Inter-departmental Postgraduate Course in Medical Physics, Faculty of Medicine and Department of Physics, University of Patras, Greece

PhD Thesis

Title: Development of supervised and unsupervised pixel-based classification methods for medical image segmentation

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Abstract

Breast cancer is among the well-researched type compared to other common types of cancer. However, there still remain important open issues for investigation. One of these issues is the clarification of the importance of certain biological factors, such as histological tumour grade and estrogens reception (ER) status, to clinical management of the disease. Until now, histological grading and ER status assessment is based on the visual evaluation of breast tissue specimens under the microscope. More specifically, grading is determined on the visual estimation of certain histological features, on H&E (Hematoxylin & Eosin) stained specimens according to the World Health Organization (WHO) guidelines, whereas ER-status is assessed as the percentage of expressed nuclei on immunohistochemically stained (IHC) specimens as suggested by the American Society of Clinical Oncology (ASCO) protocol. Recent studies have attempted to examine whether histological tumour grade relates to ER status. Such a relation seems to be of importance in the various treatment strategies followed in breast tumours. However, the quantification of ER status presents certain weaknesses: a) there is a lack of consensus among experts regarding the protocol to be followed for calculating the ER status; b) an exact estimate of the ER status is difficult to be obtained, since the latter would require manual counting of positively expressed nuclei. In clinical practice often a gross estimate is obtained by the pathologists through visual inspection on representative specimen areas. Consequently, the evaluation of ER status, which has been considered by previous studies as the key measure for assessing the correlation between ERs and tumour grade, is prone to the physician's subjective estimation. Therefore, more reliable methods are needed. This thesis has been carried out in the search of such alternative, more reliable, methods. Accordingly, the aims of the present thesis were: (i) to develop a reliable segmentation methodology for detection of ER-expressed nuclei in breast cancer tissue images stained with IHC, (ii) to objectively quantify ER status in breast cancer tissue images stained with IHC, (iii) to investigate potential correlation between ER status and histological grade by combining information from IHC and H&E stained breast cancer tissue images obtained from the same patient, (iv) to establish evidence for linking chromatin texture variations with textural variations on ER-expressed nuclei, (v) to investigate the potential of the proposed hybrid supervised pattern recognition strategies to other challenging fields of medical image processing and analysis. To address the above issues and in search of reliable methods for quantitatively assessing ER status and its correlation with histology based grading, a novel hybrid (unsupervised-supervised) pattern recognition methodology has been designed, developed and implemented for the analysis of breast cancer tissue images.

Moreover, it has been shown that proper modification of the proposed methodology may result to generalize pixel classification approach suitable for processing and analysis of medical images other than microscopic such as Computed Tomography Angiography images.

Keywords: Breast cancer, Molecular factors, Computer-aided microscopy, Medical image processing and analysis, Pattern recognition

List of publications relative to PhD Thesis

Journal Published Papers:

1. Spiros Kostopoulos, Dionisis Cavouras, Antonis Daskalakis, George C. Kagadis, Ioannis Kalatzis, Pantelis Georgiadis, Panagiota Ravazoula, and George Nikiforidis, "Cascade pattern recognition structure for improving quantitative assessment of ERstatus in breast tissue carcinomas", *Analytical Quantitative Cytology Histology*, 30, pp. 218-225, 2008.

2. Spiros Kostopoulos, Dimitrios Glotsos, Dionisis Cavouras, Antonis Daskalakis, Ioannis Kalatzis, Pantelis Georgiadis, Panagiotis Bougioukos, Panagiota Ravazoula, and George Nikiforidis, "Computer based association of estrogen receptors expressed nuclei texture with histological grade using IHC-stained breast carcinomas", *Analytical Quantitative Cytology Histology, in press*, 2009.

3. S. Kostopoulos, D. Glotsos, G. C. Kagadis, A. Daskalakis, P. Spyridonos, I. Kalatzis, M. Karamessini, T. Petsas, D. Cavouras and G. Nikoforidis, "A Hybrid Pixel-Based Classification Method For Blood Vessel Segmentation And Aneurysm Detection On CTA", *Computers & Graphics* 31 (3), pp. 493-500, 2007.

Proceedings in International conferences with referees:

4. S. Kostopoulos, D. Cavouras, A. Daskalakis, I. Kalatzis, P. Bougioukos, G. Kagadis, P. Ravazoula, and G. Nikiforidis, "Assessing Estrogen Receptors' Status by Texture Analysis of Breast Tissue Specimens and Pattern Recognition Methods", *Lecture Notes in Computer Science*, Vol. 4673, pp. 221-228, 2007.

5. S. Kostopoulos, D. Cavouras, A. Daskalakis, P. Bougioukos, P. Georgiadis, G. Kagadis, I. Kalatzis, P. Ravazoula, and G. Nikiforidis, "Colour-Texture Based Image Analysis Method for Assessing the Hormone Receptors Status in Breast Tissue Sections", *proceedings of the 29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, Lyon, France, August 23-26, 2007.

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9. S. Kostopoulos, D. Glotsos, G. Kagadis, N. Dimitropoulos, T. Petsas, , D. Cavouras and G. Nikiforidis, "Development of a for brain blood vessel segmentation method in CT-angiography" in *3rd European Medical & Biological Engineering Conference, Regional IFMBE European Conference on Biomedical Engineering (EMBEC)*, Prague, 2005.

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