Small-Data Deep Learning for Detection and Classification of Lesions in Medical Images

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Contents

- AI-aided Medical Image Diagnosis
  – "Small-data" deep learning
  – Small-data deep learning application to rare cancer
- AI/Deep-Learning Imaging
  – Bone suppression in chest radiographs
  – Radiation dose reduction in CT and Tomosynthesis

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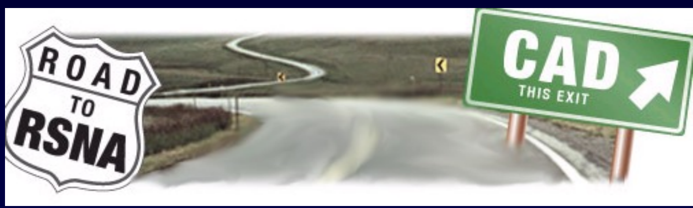
Computer-Aided Diagnosis (CAD)[1-5]
→ AI-aided Diagnosis "AI Doctor"



1) Doi K et al., Eur J Radiology (1999)
2) Giger ML & Suzuki K, *Biomed Info Tech* (2007)
3) Suzuki K, *Machine Learning in CAD* (2012)
4) Chang JZ et al., *Nature* (2016)
5) Chen Y & Suzuki K, *AI in Decision Support Systems* (2018)

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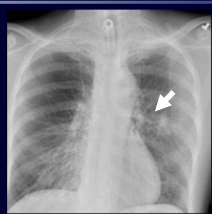
Computer/AI-Aided Diagnosis/Detection (CAD)[1-5]
"AI Doctor"

Medical image



"Second opinion"
(e.g., "I found a pattern similar to a cancer")

Physician

Diagnosis

1) Doi K et al., Eur J Radiology (1999)
2) Giger ML & Suzuki K, *Biomed Info Tech* (2007)
3) Suzuki K, *Machine Learning in CAD* (2012)
4) Chang JZ et al., *Nature* (2016)
5) Chen Y & Suzuki K, *AI in Decision Support Systems* (2018)

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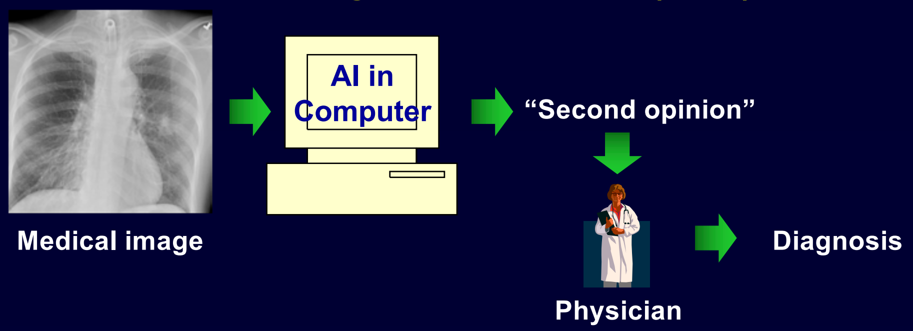
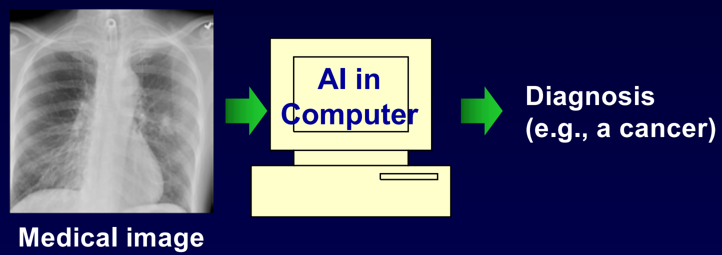
Computer-Aided Diagnosis/Detection (CAD)



Automated Diagnosis



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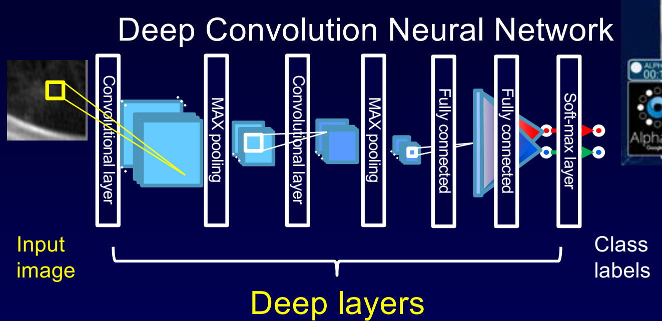
Machine Learning (ML) with Image Input: "Deep Learning"[1)]

- Deep learning: ML algorithms that attempt to model high-level representations of information processing in the brain by using deeply layered machine-learning architectures
- Input to the model is images, and the output is classes



1) Y LeCun, et al. *Nature* (2015)

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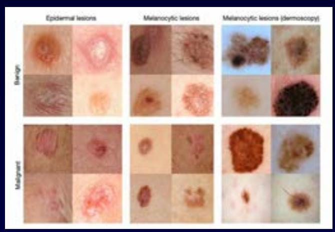
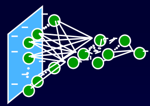
Deep Learning Application to Diagnosis of Disease on Medical Images

- Deep learning performance was equivalent to dermatologists' in diagnosis of skin cancer when it was trained with 130,000 medical + 1.28 M natural images (*Nature*, 2017)



Huge number of medical images

Deep Learning



Malignant
Benign

Huge amount of work for annotations

Dermatologists

Problem

✓ Deep learning training requires 10,000-100,000 cases per disease, which would take years to collect. Furthermore, it requires a huge amount of work for annotations of each of the images

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Bottleneck of Deep Learning in Medicine

= Necessity of "Big Data"
(10,000 -100,000 cases)

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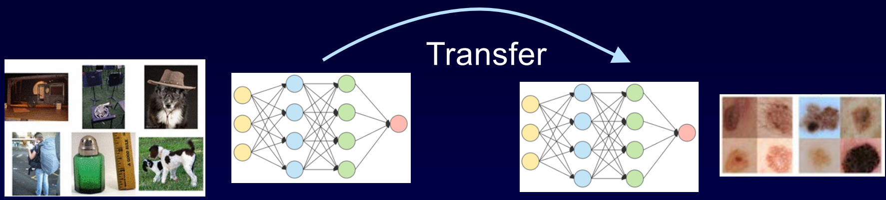
Method to Reduce the Big Data Issue

- Transfer Learning[1)]
  – Train a convolutional neural network (CNN) with 1.28M natural images; and then transfer the weights of the model and fine-tune it with 130,000 medical images

Nature (2017)



1.28M natural images

CNN

CNN

130K medical images

1) B Huynh et al. *J Med Imag* (2016)

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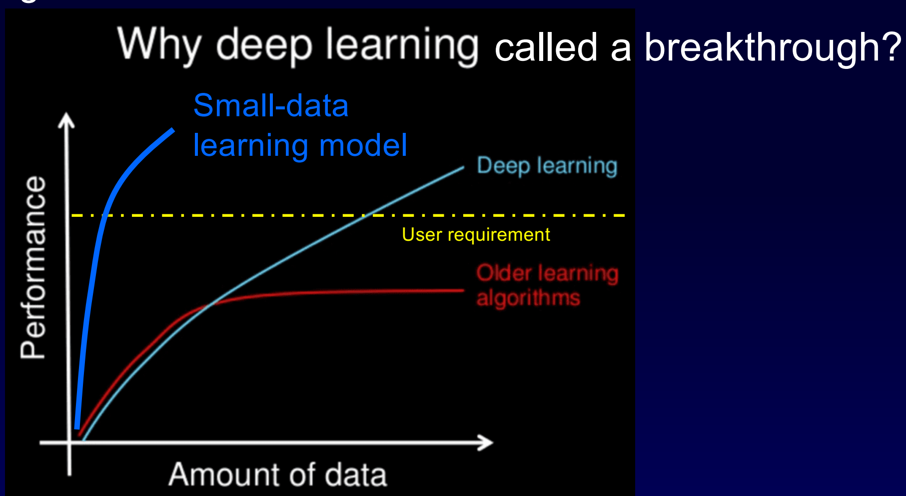
"Small-Data Deep-Learning" Model[1)]

– Deep-learning model that can be trained with a small number of cases



Source: A. Ng (Stanford U), What Data Scientists Should Know about Deep Learning (slide 30), 2015; the small-data learning model & user requirement added by K Suzuki (Tokyo Tech)

1) K Suzuki, *Proc IEEE Big Data Services* (2022)

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National Cancer Center Japan

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Is it possible to develop a deep-learning model that does not require 100,000 cases or transfer learning?

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Small-Data MTANN: Early "Deep Learning" Model

Noise reduction: Suzuki et al. ICSPAT (1996), Suzuki et al. Neural Proc Lett (2001), Suzuki et al. IEEE Trans Signal Proc (2002), Suzuki et al. IEICE Trans Info & Sys (2002), and Suzuki Neural Eng (2004)
Edge enhancement: Suzuki et al. IEEE Trans Pat Anal & Mach Intell (2003), Suzuki et al. IEEE Trans Med Imag (2004)
Lung CT CAD: Suzuki et al. *Med Phys* (2003), Arimura et al. *Acad Radiol* (2004), Li at al. *Radiology* (2005), Suzuki et al. *Acad Radiol* (2005), Suzuki et al. *IEEE Trans Med Imag* (2005), Suzuki et al. *Phys Med Biol* (2009)
CXR CAD: Suzuki et al. *Acad Radiol* (2005), Chen et al. *IEEE Trans Biomed Imag* (2013)
Bone separation (VDE) CXR: Suzuki et al. *IEEE Trans Med Imag* (2006), Oda et al. *AJR* (2009), Chen et al. *Med Phys* (2011), Chen et al. *IEEE Trans Med Imag* (2014), Chen et al. *Phys in Med & Biol* (2016)
CT colonography CAD: Suzuki et al. *Med Phys* (2006), (2008), (2010), Suzuki et al. *IEEE Trans Med Imag* (2010), Xu and Suzuki. *Med Phys* (2011)
Overview: Suzuki. *Int J Biomed Imag* (2012), Suzuki. *Quant Imag Med & Surg* (2012), Suzuki. *IEICE Trans Info & Sys* (2013), Suzuki. *J Med Imag & Info Sci* (2017), Suzuki. *Radiol Phys Tech* (2017), Suzuki. Med Imag Tech (2017)

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What is MTANN /émtæn/?

- Massive-training artificial neural network is
  - supervised image-processing / pattern-recognition technique based on machine learning (e.g., an artificial neural network)
  - One of earliest deep-learning models

- **MTANN is award winning technology**
  - **Paul C Hodges Award from U of Chicago in 2002**
  - **Certificate of Merit Award at RSNA in 2003**
  - **Research Trainee Prize at RSNA in 2004**
  - **Young Investigator Award from Cancer Research Foundation in 2005**
  - **Certificate of Merit Award at RSNA in 2006**
  - **Certificate of Merit Award at RSNA in 2009**
  - **Best Paper Award, IEICE Journal in 2014**
  - **Most Cited Paper Award, EANM Springer-Nature in 2016**
  - **Most Citation Award, RPT Journal (Springer) in 2019**
  - **Award for Science & Technology, Ministry of Education, Culture, Sports, Science and Technology of Japan in 2021**

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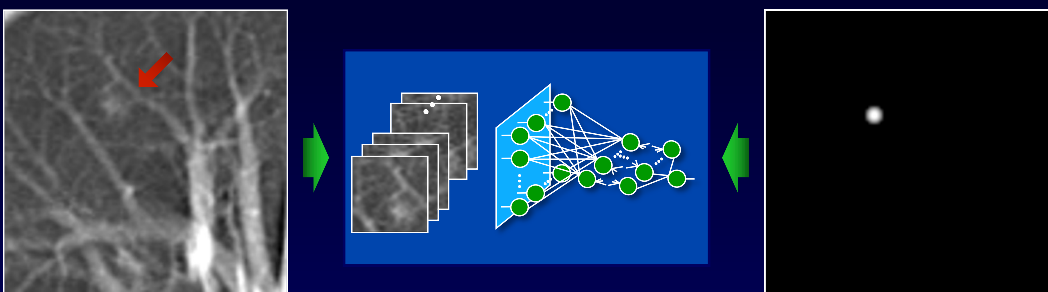
How does MTANN work?

- MTANN directly learns the relationship between input images and "teaching images." (c.f., other DL output is a class; e.g., cancer or not)
- MTANN enhances a specific pattern and suppresses other patterns in a medical image.



Input Image
(Arrow: Lung Cancer)

Teaching Image for
Enhancing Cancer

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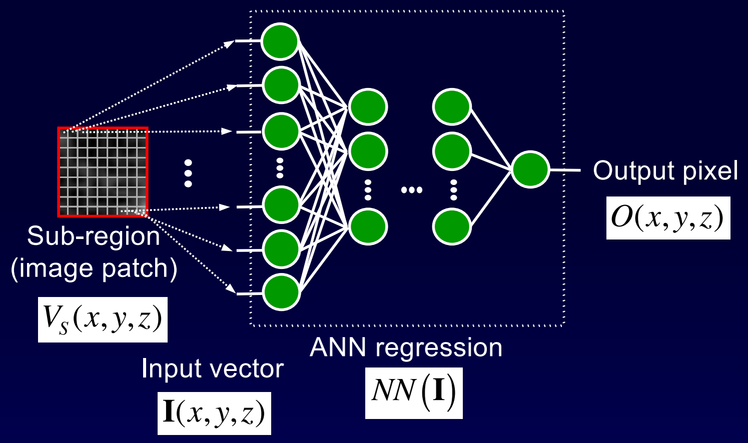
Architecture of MTANN
(Image-patch-based machine learning)

- Unlike deep CNN, pixel output (not category)



$$O(x,y,z) = NN\left\{\mathbf{I}(x-l, y-m, z-n) \mid l,m,n \in V_S\right\}$$

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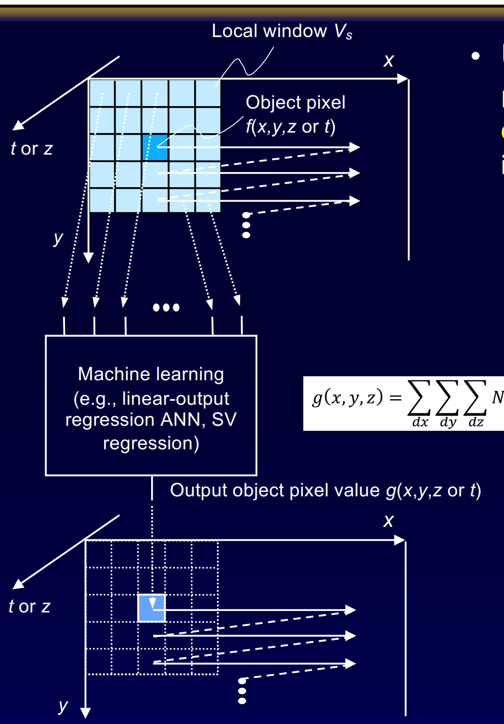

- Unlike convolutional neural network (CNN), convolution is done outside the network in the inference phase

$$g(x,y,z) = \sum_{dx}\sum_{dy}\sum_{dz} NN(dx,dy,dz) f(x+dx, y+dy, z+dz)$$

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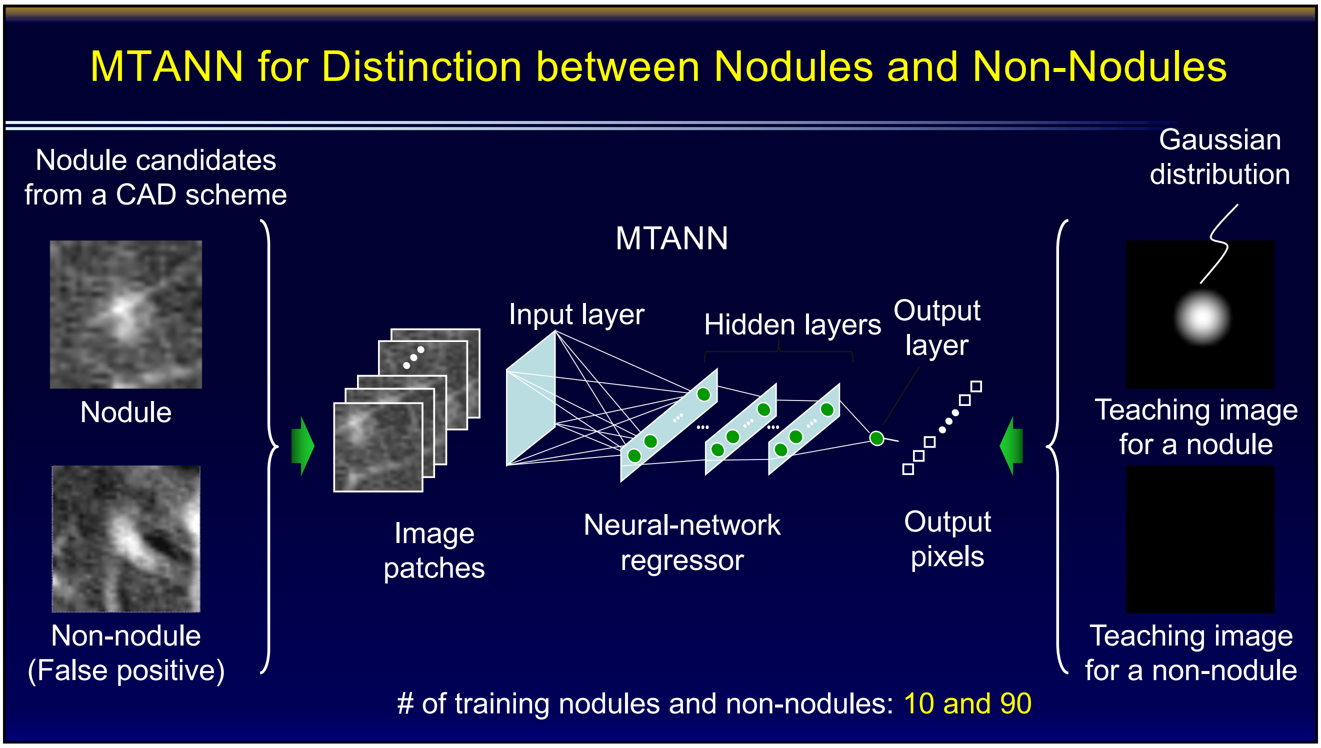
MTANN for Distinction between Nodules and Non-Nodules
Nodule candidates from a CAD scheme
Nodule
Non-nodule (False positive)
MTANN
Input layer
Hidden layers
Output layer
Image patches
Neural-network regressor
Output pixels
Gaussian distribution
Teaching image for a nodule
Teaching image for a non-nodule
# of training nodules and non-nodules: 10 and 90

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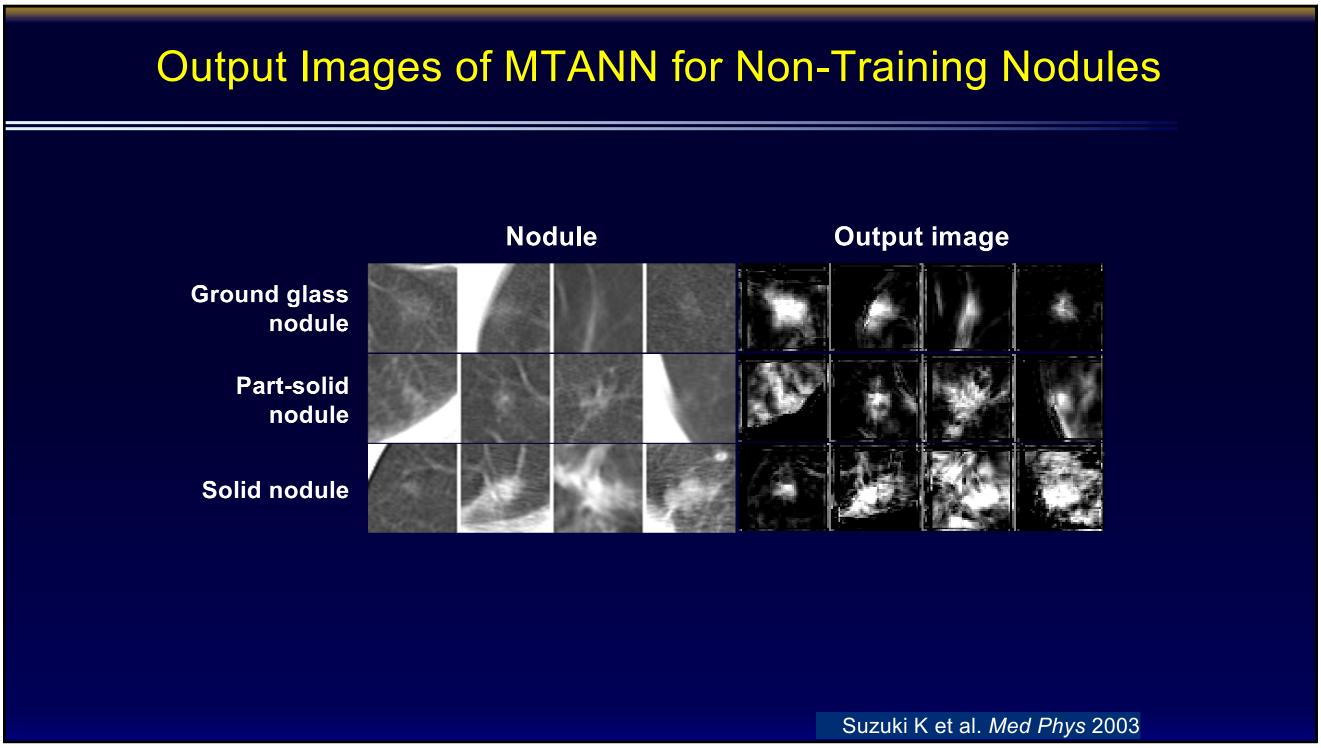
Output Images of MTANN for Non-Training Nodules
Nodule
Output image
Ground glass nodule
Part-solid nodule
Solid nodule
Suzuki K et al. Med Phys 2003

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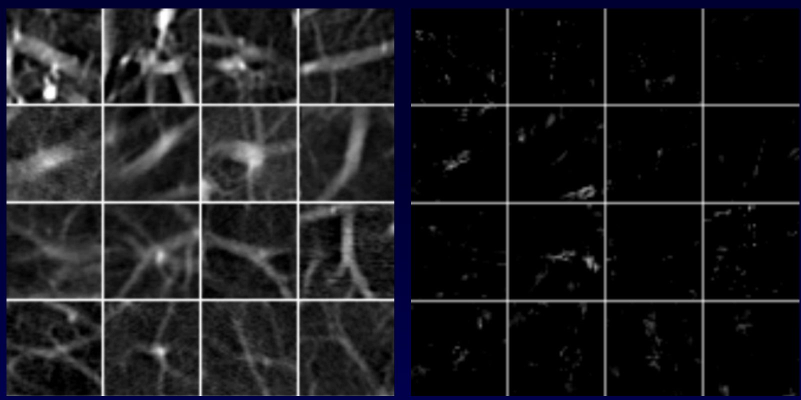
Output Images of MTANN for Various Non-Training Vessels

Different types of vessels | **Output images**



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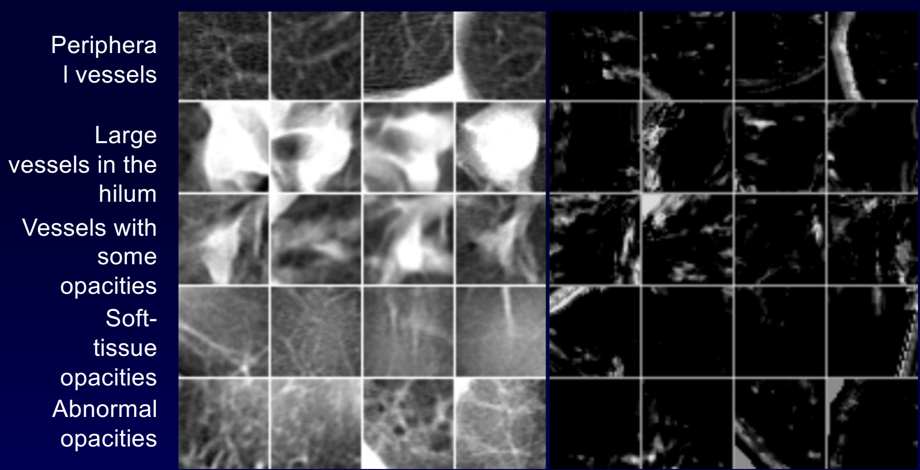
Output Images of Multi-MTANN for Various Types of Non-Nodules

Different types of non-nodules | **Output images**



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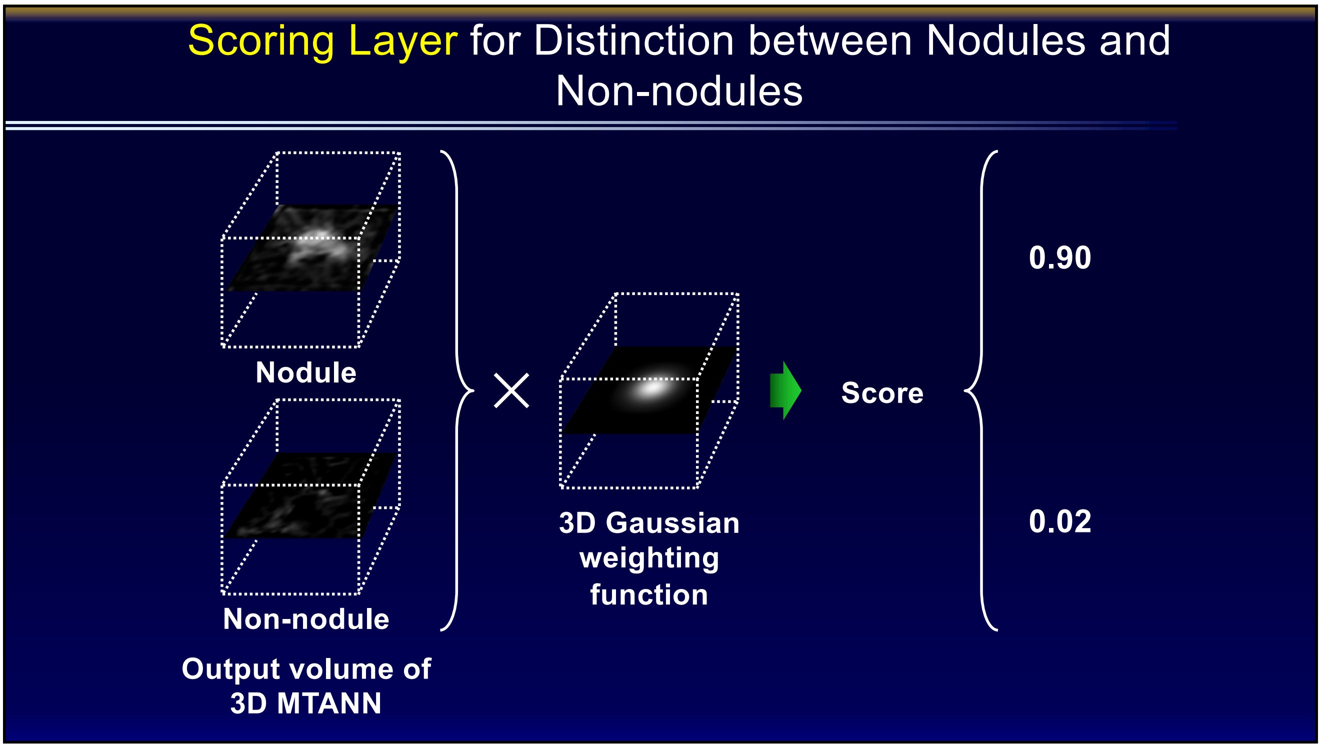
Scoring Layer for Distinction between Nodules and Non-nodules
Nodule
Non-nodule
Output volume of 3D MTANN
×
3D Gaussian weighting function
Score
0.90
0.02

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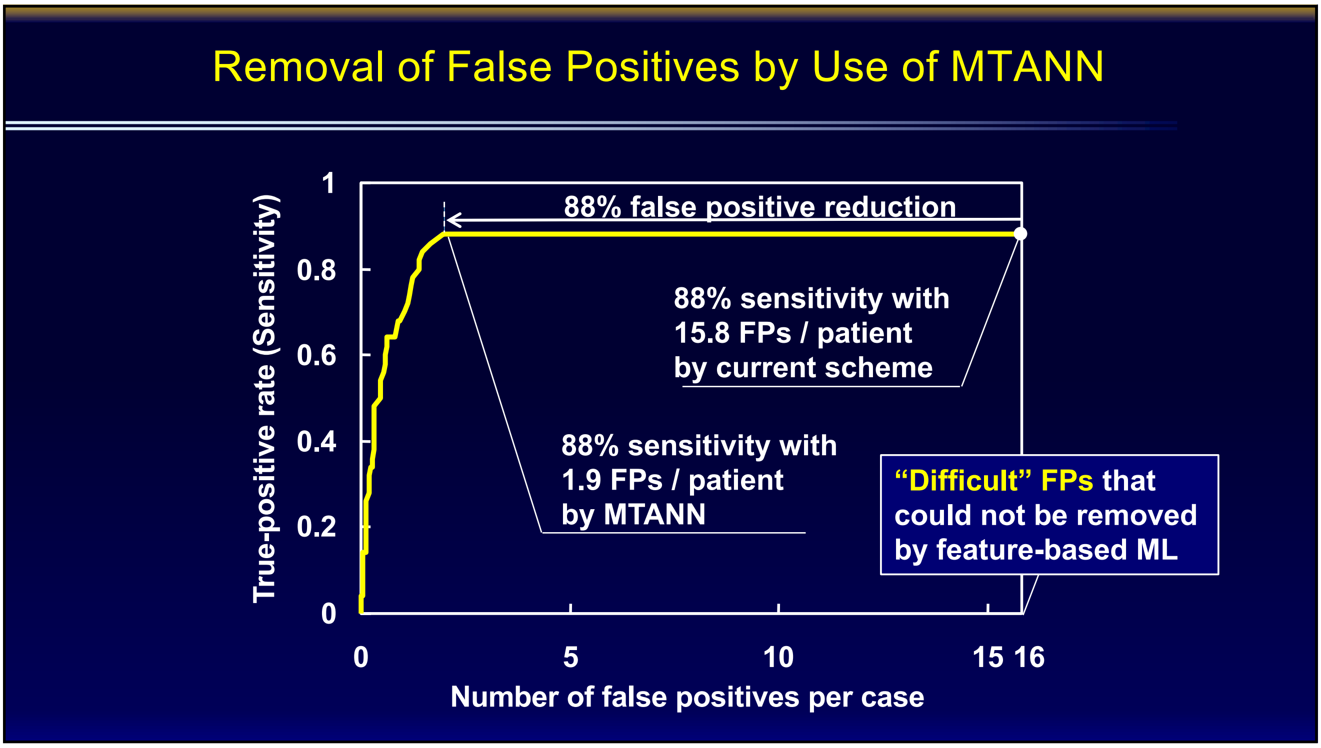
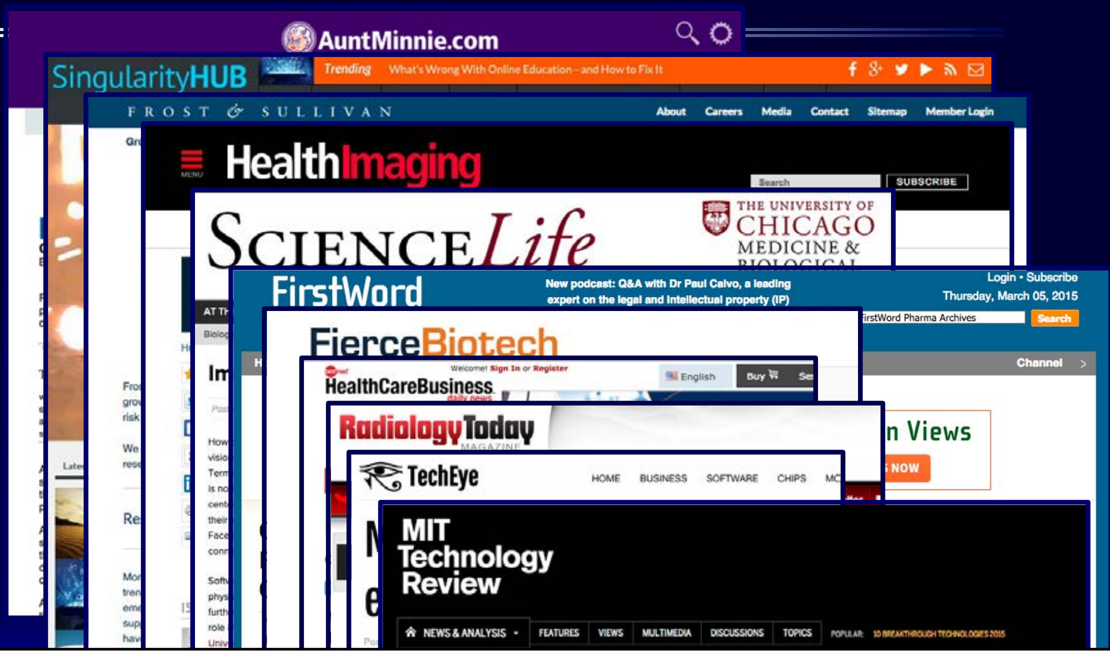

Removal of False Positives by Use of MTANN
88% false positive reduction
88% sensitivity with 15.8 FPs / patient by current scheme
88% sensitivity with 1.9 FPs / patient by MTANN
"Difficult" FPs that could not be removed by feature-based ML
True-positive rate (Sensitivity)
1
0.8
0.6
0.4
0.2
0
0
5
10
15 16
Number of false positives per case

22

Press Coverage (selected from 49)



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Comparing Two Classes of End-to-End Machine-Learning Models in Lung Nodule Detection and Classification: MTANNs vs. CNNs[1)]

1) N Tajbakhsh & K Suzuki. *Pattern Recognition* (2016)

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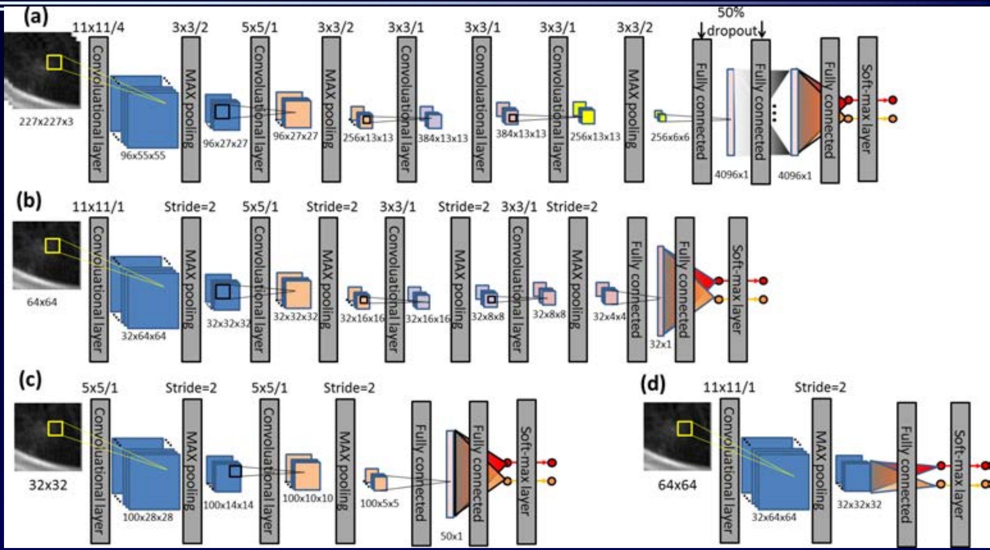
Reference Representative CNNs trained with 100 cases only



(a)Deep CNN (AlexNet)[1] (b) Relatively deep CNN (rd-CNN)
(c) LeNet[2] (d) Shallow CNN (s-CNN)

1) Alex Krizhevsky et al. NIPS (2012)
2) Y LeCun et al. Proc. IEEE (1998)

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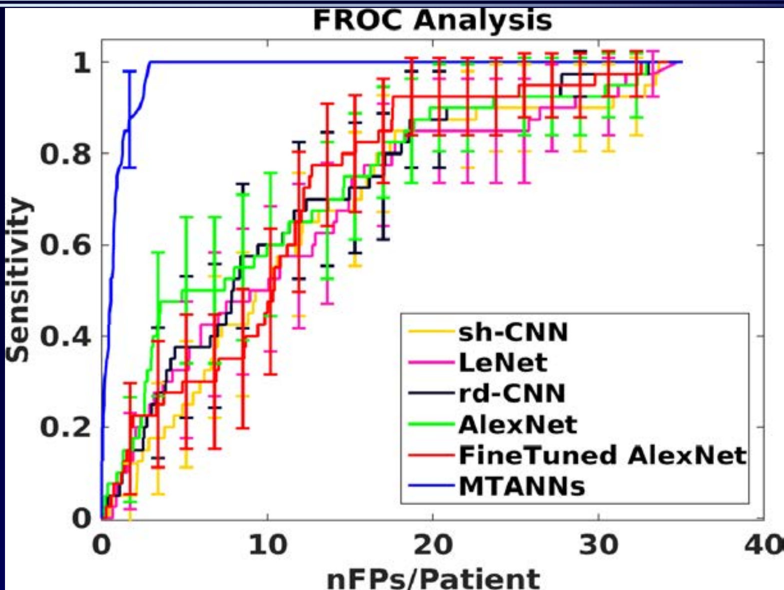
Comparison of MTANNs vs. CNNs: Lung Nodule Detection (Same # of 100 training cases)



N Tajbakhsh & K Suzuki. *Pattern Recognition* (2016)

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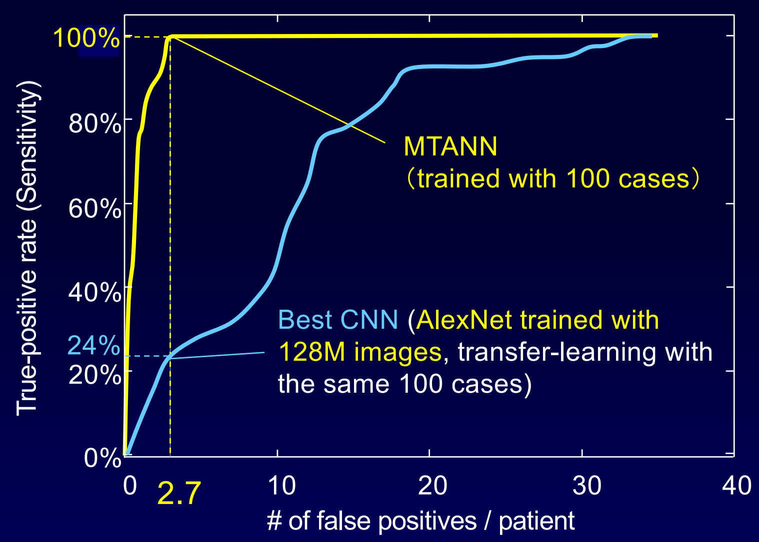
Comparison of MTANNs vs. CNNs with Small Data Learning

Lung Cancer Detection (training with 100 samples)



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What is the minimum number of cases to train an MTANN?

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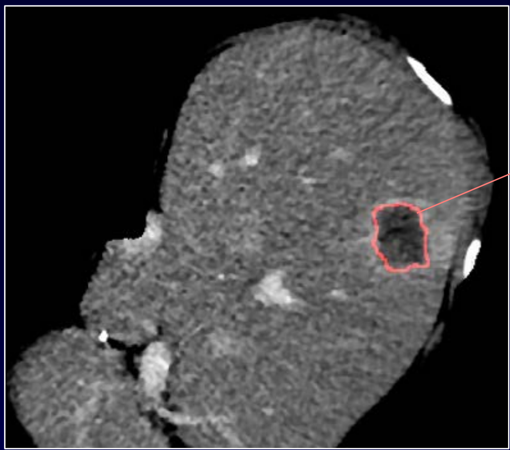
Semantic Segmentation[1-3] of Liver Cancer



Liver CT Image

[1] K Suzuki, et al. *IEEE Trans Med Imag* (IF: 10.0) (2004)
[2] D Calabrese, K Zhou, Y Liu, K Suzuki. *Proc. IEEE EMBC* (2013)
[3] J Long, et al. *Proc IEEE CVPR* (2015)

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Liver Cancer Segmentation World Competition

Top 5 deep-learning models in MICCAI 2017 competition (LiTS)

Ranking	Researchers	Institution	Dice coefficient	# of training tumors	# of training patients
1	Tian et al.	Lenovo	**0.70**	**908**	**131**
2	Li et al.	CUHK	0.69	908	131
3	Chlebus et al.	Fraunhofer	0.68	908	131
4	Vorontsov et al.	MILA	0.66	908	131
5	Yuan et al.	MSSM	0.66	908	131
…	…	…	…	…	…

Used about 900 tumors for training a deep learning model

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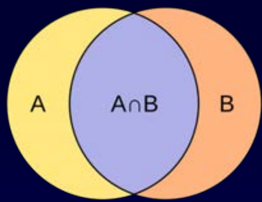
Experiment on Small Sample Training

- Training:
  - 7 tumors in 7 patients
  - 14 tumors in 12 patients

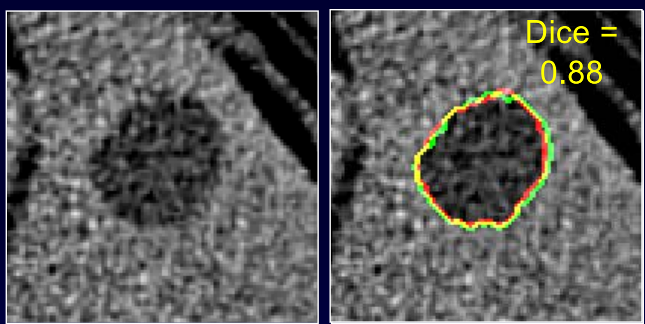
  …
- Testing:
  - 59 tumors in 24 patients
  - Quantitative Evaluation



$$\text{Dice coefficient} = \frac{2*|A \cap B|}{|A| + |B|}$$

A: gold-standard manual segmentation by radiologist
B: segmentation result

Comparison with "Gold-standard" Manual Segmentation



Abdominal CT Image

Tumor Segmentation Comparison

Red: "Gold-standard" manual segmentation, Green: 3D MTANN
(Yellow: Complete agreement)

Comparisons with the State-of-the-Art Models

Comparison with the top 5 deep-learning models in MICCAI 2017 worldwide competition

Ranking	Team	Institution	Dice coefficient	# of training tumors	# of training patients
1	Tian et al.	Lenovo	**0.70**	**908**	131
2	Li et al.	CUHK	0.69	908	131
3	Chlebus et al.	Fraunhofer	0.68	908	131
4	Vorontsov et al.	MILA	0.66	908 **1/65**	131
5	Yuan et al.	MSSM	0.66	908	131
…	…	…	…	…	…
Our MTANN Model 1			0.69	7	7
Our MTANN Model 2			**0.70**	**14**	12

Sato M, Jin Z, Suzuki K: *ECR* 2021

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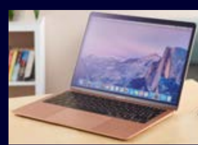
Advantages of MTANN Over Other Deep Learning Models



- Small required number of training samples
  - MTANN was trained with as small as 6 cases
- Low computational cost
  - half an hour to train, 1 sec. to execute on GPU
- Easy design of the architecture
  - easy to design the architecture and stable
- Stable in training
  - training is very stable, robust against parameter changes

	Required # of training samples	Training time	Performance
MTANN	10～100	< 10 min.	Higher
Other DL	5k～10k	a dozen hours to several days	Medium ～ High

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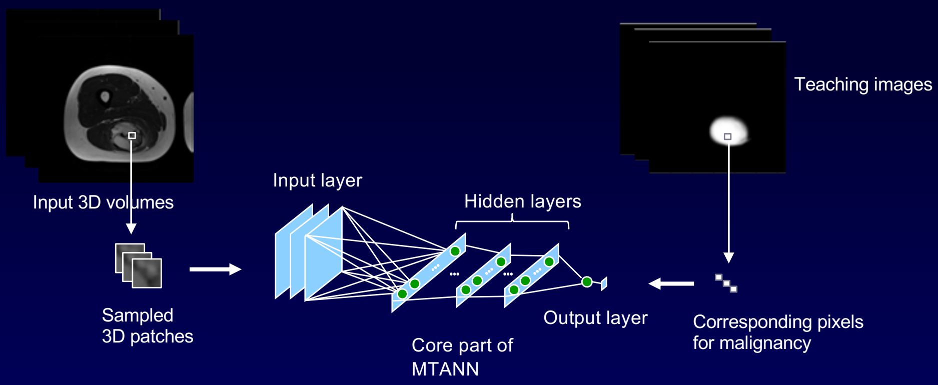
3D MTANN for Rare Cancer Diagnosis

- We trained a 3D MTANN to distinguish rare cancer (soft-tissue sarcoma) and benign tumors in femur T2w MRI
  - Training: 40 malignant tumors (soft-tissue sarcoma) + 40 benign tumors



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Performance Comparison with State-of-the-art Transfer-learned Deep Learning Models in Distinction between Benign and Malignant Tumors

Model	AUC
AlexNet	0.59*
VGG-16	0.63*
ResNet-50	0.66*
MTANN	**0.78**

*p-value < 0.05 against MTANN
AUC: Area under the ROC curve

Y Yang,…, K Suzuki, *RSNA* (2023)

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Virtual Deep-Learning/AI Imaging

1. Separation of Ribs from Soft Tissue in Chest Radiographs by Using MTANN
2. Radiation dose reduction in CT and mammography by Using MTANN

1-6) Suzuki et al. *IEEE Trans Med Imag* (IF:10.0) (2006), Oda et al. *AJR* (IF:4.0) (2009), Chen et al. *Med Phys* (IF:4.1) (2011), Chen et al. *IEEE Trans Med Imag* (IF:10.0) (2014), Chen et al. *Phys in Med & Biol* (IF:3.6) (2016), Zarshena et al. *Med Phys* (IF:4.1) (2019)

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What Is Virtual Deep-Learning/AI Imaging?

- Definition*: Virtual deep-learning/AI imaging may be defined as imaging for enhancing/suppressing physical/semantic objects and/or materials by using deep learning regression
  - It may realize specific imaging virtually without certain physical equipment/materials/procedure

*K Suzuki, Tokyo Tech, Japan

1-6) Suzuki et al. *IEEE Trans Med Imag* (IF:10.0) (2006), Oda et al. *AJR* (IF:4.0) (2009), Chen et al. *Med Phys* (IF:4.1) (2011), Chen et al. *IEEE Trans Med Imag* (IF:10.0) (2014), Chen et al. *Phys in Med & Biol* (IF:3.6) (2016), Zarshena et al. *Med Phys* (IF:4.1) (2019)

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Motivation

- In one study[1)], more than 80% of the missed lung cancers by radiologists in CXR were partly obscured by overlying bones.

1) Austin et al. *Radiology* (1992)

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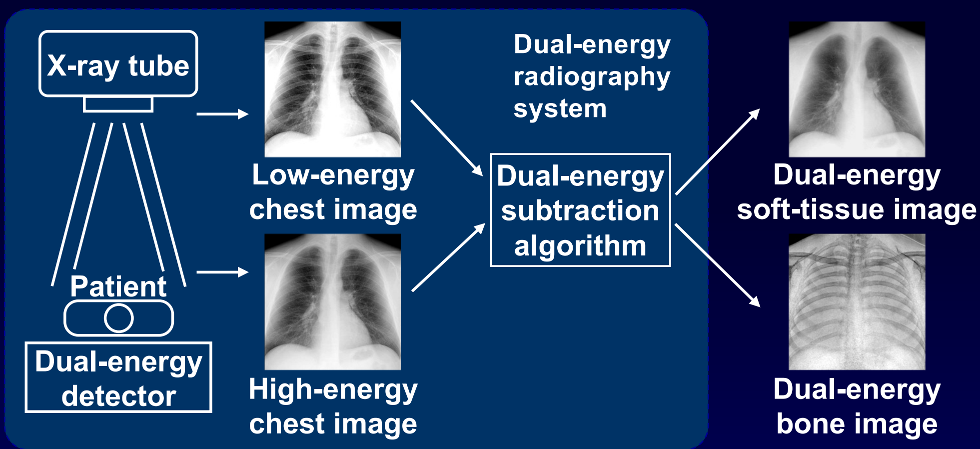
Dual-Energy Subtraction Imaging



Kido S Et Al *Radiology* 1991, 1992

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Limitation of Dual-Energy Imaging

- Despite great advantages, a limited number of hospitals use dual-energy radiography systems at present, probably because
  - Specialized equipment is required for obtaining dual-energy x-ray exposures,
  - Radiation dose may be greater than that for standard chest radiography,
  - Subtraction of high and low energy images causes an increased noise level.

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Can we separate bones from soft tissue in CXR by software?

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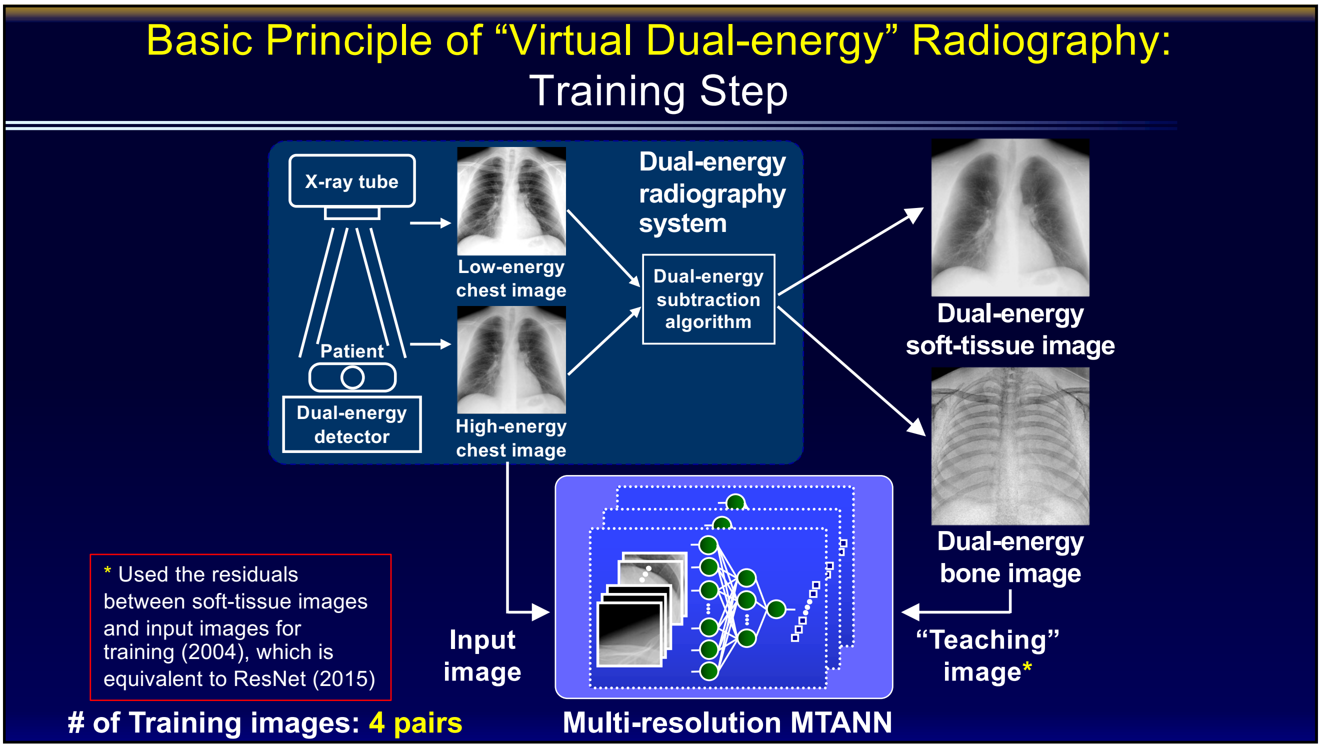

Basic Principle of "Virtual Dual-energy" Radiography: Training Step
X-ray tube
Patient
Dual-energy detector
Low-energy chest image
High-energy chest image
Dual-energy radiography system
Dual-energy subtraction algorithm
Dual-energy soft-tissue image
Dual-energy bone image
"Teaching" image*
Input image
Multi-resolution MTANN
* Used the residuals between soft-tissue images and input images for training (2004), which is equivalent to ResNet (2015)
# of Training images: 4 pairs

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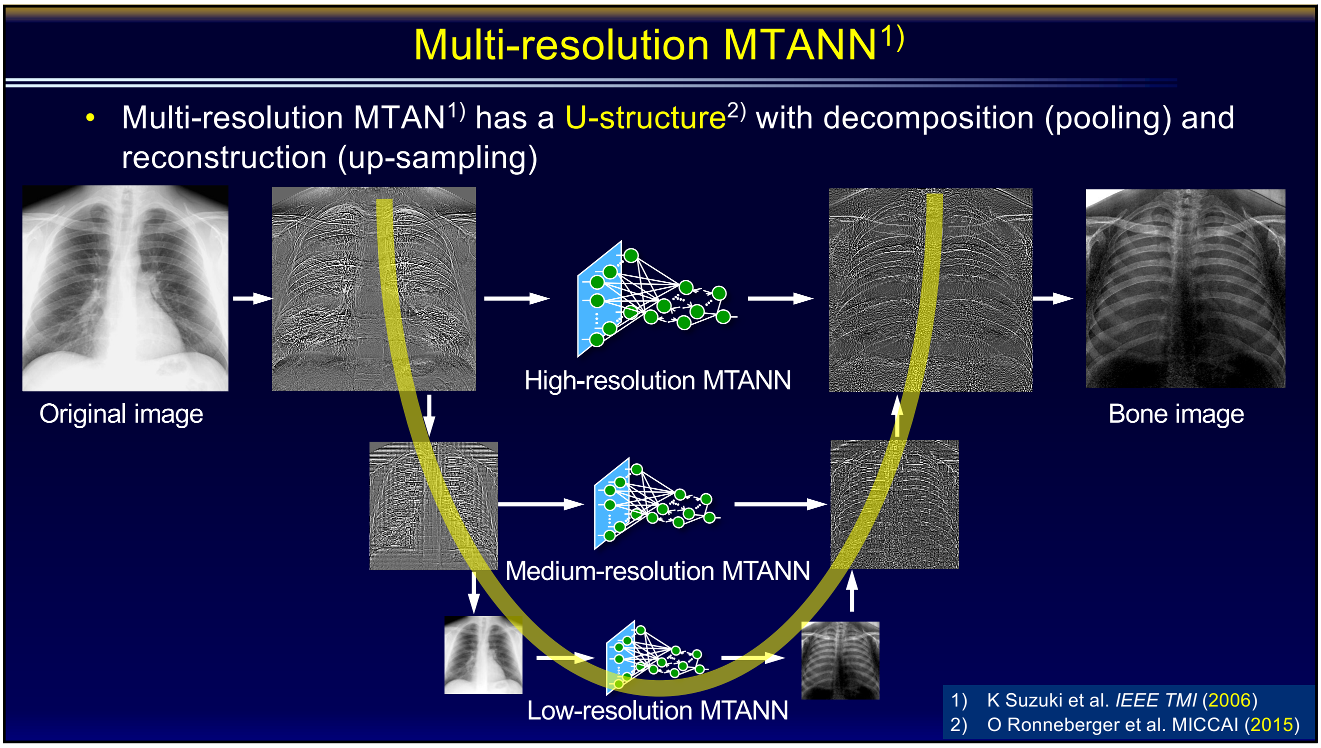

Multi-resolution MTANN1)
• Multi-resolution MTAN1) has a U-structure2) with decomposition (pooling) and reconstruction (up-sampling)
Original image
High-resolution MTANN
Medium-resolution MTANN
Low-resolution MTANN
Bone image
1) K Suzuki et al. IEEE TMI (2006)
2) O Ronneberger et al. MICCAI (2015)

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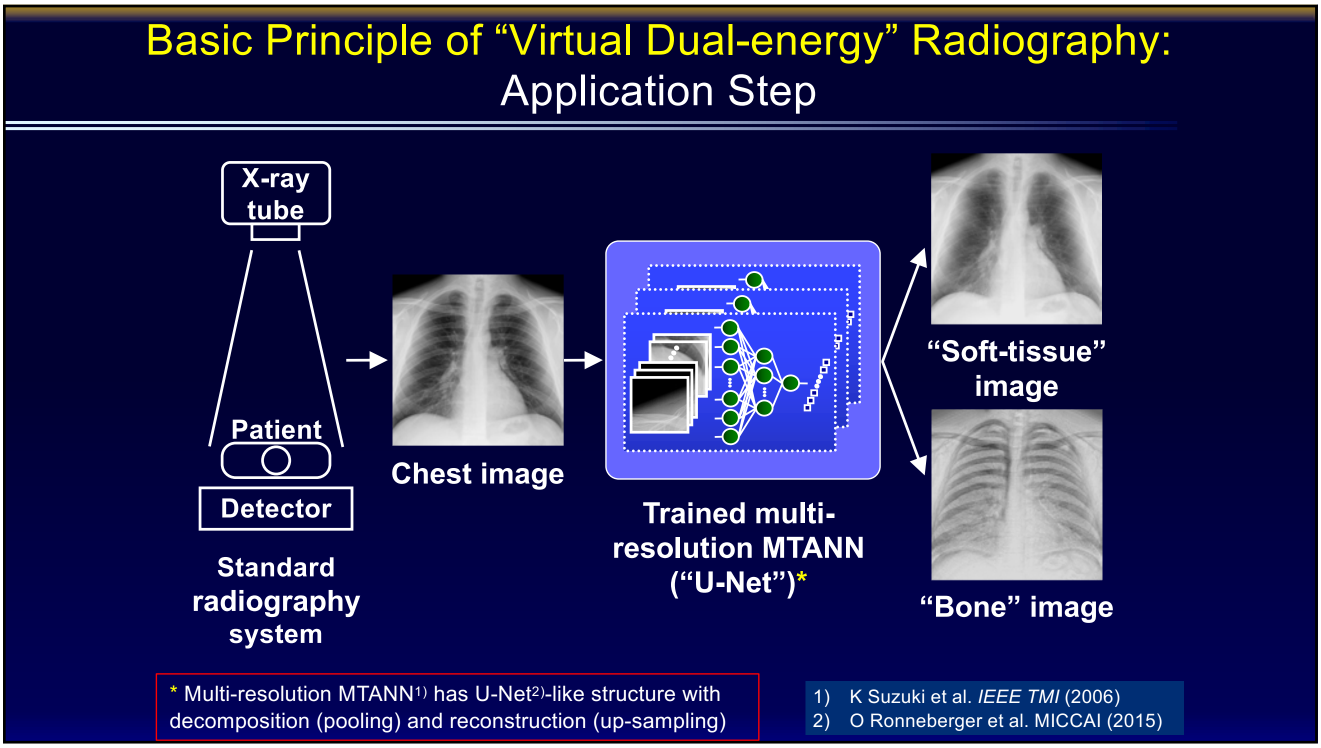
Basic Principle of "Virtual Dual-energy" Radiography: Application Step
X-ray tube
Patient
Detector
Standard radiography system
Chest image
Trained multi-resolution MTANN ("U-Net")*
"Soft-tissue" image
"Bone" image
* Multi-resolution MTANN1) has U-Net2)-like structure with decomposition (pooling) and reconstruction (up-sampling)
1) K Suzuki et al. IEEE TMI (2006)
2) O Ronneberger et al. MICCAI (2015)

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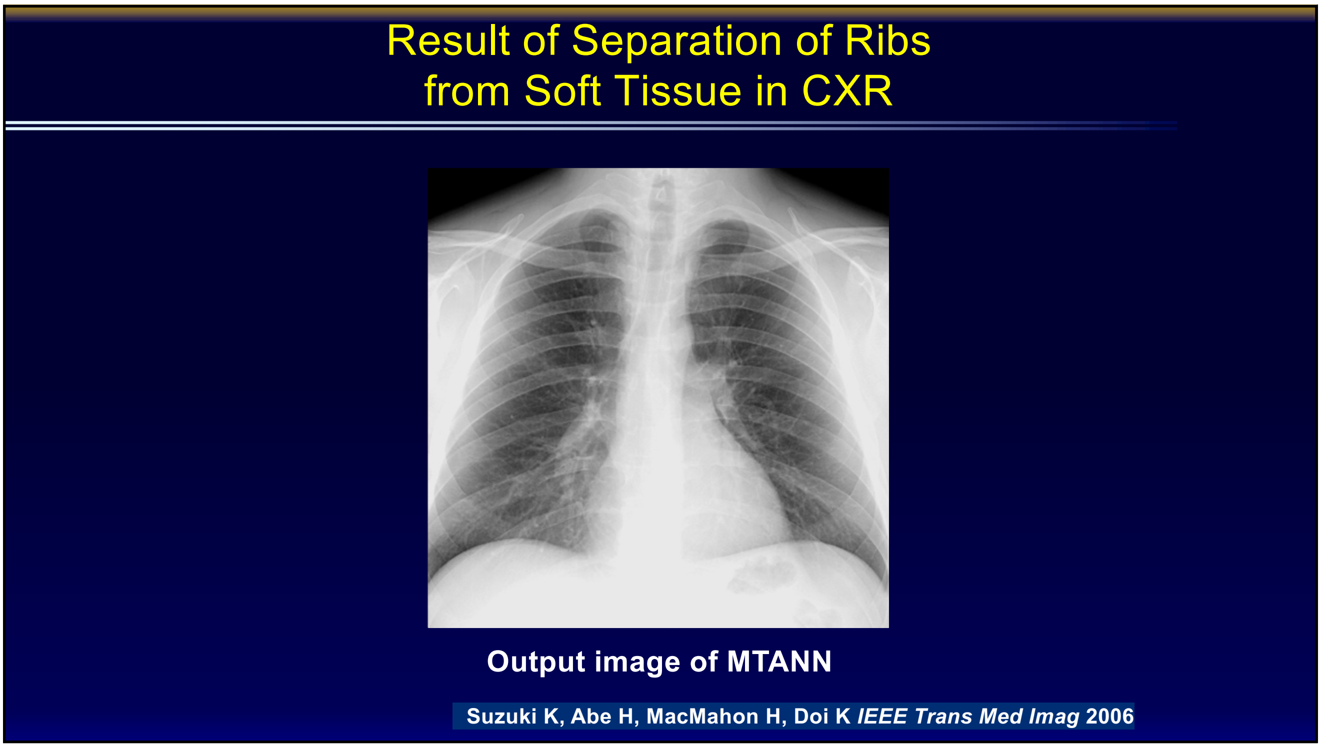
Result of Separation of Ribs from Soft Tissue in CXR
Output image of MTANN
Suzuki K, Abe H, MacMahon H, Doi K IEEE Trans Med Imag 2006

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Rib Suppression by MTANN

Original chest image | MTANN soft-tissue image

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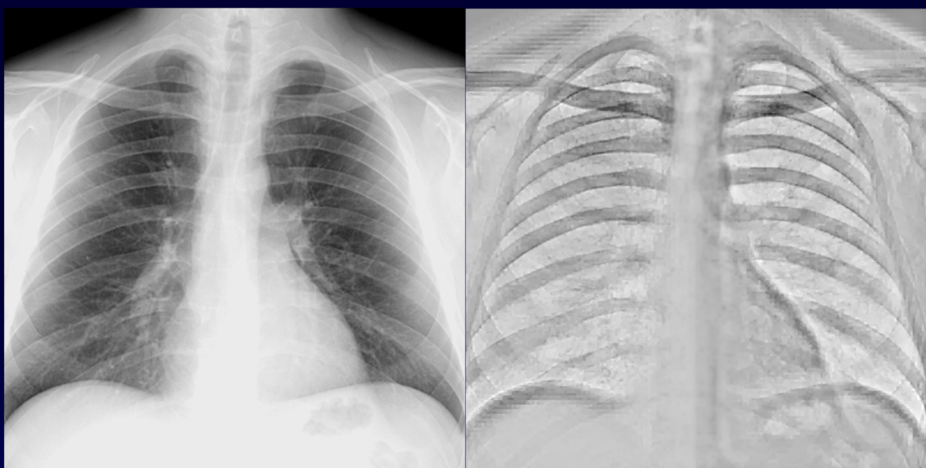
Rib Separation by MTANN



Original chest image | MTANN bone image

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Comparison with Dual-Energy Soft-Tissue Image

MTANN soft-tissue image

“Gold-standard” dual-energy soft-tissue image

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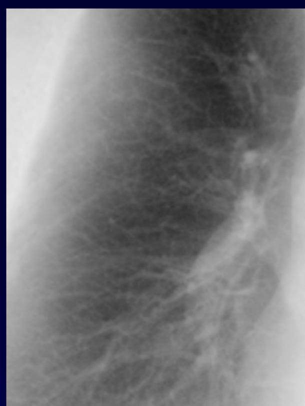
Comparison of MTANN Soft-tissue Image with Dual-energy Soft-tissue Image[1)]

Original CXR

MTANN soft-tissue image



“Gold standard” dual-energy soft-tissue image

*Deep learning bone removal[2)] after our work

1) Suzuki K, et al. *IEEE Trans Med Imag* (2006)
2) Yang W, et al. *Med Imag Anal* (2017)

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Results for Cancer Cases

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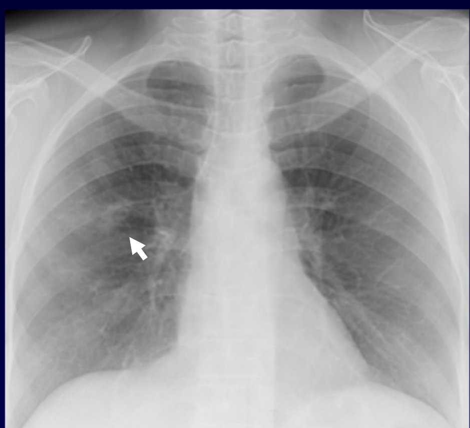
Improved Conspicuity of Nodule with MTANN



Original chest image with nodule

Our MTANN soft-tissue image

Chen S, Suzuki K. *IEEE TMI* 2014

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Comparison of Our MTANN "Virtual Dual-Energy" Imaging with Conventional Dual-Energy Imaging

- Our technique for separation of ribs from soft tissue requires:

  1. **No specialized equipment,**
  2. **No additional radiation dose to patients,**
  3. **But only software.**

- Our technique is applicable to any chest radiographs acquired with a standard radiography system ($3B global market).

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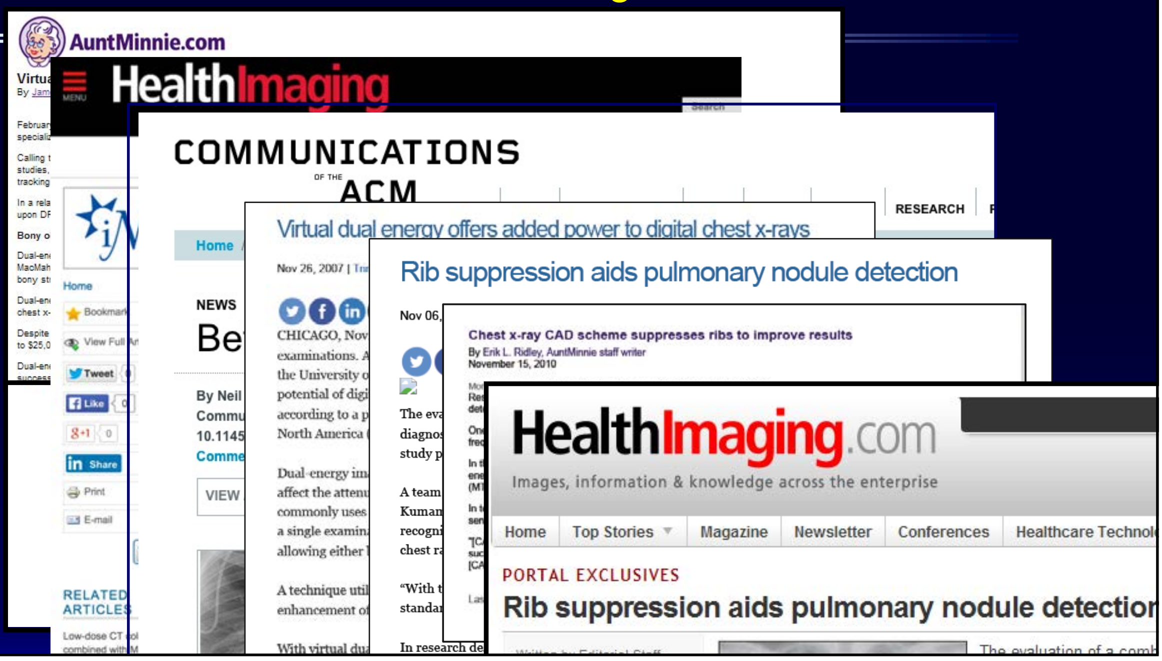
Press Coverage



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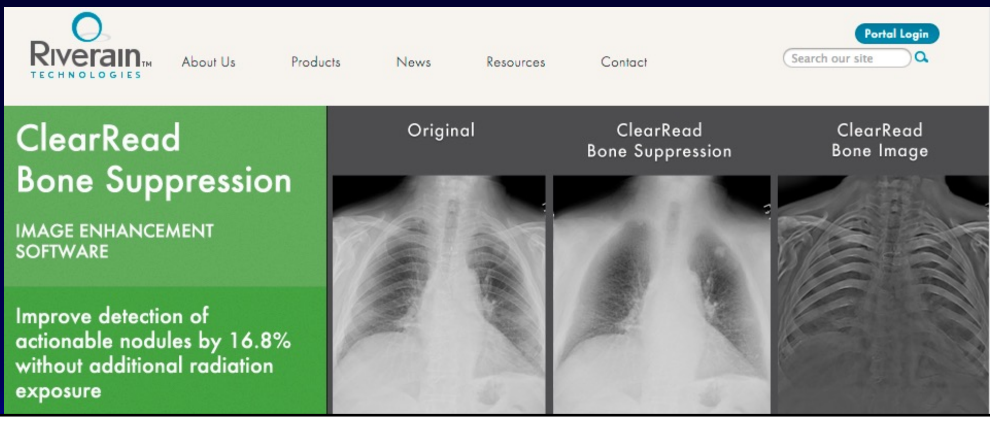
Translation of Research in Clinical Practice - SoftView by Riverain Technologies -

- U of Chicago licensed my patents and code for the VDE technology to Riverain Technologies (Miamisburg, OH)
  - 08/2008: SoftView announcement
  - 03/2010: FDA approval (First FDA-approved deep-learning product)



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Radiation Dose Reduction in CT: Toward Sub-mSv CT Exams

in collaboration with Kazuo Awai[b)], MD, PhD, Wataru Fukumoto, MD, Toru Higaki, PhD

Department of Radiology
Hiroshima University, Japan

1) K Suzuki et al. *RSNA* (2012)
2) K Suzuki, et al. LNCS-MLMI (2017)

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Radiation Dose Reduction in CT: Motivation

- CT scanners can expose patients to cumulative radiation doses which may elevate individuals' lifetime risk of developing cancer
- Studies[1-3] estimated
  - CT scans in the U.S. might be responsible for up to 1.5-2.0% of cancers
  - CT scans performed in the U.S. in 2007 alone would result in 29,000 new cancer cases in future years
  - CT scans of children each year would cause 4,870 future cancers in the U.S.

1) DJ Brenner et al. *N. Engl. J. Med.* (2007)
2) AB de González et al. *JAMA Intern. Med.* (2009)
3) DL Miglioretti et al. *JAMA Pediatrics* (2013)

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Would you be happy if we could reduce the radiation dose in CT scans by 90%?

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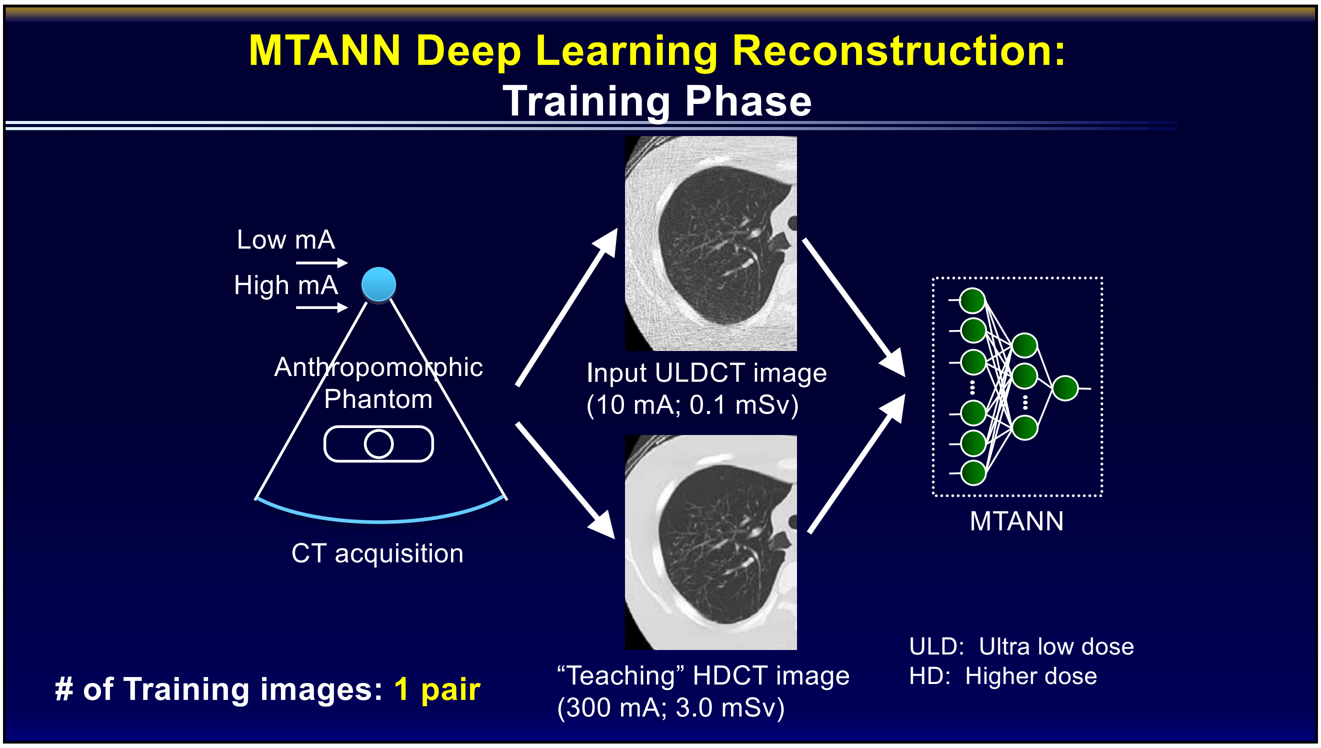
MTANN Deep Learning Reconstruction:
Training Phase
Low mA
High mA
Anthropomorphic
Phantom
CT acquisition
Input ULDCT image
(10 mA; 0.1 mSv)
MTANN
"Teaching" HDCT image
(300 mA; 3.0 mSv)
# of Training images: 1 pair
ULD: Ultra low dose
HD: Higher dose

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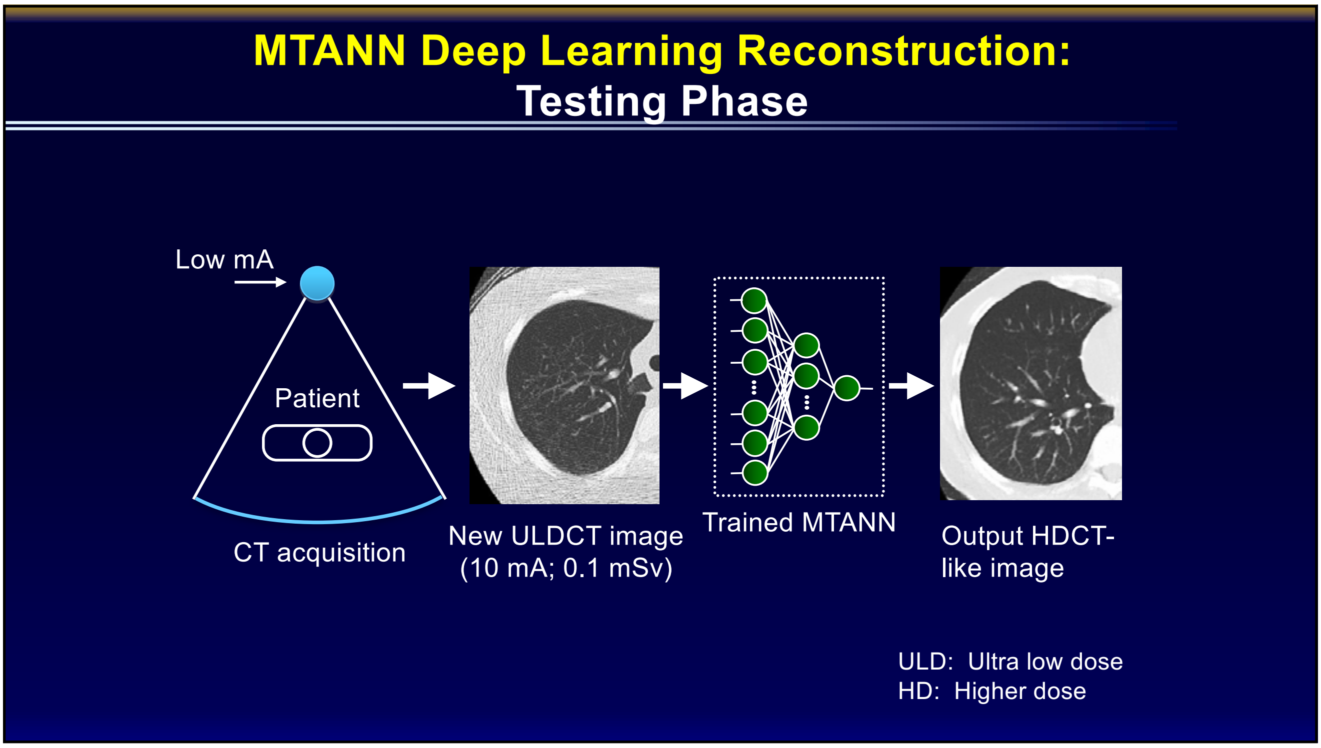
MTANN Deep Learning Reconstruction:
Testing Phase
Low mA
Patient
CT acquisition
New ULDCT image
(10 mA; 0.1 mSv)
Trained MTANN
Output HDCT-
like image
ULD: Ultra low dose
HD: Higher dose

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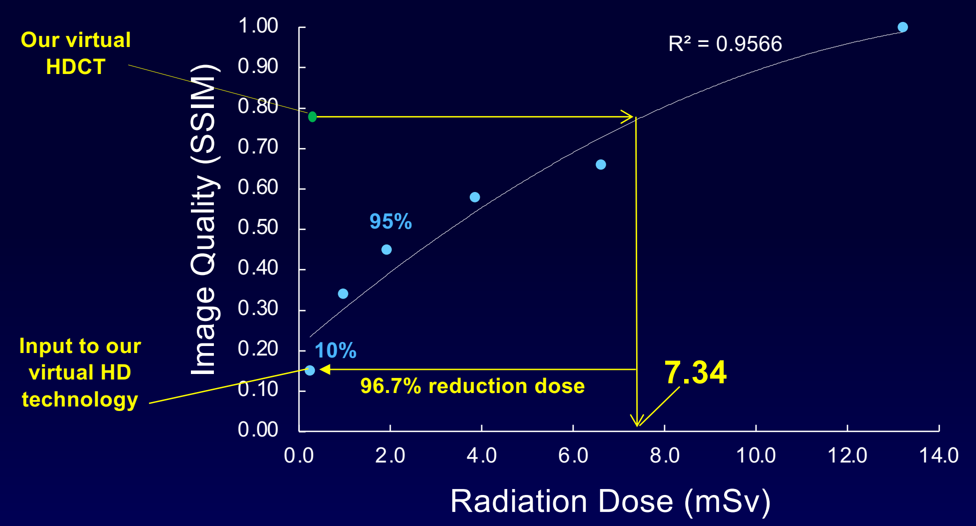
Estimation for Equivalent Radiation Dose from Image Quality (SSIM)



SSIM = structural similarity index (Wang Z et al. *IEEE TIP*, 2004)

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Translation of Research in Clinical Practice with AlgoMedica

- University of Chicago licensed my patents and code to a venture company, AlgoMedica (Sunnyvalle, CA)
- 09/2016 obtained FDA approval
- 12/2016 commercial product PixelShine™ announced

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Conclusion

- Small-data deep learning requires small data to achieve high performance
  - MTANN small-data deep learning was able to achieve the state-of-the-art performance with only a dozen images to train
  - Small-data MTANN was able to diagnose rare cancer
- Deep learning (AI) imaging would provide novel medical imaging that would enhance lesions and anatomy
  - “virtual dual-energy” imaging for separating bones & “virtual high-dose” imaging for reducing radiation dose (> 90%) in CT
- Small-data deep learning would be useful for applications in the small-data domain

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