GRAPH THEORETICAL METHODS FOR TISSUE MODELING AND CLASSIFICATION

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A Thesis Submitted to the Graduate

Faculty of Rensselaer Polytechnic Institute

in Partial Fulfillment of the

Requirements for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject: COMPUTER SCIENCE

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June 2011
(For Graduation August 2011)

ABSTRACT

While the structure-function relationship paradigm forms the basis for understanding biological systems at virtually all levels, the relationships linking tissue structure with tissue function are largely unknown. Therefore, methods and techniques that link tissue structure to biological function for successful tissue modeling and classification are in need. In this thesis, an overview of the techniques we developed to analyze biological specimens, classification of histopathological breast and bone tissues, tracking and quantification of organizational and morphological changes that occur over time and visualization and querying of biological events such as cell-to-cell interactions, collagen organization, cell to extra-cellular-matrix interactions are provided. These methods allow the study of complex biological problems that require the preservation and quantification of temporal and spatial information in 4D and establish a new paradigm to understand structure-function relationships in such systems.

We start with the histopathological tissue classification for bone and breast tissue samples. Pathological examination of a biopsy is the most reliable and widely used technique to diagnose cancer. However, it suffers from both inter- and intra-observer subjectivity. Techniques for automated tissue modeling and classification can reduce this subjectivity and increases the accuracy of cancer diagnosis. We present graph theoretical methods, called extracellular matrix (ECM)-Aware Cell-Graphs and Hierarchical Cell-Graphs for bone and breast tissues, respectively. ECM-Aware Cell-Graphs combine the ECM formation with the distribution of cells in hematoxylin and eosin (H&E) stained histopathological images of bone tissues samples whereas Hierarchical Cell-Graphs capture the lobular/glandular architecture of breast tissues.

We also assess the applicability of cell-graph techniques to branching morphogenesis. Branching morphogenesis is a developmental process shared by many organs, including the submandibular salivary gland. During morphogenesis, cells within the gland undergo rearrangements to cause changes in the overall tissue mor-

phology. We first present a methodology based on cell-graphs to quantify these changes in cellular arrangements. We then take the first steps in having a multi-scale model for branching morphogenesis. This model requires the understanding of features from different scales. We present a methodology to quantify structural properties locally, globally and extract morphological and spectral properties in mouse submandibular gland tissues. We find that a characteristic subset of mathematical features can be used to differentiate between the cellular organization of epithelium and mesenchyme in explants. We here demonstrate that cell-graphs are an effective computational tool to identify and quantify changes at multiple biological scales to distinguish between different tissue states in developing tissues.

We then move our focus to representations of tissue samples in three dimensional space. We present a method of tracking three dimensional biological structures to quantify changes over time using cell-graphs. From these cell-graphs quantitative features are extracted that measure both the global topography and the frequently occurring local structures of the tissue constructs. Using this methodology, the underlying structural changes in a simple three dimensional biological event can be tracked and quantitatively analyzed. We also introduce graphs that not only model the structural properties of a tissue but can also represent the extracellular matrix around it. We describe cooperative collagen alignment process with respect to the spatio-temporal organization and function of mesenchymal stem cells in three dimensions. We defined metrics for quantitatively tracking type I collagen and fibrillogenesis remodeling by mesenchymal stem cells over time. Definition of early metrics that are able to predict long term functionality by linking engineered tissue structure to function is an important step towards optimizing biomaterials for the purposes of regenerative medicine.