Quantitation of Collagen Alignment: a Tool for characterizing Cancer Invasion and Progression

Carolyn Pehlke[1], Jared Doot[1,2], Curtis Rueden[1], Robert Nowak[1,2], David Beebe[1], Patricia Keely[1] and Kevin W. Eliceiri[1]

***Short Abstract* — The morphology and orientation of collagen fibers in the extracellular matrix have been shown to be an important factor in tumor progression, muscular diseases and birth defects. In some cases, the structure of collagen in a particular tissue can act as a predictive biomarker of a disease state. In order to fully exploit the predictive value of collagen, we have developed an semi-automated tool based on the Fast Discrete Curvelet Transform (FDCT) for the measuring of collagen fibers in biological tissues.**

***Keywords* — Curvelet analysis, signal processing, Breast cancer, invasion, progression, second harmonic generation, multiphoton microscopy, collagen, stroma, extracelluar matrix.**

I. Purpose

It has recently been shown that the presence of a specific collagen structure and orientation, straightened and aligned collagen fibers that are oriented perpendicular to the tumor boundary, can be used as a prognostic indicator for human breast cancer (1). The presence of these collagen structures in breast tumors are associated with poor disease specific and disease free survival, independent of tumor grade, tumor size, ER or PR status, HER-2 status, node status and tumor subtype. The ability to quickly and accurately detect and measure collagen fibers present in routine histopathologic samples could provide quantitative data on which to base predictions of human breast cancer survival. As well there is great potential of harnessing these candidate optical biomarkers in clinical imaging for early detection and characterization of cancer invasion and progression.

II. Results

The fundamental advantage of the FDCT algorithm applied to the problem of detecting collagen alignment and orientation, is the ability of the transform to retain orientation information from the image. The Curvelet transform (2) not only varies on scale and location in the image, but also in the orientation of the edges. This results in the ability to examine all prominent edges at a particular orientation and a particular scale (varying only on location of the fixed scale and orientation Curvelet in the image). When applied to the Tumor-Associated Collagen Signatures problem, the Curvelet transform becomes a powerful tool for detecting the presence of long straight edges and their location, scale, and orientation. By obtaining accurate quantitative data regarding collagen amount, morphology, and organization/orientation, biologically relevant data can be derived. The implementation of our curvelet analysis program uses an implementation of the wrapping-based digital FDCT transform.

A. *Location of Collagen Fibers*

The FDCT algorithm retains the location of the center point of all non-zero curvelet coefficients in an image. Grouping these curvelet centers with other curvelet centers that are both spatially nearby and have a similar orientation gives a good approximation of the locations of collagen fibers in the image.

B. *Orientation of Collagen Fibers*

The angular information of each non-zero curvelet coefficient is retained by the unique tiling of the frequency domain. Once the appropriate thresholding and grouping of curvelet coefficients has been applied, the angle of each fiber can be determined by averaging the angles of all curvelet coefficients associated with a fiber.

III. Conclusion

The angle of collagen fibers relative to the tumor boundary may be used as a predictor of imminent invasion and metastasis. Hence, there is a need to quickly and accurately quantify both fiber angle and any related structural changes of the collagen matrix. The FCDT, developed by Candes and Donoho is specifically designed to determine a sparse representation of edges in images, even in the presence of complex geometries such as those associated with collagen alignment. The locations and angles of collagen fibers in an image of a breast cancer histology sample were accurately determined using a program based on the FDCT.

References

1) *Provenzano, P.P., et al.,* Collagen reorganization at the tumor-stromal interface facilitates local invasion. *BMC Med, 2006. 4(1): p. 38.*

2) *Candès, E. and D.Donoho,* Curvelets - a surprisingly effective nonadaptive representation for objects with edges, *in* Curves and Surface Fitting: Saint-Malo 1999*, A. Cohen, C. Rabut, and L. Schumaker, Editors. 1999, Vanderbilt University Press: Saint-Malo, France. p. 105-120.reference campagnola harmonic*

Acknowledgements: This work was funded by NLM Grant 5T15LM007359 and NIH R01CA136590.

[1]Laboratory for Optical and Computational Instrumentation, Department of Biomedical Engineering, University of Wisconsin at Madison, Other address information. E-mail: pehlke@wisc.edu.

[2]Department of Electrical and Computer Engineering, University of Wisconsin at Madison.