

# Towards quantitative single cell analysis using optical tweezers and microfluidics

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## ABSTRACT

Experiments on single cells have the potential to uncover information that would not be possible to obtain with traditional biological techniques, which only reflect the average behavior of a population of cells. In the averaging process, information regarding heterogeneity and cellular dynamics, that may give rise to a nondeterministic behavior at the population level, is lost. In this thesis I have demonstrated how optical tweezers, microfluidics and fluorescence microscopy can be combined to acquire images with high spatial and temporal resolution that allow quantitative information regarding the response of single cells to environmental changes to be extracted.

Two main approaches for achieving the environmental changes are presented, one where optically trapped cells are moved with respect to a stationary flow, and one where the fluid media are moved relative to cells positioned stationary on the bottom of a microfluidic device. Both approaches allow precise and reversible environmental changes to be performed. The first approach achieves environmental changes in less than 0.2 s, and is thus suited for studies of fast cellular processes. This is approximately ten times faster than the second approach, which is, however, more convenient for studies over longer periods of time where statistical information on a large number of individual cells are requested. The experimental approaches are verified on different signalling pathways in *Saccharomyces cerevisiae*, where the main focus is the HOG pathway. The cellular response is followed either via brightfield images, where the volume changes of cells are monitored, or through fluorescence images where the spatio-temporal distributions of GFP tagged proteins are extracted.

A possible approach to increase the throughput using stationary flows is demonstrated by introducing holographic optical tweezers, allowing several cells to simultaneously be trapped and exposed to environmental changes. Automated image analysis combined with 3D manipulation is shown to allow the temporal resolution to be increased, or enable studies over longer periods of time thanks to the reduced photobleaching.

**Keywords:** Optical tweezers, holographic optical tweezers, microfluidics, lab-on-a-chip, fluorescence microscopy, spatial light modulator, single cell analysis, quantitative systems biology, GFP, *Saccharomyces cerevisiae*.