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Synapse classification and localization in Electron Micrographs

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ABSTRACT

Classification and detection of biological structures in Electron Micrographs (EM) is a relatively new large scale image analysis problem. The primary challenges are in modeling diverse visual characteristics and development of scalable techniques. In this paper we propose novel methods for synapse detection and localization, an important problem in connectomics. We first propose an attribute based descriptor for characterizing synaptic junctions. These descriptors are task specific, low dimensional and can be scaled across large image sizes. Subsequently, techniques for fast localization of these junctions are proposed. Experimental results on images acquired from a mammalian retinal tissue compare favorably with state of the art descriptors used for object detection.

1. Introduction

Visual classification of structures of interest has a wide variety of applications in natural images, video sequences, aerial and biological images. At one end of the spectrum, detection and classification of objects in natural images has received a significant research interest in recent times with competitions like PASCAL and ImageNet. Algorithms such as the DPM and Sparselet have been shown to perform extremely well on such challenges. At the other end of the spectrum are emerging applications in bio-microscopic imagery, where automated image analysis is crucial due to high throughput image acquisition. Constructing an overarching classification/detection model that can work across any bio-microscopic imagery is challenging due to inherent variability in imaging protocols. For instance, a tissue imaged using different imaging conditions, such as the light, confocal or electron microscopy, can lead to visually very different images. Knowledge of associated meta-data such as molecule specific bio-markers used for imaging are critical for further processing and interpretation of such images. As a result, an algorithm developed for one modality is difficult to adopt to another modality, necessitating the development of application specific classification/detection algorithms. The scope and applications to problems in bio-microscopic imagery are fairly diverse, with many applications still relatively unexplored. We focus on one such application, namely structural connectomics.

Connectomics: Connectomics is a sub-field of neuroscience aiming to understand neuronal circuitry in the animal brain. Synapses, or edges in the neuronal circuit graph can be resolved only at nanometer (10^{-9} m) resolutions. Such resolutions require the acquisition of massive amounts of data, typically ranging into several terabytes. Due to recent developments in high throughput microscopy, such datasets can be acquired in a fully automated fashion without any human intervention. The bottleneck manifests in analyzing these large image mosaics, which could take human annotators several man years. In attempting to develop fully automated image analyzers, two main issues arise. Firstly, the low level visual features that would work best are unknown beforehand, and considerable effort is required to uncover features that work reliably. Secondly, the feature extractors and classifiers must be scalable to the size of datasets considered.

In this paper, we focus our attention on the problem of visually interpreting Electron Micrographs (EM). An example of Electron Micrograph imagery is shown in Fig. 1. These high resolution EM images tend to be highly textured and require expert interpretation in identifying cellular and sub-celluar structures of interest.

Scale of Data Considered: The dataset of interest in this paper, also referred to as the RC1 connectome is acquired from a rabbit's retinal tissue. It is physically 33 μm thick and has a diameter of 25 mm. The imaging is performed at an x–y resolution of 2.18 nm, and a z-resolution is 70 nm. As a result, the data is highly anisotropic, meaning that the sampling across z-direction is much coarser than sampling on the x–y direction. In other words, thin sections of the tissue are successively imaged with a z-spacing of about 70 nm between adjacent slices. A total of 341 z-slices are acquired using high throughput microscopy, leading to the creation

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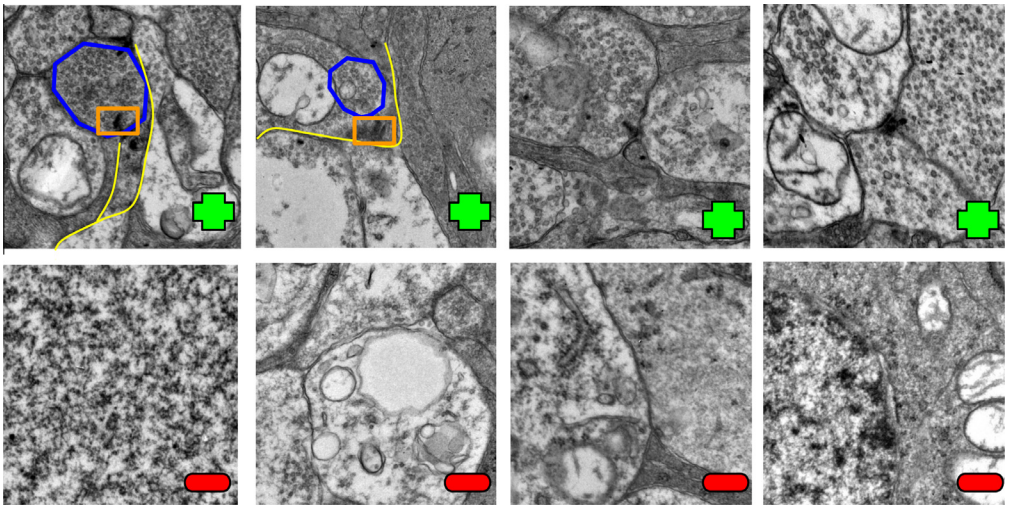

Fig. 1. The first row illustrates examples of synaptic junctions characterized by vesicles (blue contours), cell membrane (yellow contour) and ribbons (orange box). The second row of images illustrate negative examples which do not contain synaptic junctions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

of a 3D image stack where the z dimension ranges from 1 to 341. Further, the raw data is stored as a multi resolution volume, comprising a total of six pyramid levels. The total storage requirements for the multi resolution volume alone is about 15 terabytes. Hence, even storing, accessing and handling the entire dataset is a major challenge to begin with. The scalable Viking viewer (Anderson et al., 2011) elegantly solves this problem by providing an interface to interact, annotate and study the data.

Each z-slice of the connectome volume comprises around 250,000 tiles of dimension 256×256. The entire connectome volume would then comprise a total of 90 million such tiles of dimension 256×256. A single slice from the connectome, after mosaicking has 125000×125000 pixels. Processing such large datasets require distributed computing infrastructures, and the availability of algorithms that can be parallelized and scaled across a large number of computing nodes. We focus our attention on the latter issue of developing scalable algorithms that solve an important problem of synapse localization in Electron Micrographs, see Fig. 2.

Significance of Synapses: Synapses are structures in the brain that help neurons in communicating with one another using chemicals known as neurotransmitters. Vesicles are the carriers of neurotransmitters, that are transmitted from one cell to another. Since vesicles are spherical in 3D, they have a circular shape when projected onto a 2D plane and imaged. The junction where communication between neurons happen is the cell membrane, also referred to as clefts. Vesicles and clefts co-occur in any type of chemical synaptic junction. Further, in some classes of synapses one can observe electron dense black regions referred to as ribbons near the cleft. Such synapses are known as ribbon synapses. The co-occurrence of three structures, namely vesicles, clefts and ribbons are often used by biologists to detect the presence/absence of a synaptic junctions. We also refer to the three structures (vesicles, clefts, ribbons) as semantic attributes that are the building blocks in constituting a synapse.

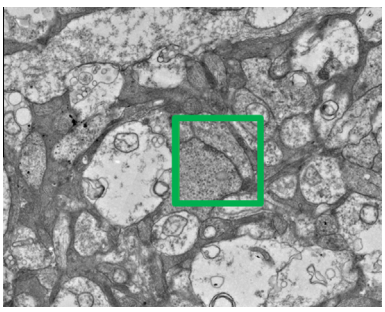

Fig. 2. Illustration of the Detection task. The aim here is to isolate synapses (green boxes) from the rest of structures in the image. The image comprises only a single channel, and has structures surrounding the synapse with similar visual properties, making the detection problem very challenging. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The primary objective of this work is to build a robust and lightweight feature descriptor for identifying synaptic junctions in large EM mosaics.

Strong Biological Priors: Object detection refers to the problem of identifying the spatial location of an object of interest in images. State of the art methods can detect faces and people with impressive accuracy. However, detection of generic object categories is still an open area of research which is being addressed in computer vision competitions such as PASCAL VOC. In most of the detection systems that work reliably, some form of gradient features based on histogram of oriented gradients are trained with linear SVMs for detection. Extensions based on deformable part models where latent part configurations are inferred during training are widely used. The deformable part model does have its share of disadvantages such as reduced accuracy on object classes without articulate parts, and considerably higher training time involved in learning.

Images for generic object detection can come in any scale/rotation/shear/clutter, while the target class (say a person) remains consistent across all images, thus necessitating rich feature sets and object localizers. In contrast, biological image datasets have highly constrained imaging protocols which are known in advance, as well as biological priors on shape and size of objects of interest. As a result, we propose to focus on exploiting strong constraints on imaging and biological knowledge to construct efficient and simple detectors. We focus on the problem of synapse detection for illustrating the usefulness of exploiting strong prior knowledge available in bioimaging scenarios.

Paper Organization: The rest of the paper is organized as follows. Section 2 presents the design of attribute based feature descriptors for synaptic patches, and their classification based on fusion of features. Section 3 discusses extension of classification to a localization framework. Section 4 presents comprehensive experimental