Belief theory enables identification of protein complexes in multi-scale microscopy with applications to metastasis and Alzheimer disease.

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Abstract*

Identifying objects in fluorescence microscopy is a non-trivial task burdened by parameter-sensitive algorithms. With experiments spanning multiple channels, datasets, operators, and microscopes, there is a clear need for an approach that adapts dynamically to changing imaging conditions. We introduce an adaptive object detection method that, given a microscopy image and an image level label, uses a kurtosis based matching of the distribution of the image differential to express operator intent in terms of recall or precision. Examples of image level labels include genome-based alteration of sub-diffraction limited cellular structures or pathological diagnosis based on image-based analysis of tissue section, where we wish to capture those aspects of the image that support the label, and to what extent. We show how a theoretical upper bound of the statistical distance in feature space enables application of belief theory to obtain statistical support for each detected object. We validate our method on 2 datasets: identifying Caveolin-1 labelled caveolae and scaffolds acquired by STED superresolution microscopy, and detecting amyloid-β deposits in confocal microscopy retinal cross sections of neuropathologically confirmed Alzheimer's disease donor tissue. Our results show consistency with biological ground truth and with previous subcellular object classification results, yet adds insight into more nuanced object transition dynamics. We illustrate the novel application of belief theory to object detection in heterogeneous microscopy datasets and the quantification of conflict of evidence in a joint belief function. By applying our method successfully to confocal and superresolution microscopy, we demonstrate multi-scale applicability.

Keywords

belief theory, object detection, statistical support, self-tuning, evidence conflict, live-cell microscopy, confocal and superresolution microscopy, diffraction limited [1] [2]

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[2]* Adapted from "SPECHT: Self-tuning Plausibility Based Object Detection Enables Quantification of Conflict in Heterogeneous Multi-scale Microscopy" – https://doi.org/10.36227/techrxiv.12971051.v1

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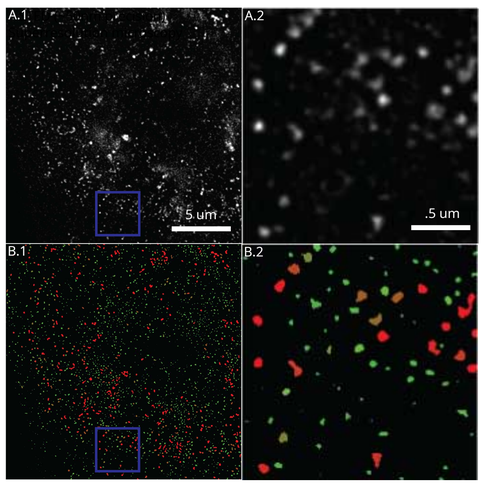
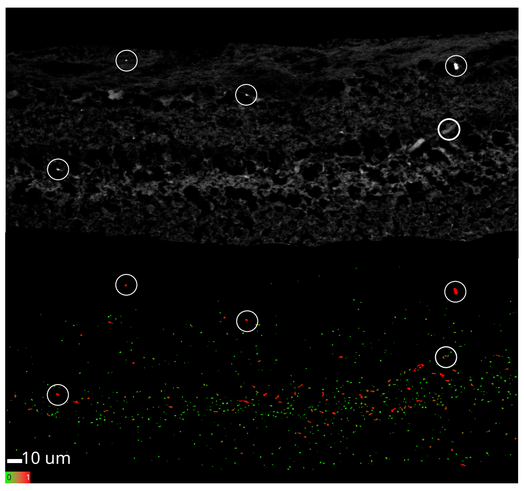
I.a Detecting Caveolae in superresolution microscopy



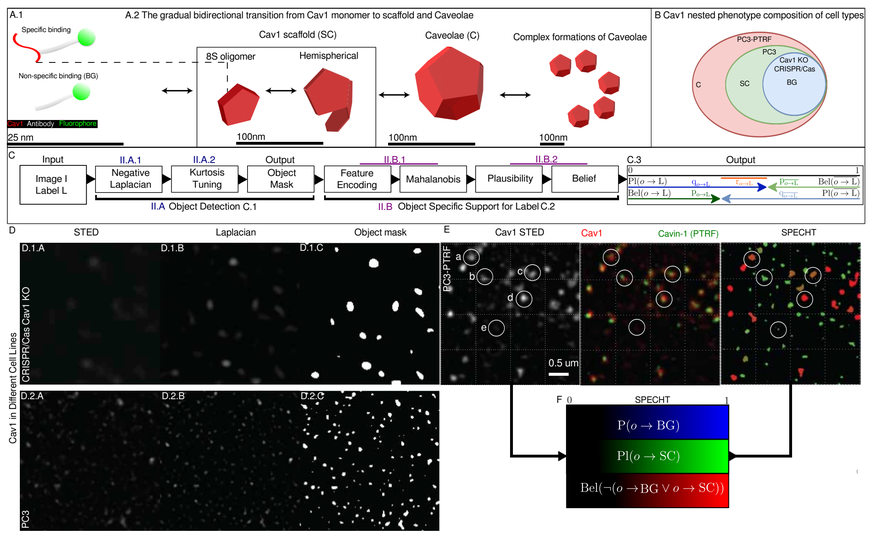
Caveolae are structures composed of Cav1 proteins that enable a cell membrane to withstand stress, and therefore motility. The formation process of Caveolae is thus a critical factor in understanding metastasis in cancer cells. We want to identify in each superresolution image (2D STED, $\sim$ 20nm) if a Cav1 concentration is a Caveolae, background, or scaffold.

I.b Detecting Alzheimer-disease specific amyloid-β in confocal microscopy



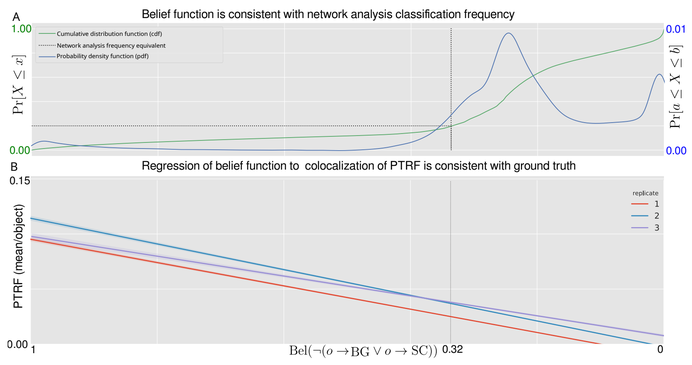
Amyloid-β deposits are associated with Alzheimer disease, but also are present in healthy tissue. We want to identify in retina tissue which AB deposits are indicative of Alzheimer disease, AD+ vs healthy tissue, AD-

II. Self-tuning detection and labelling of objects in multi-scale microscopy

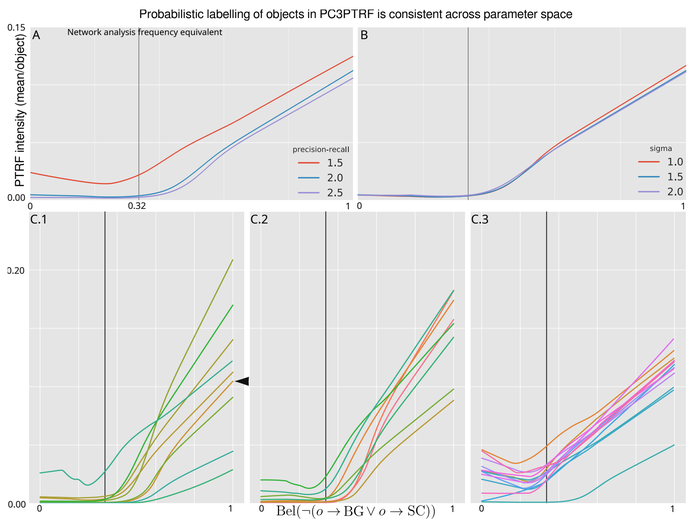


Outline of our method [1]. The formation process of Caveolae (A). Genotype alteration allows us to build a 3-valued belief label (B). The control flow of our algorithm (SPECHT) details the individual steps from self-tuning object detection to belief theory based labelling (C). The need for self-tuning object detection becomes clear as we contrast the intensity and object diversity in Cav1 knock-out (D.1.A), PTRF-KO (D.2.A), and the unaltered cells (E). E.Specht shows an example of an annotated (inset) of a prostate cancer cell. We observe high (expected) colocalization with PTRF for objects labelled as Caveolae, PTRF is necessary for the formation of Caveolae.

III. Validation

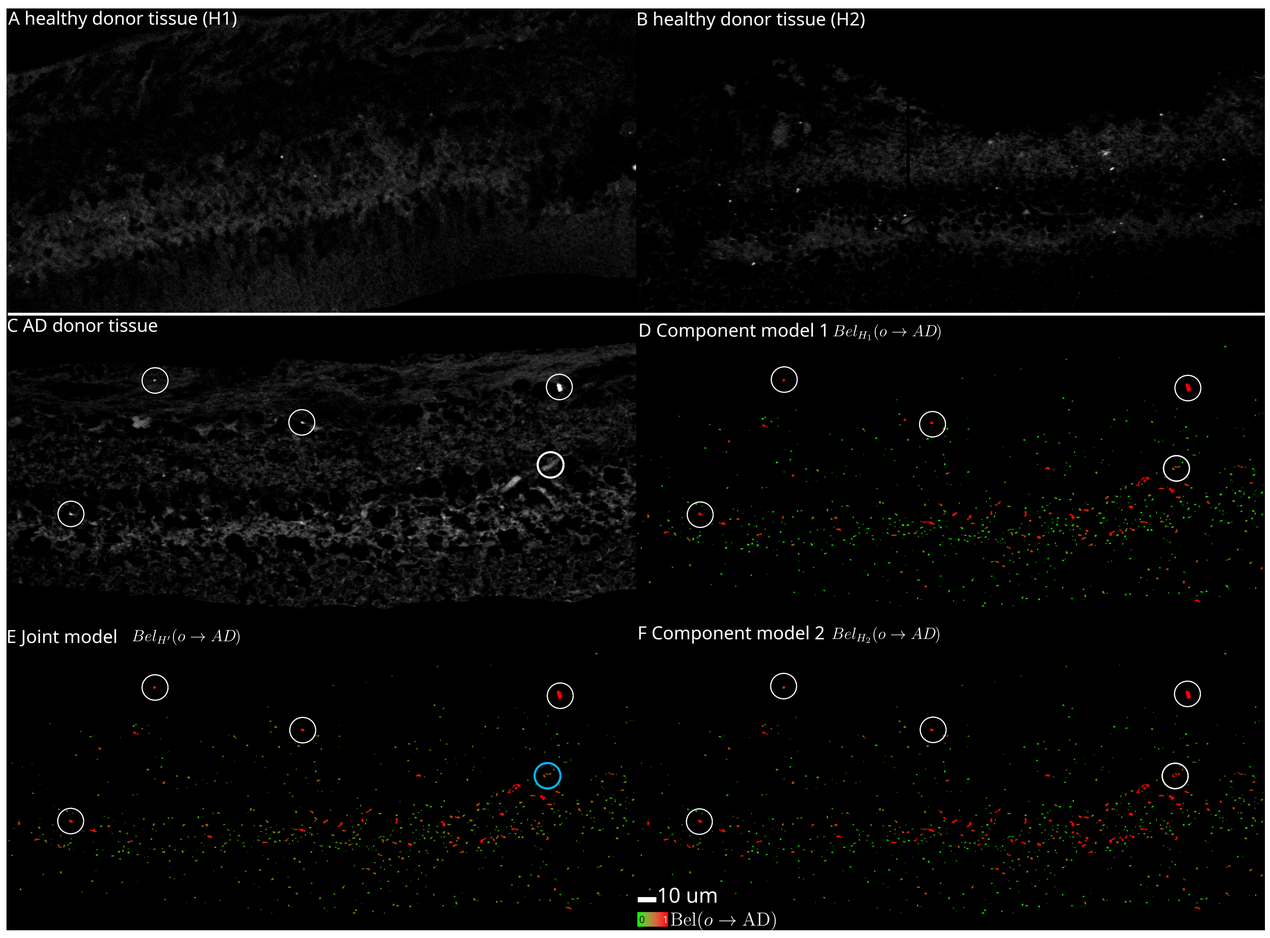


Cav1 requires PTRF to form Caveolae. Caveolae in PC3-PTRF cells is reported at a 20% [3] frequency. Our belief label (X-axis) is consistent with both. Observe how the 20% frequency coincides with a clear elbow point in the cdf and pdf curves.



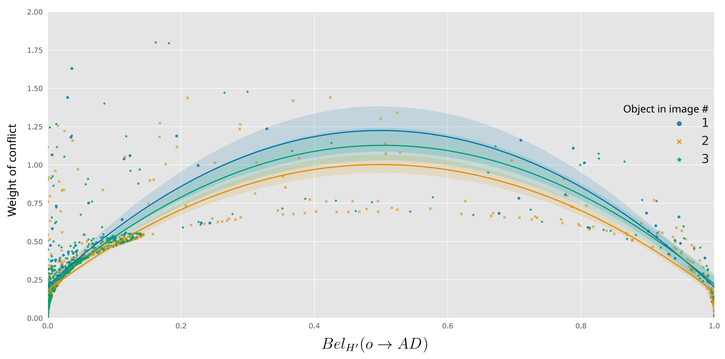
LOESS regression of the belief label (X-axis): colocalization of PTRF with Cav1 is consistent across cells and coincides with the elbow point of the cdf curve.

IV. Belief theory enables detection across multiple microscopes



Detecting AB deposits in confocal images is non-trivial, for example contrast image A (Alzheimer positive, AD+) with B (healthy, AD-). SPECHT is able to identify AB deposits associated with AD+ versus healthy across images from different microscopes.Belief theory enables the seamless joining of models built on different datasets (D, F) into a single model (E). We are able to inform the end user of deposits where the individual models disagree through the computation of conflict in Dempster-Shafer calculus [2].

V. Conflict computation between heterogeneous models



Example of conflict (Y-axis, $\sim$ disagreement) between individual object labels when SPECHT is modelled on 2 distinct datasets. A higher Y-value indicates higher disagreement, each marker represents a single object in an image. The X-axis denotes the belief label. Minimum conflict is highest where the belief label is around .5.

VI. Conclusion

- We introduce self-tuning object detection coupled with belief theory based object identification
- We show our method works for 2 scientific discovery use cases:
  - **Caveolae (de)formation associated with metastasis of prostate cancer cells**
  - **Amyloid-β deposits associated with Alzheimer disease in retina tissue**
- We show that our method spans heterogeneous data, informing the user of the level of conflict between different datasets.

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[1] Ben Cardoen et al. "SPECHT: Self-tuning Plausibility Based Object Detection Enables Quantification of Conflict in Heterogeneous Multi-scale Microscopy". In: (Sept. 2020). DOI: 10.36227/techrxiv.12971051.v1.

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