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High-throughput holographic imaging technologies for rapid monitoring of cell density, viability, and cell health in bioreactors

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Viable cell count (VCC) and viability are key cell culture process parameters during biopharmaceutical manufacturing. As such, accurate measurements of these attributes are critical both in process development and GMP manufacturing. Existing technologies to measure cell count and viability in bioreactors are not only expensive but also pose certain restrictions in terms of time required for measurements, equipment-to-equipment variability, and high sample volume requirements. This work aims to describe the use of a novel, label-free holographic imaging technology (NORMA) to enable rapid and accurate measurements of not only VCC and viability, but also cell health based on changes in refractive index of the cells. Holographic cell imaging is an inexpensive solution over current technologies for measuring cell density and viability from bioreactors. The rapid and high-throughput readout coupled with a dilution-free, low sample size makes it suitable for measurements in bioreactors across scales including microscale bioreactors. The robustness of this novel technology was tested across multiple cell lines, media types, and process conditions. Both VCC and viability were reliably measured up to 40 million cells/mL without dilution. Refractive index of the cells was observed to change with phases of cell growth which consistently correlated with cell health in the reactor. The high-throughput version of the NORMA technology (NORMA 4S) was successfully integrated with the advanced microscale bioreactor (ambr15) system for timely, automated sampling and rapid measurement of VCC and viability using just 20 µL of cell suspension enabling more frequent measurements than conventional technologies.