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Invited review: Sensor technologies for real-time monitoring of the rumen environment

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ABSTRACT

Quantifying digestive and fermentative processes within the rumen environment has been the subject of decades of research; however, our existing research methodologies preclude time-sensitive and spatially explicit investigation of this system. To better understand the temporal and spatial dynamics of the rumen environment, real-time and in situ monitoring of various chemical and physical parameters in the rumen through implantable microsensor technologies is a practical solution. Moreover, such sensors could contribute to the next generation of precision livestock farming, provided sufficient wireless data networking and computing systems are incorporated. In this review, various microsensor technologies applicable to real-time metabolic monitoring for ruminants are introduced, including the detection of parameters for rumen metabolism, such as pH, temperature, histamine concentrations, and volatile fatty acid concentrations. The working mechanisms and requirements of the sensors are summarized with respect to the selected target parameters. Lastly, future challenges and perspectives of this research field are discussed.

Key words: biosensor, rumen, precision livestock farming

INTRODUCTION

As the global population increases and the need for sustainably produced food becomes more important, ruminant animals as a food source have been highlighted as an interesting paradox (Liebe et al., 2020). By 2050 the Food and Agriculture Organization predicts that the demand for meat will increase by 73%, and the demand for dairy will increase by 58% over 2011 levels (McLeod, 2011). This trend for increased demand builds on the increasing global demand for animal products evidenced over the past several decades, which has led to the intensification of animal agriculture in the United States (MacDonald et al., 2016). Much as intensification was leveraged as a tool to address the need for enhanced productivity and efficiency of dairy production systems over the past several decades (Capper et al., 2009; Capper and Cady, 2020), precision feeding and management technologies hold promise as strategies that can be adopted to continue efficiency and productivity trends toward sustainably intensifying agriculture to meet the projected 2050 demand for animal products due to growing population.

The rumen ecosystem is central to the opportunity presented by ruminant animals to feed the growing global population and to address the major sources of environmental impact contributed by ruminant production. Namely, the fermentation of fiber within the rumen is the process that allows ruminant animals to convert poor-quality, human-inedible materials into high-quality human-edible proteins. That fermentation process is also the major driver of enteric methane production (Moe and Tyrrell, 1979) and contributes to N use efficiency of dairy cattle (Johnson, 1976; Huber and Kung, 1981). For several decades, ruminant nutritionists have studied the digestive and fermentative processes of ruminant animals by leveraging fistulated cattle (Duffield et al., 2004). These are animals that have undergone surgical placement of a cannula to allow direct, experimental access to the animal's gastrointestinal tract. This direct access to the gastrointestinal tract has allowed for revolutionized understanding of the microbial processes responsible for fiber fermentation and has given initial indications of how to adapt ration formulation to influence productivity, health, performance, and immunity (Harmon and Richards, 1997; Huhtanen et al., 1997).

Despite the advancements in fundamental understanding gleaned from studies on fistulated cattle, several practical (e.g., representativeness of a small

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number of animals) and ethical (e.g., tenets of institutional animal care and use policies related to stress alternatives) challenges with fistulated animals suggest that new approaches may be important in our efforts to continue to advance understanding of rumen fermentation. For example, the rumen is an anaerobic fermentation system with sensitive microbial communities and unique microclimates. The effects of disrupting this system through macro-interventions, such as surgical placement of the cannula, introduction of air (and O_2) through the fistula, and disruption of the regular fluid dynamics by sampling, stirring, infusion of markers, and other common experimental processes, have largely been uninvestigated because of lack of sufficiently nuanced and noninvasive research approaches to properly study the importance of these factors. As we continue to study this sensitive system, a need exists to leverage less-invasive experimental techniques to evaluate system functionality in a manner closer to the native rumen environment. This need is evidenced by the movement toward sampling through ruminocentesis or oro-ruminal sampling; however, these methods also have well-documented challenges (Shen et al., 2012). An alternative to these rumen sampling strategies is to develop a stand-alone system for monitoring important biomarkers (Penner et al., 2006). Such devices exist to monitor rumen pH, temperature, rumination, and overall activity of the animal (Rutten et al., 2013). These devices were a part of the first wave of precision livestock farming technologies that emerged during the 2000s (Werner et al., 2003), which sought to leverage technological intervention and process engineering to more precisely meet the needs of individual animals (Wathes et al., 2008). The past 2 decades have seen a monumental rise in the availability of such precision livestock farming products, but although these technologies show initial promise, several limitations preclude their widespread adoption.

This review discusses the opportunities for innovations in sensor technology development for the rumen ecosystem and investigates opportunities for technology advancement, including expanding the array of physical and chemical attributes sensed through real-time monitoring capacities.

HISTORICAL ADVANCES IN RUMEN MONITORING

Since the mid-1920s, researchers have focused on the rumen environment due to its important role in the digestive process of herbivorous animals (Schwarz and Kaus, 1926; Duke, 1934). Throughout the history of such study, rumen pH has been a major focus because of the relationship between pH and cellulose digestion. Real-time monitoring of rumen pH has been proposed as a critical management tool to address animal health challenges such as subacute ruminal acidosis (Humer et al., 2015) and to improve understanding of fermentation processes (Oba et al., 2015). In very early studies, Schwarz and Kaus (1926) found an average pH value of 8.28 in rumen ingesta obtained from slaughtered animals that were fed hay and straw before slaughter. Duke (1934) also found an alkaline rumen environment in oxen (average pH 8.89) and explained this as due to the addition of highly alkaline saliva secreted by ruminants. In the late 1930s, the first in vitro measurements of rumen pH from ingesta were obtained from living cows outfitted with fistula, as shown in Figure 1(a) (Kick et al., 1938; Monroe and Perkins, 1939). Kick et al. (1938) reported that pH values of ingesta obtained from live cows varied from 5.5 to 7.7 depending on the composition and the time of feeding. Monroe and Perkins (1939) found that pH values were not the same in all parts of the rumen and that pH values of rumen ingesta averaged between 6.83 and 7.01 when cows were fed roughage-based diets. They also found that pH values of ingesta obtained from the slaughtered cows were uniformly more alkaline than the average pH values obtained from living cows.

The first in vivo measurements of rumen pH were performed by Smith (1941) in 1941 to avoid rapid changes in the pH in body fluids when exposed to air, as shown in Figure 1(b). A pH meter with an extended electrode was used for reading pH inside the rumen. The electrode was inserted into the rumen through a permanent rumen fistula, and pH readings were performed in 6 different localities. Smith (1941) found that average pH values varied from 6.0 to 6.30, depending on the ration and the time of feeding, and the average pH values obtained by in vivo measurements were lower than those of other in vitro measurements. The lower pH values in vivo were assumed to be due to the loss of CO_2 from the in vitro samples. In 1955 another set of in vivo measurements were collected using a fistulated cow and a measuring probe connected to a pH meter, as shown in Figure 1(c) (Lampila, 1955). The in vivo and in vitro measurements were performed simultaneously, using a single cow, to compare the measured pH values directly. The result showed that the pH values obtained from in vitro measurements were 0.15 to 0.65 pH units higher than those obtained from in vivo measurements.

These prior studies indicated the need for in vivo measurements and emphasized the need for real-time tracking of changes. One of the first continuous recordings of pH in the cow rumen was conducted in 1968 (Johnson and Sutton, 1968). In this work, an extended glass and reference electrode protected by stainless-steel housing and polyvinyl chloride tubing [Figure 1(d)] was inserted into the rumen through the

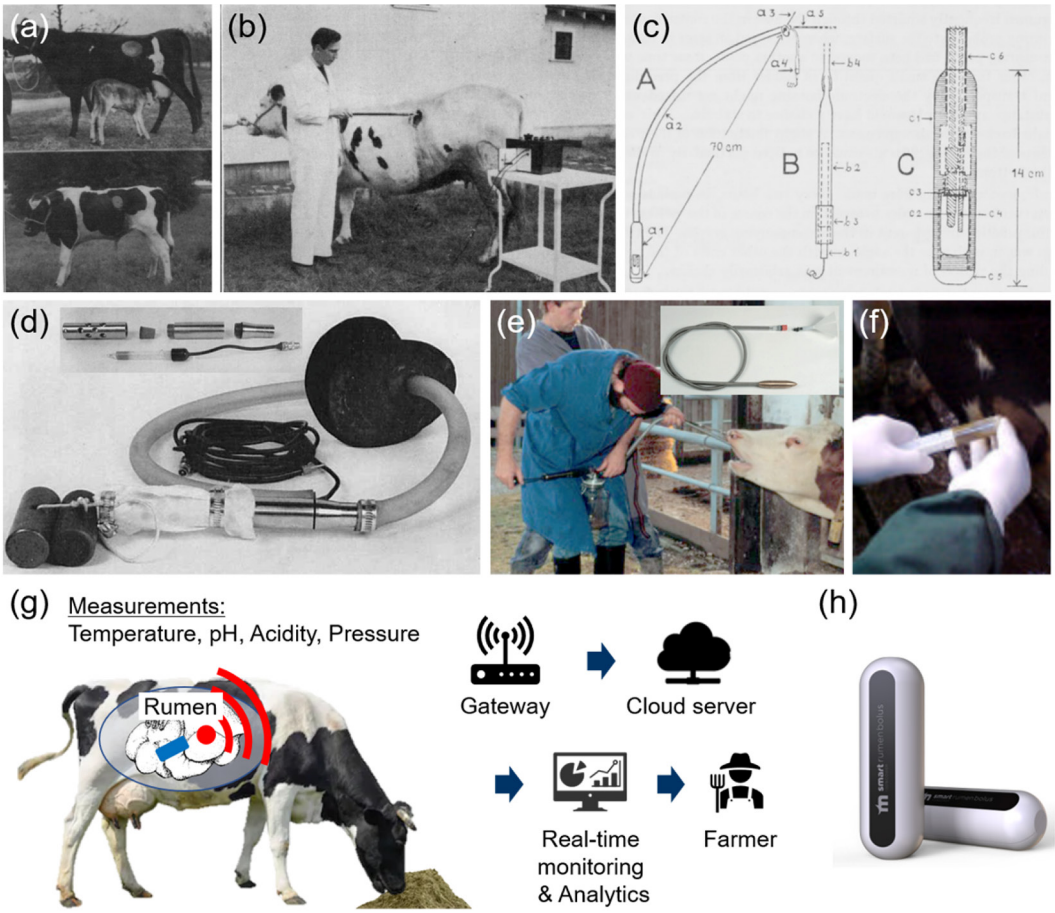

Figure 1. History of rumen monitoring methods. (a) Fistulated cows used in the first in vitro measurements of the hydrogen ion concentration (Monroe and Perkins, 1939); (b) the first in vivo measurements of hydrogen ion concentration in the rumen of a fistulated cow (Smith, 1941); (c) the measuring probe used in in vivo measurement (Lampila, 1955); (d) the measuring probe used in the first continuous recording of pH in the cow rumen (Johnson and Sutton, 1968); (e) collection of ruminal fluid using an oro-ruminal probe and suction pump (Geishauser, 1993); (f) aspiration of ruminal fluid using the rumenocentesis (Kleen et al., 2004); (g) schematic diagram of Internet of Things (IoT) sensor systems for monitoring the rumen environment; and (h) the Smart Rumen Bolus, by Moonsyst (courtesy Moonsyst). Reproduced with permission from Elsevier (a, b), Agricultural and Food Science (c), Cambridge University Press (d), the American Association of Bovine Practitioners (e), Schlütersche Verlagsgesellschaft (f), and Moonsyst International (h).

rumen fistula. This technique was successful in measuring changes in the rumen pH over a 4-wk period. Since these early studies, in vivo measurements using fistulated cows have become the preferred method for research on monitoring the rumen environment. However, this solution is not well-suited to other applications, because it is impractical to maintain large herds of cannulated cows in production settings. Cannulated animals also may be an imperfect research tool because repeated use of the fistula cover disturbs the rumen environment and may allow rumen digesta to escape (Tajik and Nazifi, 2011).

To address these challenges with fistulated animals, oro-ruminal probes [Figure 1(e)] and rumenocentesis [Figure 1(f)] have been used to measure the pH value in collected ruminal fluids, with calibration of possible measurement errors in in vitro measurements (Geishauser, 1993; Kleen et al., 2004; Yáñez-Ruiz et al., 2016). However, these methods are not suitable for long-term, continuous monitoring of the rumen environment. Additionally, they have limited capacity to address spatial diversity within the rumen. For oro-ruminal probing, pH values may vary depending on the intraruminal localization of the probe and saliva contamination (Enemark et al., 2002; Tajik and Nazifi, 2011). In the case of rumenocentesis, health problems and reduced productivity have been reported in sampled cows (Strabel et al., 2007; Tajik and Nazifi, 2011). In response to the shortfalls of these historical methods, the newest precision livestock farming technologies seek to provide strategies for continuous, remote, and real-time monitoring of the rumen environment.

Table 1. Summary of key features of commercially available rumen boluses

Sensor name	Measurement	Data collection	Size (length × diameter; mm)	Life span	Manufacturer
eBolus	pH Temperature	Wifi handset	135 × 27	5 mo	eCow Devon Ltd.
SmaXtec	pH Temperature Activity levels	Wireless network	132 × 35	5 mo	smaXtec Animal Care GmBH
Moow Rumen Bolus	pH Temperature	Wireless network	—	3 yr	Moow
Smart Rumen Bolus	pH Activity Temperature	Wireless network	—	6 yr (temperature, activity) 90 d (pH)	Moonsyst
LiveCare Bio Capsule	pH Temperature	LoRaWAN network	100 × 25	5–6 yr	UlikeKorea Co. Inc.

CONTEMPORARY TECHNOLOGIES FOR RUMEN MONITORING

Contemporary, commercially available rumen monitoring systems focus on detecting estrus or heat, detecting the onset of diseases such as SARA and mastitis, and monitoring activity and productivity through indirect means that leverage measured biomarkers (e.g., temperature, pH, and activity). Temperature and its variation patterns are often primary indicators of estrus (Wrenn et al., 1958) and onset of diseases (Sathiyabarathi et al., 2016). Rumen pH is used to detect SARA (AlZahal et al., 2008, 2009; Phillips et al., 2010). Activity data gathered using accelerometers is used for detection of estrus (Kamphuis et al., 2012; Valenza et al., 2012) and lameness (Pastell et al., 2009). Initially, ear tags, neck collars, and leg tags were introduced to measure temperature and activity. However, such sensors could only measure temperature from contact with skin, which was subject to variations due to environmental conditions as well as placement (Sellier et al., 2014). To address this issue, rumen bolus technologies were developed to continuously monitor pH and temperature. These technologies were also developed in response to the need to detect SARA associated with feeding highly fermentable carbohydrate diets (Oetzel, 2007; Zabasta et al., 2019) due to the negative effects of SARA on ruminitis (Oetzel, 2007), immunity (Humer et al., 2018), mastitis (Abdela, 2016), productivity, and reproductive performance (Abdela, 2016). Because pH monitoring is one of the most effective ways to diagnose SARA, sensor boluses placed in the rumen or reticulum were preferred over other methods of diagnosis because they are easy-to-use and noninvasive, and they allow for continuous monitoring (Zabasta et al., 2019). Although initial boluses could be used only in fistulated cows, because they were connected to data loggers placed on the outside of the cow and had to be removed after a short period due to sensor drift issues (Dado and Allen, 1995; Mottram, 1997), more recent advancements in these sensors allow for use in non-cannulated animals. An early wireless telemetric bolus was presented by Mottram et al. (2008). This bolus included a single-junction glass bulb electrode wherein the glass formation protected the reference junction, allowing the sensor bolus to perform, with stability, for at least 60 d (Mottram et al., 2008). Wireless rumen or reticulum indwelling boluses then entered the commercial space (e.g., eCow, eCow Devon Ltd.). These boluses now commonly include capacity to monitor pH, temperature, and activity. Most of the development of commercial sensors has been concentrated on eliminating the drift of sensors over time, to extend their life cycles. A survey of some commercially available products, with their measurement parameters, size, life span, and data collection technology, is included in Table 1.

A major challenge in most historical rumen bolus devices was the short life cycle of the device, which makes them financially infeasible for farmers and highly impractical. For example, historical pH monitoring boluses typically had a life span of roughly 6 mo and experienced considerable drift during that period (Kaur et al., 2010). Another challenge, particularly with orally administered boluses, is that the bolus typically settles into the reticulum, rather than the rumen. Recent developments in battery technology and low-power wide-range wireless communication have significantly addressed battery concerns; however, the stationary nature of the orally administered bolus remains a challenge. In addition to advancing battery life, the development of Internet of Things (IoT) systems for agriculture has propelled research in creating smart and connected sensors [Figure 1(g)], which leverage wireless data transmission to enable more flexible use. One such product that uses low-power wide-range technology is the LiveCare Bio Capsule (UlikeKorea Co. Inc.), which

is a sensor bolus that settles in the rumen of the cow. The bolus can measure pH and temperature to detect estrus, calving, abnormal activity, and the onset of various diseases, as validated by Kim et al. (2018). The main differentiator of this product is that battery tests suggest a potential life span of 5 to 6 yr (for monitoring functions excluding pH), meaning the sensor can monitor temperature for the majority of the productive life of the animal without needing replacement (Kim et al., 2018). Another such product is the Smart Rumen Bolus by Moonsyst, as shown in Figure 1(h), which also has a potential life cycle of more than 6 yr for temperature and activity monitoring based on battery testing (Stachowicz and Umstätter, 2020). Despite providing ongoing disease and estrus detection capacity based on temperature and activity, the pH monitoring ability of this product is still limited to about 90 d.

RESEARCH ADVANCEMENTS FOR RUMEN SENSORS

Research advancements related to advancing rumen sensing capacity focus on the improvement of rumen pH, motility, and temperature sensors, along with diagnostic technologies to support sensor systems (Nogami et al., 2017; Kim et al., 2019). Other research advancements in rumen sensors include the expansion of sensing capacity for important metabolites such as VFA and ammonia or biomarkers such as histamine.

Sensors for Monitoring Rumen pH

Monitoring ruminal pH is beneficial to avoid SARA (Garrett et al., 1999; Dijkstra et al., 2020). Several sensor construction strategies have been investigated for rumen pH sensors; however, conventional glass membrane electrode-based pH sensors are currently most common (Sato et al., 2012; Andersson et al., 2018). Most commercial boluses reviewed use conventional glass membrane electrode-based pH sensors. These glass membrane electrodes are large and bulky, easy to break, difficult to miniaturize, and slow in response. Moreover, they require regular maintenance, such as calibration and refilling of the reference buffer solution. Therefore, it is necessary to develop alternative pH sensors that can be safely used in the rumen for long-term, real-time monitoring. In addition, the development of a miniaturized pH sensor is required to integrate pH sensing into wireless multiparameter rumen monitoring systems (Dijkstra et al., 2020; Knight, 2020). In this section, we review recent advances in micro-scale pH sensors that are suitable for in vivo rumen pH monitoring.

Potentiometric Sensors. Potentiometric sensors have been most widely used for measuring pH of solutions due to their simple configuration, small size, and fast response time. A typical potentiometric sensor consists of 2 electrodes, the working electrode (sensing electrode) and the reference electrode, as shown in Figure 2(a). The Ag/AgCl reference electrode is most commonly used in micro-size pH sensors (Safari et al., 2013; Qin et al., 2015a). When both electrodes contact a solution, the electrical potential difference (open circuit potential) between them is generated by either redox reactions or ion-selective permeation (Qin et al., 2015a). Recent advances in micro- and nano-fabrication and materials have enabled researchers to miniaturize solid-state potentiometric pH sensors for wireless real-time pH monitoring systems. For example, Amor et al. (2016) developed a novel miniaturized low-temperature co-fired ceramic-based wireless pH sensing system, as shown in Figure 2(b). Huang et al. (2011) also developed a miniaturized solid-state potentiometric pH sensor based on an AgCl reference electrode and an IrO_x working electrode. In both cases, the sensors were fabricated using novel approaches, and the resulting prototypes showed promise for micro-scale pH monitoring. These sensors have particular importance for pH monitoring in the rumen because of their small physical size. The small size contributes to the development of small form factor sensors, which can be administered orally or contribute to constraining power requirements of mobile (active) rumen sensors. The latter application simultaneously addresses the challenges associated with cannulating animals and the need for better strategies to noninvasively assess microclimates within the rumen.

Ion-Sensitive Field-Effect Transistor-Based PH Sensors. Ion-sensitive field-effect transistor (**ISFET**)-based pH sensors measure pH of a solution through an ion-sensitive membrane and the field-sensing characteristic of a transistor (Li et al., 2007). Practically, configuration of an ISFET is the same as that of a modified metal oxide semiconductor field-effect transistor (**MOSFET**), in which the ion-sensitive membrane is used as the gate dielectric layer and the gate metal is separated from the MOSFET, as shown in Figure 2(c) (Qin et al., 2015a). The gate dielectric layer is directly exposed to the solution so that the solution and a reference electrode immersed in this solution act as the gate metal. When positive voltage is applied to the reference electrode, hydrogen ions in the solution reside at the surface of the gate dielectric layer in proportion to the pH, inducting polarization in the gate dielectric layer. This polarization attracts mobile charges (electrons in n-type semiconductor layer) toward the interface between the semiconductor and the

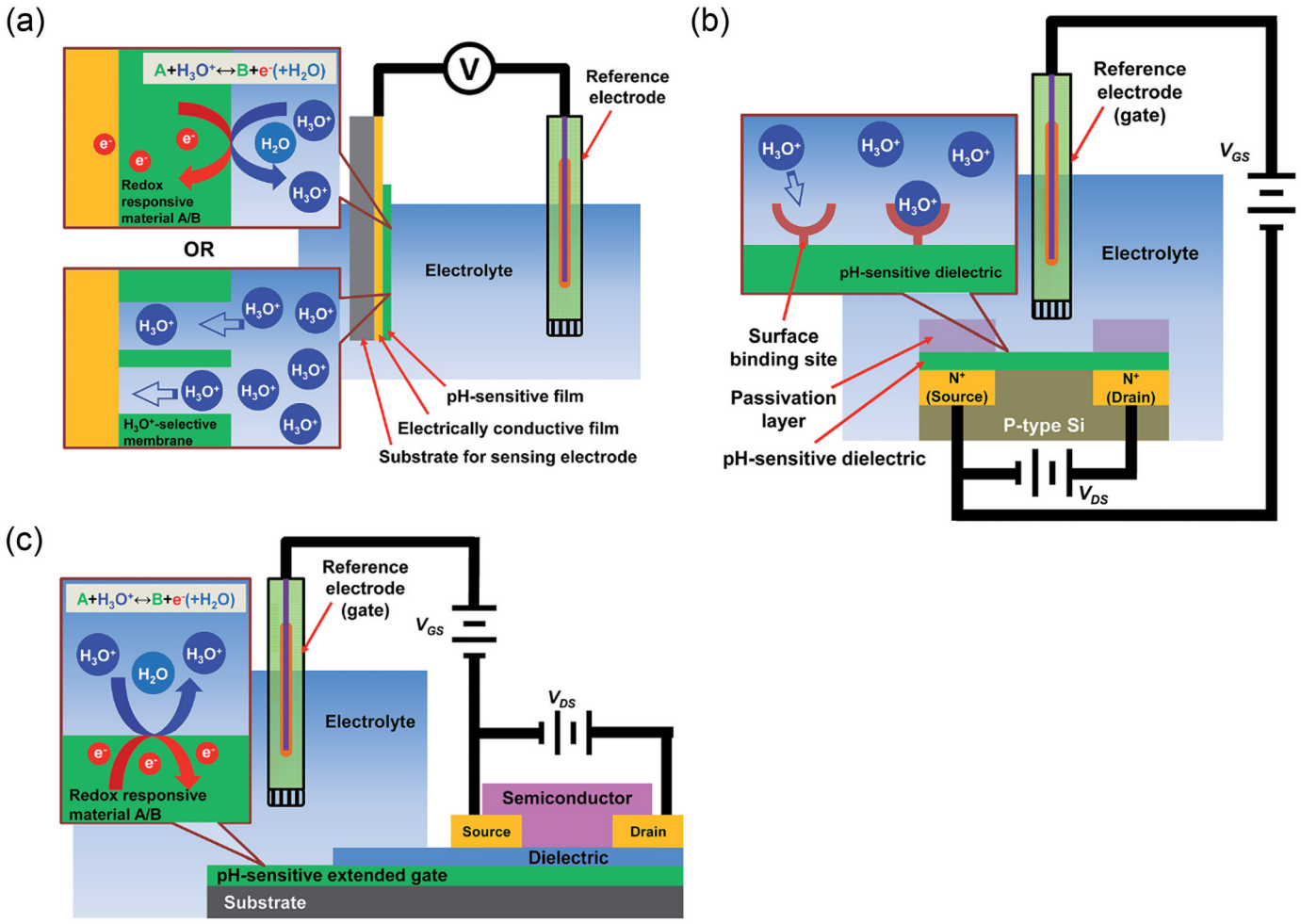

Figure 2. Schematics of (a) a potentiometric pH sensor and its possible sensing mechanisms, (b) an ion-sensitive field-effect transistor-based pH sensor, and (c) an extended gate field-effect transistor (EGFET)-based pH sensor with their respective sensing mechanisms (Qin et al., 2015a). A and B = materials that participate in redox reactions; e^- = electron; V_{GS} = potential difference between gate and source electrode; V_{DS} = potential difference between drain and source electrode; P-type Si = silicon doped with acceptor impurities such as boron (B), gallium (Ga), indium (In), aluminum (Al), etc. Reproduced with permission from the Royal Society of Chemistry.

gate dielectric layer. Consequently, a conducting channel layer is created between the source and the drain. Because the drain and the reference electrode are connected to constant voltage sources and the source is connected to ground, the amount of current passed through the conducting channel layer is determined by the concertation of the hydrogen ions in the solution. Therefore, the gate dielectric layer plays the most crucial role in determining the sensitivity and selectivity of the ISFET-based pH sensor (Ghoneim et al., 2019; Manjakkal et al., 2020). Although ISFET-based pH sensors have many advantages, such as small size, robustness, and easy storage without many necessary conditions (e.g., low measurement bias at extreme pH and low temperature dependence), they are difficult to use for in vivo monitoring because they must be encapsulated. That is, the chip metal and wires must be protected from the fluid to avoid possible damage (Korostynska et al., 2008). As such, integration of sensor testing exercises with appropriate materials and housing tests are necessary to identify the best encapsulation strategy before ISFET sensors will be useful in rumen monitoring applications.

Extended Gate Field-Effect Transistor-Based PH Sensors. Extended gate field-effect transistor (**EGFET**)-based pH sensors were introduced as an alternative to ISFET-based sensors (van der Spiegel et al., 1983; Chi et al., 2000). Unlike the ISFET structure, EGFET sensors consist of a standard MOSFET, a sensing electrode that is physically separated and connected to the gate metal of the MOSFET, and a reference electrode, as shown in Figure 2(d) (Qin et

Table 2. Summary of the representative works on extended gate field-effect transistor (EGFET)-based pH sensors with various sensing materials and nanostructures[1]

Sensing material (Substrate)	Reference electrode	FET device	Sensitivity (mV/pH)	pH range	Reference
ITO film (Glass)	Saturated calomel electrode	Commercial p-type	58	2–12	Yin et al., 2001
ITO film (PET)	Ag/AgCl	Commercial n-type	50.1	2–12	Lue et al., 2012
InN nanorod (Quartz)	Ag/AgCl	Commercial n-type	22.6	4–10	Chen et al., 2014
ZnO film (Al foil)	Ag/AgCl	Commercial Not reported	38	2–12	Batista and Mulato, 2005
ZnO nano-array (ITO/glass)	Ag/AgCl	Commercial p-type	45	4–12	Qi et al., 2015
Al-doped ZnO nanowire (Glass)	Ag/AgCl	Not reported	57.95	1–13	Yang et al., 2011
SnO_2 film (Al/Si)	Saturated calomel electrode	Commercial p-type	58	2–12	Chi et al., 2000
TiO_2 film (ITO/glass)	Ag/AgCl	Commercial p-type	59.89	1.8–12	Yusof et al., 2016
V_2O_5 film (Glassy carbon)	—	Commercial p-type	58.1	2–10	Guerra et al., 2009
Multiwall carbon nanotube film (PI)	Ag/AgCl	Commercial n-type	55.7	1–13	Tsai et al., 2014

[1]ITO = indium tin oxide; PET = polyethylene terephthalate; PI = polyimide.

al., 2015a). In the EGFET sensor, only the sensing and reference electrodes need to be immersed in the solution to measure pH. Therefore, this system is easy for passivation and packaging, is flexible in shape, and has high stability (Chi et al., 2000), making it much better suited to rumen monitoring applications. The major difference between EGFET and ISFET sensors is in the material properties required for the sensing membrane (Chiang et al., 2001; Chou and Chen, 2009; Qin et al., 2015b). The sensing membrane in the ISFET-based pH sensor is the gate dielectric layer, so that it has to be an insulator, defect-free, and of high impedance, whereas the sensing membrane in the EGFET-based pH sensor has to be fabricated using a low-impedance material for high conductivity and sensitivity. Because the rumen environment is not expected to negatively influence a low-impedance material, there is further value in considering EGET sensors for ruminal monitoring.

Various thin film and nanostructured materials have been investigated as sensing electrodes of EGFET-based pH sensors. The structural and sensing characteristics of these materials are listed in Table 2. In addition, many efforts have been made to develop a miniaturized all-solid-state sensor, including reference electrode, because the conventional reference electrode is challenging to use for in vivo measurement due to its bulky size and internal electrolyte solution (Zhang et al., 2017; Rosli et al., 2018; Tsai et al., 2019). Recently, an all-solid-state EGFET-based pH sensor with a wireless data communication module was developed for real-time monitoring of the cow's ruminal pH, as shown in Figure 2(e) (Zhang et al., 2017). Using this sensor, researchers reported that rumen pH was successfully monitored for several days. Further evaluation of this technology to understand interfering compounds, drift, longer-term battery life, and appropriate housing is essential to progress toward more functional real-time monitoring of the rumen pH.

Impact, Importance, and Future Directions. Rumen pH sensing has been well-characterized as a much-needed management tool for ruminant operations of all kinds. Despite commercially available products, widespread adoption of pH monitoring has been limited. In addition to the documented challenges highlighted above, anecdotal evidence suggests that alarm fatigue and limited data interpretability preclude effective use of real-time sensed pH data. As such, the potential impact of real-time pH monitoring as a tool to improve cattle health management is limited not only by sensor limitations but also by the translation of effectively sensed data into actionable decisions or management recommendations. This is perhaps because fluctuations in ruminal pH are nonspecific, and integration of analytics with other sensed parameters may be essential to convert real-time sensed pH measurements into an effective diagnostic or management tool.

Sensors for Rumen Motility

Monitoring of rate and amplitude of ruminal contractions, called motility, is one of the pathways to diagnose metabolic diseases such as ruminal acidosis

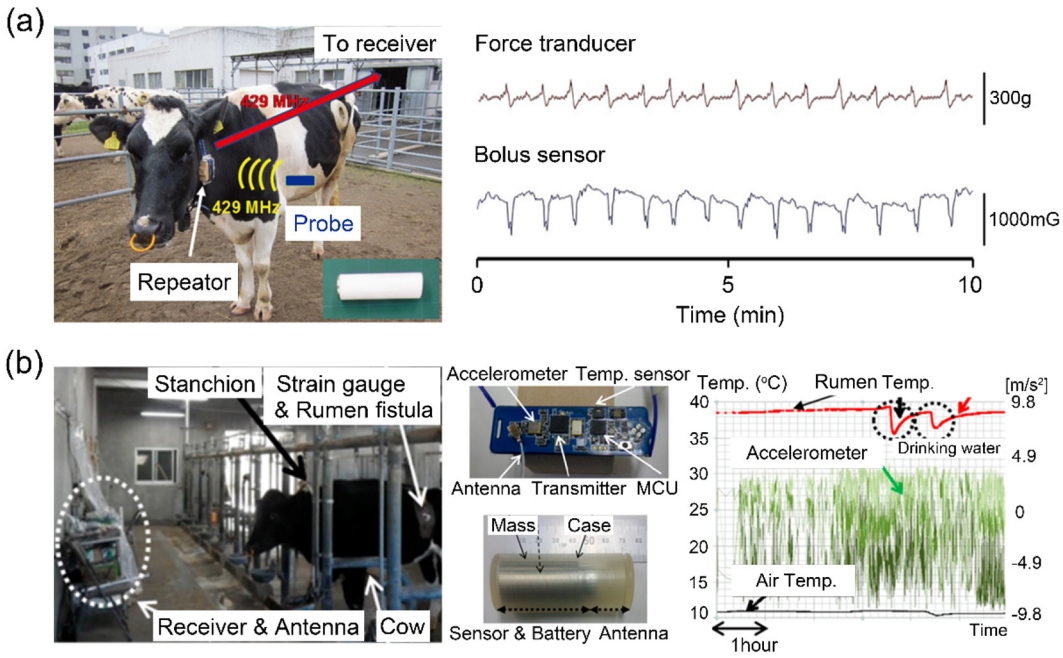

Figure 3. Rumen sensor nodes for early detection of diseases. (a) Bolus-type wireless sensor node for monitoring rumen motility (Arai et al., 2019b). (b) Bolus-type wireless sensor node for monitoring rumen motility and temperature (Temp.; Nogami et al., 2017). MCU = microcontrol unit. Reproduced with permission from J-STAGE (a) and MDPI (b).

and hypocalcemia, as well as many other stressful or productivity-limiting conditions (Mudziwepasi and Scott, 2014; Nogami et al., 2017; Arai et al., 2019b). Rumen motility has generally been evaluated physiologically using strain gauge-based force transducers or ultrasonography methods (Braun and Schweizer, 2015; Arai et al., 2019a). However, these methods are not practical because of their significant disadvantages. For example, the force transducer must be sutured onto the serosa of the dorsal sac of the rumen through a surgical procedure, and the ultrasonography methods limit continuous measurements over longer periods because the ultrasound must be held against the animal's body wall. In addition, these methods of continuously measuring the movement of the rumen consume more power than other equivalent approaches. To monitor rumen motility more simply and over a longer period of time, bolus-type wireless sensor nodes with a 3-axis accelerometer have been developed, as shown in Figure 3(a) and (b) (Nogami et al., 2017; Arai et al., 2019b). Compared with the force transducer, the 3-axis accelerometer has been reported to be more suitable for early detection of rumen dysfunctions such as ruminal atony, ruminal tympany, and anorexia. In addition to leveraging accelerometer-based sensors, pressure monitoring within the rumen has been tested as a strategy to limit power consumption while characterizing rumen motility patterns (Egert et al., 2014; Ahn et al., 2020).

Sensors to characterize rumen motility patterns provide a complementary set of information to those designed to determine biomarker or metabolite concentrations. By synthesizing data coming from motility sensors with pH, temperature, VFA, or other data, we may be better able to convert these sensor data to actionable information for use on farm, such as alerts for medical conditions like displaced abomasum, tympany, atony, or anorexia. Because rumen motility is critical for fermentation, coupling motility data with data on animal performance and feed intake (from autonomous monitoring systems) may also enable use of rumen motility data, likely coupled with other ruminal parameters, as indicators of feed efficiency and productivity.

Sensors for Monitoring Body Temperature

Real-time monitoring of body temperature changes in ruminants is an effective method to detect diseases, estrus, and parturition (Piccione et al., 2003; Kim et al., 2019). For example, mastitis can be detected in its early stages using a bolus-type wireless temperature sensor node, as shown in Figure 4. Rectal thermometers have been widely used for core temperature monitoring; however, this method requires individually handling animals within a chute, which is time-consuming. Therefore, measurement of rumen temperature using orally administered sensors has been proposed as an

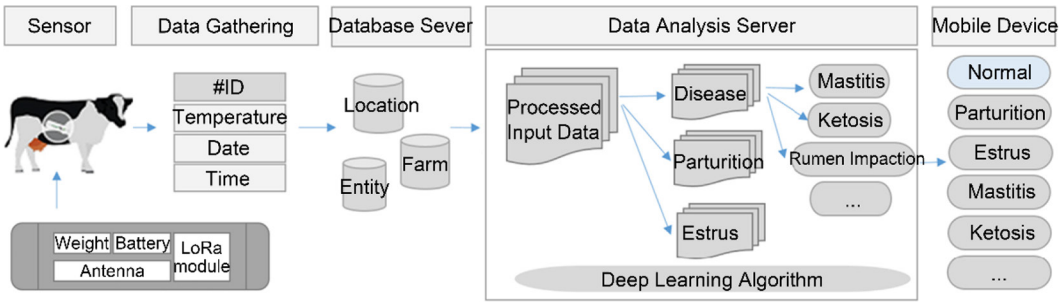

Figure 4. Rumen sensor nodes for early detection of diseases. Orally administrable indwelling wireless sensor node for monitoring rumen temperature (Kim et al., 2019). LoRa = long-range radio; LoRa technology is the wireless protocol designed specifically for long-range, low-power communications. Reproduced with permission from Elsevier.

alternative method (Bewley et al., 2008a; Adams et al., 2013; Voss et al., 2016). It should be noted that various technologies to monitor tympanic, vaginal, and rectal temperatures have been developed; however, such technologies are not the focus of this discussion and will not be comprehensively reviewed. Table 3 summarizes the literature leveraging temperature-sensing technologies, including the species of the studied animal, the temperature-sensing technology used, the location of the measurement performed, and the purpose of the study (physiological monitoring or sensor validation). The sensors listed in Table 4 are all noninvasive, in the sense that they do not require surgical procedures to be implanted into the animal, albeit some of the rumen boluses were inserted in cannulated cows through a fistula.

Sensing Mechanisms. Most temperature sensors used for core body temperature measurement primarily consist of thermocouples or thermistors, which require contact to obtain measurements. Thermocouples have been used for temperature measurement for a long time, since the discovery of the thermoelectric effect by Seebeck in 1821. The principle of the thermoelectric effect is that when 2 dissimilar metals at different temperatures are joined together, a potential difference is generated between them. This potential difference is proportional to the temperature gradient and hence is used to measure temperature. Although thermocouples are easy to fabricate at low cost, they require continual recalibration, meaning that they are not an effective temperature monitoring technology for long-term sensing of the rumen environment.

An alternative to the thermocouple is the thermistor, which is a semiconductor made from metal oxides that are pressed into various shapes and sintered at high temperatures. The electrical resistance of the thermistor changes with change in temperature. Thermistors have proven to be far more accurate than thermocouples and do not require continual recalibration, which makes them much more suitable for rumen monitoring. Moreover, they have high sensitivity and are stable, meaning they are unlikely to be influenced by other environmental conditions, such as ions within solution, solution density, or pressure. This stability addresses the important need for selective and precise sensors that are able to reflect only the target response (i.e., temperature) despite the complex and dynamic rumen environment. However, thermistors have some limitations of their own. For example, the output of thermistors is nonlinear, meaning that more complex mathematics are needed to translate the sensor output to a numerical representation of temperature. This is typically accomplished with the aid of a microprocessor, which contributes to slightly larger form factor and increases power requirements of this sensor relative to the linear thermocouple. Nevertheless, the majority of devices available currently use thermistors for measurement of temperature.

Incorporation into Rumen Bolus Technologies. Numerous studies have been performed to record rumen temperature, especially using telemetric boluses, which can be inserted in the animal orally or through a cannula (Prendiville et al., 2002; Eihvalde et al., 2016; Lees et al., 2018). The major advantage of using rumen-dwelling sensors is that they can be placed for long periods (e.g., lasting up to 6 yr in the rumen). Most rumen-dwelling bolus sensors are telemetric and can communicate to nodes outside the animal (Cooper-Prado et al., 2011; Eihvalde et al., 2016; Tao et al., 2019). They use radio-frequency communication to transmit temperature and other data to a server outside the cow. These data, in some cases, are made available to the farmer using real-time cloud-based databases.

Ruminal temperature monitoring has been evaluated for use in a wide variety of applications. For example, the relationship between ruminal temperature and onset of estrus was investigated by Cooper-Prado et al. (2011). In that study, rumen boluses from Smartstock

Table 3. Summary of literature search on core (internal) temperature measurements in bovines

Sensor placement	Sensing technology	Sensor model and maker	Purpose	Reference
Abdominal cavity	Thermistor	CorTemp, HQ Inc.	Validation	Brown-Brandl et al., 2005
Eardrum	Thermistor	Steri-Probe, Cincinnati Sub-Zero	Nutrition	Bergen and Kennedy, 2000
Eardrum	Thermistor	Teagasc–Silsoe Institute	Validation	Prendiville et al., 2002
Eardrum	Thermistor	Stowaway XTI, Onset	Nutrition	Davis et al., 2003
Eardrum	Thermistor	Stowaway XTI, Onset	Thermoregulation	Mader et al., 2005
Eardrum	Thermistor	Stowaway XTI, Onset	Nutrition	Mader et al., 2010
Eardrum	Thermistor	BoviMinder ear tag, Gavco	Reproduction	Moe et al., 2012
Rumen	Thermistor	smaXtec Animal Care GmBH	Validation	Ammer et al., 2016
Reticulum	Thermistor	Phase IV CTMS, MaGiiX Inc.	Health	Bewley et al., 2008b
Rumen	Thermistor	SI7051-A20-IM, Silicon Labs	Validation	Tao et al., 2019
Rumen	Thermistor	Bolus, SmaXtec Animal Care GmbH	Validation	Eihvalde et al., 2016
Rumen	Thermistor	SmartStock LLC	Validation	Cooper-Prado et al., 2011
Rumen	Thermistor	Smartstock LLC	Validation	Lees et al., 2018
Rumen	Thermistor	Cow Temp, Innotek	Validation	Prendiville et al., 2002
Rumen	Thermistor	SmartStock LLC	Validation	Alzahal et al., 2009
Rumen	Thermistor	LiveCare Biosensor Bolus	Validation	Kim et al., 2018
Rectal	Thermistor	iButton and Vemco temperature logger	Validation	Lea et al., 2008
Rectal	Thermistor	TidbiT v2, Onset Corp.	Validation	Reuter et al., 2010
Vaginal	Thermocouple	L820, Unipulse Inc.	Validation	Aoki et al., 2005
Vaginal	Thermistor	ACR Systems Inc.	Validation	Burke et al., 2007
Vaginal	Thermistor	HOBO Pro V2, Onset	Health	Dikmen et al., 2009
Vaginal	Thermistor	TX minilog, Vemco Ltd.	Well-being	Hillman et al., 2009
Vaginal	Thermistor	DST micro-T, Star Oddi	Validation	Burdick et al., 2012
Vaginal	Thermistor	Thermoclone Data Logger	Reproduction	Sakatani et al., 2016
Vaginal	Thermistor	StarOddi DST Centi, StarOddi	Validation	Tresoldi et al., 2020
Vaginal	Thermistor	ADT7320	Validation	Wang et al., 2020

Table 4. Summary of different types of electrochemical histamine sensors

Measurement	Transducer[1]	pH	Sample	Linearity range (μM)	Limit of detection (μM)	Reference
Impedimetry	MIP-coated Al electrode	5, 7, 9, 12	—	0–0.012	0.002	Bongaers et al., 2010
Impedimetry	MIP-coated Al electrode	—	Canned tuna	—	0.001	Horemans et al., 2010
Impedimetry	MIP-coated Al electrode	5, 7	Bowel fluids	0–0.4	0.015	Peeters et al., 2013
Impedimetry	Reduced graphene oxide	7	—	0.1–1	0.1	Delle et al., 2015
Impedimetry	Nonporous Al membranes	7	Saury fish	10^{-6}–0.04	0.003	Ye et al., 2016
Impedimetry	MIP-coated Ti electrode	7	—	—	0.0034	Ramakers et al., 2019
Impedimetry	MIP-coated Ti electrode	7	Intestinal fluid	0.005–0.2	—	Wackers et al., 2020
Impedimetry	PEDOT:PSS-coated Au electrode	5, 7, 8	—	0.1–1,000	0.1	Bai et al., 2020
Amperometry	POD-CPE	7	Tuna fish	0–0.95	0.069	Hibi and Senda, 2000
Amperometry/ voltammetry	nAu-GCE	>7	Sardine	2–100	0.6	Carralero et al., 2005
Amperometry	PS/MWCNT/Fc/DMF/SPE −0.05 V	8	Anchovies, tuna, sardines, etc.	0.3–20	0.17	Pérez et al., 2013
Amperometry/ voltammetry	GCE/CeO_2–PANI/DAO −0.1 V	7	Tiger prawn	450–1,050	48.7	Gumpu et al., 2014
Amperometry/ voltammetry	FrGO/GCE +0.746 V	8	Cider vinegar	0.2–80	0.007	Shahzad et al., 2017
Amperometry	Cu@Pd/PGE +0.55 V	>7	Canned tuna fish	0.1–100	0.0032	Gajjala and Palathedath, 2018
Amperometry/ voltammetry	MADH-PPy/Au electrode				25	Veseli et al., 2016
Amperometry	ReO_2/SPCE −0.1 V	7	Fish sauce	4.5–9.0	1.8	
Amperometry	MADH-TCNQ enzyme electrodes +0.2 V			0–200	4.8	
Amperometry	DAO/BSA/GA/SPCE −0.3 V	7	Hake and mackerel	9–675	8.46	Lin et al., 2018; Torre et al., 2019
Amperometry	DAO/PhotoHema/SPE +0.35 V	7	Tiger prawn	0–540	5.85	Torre et al., 2019
Amperometry	DAO-HRP-BSA/SPCE −0.025 V	7	Tuna	18–180	0.99	Trevisani et al., 2019
Amperometry	DAO/ITONP/PB/SPCE −0.15 V	7	Cheese	6–690	1.9	Trevisani et al., 2019; Kaçar et al., 2020
Amperometry	MAO/ITONP/PB/SPCE −0.15 V	8.5	Cheese	2–32,000	2.0	Kaçar et al., 2020
Voltammetry	Au microelectrode	2	Tuna fish	9.9×10^{-6}–0.049	3.1×10^{-6}	Akbari-adergani et al., 2010
Voltammetry	GCE	5	Human urine and wine	5–200	0.3	Akbari-adergani et al., 2010; Degefu et al., 2014
Voltammetry	MWCNTs/p-(AHNSA)/GCE	5–11	Fish muscle extract	0.1–100	0.076	Degefu et al., 2014; Geto et al., 2014
Voltammetry	CeO_2-PANI	7	Fish	450–1,050	—	Geto et al., 2014; Jayaprakasan et al., 2015
Voltammetry	SWCNT/CPE	4–9	Alcoholic beverages	4.5–180	1.26	Jayaprakasan et al., 2015; Stojanović et al., 2016
Voltammetry	MIP/CPE	7	Human serum	0.001–0.007	7.4×10^{-5}	Stojanović et al., 2016; Akhoundian et al., 2017
Voltammetry	PB/CS/AuNP	—	Fish	0.09–900	—	Akhoundian et al., 2017; Dong et al., 2017
Voltammetry	GNRs-AgNP	7	Blood plasma	1–50, 60–500	0.049	Dong et al., 2017; Kumar and Goyal, 2018
Voltammetry	Ag-Ag_2O/MWCNT/GCE	7	Fish sauce	45–1,800	0.018	Kumar and Goyal, 2018; Butwong et al., 2019

[1]PEDOT:PSS = poly (3,4-ethylenedioxythiophene) polystyrene sulfonate; FrGO = fluorine-doped reduced graphene oxide; GCE = glassy carbon electrodes; PGE = pencil graphite electrode; SPCE = screen-printed carbon electrode; DAO = diamine oxidase; BSA = bovine serum albumin; GA = glutaraldehyde; HRP = horseradish peroxidase; CNT = carbon nanotubes; p-(AHNSA) = poly(4-amino-3-hydroxynaphthalene sulfonic acid); SWCNT = single-walled carbon nanotubes; MWCNT = multiwalled carbon nanotubes; PhotoHema = photocured poly(2-hydroxyethyl methacrylate); GNR = graphene nanoribbon; AuNP = gold nanoparticles; AgNPs = silver nanoparticles; MADH = methylamine dehydrogenase; PPy = polypyrrole; TCNQ = tetracyanoquinodimethane; POD = peroxidase-modified; CPE = carbon paste electrode; nAu = gold nanocrystal; ITONP = indium tin oxide nanoparticles; PB = Prussian blue; MAO = monoamine oxidase; Fc = ferrocene; PS = polysulfone; DMF = N,N-dimethylformamide; CS = chitosan; MIP = molecularly imprinted polymer; SPE = screen-printed electrode; PANI = polyaniline; Cu@Pd = core-shell nanostructures, where Cu is the core and Pd is the shell.

LLC were orally inserted in 30 Angus cows, and data were recorded from 48 h before to 48 h after the first detection of estrus. The investigators found a positive association between rumen temperature and onset of estrus. Eihvalde et al. (2016) evaluated the effectiveness of rumen temperature measurements to detect the onset of SARA. Moreover, the correlation among different temperatures (ruminal, rectal, and vaginal) was first studied using the SmaXtec rumen bolus by Ammer et al. (2016). Those authors noted strong correlation among rectal and vaginal temperatures ($P < 0.001$, $r = 0.75$). Kim et al. (2018) demonstrated that an ingestible biosensor could be used to monitor cattle diseases. They conducted a test on 10 cows for 60 d and monitored their temperature data, which was collected in 10-min intervals. Using this setup, they were able to detect onset of disease in 3 cows. AlZahal et al. (2009) conducted a study to evaluate telemetric monitoring systems and compared their performance to that of indwelling electrodes, which have traditionally been used for such measurements. They were able to confirm sensor effectiveness in measuring temperature, and proposed the prediction of rumen pH from rumen temperature due to a strong relationship between these variables. Despite the relationship between pH and temperature, independent monitoring technologies are still essential because specific events (estrus, illness, and more) can induce changes in temperature without changes in pH and vice versa.

One specific situation in which it is useful to evaluate pH and temperature independently is that of heat stress. The effect of heat stress on rumen temperature was studied by Lees et al. (2018), who measured rumen temperature using a radio-frequency identification-enabled bolus at 10-min intervals for 130 d. Animals showed diurnal temperature patterns, but unshaded Angus steers' rumen temperature at night was lower than that of those who were kept in the shade. This difference is explained by one of the major limitations of rumen-dwelling temperature sensors: they are affected by water consumption (Bewley et al., 2008b; Cooper-Prado et al., 2011). Bewley et al. (2008b) noted that drinking water lowered the rumen temperature up to 8.5°C, and it took up to 2 h for the temperature to reach core body temperature levels. This drop in temperature was dependent upon the amount consumed, the temperature of the water, and the frequency of consumption. Further, it has also been noted that temperature measurement also depends on the lying position of the animal (Ipema et al., 2008). Although this interference of water in rumen monitoring is a challenge, it also presents an opportunity, because temperature fluctuations may be sufficient to predict water intake. These temperature fluctuations may help managers understand the daily distribution of water drinking events, if not actually quantities of water consumed, or any unexpected changes in water drinking patterns that may reflect illness or stress.

Sensors for Ruminal Biomarker Concentrations

Monitoring concentrations of biomarkers within the rumen is gaining interest due to the need for additional information to help contextualize generic responses observed from temperature, pH, and activity monitoring. Although the techniques for monitoring biomarker concentrations reviewed herein are applicable to a variety of molecules, we focus on histamine as an example to demonstrate some of the opportunities and challenges in biomarker sensing. Additional biomarkers that may be of interest in the rumen include ammonia, lactic acid, carbon dioxide, and numerous others. Although this review discusses biosensing using histamine as an example, similar approaches can be leveraged to monitor other complex compounds. Histamine is one of many biomarkers that has been researched rather extensively in sensing applications. Ruminal histamine concentrations are of interest for monitoring SARA and other rumen afflictions (Wang et al., 2013). Histamine is an organic compound produced from the amino acid histidine by the removal of a carboxyl group through histidine decarboxylase (Peeters et al., 2013). Histamine plays an important role in animal physiology because it is released by certain cells when tissues are damaged or certain types of antibodies neutralize antigens. For example, high levels of histamine are closely associated with inflammation of the mammary gland (Chang et al., 2018). As such, biosensing of histamine has applications across physiological systems.

Traditional techniques for histamine detection include thin layer chromatography; HPLC and GC; fluorometry; capillary zone electrophoresis; and ELISA (Mattsson et al., 2017). However, these techniques are expensive and time-consuming and require complex sample pretreatment, making them impractical for real-time monitoring in the rumen environment. Electrochemical sensors are a promising alternative due to their high sensitivity, simplicity, fast response, and low cost. Here we summarize various types of electrochemical sensors, including impedimetric, amperometric, and voltammetric sensors, for histamine determination (Table 4), which have more utility for monitoring within the rumen environment. Although these sensors are discussed in the context of histamine sensing, the types are applicable across numerous biomarkers.

Impedimetric Sensors. Due to their high specificity and affinity, impedimetric sensors offer a promising way to detect biomolecules (Sharma et al., 2016). Im-

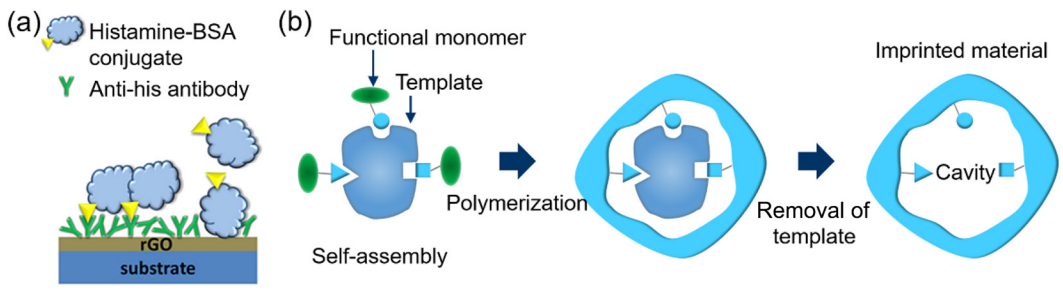

Figure 5. (a) Schematic illustration of physically adsorbed capture antibodies on the reduced graphene oxide (rGO) pattern exposed to histamine (his)-BSA conjugates. Total binding is the sum of specifically captured complexes via the antigen-antibody interaction and the unspecific binding of BSA alone (Delle et al., 2015). (b) Schematic representation of molecular imprinted polymer synthesis. Reproduced with permission from Wiley.

pedimetric sensors have previously been used to monitor a wide array of biomolecules, including histamine. Delle et al. (2015) developed a low-cost reduced graphene oxide-based histamine biosensor with an impedimetric readout technique [Figure 5(a)]. During sensor evaluation, the interaction between antihistamine antibodies on the graphene oxide surface as capture molecules and histamine-BSA conjugates as analyte molecules was observed, and researchers identified that free and bound histamine will form a complex with the antihistamine antibody. As a result, the impedance value increases with increasing histamine-BSA conjugate concentrations, and the developed biosensor showed a limit of detection (**LOD**) of 0.1 μM and linear range of histamine concentrations from 0.1 to 1 μM. The histamine level within the rumen ranges from 0 to 2.70 μM in normal rumen fluid (Dain et al., 1955) and can rise as high as 27 to 629 μM when pH levels drop to 4.5 (Suber et al., 1979). As such, considerable additional work will be needed to confirm whether these sensors are applicable for sensing within the biological range.

Toward this challenge, Ye et al. (2016) used antihistamine antibody-functionalized nanoporous alumina membranes to capture histamine by leveraging antihistamine antibody-modified magnetic nanoparticles. The impedance of the device increased as the histamine concentration increased, and displayed good linearity for histamine concentration from 1 μM to 40 mM, with the LOD reaching 3 nM, which covers the entirety of the biological range, making this sensing approach attractive as a strategy for monitoring ruminal histamine concentrations. The nanoparticles leveraged within the sensor also enhanced the blocking effect within the sensor, causing fewer ions to flow in the nanoporous alumina, further improving the detection sensitivity. The selectivity of biosensors within the rumen is critical because numerous existing technologies have challenges with interference of other molecules. Therefore, moving forward with technologies that allow for superior selectivity is essential for collecting good data that can lead to effective and informed management decisions. A major challenge with this nanoparticle-based sensor, however, is the feasibility for use within the rugged rumen environment and the ability to leverage the sensor for continuous monitoring.

Molecularly imprinted polymers functionalized as a biosensor could offer low-cost and rapid histamine determination that is more durable than other impedimetric sensors. In this approach, the polymer represents a synthetic receptors for a targeted molecule, similar to natural antibody-antigen systems (Horemans et al., 2010). As shown in Figure 5(b), fabrication of these sensors includes self-assembly of functional monomers around a molecular template, followed by initiating the polymerization of monomers with a crosslinker. The template is extracted from the resulting polymer, leaving behind complementary cavities (Feng et al., 2018; Sun et al., 2018). Because molecularly imprinted polymers are robust and inert in harsh environments, they are widely used in biosensing. Using histamine as an example, Bongaers et al. (2010) reported a fast histamine detection sensor. However, the binding of histamine was significantly correlated with the pH-dependent degree of protonation of both the histamine and the polymer. As such, moving toward these more robust and inert molecularly imprinted polymers presents new challenges, such as greater interference by other factors within the rumen.

Amperometric Sensors. Amperometry is another commonly used technique to measure concentrations of biomarkers. In this technique, current as a function of time is measured with a constant potential applied to the working electrode. In the histamine example, various types of histamine electrochemical biosensors with immobilized amine oxidases and dehydrogenases have been reported. Hibi and Senda (2000) presented a rapid detection of histamine bi-enzymatic biosensor by using a histamine oxidase assay with a peroxidase-modified

carbon paste electrode. The device showed that the current increased linearly as histamine increased, with an LOD of 0.069 μM. Pérez et al. (2013) employed diamine oxidase and horseradish peroxidase and a multiwalled carbon nanotube membrane that covered the screen-printed electrodes. This membrane type has high current response and excellent chemical stability. The sensor exhibited an LOD of 0.17 μM and an excellent positive linear relationship between current and histamine concentration from 0.3 to 20 μM, with R^2 equal to 0.99. In this work, the devices also showed excellent storage stability with evolution of sensitivity in 1 month, with decreases of 9.9 and 10.7% for continuous and interrupted use, respectively. Despite performing well relative to other similar sensors, biological sensing within the rumen will require considerable advancement upon these techniques because enzyme-based biosensors are not yet reliable for long-term continuous use, and tested ranges do not always map well to the biological range.

Biosensors that can detect histamine rapidly without enzyme have also been developed. For example, Shahzad et al. (2017) developed a fluorine-doped reduced graphene oxide-modified histamine sensor. This sensor demonstrated current increases with increased histamine concentration from 0.2 to 80 μM, and an LOD of 7 nM. This device has a long time stability and can be used over 2 mo without significant change in its response. As such, moving toward nonenzymatic amperometric biosensors may hold promise as a strategy to improve the life spans of sensors for rumen biomonitoring.

Voltammetric Sensor. A final common strategy for biomarker sensing relies on voltammetric sensing. In voltammetry, the concentration of the analyte is quantified by measuring the current when the potential is varied. Akbari-adergani et al. (2010) first reported a fast Fourier-transform continuous cyclic voltammetric method for the determination of histamine using a bare Au electrode. This sensor displayed an LOD of 3.1×10^{-3} nM, with a wide linearity range from 9.9×10^{-3} nM to 0.049 μM. As is commonly identified as a problem, this range is still far below the biological range within the rumen, making it of limited applicability for ruminal sensing. In an alternative approach, Degefu et al. (2014) used lignin deposited on the surface of glassy carbon electrodes and demonstrated linear dependence on concentration in the range 5 to 200 μM, with an LOD of 0.28 μM. The peak current decreased by only 4% for 1 wk, demonstrating decent long-term stability of the device, which, when coupled with the biological range of histamine, supports the strategy as a promising approach for real-time continuous monitoring of the rumen environment. Numerous similar approaches have been published, with similar advantages. For example, Geto et al. (2014) reported a sensor with linearity over the range 0.1 to 100 μM, with an LOD of 76 nM. Stojanović et al. (2016) developed a simple and rapid method for voltammetric determination of histamine with linearity over the range from 4.5 to 720 μM and a 3.8% difference in current response over 12 d. Dong et al. (2017) developed a histamine sensor with linearity from 0.09 to 900 μM and a 15.7% decrease in catalytic current over 2 wk. The consistency of these approaches in generating sensors that are able to detect biomarkers (in this example, histamine) within the biological range displayed in the rumen, with modest drift over the short term, holds promise for continued advancement toward real-time monitoring of the rumen environment.

Impact, Importance, and Future Directions. Ruminal biomarker sensing holds tremendous promise as a strategy to help contextualize generalized pH, temperature, and activity measurements to better explain the physiological experience of the animal at any given time. Although these different biomarker sensing techniques show excellent linearity, often within the biological range, high selectivity, and limited drift over short time scales, considerable additional development is needed to move toward their use in long-term, continuous monitoring of the rumen environment. In fact, given the drift occurring over a period of a few weeks, it may be infeasible to expect these sensors to reliably monitor biomarker concentrations for years at a time. However, that does not preclude their use in ruminal sensing. For example, a more intelligent sensor design would activate the biomarker sensors only when there is ambiguity in the data obtained from parameters monitored in real time. For example, perhaps a drop in pH occurs with depressed ruminal motility; a biomarker sensor for histamine could be activated in the short term to determine whether the signature of histamine concentration patterns aligns with what would be expected from an acidosis condition. Numerous challenges undoubtedly exist in realizing this time-sensitive and responsive approach to sensing, but it may be a more feasible way to integrate biomarker sensing into ruminal monitoring systems than expecting to develop continuous, real-time systems, at least in the immediate future.

Sensors for Monitoring Metabolite Concentrations

Monitoring of metabolite concentrations within the rumen would provide never-before-realized density of information to aid in the study and monitoring of fermentation. A major metabolite of interest is that of VFA, the primary energy source for ruminants (Dijkstra, 1994). Both yields of total VFA and composition

between the predominant VFA (acetate, propionate, and butyrate) in rumen fluid are known to determine the energy absorption efficiency of the utilization of VFA (Dijkstra et al., 1993). Therefore, real-time monitoring of the concentration and balance of the VFA in rumen fluid is important for understanding the relationship between feed intake and metabolism. Measurement of VFA has been widely researched (Chatterjee et al., 2018), with measurement methods including distillation (Siedlecka et al., 2008), titration (Lahav and Morgan, 2004), the Montgomery method (Montgomery et al., 1962), paper chromatography (Hiscox and Berridge, 1950), HPLC (Guerrant et al., 1982; Chen and Lifschitz, 1989; Peu et al., 2004), GC (Yang and Choong, 2001), and spectrofluorimetry (Robert-Peillard et al., 2009). However, those techniques are inappropriate for real-time monitoring of the rumen environment because of equipment requirements, incompatible output signal types (usually optical signal), and complicated sampling methods. For VFA detection in the rumen, an ideal sensor would include (1) strong chemical resistance, facilitating stable operation in the acidic environment, (2) outstanding sensitivity and selectivity for metabolites or biomarkers of interest, (3) small physical size that can be bolused through the esophagus, and (4) desired output signal type that enables easy signal acquisition, rapid signal processing, and wireless data transmission from the rumen. In this context, electrochemical biosensors are among the attractive candidates for potential application for VFA monitoring in the rumen. In this section, we review the current progress on VFA sensing techniques utilizing electrochemical biosensors that are suitable for real-time VFA monitoring in the rumen (Table 5).

Microorganism Electrochemical Biosensors. Microorganism electrochemical biosensors for VFA detection are classified into 2 different types: microbial electrochemical sensors and microbial fuel cells (**MFC**). In microbial electrochemical sensors, the permanent connection of the microbial metabolism and electrode is used to generate an analytical signal. The electroactive bacterial film is formed on the electrode and poised to a constant potential between the reference electrode (e.g., Ag/AgCl) and anode through oxidation of the analytes (Kretzschmar et al., 2018). Kretzschmar et al. (2016) reported an amperometric electrochemical sensor for inline detection of acetate using a microbial electrode. The sensor exhibited excellent linearity, with fixed 0.2 V vs. Ag/AgCl potential when the acetate concentration is in a range from 0 to 0.5 mM. In the cross-sensitivity test between acetate, butyrate, propionate, and VFA mixture, the sensor shows a proportional dependency only to the applied acetate concentration (Kretzschmar et al., 2017), suggesting it is highly sensitive to acetate only. However, given that the sensor was tested at acetate concentrations well below the usual biological range within the rumen, additional work is required to determine the feasibility of this MFC for monitoring acetate in the rumen in real time.

An alternative approach to acetate monitoring was taken by Atci et al. (2016), who developed a microbiosensor to measure acetate concentration utilizing acetate oxidation by *Geobacter sulfurreducens*-dominated biofilm [Figure 6(a)]. The sensor is enclosed in a glass case with a 30-μm tip diameter. This small form factor corresponds with the need for sensors that are small enough to be bolused via the esophagus, making it an attractive choice from a size perspective. The oxidation of the acetate by the biofilm occurs via the following reaction, where E is the electrical potential (He and Angenent, 2006):

$$\begin{aligned} &CH_3COO^- + 4H_2O \overset{G.sulfurreducens}{\rightarrow} \\ &2HCO_3^- + 9H^+ + 8e^- \left(E = -483\ mV_{Ag/AgCl}\right). \end{aligned} \quad [1]$$

Electrons (e^-) are generated from the biofilm and moved to the reference electrode, resulting in an analytic signal. The micro-biosensor exhibited excellent linearity in a range from 0 to 1.6 mM acetate concentration, with low LOD of ~79 μM. However, this sensor showed a significant interfering effect from other electron donors such as lactate, formate, pyruvate, or hydrogen. This interference, combined with testing well below the biological range again, suggests that considerable additional refinement, testing, and design updates may be required before this sensing system has utility in monitoring acetate in real time within the rumen environment.

The MFC electrochemical biosensors are classified into 3 different types, depending on their number of reaction chambers: single-chamber, dual-chamber, or triple-chamber biosensors (Cui et al., 2019). The single-chamber MFC biosensor is composed of the anodic (or cathodic) chamber, where the electroactive biofilms are incubated, and air cathodes. The basic structure of the single anodic chamber MFC, developed by Goud and Mohan (2011), is illustrated in Figure 6(b). The consortia of anaerobic bacteria are used as inoculum or biocatalyst in the anodic chamber. A semipermeable proton exchange membrane is placed between the anode and cathode. The anode is wholly submerged in the target solution, and the top region of the cathode is exposed to air. The electroactive biofilm generates the electrons and protons by oxidizing organic compounds in the anodic chamber, and the electrons are transferred to the cathode through an external circuit,

Table 5. Summary of microbial electrochemical biosensors for VFA detection[1]

Type	Inoculation	Anode	Cathode	Separator	Linear detection range	Response time (min)	Reference
MES	*Geobacter* sp.	Graphite rod/biofilm	Ag/AgCl (reference)	—	0–0.5 m*M*	—	Kretzschmar et al., 2016
MES	*Geobacter* sp.	Graphite rod/biofilm	Ag/AgCl (reference)	—	1–4 m*M*	—	Kretzschmar et al., 2017
MES	*Geobacter sulfurreducens*	Carbon microelectrode /biofilm	Ag/AgCl (reference)	—	0–1.6 m*M*	—	Atci et al., 2016
Single-chamber MFC	—	Carbon paper/PPy	Carbon paper/Pt	CEM (CMI-7000)	0–60 mg/L	—	Kaur et al., 2014
Single-chamber MFC	—	Carbon cloth	Carbon cloth	Carbon powder/ PTFE	0–1 g/L	—	Schievano et al., 2018
Single-chamber MFC	*Geobacter*, *Shewanella*, *Pseudomonas*	Carbon felt	Carbon cloth	PTFE	0.2–0.8 g/L 0.8–1.6 g/L	—	Jia et al., 2018
Single-chamber MFC	*Acinetobacter*, *Geobacter*, *Azospira*, *Agrobacterium*, *Acidovorax*, *Comamonas*	Graphite electrode	Stainless-steel tube	AEM (3361BW)	0–200 m*M*	10–120	Jiang et al., 2019
Dual-chamber MFC	—	Carbon paper (TGPH-120)	Carbon paper with 10% Pt	CEM (CMI-7000)	—	1–2	Kaur et al., 2013
Dual-chamber MFC	—	Graphite felt	Carbon fiber brush	CEM (CMI-7000)	0.25–0.75 m*M* 01–10 m*M*	5–25	Jiang et al., 2017
Dual-chamber MFC	—	Carbon brush	Graphite plate with Pt coating	AEM (AMI 7001)	0–20m*M*	60	Sun et al., 2019b
Dual-chamber MFC	—	Carbon brush	Titanium woven wire mesh with Pt coating	AEM (AMI 7001)	5–100 m*M*	60	Jin et al., 2017
Triple-chamber MFC	—	Carbon brush	Stainless-steel mesh	CEM (CMI-7000) AEM (AMI 7001)	1–30 m*M* 20–300 m*M*	300	Jin et al., 2016
Triple-chamber MFC	—	Carbon fiber brush	Graphite plate with Pt coating	CEM (CMI-7000) AEM (AMI 7001)	0–160 m*M*	180–300	Sun et al., 2019a

[1]MES = microbial electrochemical sensor; MFC = microbial fuel cells; PPy = polypyrrole; TGPH = carbon fiber composite paper sold by the Toray company; PTFE = polytetrafluoroethylene; CEM = cation exchange membrane; CMI-7000 = cation exchange membranes, sold by Membrane International Inc.; AEM = anion exchange membrane; AMI 7001 = anion exchange membranes, sold by Membrane International Inc.; 361BW = anion exchange membranes, sold by Shanghai Shanghua Water Treatment Materials Co. Ltd.

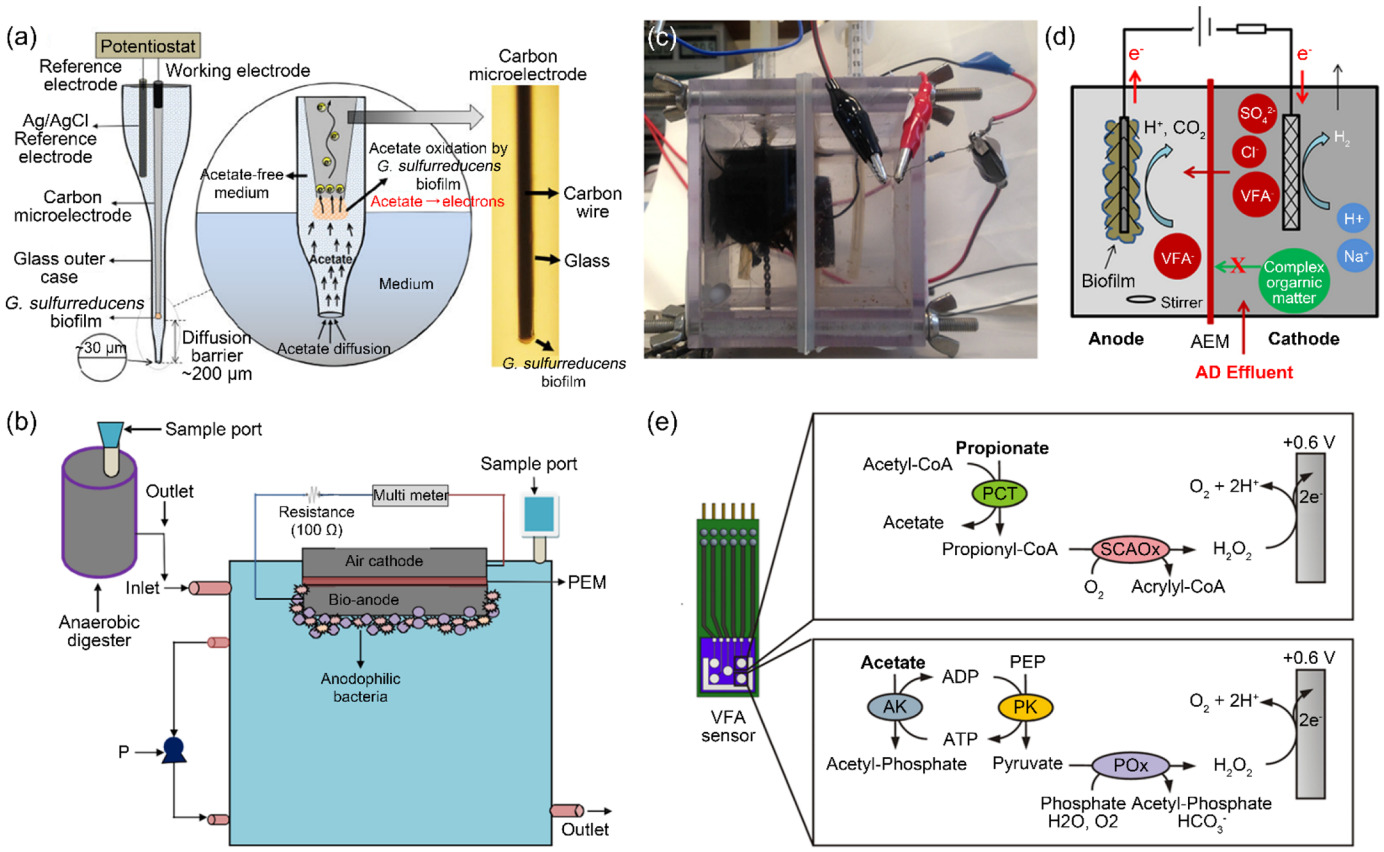

Figure 6. (a) Acetate micro-biosensor based on *Geobacter sulfurreducens*-dominated biofilm (Atci et al., 2016). Microbial fuel cell (MFC)-based electrochemical sensor for VFA detection. (b) Single-chamber MFC with proton exchange membrane (Goud and Mohan, 2011). (c) Electrochemical sensor with dual-chamber MFC reactor and (d) its schematic diagram (Jin et al., 2017). (e) Integrated enzymatic electrochemical biosensor for VFA detection (Rohlen et al., 2018). AEM = anion exchange membrane (X indicates that the complex organic matter could not pass through the AEM); e^- = electron; AD = anaerobic digestion; PEM = proton exchange membrane; CoA = coenzyme A; PCT = propionate CoA-transferase; SCAOx = short-chain acyl-CoA oxidase; AK = acetate kinase; PK = pyruvate kinase; Pox = pyruvate oxidase; PEP = phospho(enol)pyruvic acid monopotassium salt. Reproduced with permission from Elsevier (a, b, c, d) and Frontiers (e).

while protons and other cations migrate to the cathode through the membrane. In the MFC biosensor, the current signal, indicating the concentration of the analytes, is generated through this oxidization process. Although exposure to air is theoretically possible in the rumen (if the sensor is buoyant), the requirement of air exposure dramatically precludes the usefulness of this technique for rumen monitoring, due to challenges associated with disruptions when rumen fluid is mixing during contractions.

Despite this practical limitation, many efforts have recently been made to demonstrate high-performance single-chamber MFC biosensors for VFA detection (Jia et al., 2018; Schievano et al., 2018; Jiang et al., 2019). For example, Kaur et al. (2014) modified the surface condition of the electrodes in single-chamber MFC biosensors to improve temporal stability, repeatability, and response time. A functionalized polypyrrole coating on the carbon electrode surface, which forms a positively charged surface, is used to increase the total number of negatively charged electroactive bacteria on the electrode. Immobilization of the microbial community, by covering the natural polymer polyacrylamide with mediators, improved the catalytic action and stability of MFC biosensors. The biosensor exhibited repeatable signals in response to changes in concentrations of VFA ranging from 0 to 1 mmol; however, like the other MFC sensors, this range is well below the biological range of the rumen, and therefore further assessment of the suitability of this sensing platform is required to characterize relevance for rumen monitoring.

Toward the challenges of linearity, sensitivity, and specificity at higher VFA concentrations, Schievano et al. (2018) used MFC electrochemical biosensors for monitoring VFA concentrations in anaerobic digesters, and they found that the upper LOD of this device is much higher than in microbial electrochemical sensors. The MFC signal increased in parallel to VFA produc-

tion up to roughly 17 m*M* and then maintained constant signal output above the limit. Although 17 m*M* is still less than a third of normal rumen acetate concentrations, the higher LOD with this technology suggests the possibility of testing alternative microbially based technologies for real-time rumen sensing. To further support the goal of sensing at higher concentrations, Jia et al. (2018) developed an integrated dual single-chamber MFC biosensor, to improve linearity and stability. They reported an excellent linear relationship between output voltage from the MFC and VFA concentrations in ranges from 3 to 13 m*M* and 13 to 27 m*M*. Most recently, Jiang et al. (2019) reported that a submersible probe-type MFC-based electrochemical biosensor demonstrated outstanding linearity in a wide range of VFA concentrations, which also addresses the challenge of air access for this sensor type. The signal exhibited excellent linearity in a concentration range from 0 to 200 m*M* at the specific reaction time from 10 to 120 min. Moreover, the sensor demonstrated a good selectivity when VFA were in solution with other organic materials, such as cellulose, yeast extract, peptone, glyceryl trioleate, and formaldehyde. As the science of leveraging MFC-based sensing for VFA continues to advance, modifications and refinements on the approach leveraged by Jiang et al. (2019) may provide a promising method for evaluating the VFA concentrations within the rumen in real time. One challenge associated with the deployment of the existing sensor is related to the time-based specificity of sampling. Moving toward a more rapidly responding sensor with longer life span should be an additional goal to improve relevance of these technologies for monitoring the rumen environment.

Multichamber MFC biosensors have been suggested to improve the detection capacity in VFA sensing. The structure of the dual-chamber MFC biosensor includes anodic and cathodic chambers separated by an ion-exchange membrane, as shown in Figure 6(c) and (d) (Jin et al., 2017), whereas the triple-chamber MFC biosensor is composed of the anodic, middle, and cathodic chambers. The VFA or other negatively or positively charged ions pass through the ion-exchange membranes, and redox reactions occur in separated chambers, resulting in signal generation in the MFC biosensor. Because this sensor requires multiple reaction chambers, it has a larger form factor, which is a drawback for the VFA sensor to be integrated into a real-time metabolic monitoring module small enough to easily dose into the rumen. However, the multichamber MFC biosensor technique could improve detection range, reaction time, and stability, compared with single-chamber MFC biosensors. Kaur et al. (2013) reported that the reaction time of the dual-chamber MFC biosensor for the measurement of VFA concentration is in the range of several minutes. Jiang et al. (2017) developed cathode-shared dual-chamber MFC sensor arrays and obtained 2 linear detection ranges (0.25–0.75 m*M* and 1–10 m*M*) with acetate concentration change. Sun et al. (2019b) developed an MFC-based biosensor with a linear correlation between the current density and acetate concentrations in a range from 0.5 to 20 m*M* at different reaction times (1–5 h). This MFC biosensor exhibited higher sensitivity to acetate compared with other VFA such as butyrate and propionate. Jin et al. (2017) demonstrated a microbial electrolysis cell with 2 MFC chambers with an anion exchange membrane as a separator to improve VFA sensing performance of the biosensor [Figure 6(c) and (d)]. They achieved excellent sensitivity and linearity in a range from 5 to 100 m*M* of VFA concentrations as well as reducing the reaction time to 1 hr. The advantage of the microbial electrolysis cell is that the external power supply accelerates the reaction resulting from migration and microbial oxidation of carboxylic acids; however, reaction times still exceed 1 hr, meaning that readings of VFA concentrations within the rumen could occur at most once per hour. This frequency of determination is not much greater than can be achieved by hand-sampling through a fistula, and therefore additional refinements of the reaction rate are essential to improve the utility of these sensing mechanisms.

In the triple-chamber MFC, VFA ions in the middle chamber are transferred into the anodic chamber, whereas other complex organic compounds remain in the middle chamber. Thus, the current generated from the MFC is mostly proportional to VFA concentration in the solution of the middle chamber, and this helps the sensor by avoiding interference from other chemicals as well as by enhancing sensitivity and stability. Jin et al. (2016) demonstrated a triple-chamber MFC biosensor, which exhibited excellent linearity in 2 ranges of VFA concentration (1–30 m*M* and 30–200 m*M*) with a 5-h response time. Moreover, the sensor was very stable for a long period. They confirmed that the current signal from the sensor is reproducible and stable for 7 mo without membrane cleaning or replacement. Sun et al. (2019a) also developed an acetate sensor based on a triple-chamber MFC for anaerobic digestion monitoring. The sensor exhibited a linear relationship between current output and acetate concentration up to 160 m*M*. However, because other VFA, such as propionate and butyrate, can also be transferred through the anion exchange membrane, the sensor did not differentiate among VFA. Although these triple-chamber sensors are somewhat more protected against interfering compounds, the lack of selectivity among individual VFA, as well as the long reaction times, preclude their cur-

rent use in ruminal sensing. Future work focusing on power optimization to reduce the reaction time and membrane selection to improve selectivity among VFA is needed before the benefits of these sensors can be realized.

Enzymatic Electrochemical Biosensors. An alternative approach to microbially based VFA sensing is enzymatic electrochemical biosensors. A unique characteristic and advantage of the enzymatic electrochemical biosensors is that their biocatalyst reacts only with a specific analyte. Thus, usually, enzymatic electrochemical biosensors exhibit excellent selectivity, making them a good target technology for testing strategies to differentiate among VFA. Enzymatic electrochemical biosensors have been investigated for VFA sensing, especially acetate and propionate. For acetate detection, an immobilized trienzyme mixture (acetate kinase, pyruvate kinase, and pyruvate oxidase) has been used as the biocatalyst (Mizutani et al., 2001; Mieliauskiene et al., 2006). The catalytic reaction among the enzymes produces H_2O_2 from the acetate, and this process enables amperometric detection of acetate through oxidation of H_2O_2. Mizutani et al. (2001) immobilized a trienzyme mixture on a coated electrode, and the concentration of acetate was monitored at −0.4 V vs. Ag/AgCl by measuring oxygen consumption of the reaction. They were able to successfully quantify the oxygen consumption in a concentration range from 5 to 0.5 m*M* without interference from the reaction product, H_2O_2. Mieliauskiene et al. (2006) demonstrated a trienzyme modified biosensor by using immobilized acetate kinase (AK), pyruvate kinase (PK), and lactate dehydrogenase with a poly(ethyleneglycole) diglycidyl ether film containing brilliant cresyl blue as an electrochemical mediator. The sensor exhibited excellent linearity to acetate concentration in the range of 0.2 to 8 m*M*, with an LOD of 0.13 m*M* at +50 mV vs. Ag/AgCl of working potential. Although these sensors have the advantage of being selective for individual VFA (i.e., acetate), they are still below the normal biological range, and additional work is needed to evaluate the suitability of the sensing approach for monitoring acetate in the biological range.

To further demonstrate the promise of this approach, the technique has been adapted to propionate monitoring. An immobilized enzyme mixture, including propionate CoA transferase and short-chain acyl-CoA oxidase, was used as the biocatalyst for detection of propionate using the following sequential reactions (Rajashekhara et al., 2006; Sode et al., 2008):

$$\text{Propionate} + \text{Acetyl} - \text{CoA} \overset{\text{PCT}}{\rightarrow} \text{propionyl} - \text{CoA} + \text{Acetate}; \quad [2]$$

$$\text{Propionyl} - \text{CoA} + O_2 \overset{\text{sACO}}{\rightarrow} \text{Acrylyl} - \text{CoA} + H_2O_2. \quad [3]$$

Quantification of propionate was determined by detecting H_2O_2 using colorimetric methods. The researchers reported excellent linearity up to 50 μ*M* with a low LOD down to 1 μ*M*. Sode et al. (2008) also demonstrated electrochemical detection of propionate using these reactions but quantified H_2O_2 production from the enzymes using amperometric measurement at 0.6 V versus Ag/AgCl. This approach demonstrated linearity up to 100 μ*M* with an LOD of 10 μ*M* propionate. Despite advances, these examples still detect propionate well below the biological range, and further work expanding upon the linearity of responses is needed to determine the suitability of these technologies for ruminal monitoring.

Additional challenges for ruminal monitoring include interference, sensor utility (e.g., multipurpose sensors), and senor life span. Based on the same catalytic reactions produced by multiple enzymes, Röhlen et al. (2018) demonstrated an integrated enzymatic biosensor array that can monitor acetate and propionate simultaneously [Figure 6(e)] for 2 mo, with minimal interference from other organic compounds. Oxidation of H_2O_2 is used to quantify concentration of VFA through applied working potential (+0.6 V vs. Ag/AgCl). The H_2O_2 is oxidized through the following reaction and generates free electrons (e^-):

$$H_2O_2 \overset{\text{+0.6 V vs. Ag/AgCl}}{\rightarrow} O_2 + 2H^+ + 2e^-. \quad [4]$$

The sensor exhibited excellent sensitivity (2.2 ± 0.41 μA/m*M* for propionate and 0.27 ± 0.05 μA/m*M* for acetate) and linearity (0 to 1.5 m*M* for propionate and 0 to 1.4 m*M* for acetate). Furthermore, the sensor exhibited low interference from other interferents, such as formate, ethanol, butyrate, valerate, caproate, and glycerol, and signal stability for 2 mo.

FUTURE CHALLENGES IN RUMEN BIOSENSING

Despite marked progress in sensing technologies for important analytes within the rumen, several limitations to current research prototypes and commercial technologies must be addressed before widespread biomonitoring of the rumen environment is feasible. These challenges primarily relate to (1) sensor size, (2) sensor life span, (3) sensor selectivity or durability to environmental interference, (4) sensor relevance to the biological range, and (5) interpretation of information obtained from sensors. Before benefits associated with ruminal sensing can be realized, considerable advance-

ment in these areas is needed for most sensing applications.

These challenges are also not independent of one another. For example, current pH sensors are large and bulky, easily broken, difficult to miniaturize, and slow in response. Alternative pH sensors, such as miniaturized all-solid-state potentiometric pH sensors and all-solid-state EGFET-based pH sensors, have been developed; however, stability and repeatability of sensing performance remain challenging (Kaur et al., 2010; Zhang et al., 2017; Dijkstra et al., 2020). Therefore, future research addressing demonstration of small form factor, stable electrode materials that can survive in the rumen environment for an extended period is imperative for practical application.

For biomarkers such as histamine, various electrochemical sensors with low limits of detection, suitable linearity ranges, and excellent selectivity have been developed. However, these sensors are typically tested in clinical and laboratory environments, which provide much greater control than could be expected in the rumen. Additionally, the long-term stability of biomarker sensors is a challenge, and finding more intelligent sensing strategies to get around the need for long-term continuous biomarker sensing may be a more promising strategy than attempting to create sensors with zero drift over time.

For metabolites such as VFA, various biosensors are available, which may be appropriate for in vivo monitoring; however, evaluation of VFA sensors based on microorganisms and enzyme biocatalysts within the rumen is warranted. Additionally, although these technologies have excellent sensitivity, stability, and linearity, they are typically tested at VFA concentrations well below the biological range, meaning that their usefulness for VFA sensing within the biological range is still a question. Depending on the approach, these sensors also face the challenge of selectivity, with few demonstrated sensors capable of differentiating among VFA. Refining and improving these sensing approaches, to focus on solutions with high sensitivity, selectivity, linearity, and stability, and appropriate LOD, is necessary before in vivo detection of VFA will be practical.

The final, and perhaps greatest, challenge associated with rumen biosensing comes after the successful development of a sensor: namely, the interpretation of data. As has been repeatedly demonstrated and discovered with existing sensing systems (e.g., pH, temperature, activity), making actionable decisions based on sensor data is a major challenge. This is further complicated by the fact that we do not currently have the research capacity to measure at the same density and frequency without sensors, as could be realized with them. In other words, it is challenging to know the value of the data a sensor might generate until we have a working version of the sensor. In that regard, the development, refinement, testing, and use of rumen sensors is a bit of a risk. Although we can speculate on the biological responses that might be relevant (e.g., temperature spikes during estrus), it is challenging to really conceptualize how messy or clean sensor data may be with regard to that desired outcome until viewing it during analysis. For example, spikes in temperature may also be dependent on feed and water intake, thermal environment, health status, stress, and more. When considering such a generalized physiological indicator, it is difficult to imagine a scenario where sufficient granularity in responses is tracked to reliably determine that a particular shape and size of spike is associated with estrus and a different shape or size of spike is associated with another factor. As such, contextualizing these generalized physiological indicators may require multimodal sensing, because conformational information from another sensor may help explain the behaviors observed by generalized sensors. Irrespective of this potential, the development and refinement of the sensor cannot end with appropriate physical performance factors; it must also acknowledge how the sensed data can be leveraged on farm to make actionable decisions, which will require considerable testing, monitoring of ground-truth responses, and development of reliable and transparent analytics. These subjects, along with the challenges associated with data transfer and sensor location and localization, should be the subject of future reviews.

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