# EXPLORING METABOLIC DEMANDS OF HIGH DENSITY CHO-CELL CULTURES

Matthias Noebel, ARC Training Centre for Biopharmaceutical Innovation (CBI), Australia Australian Institute for Bioengineering and Nanotechnology (AIBN), The University of Queensland, Brisbane, Australia
m.noebel@uq.edu.au
Verónica S. Martínez, ARC Training Centre for Biopharmaceutical Innovation (CBI), Australia Australian Institute for Bioengineering and Nanotechnology (AIBN), The University of Queensland, Brisbane, Australia
Stephen Mahler, ARC Training Centre for Biopharmaceutical Innovation (CBI), Australia Australian Institute for Bioengineering and Nanotechnology (AIBN), The University of Queensland, Brisbane, Australia
Cristiana Dal'Molin, ARC Training Centre for Biopharmaceutical Innovation (CBI), Australia Australian Institute for Bioengineering and Nanotechnology (AIBN), The University of Queensland, Brisbane, Australia
Esteban Marcellin, ARC Training Centre for Biopharmaceutical Innovation (CBI), Australia Australian Institute for Bioengineering and Nanotechnology (AIBN), The University of Queensland, Brisbane, Australia and Metabolomics Australia (Queensland Node), The University of Queensland, Brisbane, Australia

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As the world population continues to grow and age, access to medical therapies, like therapeutic monoclonal antibodies (mAb), increases in importance. Chinese hamster ovary (CHO) cells are the preferred expression platform for biopharmaceutical production, such as mAb, due to their ability to generate human-like post-translational modifications and strong legislation background. Unfortunately, biopharmaceuticals production using CHO cells is costly leading to an expensive product. Detailed knowledge of their metabolic demands is still lacking. Hence, increasing understanding would help to develop rational approaches to enhance expression, lower production costs and subsequently make therapies more accessible.

Industrial large scale CHO cell cultures are typically run in fed-batch mode, which is limited by the accumulation of inhibitory by-products. Driven by higher volumetric productivities, shorter residence time of products, industry is shifting towards perfusion cultures. This shift in cultivation mode is accompanied by new metabolic conditions for the cell in form of higher cell densities and different exometabolite levels. Comparison of both culturing modes, as well as different perfusion dilution rates, revealed differences in growth and productivity patterns. Cell densities and cell specific productivities increased from fed-batch to perfusion and from low to high dilution rates. Aiming to progress from pattern observations to a systems biology view, the metabolome and proteome profiles of both cultures modes will be analysed and mapped onto the CHO genome-scale model. Thus, protein expression and metabolite levels will be compared on a genome wide level and provide a metabolic profile, specific for the culture condition. Alterations between metabolic profiles of different culture conditions can then be identified, understood and utilized to reverse engineer variations by using genetic engineering approaches or media design and process optimization.

Overall, this study aims to establish a systems biology approach to better understand the CHO cell metabolism in the aspect of emerging perfusion systems based on comparison of different culture modes.