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**TITLE: Improved metabolic understanding in biopharmaceutical product development through hybrid modelling**

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**ABSTRACT:** Monoclonal antibodies (mAbs) are biopharmaceuticals used to treat a wide range of infectious, immunological, and oncological diseases, thanks to their ability to mimic key functions of the immune system. mAbs are typically produced in mammalian cell cultures, e.g., Chinese Hamster Ovary (CHO) cells, which exhibit complex dynamic biological behaviour (McDonnel et al., 2022). Improving the mechanistic understanding of CHO systems is crucial to accelerate mAb process development (Kontoravdi et al., 2010). In this context, metabolomics offers a valuable source of information, giving insight into cellular phenomena understanding (Barberi et al., 2022). However, integrating intracellular metabolomic information within the interpretation of CHO culture behaviour remains challenging. To address this issue, this study proposes a hybrid framework that combines knowledge- and data-driven methodologies (Facco et al., 2020) to enhance metabolic understanding of CHO cell cultures by correlating macroscopic culture phenomena with dynamic intracellular metabolomic profiles. First, a kinetic model is calibrated using process data to capture the macroscopic behaviour of the culture; in this way the biological and physicochemical phenomena described by the model are embedded in its estimated parameters. Then, the parameters are linked to the dynamic intracellular metabolomics using supervised machine-learning models.
The proposed approach is demonstrated on an industrial mAb development case study performed in AMBR 15® miniature bioreactors. Results show that the hybrid framework establishes strong relationships between the macroscopic chemical, physical and biological phenomena and dynamic cell metabolism. In addition, the method identifies metabolites that significantly influence specific macroscopic phenomena, providing interpretable insights into culture behaviour and supporting more informed bioprocess development.

## References

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**BRIEF SPEAKER BIO:** Edoardo Tamiazzo is a PhD student in the CAPE-lab (Computer Aided Process Engineering) at the University of Padova, with a strong focus on data analysis, data-driven machine learning, and hybrid modelling. His work in metabolomics focus on understanding CHO cell culture metabolic traits by integrating first-principles models with data-based parameter estimation, aiming to identify and interpret key metabolic features associated with relevant cellular phenomena. Currently he is working to provide hybrid knowledge and data-driven frameworks to support improved experimental protocols and more informative experimentation.