LARGE SCALE TRACKING OF STEM CELLS USING SPARSE CODING AND COUPLED GRAPHS

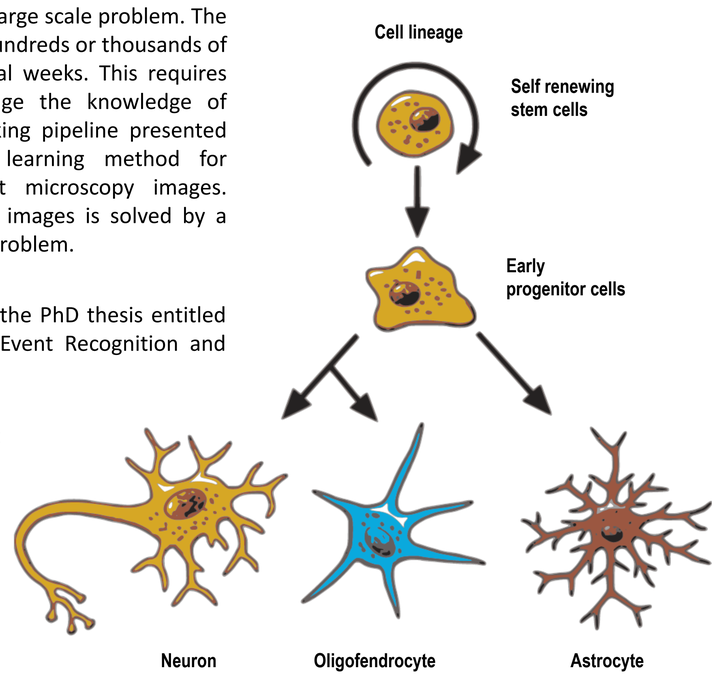
Vestergaard, Jacob S.[1], Dahl, Anders L.[1], Holm, Peter[2] & Larsen, Rasmus[1]
[1]Technical University of Denmark, Department of Informatics and Mathematical Modelling
[2]Copenhagen University, Faculty of Life Sciences

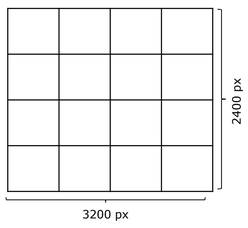
Abstract

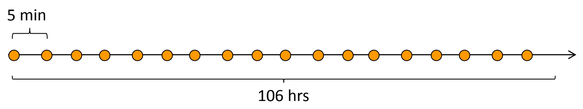
Stem cell tracking is an inherently large scale problem. The challenge is to identify and track hundreds or thousands of cells over a time period of several weeks. This requires robust methods that can leverage the knowledge of specialists on the field. The tracking pipeline presented here consists of a dictionary learning method for segmentation of phase contrast microscopy images. Linking of the cells between two images is solved by a graph formulation of the tracking problem.

This poster is prepared as part of the PhD thesis entitled "A Grand Challenge: Large Scale Event Recognition and Tracking".

The phase microscopy images are kindly provided by the Department of Basic Animal and Veterinary Sciences, Faculty of Life Sciences, Copenhagen University.







High dynamic range (HDR) phase contrast microscopy

Acquisition of the best possible imagery is ensured using high dynamic range (HDR) correction of the images. The phase contrast microscope is setup to acquire images in a 4 by 4 grid. In each of these observation points, four exposures are collected ranging from over exposed to under exposed. The over exposed images posses a large amount of saturated pixels, but captures the nuances in the center of the soma. The under exposed images neglects these nuances, but decreases the extent of the halo surrounding the somas.

The response function *g(z)* is modeled as a smooth monotonic function of the irradiances and is recovered by minimization of the quadratic objective function

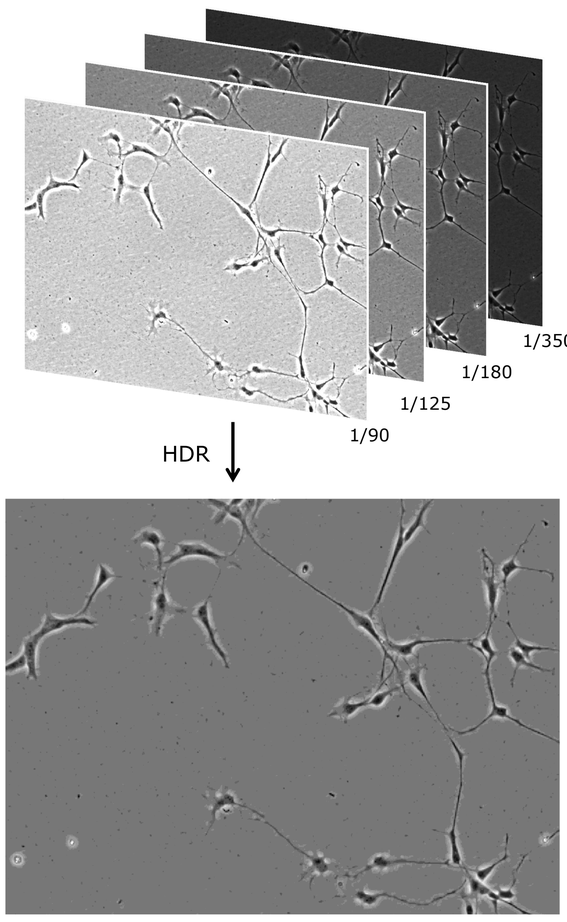
$$\mathcal{O} = \sum_{i=1}^{N}\sum_{j=1}^{P}[g(Z_{ij}) - \ln E_i - \ln \Delta t_j]^2 + \lambda \sum_{z=Z_{min}+1}^{Z_{max}-1} g''(z)^2$$

where Δt_j is the exposure time of the *j*'th image, E_i the unknown irradiance in the *i*'th pixel and Z_{ij} the pixel value. Smoothness is enforced by regularization of the second order derivative in the pixel intensity range.

Having recovered *g(z)* the four images are combined into a single image of irradiances:

$$\ln E_i = \frac{\sum_{j=1}^{P} w(Z_{ij})(g(Z_{ij}) - \ln \Delta t_j)}{\sum_{j=1}^{P} w(Z_{ij})}$$

Where *w(z)* is an introduced weighting function ignoring saturated pixels. By this transformation the dynamic range is effectively increased.



Dictionary learning

Learning a dictionary of discriminative image patches is a flexible and intuitive method for supervised segmentation. The idea is to build a basis for classification from the type of data at hand, rather than using a fixed basis, such as wavelets, curvelets, or similar.

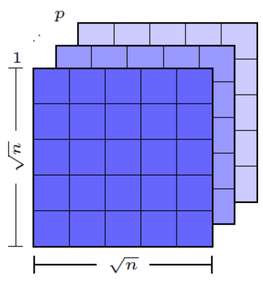
The dictionary atoms can be configured to contain any type of features. E.g., for multispectral data – or data in multiple modalities – the dictionary atoms can contain all channels. These will simply be part of the vectorized atom.

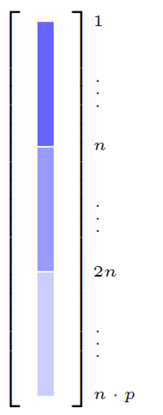
Learning a discriminative dictionary from an image:

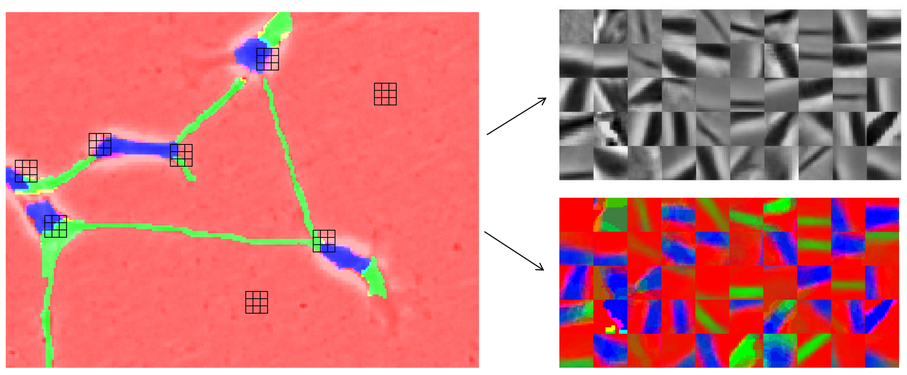
1. Label an image with a number of classes.
2. For each pixel, select an image patch.
3. Cluster these image patches in an intensity dictionary and an associated label dictionary with probabilities of each class.
4. Increase the discriminative power of the dictionary, by further separating cluster centers.

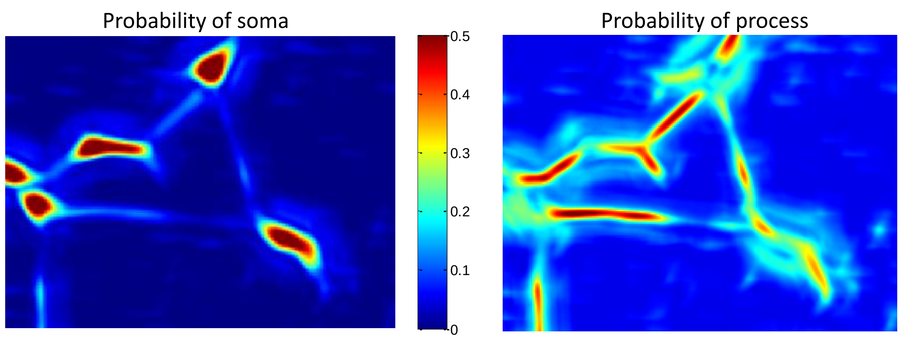
To segment an image using the dictionary is simple: Each image patch in the image is "looked up" in the intensity dictionary using a nearest neighbor search and assigned the corresponding probabilities from the label dictionary. For overlapping image patches, the probabilities are accumulated.

The result of the dictionary segmentation is a probability map with a pixel probability for each class.









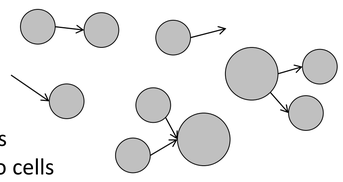
Coupled graphs for topology changes

Tracking cells through the entire time series is solved using a graph formulation of the correspondence problem. The minimum cost solution to the graph can be obtained using linear programming.

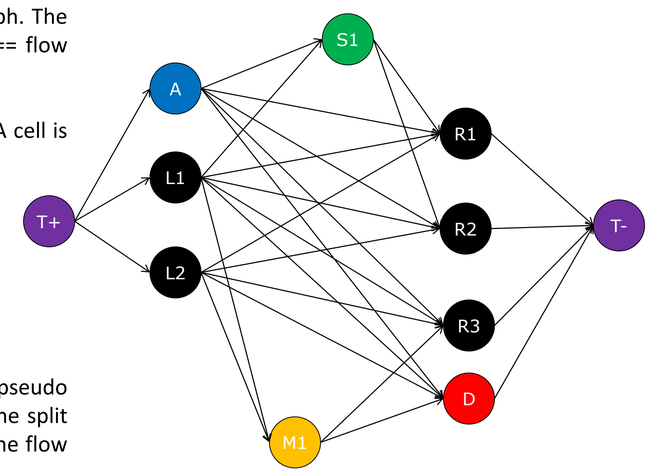
BLOBs detected in two adjoining images are the nodes connected in the graph. The edge capacities are set such that the flow conservation constraint (flow in == flow out) is honored and a minimum flow constraint is enforced.

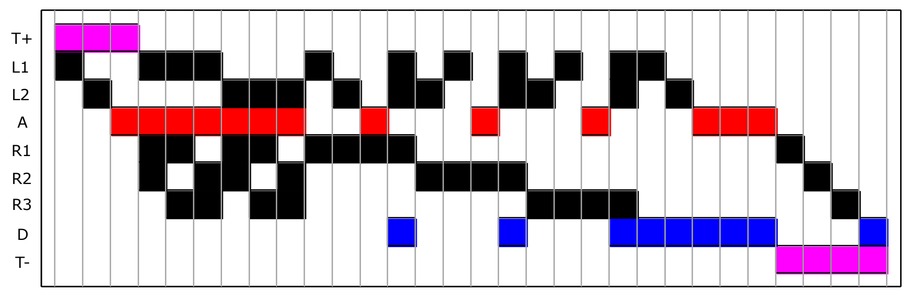
The graph is setup to accommodate for cell behavior and topology changes. A cell is allowed to

- Move
- Appear
- Disappear
- Split to two cells
- Merge from two cells



The split behavior is implemented by coupling two edges on the graph: a pseudo edge from the appear node to the split node and an edge from the cell to the split node. Similarly for the merge behavior. This coupling is done to ensure that the flow conservation constraint is honored.





The minimum cost problem can be formulated as a minimization problem:

$$\min \mathbf{c}^T\mathbf{x} \quad \text{s.t. } \mathbf{A}\mathbf{x} \leq \mathbf{b}$$

where **c** is the vector of edge costs, **x** is the binary solution vector, **b** is the vector of constraints (zeros except for source and sink) and **A** is the incidence matrix representing the graph.

Defining the edge costs

The edge cost is a scalar representing the cost of including an edge in the solution. The cost can therefore be defined from the similarity of the two objects. To represent the similarity, the feature vector difference is used. The features included are position in the x- and y-direction and area.

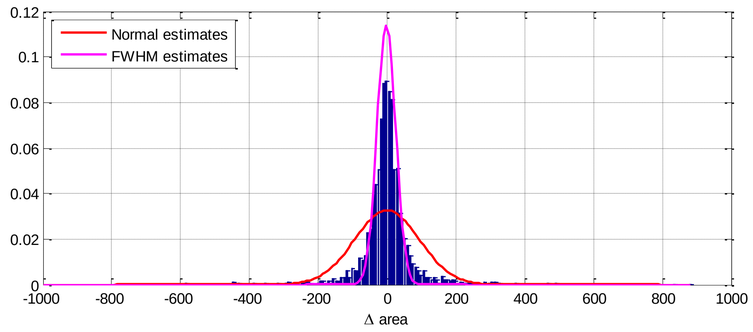
The edge cost is defined as the Mahalanobis distance from this difference vector to the mean of a population of typical changes.

$$cost(\mathbf{f}_i^t, \mathbf{f}_j^{t+1}) = (\mathbf{d}_{ij} - \boldsymbol{\mu})^T \boldsymbol{\Sigma}^{-1} (\mathbf{d}_{ij} - \boldsymbol{\mu})$$

where

$$\mathbf{d}_{ij} = \mathbf{f}_i^t - \mathbf{f}_j^{t+1}$$

The parameters **μ** and **Σ** are estimated from a simple nearest-neighbor tracking using the principle of Full Width at Half Maximum (FWHM) to extract the dominant distribution.



Tracking results

The stem cells were tracked over a time series of 40 hours, with 5 minutes interval between acquisitions. The phase contrast microscopy image acquired was of size 600 x 800 pixels.

Topology changes detected during tracking are summarized in the table below. The number of splits does not necessarily correspond to mitotic events, but rather segmentation errors. Further post processing is necessary to distinguish mitotic events.

Tracks	Splits	Merges	Appears	Disappears
144	1300	1296	184	185

Future work

Near future work include collection of ground truth to quantitatively evaluate the cell linking and definition of interesting features to collect.

The motivation for the stem cell tracking is to extract measures from the stem cell cultivation, enabling the bio analysts to optimize the growth process. Measures could include cell-to-cell proximity, in order to determine the cause for unexpected growth patterns or malicious cells.

A longer-term perspective is in-coloring of specific cell types at the end of the cultivation process. Ideally, the collected cell lineage will 1) enable the analyst to back track the life of each cell of interest back in time and 2) contribute to statistics causing the final types of cells.

References

Illustration: Genetic Engineering, http://www.humansfuture.org/genetic_engineering_stem_cells.php.htm

Dahl, A. (2011). Learning dictionaries of discriminative image patches. *British Machine Vision Conference,(BMVC)*.

Debevec, P. (2008). Recovering high dynamic range radiance maps from photographs. *ACM SIGGRAPH 2008 classes*.

Padfield, D., Rittscher, J., & Roysam, B. (2011). Coupled minimum-cost flow cell tracking for high-throughput quantitative analysis. *Medical image analysis*, *15*(4), 650-68.