Applications in Deep Learning in Imaging and Therapy

(SAM Joint Imaging-Therapy Scientific Symposium)

1. Quantitative Imaging in Radiomics and Machine Learning
   - Erickson Bradley from Mayo Clinic
2. Deep Learning for Therapeutic Toxicity in GI Radiation Therapy
   - Bulat Ibragimov from Stanford University
3. Computerized Breast Image Analysis Using Deep Learning
   - Maryellen L. Giger from University of Chicago

Computerized Breast Image Analysis Using Deep Learning

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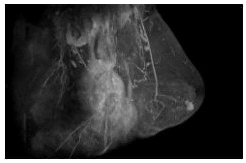
- MLG is scientific advisor, co-founder, and equity holder in Quantitative Insights, makers of QuantX -- the first FDA-cleared machine learning system for aiding in cancer diagnosis.
- MLG is President of SPIE – the international society of photonics and optics.
- It is the University of Chicago Conflict of Interest Policy that investigators disclose publicly actual or potential significant financial interest that would reasonably appear to be directly and significantly affected by the research activities.

Overview of Deep Learning and Breast Imaging

Breast Images

- FFDM, ultrasound, MRI, tomosynthesis
- Clinical images
- Large, useful databases



Deep Learning in Precision Medicine & Imaging

 → Deep Learning → Answer to Clinical Question

Need to consider:

- Cautious of "Garbage in, Garbage out"
  - Issue of Robustness
- There are multiple implementations of "Deep Learning" (e.g., CNNs)
  - Filtering
  - Classifier
  - Feature Extraction
  - Segmentation

Deep Learning

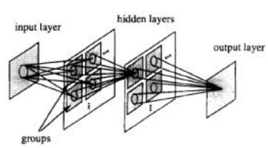
- Deep learning is a subfield of Machine Learning within AI
- Learn patterns (features) directly from input image data
- Often implemented through convolutional neural networks (CNN)
- Layers of the CNN and their "hidden" features may yield descriptors useful in medical decision making
- **In the 1990s, early forms of CNNs were introduced for CADx by learning imaging features directly from image data without explicit manual intervention**
- **Now deep learning methods use deeper and more advanced CNN architectures**

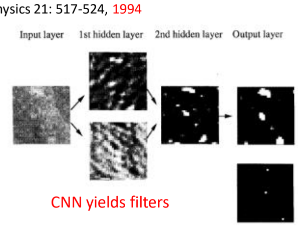
Role of deep learning at various stages of quantitative image analysis (radiomics) for disease assessment

- Applications in breast image analysis
  - Computer-aided detection (CADe)
  - Computer-aided diagnosis (CADx)
  - Risk Assessment
  - Response to neoadjuvant therapy
- Methods to handle limitations and potential pitfalls
  - Pre-processing
  - Transfer learning
    - Fine tuning and feature extraction
  - Data Augmentation

Deep learning example in CADe

Shift-Invariant Artificial Neural Network (SIANN) for CADe in Mammography, Zhang W, Doi K, Giger ML, Wu Y, Nishikawa RM, Schmidt RA. Medical Physics 21: 517-524, 1994

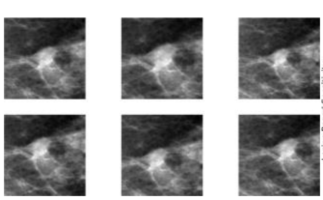


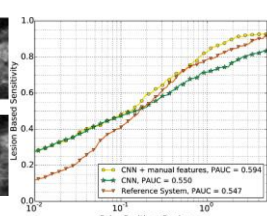


Zhang W et al. Proc. JSAP, 1988
Zhang W et al. Applied Optics, 29: 4790-4797, 1990
Zhang W et al. SPIE Proceeding 1709: 257-268, 1992
Zhang W et al. Medical Physics 21: 517-524 1994

CNN yields filters

CNN with Data Augmentation in FFDM CADe





Both systems are trained on a large data set of around 45,000 images and results show the CNN outperforms the traditional CADe system at low sensitivity and performs comparable at high sensitivity.

Kooi et al. MIA 35: 303-312, 2017

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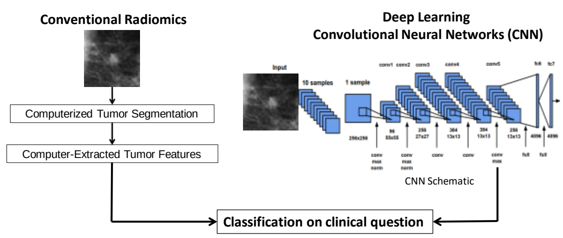
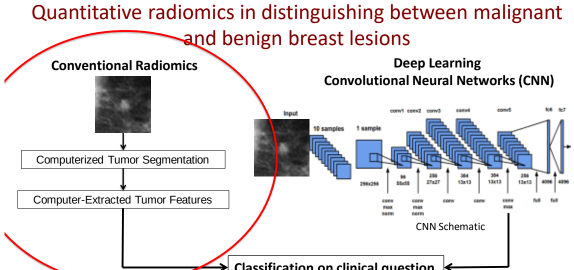
CADx: task of distinguishing between malignant and benign breast lesions



Huynh B, Li H, Giger ML: Digital mammographic tumor classification using transfer learning from deep convolutional neural networks. J Medical Imaging 3(3), 034501 (2016).

Quantitative radiomics in distinguishing between malignant and benign breast lesions



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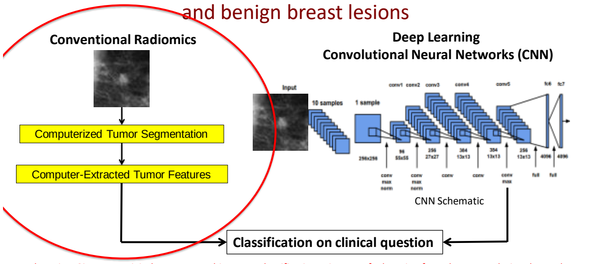

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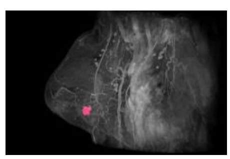
Conventional Mathematically-Engineered Radiomics CADx

- Center of the lesion is indicated
- Followed by automatic lesion segmentation
- After the lesion is segmented, image features (i.e., mathematical descriptors) areextracted from the lesion:
  - Lesion size
  - Lesion shape
  - Intensity features (e.g., average gray level, contrast)
  - Texture within the lesion
  - Margin morphology (e.g., spiculation and sharpness) of the mass
  - Kinetic enhancement features
- Features then merged by a classifier (e.g., LDA, SVM) to yield a signature indicating an estimate of the likelihood of malignancy



Giger AAPM Deep Learning Sym 2018

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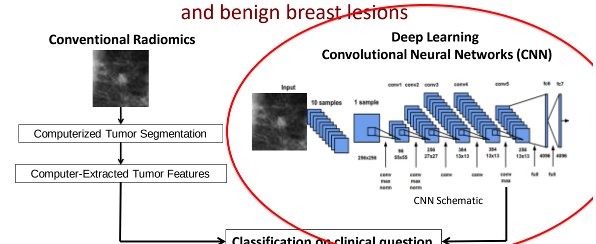

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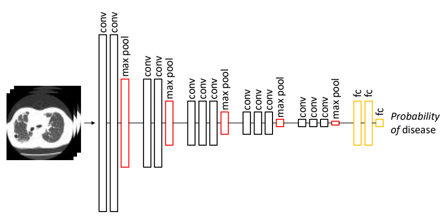
Deep Learning and CNNs

- Learn from Scratch – requires millions of images
- Transfer Learning
  - Apply CNN settings learned from one classification task to another classification task
    - Conduct **fine-tuning** by training only later layers of a pre-trained CNN to a new classification task

    OR
    - Use CNN as a **feature extractor** by extracting features from hidden layers and use a separate classifier (LDA, SVM…) for the classification task.

CNN Structure – Learn from scratch



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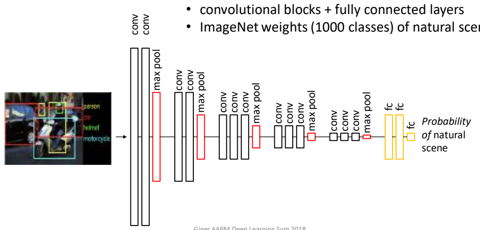
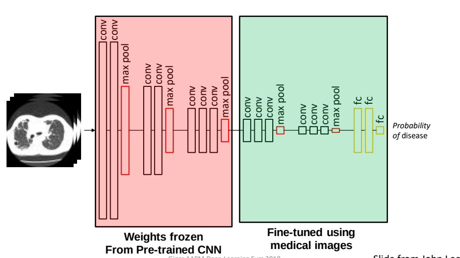
CNN structure – Transfer Learning

- Use: trained Alexnet or VGG19
- convolutional blocks + fully connected layers
- ImageNet weights (1000 classes) of natural scenes



Transfer Learning: **Fine-tuning**



Slide from John Lee

CNNs

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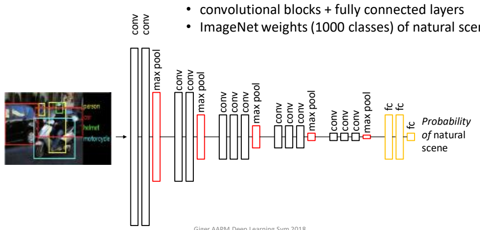
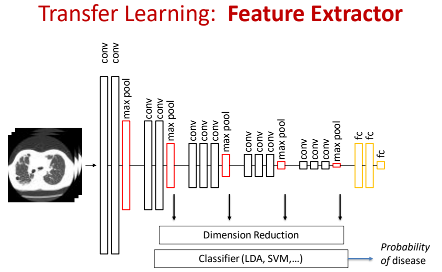
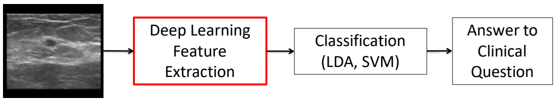


Transfer Learning: **Feature Extractor**

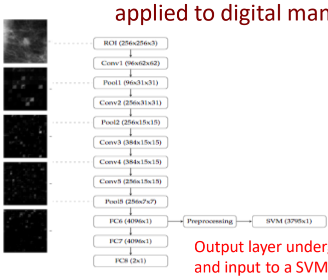


Deep learning example: *Feature Extraction*



- CNNs extract features from entire ROIs without localization or segmentation of lesions.
- Advantage: No lesion segmentation is required
- Advantage: No extraction of segmentation-based features, such as size, shape, margin sharpness, texture, and kinetics
- CNNs require very large datasets -- Can we incorporate pre-trained CNNs?

Already-Trained CNN Structure (e.g., AlexNet) applied to digital mammograms

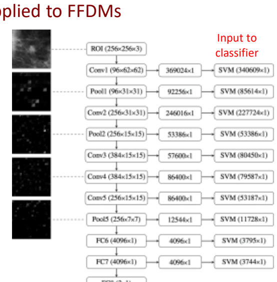


Huynh B, Li H, Giger ML: Digital mammographic tumor classification using transfer learning from deep convolutional neural networks. J Medical Imaging 3(3), 034501 (2016).

Output layer undergoes post processing and input to a SVM classifier

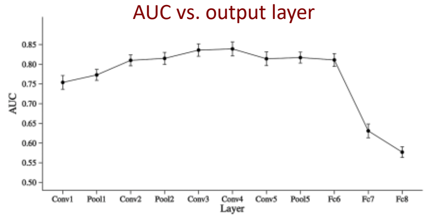
Example of Transfer Learning: Already-Trained CNN Structure (e.g., AlexNet) applied to FFDMs

- A schematic of how features are extracted using a pre-trained AlexNet.
- The numbers in parentheses for the right column denote the length of the feature vector per ROI used as an input for the SVM after zero-variance removal.
- After a feature vector has been extracted from each ROI, the SVM is then trained and evaluated by cross validation.



Huynh B, Li H, Giger ML, J Medical Imaging 3(3), 034501 (2016).

Example of Transfer Learning: AUC vs. output layer

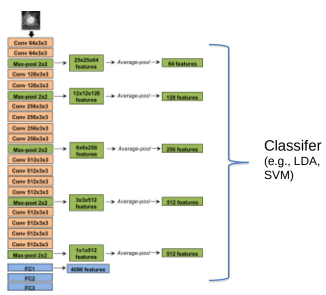


Performance in terms of AUC for classifiers based on features from each layer of AlexNet in the task of distinguishing between malignant and benign tumors on FFDMs.

Huynh B, Li H, Giger ML: Digital mammographic tumor classification using transfer learning from deep convolutional neural networks. J Medical Imaging 3(3), 034501 (2016).

VGG19 for Feature Extraction:

Pooled Layers
or
Fully Connected
Layer



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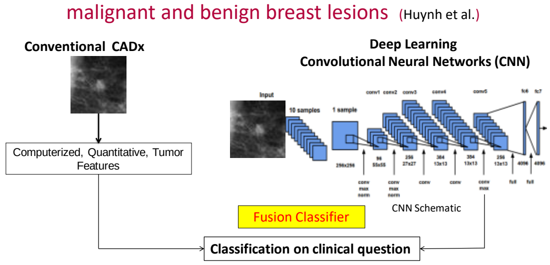
Conventional CADx vs. CNN CADx in distinguishing between malignant and benign breast lesions (Huynh et al.)



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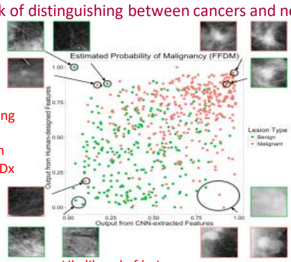
Conventional CAD/Radiomics & Deep Learning CAD/Radiomics
(task of distinguishing between cancers and non cancers)

Likelihood of being cancer as determined from conventional CADx



RED = CANCER

GREEN = Non-CANCER

Huynh et al. RSNA annual meeting 2016

Likelihood of being cancer as determined from deep learning

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Conventional CADx & Deep Learning CADx
(**diagnostic** task of distinguishing between cancers and non cancers across breast imaging modalities; ROC analysis)

Breast Imaging Modality	Number of Cases	Conventional CADx (AUC)	Deep Learning CNN (AUC)	Combination Conventional CADx & CNN (AUC)
Digital Mammography	245	0.79	0.81	0.86
Ultrasound	1125	0.84	0.87	0.90
DCE-MRI	690	0.86	0.87	0.89

Antropova N, Huynh BQ, Giger ML: A deep fusion methodology for breast cancer diagnosis demonstrated on three imaging modality datasets. Medical Physics online doi.org/10.1002/mp.12453, 2017.

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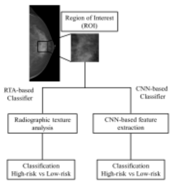
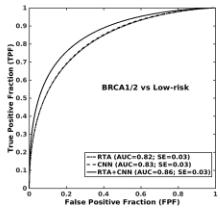
Deep Learning in Breast Cancer Risk Assessment: Evaluation of Convolutional Neural Networks on a Clinical Dataset of FFDMs



Li H, et al: Deep learning in breast cancer risk assessment: evaluation of convolutional neural networks on a clinical dataset of full-field digital mammograms. J Med Imaging 4(4), 041304 (2017), doi: 10.1117/1.JMI.4.4.041304, 2017

- 53 BRCA1/2 and 328 normal risk women
- Comparison to RTA (texture analysis)



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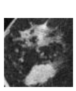
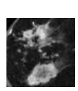
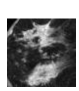
DCE-MRI in Response to Neoadjuvant Therapy

- Incorporate the dynamic (temporal) aspect of DCE-MRI.
- Multiple scans per exam.
- Multiple exams per subject.
- Each contrast time-point provides different physiological information.


Pre-contrast time-point (t_0)


Contrast time-point 1 (t_1)


Contrast time-point 2 (t_2)

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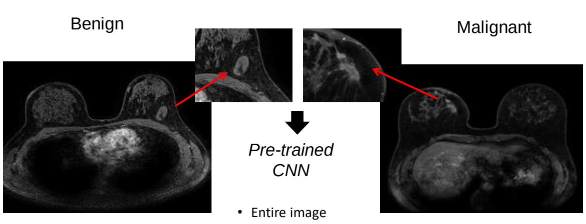
Various CNN Parameters Investigated

- Pre-Processing
  - Since ROIs of different sizes
  - Add frame or mirror padding to obtain equal input ROI sizes
  - Image enhancement
- Transfer learning
  - Pooled features
  - Fully-connected features
- Data augmentation
  - Images from multiple time points, views, slice, or rotations
- Classifier fusion

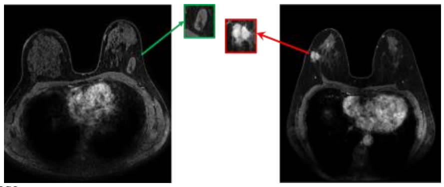
Image Data for input to CNN: Large ROIs



- Entire image
- Large ROI localized to tumor
- ROI mainly including only the tumor

Antropova N et al. SPIE Proc. Med Imag 2017

Image Data for input to CNN: Small ROIs



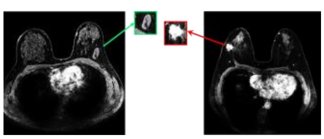
- Entire image
- Large ROI localized to tumor
- ROI mainly including only the tumor

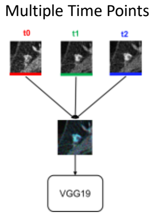
Task of distinguishing malignant vs. benign	Large ROIs	Small ROIs
AUC	0.72	0.87

Antropova N et al. SPIE Proc. Med Imag 2017
Antropova N, et al Medical Physics 2017

Data Augmentation: Use images from multiple time points to incorporate the dynamic characteristics

Use Images from Multiple Time Points

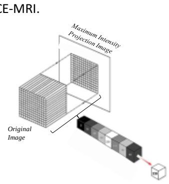




Antropova N et al. SPIE Proc. Med Imag 2017
Antropova N, Huynh BQ, Giger ML: Medical Physics 2017

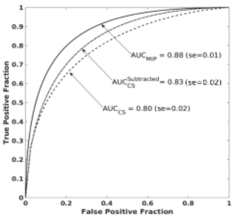
Data Preprocessing: Maximum Intensity Projection Images as DCE-MRI Representations

- Maximum intensity projection (MIP) images allow us to incorporate volumetric and partially temporal components of a DCE-MRI.



2-dimensional information	✔
Temporal information	✔
Volume information	✔

Effect of Three MRI Input Protocols on CNN Performance
(Malignant Lesion)

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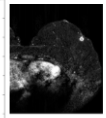


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ubtraction MRI
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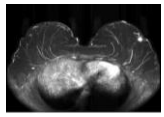


Maximum intensity projection (MIP)
2-D information
Temporal information
Volume information

Antropova , , maximum intensity projections for improved breast lesion classification with deep CNNs J Med Imaging 2018 Jan;5(1):014503.

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Summary

- Image analysis tasks are continuing to be developed using both hand-crafted methods and deep learning methods
- Understanding the CNN is important in optimizing and in using in interpretations (don't just say "black box")
- Methods available to handle limited data sets
  - Transfer learning, data augmentation
  - Pre and post processing to handle images of differing sizes

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