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Spring 5-10-2016

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Ann D'Ambruoso, Jeremie Barbau, and Denis Haumont, "Continuous suspension cell culture monitoring in bioreactors using quantitative imaging" in "Cell Culture Engineering XV", Robert Kiss, Genentech Sarah Harcum, Clemson University Jeff Chalmers, Ohio State University Eds, ECI Symposium Series, (2016). http://dc.engconfintl.org/cellculture_xv/117

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CONTINUOUS SUSPENSION CELL CULTURE MONITORING IN BIOREACTORS USING QUANTITATIVE IMAGING

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Abstract

Monitoring of suspension cell cultures often relies on sampling followed by a staining procedure. Estimations of cell count and cell viability are traditionally performed once a day using Trypan-Blue cell exclusion as a method of choice. Stained samples are destroyed afterwards creating toxic waste. Sampling a bioreactor and counting cells involve manual operations and weekend work is regularly needed.

Differential Digital Holographic Microscopy (DDHM) is a new quantitative imaging technique that allows cell counting as well as cell viability monitoring in a continuous, label-free set-up. No need for sampling (thus eliminating the risk of contamination), staining and waiting for results generated by an off-line counter: results are available in nearly real-time during the whole run.

Compared to classical light microscopy, Differential Digital Holographic Microscopy offers:

- The ability to refocus images post acquisition
- The collection of quantitative phase information (optical density), covering the shape and density of an object. This quantitative phase parameter (not captured by the human eye) is the key advantage in numerous applications developed at OVIZIO.

DDHM helps the operator to continuously track total cell density and cell viability, while the OsOne software plots the cell growth curve, live on the screen. Moreover, OsOne also shows real-time images of cells, offering the experienced operator a particularly convenient tool to check the condition of the cell culture.

In this study, we compared the results generated by the iLine F microscope with off-lines methods applying sampling and Trypan-Blue staining. OVIZIO's iLine F was benchmarked versus the Vi-Cell XR (Beckman Coulter). A bioreactor equipped with a BioConnect (OVIZIO's continuous, closed loop, sampling device) plugged into an iLine F was inoculated with CHO cells at $0.3x10^6$ viable cells/mL in CD-CHO medium (Life Technologies) for a final volume of 2L. The culture was sampled daily via the usual sampling port for Vi-Cell cell count. The iLine F was set to generate 2 data points (cell counts and viability measurement) per hour. The culture was left to grow in batch mode so it was possible to also capture the decrease in cell viability at the end of the bioreactor run.

An excellent correlation factor R^2 was obtained for the viable cell density demonstrating that the results achieved with the label-free DDHM method are in line with current methods applying Trypan-Blue staining.

Furthermore, the iLine F shows the benefit of having the full trend of the culture which can be more relevant than a single point, on a single sample, once a day. The availability of full data at the single cell level, for the whole experiment, allows to envision the use of the iLine F in a PAT approach. Indeed the large amount of data produced can be used to perform various statistical analysis on the cell population in order to define and control critical parameters of the cell culture process.