¹ d⁻¹ | 4–10 | 163 L H₂ kg⁻¹ COD<sub>lactose</sub> | HAc: 4.5 g L⁻¹ HP: 6.2 g L⁻¹ HBu: 10.6 g L⁻¹ | Davila-Vazquez et al. (2009) |
| Cheese whey                | Pretreated digested sludge    | UASB     | 35     | 5.0    | (controlled) | 20–80 g<sub>COD</sub> L⁻¹ d⁻¹ | 24      | 40 L H₂ kg⁻¹ COD | HAc: 9.1 g L⁻¹ HBu: 13.5 g L⁻¹ | Dessì et al. (2020)        |
| Deproteneized cheese whey  | None                          | SBR      | 35     | 4.5–5.5 (pulse controlled) | 12.7–25.3 g<sub>COD</sub> L⁻¹ d⁻¹ | 1.5–3.0 | 12 L H₂ kg⁻¹ COD | HAc: 2.3–3.4 g L⁻¹ HP: 1.0 g L⁻¹ HBu: 0.5 g L⁻¹ | Fernández et al. (2015)   |

<sup>a</sup> H₂ yield values express the capacity of the system to produce hydrogen, measured in kg H₂ kg⁻¹ COD.

<sup>b</sup> VFA production indicates the amount of volatile fatty acids produced, measured in g L⁻¹.

<sup>c</sup> pH values are provided for steady-state operation.

<sup>d</sup> OLR values are measured in g COD L⁻¹ d⁻¹.
| Treatment Description                                      | Reactor Type | pH | Temperature (°C) | COD removal (g COD L\(^{-1}\) d\(^{-1}\)) | H\(_2\) Production (L H\(_2\) kg\(^{-1}\) COD\(_{lactose}\)) | Lactic acid (mol lactose g\(^{-1}\) lactose) | Butyric acid (mol lactose g\(^{-1}\) lactose) | Propionic acid (mol lactose g\(^{-1}\) lactose) | References                                           |
|------------------------------------------------------------|--------------|----|------------------|--------------------------------------------|------------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|------------------------------------------------|
| Cheese whey powder supplemented with medium                | AFBR         | 30 | 4–4.5 (controlled) | 30–120                                     | 1–4                                          | 77 L H\(_2\) kg\(^{-1}\) COD\(_{lactose}\) | HAc: 0.2 mol mol\(^{-1}\) lactose            | HBu: 0.4 mol mol\(^{-1}\) lactose            | Ferreira Rosa et al. (2014a)                   |
| Cheese whey powder supplemented with medium                | AFBR         | 30 | 4–4.5 (controlled) | n.a.                                       | 6                                            | 74 L H\(_2\) kg\(^{-1}\) COD\(_{lactose}\) | n.a.                                          | n.a.                                          | Ferreira Rosa et al. (2014b)                   |
| Cheese whey + buffalo manure                               | CSTR         | 55 | 4.8–5 (at steady state) | 0.7–2.6 g\(_{VS}\) L\(^{-1}\) d\(^{-1}\) | 192–288                                      | 131.8 L H\(_2\) kg\(^{-1}\) VS            | HAc: 4.2 mmol g\(^{-1}\) VS                 | HBu: 14.1 mmol g\(^{-1}\) VS                 | Ghimire et al. (2017)                          |
| CW powder                                                  | CSTR         | 30 | 4.5–7 (controlled) | 15 g\(_{COD}\) L\(^{-1}\) d\(^{-1}\)      | 1                                            | n.a.                                          | HAc: 3.5–12 g L\(^{-1}\)                    | HBu: 2–3 g L\(^{-1}\)                        | Gouveia et al. (2017)                          |
| Ultrafiltered cheese whey                                  | None         | 36 | 5.5 (controlled)   | n.a.                                       | 6–12                                         | 78–107 L H\(_2\) kg\(^{-1}\) COD\(_{lactose}\) | n.a.                                          | n.a.                                          | Montecchio et al. (2018)                      |
| CW powder solution                                          | AFBR         | 55 | 4–4.5 (controlled) | 235.2                                     | 4                                            | 214 L H\(_2\) kg\(^{-1}\) COD\(_{lactose}\) | HAc: 0.5 g L\(^{-1}\)                      | HBu: 0.7 g L\(^{-1}\)                        | Ottaviano et al. (2017)                        |
| Cheese whey powder supplemented with sodium bicarbonate    | PBR          | 30 | 5.6 (controlled)   | 22–37                                      | 24                                           | 39 L H\(_2\) kg\(^{-1}\) COD\(_{lactose}\) | HAc: 10 g L\(^{-1}\)                     | HBu: 2 g L\(^{-1}\)                         | Perna et al. (2013)                           |
| Type of wastewater | Source of wastewater | Reactor | pH | COD Consumption | COD Consumed | ACID Consumed | Authors |
|--------------------|----------------------|---------|-----|----------------|--------------|----------------|---------|
| Cheese whey        | None                 | CSTR    | 5–6 (controlled) | 60 g COD L⁻¹ d⁻¹ | 48 L H₂ kg⁻¹ d⁻¹ | HAc: 9.2 g L⁻¹ | Venetsaneas et al. (2009) |
| Dry whey permeate  | Anaerobic sludge     | CSTR    | Uncontrolled condition | 14 g COD L⁻¹ d⁻¹ | 52 L H₂ kg⁻¹ COD | HAc: 2.1 g L⁻¹ | Yang et al. (2007) |

AFBR, anaerobic fluidized bed reactor; ASTBR, anaerobic structured-bed reactor; CSTR, continuously stirred tank reactor; PBR, packed bed reactor; SBR, sequence batch reactor; UASB, upflow anaerobic sludge blanket reactor. a HAc, acetic acid; HBu, butyric acid; HCa, caproic acid; HPr, propionic acid. b Not available. d pH adjusted to 5.5 whenever it dropped to 4.5.
3.2.2 Lactate fermentation

Lactic acid is characterised by an increasing global demand from 0.7 Mt in 2013 to 1.9 Mt in 2020 (grandviewresearch.com), mainly as the building block for polyactic acid (PLA) production, but also for application in food, pharmaceutical and chemical industries. Most commercial lactic acid is currently produced by bacterial fermentation of corn, sugarcane, molasses and other crops. CW has been proposed as an alternative feedstock to avoid competition with food production.

Lactic acid is mainly produced by bacteria belonging to the genera *Lactobacillus*, *Lactococcus*, *Streptococcus*, *Bacillus*, and *Enterococcus* (Miller et al., 2011; Ryan and Walsh, 2016). Lactose is hydrolysed by enzymes such as β-galactosidase, produced by lactic acid bacteria, into glucose and galactose, and then converted into lactic acid via homolactic fermentation (Fig. 2), resulting in a yield of 4 mol lactate mol\(^{-1}\) lactose. However, ethanol or acetate can be produced along with lactate via heterolactic fermentation (Castillo Martinez et al., 2013; Sikora et al., 2013), halving the lactate yield.

The type of fermentation pathway and the specific lactate isomer (L- or D-) produced depends on the lactic acid bacteria involved and the operating conditions, in particular pH (Mazzoli et al., 2014; Miller et al., 2011; Xu et al., 2018).

Since lactic acid bacteria have limited potential to biosynthesize amino-acids, the presence of a nitrogen source is crucial for their growth (Mazzoli et al., 2014; Prazeres et al., 2012). Due to its high protein content, raw CW can be used as for lactate production, although enzymatic hydrolysis of lactose might be necessary. Xu et al. (2018) reported a D-lactic acid productivity of 2.4 g L\(^{-1}\) d\(^{-1}\) from hydrolysed CW powder by *Lactobacillus bulgaricus* in non-sterile conditions and without the addition of extra nutrients, which was further enhanced by the addition of 9 g L\(^{-1}\) yeast extract. The yield can be further improved by continuous extraction of the lactic acid produced, since its accumulation inhibits the biomass activity. Taleghani et al. (2018) reported a lactic acid production rate of 6.1 g L\(^{-1}\) h\(^{-1}\) in a fermentative reactor with an integrated membrane extraction system, as opposed to 3.4 g L\(^{-1}\) h\(^{-1}\) obtained in the control reactor without membrane extraction.

3.2.3 Ethanol fermentation

Bioethanol is considered one of the most promising candidates for replacing fossil fuels, and thus its global demand is constantly increasing (marketsandmarkets.com). CW fermentation into ethanol is currently hardly competitive with the established processes that use sugarcane, corn starch or lignocellulosic biomass as raw materials (Guimarães et al., 2010). Solventogenesis from CW has been attempted with yeasts such as *Saccharomyces cerevisiae* (Staniszewski et al., 2007), but low ethanol yields were obtained due to the low lactose conversion and product inhibition. Conversely, the *Kluyveromyces marxianus* yeast was shown to hydrolyse lactose, form a biofilm and tolerate ethanol, and is thus a potential candidate for CW conversion into bioethanol (Joshi et al., 2011; Lane and Morrissey, 2010). Continuous fermentation is potentially superior to batch processes, as it results in a higher ethanol production while reducing the fermentation time (Gabardo et al., 2014). Several strategies have been proposed to retain the microorganisms into the bioreactor, including cell immobilization (Dahiya and Vij, 2012), cell recycle (Santos et al., 2016) and membrane retention (Wei et al., 2014). Christensen et al. (2011) obtained continuous ethanol production from CW, with a rate of 2.5–4.5 g L\(^{-1}\) h\(^{-1}\), using a pure culture of *K. marxianus* immobilized in Ca-alginate.

The ethanol yield strictly depends on the operating parameters such as substrate concentration, pH and temperature (Table 3). Using a continuous FBR with Ca-alginate immobilized-cells, Gabardo et al. (2014) obtained the highest ethanol productivity of 6.0 g L\(^{-1}\) h\(^{-1}\) from CW permeate at a concentration of 150 g L\(^{-1}\) although the highest ethanol yield was obtained at 90 g L\(^{-1}\). Dragone et al. (2011) reported that a lactose concentration of 200 g L\(^{-1}\) and a temperature of 35 °C were optimal for ethanol production (81 g L\(^{-1}\) in 44 h) from CW powder by *K. fragilis*. Using the response surface methodology, Diniz et al. (2014) reported that temperatures between 33.3 and 38.5 °C, pH between
4.7 and 5.7, lactose concentrations between 50 and 108 g L\(^{-1}\) and biomass concentrations between 2.4 and 3.3 (optical density at 600 nm) are optimal for ethanol production from CW by \textit{K. marxianus}, with yields above 90% of the theoretical value.

### Table 3. Batch and continuous bioethanol fermentation from CW-based substrates using \textit{Kluyveromyces marxianus}

| Substrate               | Substrate concentration (g lactose L\(^{-1}\)) | Reactor                      | T (°C) | Operating conditions          | Ethanol production | Reference                      |
|-------------------------|-----------------------------------------------|-------------------------------|--------|-------------------------------|--------------------|--------------------------------|
| Cheese whey             | 46.8                                          | Continuous fluidized-bed bioreactor (alginate-immobilized cells) | 32     | Dilution rate: 0.2 h\(^{-1}\) | 4.5 g L\(^{-1}\) h\(^{-1}\) | Christensen et al. (2011)      |
| Cheese whey powder      | 150                                           | Batch flask                   | 35     | pH: 4.5                       | 43.7 g L\(^{-1}\)  | Das et al. (2016)              |
| Cheese whey permeate    | 150                                           | Continuous fluidized-bed bioreactor (alginate-immobilized cells) | 30     | Dilution rate 0.3 h\(^{-1}\) | 6.0 g L\(^{-1}\) h\(^{-1}\) | Gabardo et al. (2014)          |
| Cheese whey             | 48                                            | Fed-batch reactor             | 30     | Uncontrolled condition        | 8.0 g L\(^{-1}\)  | Hadiyanto et al. (2014)        |
| Cheese whey             | 43.6                                          | Batch reactor                 | 28     | Uncontrolled condition        | 17 g L\(^{-1}\)   | Zoppellari and Bardi (2013)    |

#### 3.3 Biopolymers

CW fermentation products, mainly VFAs, can be used as building blocks for biopolymer production (Colombo et al., 2016; Duque et al., 2014; Gouveia et al., 2017; Ryan and Walsh, 2016). Biopolymers such as polylactic acid (PLA) and polyhydroxyalkanoates (PHA) are a bio-based, biodegradable alternative to petroleum-based plastics, and their market size is expected to increase from 2.11 Mt in 2018 to 2.63 Mt in 2023 (European Bioplastics, 2018).

#### 3.3.1 PLA

PLA is a versatile biopolymer used in a wide range of industrial sectors, such as food packaging, textile, agriculture, electronics, transportation as well as in the biomedical field. PLA is currently the largest compostable synthetic plastic produced worldwide and its production is projected to increase up to 0.6 Mtons year\(^{-1}\) in 2025 (IEA Bioenergy Task42, 2012). However, the high costs of the building block used for PLA production, mostly lactic acid from microbial corn starch fermentation, hinders full exploitation of its potential. This may be fostered by optimized lactate production from residual organic materials (including CW), as outlined in section 3.2.2.

#### 3.3.2 PHA

PHAs are polyesters produced from organic substrates by various microorganisms, which accumulate them inside the cell for energy storage purposes. PHA production from CW has been reported from microorganisms able to synthesize polymers from lactose, such as \textit{Thermus thermophilus} (Pantazaki et al., 2009), \textit{Pseudomonas hydrogenovora} (Koller et al., 2008), and \textit{Bacillus megaterium} (Das et al., 2018) or engineered \textit{Cupriavidus necator} (Povolo et al., 2010). Although higher PHA accumulation...
can be attained with pure cultures, mixed microbial communities can produce PHAs from complex and cheaper substrates, such as dairy biowaste, and do not require sterilisation. PHA-producing microorganisms are selected and enriched by alternating short feast (presence of carbon) and long famine (absence of carbon) regimes (Reis et al., 2003). Despite nutrient addition being commonly reported in the literature for selecting high-capacity PHA-storing microbial communities (Oliveira et al., 2018), the high N and P contained in CW might reduce, or even eliminate, the need for an external nutrient supply (Colombo et al., 2016).

PHA production from fermented CW by mixed cultures resulted in storage yields of 0.7–0.8 mol PHA mol\(^{-1}\) VFA, with a PHA content of 65–75% (Table 4). The PHA composition (polyhydroxybutyrate, PHB, or polyhydroxyvalerate, PHV) depends on the carboxylic acid present in the CW fermentate: the higher the concentration of acetate and butyrate, the higher the PHB fraction, whereas high concentrations of propionate result in PHV accumulation. PHV fractions up to 40% have been reported from fermented CW (Table 4). Recently, fermented CW has also been used as the substrate for PHA production by phototrophic mixed cultures, using light intensities comparable with those typical of sunny regions, yielding 0.6 g COD\(_{PHA}\) g\(^{-1}\) COD\(_{VFA}\) and PHA contents of 20–25% (Fradinho et al., 2019).
Table 4. PHA production from CW derived fermentates using mixed microbial communities.

| Substrate                  | Fermentation yield (g COD g⁻¹ COD) | Fermentation products (PHA precursors) HLa/HAc/HBu/HPr/HVa/HCa/EtOH* (% Organic Acid as COD) | Max PHA content (g PHA kg⁻¹ VSS) | PHA storage yield (g CODPHA g⁻¹ COD) | Productivity (g PHA L⁻¹ d⁻¹) | Polymer composition (%HB:%HV)* | Reference               |
|----------------------------|------------------------------------|--------------------------------------------------------------------------------|----------------------------------|-------------------------------------|-------------------------------|-------------------------------|---------------------------|
| Cheese whey                | 0.4                                | 58/16/26/0/0/0/0                                                              | 659 ± 46                         | 0.6 ± 0.0                           | 10.9 ± 0.8                    | 100:0                         | Colombo et al. (2016)     |
| Sterilised cheese whey     | 0.6 ± 0.1                          | 6/58/13/19/4/0/0                                                              | 814 ± 57                         | 0.7 ± 0.1                           | 28.2 ± 2.0                    | 60:40                         | Colombo et al. (2016)     |
| Cheese whey                | 0.7 ± 0.2                          | 1/58/22/6/4/0/9                                                               | 650                              | 0.7 ± 0.1                           | 13.4                          | 81:19                         | Duque et al. (2014)       |
| Cheese whey                | 0.6–0.7                            | 16/45/23/14/6/0/5                                                             | 300                              | 0.6                                 | n.a.                         | 88:12                         | Fradinho et al. (2019)   |
| Sweet cheese whey powder   | 0.64 ± 0.05                        | 0/46/44/4/5/0/0                                                               | 430                              | 0.85 ± 0.12                         | 0.20                          | 89:11                         | Oliveira et al. (2018)    |
| Filtered whey permeate     | 0.5                                | 0/44/50/2/1/3/0                                                               | 530–630                          | 0.41–0.63                           | n.a.                         | 85:15                         | Valentino et al. (2015)   |

* HLa, Lactic acid; HAc, Acetic acid; HBu, Butyric acid; HPr, Propionic acid; HVa, Valeric acid; HCa, Caproic acid; EtOH, Ethanol. ** HB, hydroxybutyrate; HV, hydroxyvalerate. c Not available.
3.4 Bioelectrochemical systems

Microbial electrolysis technologies (METs) can be implemented to recover the energy contained in CW as electricity in microbial fuel cells (MFCs) (Table 5) or as H₂ in microbial electrolysis cells (MECs) (Table 6). In MFCs, specific microorganisms, namely exoelectrogens, oxidise the organic substrate and transfer the electrons to an anode electrode. Electrons then flow to a cathode electrode through an external circuit, producing electric power, and combine with an electron acceptor, such as oxygen, closing the circuit (Logan et al., 2006). In MECs, the protons resulting from substrate oxidation are the final electron acceptors, producing H₂, if enough energy is provided as input current to drive the reaction (Rago et al., 2016).

Antonopoulou et al. (2010) were the first to test CW, diluted to 0.73 g COD L⁻¹ and amended with nutrients, as the substrate for MFC, yielding a maximum power density of 18.4 mW m⁻² and a coulombic efficiency (CE) of only 1.9%, due to the presence of undesired microorganisms in CW. To address this issue, Stamatelatou et al. (2011) filter-sterilised CW prior to dilution, obtaining power densities up to 40 mW m⁻². The effect of COD concentration (0.35–6.7 g L⁻¹) was investigated by Tremouli et al. (2013), who reported the highest power production (46 mW m⁻²) and CE (11.3%) from diluted CW at 6.7 g COD L⁻¹, with a 95% COD removal efficiency. Ghasemi et al. (2017) compared CW (50 g lactose L⁻¹) and concentrated CW (100 g lactose L⁻¹) as the substrate in a two-chamber MFC, reporting a higher power density from raw CW (288 mW m⁻²) than from concentrated CW (188 mW m⁻²).

Since carboxylic acids are favourable substrates for exoelectrogenic microorganisms, Wenzel et al. (2017) proposed fermented CW as the substrate for a single-chamber MFC, obtaining a dramatically higher power production (439 mW m⁻²) than a control reactor fed with raw CW (0.34 mW m⁻²). Indeed, exoelectrogenic microorganisms were enriched in the MFC fed with fermented CW, due to the high concentration of VFAs, whereas the high lactose and lactate concentrations of the raw CW resulted in a prevalence of fermentative microorganisms.

Both CW and fermented CW, as well as digestate from AD of CW, have been used as the substrates for H₂ production in MEC (Table 6). Diluted CW (2 g COD L⁻¹), amended with a phosphate buffer solution, was used as the substrate for H₂ production in a MEC, resulting in a production of 0.8 L H₂ L⁻¹ d⁻¹, with energy recoveries up to 71% (Rago et al., 2016). Moreno et al. (2015) combined DF and MEC for two-stage H₂ production from CW, obtaining 0.5 L H₂ L⁻¹ d⁻¹ from filtered, eight-times diluted CW fermentate, supplemented with acetate, in a MEC. However, a rapid decrease in the MEC performance occurred, probably due to the lack of nutrients in the diluted substrate. Rivera et al. (2017) compared raw, fermented and digested CW for H₂ production in a single-chamber MEC. H₂ production yields of 61 and 48 mL H₂ g⁻¹ CODremoved were obtained from digested and fermented CW, with a CE of 93 and 32%, respectively, whereas a negligible H₂ production (CE 1%) was obtained from raw CW (Rivera et al., 2017). However, besides their composition, the different initial organic load (19.9, 1.6 and 4.0 g L⁻¹ COD for raw, fermented and digested CW, respectively) may have affected the results. Fermented CW, rather than raw CW, should thus be used as the substrate for energy recovery in METs. METs can also be seen as a final polishing step after the AD process. Filtration and dilution should be avoided, since they may result in a lack of nutrients which can hinder the electrogenic activity.
Table 5. Electricity production from dairy wastewater or CW-based substrates in MFCs.

| Substrate                  | Inoculum             | Reactor characteristics | T (°C) | HRT (h) | Maximum power production | CE (%) | Reference                  |
|----------------------------|----------------------|-------------------------|--------|---------|--------------------------|--------|---------------------------|
| Cheese whey                | Anaerobic sludge     | H-type (310 mL) Anode: Teflon treated carbon filter paper Cathode: Carbon cloth with Pt Membrane: PEM | 35.5   | Batch   | 18.4 mW m^{-2}           | 1.9    | Antonopoulou et al. (2010) |
| Cheese whey powder         | Anaerobic sludge     | Single chamber (125 mL) Anode: Carbon cloth Cathode: Carbon cloth with GDL Membrane: None | 35     | Batch   | n.a.\(^{b}\)            | 0.8–2.0 | Colombo et al. (2017)      |
| Synthetic dairy wastewater | Municipal wastewater | Dual chamber (480 mL) Anode: Untreated carbon paper Cathode: Untreated carbon paper Membrane: PEM | 22     | 8.4     | 90 mW m^{-2}            | 10.5 ± 10 | Faria et al. (2017)       |
| Whey                       | Anaerobic sludge     | Cube-shaped dual chamber (420 mL) Anode: Carbon paper Cathode: Carbon paper with Pt Membrane: PEM | 30     | Batch   | 188.8 mW m^{-2}         | 26     | Ghasemi et al. (2017)      |
| Concentrated whey          | Anaerobic sludge     | Cube-shaped dual chamber (420 mL) Anode: Carbon paper Cathode: Carbon paper with Pt Membrane: PEM | 30     | Batch   | 288.1 mW m^{-2}         | 15     | Ghasemi et al. (2017)      |
| Cheese whey (diluted 10 times) | Digested sludge   | Tubular dual chamber (500 mL) Anode: Carbon fibre brush Cathode: Carbon cloth and activated carbon powder Membrane: PEM | 21     | Batch   | 0.4 W m^{-3}            | 3.9 ± 1.7 (based on total COD) | Kelly and He (2014) |
| Cheese whey                | MFC enriched community | Single chamber (28 mL) Anode: Graphite fibre brush Cathode: Graphite fibre cloth with PTFE and Pt Membrane: None | n.a.\(^{b}\) | Batch | 3.46 mW m^{-2} | 49 ± 8 | Rago et al. (2016)        |
| Cheese whey                | Anaerobic sludge     | Dual chamber (310 mL) Anode: Carbon paper | 30     | Batch   | 46 mW m^{-2}           | 5.5–11.3 | Tremouli et al. (2013)   |
| Source of wastewater | Anaerobic consortia | Anode | Cathode | Membrane | Cell configuration | Batch duration (days) | Power output (mW m\(^{-2}\)) | COD removal (\%) | Reference |
|----------------------|---------------------|-------|---------|----------|-------------------|----------------------|-----------------------------|----------------|-----------|
| Dairy wastewater     | Anaerobic mixed consortia | Graphite plate | Graphite plate | PEM | Single chamber (550 mL) | 29 | Batch | 6.71 mW m\(^{-2}\) | 4.3–14.2 | Venkata Mohan et al. (2010) |
| Cheese whey          | Planktonic MFC community | Graphite felt | Carbon cloth with Nafion and Pt | PEM | Single chamber air cathode (25 mL) | 30 | Batch | 0.34 mW m\(^{-2}\) | 14 | Wenzel et al. (2017) |
| Fermented cheese whey | Planktonic MFC community | Graphite felt | Carbon cloth with Nafion and Pt | PEM | Single chamber air cathode (25 mL) | 30 | Batch | 439 mW m\(^{-2}\) | 24 | Wenzel et al. (2017) |

\(^a\) GDL, gas diffusion layer; PEM, proton exchange membrane; PTFE, polytetrafluoroethylene. \(^b\) Not available.
| Substrate | Inoculum | Reactor characteristics | T (°C) | HRT (h) | Maximum hydrogen production | CE (%) | Reference |
|-----------|----------|-------------------------|--------|---------|----------------------------|---------|-----------|
| Ricotta cheese production wastewater (spotted) | Anaerobic sediments | Cylindrical double chamber (400 mL) Anode: Carbon felt Cathode: Pt-Ir (90%:10%) mesh Membrane: AEM | 37 | Batch | 0.023 L H₂ L⁻¹ d⁻¹ | 75 (estimated) | Marone et al. (2017) |
| Cheese whey fermentate (diluted) | Planktonic MEC community | Continuous flow membrane-less (50 mL) Anode: Carbon felt Cathode: GDL with Ni nanoparticles Membrane: None | 25 | 10 | MEC failure | n.a. b | Moreno et al. (2015) |
| Fermented cheese whey and acetate | Planktonic MEC community | Continuous flow membrane-less (50 mL) Anode: Carbon felt Cathode: GDL with Ni nanoparticles Membrane: None | 25 | 10 | MEC failure | n.a. b | Moreno et al. (2015) |
| Fermented cheese whey and salts | Planktonic MEC community | Continuous flow membrane-less (50 mL) Anode: Carbon felt Cathode: GDL with Ni nanoparticles Membrane: None | 25 | 10 | 0.5 L H₂ L⁻¹ d⁻¹ | n.a. b | Moreno et al. (2015) |
| Fermented cheese whey, salts and acetate | Planktonic MEC community | Continuous flow membrane-less (50 mL) Anode: Carbon felt Cathode: GDL with Ni nanoparticles Membrane: None | 25 | 10 | 0.5 L H₂ L⁻¹ d⁻¹ | n.a. b | Moreno et al. (2015) |
| Cheese whey | MFC enriched community | Single chamber (28 mL) Anode: Graphite fibre brush Cathode: Graphite fibre cloth with PTFE and Pt | n.a. b | Batch | 0.8 L H₂ L⁻¹ d⁻¹ | 120c | Rago et al. (2016) |
| Cheese whey  | Anaerobic sludge | Single chamber (300 mL) Anode: Graphite felt Cathode: Stainless steel mesh Membrane: None | 32 | Batch | MEC failure | l | Rivera et al. (2017) |
|--------------|------------------|-------------------------------------------------------------------------------------|----|-------|------------|--|---------------------|
| Cheese whey digestate | Anaerobic sludge | Single chamber (300 mL) Anode: Graphite felt Cathode: Stainless steel mesh Membrane: None | 32 | Batch | 0.16 L $H_2$ L$^{-1}$ d$^{-1}$ | 31.8 | Rivera et al. (2017) |
| Cheese whey fermentate | Anaerobic sludge | Single chamber (300 mL) Anode: Graphite felt Cathode: Stainless steel mesh Membrane: None | 32 | Batch | 0.06 L $H_2$ L$^{-1}$ d$^{-1}$ | 92.7 | Rivera et al. (2017) |

*a* AEM, anion exchange membrane; GDL, gas diffusion layer; PEM, proton exchange membrane; PTFE, polytetrafluoroethylene. *b* Not available. *c* Due to $H_2$ recycling by homoacetogenic bacteria.
3.5 Integrated processes

A combination of treatment processes to produce an array of valuable products is required for the implementation of a zero-waste-approaching dairy biorefinery (Morais and Bogel-Lukasik, 2013). Combinations of physical, chemical and biological processes (Table 7; Fig. 3) can be implemented. Protein recovery, e.g. by isoelectric or thermocalcic precipitation or nano- or ultrafiltration, may be applied prior to the biological treatment (Bosco et al., 2018; Chen et al., 2016), although negatively affecting the availability of nutrients for the subsequent biological processes.

DF was applied as the first step in most of the studies combining biological treatments for CW valorisation (Table 7), standing as the core of the biorefinery. Several biological downstream processes can be then applied for further valorisation of the DF effluent. Among these, AD is the most applied process on fermented dairy effluent (Bosco et al., 2018; Chen et al., 2016). Combination of DF and AD typically leads to high COD removal efficiencies (> 80%), due to the final conversion of VFAs to methane. However, considering the higher pH and HRT required for AD than for DF, pH buffering and high reactor volumes are commonly required for the AD step. Furthermore, the high concentrations (up to 20–30 g L⁻¹) of VFAs produced in DF, as well as the low buffering capacity of CW, may inhibit the AD process (Bertin et al., 2013).

The DF effluent can also be used for further H₂ production, although an external source of energy e.g. in the form of light (photofermentation) or electricity (MEC) is required to overcome the thermodynamic constraints. Rai et al. (2012) combined dark and photofermentation of diluted CW (10 g L⁻¹ lactose) using immobilized pure cultures, obtaining a yield of 199 L H₂ kg⁻¹ COD, although the COD removal efficiency was low (36%). The application of METs to fermented CW could be favoured by the low ohmic resistance associated to the typically high salinity of CW. A remarkably high yield of over 800 L H₂ g⁻¹ COD was obtained from deproteinized ricotta CW, diluted to 3 g COD L⁻¹, by combining DF and MEC, with a 63% COD removal efficiency (Marone et al., 2017).

Since DF effluents are rich in VFAs, DF can also be coupled to PHA production. Colombo et al. (2019) proposed an integrated two-step bioprocess aimed at simultaneously recovery of H₂ (2.4–5.1 L H₂ L⁻¹ d⁻¹) and PHB (274–268 g kg⁻¹ CODₘᵢₙ) from deproteinized CW. In order to produce PHAs at high concentrations, a VFA extraction and concentration step, e.g. via electrodialysis, can be included in the integrated process. Domingos et al. (2018) applied electrodialysis to fermented CW obtaining a concentrated VFA stream (up to 63 g L⁻¹ from the original concentration of 13 g L⁻¹), from which a PHA yield of 0.60 g PHA g⁻¹ VFAs was obtained, comparable to the yields reported from VFA-containing synthetic solutions.
Table 7. Combination of at least two chemical or biological processes for energy or resource recovery from CW-based substrates.

| Processa                                      | Substrate                              | Inoculum                             | Temperature (°C) | HRT                     | Output                          | COD removal (%) | Reference                     |
|------------------------------------------------|----------------------------------------|--------------------------------------|------------------|-------------------------|---------------------------------|-----------------|--------------------------------|
| Dark fermentation (CSTR, 3 L) + methanogenesis (PABR, 15 L) | Cheese whey (61 g COD L⁻¹)            | Indigenous microflora                 | 35 (both processes) | 1 day (fermentation) 4.4 days (methanogenesis) | Hydrogen: 41 L kg⁻¹ COD, Methane: 383 L kg⁻¹ COD | 94              | Antonopoulou et al., 2008 |
| Acidogenesis + methanogenesis (two-stage concentric reactor, 190 mL for acidogenic reactor, 790 mL for methanogenic reactor) | Cheese whey + cattle manure (1:1; 35.2 g COD L⁻¹) | Methanogenic sludge (both processes) | 35 (both processes) | 5 days (acidogenesis) 20 days (methanogenesis) | Methane: 258 kg⁻¹ VS | 83              | Bertin et al., 2013 |
| Thermocalcic precipitation, ultrafiltration + PHA production | Cheese whey (50 g COD L⁻¹)            | Dairy plant activated sludge enriched on acetate (bioplastic production) | 45–55 (thermocalcic precipitation) Not reported for PHA production | 24–48 hours (bioplastic production) | Proteins: 80 g L⁻¹, PHA: 0.75–0.90 g L⁻¹ | n.a.² | Bosco et al., 2018 |
| Isoelectric precipitation, nanofiltration + dark fermentation (UASB, 7.4 L) | Milk powder (3.0 g COD L⁻¹)            | Sewage sludge                        | 25 (precipitation and nanofiltration) 37 (fermentation) | 12 hours (fermentation) | Proteins: 192 g kg⁻¹ COD, Reusable water, Hydrogen (not quantified), VFAs: 2.2 g L⁻¹ | n.a. | Chen et al., 2016 |
| Enzymatic hydrolysis step with β-galactosidase + Dark fermentation (CSTR, 4 L) + PHA production (SBR, 1 L; Fed-batch assay, 0.5 L) | Second cheese whey; concentrated cheese whey permeate; OLR: 8, 11, 15 g sugars L⁻¹ d⁻¹ (Dark) | Termally pretreated anaerobic digested sludge (dark fermentation); activated sludge (PHA selection step) | 55 (Dark fermentation) 25 (PHA production) | 2 days (Dark fermentation) 1 day (PHA selection step) | Hydrogen: 163–233 L kg⁻¹ COD, PHA: 268–274 g kg⁻¹ COD | n.a. | Colombo et al. (2019) |
| Process Description                                                                 | Feedstock (COD concentration) | Microorganism (PHA production) | Temperature (FERM) | Temperature (METH) | VFA (FERM) | PHA (FERM) | Hydrogen (FERM) | Methane (FERM) | Current (MEC) | COD Reduction (%) | Authors (Year) |
|-----------------------------------------------------------------------------------|-------------------------------|-------------------------------|---------------------|-------------------|------------|------------|----------------|----------------|--------------|------------------|----------------|
| Dark fermentation (CSTR, 3 L) + methanogenesis (UASB, 1 L)                       | Cheese whey powder (45.5 g COD L⁻¹) | Anaerobic granular sludge    | 37 (fermentation)   | 25–30 (methanogenesis) | 6 hours (both processes) | Hydrogen: 137 L kg⁻¹ COD, Methane: 250 L kg⁻¹ COD | 92               | Cota-Navarro et al., 2011 |
| Dark fermentation (anaerobic column biofilm packed reactor, 1 L) + electrodialysis + PHA production (3 L) | Cheese whey powder (28 g COD L⁻¹) | Acidogenic sludge (dark fermentation) | *Cupravidus necator* (PHA production) | 37 (fermentation) | 6 hours (fermentation) | VFA: 13 g L⁻¹ (60 g L⁻¹ after electrodialysis), PHA: 500 g kg⁻¹ COD | n.a.             | (Domingos et al., 2018) |
| Dark fermentation (batch, 2 L) + methanogenesis (batch, 2 L)                      | Dairy wastewater (11.2 g COD L⁻¹) | *Enterobacter aerogens* (dark fermentation) | 30 (fermentation) | 35 (methanogenesis) | 13 hours (fermentation) | 7 days (methanogenesis) | Hydrogen: 105 L kg⁻¹ COD, Methane: 190 L kg⁻¹ COD | 64               | Kothari et al., 2017 |
| Dark fermentation (batch, 500 mL) + biocatalyzed electrolysis (MEC, 400 mL)      | Deproteinized ricotta cheese whey (57.8 g COD L⁻¹) diluted to 3 g COD L⁻¹ | Anaerobic digested sludge (dark fermentation) | 37 (both processes) | 48 hours (fermentation) | 14 days (MEC) | Hydrogen: 95.1 + 714.7 L kg⁻¹ COD, Electric current: 7.46 A m² | 63               | Marone et al., 2017 |
| Dark fermentation (batch, 250 mL) + biocatalyzed electrolysis (MEC, 50 mL)       | Cheese whey (fermentation; 122 g COD L⁻¹) | Digested sludge (dark fermentation) | 35 (fermentation) | 25 (MEC) | not reported for fermentation | 10 hours (MEC) | Hydrogen: 94.2 L kg⁻¹ VS, Electric current: 10 mA | 82               | Moreno et al., 2015 |
| Process Description                                                                 | Diluent and Conditions                                      | Organisms                                                                 | Time Frames                                                                                       | Hydrogen Yield | Methane Yield | References                  |
|-----------------------------------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------|---------------|-----------------------------|
| Dark fermentation (batch, 100 mL) + photofermentation (batch, 100 mL)             | Diluted cheese whey (10 g lactose L⁻¹)                      | Enterobacter aerogens (dark fermentation) Rhodopseudomonas (photofermentation) | 30 (dark fermentation) 34 (photofermentation) 84 hours (both processes)                           | 199 L kg⁻¹ COD |               | Rai et al., 2012            |
| Dark fermentation (CSTR, 0.5 L) + methanogenesis (CSTR, 3 L)                      | Cheese whey (60.5 g COD L⁻¹) Indigenous microflora           | 35 (both processes) 1 day (fermentation) 20 days (methanogenesis)         | Hydrogen: 48 L kg⁻¹ COD, Methane: 31 L kg⁻¹ COD                                                  | 95             |               | Venetsaneas et al., 2009    |

a CSTR, continuously stirred tank reactor; MEC, microbial electrolysis cell; PABR, periodic anaerobic baffled reactor; UASB, upflow anaerobic sludge blanket.
b Not available.
4. Full-scale applications

Despite the potential for CW valorisation, the implementation of integrated, multiple treatment schemes is still limited. Existing full-scale plants are mostly AD plants producing biogas to cover part of the dairy industry energy needs. More complex processing sequences would require, to be economically viable, a plant size that often exceeds the potential of small- to medium-size dairy industries.

Among the full-scale applications in Europe, the company Valbio provides AD systems to dairy industries through its patented technology Valbio Methcore®, based on UASB technology. Valbio has commissioned more than 10 full-scale plants for dairy companies mostly located in France, Canada and Bulgaria, treating 0.3–10.5 million L of CW year⁻¹ with an energy production of 0.3–3.5 MWh year⁻¹ and COD removal efficiency higher than 90% (Valbio.com). Dairygold Co-Operative Society Limited recently installed the world’s largest above ground anaerobic digester (ADI/BVF®, Evoqua) in Ireland. The Dairygold low-rate anaerobic digester was designed to treat 5,500 m³ d⁻¹ wastewater containing powdered milk, cheese waste and CW (Evoqua.com), meeting the discharge limits and contributing to satisfy the dairy industry energy needs. First Milk’s Lake District creamery (Cumbria, UK) was the first dairy industry to feed upgraded biomethane generated from cheese process residues, to the national gas grid in 2016 (Clearfleau.com). The CSTR was designed to treat 1,650 m³ d⁻¹ of dairy wastewater and whey producing 5.4 MWh of bioenergy (Clearfleau.com).

Industrial-scale bioethanol plants are in operation in Ireland, New Zealand, USA, Denmark and Germany. The Carbery Group factory, the largest single cheese-producing facility in Ireland, started the operation of an industrial-scale whey-to-ethanol plant in 1978 (Carbery, 2018). In addition to cheese, the company produces high-quality ethanol, accounting for 50% of Ireland’s industrial ethanol needs for beverage, pharmaceutical and food industries (Carbery, 2018). Since 2005, the company has also been supplying ethanol to petrol companies in Ireland. Anchor Ethanol operates three whey-to-ethanol plants in New Zealand, using deproteinated whey, concentrated from 4 to 8% lactose and fermented for 24 h by Kluyveromyces sp., as feedstock attaining an ethanol titre of 4%, successively concentrated to various ethanol grades by distillation (Guimarães et al., 2010).

5. Future perspectives

CW is an abundant substrate, easily available and at low-cost, but at the same time needs proper management. Many of the processes applicable for biotechnological valorisation of CW are currently at a medium/high TRL and some integration schemes between these processes are promising. However, some critical aspects need further investigation in order to make the application of the biorefinery concept to the dairy supply chain fully feasible.

CW displays very variable characteristics depending on both the livestock originating the milk, and the geographical context. The milk and the resulting CW production is characterized by a strong seasonal variability in terms of quantity and composition, that follows the lactation period. The seasonal variation could be managed by freezing CW during peak production, and subsequently thawing on demand. A better solution could be based on assessing the availability of CW in the area under concern, and promoting consortia to ensure an even CW supply throughout the year (Ubando et al., 2020).

The optimal combination of the biotechnological processes strictly depends on CW availability and characteristics, as well as legislation and market demand. Pre-treatment of CW might simplify downstream valorisation. For example, a protein extraction step, already well developed at the industrial scale (TRL 9), could be integrated into the process chain, fostered by the relatively high value of whey proteins (6–22 € kg⁻¹) (Table 8), but addition of nutrients may be required for the subsequent biological treatment steps. Similarly, the need for post-treatments aimed at removing
undesired impurities or extracting the compounds of interest must be carefully evaluated, being an important cost item in the entire process scheme.

Among the soluble products of CW fermentation, acetic acid and ethanol are currently characterised by low economic values, but relatively big market sizes, whereas butyric and lactic acid have smaller, but rapidly growing (15–19% compound annual growth rate, CAGR) markets (Table 8). It should be noted, however, that obtaining individual marketable products from the mixture of carboxylic acids typical obtained from CW fermentate would require highly selective and efficient extraction systems, currently available at TRL 2–3.

As an alternative, the carboxylic acids mixture can be used as a feedstock for biopolymer production, and in particular for PHA production. The technology for PHA production from biowaste is still in the development stage (TRL 3–5). However, the high value of PHAs (2.8–3.2 € kg⁻¹), and the rapidly increasing bioplastics market (16.5% CAGR) could make biological PHA production profitable in the near future. Specific tailored solutions can be investigated within the same dairy industry supply chain, e.g. using the PHA produced from CW as a sustainable packaging for dairy products.

METs are still under development (TRL 3–4). Due to the high cost, and the typically low power density and H₂ yield achievable through MFC and MEC, respectively, their use for treatment of undiluted CW fermentate, characterised by high carboxylic acid concentration, does not appear profitable. In particular, MFCs can hardly compete with technologies such as solar energy and wind power for electricity production at a large scale, unless many cells are stacked together (Gajda et al., 2018). However, due to the high COD removal efficiencies, both MFCs and MECs can be seen as a polishing step prior to effluent disposal. Among bioelectrochemical systems, microbial electrosynthesis (MES) can be a key player in limiting the carbon emissions by recycling the CO₂ produced by other bioprocesses, and from the dairy industry itself, and converting it to carboxylic acids for downstream applications (Batlle-Vilanova et al., 2016; Vassilev et al., 2018). This would close the loop in the carbon recovery chain towards a zero-waste-approaching biorefinery.
**Figure 3.** Integrated treatment processes for cheese whey valorisation according to the circular economy principle. Symbols and colours are represented according to Cherubini et al. (2009). The dashed parts represent optional processes, not essential for the following treatment steps.

**Table 8.** Treatment processes applicable in a biorefinery concept (Fig. 3), including their technological readiness level (TRL), and market value and market size (converted into € from original data in USD) of the main products obtained.

| Process                                   | TRLa | Products            | Indicative price (€ kg⁻¹) | Global market size (€) | Global market forecast (€) | CAGRb (%) | References                               |
|-------------------------------------------|-----|---------------------|---------------------------|------------------------|----------------------------|-----------|------------------------------------------|
| Protein recovery                          | 9   | Functional proteins | 6.4–22.0                  | 3.9 x 10⁹ (2017)       | 5.3 x 10⁹ (2022)           | 6.3       | Marketsandmarkets.com                    |
| Dark fermentation                         | 4–5 | Hydrogen            | 0.9–7.3                   | 124.4 x 10⁹ (2018)     | 183.4 x 10⁹ (2025)         | 8.0       | Marketsandmarkets.com                    |
| VFA extraction from fermentation broth    | 2–3 | Acetic acid         | 0.4–0.7                   | 8.8 x 10⁸ (2015)       | 12.2 x 10⁸ (2022)          | 4.8       | Grandviewre.com                          |
|                                           |     | Butyric acid        | 1.4–1.6                   | 114.8 x 10⁶ (2014)     | 218.1 x 10⁶ (2020)         | 15.1      | Marketsandmarkets.com                    |
|                                           |     | Propionic acid      | 1.8–2.3                   | 1.2 x 10⁹ (2014)       | 1.4 x 10⁹ (2020)           | 2.8       | Grandviewre.com                          |
| Lactic acid fermentation                  | 8   | Lactic acid         | 0.9                       | 1.9 x 10⁹ (2015)       | 3.5 x 10⁹ (2020)           | 18.6      | Marketsandmarkets.com                    |
| Alcohol fermentation                      | 9   | Bioethanol          | 0.6–1.4                   | 48.5 x 10⁹ (2016)      | 63.5 x 10⁹ (2022)          | 5.3       | Marketsandmarkets.com                    |
| Polymerisation                            | 9   | PLA                 | 2.0                       | 5.5 x 10⁹ (2017)       | 13.8 x 10⁹ (2023)          | 16.5      | Marketsandmarkets.com                    |
| Biological biopolymer production          | 3–5 | PHA                 | 2.8–3.2                   |                         |                            |           | Marketsandmarkets.com                    |
| Microbial fuel cell                       | 3–4 | Renewable electric power | 48.9c                   | 5 x 10³ TWh (2018)     | 7 x 10³ TWh (2023)          | 13.1      | International Energy Agency, IEA         |
| Microbial electrolysis cell               | 3–4 | Hydrogen            | 0.9–7.3                   | 124.7 x 10⁹ (2018)     | 183.3 x 10⁹ (2025)         | 5.7       | Marketsandmarkets.com                    |
| Anaerobic digestion                       | 9   | Biogas              | 0.4–0.7                   | 1.4 x 10⁹ (2017)       | 2.4 x 10⁹ (2025)           | 7.1       | Transparencymarketresearch.com           |
|                                           |     | Fertiliser          | 0.6d                      | 5.6 x 10⁹ (2019) c     | 8.5 x 10⁹ (2024)           | 6.8       | Globenewswire.com                        |
| Microbial electrosynthesis                | 2–3 | Acetic acid         | 0.4–0.7                   | 8.8 x 10⁹ (2015)       | 12.2 x 10⁹ (2022)          | 4.8       | Grandviewre.com                          |
|                                           |     | Butyric acid        | 1.4–1.6                   | 114.8 x 10⁶ (2014)     | 218.1 x 10⁶ (2020)         | 15.1      | Marketsandmarkets.com                    |
|                                           |     | Caproic acid        | 1.5                       | 9.2 x 10⁹ (2018)       | 11.5 x 10⁹ (2024)          | 3.2       | Marketwatch.com                          |

a Technology readiness level; b Compound annual growth rate; c €/MWh, average price in EU; d €/m³; e Data from compost global market.

**Conclusions**
Cheese whey is an outstanding resource for production of green energy and platform chemical compounds, but currently its potential is not fully exploited. In this review, the most promising biotechnologies for cheese whey valorisation were compared, and the strong and weak points of each one were critically analysed. Due to its simple and efficient application on raw CW, the current and potential huge market size of its products (H₂ and VFAs), and the more and more stringent regulations on carbon emissions, fermentation is likely to gradually replace anaerobic digestion as the core of the dairy biorefinery. H₂ is indeed a key player towards the decarbonisation of the energy production system, whereas VFAs have several industrial applications, and may also be regarded as precursor for bioplastic production, the market size of which is expected to increase in response to the policies to reduce use of traditional plastics. Due to the huge organic load of CW, inhibitory for electrogenic microorganisms, MFC and MEC can only find application as the final polishing step of the dairy biorefinery. MES is a promising technology to recycle the CO₂ generated in the other biological treatment processes, and in the energy production plants providing heat and electricity to the dairy industry, such as boilers and co-generation heat and power (CHP) plants, closing the carbon loop.

Acknowledgements

This work was supported by the Science Foundation of Ireland (SFI) Research Professorship Programme on Innovative Energy Technologies for Bioenergy, Biofuels and a Sustainable Irish Bioeconomy (IETSBIO³, award 15/RP/2763). It was conducted on the framework of the “Waste Biorefinery” task group of the International Waste Working Group (IWWG). Fabiano Asunis gratefully acknowledges Sardinian Regional Government for the financial support of his PhD scholarship (P.O.R. Sardegna F.S.E. - Operational Programme of the Autonomous Region of Sardinia, European Social Fund 2014-2020 - Axis III Education and training, Thematic goal 10, Investment Priority 10ii), Specific goal 10.5.

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