

ON-LINE MONITORING AND CONTROLLING OF CELL APOPTOSIS IN MAMMALIAN CELL CULTURE PROCESSES USING DIELECTRIC SPECTROSCOPY

An Zhang, Biogen, an.zhang@biogen.com
Fuduo Ma, North Carolina State University
Orlin D Velev, North Carolina State University
Vivian Shen, Biogen
Caitlin Kurtz, Biogen
Kelly Wiltberger, Biogen
Rashmi Kshirsagar, Biogen
Jun Ren, Biogen
Michael Farrow, Biogen
Rob Guenard, Biogen

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We investigate a method to control critical quality attributes and apply Process Analytical Technology (PAT) via online dielectric spectroscopy (DS) feedback. This system has been intensively explored and successfully implemented in GMP manufacturing processes at Biogen. The present bioreactor application however, is basic and only allows the prediction of biomass. To further enhance the cell culture process robustness, we investigated the feasibility of using the full-spectrum dielectric spectroscopy scanning function to detect dielectric property changes in the cells associated with shifts in cell health and/or metabolism. In this proof of concept study, we used several CHO cell processes to demonstrate that DS probes can be used to not only measure the biomass but also reflect the cell's physiological state changes (e.g. cell apoptosis). The results showed that one or more of the key parameters of delta capacitance (ΔC), critical frequency (f_c), and Cole-Cole Alpha (α) from the multi-frequency scanning data could reflect the cell's early apoptosis induced by chemical treatment, nutrient depletion, or shear stress, which were seen earlier than that obtained from off-line methods (e.g. trypan blue exclusion). In some cases, by responding to the earlier detection, the cell apoptosis was reversed in time and the batch was saved. This enables a potential application, transferrable across programs, of full-spectrum dielectric spectroscopy for earlier detection of physiological changes, allowing for timelier bioreactor process adjustments. In addition, the feasibility of the application of multifrequency scanning in cGMP process for monitoring and control was also explored in this study.