Predicting 3D nuclear architecture patterns in cancer

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***Short Abstract* — The three-dimensional organization of the human genome and localization of proteins in cell nuclei are being increasingly investigated to better understand their role in cancer. We perform optical micro-CT to image epithelial cells individually in 3D at sub-micron, isotropic spatial resolution and employ computer vision algorithms to precisely quantify nuclear structure, chromatin packing, and spatial localization of specific proteins that regulate nuclear architecture. As part of our effort to better ascertain the functional ramifications of nuclear architecture through the cell cycle and in cancer, we seek collaborations with modelers to further exploit our image data and streamline our investigations.**

***Keywords* — 3D nuclear architecture, cancer, protein localization, temporal dynamics, optical micro-CT, 3D morphometry**

I. Introduction

THE classical characteristics of cancer cells such as their aberrant genetics, enhanced replication potential, immune response evading capabilities, altered metabolism, and others [1] are well known. A rapidly emerging perspective is the impact of epigenetic processes on the advent and progression of the disease. Aspects such as nuclear structure, chromatin packing in 3D nuclear space, and spatial localization patterns of regulatory proteins have been shown to be non-random, impact cellular function, and altered in cancer [2, 3]. However, a detailed understanding of the science is obfuscated by biological factors including spatio-temporal regulation of nuclear architecture through the cell cycle and in disease progression. Recent advances in microscopy and automation sciences have facilitated accurate quantification of nuclear architecture patterns but the dearth of quantitative computer models on nuclear organization severely limits systematic investigations. A combination of high-resolution, quantitative 3D microscopy and strategic modeling techniques that account for space-time dynamics could help deconvolve this complexity and offer novel insights on the functional consequences of altered nuclear organization in cancer.

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II. Methods and Results

We stained interphase cells with appropriate absorption and fluorescent markers and imaged them individually in 3D at sub-micron, isotropic resolution using the Cell-CT instrument (VisionGate, Phoenix, AZ). We used hematoxylin stain to study gross nuclear architecture and immunocytochemistry methods to fluorescently tag proteins such as SATB-1, Lamin A/C, and HMGA that are known to regulate nuclear architecture and whose expression is altered in cancer. We developed robust 3D image reconstruction algorithms to generate volumetric cell imagery with high signal to noise ratio. We designed custom computer vision algorithms to accurately delineate volumes of interest from the reconstructed cell imagery and precisely quantify nuclear architecture patterns. We applied statistical methods to derive quantitative morphological signatures of 3D nuclear architecture patterns to distinguish normal cells from their cancerous counterparts. To date, we have performed our studies with representative, immortalized cell lines of the human esophagus, breast, and colon.

Our investigations revealed several novel aspects of nuclear architecture and its aberrations in cancer. We found significant morphological heterogeneity in nuclear architecture even within normal cell populations. Contrary to the current grading paradigm in clinical cytopathology, our approach revealed a unique morphological signature for each of esophageal, breast, and colon cancer cells. DNA organization and spatial localization patterns of Lamin A/C and SATB-1 proteins in the nucleus were determined to be more chaotic in cancer cells.

III. Conclusion

Our single-cell, high-resolution, quantitative 3D microscopy methods enable a better understanding of nuclear architecture and its alterations in cancer. Strategic application of computer models that use our morphological data to provide additional insights on regulation of nuclear architecture would enhance our knowledge about the disease.

References

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