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PREDICTIVE ENGINEERING OF CHO CELLS USING SYSTEMS BIOLOGY MODELS

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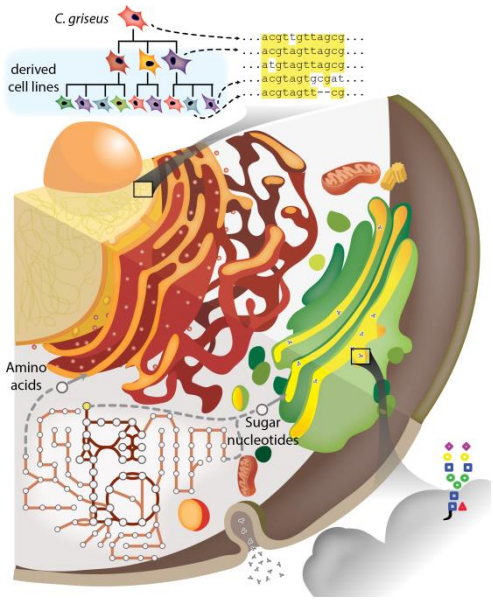

Figure 1 – We have reconstructed the pathways underlying the CHO secretory pathway, including protein translation, glycosylation and cell metabolism. These pathways are valuable resources for the analysis of genomic variants, glycosylation, and cell processes impacting product quality.

Decades of bioprocess optimization have resulted in substantial improvements in recombinant protein production. However, some proteins remain difficult to express, and there is an increasing awareness of the need for improved control of critical quality attributes of recombinant protein drugs. To enable cell engineering efforts to enhance protein production and control product quality, we have enumerated the CHO cell parts through genome sequencing efforts,[1,2] and are now providing context to these parts by reconstructing genome-scale networks of the secretory pathway, glycosylation, and metabolism CHO (Figure 1). Using these models, which account for the activities of more than 2000 genes, we have approached questions relevant to bioprocessing and guided cell engineering efforts.

First, several bioprocess treatments have increased CHO cell specific productivity, but the yields still pale in comparison to professional secretory cells. Have these bioprocess treatments maximized specific productivity? To answer this question, transcriptomic, proteomic and metabolomic data were used build cell-line specific models. Through simulations we found that common treatments, such as NaBu and decreased temperature increase the yield inefficiently, as opposed to cell engineering efforts.

Second, cell engineering efforts aim to match product quality attributes relevant to product activity. To aid in this, we developed a simple but powerful computational modeling platform to predict glycosylation and study how metabolism impacts glycans on products. Using this platform and an initial glycoprofile of a product under development, we can successfully predict the effects of genetic manipulations and media, thereby providing insights into which treatments are most likely to yield the desired glycoforms.

In summary, these genome-scale models serve as valuable platforms for data analysis and simulation, thereby providing insights into the molecular basis of various bioprocess phenotypes and for guiding cell engineering efforts.

References

1. Lewis, N. E.; Liu, X.; Li, Y.; Nagarajan, H.; Yerganian, G.; O'Brien, E.; Bordbar, A.; Roth, A. M.; Rosenbloom, J.; Bian, C.; Xie, M.; Chen, W.; Li, N.; Baycin-Hizal, D.; Latif, H.; Forster, J.; Betenbaugh, M. J.; Famili, I.; Xu, X.; Wang, J.; Palsson, B. O. Genomic Landscapes of Chinese Hamster Ovary Cell Lines as Revealed by the Cricetulus Griseus Draft Genome. *Nature biotechnology* **2013**, *31*, 759–65.

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