Instant Implementation of Raman-Based PAT With MAVERICK® System for Monitoring Glucose and Lactate

Application Note

Repligen Corp. now owns the life sciences PAT product portfolio of 908 Devices Inc. Please contact Repligen for further inquiries.

The MAVERICK® System from Repligen provides an in-line, Raman-based PAT solution, for monitoring and control of glucose, lactate, and biomass in up to 6 bioreactors right out of the box.

Introduction

When managing a bioprocess, it is essential to monitor and control several critical process parameters (CPP) to maintain optimal cell culture conditions, ensure product quality, and maximize yield. Multivariate optical sensing technologies often require substantial expert configuration and set-up time that can take months or years, and significant expense.[1,2] The MAVERICK System offers the advantages of in-line Raman process analytical technology (PAT) without the cost and headaches inherent to the implementation of conventional process spectroscopy-based methods. Unlike conventional Raman analyzers, which rely on empirical calibration of spectral data to off-line reference measurements, the MAVERICK System utilizes a *de novo* model that does not require empirical trial-and-error "training" on bioprocess data.[3] In other words, the levels of glucose and lactate are measured by their chemically specific Raman scattering signal. For a technology with a traditionally complex setup built on process-specific conditions and the combined signals (specific or unspecific) from a complex cell culture, the MAVERICK System offers an accessible, plug-and-play solution.

Here we describe the straightforward workflow to set up the MAVERICK System and start generating robust in-line data in as little as 60 minutes. We also present data from examples spiking fresh media with serial concentrations of glucose and lactate. We tested more than 15 media types used to support the growth of popular bioprocess cells including CHO, HEK293, and T-cells.

Instant Implementation of In-Line Monitoring of Process Parameters with the MAVERICK System

The MAVERICK System consists of an optical immersion probe, a central control/display hub, and measurement module (Figure 1). Because the MAVERICK System does not require the user to develop a chemometric model to interpret Raman spectra, the implementation of this PAT device in a bioprocess is quick and straightforward. Figure 2 shows the few steps required to set up and start using the MAVERICK System for monitoring of key process parameters.

The MAVERICK System Hub allows for independent monitoring and control of up to six bioreactors simultaneously, with no loss of duty cycle or optical throughput. This delivers valuable insights into your bioprocess, reduces the risks of contamination and human error, eliminates the need for unreliable auto-samplers, and decreases overall costs. The output values for glucose, lactate, and biomass are provided via standard CSV, OPC UA, or analog outputs for immediate control of feed pumps or trigger signals. The full Raman spectra are also provided for additional offline modeling as desired.

Figure 1. Components of MAVERICK System: Optical immersion probe (A), measurement module (B), and a central monitoring hub (C). One hub can manage up to 6 modules and bioreactors.

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Figure 2. Setting up of MAVERICK System for in-line monitoring of process parameters is as simple as 1-2-3: (1) MAVERICK System is calibrated using the provided calibration standards. (2) The probe is autoclaved. (3) MAVERICK System can begin monitoring key process parameters in real time. The average time to start collecting in-line data (excluding autoclaving time) is 60 minutes.

Evaluation of MAVERICK System Precision, Linearity, Accuracy, and Selectivity

The measurements obtained from the MAVERICK System typically will provide a precision of <0.1 g/L for both glucose and lactate. For example, when fresh BalanCD HEK293 medium (Fujifilm) was measured for 20 hour under stable conditions (pH 7.05, 37°C, 125 RPM stirring) in a 3 L bioreactor, MAVERICK measurements at 1 minute reporting interval showed a standard deviation of 0.09 g/L for glucose and 0.04 g/L for lactate.

To evaluate the consistency, linearity, and selectivity of MAVERICK System measurements, known quantities of glucose and lactate were serially spiked into a range of CHO, HEK293, T-cell, and other cell culture media samples (Table 1). These media already contained glucose but no lactate based on the off-line measurements. The concentration of glucose in the un-spiked media was measured using an off-line analyzer, the BioProfile FLEX2 analyzer (Nova Biomedical),

Table 1. Media evaluated in spiking experiment.

Media Type	Media Name	Media Type	Media Name
CHO	• Gibco CD CHO Medium • Gibco OptiCHO Medium • Gibco CD FortiCHO • Gibco Efficient Pro Medium • Gibco ExpiCHO Stable Production Medium • SAFC EX-CELL Advanced CHO Medium • Cytiva Hyclone ActiPro	**T-cell/Stem cells**	• Gibco AIM-V Medium (serum free) • FujiFilm PRIME-XV T cell Expansion XSFM • Gibco CTS OPTmizer Pro Medium
HEK293	• Pepro PeproGrow HEK293 Media • SAFC EX-CELL CD HEK293 Viral • Vector Medium • Gibco LV-MAX Production Medium • Gibco 293SFM II SFM for Suspension Cultures	**Other**	• Gibco DMEM • SAFC EX-CELL CD Hybridoma Medium • Cytiva CDM4Mab Hybridoma Medium

and used to determine the glucose concentrations in the spiked samples. Over the 17 media tested, the glucose concentrations covered a range of 0–20 g/L in the spiked samples. Figure 3 and Figure 4 show the actual added concentration of glucose and lactate in each spiked sample against the change measured by the MAVERICK System. Linearity was excellent across the wide range of media types tested, demonstrating that the MAVERICK System is able to report glucose and lactate concentrations accurately with the *de novo* model for glucose and lactate specific measurements in diverse media conditions.

The spiking experiments provide quantitative information about the selectivity of the MAVERICK System measurements. The IUPAC (International Union of Pure and Applied Chemistry) definition of selectivity is "the extent to which a method result is influenced by other interferences in the matrix." In an ideal circumstance, the addition of a particular interferent would have a near-zero effect on the reported analyte concentration. The selections determined from the spiking experiments were -0.033 g/L glucose per 1 g/L lactate, and -0.026 g/L lactate per 1 g/L glucose. These values are very close to theoretically ideal (zero), demonstrating very high selectivity.

The spiking experiments provide an evaluation of the accuracy of glucose and lactate measurements in various HEK293, CHO, and other media (list of media shown in Table 1). Across the 17 types of media, percent recovery was excellent and comparable to the accuracy of the reference analyzer. Spiked concentrations across the full range were also very consistent in percent recovery, demonstrating robust performance regardless of media formulation. Taken together, these data suggest that the MAVERICK System measurements accurately represent the spiked glucose and lactate concentrations in the various media (Figure 5). Note that these were single measurements for each media type.

Conclusion

MAVERICK Systems provide a plug-and-play, in-line, Raman-based PAT solution for monitoring and control of glucose, lactate, and biomass in up to 6 bioreactors. The MAVERICK System is easy to set up and enables instant implementation of PAT, generating accurate, precise, linear, and selective in-line measurements across a wide range of media used typically in mammalian cell culture (including CHO and HEK293 media) for the production of biotherapeutics.

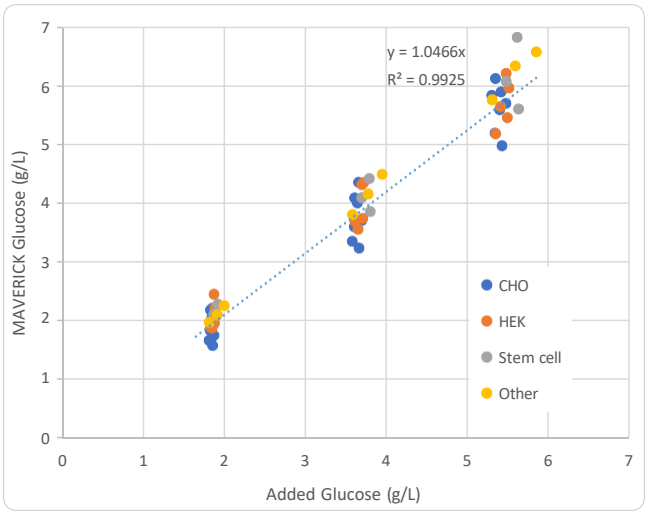

Figure 3. Spiking of known concentrations of glucose into CHO media, HEK293 media, T-cells/stem cell media, and other media. Actual spike concentrations (x-axis) plotted against the MAVERICK System reported values (y-axis).

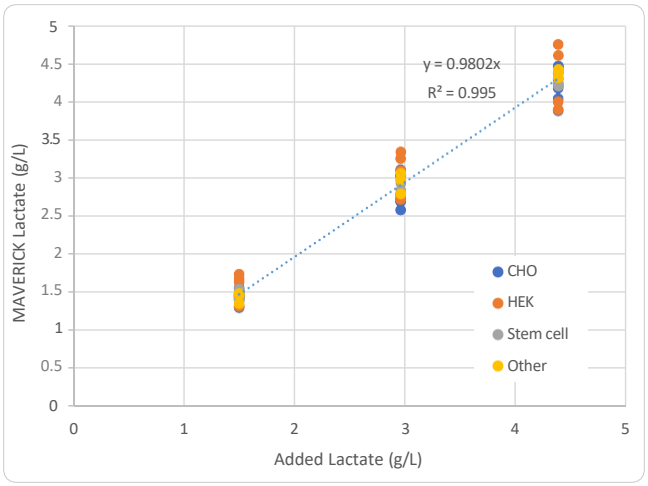

Figure 4. Spiking known concentrations of lactate into CHO media, HEK293 media, T-cells/stem cell media and other media. Actual spike concentrations (x-axis) plotted against the MAVERICK System reported values (y-axis).

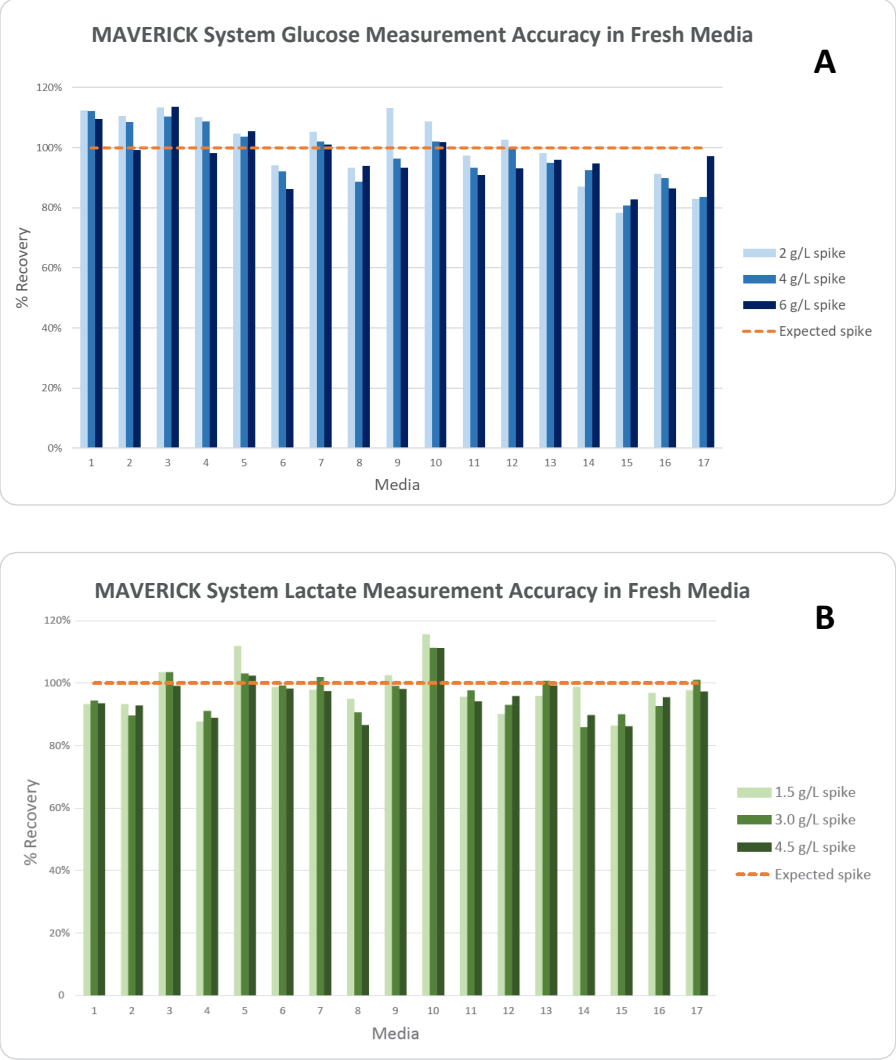

Figure 5. Percent recovery of analyte concentration using MAVERICK System. A): Glucose, B): Lactate. Results are calculated as a percent recovery (100% x measured/spiked) for the addition of analyte. Most fresh media contain glucose, but no lactate, in the formulation. Each media and spiked media were single measurements.

References

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