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UNDERSTANDING AND OVERCOMING PROCESS INSULTS THROUGH APPLICATION OF 'OMICS TECHNOLOGIES

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Modern industrial process development, at both small and large corporations, usually consists of applying a well-characterized and established cell culture platform. Despite the high productivity available from these process platforms, difficult challenges remain, including with respect to the ability of the process to endure insults or disruptions. We previously demonstrated that overfeeding resulted in an undesirable increase in lactate production late in fed batch culture, which decreased productivity[i]. Here we report on metabolic flux analysis performed utilizing this process and isotopically labeling with multiple tracers (glucose and glutamate) delivered at five distinct time points of the cell culture process. Notably, we identified unexpected behavior within the tricarboxylic acid (TCA) cycle. The corresponding labeling data indicated a significant redistribution of the fluxes in and around the TCA cycle.

Understanding the intracellular changes occurring when cells are challenged with a process insult, such as overfeeding, should lead to enhanced process development. Consequently metabolic flux analysis is only the first step in improving the process. We have identified two medium supplements which each independently permit the cell culture to endure overfeeding and result in maintaining or increasing titer despite the process insult. The overfed process and the supplemented processes were utilized to evaluate changes in the cellular metabolism with an untargeted metabolomics approach. Novel findings from the untargeted metabolomics approach when combined with metabolic flux analysis give a complete picture of the cellular metabolism as both reaction rates and relative concentrations are known over the full process duration. With this knowledge in hand, the platform process can evolve to routinely overcome process insults such as overfeeding.

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