A SOFT SENSOR OF CELL CONCENTRATION IN A PERFUSION BIOREACTOR VIA A DIGITAL TWIN

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An important stage in the manufacture of chimeric antigen receptor (CAR) T cell therapies is the expansion of the initial cell population. Estimating the CAR T cell population in real-time can help to inform decisions regarding their harvest time for subsequent cryopreservation or re-infusion into the patient. However, it can be challenging to predict the cell concentration without time consuming manual intervention or costly hardware (or 'hard') sensors. To address this challenge, we have developed a digital twin of a perfusion bioreactor which can provide a 'soft' sensor of cell concentration. A key requirement of the digital twin is access to high frequency nutrient/metabolite measurements (i.e. glucose/lactate concentrations) via at-line sensors. Additional data requirements include the at-line perfusion rate readings as well as an off-line measurement of the initial cell concentration. To demonstrate its utility, the digital twin has been applied to three historical datasets of the Aglaris Facer bioreactor (see panels 'a' and 'b' of Figure 1). Based on the perfusion rate and glucose/lactate concentration at-line data alone, the growth yield factor of lactate from glucose was estimated to be 1.88, 1.74 and 1.70 (unitless), respectively, for the three datasets. These estimates are consistent with the anaerobic glycolysis metabolic pathway where one mole of glucose is ultimately converted to two moles of lactate. Combining the at-line data with the off-line initial and final cell concentration measurements, the growth yield factor of cells from glucose was estimated to be 0.22, 0.27 and 0.16 cells/pmol, respectively. This critical process parameter (CPP) allows for an estimate of the cell concentration via a combination of the digital twin and the bioreactor data (see panel 'c' of Figure 1). In addition, estimates of the specific growth rate suggest a deceleration of cell expansion that is consistent with the Richards model of cell growth. To the best of our knowledge this is the first soft sensor of cell concentration in a perfusion bioreactor that utilizes high frequency at-line nutrient/metabolite data in the context of CAR-T cell therapy. Furthermore, the CPP estimates have provided insight of T cell metabolism and growth in a perfusion bioreactor. Our work has direct relevance to sessions 3 and 4 because, via process modeling, the digital twin provides a tool to address challenges with the analysis and interpretation of big data and heightens the level of process understanding. Also with reference to session 4, the glucose/lactate sensors demonstrate an implementation of these process analytical technology (PAT) tools in a GMP grade bioreactor. In addition, our research is also relevant to session 5 because the three historical datasets were generated via the manufacturing of therapeutic T cells and our use of at-line process monitoring data has enabled us to identify CPPs such as the growth yield factor of cells from glucose.

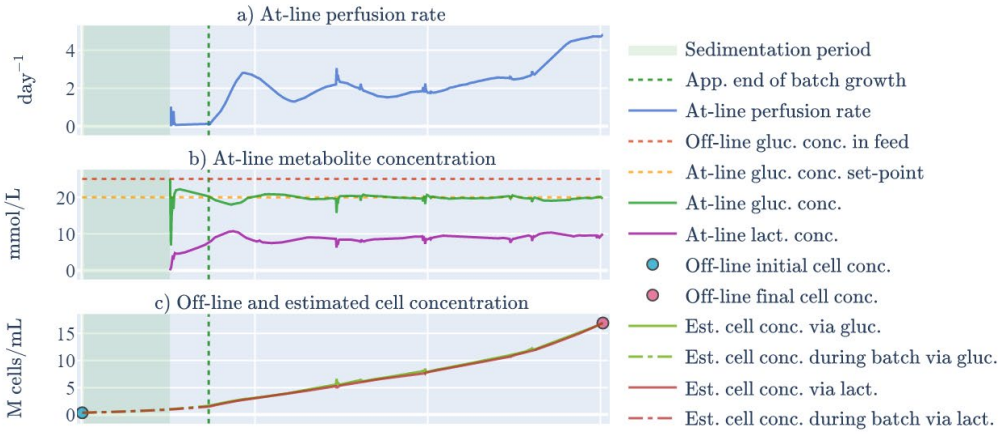

Figure 1 – Data and soft sensor for dataset 2