FEEDBACK CONTROL OF LACTATE USING RAMAN SPECTROSCOPY

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In fed batch cell culture lactate is produced during the growth phase; its consumption is observed when cells enter the stationary phase. This metabolic shift is desirable and tends to favor optimal process performance and product quality. A CHO cell line known not to demonstrate this metabolic shift and produce high lactate was used as an experimental system. Multifactor DOE experiments were run on process conditions known to influence lactate which included glucose, pH, cell generational age, base control, cell bank and scale-up. Conditions were established for high and low lactate results at bench-top and pilot scale. Multivariate models of lactate production were established. Although multiple factors influenced lactate production it was thought that a flexible manufacturing system could convert a worst-case high-lactate profile into desirable low-lactate profile. Previous work has demonstrated the feasibility of controlling lactate and glucose on-line with Raman spectroscopy. Models were established to quantitate in real-time both glucose and lactate concentrations during the bioreactor process. A feedback loop was developed, in which glucose and lactate concentrations were both monitored and used to control a glucose feed pump. The high-lactate process conditions were run with this two factor feedback control in both bench-top scale and pilot scale reactors. The results demonstrated that a culture could be shifted to lactate consumption converting a high-lactate profile to a low-lactate profile. The system also demonstrated an equivalent or potential increase in over-all titer. Work is continuing to establish this system as a back-up control to prevent high-lactate in future manufacturing.