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Engineering the cell factory for efficient culture performance

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The global relevance of the bio-based economy keeps growing and is boosted by the genetic and metabolic manipulation of the cell factories. The portfolio of molecules that are bio-produced at laboratory and commercial levels is also expanding. While the manipulation of cell factories allows overproducing natural or non-natural molecules at attractive yields, cell factories are frequently developed and evaluated under environmental conditions that differ from those that will be found in large scales. In comparison with the examples of genetic modifications aimed at the overproduction of a given molecule, there are much less examples on the engineering of cell factories for facing the production scale, which often results in reduced productivities when processes are up scaled.

A typical example of the cell factory behavior limiting the process operation is the aerobic production of acetate (overflow metabolism) in *Escherichia coli*. In order to improve the performance of the *E. coli* during batch and fed-batch cultures, we have pursued genetic modifications aiming at reducing the overflow metabolism. This opens the possibility of using unconventional cultures schemes like high cell-density cultures using up to 120 g/L of initial glucose concentration with minimal acetate accumulation. Further modifications have allowed efficient production of plasmid DNA vaccines in small-scale bioreactors and shake flask with enzyme-controlled glucose release.

Another example of process limitation is the mass transfer capacity of bioreactors, which is often lower than the oxygen demand of the cell factories. This results in microaerobic conditions, which activate metabolic modes that are less efficient for energy and biomass synthesis than those used under aerobic conditions. We have engineered *E. coli* strains in order to improve growth rate, biomass yields and reduce by-products formation. When cultured under controlled microaerobic conditions, the engineered cells have displayed growth characteristics similar to those of the wild-type strain under fully aerobic conditions. Engineered cells are being evaluated for the microaerobic production of recombinant molecules.

In order to gain a better understanding of the physiological adaptations of the engineered strains, classical (chemostat culture) and modern (flux balance analyses, on-line capacitance/conductivity measurements) have been pursued. The most representative results will be presented. The potential applications of the results for robust processes development will be discussed.