

## TOWARDS ADVANCED UNDERSTANDING OF SCALE-UP: FROM COMPUTATIONAL FLUID DYNAMICS TO SYSTEMS BIOTECHNOLOGY APPROACHES

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Key Words: Scale-up, systems biotechnology, CFD

Scale-up of mammalian cell culture processes from development scale to commercial manufacturing scale is routinely performed in biopharmaceutical process development. For this purpose, well established biochemical engineering principles, empirical formula and scale-up criteria were developed. Considering well characterized equipment as well as company specific process and platform knowledge, scale-up typically is successfully achieved. Yet, improved understanding of scale-up phenomena is desirable for various reasons. Since miniaturized systems are increasingly used in biopharmaceutical process development and, at the same time, efforts with respect to resources and timelines to achieve final manufacturing scale are to be minimized, scale-up steps need to cope with larger bioreactor volume changes in the future. From a process science perspective, an integrated analysis of scale-up phenomena considering both the biochemical engineering aspects (e.g. power input,  $k_L a$ ) as well as cell-level data is needed.

In order to gain more profound understanding of scale-up, comprehensive characterization of our cultivation systems using computational fluid dynamics (CFD) was achieved (Figure 1). To further improve and integrate the understanding of an antibody producing CHO cell in a bioreactor environment across scales, we performed thorough analysis of metabolic rates and fluxes in different cultivation scales. In addition, gene expression data using NGS were obtained (Figure 2).

These tools were applied for an in-depth analysis of a production process where differences in cell culture performance (e.g. product titer) were observed between different scales (from 250mL to 12.000L). The results of this case study will be presented and the individual contributions of these tools towards a more comprehensive understanding of scale-up will be discussed.

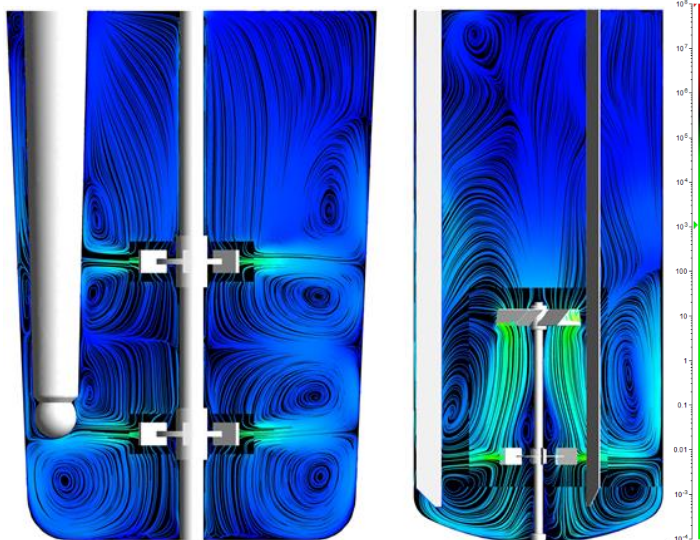


Figure 1 – Velocity profiles in 250mL and 12.000L scale

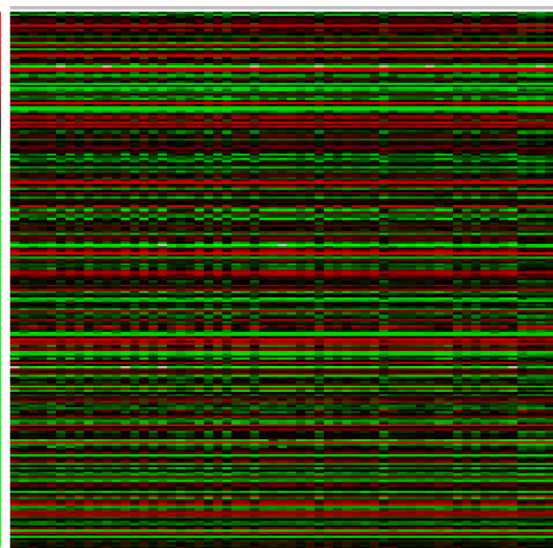


Figure 2 – NGS gene expression profiling