DYNAMIC PH PROFILES DRIVE HIGHER CELL SPECIFIC AND VOLUMETRIC PRODUCTIVITY

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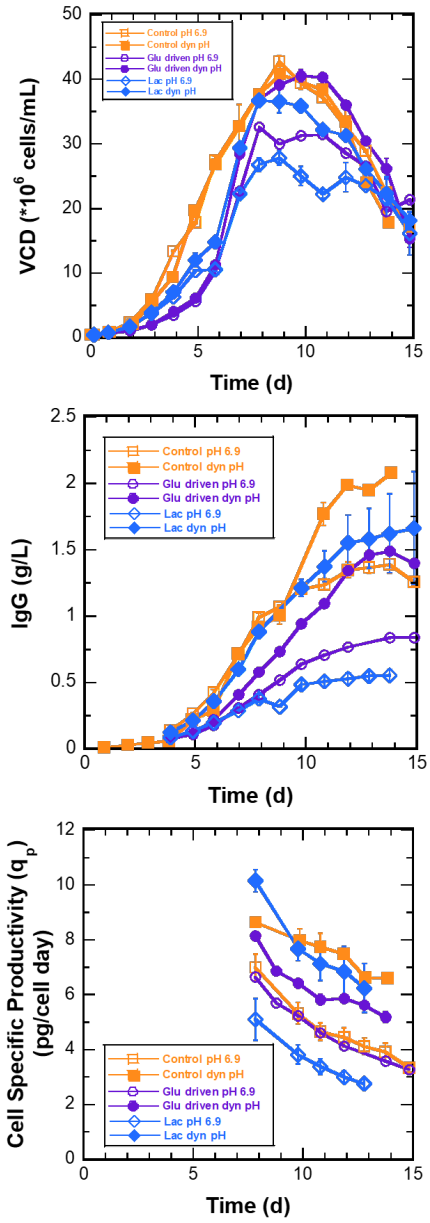

Chinese hamster ovary (CHO) cells continue to be a successful platform for the production of recombinant protein-based therapeutics due to ability to perform post-translational modifications analogous to human proteins. Since CHO cell proteins occupy such a large portion of the pharmaceutical market, recent research has focused on optimizing the mammalian cell production process for higher efficiency, better reproducibility, and lower cost. Process optimization typically occurs with modifications of basal media and feed formulations, adjustment of process parameters including pH, DO, and temperature, as well implementing novel feeding strategies. More specifically, culture pH has been shown to be a critical parameter that influences growth, productivity, and critical quality attributes. Typically, pH is either controlled to a set point throughout the culture or uses a single pH shift to achieve higher productivity. The pH is usually maintained by CO_2 and base additions. For CO_2 controlled cultures, using a set point can result in an accumulation of CO_2, which has detrimental effects on mammalian cell growth and production. In this study, a dynamic pH profile was implemented that allowed the pH to mimic the natural pH profile observed in shake flask cultures. This dynamic pH profile employs multiple pH shifts during the exponential phase of an IgG_1 producing CHO-K1 cell line as opposed to a single pH set-point shift as seen in most industrial processes. The results show that a dynamic pH profile was able to successfully alleviate CO_2 accumulation and increase the cell specific productivity, as well as the volumetric productivity. This effect was observed across multiple feeding strategies, as well as lactate stress cultures, as shown in **Figure 1**. This work also explores the impacts of dynamic pH profiles on amino acid metabolism and glycosylation profiles.

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Figure 1 – Growth Characteristics for Dynamic pH and pH 6.9 set-point controlled cultures. A) viable cell density; B) titer; and C) cell specific productivity profiles for control, amino acid (Glu) driven feed, and lactate stress (Lac) cultures