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Process intensification of perfusion: to steady-state, or unsteady-state, that is the question

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Recent advances in process intensification of perfusion cell culture have diverged into two general modes of operation. One focuses on the conventional steady-state concept of maintaining constant high cell density over a lengthier culture duration, and the other focuses on a much more intensified non-steady state cell density, at times reaching $>100e^6$ cells/mL. The latter has been coined concentrated fed-batch and the former continuous perfusion. Several underlying characteristics differentiate the two modes. In the steady-state approach, cell bleed is required and the cell density typically can range from 20 to $50e^6$ cells/mL. Culture duration of 30 days or more is usually achievable and this can be decided based on the product yield requirement. In the unsteady-state approach, cell density in the range of 50 to $100e^6$ cells/mL is typically achievable; however run duration is dictated by how long the culture can stay viable. Both modes can produce product yields that far exceed fed-batch processes. Specific productivity is not expected to differ for the two modes when using the same medium and bioreactor conditions. When designing a perfusion process that is integrated with downstream process for continuous processing, several considerations weigh into the design. The steady-state approach can leverage run duration to achieve the desired yield and produce a more constant product concentration stream, however, the longer run time challenges downstream in terms of column cycle, sterility integrity and buffer requirement. In the unsteady-state approach, higher cell density is leveraged to achieve the desired yield with a shorter run duration, however variable product concentration stream challenges column loading and the control of continuous purification. Our experience with developing both types of perfusion culture shows that which path to take largely depends on the requirement of the cell line and the type of downstream employed. The development and characterization of these two modes of perfusion operation will be discussed.