

Abstract

Fed-batch culture processes are commonly used for the production of various biotherapeutic and other industrial commodities. A widely employed nutrient feed control strategy for both cell culture and microbial fermentation processes is direct feedback control, in which the nutrient feed is directly controlled by the nutrient, i.e., glucose, concentration. However, various iterations of this feeding approach exist which may not be conducive to culture growth and productivity. In order to optimize culture performance, the means by which the substrate is fed to the culture is just as, if not more, important as maintaining the desired media substrate levels.

An automated feedback control platform, which employs a continuous feed strategy based on the culture's real-time nutrient consumption rate, has been developed by FlowNamics®. This integrated platform consists of the Seg-Flow® automated on-line sampling system, a nutrient analyzer and a feed pump. The Seg-Flow system was evaluated for its ability to precisely control media glucose concentrations in both low and high consumption rate culture simulation models. The results showed that the integrated Seg-Flow system was able to precisely control media glucose concentrations at the prescribed levels through real-time glucose consumption rate calculation and continuous feeding.

Evaluating the Seg-Flow Feed Control Platform

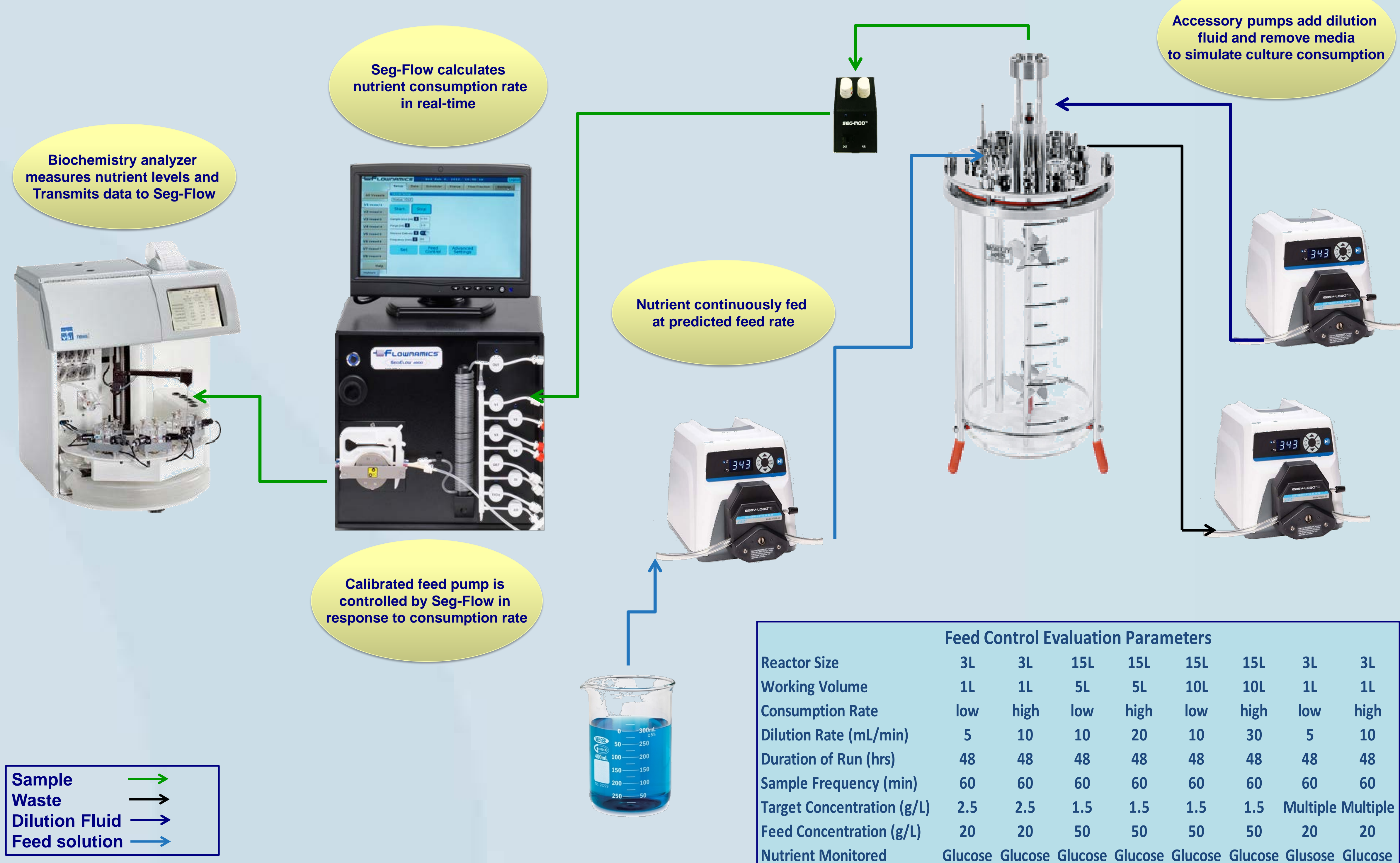
Evaluation:

- Precisely control media nutrient concentrations at $\pm 10\%$ of the prescribed setpoint in culture simulation models.
- Demonstrate the utility and versatility of the Seg-Flow Feed Control Platform across a matrix of scales and nutrient concentration setpoints.

Culture Simulation Models:

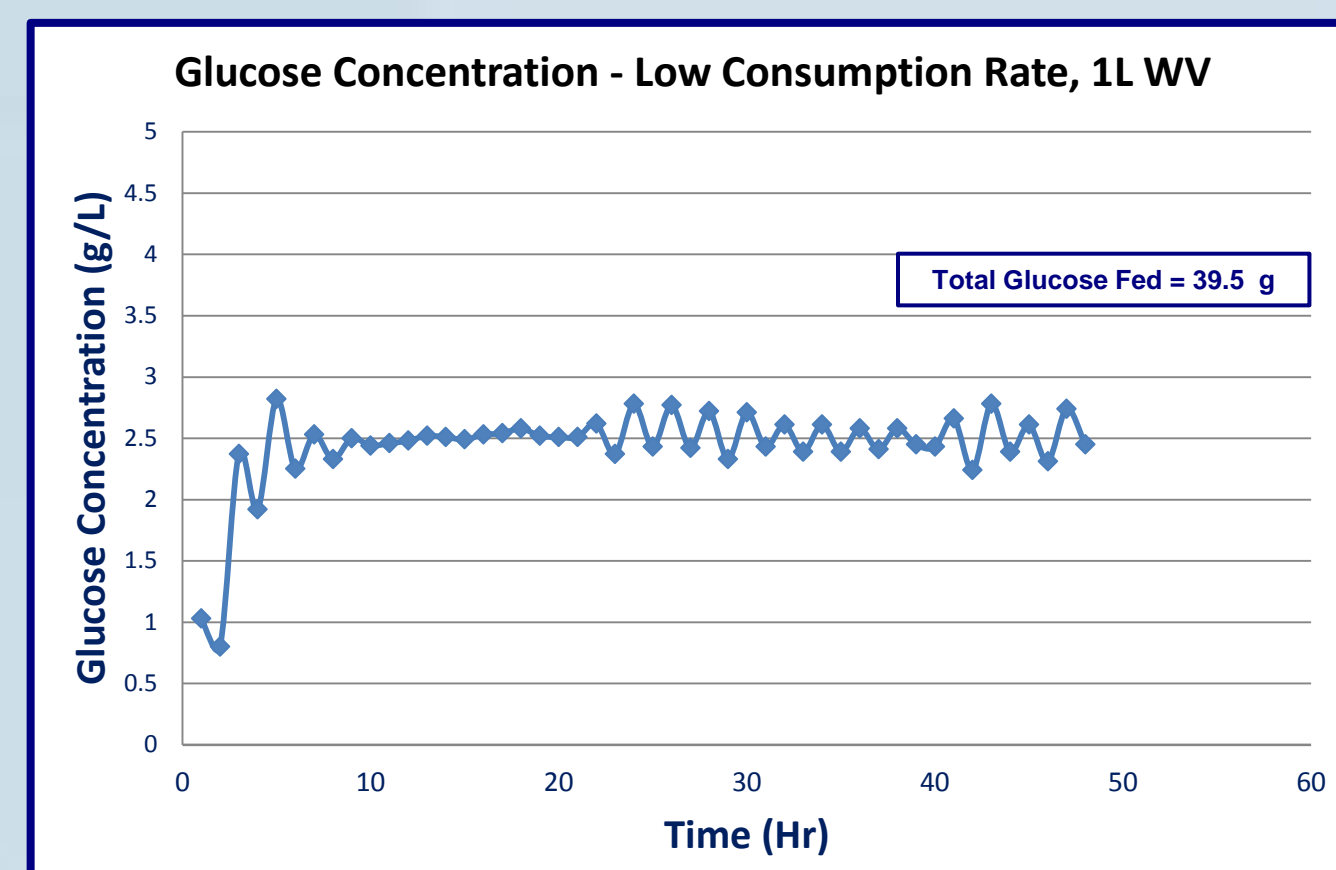
- Continuous dilution strategy of vessel media used to mimic live culture nutrient consumption at low and high consumption rates (g/L/min).

The Automated Nutrient Monitoring & Continuous Feed Control Platform

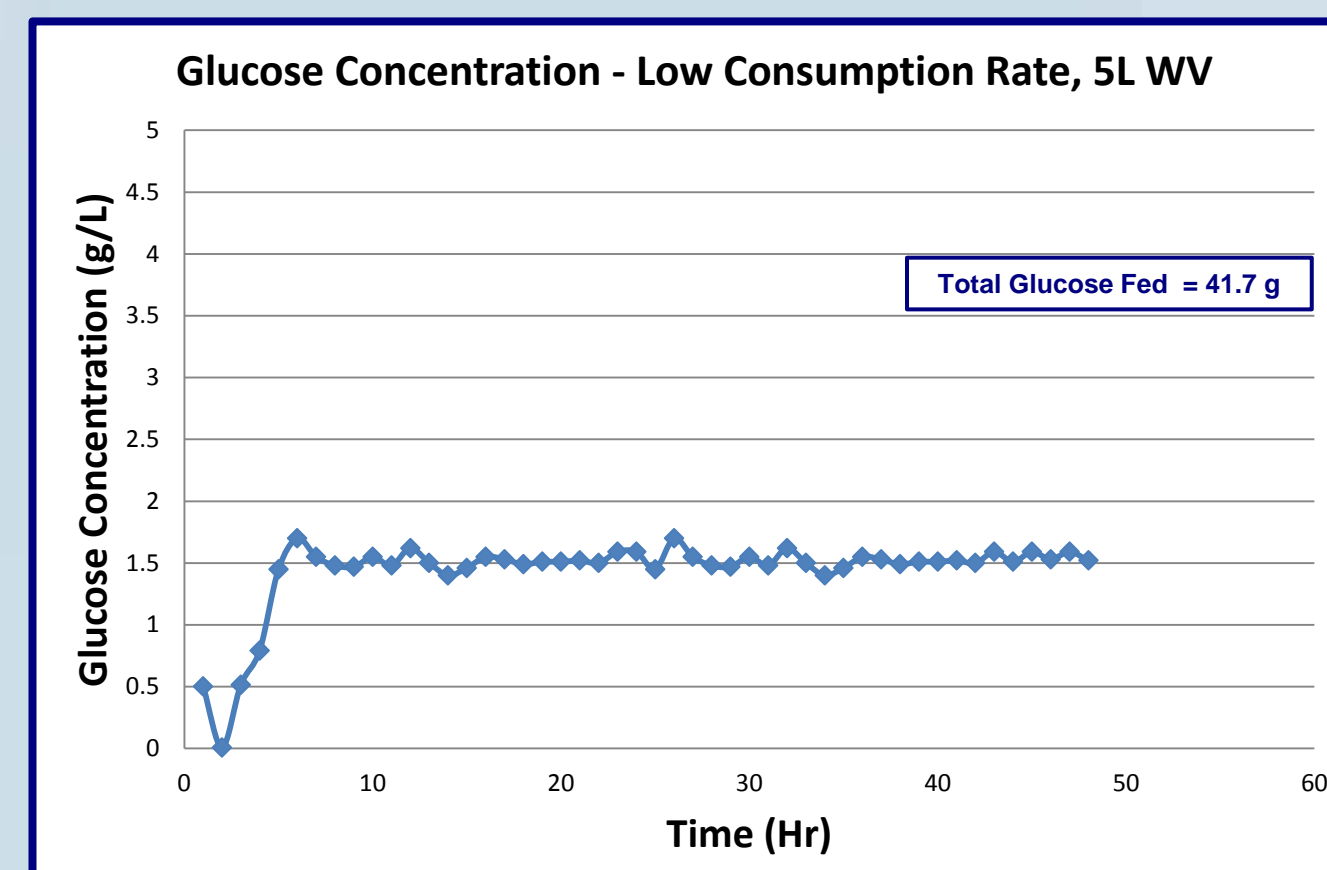


Feed Control Performance Data

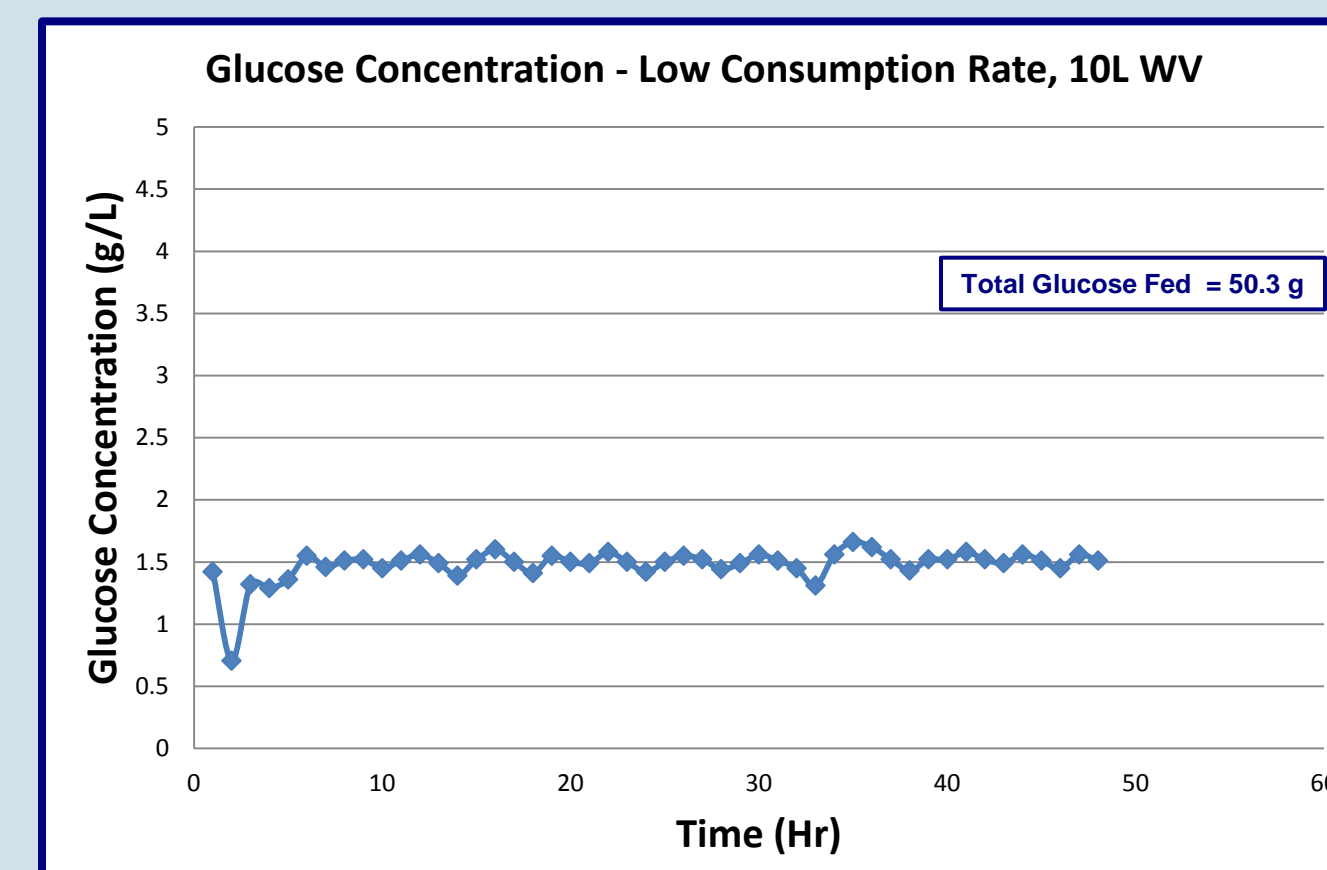
1L Volume – 2.5 g/L Setpoint



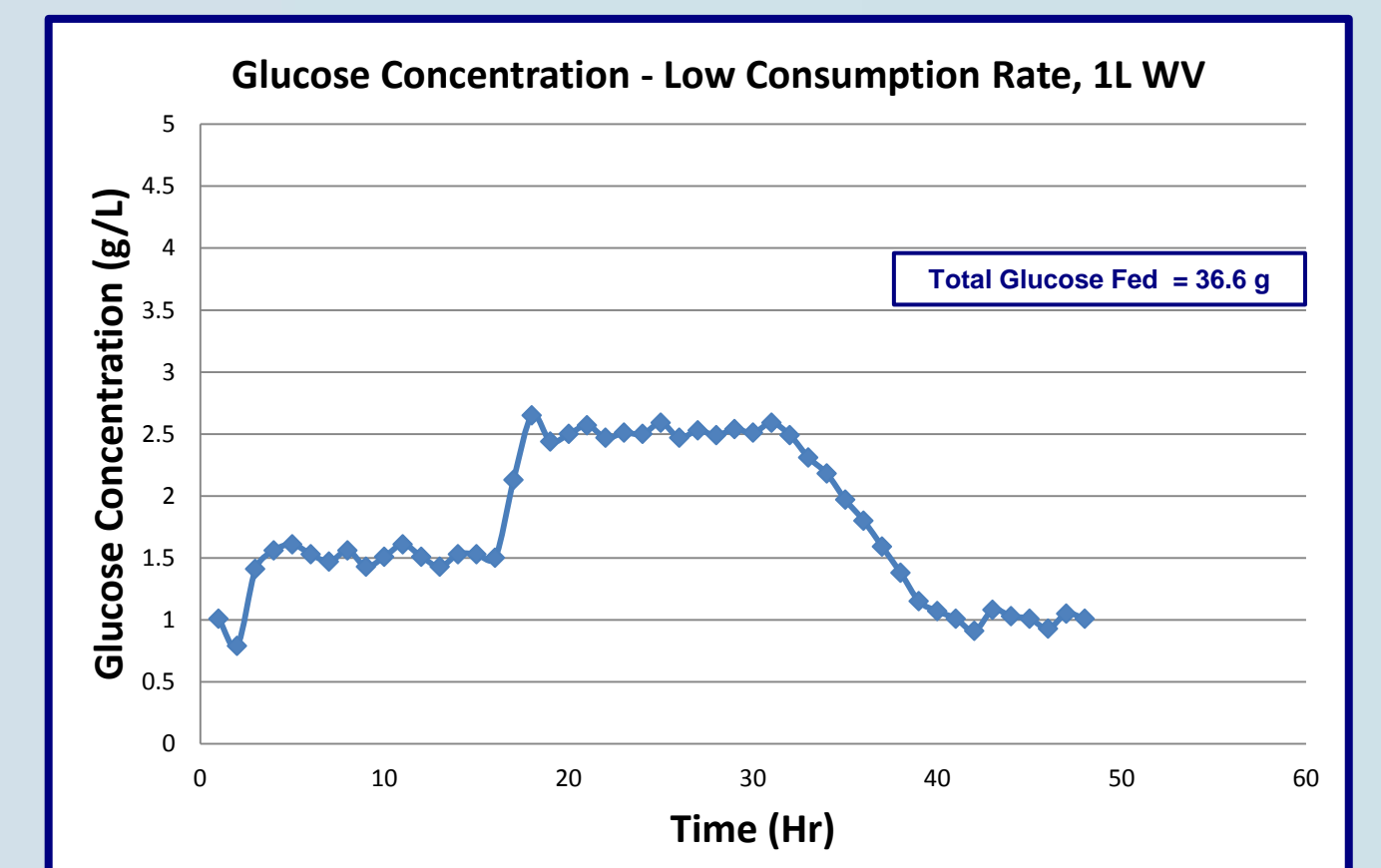
5L Volume – 1.5 g/L Setpoint



10L Volume – 1.5 g/L Setpoint



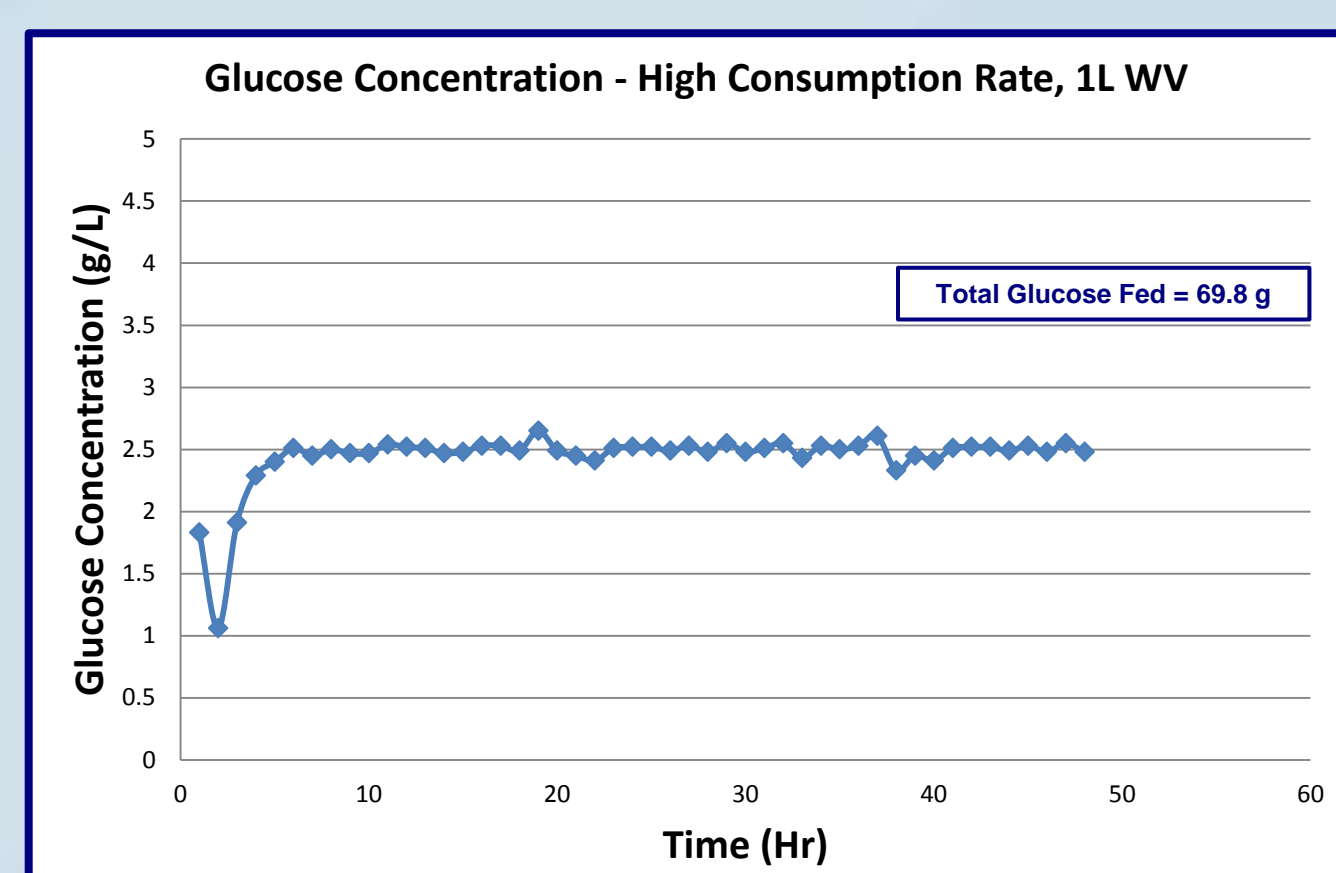
Multiple Setpoint Control Strategy



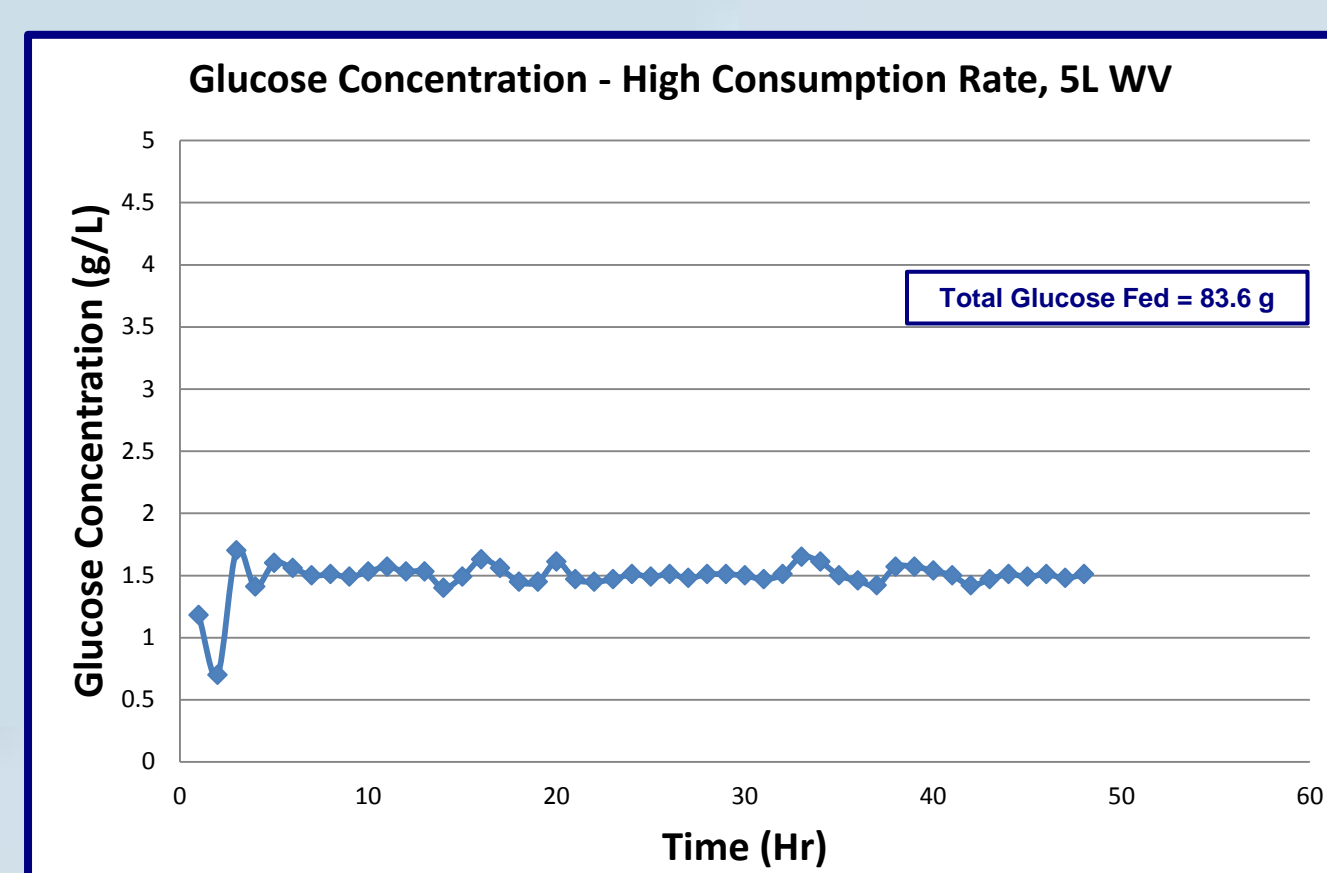
Low Glucose Consumption Rate Simulation Model

High Glucose Consumption Rate Simulation Model

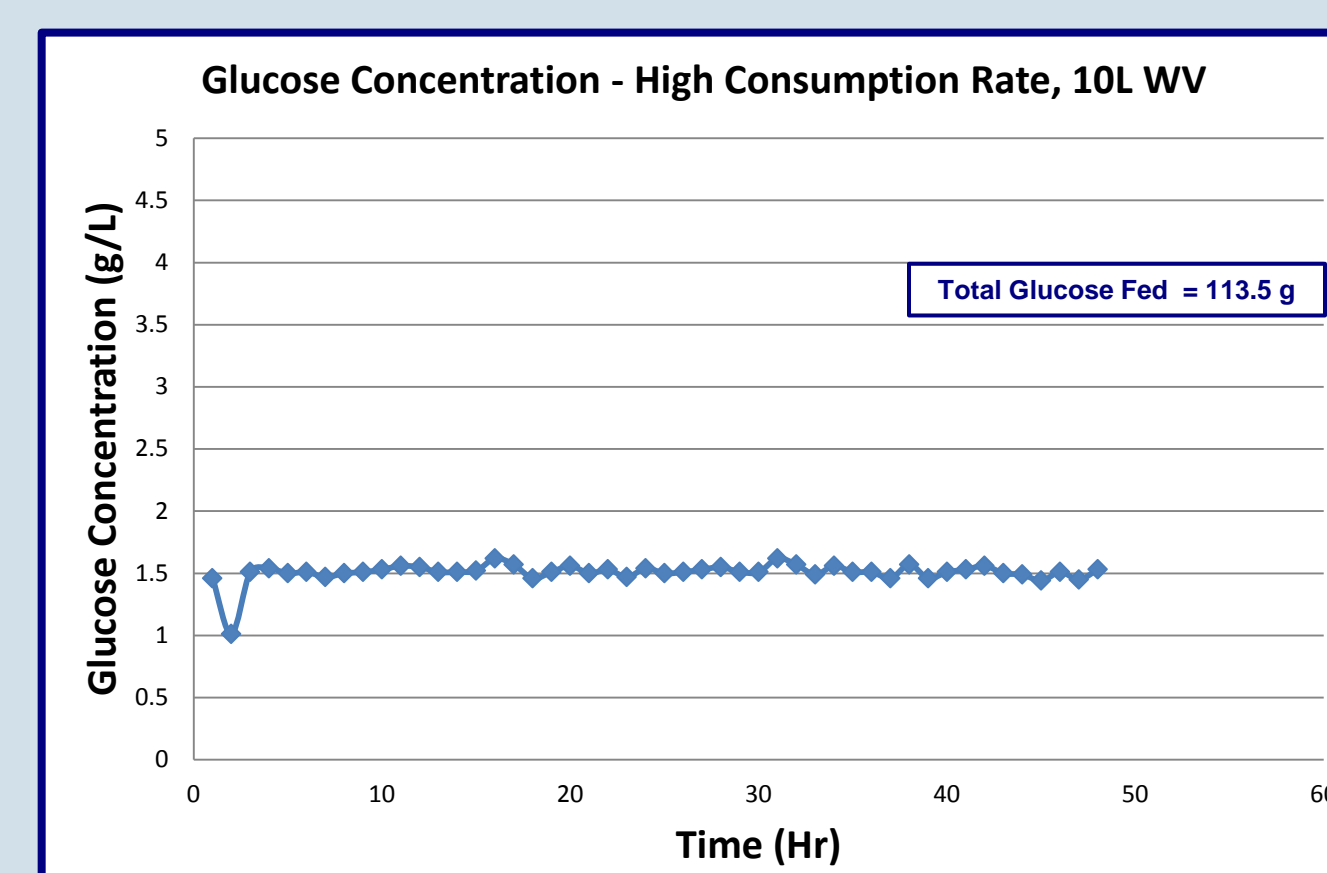
1L Volume – 2.5 g/L Setpoint



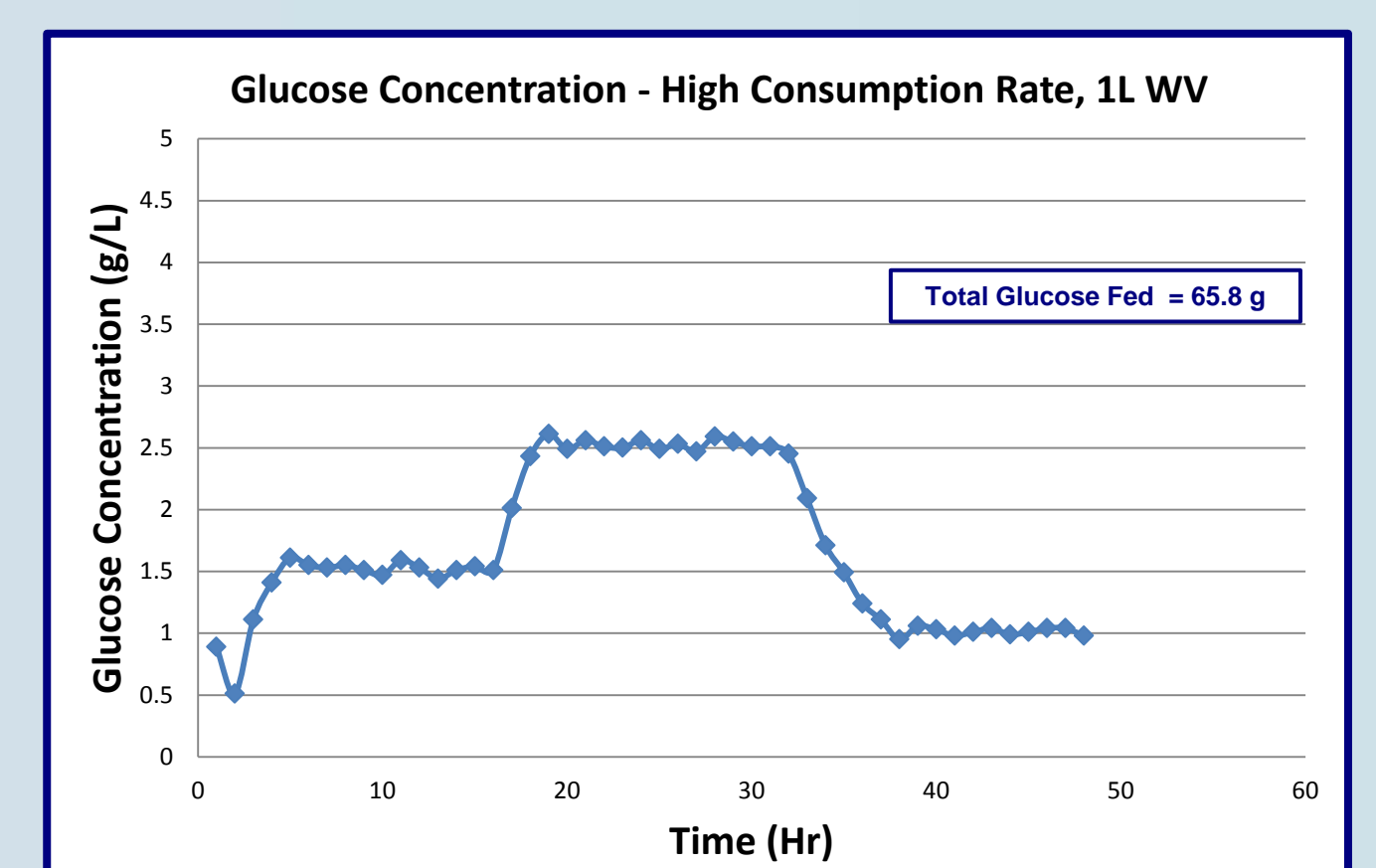
5L Volume – 1.5 g/L Setpoint



10L Volume – 1.5 g/L Setpoint



Multiple Setpoint Control Strategy



- Hourly analysis performed by the SegFlow system provided comprehensive glucose concentration profile for each 48 hour trial
- Continuous feed control platform allows quantitative monitoring of consumption rate at each sampling
- Feed pump activated after analysis of second sample, once consumption rate can be calculated

- Consumption is recalculated after every sample to ensure setpoint is maintained between cycles
- Setpoint attained in \leq four sample cycles
- The Seg-Flow Scheduler function allows multiple setpoint control throughout the process duration

SegFlow System



Conclusions

- Precise nutrient feed control achieved by the Seg-Flow automated nutrient monitoring and continuous feed control platform
- Prescribed nutrient concentration levels maintained at $\pm 10\%$ for both low and high nutrient consumption rate simulation models
- Scalability and versatility demonstrated across a matrix of working volumes and nutrient concentration setpoints
- Seg-Flow system provides real-time nutrient concentration and nutrient consumption rate monitoring in conjunction with a variety of user-defined feed strategies

Acknowledgements

FlowNamics, Inc.

- Jayson Preston
- Ashley Fisher