Automatic 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

SPECHT

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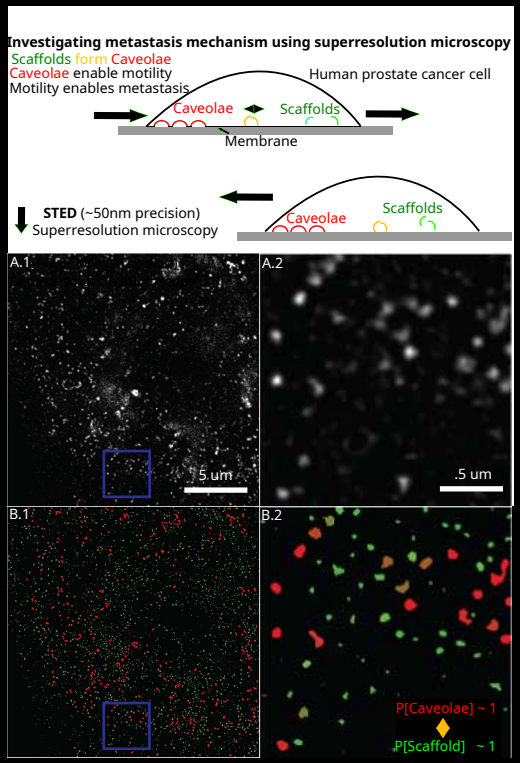
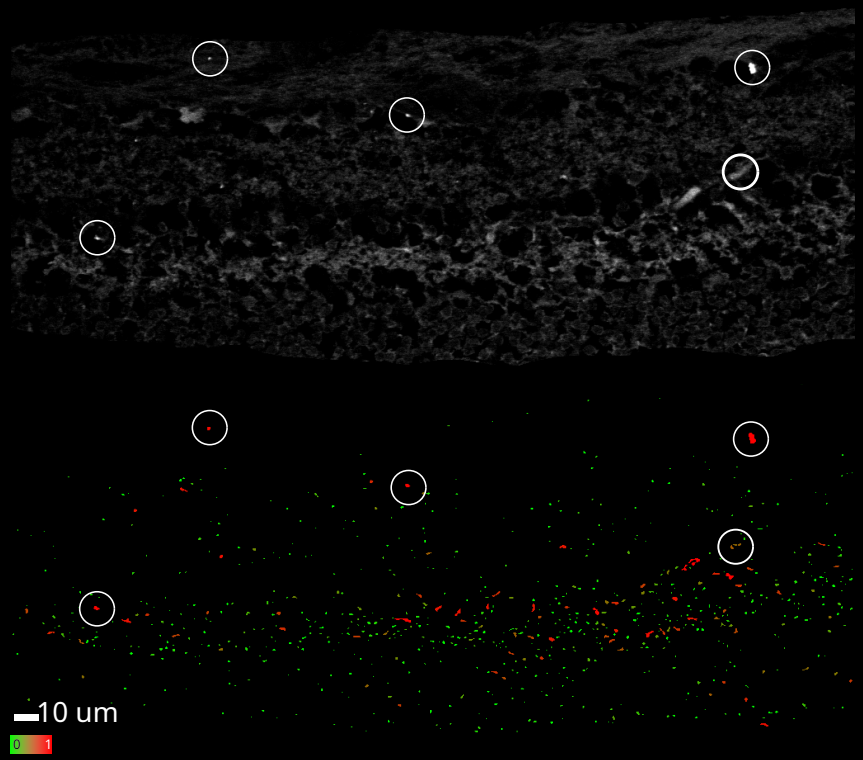
Identifying fluorescent labelled protein structures in multiscale microscopy

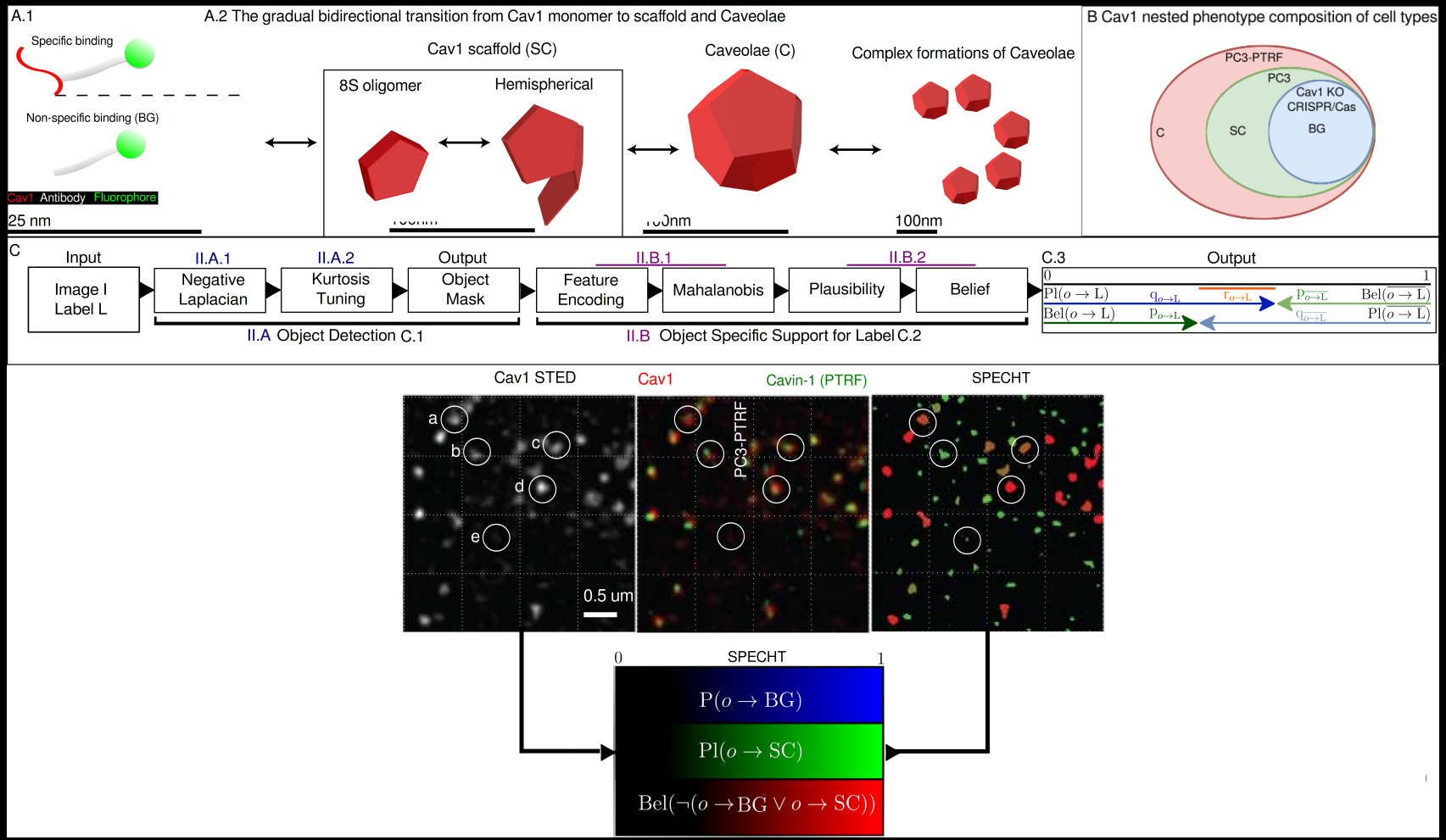


Distinguishing Cav1 protein structures in superresolution microscopy images of prostate cancer cells to discover how cell motility enables metastasis. [6]. The (de-)construction of Caveolae into Scaffolds and vice versa can give a cell membrane a capability to withstand stress associated with cell motility, and consequently cancer cell metastasis.



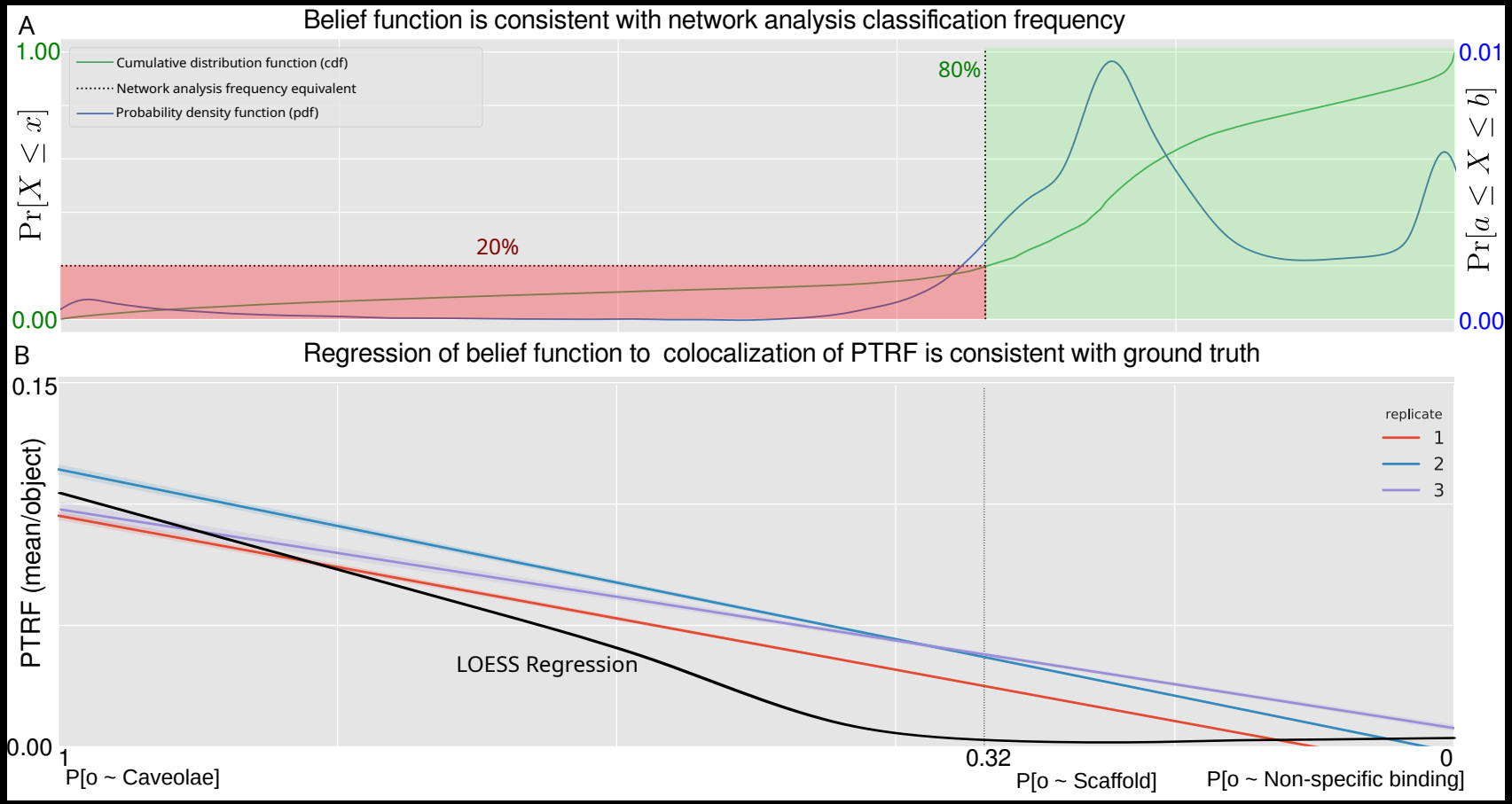
Retina tissue from Alzheimer diagnosed patients labelled for amyloid-β [5] (AB). AB is sufficient, but not necessary for Alzheimer disease (AD). Quantifying the expression of AB deposits specific to AD is critical to gain insight into this aspect of AD. We identify AB deposits specific to Alzheimer versus deposits characteristic of healthy tissue.

Method Overview



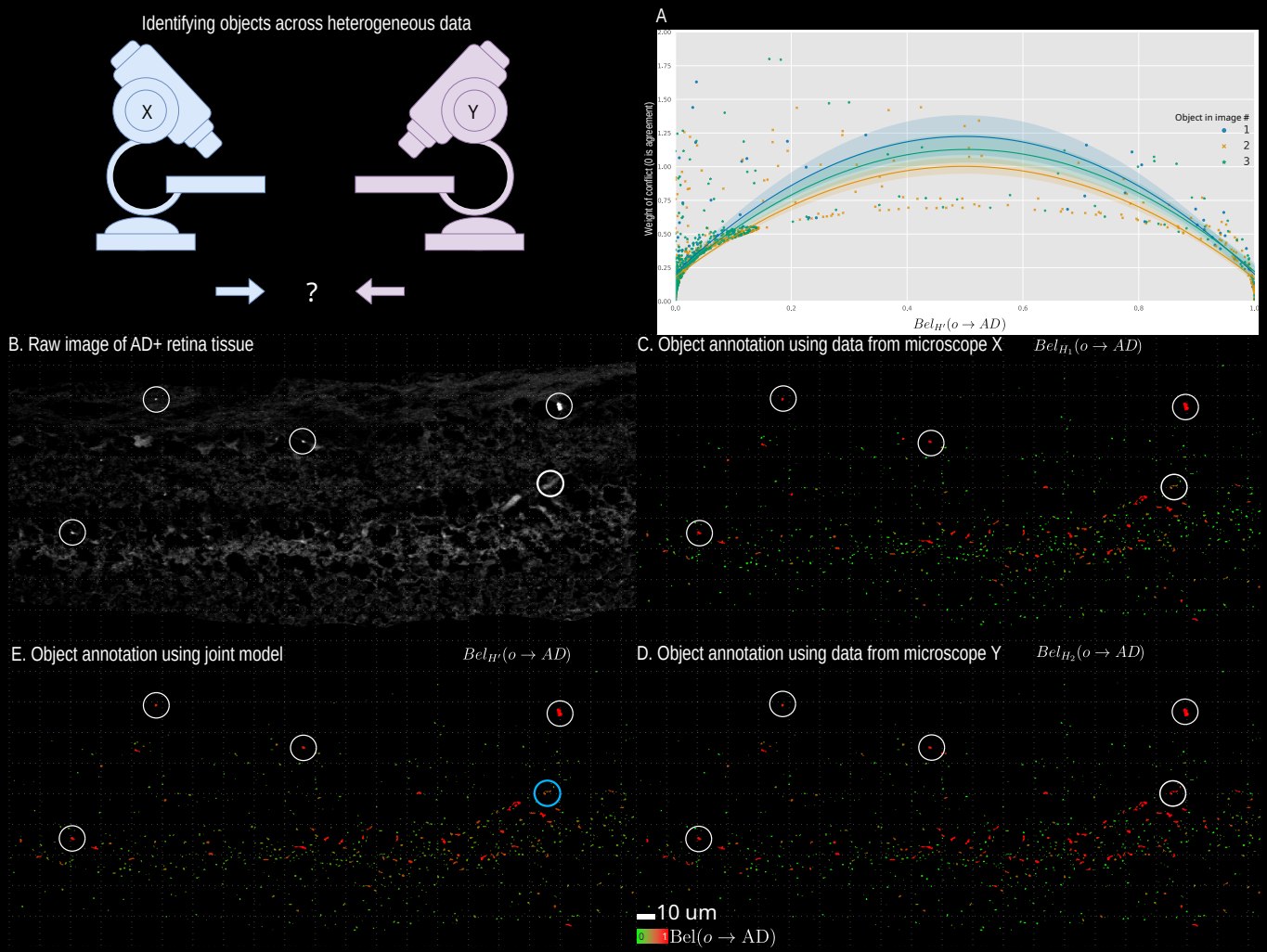
A simplified model of Caveolae formation (A). By contrasting 3 genotypes (B) we can learn a complex belief function distinguishing Caveolae, Scaffolds and background labelling (A.1). The control flow of SPECHT (C) results in a belief [3, 2] function for each object (C.3). An illustration of SPECHT applied to a prostate cancer cell.

Does it work?



Caveolae require PTRF, and have a reported frequency of 20% [4]. We observe that the 20% frequency coincides with an elbow of the [c,p]df functions of our probability label. This threshold coincides with a marked increase of PTRF colocalization, confirming the validity of the approach.

What if images come from different datasets or microscopes ?



Restricting analysis to homogeneous data reduces statistical power in an already reduced sample size context (human tissue). Belief theory enables us to formulate a joint model (E), while recording the conflict (A, E-o) for the end user to frame any subsequent discovery.

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