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Kinetic physico-chemical model for cell culture processes – applications and opportunities

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Cell culture processes for production of recombinant proteins can be modeled to provide critical insights into the interrelationship between several parameters that impact the process performance and control. For the first time, we describe a model that incorporates pH control in combination with gas transfer to provide a more complete description of the physicochemical processes that occur during the entire course of the cell culture process. The model includes multi-component chemical equilibria involving carbonate, lactate and sodium hydroxide coupled with electroneutrality for calculation of pH. Further, the pH feedback control has been incorporated depending on levels of carbonate and lactate in the culture. Additionally, pH ramp, and pH dead-band controls have been included to facilitate simulation of real process conditions. For oxygen transfer, cascaded control including agitation, air flow and oxygen flow are implemented. Very limited actual data from at-scale or small scale studies are required for the model, essentially requiring only cell density profiles and lactate profiles. Other specific rates are readily calculated based on measurements.

Simulations based on these models provide key relationships that provide a clear basis for designing control strategies for the entire process. Several scenarios, including the choice of base, the impact of lactate consumption and production, the impact of cascaded controls for oxygen transfer, as well as the buffer composition of the media have been simultaneously evaluated through simulations, resulting in valuable approaches to scale-up and scale-down design of cell culture processes. Case studies will be presented demonstrating some of the applications. Potential improvements and opportunities will also be presented.