Large Scale Identification of Brain Cells

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Transgenic mouse cerebellum at the micron scale
Slivestri et al., *Optics Express* 2012

Goal in this work: identification of all Purkinje soma in the whole cerebellum
Cell identification: challenges

• Most existing tools designed to work with small/medium scale images
• Whole mouse cerebellum image: 120 GVoxel
• Over 200,000 Purkinje cells
• Wild variability even within a single image
Mean shift cell identification

• Unsupervised mode seeker
• Cluster voxels based on 3D coordinates
• Fast: 100GVoxel/h on a 2-servers cluster
• Two preliminary steps, both sensitive to contrast:
  • image thresholding
  • seeding (based on intense local maxima)
Mean-shift on raw images

Performance measures

- Precision
- F1-Measure
- Recall

Mean-shift on raw images

Radius of the seed ball

Roughly the radius of smallest soma
Mean-shift on raw images

- Precision
- F1-measure
- Recall

Roughly the radius of smallest soma

Mean shift kernel bandwidth
Semantic deconvolution

- **Classic deconvolution**
  - Assume that the “good quality” image was “blurred” during optical acquisition
  - Blurring modeled as convolution with a point spread function
  - Invert the process

- **Semantic deconvolution**
  - Assume that the “ideal image” consisted of white spheres centered on the soma, on a black background
  - Use supervised learning to invert the process
Semantic deconvolution as supervised learning

No cell segmentation, just use centers!
How to do semantic deconvolution

- Naive idea:
  - Classify each voxel as soma vs non-soma
  - Use 3D patches of size $s$ as input to a neural net
  - Running time: for an image of size $n$ it takes $O(hn^3s^3)$ when using a one-layer net with $h$ units
• Predict $s^3$ voxels simultaneously in $O(2hn^3s^3)$ using a network with $s^3$ outputs.

• Using a stride of $d$ when moving the patch we may speed up the computation significantly $O(2hn^3s^3/d^3)$, e.g. for $d=4$ we get a 32x speedup over the naive approach.
Mean-shift on semantically deconvolved images

![Graph showing the comparison of Precision, Recall, and F1-measure before and after mean-shift on semantically deconvolved images. The x-axis represents the mean shift kernel bandwidth, and the y-axis represents the values of Precision, Recall, and F1-measure. The graph shows an increase in F1-measure and Precision, and a decrease in Recall after the mean-shift.](image-url)
Mean-shift on semantically deconvolved images

Performance measures

Recall
F1-Measure
Precision

Precision
F1-Measure
Recall

Before
After

Radius of the seed ball
Can we do even better?

• Best $F_1$ measure so far 0.93
• The cerebellum cortex folds into folia, i.e. manifolds
• Isolated / off-manifold predictions: mostly false positives
• Estimate manifold distance: charted Isomap + LOWESS
• The filter gains 3 points of $F_1$ measure
Using the manifold filter
Questions?

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Mean shift cell identification

- Mean shift is a hard version of kernel density estimation (in the same sense as k-means is a hard version of Gaussian mixture modeling)
- We use XYZ coordinates (major difference wrt other MS segmentation approaches which work on intensity/color/texture)
Sketch of the algorithm

- Start from all data points. Pick a set of seeds.
- Place a monotone kernel around each seed.
- Iterate until convergence.
  - Compute the weighted mean center of mass of the points falling within the kernel.
  - Move the seed into the center of mass.
- Remove duplicates.
Substacks

• One-shot application of the MS algorithm to 100GB not practical

• Split into 9000 overlapping substacks of size 245x280x280

• Two advantages:
  • Trivial parallelization
  • Local thresholding to discard background noisy voxels
Measuring prediction quality

We manually marked 4138 Purkinje nuclei in 56 different regions of the cerebellum image.
Comparing to other approaches?

- None developed specifically for this type of animal (mouse), type of cells (Purkinje), type of labeling (enhanced GFP), type of microscopy (confocal LSM)

- DeadEasy Mito-Glia (Forero et al. 2010) designed to detect mitotic cells labeled by anti-phospho-histone H3 in drosophila acquired by laser-scanning confocal microscopy

- Probably not a fair comparison but we still may gain some insights:
  - Several parameters to be tuned
  - Tried 140 different combinations of parameters in 56 cerebellum regions
  - Results are very sensitive to the choice of parameters
  - Taking the BEST parameter combination in each region leads to an overall performance of 0.95 precision, 0.78 recall, 0.86 F1-measure
  - By contrast, taking the best parameter on average leads to an overall performance of 0.88 precision, 0.76 recall, 0.82 F1-measure
Manifold filter algorithm

- Given \( S = \{(x^{(i)}, y^{(i)}, z^{(i)}), i = 1, \ldots, n\} \)
- Run ISOMAP to embed \( S \) into a 2D space:
  \[ H = \{(u^{(i)}, v^{(i)}), i = 1, \ldots, n\} \]
- For \( i = 1, \ldots, n \):
  - Let \( f^{(\setminus i)} \) be a LOWESS (locally-weighted regression) model trained on \( n - 1 \) points (except \( i \)) using the 2D embeddings as predictors and the corresponding 3D coordinates as responses.
  - The estimated distance from \( i \) to the manifold is

\[
 d^{(i)} = \left\| f^{(\setminus i)}(u^{(i)}, v^{(i)}) - (x^{(i)}, y^{(i)}, z^{(i)}) \right\|
\]