Deep Learning Meets Biomedical Image Computing

Fuyong Xing, Ph.D.

Department of Biostatistics and Informatics
Colorado School of Public Health
University of Colorado Anschutz Medical Campus
Deep Learning is Changing Our Lives

- Play (Go) Game
- Self-driving
- Machine Translation
- Speech Recognition
- Paying With Your Face
- Artistic Style Transfer
Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs

Varun Gulshan, PhD; Lily Peng, MD; Marc Coram, PhD; et al

December 13, 2016

Key Points

**Question** How does the performance of an automated deep learning algorithm compare with manual grading by ophthalmologists for identifying diabetic retinopathy in retinal fundus photographs?

**Finding** In 2 validation sets of 9963 images and 1748 images, at the operating point selected for high specificity, the algorithm had 90.3% and 87.0% sensitivity and 98.1% and 98.5% specificity for detecting referable diabetic retinopathy, defined as moderate or worse diabetic retinopathy or referable macular edema by the majority decision of a panel of at least 7 US board-certified ophthalmologists. At the operating point selected for high sensitivity, the algorithm had 97.5% and 96.1% sensitivity and 93.4% and 93.9% specificity in the 2 validation sets.

**Meaning** Deep learning algorithms had high sensitivity and specificity for detecting diabetic retinopathy and macular edema in retinal fundus photographs.
Why Deep Learning?

- Deep learning: a class of machine learning techniques that learn multiple levels of representations.

Image credit: Andrew Ng
Biomedical Images Are Everywhere
Biomedical Image Computing: Make Sense From Biomedical Image Pixels

- Breast cancer pathology image, 1716 x 928 pixels, 0.25 microns/pixel.
Biomedical image computing and imaging informatics is a field that includes the development of methods for automated processing, analyzing, searching, retrieving, and understanding biological and medical images, which in general contain large scale, high-dimensional image data obtained from the real world, to produce numerical or non-numerical information, in the forms to facilitate new biological discovery or clinical diagnosis, prognosis, and decision support.
Biomedical Image Computing and Imaging Informatics

- Automated detection of objects, regions, landmarks, etc.
- Automated segmentation of organs, substructures, etc.
- Automated classification of objects, diseases, etc.
- Image registration
- Image retrieval
- Biomarker discovery
- Medical Imaging report generation
- More …
What Will I Present?

- Deep learning for image quantification
  - Convolutional neural networks for **cell counting/detection**
  - Fully convolutional networks for **fast object detection**

- Deep learning for image biomarker computation
  - Deep multi-task learning for **ki67 labeling index assessment**
Deep Learning for Image Quantification

- How many cells?
- Where are they?
Deep Learning for Image Quantification

- How many cells?
- Where are they?

Challenges:
- High-dimensional
- Background clutter
- Inhomogeneous intensity
- Scale variation
- Densely clustered
- More …
Deep Learning for Image Quantification

- How many cells?
- Where are they?

Challenges:
- High-dimensional
- Background clutter
- Inhomogeneous intensity
- Scale variation
- Densely clustered
- More …
Cell detection: formulated as an image pixel-wise binary classification problem.
Machine Learning for Image Quantification

- Cell detection: formulated as an image pixel-wise binary classification problem.

Input images (pixels) → Feature representation (hand-crafted) → Learning algorithms (e.g., SVM) → Object detection/classification

Infer rules
Machine Learning for Image Quantification

- Cell detection: formulated as an image pixel-wise binary classification problem.

Input images (pixels) → Feature representation (hand-crafted) → Learning algorithms (e.g., SVM) → Object detection/classification

Non-trivial task!
Deep Learning for Image Quantification

Our goal: **improve objectivity** and **reduce human workload**.


C: convolutional layers; M: max-pooling layers; F: fully-connected layers. The last layer has two units for binary classification.

CNN Training for Cell Quantification

- Cell patches: center pixels of image patches are close to cell centers.
- Training data: millions of image patches.

Cell patch definition

Cell patches

Non-cell patches
CNN Training for Cell Quantification

- Cell patches: center pixels of image patches are close to cell centers.
- Training data: millions of image patches.

GPU-based model training

\[
W^* = \arg \min_W \sum_{i=1}^{N} \mathcal{L}(x^i, y^i; W)
\]

\[
\mathcal{L}(x^i, y^i|W) = - \sum_{k=1}^{K} y^i_k \log p(c_k^i|x^i; W)
\]
CNN Testing for Cell Quantification

- Sliding window-based prediction
CNN Testing for Cell Quantification

- Sliding window-based prediction

White dots indicate locations of cells
CNN Testing for Cell Quantification

- Sliding window-based prediction
Comparison Between CNN and Others

- Support vector machine
- Random forests
- Deep belief network
- Proposed CNN

F1 score

- Brain: Support vector machine (74%) vs. Proposed CNN (77%)
  Difference: 3%
- NET: Support vector machine (80%) vs. Proposed CNN (90%)
  Difference: 10%
- Breast: Support vector machine (50%) vs. Proposed CNN (70%)
  Difference: 20%
Can We Do Better?

- Sliding window-based CNN: 1) fixed-size image input, 2) repeated computation.
Fully Convolutional Network (FCN) Detection

Fully Convolutional Network (FCN) Detection

- CNN → FCN: **improve computational efficiency.**
Fully Convolutional Network (FCN) Detection

- **CNN** → **FCN**: improve computational efficiency.

**Objective function:**

\[
\mathcal{L}(o^i, y^i) = \frac{1}{2} \sum_{(u,v) \in y^i} (\beta y^i(u,v) + \lambda y^i)(o^i(u,v) - y^i(u,v))^2
\]

- \(y^i\): ground-truth
- \(o^i\): prediction

Arbitrary-sized image
Deep Learning for Biomarker Computation

- Is this pancreatic NET image a diseased image?
- Is it a low-, intermediate- or high-grade neuroendocrine tumor?
- What is the Ki-67 score (biomarker)?

\[ Ki67 = \frac{\# \text{immunopositive tumor cells}}{\# \text{total tumor cells}} \]

One pancreatic neuroendocrine tumor (NET) image.
Deep Learning for Biomarker Computation

- Is this pancreatic NET image a diseased image?
- Is it a low-, intermediate- or high-grade neuroendocrine tumor?
- What is the Ki-67 score (biomarker)?

$$Ki67 = \frac{\# \text{immunopositive tumor cells}}{\# \text{total tumor cells}}$$

Color coding: Non-tumor cells, Immunopositive tumor, Immunonegative tumor, lymphocytes.
Ki-67 Biomarker Computation

- Current Ki-67 scoring systems: multi-stage processing.

Color coding: Non-tumor cells (non-lymphocytes), Immunopositive tumor, Immunonegative tumor, lymphocytes.

Ki-67 Biomarker Computation

- Single-stage Ki-67 scoring: **more accurate and faster.**

Color coding: Non-tumor cells (non-lymphocytes), Immunopositive tumor, Immunonegative tumor, lymphocytes.

Ki-67 Biomarker Computation

- Deep neural network architecture: simultaneous cell detection and classification.
Ki-67 Biomarker Computation

- Model training: minimize losses for two tasks.

$$\arg \min_{\theta} \sum_{i=1}^{N} L_1(o^i, y^i) + L_2(\bar{o}^i, \bar{y}^i)$$

- Model prediction: simultaneous cell detection and classification.

Input → Inference → output
Ki-67 Biomarker Computation

- Results of single-stage Ki67 scoring.

Color coding: Non-tumor cells, Immunonegative tumor, and Immunopositive tumor.
Text Generation From Biomedical Images

- **CNN + RNN**: Diagnostic report generation.

Link: https://www.youtube.com/watch?v=yy7NUrc3KI0

Selected References of Deep Learning

Thank You

- Web: https://fuyongxing.github.io
- Email: fuyong.xing@ucdenver.edu
- Address:
  Department of Biostatistics and Informatics
  Colorado School of Public Health
  University of Colorado Anschutz Medical Campus