Simplifying Progress

High-Throughput Media Optimization for CHO Cell Lines

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Introduction

As more biologics are developed, shortening molecule development timelines can help improve process efficiency. Optimizing the composition of cell culture media is critical to maximizing yield and attaining key product quality attributes.

Manufacturers can accelerate media optimization using statistical design of experiments and multiplexed cell cultivations in microtiter plates or scale-down model bioreactors. But it can be challenging — media can contain more than 50 different compounds, and modifying both basal media and feeds and performing multiple iterations is often required.

Here we establish a methodology that combines data-rich experiments with advanced data analytics. The methods presented here can raise mAB titer, improve productivity, and help attain key quality attributes.

Method Overview

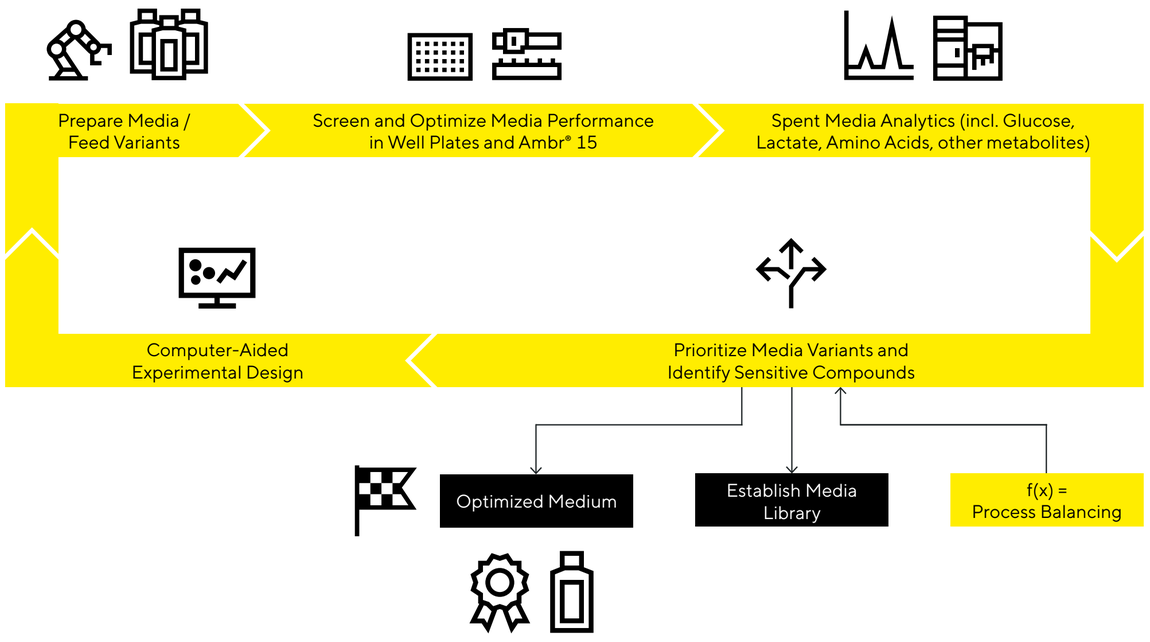
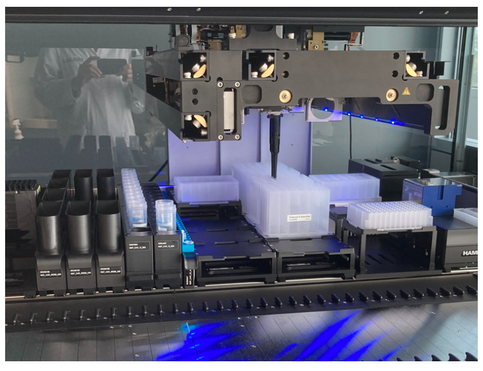
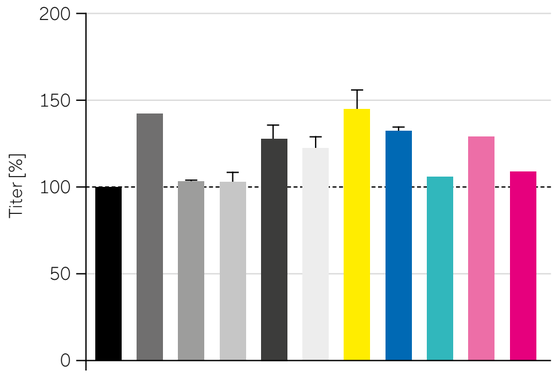


Figure 1: *Media Optimization Workflow. For a Given Optimization Target (e.g., Product Titer, Specific Glycan Pattern), Initial Data Is Collected From Screening Runs With Media Variants From a Library or Premixed Variants Based on Objective. We Assessed Cell Performance in the Scaled-Down Target Process Experimentally Using a High-Througput Approach in Deep-Well Plates. We Used Spent Media Analytics and a Computational Workflow to Identify Sensitive Compounds and Predict Targeted Follow-up Experiments With Adapted Media Compositions for Further Optimization (e.g., at Ambr® 15 Scale). Once the Desired Optimization Target Is Reached, Scale-up Testing Is Performed and Optimized Formulations Media Can Be Provided in Liquid or Powder Format.*

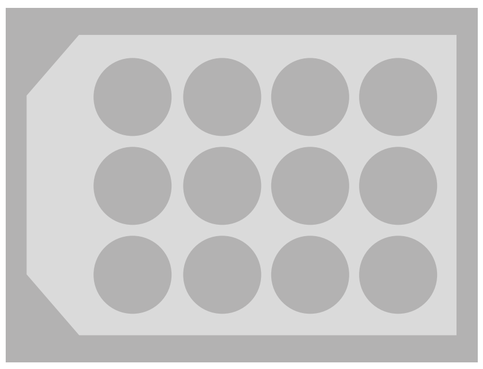
HT Media Variant Screening in Scale-Down Model



Media variant preparation from fixed library media and stock solutions incl. pH adjustment



Evaluation of media screening results e.g., regarding growth, productvity, by product formation



Media variants pipetted into 24 wellplates and inoculated with cell line(s) for fed batch screening

Fed batch screening with automated cell counting and feeding

Figure 2: *Screening of Pre-defined Library Media and Targeted Media Variants of Basal Media And/Or Feed Media With Automated Steps for Cell Counting and Feeding for Superior Reproducibility*

Time-Resolved Spent Media Analytics as Basis For Identifying Sensitive Compounds and Design of Targeted Optimizations

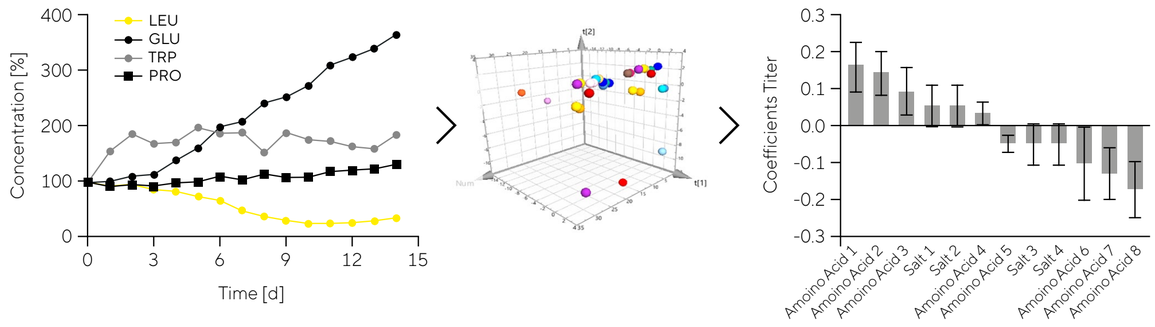


Figure 3: *Time-Resolved Spent Media Analytics (e.g., Amino Acids, Vitamins, or Trace Metals) Of the Most Promising Screening Runs Is Combined With Process-Integral Performance Data (e.g., Growth, Titer, Byproducts) To Enable Identification of Media Compounds Sensitively Affecting the Target Optimization Criteria Using Multivariate Data Analysis And Post-processing (e.g., Filtering Out Accumulating Compounds). This Results Forms the Basis for Designing a Subsequent Targeted Optimization Run, e.g., in Ambr® 15 Employing a DoE Approach or Alternative Setups*

Media variant design and screening using spent media analysis and multivariate data analysis

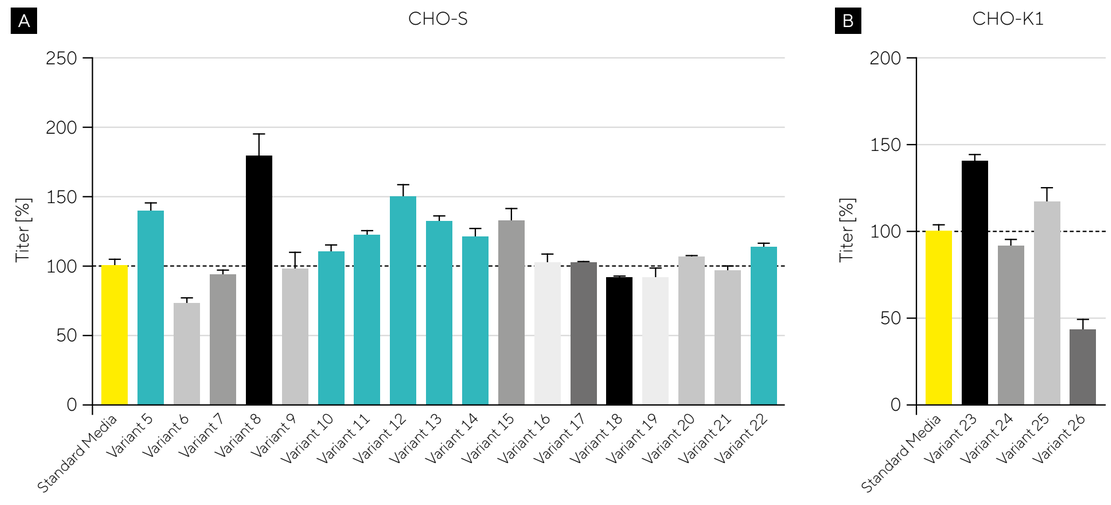


Figure 4: *Screening Run of CHO Media on a CHO DG-44 and a CHO-K1 Cell Line. Titer Increases Are Expressed in Percentage of Increase of a Variant Media Over Control Media*

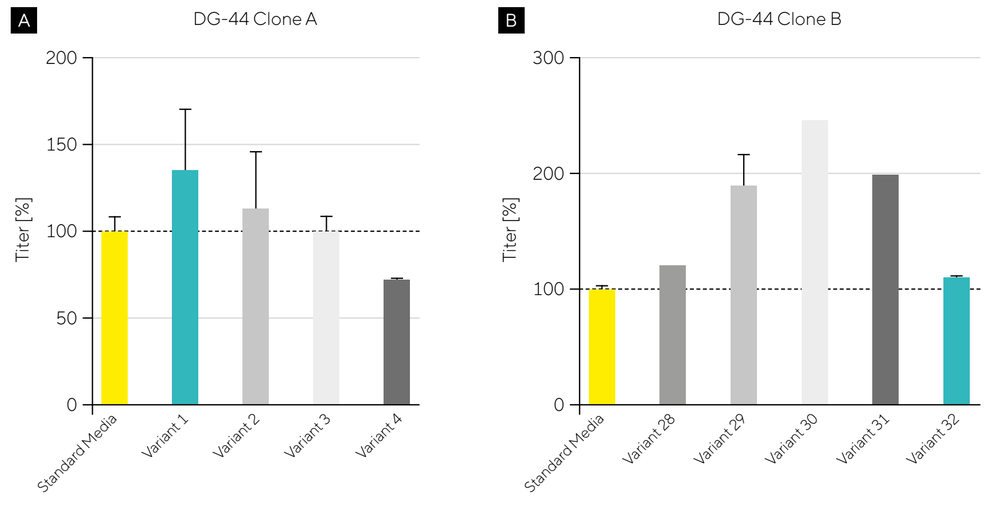


Figure 5: *Screening Run of CHO Media on 2x CHO DG-44 Cell Line Clones. Titer Increase Are Expressed in Percentage of Increase of a Variant Media Over Control Media*

Conclusion

The integrated platform provides a structured media optimization workflow. Our method leverages high-throughput cultivation media variant preparation and screening, adaptive spent media analytics, and a data analytics pipeline to support media optimization. The platform can be applied to media optimization regarding, for example, product titers or specific glycoforms by joint optimization of basal and feed media. Its modular nature also enables easy integration of upgrades and extensions in cultivation, spent media analytics, and data analysis, and provides an approach that can extend to applications beyond CHO cells.

References

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2. Y. Rouiller et al. (2013) A high-throughput media design approach for high performance mammalian fed-batch cultures, mAbs, (5): 501-511.

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