Operations | Healthcare / Pharmaceuticals | Improved process performance | Regression analysis

Industry 4.0 in Biomanufacturing: Predictive Real-Time Models Using Process Analytical Technology

BUSINESS PROBLEM

Amgen's primary business is in manufacturing biologics, a process that involves growing mammalian cells in progressively larger bioreactors in a culture that induces them to produce the target protein. To ensure high quality, cell culture metrics like viable cell density (VCD) and viability are tracked via manual samples taken every 24 hours. Data from new sensors can be correlated to real-time readings of VCD and viability, leading to direct savings in avoidable product losses and reduced manual sampling, and creating opportunities for additional savings through optimization of the cell culture feeding strategy via advanced process control.

APPROACH

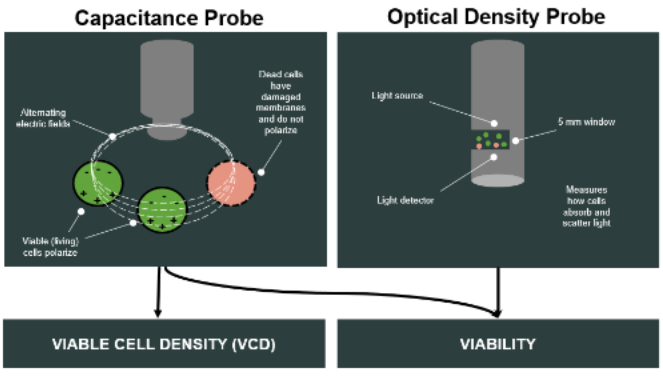
Multivariate analysis and supervised machine learning has been conducted on the data reported by the Process Development laboratories and pilot plants that are testing newer, more real-time sensors. The data from the sensors can be correlated to viable cell density (VCD) and viability, which are directly proportional to titer, the concentration of the target molecule in the cell culture media.

DATA SOURCES

The data are from Process Development laboratories and pilot plants located primarily in Cambridge, Rhode Island, and Thousand Oaks. A series of experiments have been conducted in these labs to test out the new sensors and models. Literature review is sources from both internal company white papers and external biomanufacturing sources.

Data Types and Format

Excel spreadsheets assembled by the labs consisting of numerical and datetime formats. Qualitative or categorical data is minimal outside of literature review.



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IMPACT

The models developed in this thesis enable real-time monitoring of viable cell density (VCD) and viability, currently done every 24 hours via manual sampling. This is an important component of a larger initiative to implement process analytical technology (PAT) to improve manufacturing efficiency at Amgen. Within the new $550M manufacturing plant slated to open in North Carolina in 2025, the implementation of PAT is projected to save $2M per year in avoidable product losses and reduce manual sampling by approximately 50%. Advanced process control (APC), which is improved by real-time data coming from the use of PAT, is projected to increase titer by 5% and result in $12M of additional savings per year.

DRIVERS

The FDA and global regulatory bodies encourage the use of PAT in biomanufacturing as part of their guidance to integrate with Quality by Design (QbD), a systematic approach to drug development that aims to ensure the quality of the final product by building quality into the development process. Globally, Amgen has been pushing to implement PAT, particularly in the construction of new biomanufacturing plants.

BARRIERS

A few barriers that impacted this work include limited data availability and regulatory risk. Given the small dataset size, traditional machine learning models that require large datasets are not well suited for this use case. Additionally, stringent regulations require full transparency into the model approaches and minimal external dependencies.

ENABLERS

This work is enabled by Amgen's company-wide strategy of driving toward Industry 4.0, resulting in careful planning and execution of the steps needed to thoroughly test PAT tools so they can be implemented at the new manufacturing facility in North Carolina and other facilities globally.

ACTIONS

To implement this solution, I worked closely with the process development scientists to understand the data and its context. We had weekly meetings where we reviewed the models together and I collected feedback. I also worked closely with others within the data science organization, resulting in broad testing and validation of the model approach.

INNOVATION

The implementation of these models will enable real-time cell culture analysis, where the current state is manual samples every 24 hours. The VCD model, being a gaussian process regressor, allows for a smaller training dataset, and can be used to make a confidence interval prediction instead of a traditional point prediction. The viability analysis is a novel approach that is being considered for patenting.

IMPROVEMENT

The implementation of process analytical technology in the new North Carolina plant is projected to save $2M in avoidable product loses and reduce manual sampling by approximately 50%.

BEST PRACTICES

Best practices for replicating this solution (e.g., training a model with new data coming from additional ongoing experiments at Amgen) include automating the data wrangling process as much as possible. I wrote python scripts that have been passed on to the data science organization to assist with this.

OTHER APPLICATIONS

PAT, specifically the VCD and viability models, can be used across Amgen's biomanufacturing plant networks, and other biopharmaceutical companies that produce biologics.