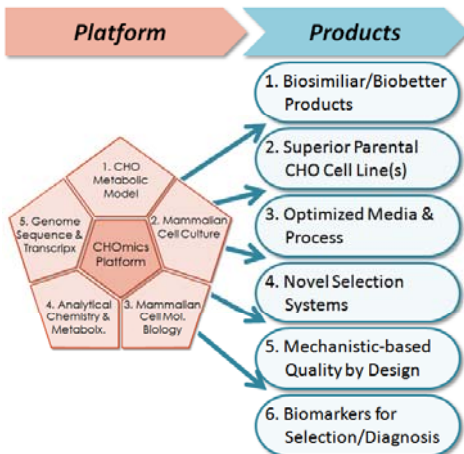


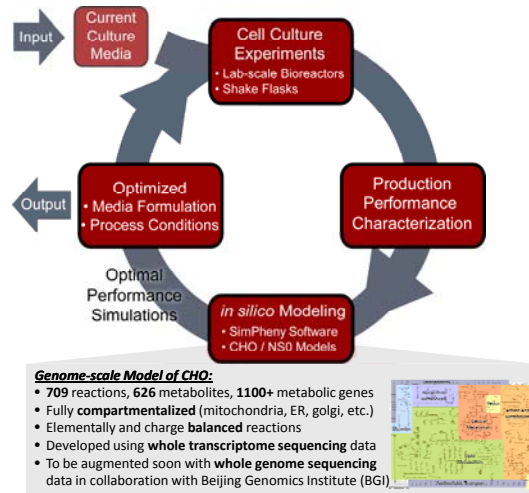
Abstract

Recent advancements in experimental and bioinformatics technologies have contributed immensely to the expansion of the knowledge base for cell components and their interactions. This information can be leveraged to study networks at a whole-cell level using *in silico* network reconstruction and computational modeling. Computational methods for analyzing cell metabolism and physiology have proven successful in discovering biological components and their interactions, predicting physiological responses to genetic and environmental changes, and improving product formation for industrial and medical applications. Using a validated computational metabolic modeling platform and advanced experimental technologies, we have simulated and studied metabolism in NSO murine myeloma and Chinese Hamster Ovary (CHO) cell lines and identified nutritional and process modifications that result in significant growth and titer improvements and byproduct reduction. Experimental validation of our model-based media formulations and process design has proven to be effective in improving the final product titers and reducing byproduct accumulation when compared to traditional media optimization methods. We have also used this approach to discover and develop novel selection systems for stable expression of therapeutic proteins in mammalian cell lines (see other poster). The results demonstrate that metabolic modeling combined with advanced experimental technologies can significantly improve and accelerate discovery and development of therapeutic proteins in mammalian cell lines.

GT Life Sciences' Computational & Experimental Platform and it's Applications:



Model-Driven Design and Discovery:



Model-driven Media Optimization Advantages:

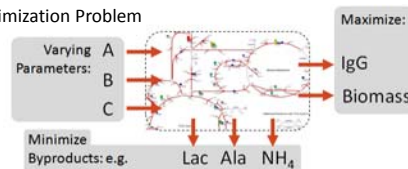
- Mechanistic understanding and calculation of growth and production requirements
- Rapid hypotheses and experimental implementation
- Integrated computational and experimental platform

Model-Driven Media Optimization: Media Formulation and Design

Goal: To increase protein production and growth, and to decrease byproduct formation in a high-producing CHO cell line using a model-driven media optimization

Formulating the Simulation:

A Linear Programming Optimization Problem



Sample Media Design:

An example of how two model-based formulations (out of a total of 5 examined for basal and feed compositions) differed from a depletion-based formula

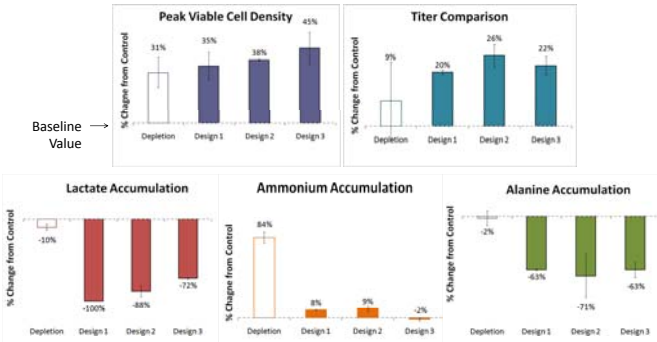
Nutrients	Depletion-based Formula	Model-based Design 1	...	Model-based Design 3
Metab A	+			
Metab B	+			
Metab C				
Metab D		+		+
Metab E	+	+		+
Metab F	+	+		+
Metab G		+		+
Metab H				+

Model-Driven Media Optimization Results:

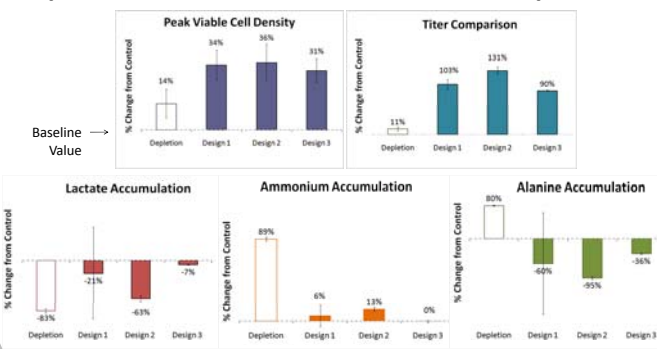
Duplicate shake flasks, batch & fed-batch experiments were performed:

- **Baseline:** cell culture with an already optimized media formulation, i.e. the CD OptiCHO™ basal and EfficientFeed™ A (Invitrogen, Corp.)
- **Depletion:** depleted nutrients added back in using spent media analysis
- **Designs 1-3:** model-based formulations

Experimental Results – Batch Media Optimization



Experimental Results – Fed-Batch Media Opt



Conclusions

- The model-based media formulations **significantly outperformed** the control, as well as the industry-standard depletion analysis in one iteration
- The formulations were designed and tested **rapidly** using a genome-scale model of CHO metabolism
- The formulations were **novel** and **non-intuitive**
- The results in CHO are **consistent** with those made in NSO cell line
- The approach is being applied to **bioreactor** studies, along with **process optimization** and **product quality** (i.e. glycosylation)