Deep Learning for Lymphoma: Diagnostic Systems for Whole Slide Imaging

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Outline of talk

- Define application of Deep Learning method, a technological breakthrough in Machine Learning, to big-data analytics
- Automated lymphoma diagnosis using digital images

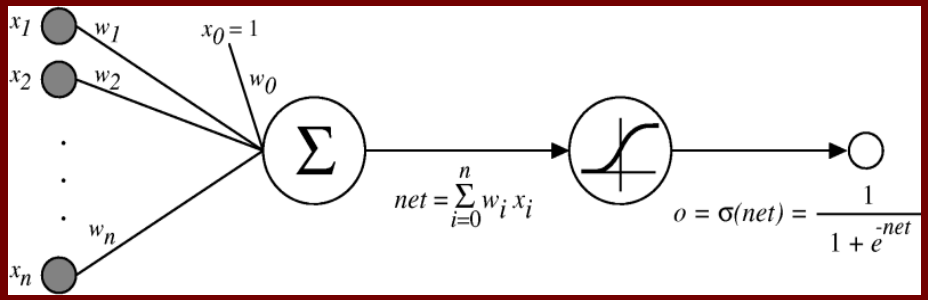
I have no relevant financial relationships with commercial interests to disclose

Deep learning and pathology image

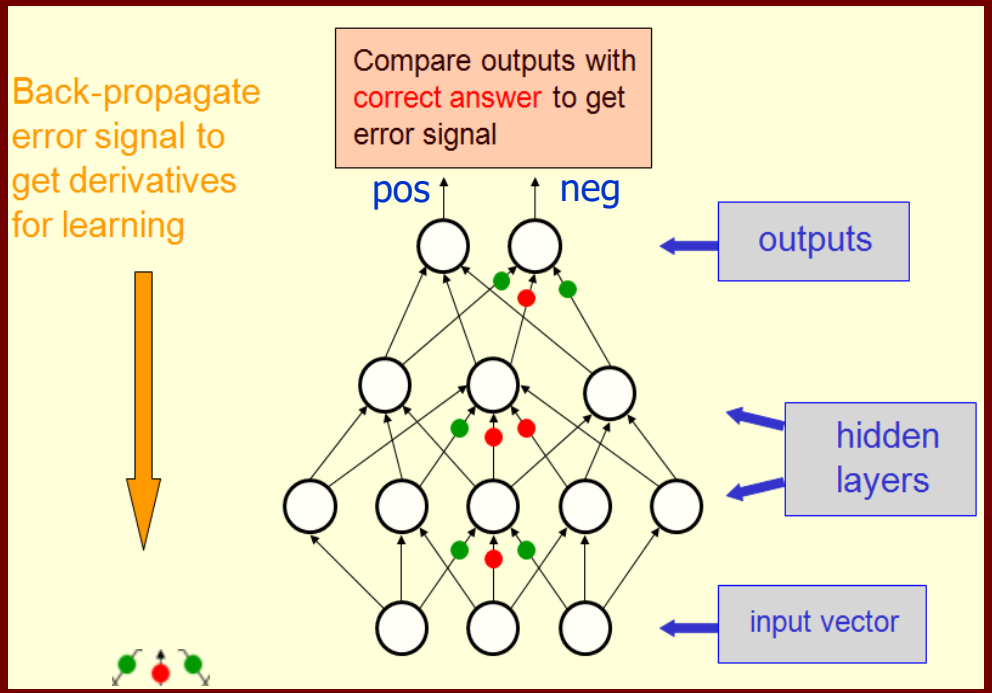
- Machine learning: software algorithms that can learn from and make predictions on data - i.e. “gives software the ability to learn without being explicitly programmed”
- Numerous machine learning methods:
  Decision tree, Cluster analysis, Support vector machine, Random forest, Bayesian, Regression analysis, Neural network….
- Deep learning is the most recent and most disruptive method of machine learning; based on Neural network
- Big companies are analyzing large volumes of data for business analysis and decisions, using Deep Learning technology (Google’s search engine, Google Photo, automobile companies: self-driving cars, IBM’s Watson).
- The application of deep learning to digital pathology image has a promising start; it could impact personalized diagnostics, and treatment.

Deep Learning: based on Neural Network

- Neural network (inspired by biological neural networks): artificial nodes ("neurons“) are connected together to form a network for prediction/classification



→ Fire/not Fire



Early Generation of Neural Networks with Supervised Training

Disadvantages

(1) Parameters often do not converge; not giving solution

(2) Model not scaling well

Deep Learning (3rd Gen Neural Network)

- Major breakthroughs in Deep Learning started in 2006 and helped it to outperform all other machine learning models

- Deep Learning algorithms:
  (1) Unsupervised learning ->allows a network to be fed with raw data (no known outcomes) and to automatically discover the representations needed for detection or classification
  (2) Extract high-level & complex data representations through multiple layers; avoid problems of last-gen networks (previous slide)

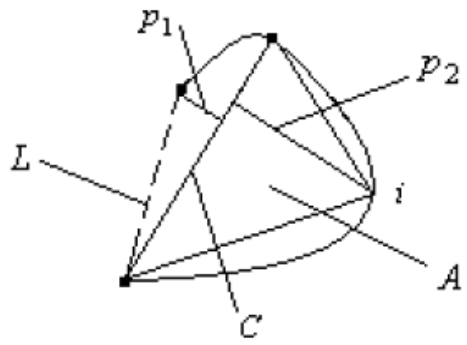
- Supporting hardware: multiple graphics processing units (GPU)

Diagnosis of Lymphoma using Digital Images

- Lymphoma is a clonal malignancy of lymphocytes (either T- or B cells). The WHO Classification of Lymphoid Malignancies includes at least 38 entities.
- Lymphoid malignancies were diagnosed in 280,000 people annually worldwide
- Lymphoma is typically first suspected by their pattern of growth and the cytologic features of the abnormal cells via light microscopy of hematoxylin-eosin stained tissue sections
- Immunophenotypes are required for diagnosis (by flow cytometry and/or immunohistochemical stains). In addition, cytogenetics, molecular results, and clinical features are often needed in finalizing the diagnosis in certain lymphoma types.

Automated Diagnosis for Morphology

- Due to subtle difference in histologic findings between various types of lymphoma, histopathologic screen often presents a challenge to the pathologists.
- An automated diagnosis for digital images would be helpful to assist the pathologists in daily work.
- Previous attempts to digitally classify histologic images were based on specific criteria (such as nuclear shape, nuclear size, texture, etc.). They were not very successful.
- Attention has turned to machine learning. In recent years, 'deep learning' techniques, especially 3rd generation neural network called convolutional neural network (CNN or ConvNet), has quickly become the state of the art in computer vision.



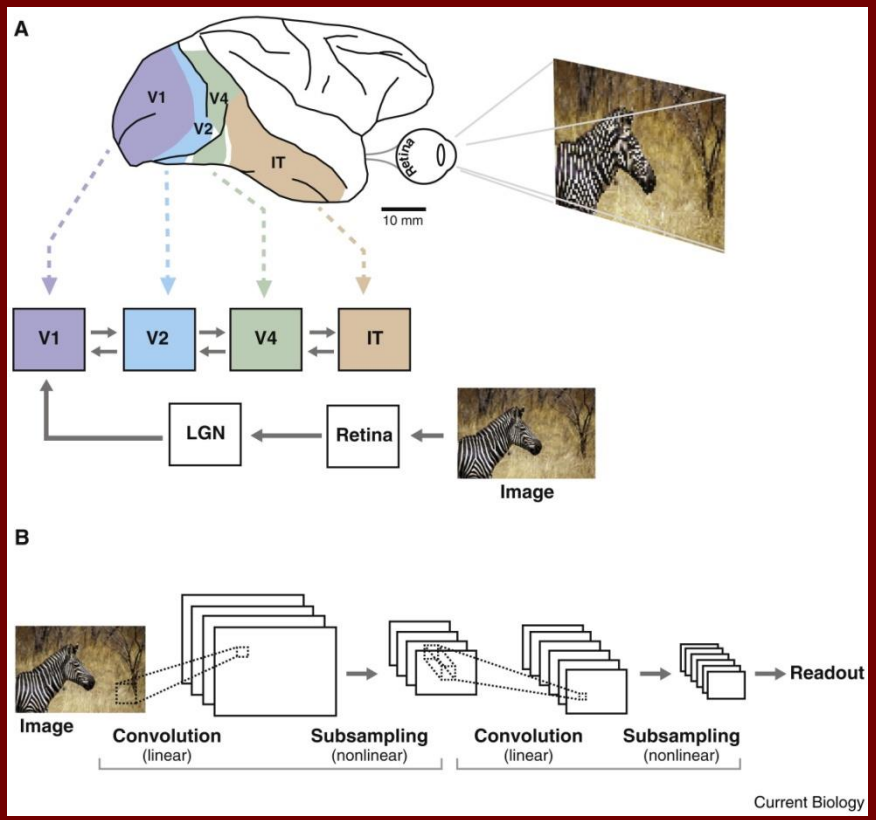
Shape and measures used to compute features.

1) Circularity $cir = \frac{4pA}{P^2}$
2) Aspect Ratio $ar = \frac{p_1+p_2}{C}$
3) Discontinuity Angle Irregularity $dar = \sqrt{\frac{(\sum|\theta_i-\theta_{i+1}|}{2\pi(n-2)}}$
   A normalized measure of the average absolute difference between the discontinuity angles of polygon segments made with its adjoining segments.
4) Length Irregularity $lir = \frac{\sum|L_i-L_{i+1}|}{K}$, where $K = 2P$ for $n > 3$ and $K = P$ for $n = 3$.
   A normalized measure of the average absolute difference between the length of a polygon segment and that of its preceding segment.
5) Complexity $com = 10^{\frac{3}{n}}$. A measure of the number of segments in a boundary group weighted such that small changes in the number of segments have more effect in low complexity shapes than in high complexity shapes.

CNN: Inspiration from the primate visual cortex

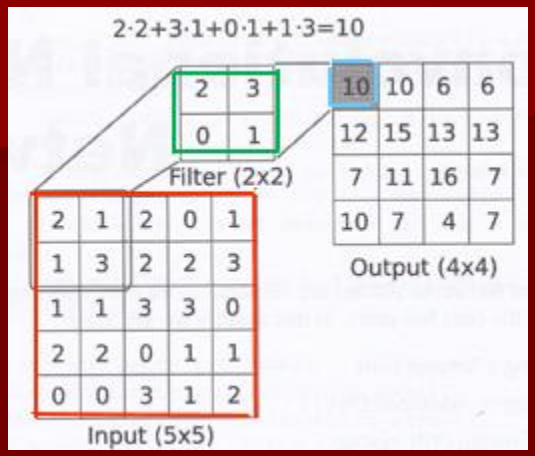
- A. The ventral visual pathway is organized as a hierarchical series of 4 interconnected visual areas called Brodmann areas. Neurons in early areas, such as area V1, respond to comparatively simple visual features of the retinal image, while later areas, such as area V4, respond to increasingly complex visual features

- B. The specialization of receptor cells are incorporated into the design of CNN as pairs of convolution operator followed by a pooling layer

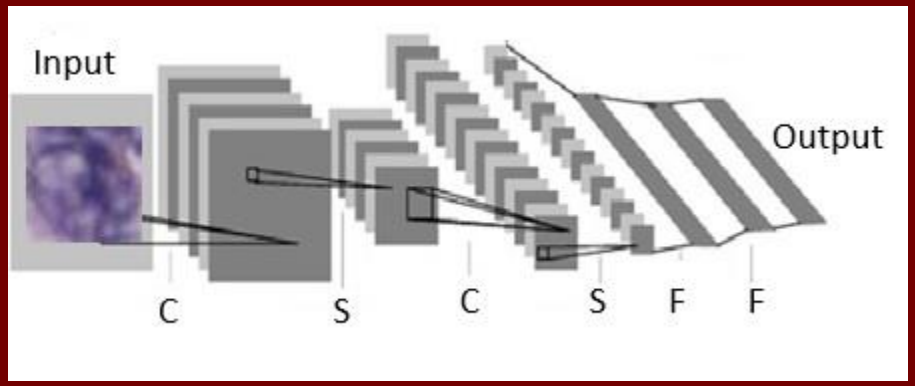


A rough correspondence between the areas associated with the primary visual cortex and the layers in a convolutional network.

Definition of Convolution



- Convolution: an operation in image processing using filters, to modify or detect certain characteristics of an image (Smooth, Sharpen, Intensify, Enhance). In CNN, it is used to extract features of images
- Mathematically, a convolution is done by multiplying the pixels' value in image patch by a filter (kernel) matrix [dot product]



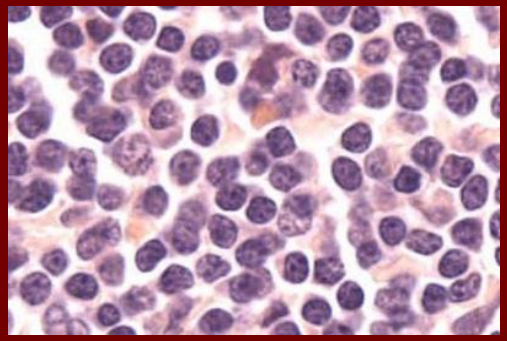
By moving the filter across input image, one obtains the final output as a modified filtered image

- The convolutional layers (C) perform 'feature extraction' consecutively from the image patch to higher level features.
- The max pooling layers (S) reduce image size by subsampling
- The last 'fully connected' layers (F): provide prediction

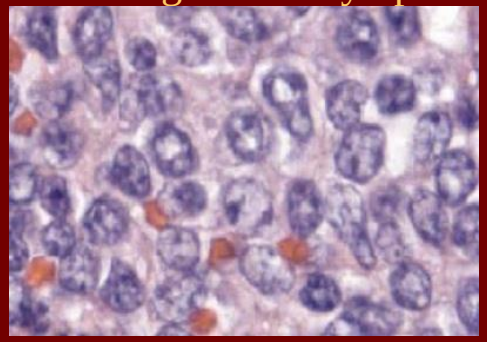
The Goal of our Study

- Recent studies have shown promising results in using machine learning to detect malignancy in whole slide imaging. However, they were limited to just positive and negative finding for a particular neoplasm.
- We explore how Deep Learning can be used to accurately classify a test case as one of the 4 entities (Representative of various morphologic patterns in lymphoma):

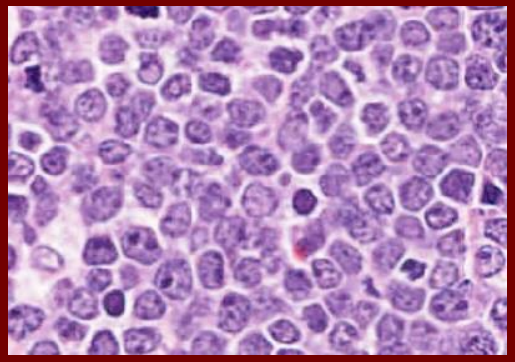
Benign lymph nodes



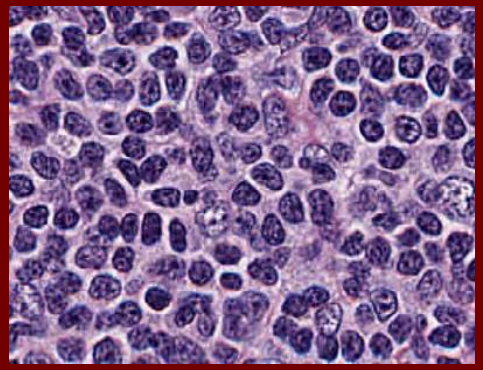
Diffuse large B-cell lymphoma



Burkitt lymphoma



Small lymphocytic lymphoma

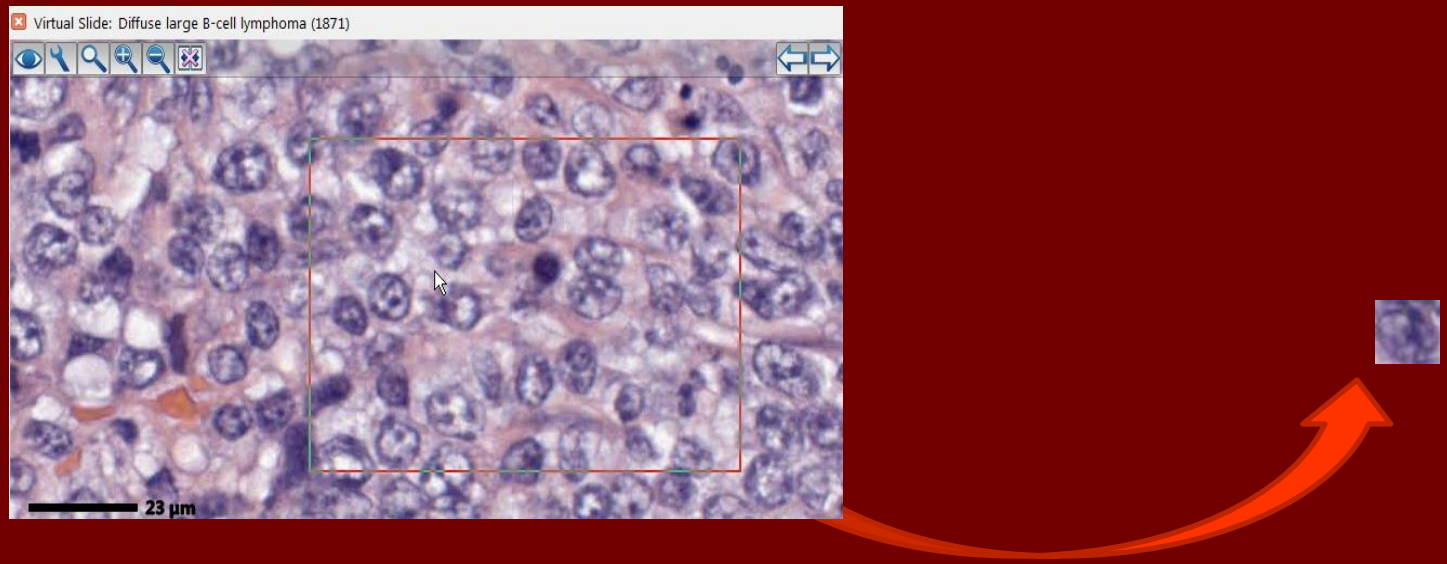


Digital Images of Lymphomas

- Data source #1: at Virtual Pathology at the University of Leeds (355,966 slides -114.92 TB)

  http://www.virtualpathology.leeds.ac.uk/slides/library/
- Web browser (at 40x) -> SnagIt (TechSmith Corp, Okemos, Michigan, USA) to capture and automatically save 40x40 image patch in a file xxx.jpg

- Data source #2: also at Virtual Slide Box-Whole Slide Imaging Collection (1,000 slides from U of Iowa) on Biolucida Cloud Portal, hosted by MicroBrightField Bioscience (Williston, VT USA) http://www.mbfbioscience.com/iowavirtualslidebox
- Biolucida viewer-> SnagIt to capture and automatically save 40x40 image patch in a file xxx.jpg



Whole Slide Imaging (WSI) of Lymphomas

- WSI's were typically obtained with Aperio (Aperio Technologies, San Diego, CA, USA) whole slide imaging systems (T3 or CS Series). Our study includes: 32 cases for each of the following:

  1. Benign lymph nodes,
  2. Diffuse large B-cell lymphoma,
  3. Burkitt lymphoma,
  4. Small lymphocytic lymphoma

- 4 sets of 5 representative 40x40 images for each of the 32 cases
  -> a total of 4x5x32x4=2,560 images

Our Programming Platform

- We design a CNN model in Python language, commonly used in deep learning (together with TensorFlow and Keras libraries)
- Keras allows for parallel computing using GPU
- Hardware:
  Intel i5-4590, 8GB RAM
  Windows 8-64 bit
  GPU: GTX745 (4 GB), 384 cores
  NVIDIA card supported by CUDA
  (Compute Unified Device Architecture)

Validation Method

- 1856 images (~70%) were used for training the model, 464 (~20%) for validation, and 240 (~10%) for testing
- For each test case, the predicted diagnosis is combined from the prediction for 5 images (at least 3 or more have to agree), a process known as “majority voting”

Display of Analysis Results

```
> set1
[[1]]
      Observed Predicted
 [1,]        0         0
 [2,]        0         4
 [3,]        0         0
 [4,]        0         0
 [5,]        0         0
 [6,]        1         1
 [7,]        1         1
 [8,]        1         1
 [9,]        1         1
[10,]        1         1
[11,]        3         3
[12,]        3         3
[13,]        3         0
[14,]        3         3
[15,]        3         3
[16,]        4         4
[17,]        4         4
[18,]        4         4
[19,]        4         4
[20,]        4         4
```

…

```
[50,]        1         1
[51,]        3         3
[52,]        3         0
[53,]        3         3
[54,]        3         3
[55,]        3         3
[56,]        4         4
[57,]        4         4
[58,]        4         4
[59,]        4         4
[60,]        4         4

[[2]]
             Observed DX
Predicted DX  0  1  3  4
           0 11  0  4  1
           1  0 13  0  0
           3  2  0 11  0
           4  2  2  0 14

[[3]]
[1] 0.82
```

	Observed	Predicted
[1,]	0	0
[2,]	0	4
[3,]	0	0
[4,]	0	0
[5,]	0	0
[6,]	1	1
[7,]	1	1
[8,]	1	1
[9,]	1	1
[10,]	1	1
[11,]	3	3
[12,]	3	3
[13,]	3	0
[14,]	3	3
[15,]	3	3

Majority vote:

->4/5 predicts 0

->5/5 predicts 1

->4/6 predicts 3

RESULTS: ACCURACY

Observed DX					
Predicted DX		Benign	DLBCL	BL	SLL
	Benign	56	0	0	4
	DLBCL	0	60	0	4
	BL	4	0	60	0
	SLL	0	0	0	52

Image-by-image:
Accuracy: 228/240=95%

Observed DX					
Predicted DX		Benign	DLBCL	BL	SLL
	Benign	12	0	0	0
	DLBCL	0	12	0	0
	BL	0	0	12	0
	SLL	0	0	0	12

Case-by-case
(majority voting):
Significantly better accuracy:
48/48=100%

SUMMARY

- We explore how Deep Learning can be utilized for histologic diagnosis of lymphoma using whole slide imaging
- Deep learning with CNN algorithm yields an impressive result **(an accuracy of 100%)**
- Generic machine learning algorithm with CNN method-> no need for manual settings of morphology parameters (nuclear architecture, shape, and texture, etc.) -> presumably can be applied to other histologic pathologies (GI, GYN, etc)
- Current limitations include:
  (a) only 4 histologic categories were included, not yet practical for clinical use,
  (b) representative images require manual selection of suspected areas
- Our preliminary study provided a proof of concept for incorporating automated lymphoma diagnosis using digital microscopic images into the pathology work flow to augment the pathologists' productivity. Future studies will need to include more histologic entities and many more cases for training, and validation

Acknowledgement

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