

**Algorithms and Framework for Cellular-Scale Mapping of Complex  
Biological Tissues from 2-D/3-D Multi-Spectral Images**

by

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## ABSTRACT

The overall objective of this thesis is to develop effective computer vision and machine learning algorithms and a framework for 2D/3D cellular-scale mapping of complex biological microenvironments and to quantify molecular biomarkers on a cellular scale with cell-type specificity. Biological microenvironments such as brain tissues and tumors have complex structures, in which several elements are present (e.g. multiple cell types and blood vessels). Studying the different elements in the tissue and extracting meaningful measurements that quantify relationships between them is an important need arising in many biological studies.

This thesis has three specific aims. The first one is to develop a robust and fast algorithm for reliable segmentation of cell nuclei. To achieve that aim, a fully automated nuclear segmentation algorithm is proposed, that advances the state of the art in the nuclear and cell segmentation field, and introduces several novel ideas that can be adopted in other computer vision applications. In addition, a simple algorithm is presented for automatic estimation of the segmentation algorithm parameters.

The second aim is to develop methods to reliably identify the types of all cells with minimal training of classifiers. This is a very important requirement since the vast majority of cell classification approaches presented in the literature are often limited by the manual training effort. In this thesis, a generic and modular cell classification framework is proposed, in which both automatic and manual training set extraction methods are used, and an active learning approach is adopted for classification refinement.

The third aim is to quantify spatial associations between the different elements in the tissue, and to quantify molecular biomarkers that are of biological and/or clinical interest on a cell-by-cell basis. In order to do that, an object-level association framework is proposed for quantifying biologically relevant relationships and associations present between the different elements in the tissue. The proposed framework uses an abstract and extensible representation of the association rules.

The proposed methodologies in this thesis were implemented and tested on 2-D and 3-D multi-spectral images. More specifically, we have focused on two applications: 3-D 5-channel images of brain tissues and 2-D multi-spectral images of cancer

histopathology samples. The segmentation and classification results were validated manually by human experts. The overall accuracy of the proposed segmentation algorithm exceeded 86%. The accuracy was found to exceed 94% when only over- and under-segmentation errors were considered and found to be highly accurate in most of the cases. Additionally, controlled experiments using 2-D and 3-D phantom images were conducted for extra performance evaluation. Finally, tools for efficient segmentation editing and validation as well as classifier training are developed, in which feature-assisted and edit-based strategies techniques are employed.