Quantifying cellular dynamics of stem cell decisions

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Time-lapse microscopy is a powerful method to continuously monitor single cells. Combined with appropriate markers, it allows for the time-resolved observation of protein expression. Such information is necessary to characterize state transitions, differentiation dynamics and gene expression models. However, to infer regulatory events or spatiotemporal effects robustly, bioimage informatics and tailored analysis methods are required.

I will first present bioimage informatics tools for the processing of time-lapse data. Uneven illumination and variable background levels in microscopy images affect subsequent analysis but can be corrected with a computational method based on low rank and sparse decomposition. Single-cell information can be retrieved from images using tracking, segmentation and quantification. These tools generate lineage trees that contain genealogical information but also the dynamics of morphological changes, cell speed, and expression of fluorescent proteins.

In the second part I will present statistical models to infer cellular properties from single-cell data. In lineage trees of differentiating blood stem cells, stem cell decisions happen before an observable state change, inducing correlations in sister cells. Using these correlations and a stochastic model for a differentiation process, we find differentiation events to happen much earlier than anticipated and identify transcription factor expression that is inconsistent with the current toggle switch paradigm. To predict differentiation prospectively, we use a deep neural network trained on image patches from brightfield microscopy and cellular movement. Surprisingly, we can detect lineage choice in blood stem cells up to three generations before conventional molecular lineage markers are observable.