Simulation of Breast Anatomy and Pathology at the Cellular Level

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- Rebecca Bates, 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 & radiology relationship demand analysis and simulation of anatomy at various scales.

**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

**Histopathology of the Breast**

- Subgross Breast Section
- Digitized Path Section
- Histology, 1975
- Subcutaneous Organization
- Fat, Perls, and lobuli (Mendieta, 2009)
- Digital Path Section (Keller, 2015)
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, separated 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.
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 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).
**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.

**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.

**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.
Work-in-progress: Simulating successive slides

(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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