GT's Model-driven Platform for Improving Biologics Production in Mammalian Cell Culture

GT Life Sciences

Overview

GT Life Sciences, Inc. (GT), a privately held San Diego based biotechnology company, has developed a proven metabolic modeling and experimental platform that can rapidly increase titers and productivity in mammalian cell culture. GT's Biologics platform is used to study, design, and develop new products, processes, and host cell lines in the cell culture industry using: (1) whole-cell metabolic models, (2) computational modeling and simulation tools, and (3) advanced experimental technologies (Fig.1). GT Life Sciences' proprietary platform has been validated over the last decade and is covered by over 50 patents and patent applications.

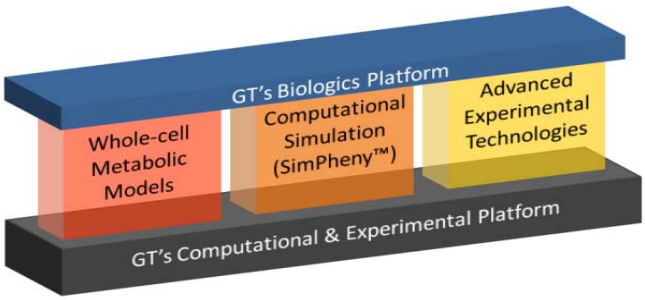

Figure 1. GT's computational and experimental platform.

Key Applications Areas

GT is enabling and accelerating the development of product opportunities for GT and its partners in a number of application areas including:

Media Optimization

- Designing novel media formulations
- Improving productivity in stationary phase

Process Design

- Optimizing cell culture process
- Analyzing scale-up variability
- Analyzing batch-to-batch variability

Cell Line Development & Engineering

- Developing superior parental/producing cell lines
- Engineering metabolic pathways
- Developing novel selection systems

Biomarker Analysis

- Understanding clonal differences
- Discovering biomarkers for high-producing cell lines

Technical Achievements

1. Developing whole-cell metabolic networks for host cell lines including CHO, NS0, and hybridoma
2. Outperforming the current approaches for media optimization (e.g., depletion analysis, nutrient screening)
3. Understanding/Predicting the nutritional requirements of the cell
4. Predicting/determining genetic engineering interventions to improve cellular traits for production of novel host cell lines

Model-driven Media Optimization – A Case Study

GT has successfully applied its platform in a pilot study. In this study, our NS0 metabolic model was used to improve product titer in cell culture. Three formulations were evaluated and compared with a base case media formulation:1) a model-based media formulation to *minimize byproduct formation*, 2) a model-based media formulation to *increase growth and product formation*, and (3) a data-based media formulation based on the industry standard *depletion analysis* where depleted nutrients are identified from cell culture bioreactor data.

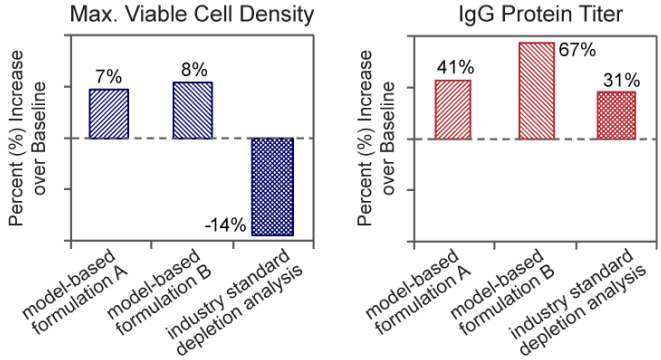

Figure 2. Results from the model-based and depletion-based media optimization for maximum viable cell density (VCD_{max}), and final IgG titer. Formulation A was designed by the model to reduce byproduct formation. Formulation B was designed by the model to increase growth and IgG production. Depletion analysis was used in the last formulation for comparison.

Fed-batch results showed up to an 8% increase in maximum viable cell density and up to a 67% increase in final titers for the model-based media formulation, with significantly better performance than the depletion analysis (Fig. 2).

Fed-batch results also showed reductions in the final titers of up to 13% for lactate, 46% for ammonia, and 24% for alanine, with significantly better performance in the model-driven formulations compared with the depletion analysis (Fig. 3).

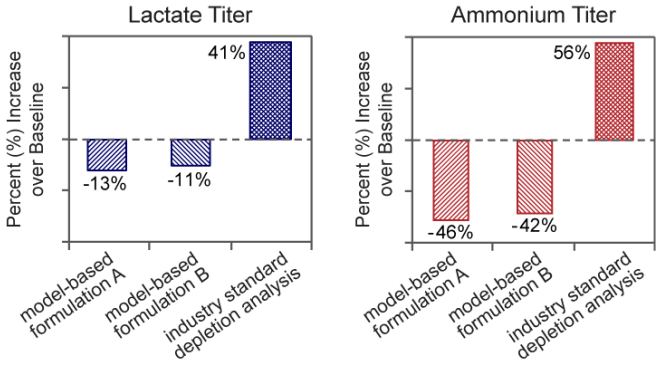

Figure 3. Results from the model-based and depletion-based media optimization for lactate, and ammonium. Formulation A was designed by the model to reduce byproduct formation. Formulation B was designed by the model to increase growth and IgG production. Depletion analysis was used in the last formulation for comparison.

Summary of Media Optimization Study

- Superior model-based media optimization performance in both final titers and maximum viable cell density compared with the depletion analysis
- Significantly better model-based performance in reducing byproducts over the deletion analysis
- Higher product titers in the predicted cases
- Lower byproducts in the predicted cases
- Prediction based on fundamental understanding of the nutritional requirements of the cell
- Unique and non-intuitive formulations

Advantages of a Model-driven Approach

- Requires a minimum set of data (amino acid analysis, glucose, lactate, ammonium, cell viability, etc.), and is therefore less expensive
- Provides a mechanistic understanding of metabolism and cellular response to environmental and genetic changes
- Drives discovery and generates prediction that often leads to non-intuitive designs
- Provide quantitative prediction
- Can answer “what if” questions

GT Life Sciences, Inc.

GT is seeking commercial collaborations with the goal of enabling and improving productivity for mammalian cell culture. For more information about our Biologics Production Platform, please contact Thomas Reed, President and CFO (treed@gtlifesciences.com), or Iman Famili, Director of R&D (ifamili@gtlifesciences.com) at:

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