TECHNOLOGY IN ANIMAL SCIENCE

Efficacy of statistical process control procedures to identify deviations in continuously measured physiologic and behavioral variables in beef steers experimentally challenged with *Mannheimia haemolytica*

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Abstract

The objective of this experiment was to determine if statistical process control (SPC) procedures coupled with the remote continuous collection of feeding behavior patterns, accelerometer-based behaviors, and rumen temperature can accurately differentiate between animals experimentally inoculated with *Mannheimia haemolytica* (MH) or PBS. Thirty-six crossbred steers (BW = 352 ± 23 kg) seronegative for MH were randomly assigned to bronchoselective endoscopic inoculation with MH (n = 18) or PBS (n = 18). Electronic feed bunks were used to measure DMI and feeding behavior traits, accelerometer-based neck collars measured feeding- and activity-behavior traits, and ruminal thermo-boluses measured rumen temperature. Data were collected for 28 d prior to and following inoculation. Steers inoculated with MH exhibited elevated ($P < 0.02$) levels of neutrophils and rumen temperature indicating that MH challenge effectively stimulated immunologic responses. However, only nine of the MH steers exhibited increased serum haptoglobin concentrations indicative of an acute-phase protein response and one displayed clinical signs of disease. Shewhart charts (SPC procedure) were used for two analyses, and sensitivity was computed using all MH-challenged steers (n = 18), and a subset that included only MH-challenged haptoglobin-responsive steers (n = 9). Specificity was calculated using all PBS steers in both analyses. In the haptoglobin-responsive only analysis, DMI and bunk visit (BV) duration had the greatest accuracy (89%), with accuracies for head-down (HD) duration, BV frequency, time to bunk, and eating rate being less (83%, 69%, 53%, and 61%, respectively). To address the diurnal nature of rumen temperature, data were averaged over 6-h intervals, and quarterly temperature models were evaluated separately. Accuracy for the fourth quarter rumen temperature was higher (78%) than the other quarterly temperature periods (first = 56%, second = 50%, and third = 67%). In general, the accelerometer-based behavior traits were highly specific ranging from 82% for ingestion to 100% for rest, rumination, and standing. However, the sensitivity of these traits was low (0% to 50%), such that the accuracies were moderate compared with feeding behavior and rumen temperature response variables. These results indicate that Shewhart procedures can effectively identify deviations in feeding behavior and rumen temperature patterns to enable subclinical detection of BRD in beef cattle.

Key words: bovine respiratory disease, feeding behavior, *Mannheimia haemolytica*

Abbreviations

AUC	area under the curve
BRD	bovine respiratory disease
BVDV	bovine viral diarrhea virus
BV	bunk visit
EID	electronic identification tag
FN	false negatives
FP	false positive
HD	head-down
MH	Mannheimia haemolytica
RUT	reticulo-rumen temperature
SPC	statistical process control
TTB	time to bunk
TN	true negatives
TP	true positive

Introduction

The bovine respiratory disease (BRD) complex represents the largest economic loss due to mortality and morbidity within the feedyard sector of the beef industry (Duff and Galyean, 2007; Schneider et al., 2009). Despite improvements in vaccines, antimicrobials, and animal management strategies designed to prevent BRD, mortality related to BRD has tended to increase (Engler et al., 2014). Current BRD detection methods rely on visual observation and are highly specific but lack sensitivity (92% and 27%, respectively; Timsit et al., 2016), indicating that a large proportion of cattle develop BRD during the feeding period, but are never diagnosed or treated. The utilization of clinical observations for disease detection is incongruent with evolution, as cattle are prey animals that have developed instincts to conceal symptoms of illness from predators (Noffsinger and Locatelli, 2004).

Recent developments in sensor technologies enable real-time measurements of behavior patterns, ruminal temperature, feed intake, and feeding behavior on an individual-animal basis (Lancaster et al., 2009; Timsit et al., 2011; Kayser and Hill, 2013; Theurer et al., 2013). These data collection systems, coupled with robust mathematical models, can accurately identify deviations in animal behavior prior to the onset of BRD (White et al., 2016). Increased accuracy of BRD detection would likely improve the efficacy of antimicrobial treatment and reduce the duration of subclinical disease leading to an improvement in animal welfare (Cusack et al., 2003; Schaefer et al., 2007).

Statistical process control (SPC) was initially proposed by Shewhart (1931) to identify atypical variation in a process. Statistical process control was initially applied within manufacturing industries, but their applications have also been used in the financial and healthcare industries (Montgomery, 2009; De Vries and Reneau, 2010). Previous studies have evaluated the use of SPC procedures to monitor feeding duration and ruminal temperature prior to the onset of BRD in high-risk and Holstein calves (Quimby et al., 2001; Timsit et al., 2011; Kayser et al., 2018a). However, these reports used visual observations to determine the health status of the animals, and, due to the aforementioned inaccuracy of visual observation, it is difficult to ascertain the accuracy of the SPC procedures for the detection of preclinical BRD. Our objectives were to determine the sensitivity, specificity, and accuracy of Shewhart control charts to detect deviations in behavioral or physiological responses in steers experimentally inoculated with *Mannheimia haemolytica* (MH) or phosphate buffer solution (PBS). An additional objective was to determine which of the three data collections systems (feed intake and feeding behavior, accelerometer-based behavior, and

rumen temperature) more effectively discriminated between the MH- and PBS-treatment animals.

Materials and Methods

All animal care and use procedures were in accordance with the guidelines for use of Animals in Agricultural Teaching and Research as approved by the Texas A&M University Institutional Animal Care and Use Committee (IACUC # 2015-0379) as well as the Texas A&M University Institutional Biosafety Committee (IBC # 2015-068).

Animals

A total of 36 Angus crossbred steers (initial BW = 386 ± 25 kg) originating from the McGregor and Beef Cattle Systems herds belonging to Texas A&M University were used in this study. All animals were considered clinically healthy based upon daily observations for 28 d prior to challenge and were seronegative for MH determined by paired serum samples collected 45 d apart. Furthermore, all animals were confirmed negative for persistently infected bovine viral diarrhea virus (BVDV), through the collection of an ear notch prior to study commencement, which was analyzed with the BVD antigen-capture ELISA (BVD-Ag ELISA, Texas Veterinary Medical Diagnostic Laboratory, College Station, TX).

Experimental design and treatment arrangements

The data used for this study were previously collected (Kayser et al., 2018b) to evaluate the effects of live yeast (LY) (*Saccharomyces cerevisiae* boulardii strain I-1079 at 25 g/hd/d; ProTernative Advantage, Lallemand Animal Nutrition) supplementation on animal performance prior to and post MH challenge. Therefore, steers were stratified by herd origin, initial BW, MH titer dilution, exit velocity (objective measure of animal temperament; Olson et al., 2019), and prestudy ADG, then a random number generator was used to assign steers to one of four treatments (9 hd/treatment) arranged in a 2×2 factorial array. Supplementation with live yeast, however, did not affect the SPC procedures sensitivity, specificity, or accuracy (Kayser et al., 2018b). Therefore, the effect of dietary yeast treatment was not considered in the current analysis, only two treatment groups were evaluated: steers inoculated with MH ($n = 18$) or PBS ($n = 18$).

The MH inoculum was prepared as described by Mosier et al. (1995). Briefly, MH serotype A1 was grown on trypticase soy agar containing 5% sheep blood for 18 h at 37°C in 7% CO₂. Colonies were inoculated into brain-heart infusion broth and incubated for 16–18 h at 37°C with aeration. The bacteria were then centrifuged at $3,000 \times g$ for 15 min at 4°C and washed twice with PBS. After the second wash, the bacteria were centrifuged as before and the pellet was resuspended in PBS at a final concentration of $1.2\text{--}1.4 \times 10^9$ CFU/10-mL dose. After preparation, the inoculum was placed on ice in a dark cooler and transported to the site of inoculation (approximately 17 km).

Steers were fed for a total 56 d, and baseline data collection began on day –28 d prior to MH inoculation on day 0. To avoid any chance of PBS animals receiving MH via contamination of the instruments used for inoculation, the PBS treatment group was inoculated prior to the MH treatment group. The inoculations were performed with an endoscope as described by Theurer et al. (2013). Steers were restrained in a standard hydraulic squeeze chute that allowed more specific restraint of the head. An endoscope 1 m in length was inserted into the ventral

meatus of one nostril and passed into the trachea to the level of the right apical lung lobe bronchi allowing visualization of the opening. A sterile bronchoalveolar lavage tube was inserted into the endoscope portal and passed until the tip of the lavage tube was visible emerging from the endoscope. Thereafter, the lavage tube was advanced another 1–2 cm into the opening of the right apical lung lobe bronchi. Once in place, steers in the PBS treatment group were administered 10 mL of PBS followed by a 60 mL flush of PBS for a total of 70 mL. Following the treatment of all the PBS animals, the endoscope was disinfected with chlorhexidine solution and rinsed with saline. Subsequently, steers ($n = 18$) in the MH treatment groups were challenged with 10 mL of MH serotype A1 at $1.2\text{--}1.4 \times 10^9$ CFU/mL followed by 60 mL of PBS for a total of 70 mL. Following this procedure, steers in both treatment groups were observed for adverse effects of the challenge procedure.

Throughout the 56-d study, all animals were group housed in four pens at Texas A&M University's Beef Cattle Systems Research Center in College Station, TX. The MH- and PBS-challenged steers were comingled within pen and there were equal number of steers from each treatment housed together. During the study, steers were offered a growing diet *ad libitum*, which was provided twice daily at 0700 and 1600 hours.

Data collection

Clinical illness scoring

All steers were monitored by two experienced evaluators twice daily for clinical signs consistent with BRD. The visual evaluation employed in the experiment has been described in detail by [Step et al. \(2008\)](#). The criteria included signs of depression, inappetence, and respiratory distress. Evaluators assigned a severity score of 1 to 4, where 1 was assigned for mild, 2 for moderate, 3 for severe, and 4 for moribund. Steers receiving a 3 or greater were removed from the pen and given a full medical evaluation ([Kayser et al., 2018b](#)). Rectal temperature was measured during the medical evaluation and if it exceeded 40.5°C , antimicrobial therapy was administered. All steers were returned to their home pen after evaluation. Temperature readings, BW, and administration of antimicrobial therapies were recorded for every animal that was examined for clinical signs consistent with BRD.

Hemogram

Blood samples (7 mL EDTA and 10 mL Vacutainer with no additive; Becton, Dickinson and Company, Franklin Lakes, NJ) were collected via jugular venipuncture using an 18-gauge needle on days -4 , 0 , 1 , 2 , 3 , 5 , 7 , 10 , and 14 , relative to challenge. The EDTA samples were immediately submitted to a commercial lab (Texas A&M Veterinary Medical Diagnostic Laboratory, College Station, TX) for total and differential white blood cell determination. Blood counts were performed with an automated hemocytometer (ADVIA 120, Siemens Healthcare Diagnostics, Tarrytown, NY) using the factory-installed cattle setting (ADVIA 120 Multispecies System software, version 2.206 MS, Siemens Healthcare Diagnostics). The hemocytometer counts leukocytes, erythrocytes, and platelets by optical scatter and fluorescence. Differential leukocyte percentages were determined by visual cell counts on modified blood smears and absolute counts were calculated using the total leukocyte count from the hemocytometer.

To harvest serum, samples were allowed to clot then were centrifuged at $3,000 \times g$ for 20 min at 20°C , then stored in duplicate aliquots at -20°C until subsequent analysis. Serum haptoglobin concentration was determined at the West Texas

A&M University Ruminant Health and Immunology Laboratory (Canyon, TX) with a commercial, bovine-specific sandwich ELISA kit (Immunology Consultants Laboratory, Inc., Portland, OR). The haptoglobin analysis had an intra- and interassay coefficient of variation of 11.4% and 16.1%, respectively. The haptoglobin measures were used as an indicator of the effectiveness of the challenge. Quantification of haptoglobin response was accomplished by calculating area under the curve (AUC) values for each steer in the MH treatment using Proc Expand in SAS 9.4 (SAS Institute, Cary, NC). Two separate analyses were performed: the first included all steers, and the second included only steers from the MH whose haptoglobin AUC exceeded 20 mg/dL/d ([Figure 3](#)).

Serum concentrations of cortisol were determined as described by [Littlejohn et al. \(2016\)](#). A solid-phase radioimmunoassay (DSL-2100; Diagnostic Systems Labs, Webster, TX) using antiserum-coated tubes was prepared according to the manufacturer's directions. Serum cortisol samples were analyzed in duplicate, and concentrations were determined based on a standard curve generated from known concentrations of cortisol using Assay Zap software (Biosoft, Cambridge, UK). The minimum detectable cortisol concentration for this assay was 1.2 ng/mL, and the inter-assay coefficient of variation was 8.8%.

DMI and feeding behavior

All pens were equipped with electronic feedbunks (GrowSafe Systems Ltd., Airdrie, AB, Canada) to facilitate the collection of feed intake and feeding behavior data on an individual-animal basis. The GrowSafe system consisted of feed bunks equipped with load bars to measure feed disappearance, and an antenna located within each feed bunk to record animal presence via detection of electronic identification tag (EID). Assigned feed disappearance rates were computed daily for each feed bunk to assess the data quality and averaged 98% throughout the 56-d study. Feeding behavior traits were based on the frequency and duration of BV events. A BV event began when the EID of an animal was first detected, and ended when the time between consecutive EID recordings exceeded 100 s, when the same animal was detected at another feed bunk, or when the EID of another animal was detected at the same feed bunk ([Mendes et al., 2011](#)). BV frequency was defined as the number of independent events recorded regardless of feed consumed, and BV duration as the sum of the lengths of all BV events recorded during a 24-h period. Feed intake was allocated to individual animals based on continuous recordings of feed disappearance during each BV event. Head-down (HD) duration was computed as the sum of the number of times the radio-frequency identification (RFID) tag for an animal was detected each day multiplied by the scan rate of the GrowSafe system (1.0 s) and is a proxy of time the animal is actively eating from the bunk. Time to bunk (TTB) was computed daily as the interval length between the time of feed-truck delivery within the pen and each animal's first BV event following feed delivery. A subroutine of the GrowSafe 6000E software (Process Feed Intakes) was used to compute daily feed intake. For this study, the eating rate was computed as the ratio of daily DMI to daily BV duration.

Rumen temperature

Radiofrequency biothermal boluses (ThermoBulus, Medria, Châteaubourg, France) were inserted into the rumen of all steers prior to initiation of the study (day -28). The ThermoBulus continuously recorded reticulorumen temperature (RUT) at 5-min intervals. A proprietary algorithm was used to remove the variation in RUT due to drinking events. To reduce the variance

induced by the diurnal pattern of rumen temperature, summary statistics were computed for 6-h time periods, with quarter 1 ranging between 0000 and 0600 hours, quarter 2 ranging between 0600 and 1200 hours, quarter 3 ranging between 1200 and 1800 hours, and quarter 4 ranging between 1800 and 2400 hours. Summary statistics were computed daily for the four quarters.

Accelerometer-based traits

The Feed Phone system (Medria, Châteaubourg, France) is composed of an Axel collar and Radio Base station. Feeding and activity behavior traits are generated from data recorded by the Axel sensor which was attached to the collar and securely fitted around the steers' neck. The sensor consists of a micro-electromechanical tri-axial accelerometer that quantifies changes of inclination, lateral, and vertical accelerations on a continuous basis. Nine metrics were recorded over 5-min intervals, and were automatically transmitted to the radio base station and thereafter a web-based data center. Processing algorithms on servers converted raw data into animal behaviors, and the most dominant behavior within a 5-min interval was reported (Delagarde and Lemonnier, 2015). There were five reported mutually exclusive behaviors: ingestion (feeding duration), rumination, rest, other activity (duration of unidentified behaviors), and over activity (estrus behavior). Standing was also reported which was not mutually exclusive with the other behaviors.

Statistical process control procedures

Charting procedure

An SPC chart is a graphic display of a process over a given time period. Shewhart (1931) first proposed the use of a control chart methodology to monitor the variance and mean of a process to identify when a system goes out of control to improve product quality. Control charts contain a centerline, which represents the mean or target value of the process while in control, and upper or lower control limits that are based on the variance of the process (Figure 1). The control limits are set by the architect of the chart based upon the behavior of the process, and the process is deemed out of control when plotted observations

Figure 1. Shewhart chart of DMI for a steer experimentally inoculated with MH challenge.

exceed the bounds of these control limits (Quimby et al., 2001; Montgomery, 2009).

This analysis utilized the Shewhart method with three signaling strategies: effect can signal in both directions, effect can only signal on the lower threshold, and effect can only signal on the upper threshold. Eating rate, rest, standing, over activity, and other activity were all set to signal in either direction. The feeding behavior traits: DMI, BV frequency, BV duration, and HD duration were set to only signal on the lower threshold. All of the rumen temperature measures were set to only signal on the upper threshold.

The performance of a Shewhart chart is predicated upon the design, which includes the selection of the σ threshold values. The σ threshold values were evaluated from 1 through 7 at intervals of 0.5 (Figure 2). This was done to identify the optimal σ threshold for each effect. All Shewhart charts were generated using PROC Shewhart in SAS 9.4 (Cary, NC).

Accumulative parameter estimation

Previous studies which have used SPC procedures to monitor the health of cattle estimated their parameters (μ and σ) in a post hoc manner, meaning that the parameters are calculated after all the data have been collected (Sowell et al., 1999; Quimby et al., 2001). Therefore, it is possible for a chart to signal based on parameters that are estimated with data collected in the future, and it is difficult to assess the validity and accuracy of the monitoring process using this methodology. Although this method serves as a statistical test and quickly identifies changes in the mean and variation of a process, it would be difficult to use this method of parameter estimation to monitor health in real-time.

For this study, initial parameter estimation was accomplished using the first 4 d (-28 through -25) of the 56-d study as a reference period to calculate baseline μ and σ for each animal. Thereafter, daily observations were used to recompute parameters in an accumulative manner (Kayser et al., 2018a; Mertens et al., 2008) using all of the available data to that time point in the data set. Therefore, every sequential time series measurement includes more data in estimating model parameters than the previous observations. These parameters were used to transform the daily observations to a standard normal basis. Plotted values

Figure 2. Average sensitivity, specificity, and accuracy values for the Shewhart chart monitoring DMI at different sigma levels.

are the daily observation subtracted from the accumulating μ and divided by the accumulating σ . Utilizing the accumulating methodology enables the chart to behave as it would in real-time application. This procedure also allows for the rapid implementation of the monitoring process due to the relatively short reference period required for initial parameter estimation (Kayser et al., 2018a; Mertens et al., 2008). Furthermore, the accuracy of those parameters increases every day the process is monitored.

Model accuracy determinations

The MH challenge group was used to assess the sensitivity of the Shewhart procedure. In order for the signal to be deemed a true positive (TP, effect signaled for steer after inoculation), the signal had to exceed the bounds of the control limits. Steers challenged with PBS were used to assess the specificity of the Shewhart procedure, if an effects value exceeded the threshold at any time the signal was classified as a false positive (FP, effect went out of control on a PBS steer). The inverse of these classifications was categorized as false negatives (FN, chart fails to signal when steer challenged with MH) and true negatives (TN, fails to signal in PBS challenge steers), respectfully. Ratios of these classifications: sensitivity (TP/TP + FN), specificity (TN/[FP + TN]), and accuracy ((TP + TN)/[TP + FP + FN + TN]) were used to evaluate the efficacy of the monitoring systems for identifying when an animal becomes morbid (Kayser, 2018a). These diagnostic measures were calculated using PROC FREQ (SAS 9.4). Furthermore, 95% confidence intervals (CI) were computed within the FREQ procedure to identify the statistical difference between the variables; this method would be synonymous to pair-wise t-tests, except that the CI were computed using a chi-square distribution instead of a Gaussian distribution. A high-performing model will exhibit high sensitivity, specificity, and therefore a high accuracy. The signal day is the average number of days after inoculation that the chart first signaled the system was out of control. Proc Univariate (SAS 9.4) was used to construct 95% CI for signal day.

Results and Discussion

Clinical illness scores were not different between the inoculation treatments ($P = 0.65$). Throughout the study, only one steer (MH treatment) received a clinical illness score ≥ 3 and during the health evaluation exhibited a rectal temperature $>40.5^{\circ}\text{C}$. The steer was treated with an antimicrobial, quickly recovered, and no re-treatments or mortalities occurred throughout the study. Gross clinical signs of disease resulting from the challenge model were not expected, as previous studies that used a similar MH strain with intra-tracheal delivery reported that MH-challenged animals appeared clinically normal or had slight increases in clinical illness scores that did not differ from clinically normal (Corrigan et al., 2007; Capik et al., 2015).

The MH challenge in this study stimulated an immune response as evident by increased ruminal temperature and circulating neutrophils. However, there was an apparent divergent haptoglobin response in MH-challenged animals. Haptoglobin AUC was computed from day -4 through 14 relative to challenge, to quantify the magnitude of the acute-phase protein response exhibited by MH-challenged animals. Individual AUC values were used to classify MH-challenged animals as responsive or nonresponsive based on an arbitrary threshold AUC of ± 20 mg/dL/d (Figure 3). Although characterizing the impact of the MH challenge on inflammation markers was not the focus of this

Figure 3. AUC of serum concentrations of haptoglobin for individual steers that were experimentally inoculated with MH. Haptoglobin was measured from day -4 through day 14 for every animal, and plotted values are presented in ascending sequential order by day for each animal.

paper, the haptoglobin response to the MH challenge appears to be indicative of the severity of the challenge, which affect the chart performance. This threshold was selected based upon plotted values and numerical separation between animals. Within the haptoglobin-responsive group, the minimum haptoglobin concentration (33 mg/dL/d) response was 3-fold greater than the maximum haptoglobin concentration (11 mg/dL/d) response in the haptoglobin-nonresponsive group. The haptoglobin response induced by MH challenge was not affected by LY supplementation or pen assignment. Furthermore, the chute-order sequence by which animals were inoculated with MH did not differ between the haptoglobin-responsive and nonresponsive groups (data not presented).

The acute-phase response is induced by pro-inflammatory cytokines, which are protein hormones that act as messengers between local site of injury and hepatocytes that synthesize acute-phase proteins (Petersen et al., 2004). Haptoglobin is an acute-phase protein that binds free hemoglobin in blood circulation and creates haptoglobin-hemoglobin complexes, which are thought to sequester and limit the amount of Fe available for bacterial proliferation (Petersen et al., 2004; Richeson et al., 2016). In the current study, only half of the MH-challenged steers exhibited an increase in haptoglobin concentration. The mechanisms responsible for this individual-animal response to MH challenge are not clear. Although not statistically significant ($P = 0.18$), MH-challenged steers that were haptoglobin nonresponsive had numerically higher cortisol concentrations than MH-challenged steers that were haptoglobin responsive the day following challenge (Figure 4). In support of these findings, Richeson et al. (2016) reported that haptoglobin concentration responses to a multivalent respiratory vaccine were attenuated in animals that received prior injections of dexamethasone. The authors concluded that dexamethasone, which has been used for many decades as an anti-inflammatory, modulated the production of pro-inflammatory cytokines, namely IL-6, which reduced the production of acute-phase proteins (Richeson et al., 2016).

Haptoglobin-responsive MH-challenged steers had greater ($P < 0.05$) circulating haptoglobin concentrations than non-haptoglobin-responsive MH-challenged and PBS-challenged steers from days 2 through 5 after challenge. There were no differences ($P > 0.05$) in haptoglobin concentrations between

Figure 4. Serum cortisol (top), neutrophil (middle), and haptoglobin (bottom) concentrations for steers experimentally challenged with MH that did and did not exhibit a haptoglobin response and steers challenged with PBS (control). Plotted values represent least squares mean $\pm$ 95% CIs for the PBS ($n = 18$), MH challenge with haptoglobin response ($n = 9$), and no response ($n = 9$). Challenge response type by day interaction P -values were: cortisol ($P = 0.18$), neutrophil ($P < 0.01$), and haptoglobin ($P < 0.01$) serum concentration. Within day values that are separated by error limits differ ($P < 0.05$).

the non-haptoglobin-responsive MH-challenged and PBS-challenged steers for any day following the inoculation. Similarly, all MH-challenged steers had increased ($P < 0.05$) concentrations of circulating neutrophils compared with PBS-challenged steers following the inoculation. Furthermore, MH-challenged haptoglobin-responsive steers had greater ($P < 0.05$) circulating neutrophil concentrations 1 d after inoculation than MH-challenged non-haptoglobin-responsive steers. Similarly to the neutrophil response, steers challenged with MH exhibited greater ($P < 0.05$) ruminal temperature (Figure 5) than PBS inoculated steers following inoculation. Furthermore, MH-challenged haptoglobin-responsive steers had a greater ($P < 0.05$) rumen temperatures than nonresponsive MH-challenged steers.

Steers challenged with MH were used to estimate the sensitivity of the SPC algorithms. Due to the aforementioned

Figure 5. Rumen temperature for steers experimentally challenged with MH that did and did not exhibit a haptoglobin response and steers challenged with PBS (control). Plotted values represent least squares mean $\pm$ 95% CIs for 18 animals in the PBS group and 9 animals for the MH response and no response groups. There was a challenge by hour interaction ($P < 0.01$) and within day, values that are separated by error limits differ ($P < 0.05$).

differential haptoglobin responses to the MH challenge, sensitivities of detection algorithms were evaluated separately for all MH-challenged steers (Table 1) and the haptoglobin-responsive MH-challenged steers (Table 2). Both analyses included all PBS-challenged steers to estimate specificity, with the specificity results presented in both tables for comparative purposes. Table 1 is included for completeness and to allow the reader to evaluate the results. However, it would be redundant to discuss both tables; therefore, only Table 2 will be discussed, where sensitivity was estimated using only the haptoglobin-responsive MH-challenged steers ($n = 9$). Three categories of continuous-measured response variables are represented and evaluated for their effectiveness in combination with the SPC procedures for detecting BRD. Throughout this discussion, it is relevant for the reader to consider the severity of the challenge, which was mild, and that these systems would potentially be more accurate when monitoring a naturally occurring BRD case.

In general, there are two types of charting procedures that are used to monitor a process. Shewhart charts are designed to identify mean shifts greater than 3σ and have no memory, meaning current observations are not affected by preceding observations. Cumulative summation charts (Page, 1954) incorporate all information in the sequence of sample values by plotting the cumulative sums of the deviations of the sample values from a target value (Montgomery, 2009). Shewhart charts are more accurate at detecting large mean shifts, while cumulative summation charts detect small sustained mean shifts. While both cumulative summation and Shewhart charts were evaluated in this study, the cumulative summation procedures were less accurate in detecting physiological and behavioral responses to MH challenge. Thus, only the Shewhart procedure results are presented.

All SPC procedures require the design architect to set the thresholds for the process that will signal when the process has changed. The process threshold limits are designed to separate between normal and atypical variation. When the limits are low, the SPC procedure will have high sensitivity and low specificity,

Table 1. Performance of feeding behavior, accelerometer, and physiologic response variables in differentiating between MH-challenged and PBS-challenged steers over a 56 d feeding study

Effect	Sensitivity	Specificity	Accuracy	Signal day ¹	Signal direction ²	Sigma level ³
Number of steers	18	18				
Feeding behavior traits						
DMI, kg/d	72.2 ^{de}	77.8 ^{bc}	75.0	0.08 ^a	↓	3.5
BV duration, min/d	61.1 ^{cde}	88.9 ^{bc}	75.0	0.09 ^a	↓	3.5
BV frequency, events/d	38.9 ^{abc}	72.2 ^{bc}	55.6	0.14 ^a	↓	3.0
HD duration, min/d	72.2 ^{de}	77.8 ^{bc}	75.0	0.15 ^a	↓	3.0
Time to bunk, min	94.4 ^e	5.56 ^a	50.0	0.88 ^{bc}	↑	3.0
Eating rate, g/min	16.7 ^{abc}	88.9 ^{bc}	52.8	4.00 ^{abc}	↕	4.5
Accelerometer-based traits						
Ingestion, min/d	37.5 ^{abc}	82.4 ^{bc}	59.9	1.33 ^{abc}	↓	2.5
Rumination, min/d	12.5 ^{ab}	100 ^c	56.3	0.50 ^{abc}	↓	4.0
Rest, min/d	31.3 ^{abc}	88.2 ^{bc}	59.7	0.20 ^a	↕	3.0
Standing, min/d	0.00	100 ^c	50.0		↕	4.0
Over activity, min/d	0.00	94.1 ^{bc}	47.1		↕	4.0
Other activity, min/d	18.8 ^{abc}	76.5 ^{bc}	47.6	3.67 ^{abc}	↕	3.0
First quarter rumen temperature ⁴						
Average, °C	50.0 ^{bcde}	55.6 ^b	52.8	1.00 ^b	↑	6.5
Minimum, °C	50.0 ^{bcde}	72.2 ^{bc}	61.1	1.00 ^b	↑	5.5
Maximum, °C	44.4 ^{abc}	77.8 ^{bc}	61.1	1.00 ^b	↑	7.0
Second quarter rumen temperature ⁵						
Average, °C	38.9 ^{abc}	61.1 ^{bc}	50.0	1.00 ^{bc}	↑	6.0
Minimum, °C	11.1 ^a	88.9 ^{bc}	50.0	0.50 ^{abc}	↑	6.0
Maximum, °C	33.3 ^{abc}	66.7 ^{bc}	50.0	1.17 ^{bc}	↑	5.0
Third quarter rumen temperature ⁶						
Average, °C	50.0 ^{bcde}	77.8 ^{bc}	63.9	0.22 ^a	↑	5.5
Minimum, °C	44.4 ^{abc}	77.8 ^{bc}	61.1	0.00 ^a	↑	4.0
Maximum, °C	50.0 ^{bcde}	72.2 ^{bc}	61.1	0.22 ^a	↑	5.0
Fourth quarter rumen temperature ⁷						
Average, °C	66.7 ^{de}	72.2 ^{bc}	69.4	0.00 ^a	↑	5.0
Minimum, °C	55.6 ^{bcde}	94.4 ^c	75.0	0.00 ^a	↑	5.0
Maximum, °C	61.1 ^{cde}	83.3 ^{bc}	72.2	0.00 ^a	↑	6.0

¹Signal day is computed as the average of days post-inoculation that the effect signaled for steers challenged with MH only.

²Upper arrow indicates that the chart could only signal on the upper threshold. Lower arrow means chart could only signal on lower threshold and arrow in both directions indicates that the chart could signal on either threshold.

³Sigma level is the magnitude of standard deviations that the signal thresholds were most accurate.

⁴Firstquarter = 0000 through 0600 hours.

⁵Second = 0600 through 1200 hours.

⁶Third quarter = 1200 through 1800 hours.

⁷Fourth quarter = 1800 through 2400 hours.

^{a-e}Estimates within column with unlike superscripts differ ($P < 0.05$).

and as the thresholds are increased, sensitivity decreases and specificity increases (Figure 2). Results for the physiological and behavioral traits are presented at the σ threshold at which the response variable was most accurate (Tables 1 and 2).

One of the most accurate feeding behaviors was DMI with a sensitivity of 78% and specificity of 100% (equal with BV duration, accuracy = 89%). Reductions in DMI are frequently observed in clinically ill cattle, and inappetence is often used within clinical illness scoring rubrics (Sowell et al., 1999; Daniels et al., 2000; Jackson et al., 2016). However, commercial feeding operations are not equipped to measure individual-animal feed intake, and the current cost associated with feed intake systems would preclude them from wide-spread deployment in commercial feeding operations. BV and HD duration had equal sensitivity of 89%, although BV duration had greater specificity of 89% compared with HD duration, which was 78%. Similar to these results, Quimby et al. (2001) monitored BV frequency of high-risk calves with a cumulative summation (CUSUM) chart for the 3-h post-feed delivery, and reported a sensitivity of 85% and specificity of 95% resulting in the overall accuracy of 90%.

Furthermore, the CUSUM chart in this study detected morbidity 4.5 d prior to standard detection by feedyard personnel. Utilizing a CUSUM, Kayser et al. (2018a) reported that DMI exhibited the greatest accuracy (80%) in detecting a naturally occurring BRD outbreak in young purebred bulls. However, in that study, HD duration was 79% accurate, exhibited greater sensitivity than DMI (77% vs. 67%) and signaled 4 d prior to observed clinical symptoms. Comparisons between the current study and others with regard to signal day are difficult. Previous studies have compared a disease detection system against visual observation, and the disease detection system consistently identifies animals prior to observed clinical signs; therefore, a negative value is desirable. For the current experimental design, healthy animals were experimentally challenged with MH, thus the SPC detection of signal day represents the average duration from inoculation to when the algorithm signals. Therefore, it is not possible for the signal day to be <0. However, we can make comparisons between the magnitudes of duration across behavioral traits in this study. Of the six feeding behavior traits evaluated, DMI, BV duration, BV frequency, and HD duration,

Table 2. Performance of feeding behavior, accelerometer, and physiologic response variables in differentiating between MH-challenged haptoglobin responsive and PBS-challenged steers over a 56-d feeding study

Effect	Sensitivity	Specificity	Accuracy	Signal day ¹	Signal direction ²	Sigma level ³
Number of steers	9	18				
Feeding behavior traits						
DMI, kg/d	77.8 ^{bc}	100 ^c	88.9	0.14 ^a	↓	4.0
BV duration, min/d	88.9 ^{bc}	88.9 ^{bc}	88.9	0.13 ^a	↓	3.5
BV frequency, events/d	66.7 ^{bc}	72.2 ^{bc}	69.4	0.17 ^a	↓	3.0
HD duration, min/d	88.9 ^{bc}	77.8 ^{bc}	83.3	0.25 ^a	↓	3.0
Time to bunk, min	100 ^c	5.56 ^a	52.8	1.33 ^{ab}	↑	3.0
Eating rate, g/min	33.3 ^{abc}	88.9 ^{bc}	61.1	4.00 ^{abc}	↓	4.5
Accelerometer-based traits						
Ingestion, min/d	50.0 ^{bc}	82.4 ^{bc}	66.2	1.75 ^{ab}	↓	2.5
Rumination, min/d	25.0 ^{ab}	100 ^c	62.5	0.50 ^{ab}	↓	4.0
Rest, min/d	37.5 ^{abc}	100 ^c	68.8	0.33 ^{ab}	↓	4.0
Standing, min/d	0.00	100 ^c	50.0		↓	4.0
Over activity, min/d	25.0 ^a	70.6 ^{bc}	47.8	7.00 ^c	↓	3.0
Other activity, min/d	25.0 ^{ab}	76.5 ^{bc}	50.7	3.50 ^{abc}	↓	3.0
First quarter rumen temperature ⁴						
Average, °C	66.7 ^{bc}	44.4 ^{ab}	55.6	1.00 ^b	↑	5.5
Minimum, °C	44.4 ^{bc}	88.9 ^{bc}	66.7	1.00 ^b	↑	6.5
Maximum, °C	55.6 ^{bc}	77.8 ^{bc}	66.7	1.00 ^b	↑	7.0
Second quarter rumen temperature ⁵						
Average, °C	33.3 ^{abc}	66.7 ^{bc}	50.0	1.00 ^{ab}	↑	6.5
Minimum, °C	11.1 ^{ab}	94.4 ^{bc}	52.8	1.00	↑	7.0
Maximum, °C	33.3 ^{abc}	66.7 ^{bc}	50.0	1.30 ^{ab}	↑	5.5
Third quarter rumen temperature ⁶						
Average, °C	55.6 ^{bc}	77.8 ^{bc}	66.7	0.40 ^{ab}	↑	5.5
Minimum, °C	44.4 ^{bc}	77.8 ^{bc}	61.1	0.00 ^a	↑	4.0
Maximum, °C	55.6 ^{bc}	72.2 ^{bc}	63.9	0.40 ^{ab}	↑	5.0
Fourth quarter rumen temperature ⁷						
Average, °C	77.8 ^{bc}	77.8 ^{bc}	77.8	0.00 ^a	↑	6.5
Minimum, °C	77.8 ^{bc}	94.4 ^{bc}	86.1	0.00 ^a	↑	5.0
Maximum, °C	77.8 ^{bc}	83.3 ^{bc}	80.6	0.00 ^a	↑	6.0

¹Signal day is computed as the average of days post-inoculation that the effect signaled for steers challenged with MH only.

²Upper arrow indicates that the chart could only signal on the upper threshold. Lower arrow means chart could only signal on lower threshold and arrow in both directions indicates that the chart could signal on either threshold.

³Sigma level is the magnitude of standard deviations that the signal thresholds were most accurate.

⁴First quarter = 0000 through 0600 hours.

⁵Second quarter = 0600 through 1200 hours.

⁶Third quarter = 1200 through 1800 hours.

⁷Fourth quarter = 1800 through 2400 hours.

^{a-e} Estimates within column with unlike superscripts differ ($P < 0.05$).

all signaled in less than 1 d (0.14–0.25 d). For an animal-health monitoring system to be successful, it will need to have high sensitivity and specificity, and be able to alert early during the preclinical stages of the disease process for antimicrobial therapy to be effective. The accuracies of BV duration and DMI responses were similar, with HD duration being the second most accurate feeding behavior. This suggests that monitoring attendance at the feed bunk could be as effective as monitoring DMI for preclinical disease detection. Furthermore, BV duration would be expected to be less expensive to measure than DMI because it would not require the use of electronic scales to measure feed disappearance. In a direct comparison of observation by pen riders with a geolocation-based system that monitored BV frequency and duration, MacGregor et al. (2015) reported that the technology system reduced the incidence of initial treatments (19.6% vs. 38.2%; $P < 0.01$), improved treatment success rates (81.5% vs. 67.6%; $P < 0.01$), and reduced medication costs (\$34 vs. \$40; $P < 0.04$). These results suggest that BV frequency is a useful behavioral response variable for monitoring the onset of BRD with repeatable results.

TTB had the greatest sensitivity (100%), although it had the lowest specificity, resulting in a low overall accuracy of 53%. In this study, steers were weighed on a weekly basis prior to inoculation, and so were acclimated to being handled through the processing facility. The increased time required to inoculate steers on the day of challenge or the frequency of weighing steers post-inoculation may have disrupted the PBS-inoculated steers' TTB to a greater extent, resulting in a lower specificity and an overestimation of sensitivity. Eating rate had relatively low sensitivity (33%), although the specificity was high at 89%. Interestingly, eating rate did not signal as out of control until 4 d after the challenge suggesting that this behavior has a delayed response to the challenge. Jackson et al. (2016) reported deviations in eating rate 1–3 d prior to the onset of BRD in growing bulls utilizing a broken-slope linear regression model. Furthermore, they observed an increase in eating rate for bulls prior to observed clinical signs of BRD, suggesting that these bulls were eating at a faster rate in an effort to conserve energy. In the current analysis, there was no specific direction in which eating rate signaled, which is why

the algorithm was allowed to signal on both the upper and lower thresholds. Estimates of sensitivity for eating rate in the current analysis are poor; however, future research endeavors should continue to evaluate the mechanism for the delayed impact and direction in which the behavior changes as an animal becomes morbid.

The Feed Phone system is an accelerometer-based behavior monitoring system that is primarily used in dairy ruminant production. The accelerometer is attached to a neck collar and can differentiate between feeding and ruminating durations (Delagarde and Lemonnier, 2015). Although, neck collars have not been used in beef cattle production, accelerometer-based neck collars or ear tags have considerable potential to be used in animal-health monitoring systems for preclinical disease detection. Ingestion, which is a proxy for DMI, was the most sensitive (82%) of the accelerometer-based response variables evaluated in this study. Rumination had high specificity (100%), and in fact, never falsely signaled in the PBS-challenged steers. However, the sensitivity of rumination was low (25%). Rumination is paramount to maintaining a healthy environment for the rumen microbiome and follows a circadian rhythm (Beauchemin, 1991). Van Hertem et al. (2013) reported that night-time reductions in rumination duration occurred immediately prior to the detection of lameness in dairy cows. The duration of rumination has also been shown to be effective in the detection of the onset of calving (Büchel and Sundrum, 2014). However, in the current analysis, rumination provided little value in detecting responses to the MH challenge. Rest and standing had equal specificities of 100%; however, their sensitivities were also poor. In fact, the sensitivity for standing was 0% (which is why signal day for standing is blank; Table 2). Over activity and other activity had equal sensitivities of 25%, and had comparable specificities of 71% and 77%, respectively, which resulted in overall accuracies of 48% and 51% for over activity and other activity, respectively. Reduced activity is a common observation in cattle afflicted with lameness or diseases such as BRD (Richeson et al., 2018). Carroll and Forsberg (2007) proposed that the reduction in activity is a compensatory response related to increased energy demands required to produce pro-inflammatory cytokines, acute-phase proteins, antibodies, and mount a febrile response associated with the hyper-metabolic state in disease-infected animals. Pillen et al. (2016) utilized pedometers to monitor alterations in behavioral activities of high-risk cattle that were clinically diagnosed with BRD. Calves that succumbed to BRD reduced their activity up to 6 d prior to visual detection of clinical signs, and the mean separation was greatest the day before detection. Furthermore, Pillen et al. (2016) reported reductions in standing time, step count, and lying bouts the day before clinical detection, and concluded that accelerometer-based activity sensors would be effective for detection and management of sick cattle. The differential results in the described and current study may be related to the analysis method; Pillen et al. (2016) used a post hoc time-series model and compared healthy to clinically ill calves. Other reasons for differentiation may be the pedometer is more precise in collecting activity data than an accelerometer on a collar or a naturally occurring BRD event exerts greater influence on activity than the MH challenge.

In general, the feeding and activity behavior traits measured by the accelerometer-based system were highly specific but not sensitive; therefore, either the sensor does not measure the behaviors with enough precision to detect those behavior changes or the behavior was not affected by the challenge. DMI and BV duration were both effective measurements at detecting

the challenge and did not falsely signal on the PBS animals; therefore, it was surprising that ingestion did not perform better.

Rectal temperature is regularly used as a criterion to diagnose BRD, and is typically the only objective measurement used to determine the health status of animals (Smith, 2015). One of the challenges with rectal temperature is that it can be difficult to obtain because it requires moving an animal from the pen to a handling facility for restraint (Rose-Dye et al., 2011). Further, rectal temperature is a single point-in-time measurement and not always indicative of BRD. Capik et al. (2015) examined the rectal temperature patterns among beef calves experimentally challenged with MH and reported that clinical illness scores were not associated with rectal temperature. Hanzlicek et al. (2010) measured rectal temperature three times daily in beef steers experimentally challenged with MH, and found that time of day affected rectal temperature, being greatest in the early evening (morning = 39.6, noon = 39.4 and evening = 40.2°C). Furthermore, regardless of time of day, rectal temperature always exceeded their upper reference (39.5°C) limit, which was attributed to high environmental temperatures and the restraint stress associated with the physical examination. One of the benefits of using rumen biothermal sensors to monitor body temperature is that it is a continuous measurement, which enables the determination of core body temperature patterns and deviations of patterns on an individual-animal basis. Sensitivity (78%) was equal for the average, minimum, and maximum rumen temperature measured during the fourth quarter of the day. Subsequently, temperature measured in the fourth quarter had greater accuracy than temperature measured during the other three quarters. Accuracies for average, minimum, and maximum rumen temperature were 78%, 86%, and 81%, respectively. Furthermore, all fourth quarter rumen temperature metrics signaled the day of inoculation. Temperature measured during the other three quarters were less accurate, which may be due to an increase in ruminal temperature variance associated with the steers' feeding activities. Timsit et al. (2011) monitored RUT in an effort to examine the efficacy of this biosensor to detect the onset of BRD in young Holstein bulls after arrival to a feedyard. Reticulo-rumen hyperthermia exhibited a positive predictive value of 73%, and in the bulls that were correctly identified, the hyperthermia response was observed 1–3 d prior to clinical symptoms. In concordance with these studies, Schafer et al. (2007) monitored ocular surface temperature with an infra-red camera and reported a positive predictive value of 80%. Furthermore, animals were identified by the camera 4–6 d prior to the onset of clinical symptoms of BRD. The relatively high sensitivity measured in the current study and previous reports confirms the value of using temperature-based sensors in animal-health monitoring systems for preclinical detection of BRD.

Conclusion

The utilization of sensors to continuously monitor physiological and behavioral responses offers opportunities to develop robust animal-health monitoring systems for more accurate detection of BRD cases. Adoption of these systems would improve efficacy of antimicrobial protocols, and minimize the economic impact and animal suffering from BRD. Despite the fact that clinical disease was not detected in this study, results indicate that subtle shifts in behavioral/physiological parameters can be effectively detected using SPC procedures, which have application for preclinical detection of BRD in feedlots. Results from this study demonstrated that DMI and BV duration were more accurate

than the accelerometer-based behavioral traits for the detection of individual-animal responses to the MH challenge, with the accuracy of fourth-quarter-minimum rumen temperature being intermediate. Additionally, results from this study demonstrated the utility of Shewhart procedures to identify sensors that can most precisely measure physiological or behavioral responses that are indicative of preclinical onset of disease. Results from the current study will aid in future sensor development to provide cost-effective monitoring systems for the detection BRD in cattle.

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