Simulation of Breast Anatomy and Pathology at the Cellular Level

Symposium on ***Recent Advances in the Virtual Tools for Validation of New 3D/4D X-ray Breast Imaging System***

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  (The content is solely the responsibility of the author and does not necessarily represent the official view of the NIH, DoD, or NSF.)
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- David D. Pokrajac, Ph.D., *Applied Math, Delaware State Univ.*
- Rebecca Batiste, M.D., and Michael D. Feldman, M.D., Ph.D., *Pathology, Univ. of Pennsylvania*
- Andrew D.A. Maidment, Ph.D., *Radiology, Univ. of Pennsylvania*

Simulation of Breast Anatomy

- Computer phantoms are used for pre-clinical testing of new systems for breast imaging or image analysis – *Virtual Clinical Trials (VCTs)*
- Various phantom designs exists (*Penn, Duke, Varna, FDA, Surrey, etc.)*
- Penn phantoms developed since 1996; currently used by 70+ researchers from 15+ countries.
- Digital pathology & rad-path relationship demand analysis and simulation of anatomy at various scales.

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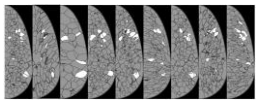
Penn Software Breast Phantom

- Generated using octree-based recursive partitioning & GPU implementation
- Very fast simulation of a large number of phantoms with small voxel size.
- Provide support for VCTs
  - The known ground truth about simulated tissues
  - The flexibility to cover anatomic variations



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Histopathology of the Breast

Subgross Breast Section (Wellings, 1975)

Subcutaneous Organization: Fat Perls and Lobuli (Mendieta, 2009)

Digitized Path Section (Keller, 2015)

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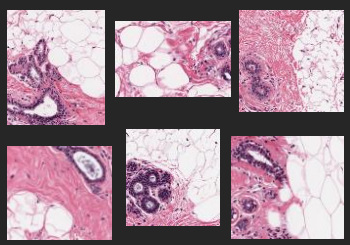
Histopathology of the Breast: Variation



(Bakic, Pokrajac, Batiste, Feldman, Maidment, 2016)

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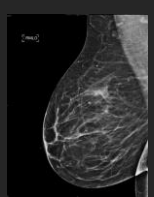
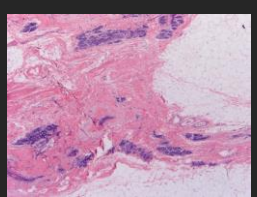
Histopathology of the Breast: Sequential





d + 500μm

(Bakic, Pokrajac, Batiste, Feldman, Maidment, 2016)

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Histopathology of the Breast: Structures

- In this work we focus on the simulation of normal anatomy at the cellular scale, including the following structures:
  - *Predominantly adipose regions*: Adipocytes (70-120μm), hierarchically organized into compartments and subcompartments of decreasing size, septated by collagen fibers and sparse fibroblasts (10-15μm).
  - *Predominantly fibroglandular regions*: Irregularly shaped ducts, lined with epithelial (20-60μm) and myoepithelial cells; TDLUs with terminal ducts and lobuli/acini (lined with epi and myoepi cells), surrounded by basement membrane of dense and loose fibrous tissue, sparse fibroblasts, and lymphocytes (7-20μm).
  - Arteries, veins, and lymph vessels can be added optionally.

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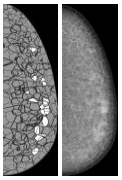
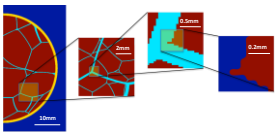
Simulation at the Cellular Scale

- Performed in two stages:
  1. *A computer radiological scale (RS) phantom is generated*, including:
     - The breast outline with a layer of skin;
     - The matrix of compartments (defined by Cooper's ligaments), labeled as adipose or dense.
  2. *Second, a region within the RS phantom is selected and used to simulate the corresponding pathology image.*



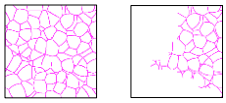


Simulation at the Cellular Scale

- The selected region is resampled to the resolution of pathology images, and filled with structures simulated at the cellular scale: (*adipocytes, ductal epithelium & myoepithelium, lymphocytes, fibroblasts and collagen fiber bundles*).
- In our proof-of-concept, we simulated a pathology image at *1μm* resolution, starting from an RS phantom at *50μm* voxel size. The region (below) contains a *predominantly adipose portion (AP)* and a *predominantly fibroglandular portion (FGP)*.

Simulation of the Adipose Tissue

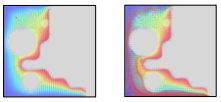
- The predominantly AP consist of a random collection of adipocytes, simulated by recursive partitioning (same as used to model adipose compartments in RS phantoms).



Randomly positioned adipocytes (left) fit into the predominantly adipose portion of the path image (right)

Simulation of the Fibroglandular Tissue

- The predominantly FGP includes duct segments, acini and lymphocytes, surrounded by fiber bundles & fibroblasts. *First*, locations of ducts/acini and lymphocytes are selected randomly. *Second*, fiber bundles & fibroblasts are placed along equipotential lines, assuming:
  - The adipose-fibroglandular border is kept at a given potential (e.g., +V);
  - Locations of ducts/acini & lymphocytes are at the opposite (e.g., -V); and
  - Borders of the selected fibroglandular region are at 0 potential.



Assumed potential distribution (left) used to simulate fibers & fibroblasts positioned along equipotential lines (right)

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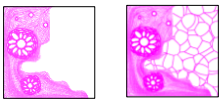
Simulation of the Path Image: AP & FGP

- Our proof-of-concept did not simulate intracellular structures, thus, not distinguishing collagen fibers vs. fibroblasts.
- Simulated ducts/acini (surrounded by ellipsoidal epithelial and flat myoepithelial cells), and lymphocytes were inserted into their selected locations.
- Complete path image is obtained by combined simulated AP & FGP.



Simulated FGP (left) is combined with AP to obtain simulated path image (right)

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Discussion & Conclusions

- Anatomy simulation at the cellular level, by octree-based recursive partitioning, can be incorporated into our RS phantoms, bridging synthetic rad and path images.
- The method "zooms-in" selected phantom regions. In the proof-of-concept example, all cells were in the same plane, (although, that is not generally required).
- The simulation of the whole breast volume at the cellular scale is not justifiable, due to the storage and transfer limitations.
- Simulating structures at arbitrary 3D locations would allow the generation of successive pathology images at different depths, rendering 3D pathology.

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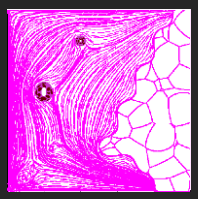
Work-in-progress: Simulating successive slides



d + 500μm

(Preliminary results as of 7/30/2016)

Discussion and Conclusion

- The spatial distributions of simulated cells may be matched to specific parenchymal properties, for improved rad-path correspondence.
- Color schemes may be matched to clinically used stains.
- Optimized simulation may provide more details, (e.g., cell nuclei) for improved realism.
- The method may be extended to simulate breast lesions (benign and/or malignant). Lesion visualization in synthetic radiology images may support VCTs for biomarker discovery.

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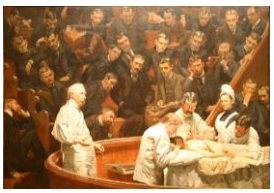

T. Eakins, "The Agnew Clinic", 1889;
John Morgan Building, UPenn

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