INTEGRATED PLATFORM FOR HIGH-THROUGHPUT MEDIA OPTIMIZATION

Dirk Müller, Sartorius Stedim Cellca GmbH
dirk.mueller2@sartorius.com
Swapnil Chaudhari, Sartorius Stedim Cellca GmbH
Ali Safari, Sartorius Stedim Cellca GmbH
Jaeho Shin, Sartorius Stedim Cellca GmbH

Key Words: Media Optimization, High-Throughput Analysis, Artificial Intelligence, CHO cells

The increasing numbers of biologicals currently under development require to shorten molecule development timelines and to maximize process efficiency in production plants. Optimizing the composition of cell culture media is central to maximize product yield and attain key product quality attributes. Nowadays, optimization of media formulations can be accelerated through optimized statistical design of experiments (DoE) and use of multiplexed cell cultivations in microtiterplates or scale-down model bioreactors. Still, performing a comprehensive optimization of a cell culture medium represents a formidable challenge: media usually contain >50 different compounds and often joint modification of both basal media and feeds is required to leverage the full potential. For lack of time, often only whole groups of compounds are jointly optimized or one resorts to blending approaches which resulting in even more complex media. Selecting the right components sensitively affecting the target outcome like titer requires much experience. Consequently, media optimization is frequently performed by few experts and does not scale well if multiple optimizations need to be performed in a short time. Routinely, many iterations are required to achieve meaningful improvements.

We have developed an integrated media optimization platform that combines high-throughput cell cultivations, automated media variant preparation, and versatile spent media analytics with a computational data analytics pipeline. The combined platform enables fast optimization of media for different process outcomes like product titer or critical quality attributes (CQAs). Furthermore, it simplifies targeted media optimization also for non-experts. Cultivation in fed-batch mode already at the screening stage ensures that only media variants are propagated that can yield meaningful results in the target process format. Numerous steps in media variant preparation and fed batch cultivation have been automated using robotic liquid handling systems. Spent media analytics can be tailored to the individual problem and may cover carbon sources, amino acids, vitamins and selected cellular metabolites. A computational data analytics pipeline has been developed that combines time-resolved cultivation data, spent media results and product analytics to identify media variants and components most sensitively affecting the outcome to be optimized, e.g., product titer. This information is then used by the algorithm to predict focused compound modifications for more targeted optimization than possible with conventional optimization approaches like DoE or media blending. Best media variants are then taken forward for further assessment at larger scales and for production of corresponding pilot media powders. Consistent use of manufacturing-grade raw materials throughout the optimization minimizes the risk of unexpected performance deviations when transferring the optimized media to large-scale manufacturing.

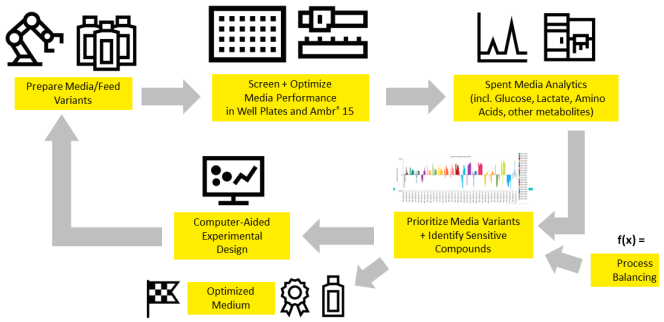

Figure 1 – Workflow Integrated Media Optimization Platform

We demonstrate the application of this platform for the optimization of product titer and glycan profile in CHO cells employing different cultivation systems including deepwell plates, Ambr minibioreactors systems and benchtop bioreactors. While this contribution illustrates application of the methodology to CHO cells, the platform can readily be extended to optimize media compositions for other cell line types.