6-12-2022

Maximizing viral titer yield at harvest through metabolic process analytical technology (PAT)

Katherine Forrester

Marena Trauger

Thomas Randolph Blanda

Neil Templeton

MAXIMIZING VIRAL TITER YIELD AT HARVEST THROUGH METABOLIC PROCESS ANALYTICAL TECHNOLOGY (PAT)

Katherine Forrester, MSD
katherine.forrester@merck.com
Marena Trauger, MSD
Thomas Randolph Blanda, MSD
Neil Templeton, MSD
770 Sumneytown Pike, West Point, USA

Key Words: Process Analytical Technology, Bioreactor, Oxygen Uptake Rate, Capacitance, Dissolved Oxygen

This work pertains to the optimization of enterovirus production using MRC5 cultured on microcarriers within a bioreactor. This enterovirus, like other lytic viruses, has a rapid decay rate within a production batch, such that a 30% loss of potency is observed per day. Therefore, to maximize the yield of infectious product from the bioreactor, harvest needs to be timed to maximize the amount of viral production while minimizing the decay. Viral potency assays have slow turnaround times relative to a production batch, making an online process analytical technology (PAT) critical to maximize titers. In pursuit of an online method for tracking viral titer, three different PAT-enabled streams were investigated: dissolved oxygen (DO), viable cell volume (VCV), and oxygen uptake rate (OUR). DO monitoring was the simplest and leverages the ubiquitous DO trends of production, however it remains scale and gassing strategy dependent. Dual-frequency capacitance measurements were utilized to calculate VCV and thereby quantify the magnitude and timing of massive cell lysis that was correlated in time with peak viral potency. OUR, which quantifies the amount of oxygen being consumed per cellular volume, leverages both capacitance and DO measurements (in addition to oxygen mass balances pertaining to the gassing strategy) to provide a holistic scale-independent metabolic PAT readout. The sharp increase we observe in OUR prior to its decline due to cell lysis appears to be related to increased oxygen demand during viral production—this sharp increase precedes peak viral potency and peak specific productivity in our process. Data generated by our PAT tools—DO, VCV, OUR— were compared to potency and specific productivity trends across 22 batches. In this talk, we will discuss the utility and application of the tools, repeatability of our models across datasets, and the strengths and weaknesses of each model.

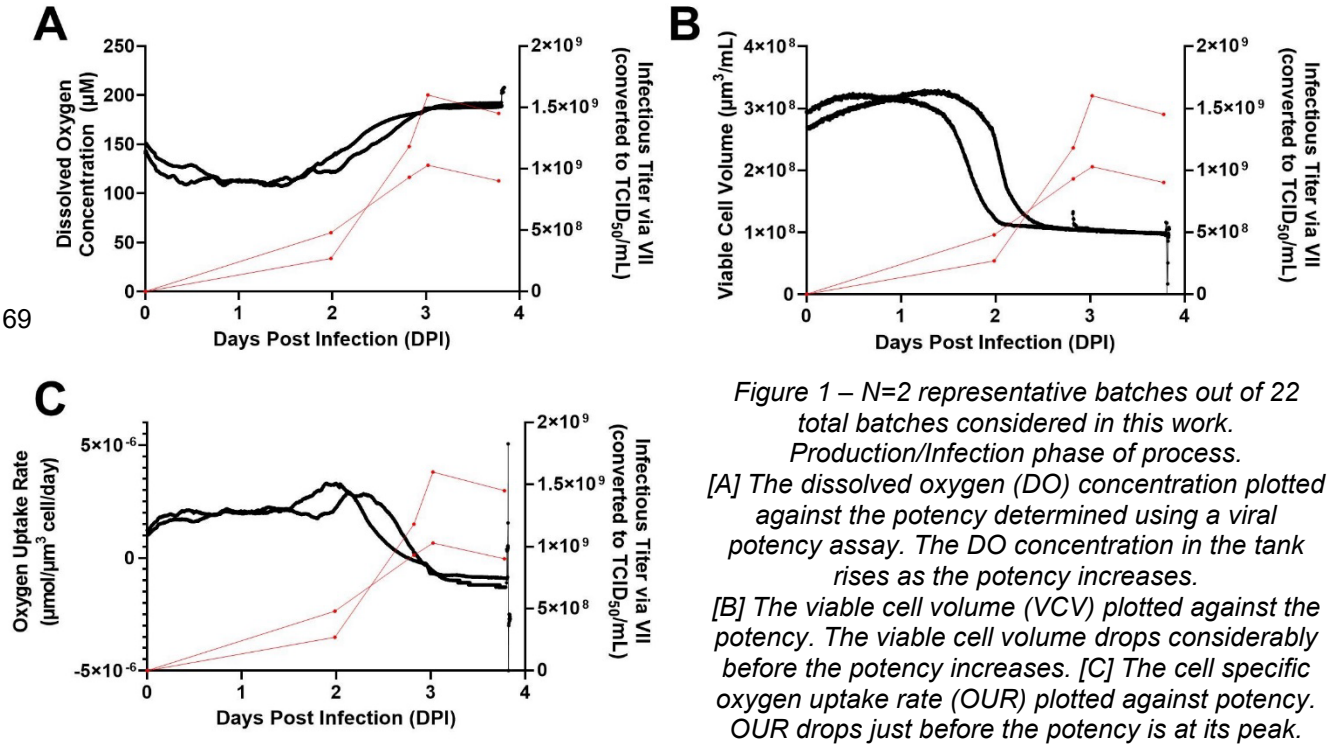

Figure 1 – N=2 representative batches out of 22 total batches considered in this work. Production/Infection phase of process. [A] The dissolved oxygen (DO) concentration plotted against the potency determined using a viral potency assay. The DO concentration in the tank rises as the potency increases. [B] The viable cell volume (VCV) plotted against the potency. The viable cell volume drops considerably before the potency increases. [C] The cell specific oxygen uptake rate (OUR) plotted against potency. OUR drops just before the potency is at its peak.