Analysis of array CGH data for the detection of single-cell chromosomal imbalances

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Based on Fluorescent *In Situ* Hybridization (FISH) analyses, previous studies on single human blastomeres have shown a high rate of chromosomal aneuploidy during early embryogenesis. Recently, it was shown that array CGH using BAC arrays enables the detection of chromosomal aneuploidies in single cells. To increase the resolution and the accuracy of the detection of chromosomal imbalances in single cells, we developed a finite mixture model enabling the detection of chromosomal and segmental aneuploidies.
The data are analyzed per single cell by fitting a finite mixture of Normal distributions per chromosome. Our finite mixture model consists of three Normal distributions corresponding to the duplication, the normal and the deletion group. The model corrects for the systematic bias, introduced by amplification, through an additional estimated clone-specific mean and clone-specific variance, both derived from a reference set of normal clones. The detection of aneuploidies is equivalent to searching for regions of successive clones that belong to one of the three groups. To obtain these regions, the posterior probabilities of the clones are smoothed by means of a loess smoothing. This approach has the advantages that loess smoothing is robust for outliers and the posterior probabilities take the a priori proportions of the three different groups into account.
The methodology was tested on single cells with a priori known abberations. Next, we analyzed single cells from three different cell types. The non a priori known aneuploidies that we detected, were confirmed by single cell SNP arrays. Using our methodology, we are able to screen single cells for genome wide copy number variations.