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LENSSLESS IMAGING FOR CONTINUOUS CHO VIABLE CELL DENSITY MONITORING IN BIOREACTOR

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During suspension cell cultures in bioreactors, traditional measure for cell count and cell viability still rely on sampling and staining protocol where the Trypan Blue exclusion method is performed once a day. While automatic cell counters have reduced the statistical error of the original manual method, sampling the bioreactor is a risk for contamination and is prohibiting the use of such method for process control as the sampled volume becomes significant. Lensless Imaging Technology is a new breakthrough method for accurately and precisely determine cell concentration and viability without staining. This technique has the unique capability of acquiring microscopy images without any objective, lens or focus settings. A light source illuminates the cells, the interference between the light diffracted by the cells and the incident light coming from the same light source generates holograms that are directly recorded onto a CMOS sensor. A holographic reconstruction algorithm retrieves in real time the objects that have created the holograms and reconstructs the microscopy image. Living and dead cells have significant diffraction properties creating very different hologram patterns that are distinguished by the algorithm. Our contribution reports the comparison of cell counts and viability determination between the Trypan Blue reference method and our Lensless Imaging device. Cell counts is performed once a day on samples from 12 separated bioreactors, starting from the inoculation to the end of a 13 days CHO culture. The Lensless Imaging prototype is immersed in a measurement chamber, manually receiving the bioreactor samples, to both reproduce an in situ measure and avoid steam sterilization at this time of the experiment. With a concentration range from $0,43 \times 10^6$ up to 20×10^6 cells /ml and viability from 100% declining to 75% at the end of the cultures, we obtained a correlation factor of 0.986 (figure1). A specific study reports on the repeatability of the Lensless Imaging measurement method. The very large field of view (30m^2), allows the analyze of several thousand cells within a single image, keeping the statistical variability of the measure as low as 3% in low as well as high cell concentration range. We are now working at designing a steam sterilizable probe, and we envision Lensless Imaging to become the future method of choice for on-line and in-situ monitoring of suspension cells and a perfect tool for process control in fed-batch or perfusion mode.

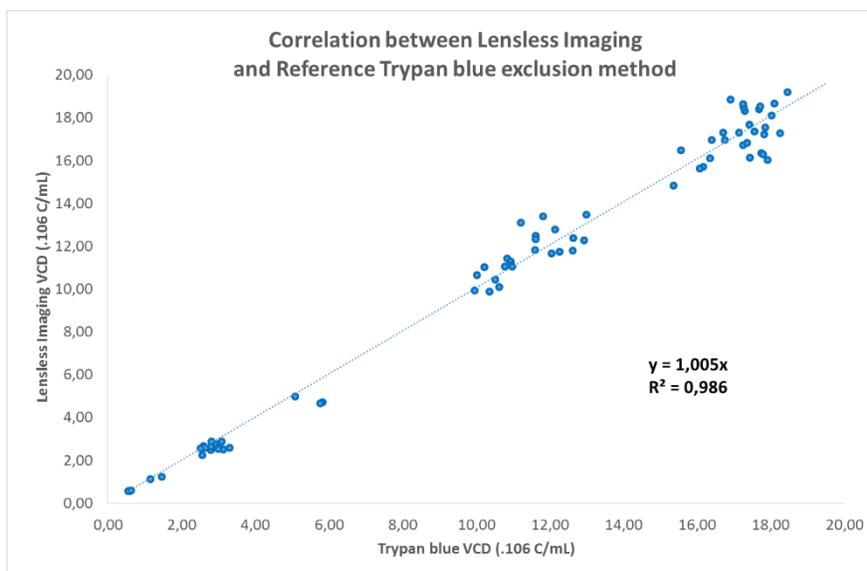


Figure 1