醫療影像人工智慧及深度學習技術

Medical image AI and Deep Learning

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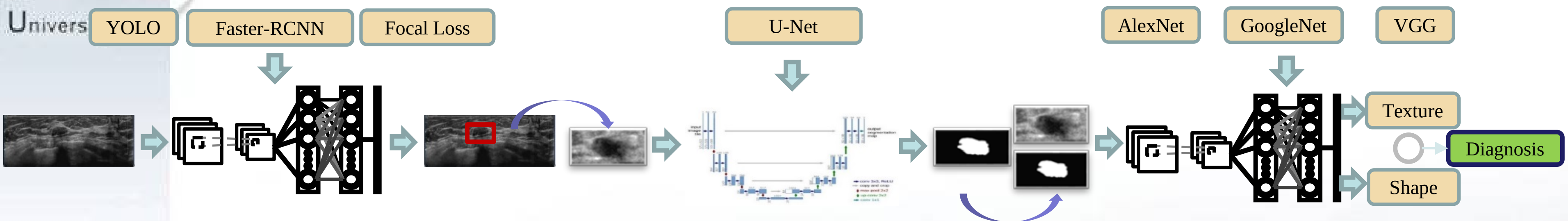
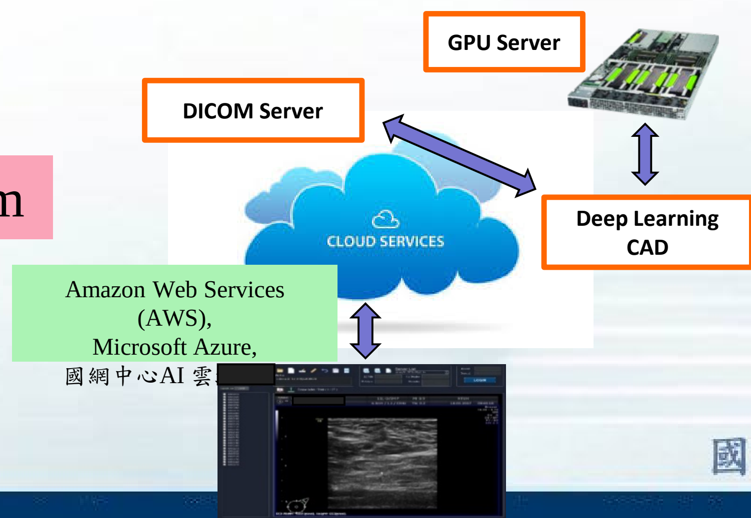
AI Innovation Research Project (2018-2021)
科技部AI創新研究中心專案計畫(107-110)

- **supported by the AI Innovation Research Program of Ministry of Science and Technology (MOST)**
- **Automated Breast Ultrasound Computer-aided Detection and Diagnosis Using Deep Learning**
  - **Co-PI: Dr. Huang, and Dr. Chang**



ABUS DL System

2D BUS Cloud System

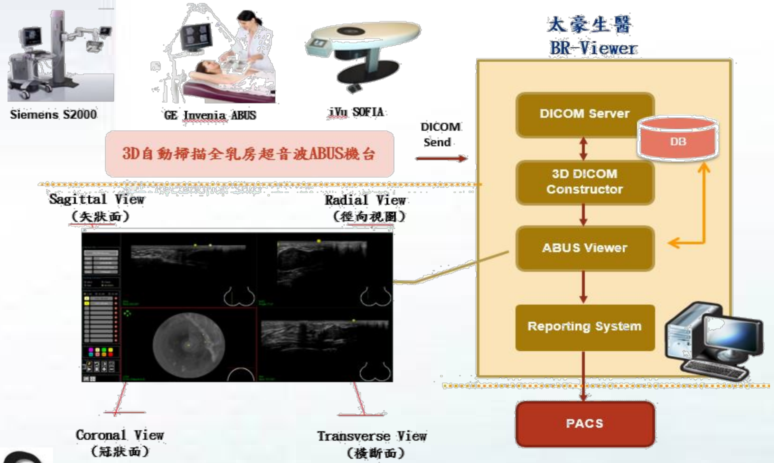


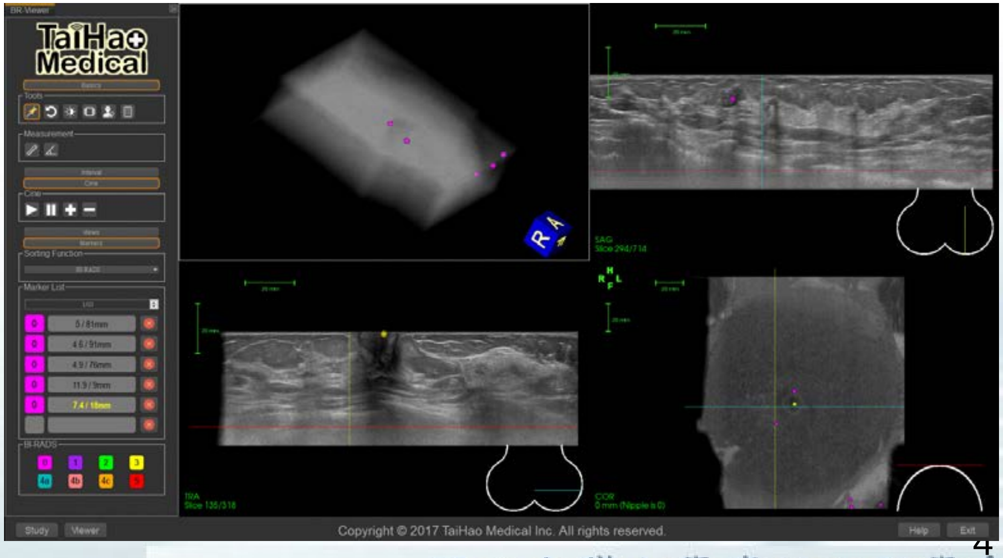
Technology Development Program for Academic (TDPA, 2011-2014)

- This TDPA project was supported by the Ministry of Economic Affairs (MOEA) to develop
  - a CADe system for ABUS
  - a CADx system for B-mode US/elastography
  - breast US GPS/recoding System
- The Co-PIs are Dr. Chou from VGH, Dr. Huang, and Dr. Chang from NTUH.
- 25 international journals and 12 international conference papers
  - Three IEEE Trans. MI papers have been published.
- The CADe and CADx systems have been transferred to TaiHao Medical Inc. (http://taihaomed.com/)

Automated Breast US Viewing System

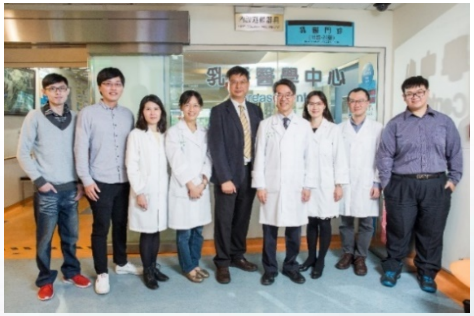
- developed by NTU has been transferred to TaiHao Medical Inc, Taiwan.
  - ✓ 2016 FDA- K151075, BR-ABVS Viewer 1.0
  - ✓ 2017 TFDA- 衛部醫器製字第005760號(BR-Viewer), 2018第006147號(BR-Viewer 1.2)
- to assist the physician to visualize 3-D ABUS images.
- Changhua Christian Hospital, Taiwan will use this system with CADe for dense breast screening.

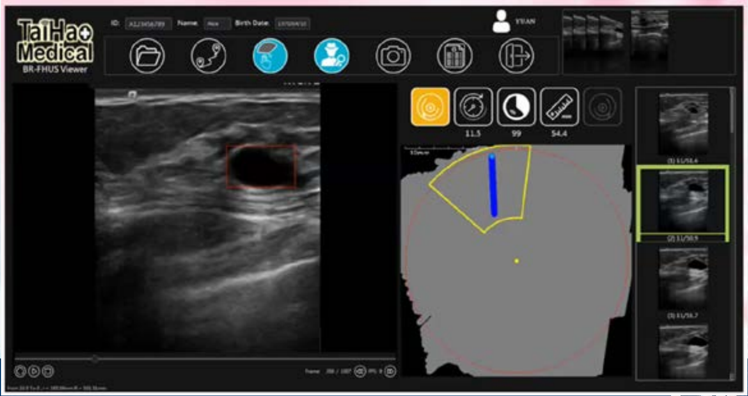




Free-hand Whole Breast US Smart System

- developed by NTU has been transferred to TaiHao Medical Inc, Taiwan.
  - ✓ 2017 FDA Approvals
    - ✓ K171309 BR-FHUS Navigation 1.0
    - ✓ K171709 BR-FHUS Viewer 1.0
  - ✓ 2018 TFDA Approval
    - ✓ 衛部醫器製字第005966號(BR-FHUS Navigation 1.0, BR-FHUS Viewer 1.0)
- indicated for use to alert sonographer of possible missing area during breast screening and assists radiologists to review 2-D breast ultrasound images efficiently





產學合作計畫-太豪生醫

- **2D乳房超音波影像電腦輔助診斷系統 (107/10/01~108/09/30)**

工商時報 智慧照護篇
https://ctee.com.tw
中華民國108年6月27日 星期四

超音波乳房腫瘤輔助診斷系統 太豪生醫下半年啓動臨床實驗

文／李水蓮

致力超音波乳腺腫瘤篩檢解決方案的太豪生醫，繼之前兩項新醫材產品通過美國FDA510K及台灣衛福部醫療器材上市許可後；該公司利用新一代AI技術研發的「全乳超音波乳房腫瘤電腦輔助診斷系統」，日前亦通過「財團法人醫藥品查驗中心」之指標輔導案件，預計於下半年可啟動臨床實驗等工作。

太豪生醫研發的「全乳超音波乳房腫瘤電腦輔助診斷系統」，目前應用在乳篩超音波影像上的良惡性判讀數據，其敏感度已達96%，特異性亦可達71%，目前國內外尚無類似之產品通過美國FDA上市許可。

6月初BIO生技展中，太豪生醫在費城天普大學「2019台灣生技創新創業論壇─全球生技領袖高峰會」應邀上台報告人工智慧於醫療影像的應用，吸引超過300位海內外專家參與。另外在生技展會場展示該公司超音波全乳腺腫瘤篩檢解決方案，也受到來自全球的專家及投資人矚目。

太豪生醫去年底與日商笛卡爾公司簽定戰略合作合約後，其「超音波全乳智慧掃描檢視系統」已於日本申請上市許可中。今年再度引進益鼎創投與經濟部工業局「加強投資策略性製造業實施方案」的資金，除持續在台灣擴展人工智慧研發團隊外，並預計於下半年度在日本成立『AI人工智慧醫療軟體開發研究所』，持續研發更多的高階智慧醫療器材。

有鑑於近幾年肺癌發生率及死亡率躍昇為台灣及日本十大癌症之前三名，公司亦決定研發新一代的肺部CT 人工智能發展計畫，以因應人工智慧應用在醫療影像業務需求的蓬勃發展。

以1A期肺癌為例，病人5年存活率可達到80%以上，遺憾的是有一半以上的肺癌病人在診斷時已經是末期，5年的存活率不到5%。配合新一代的肺部電腦斷層輔助偵測診斷腫瘤人工智能系統的應用，相信必能有效的協助臨床醫師診斷。

●太豪生醫技術專家於2019台灣生技創新創業論壇中介紹全乳超音波乳房腫瘤電腦輔助診斷系統。圖／太豪生醫提供

- **3D全乳房自動超音波電腦輔助偵測系統 (108/06/01~109/05/31)**

Collaboration with Japanese Company

- Our collaboration with a Japanese company focuses on medical AI
- They have invested the TaiHao Medical Inc, Taiwan
- Also signed a 10- year agency agreement for the free-hand whole breast US smart system
- They begin to apply for the Japan PMDA regulation

中華民國107年11月8日／星期四 http://ctee.com.tw 健康照護 D1 工商時報

太豪結盟日商 推AI新醫材

與笛卡爾簽訂「超音波全乳智慧掃描檢視系統」合約，共同造福女性同胞

文／李水蓮

屢獲國內外各項醫療AI新創醫材大獎的太豪生醫，致力於提供超音波乳腺腫瘤篩檢解決方案，目前已有兩項新產品「超音波全乳智慧掃描檢視系統」及「3D自動超音波閱片系統」通過美國FDA510K及台灣衛福部醫療器材上市許可，並獲國內外臨床醫師及放射科醫師們的肯定，本月底亦將進軍美國放射科醫學會RSNA年度展覽，預期將為公司帶來更多之商機與訂單。

太豪生醫日前已與日商笛卡爾公司共同簽訂「超音波全乳智慧掃描檢視系統」共十年期逾30億新台幣之經銷合約，雙方將進行緊密之合作關係並在台灣與日本共同啟動臨床實驗。

太豪生醫總經理賴信宏表示，由於目前日本與台灣乳房X光篩檢率皆不到4成，待本項超音波乳篩新醫材產品通過日本衛生主管機關PMDA（日本政府獨立行政法人醫藥品醫療機器總合機構）上市許可後，將可有效彌補及改善現有乳房X光篩檢率不足之問題，以達成早期發現、早期治療快速篩檢腫瘤並造福女性同胞之目的。

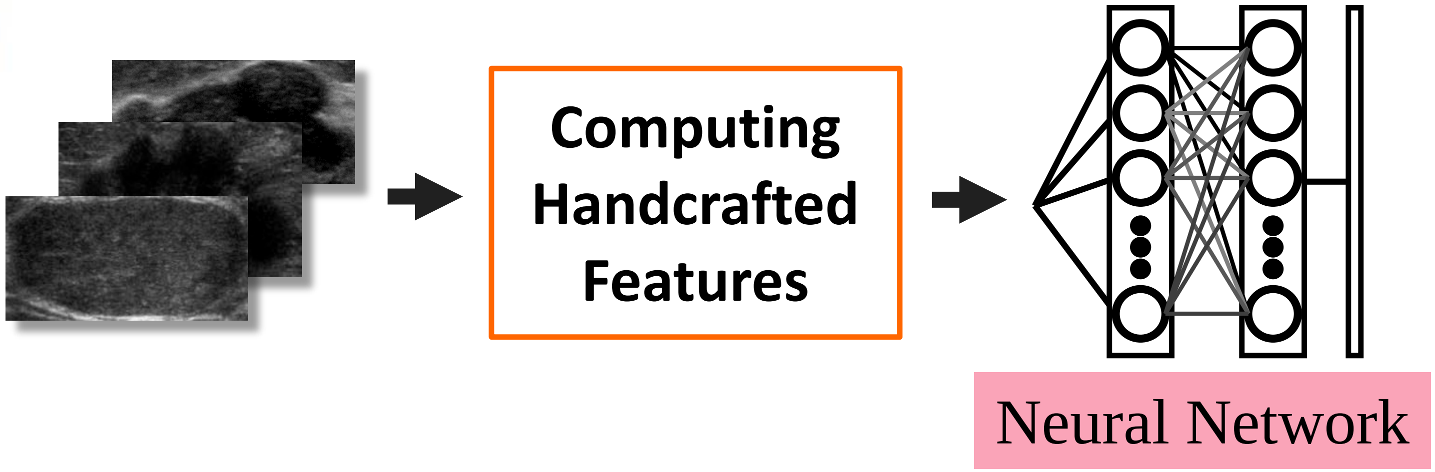
同時雙方並已簽訂戰略合作合約，將共同推動數項新AI醫療器材開發專案，日商笛卡爾公司並結合日本財團法人醫療AI機器開發機構（MDSA）一起舉辦AI醫療人才養成講座，此Web講座將針對醫師、放射線技師、臨床檢查技師等開辦一系列之AI醫療網路講座，目前已進入第二期招生中。

●太豪生醫總經理賴信宏（前排左起）、日企MDSA理事長所康生博士、研究員崔日博士、以及太豪生醫團隊合照。 圖／業者提供

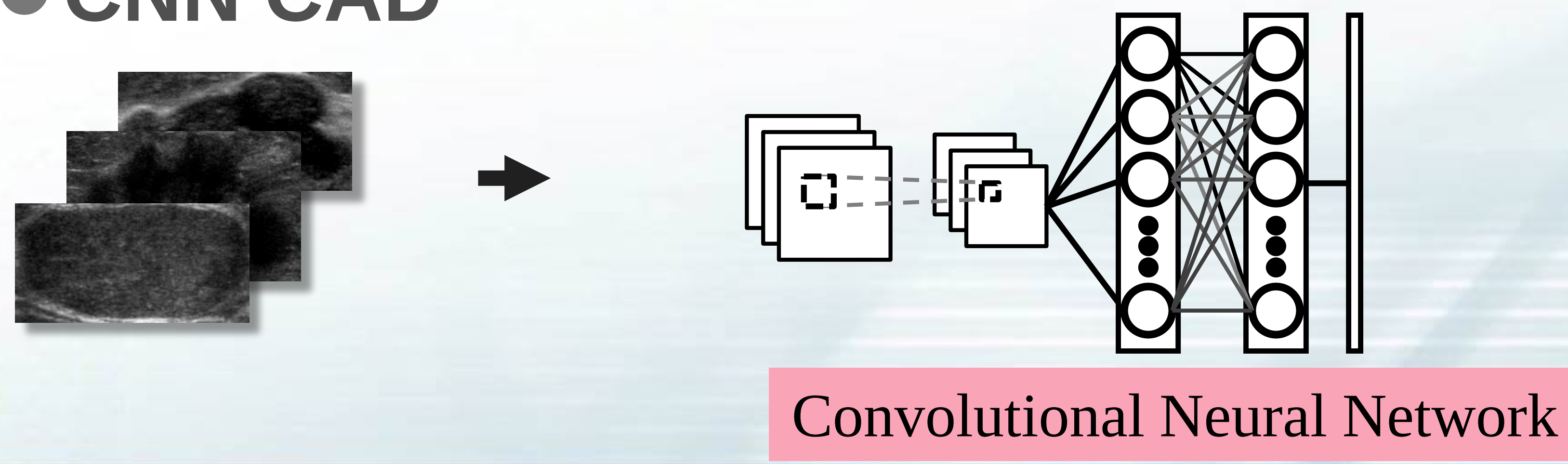
MDSA理事長所康生博士日前亦率領其團隊成員一起至太豪生醫共同商討後續各項講座及新專案開發事宜，如利用人工智慧解析肺部的CT畫像，以進行肺癌初期診斷、透過人工智慧解析口腔病變等，深信在明後年將可推出更多項AI新醫療器材產品，輔助更多不同科別之臨床醫師進行早期病變之判讀，並利用AI新技術造福全人類。

CNN vs. NN

- **Conventional CAD**

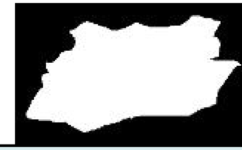
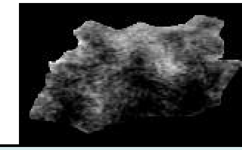


- **CNN CAD**



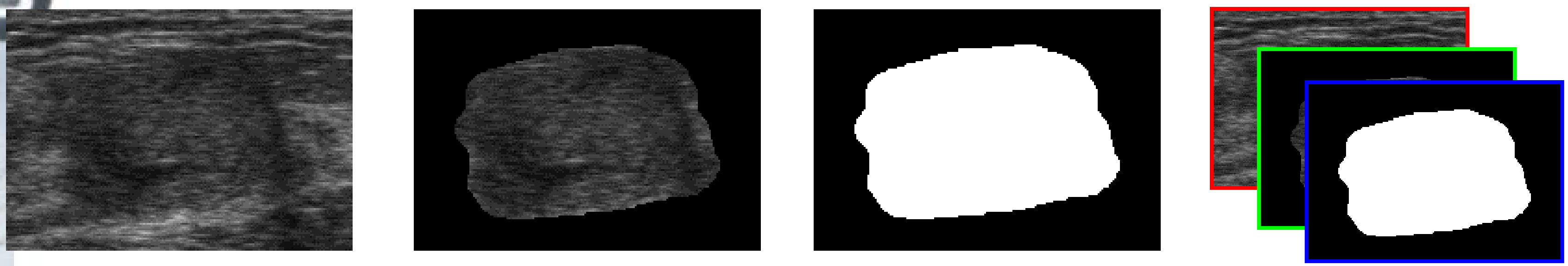
Comparison of Different CNNs

- **Tumor ROI, tumor shape, and tumor region**

Method	Depth	Performance		
		Accuracy	Sensitivity	Specificity
VGG	16	88.72% (299/337)	83.78% (124/148)	92.59% (175/189)
VGG	8	86.05% (290/337)	80.41% (119/148)	90.48% (171/189)
ResNet	18	86.65% (292/337)	81.76% (121/148)	90.48% (171/189)
ResNet	50	86.05% (290/337)	86.49% (128/148)	85.71% (162/189)
ResNet	101	86.05% (290/337)	84.46% (125/148)	87.30% (165/189)
DenseNet	40	87.83% (296/337)	89.19% (132/148)	86.77% (164/189)
DenseNet	121	89.32% (301/337)	87.84% (130/148)	90.48% (171/189)
DenseNet	161	**90.80% (306/337)**	**89.86% (133/148)**	**91.53% (173/189)**

Comparison of Different Image Types



Method	Dataset	ACC (%)	SEN (%)	SPEC (%)	Precision (%)	F1 score (%)
DenseNet-121	1	86.35 (291/337)	77.70 (115/148)	93.12 (176/189)	89.84	83.33
DenseNet-40	2	87.24 (294/337)	83.11 (123/148)	90.48 (171/189)	87.23	85.12
VGG-Like	3	84.27 (284/337)	81.08 (120/148)	86.77 (164/189)	82.76	81.91
DenseNet-161	4	90.80 (306/337)	89.86 (133/148)	91.53 (173/189)	89.26	89.56

CNN Experiments

- **1,512** tumors from 1,227 cases
  - 477 malignant tumors and 1,035 benign tumors
- The methods have the **same performance statistically** (all *p-values > 0.05*)

Method	AUC	ACC (%)	SENS (%)	SPEC (%)
CNN (VGG-Lite)	0.91	83.73 (1266/1512)	74.00 (353/477)	88.21 (913/1035)
NN (Ranklet)	0.90	83.60 (1264/1512)	75.47 (360/477)	87.34 (904/1035)
VGG-Lite + RANK	0.92	84.39 (1276/1512)	73.38 (350/477)	89.47 (926/1035)

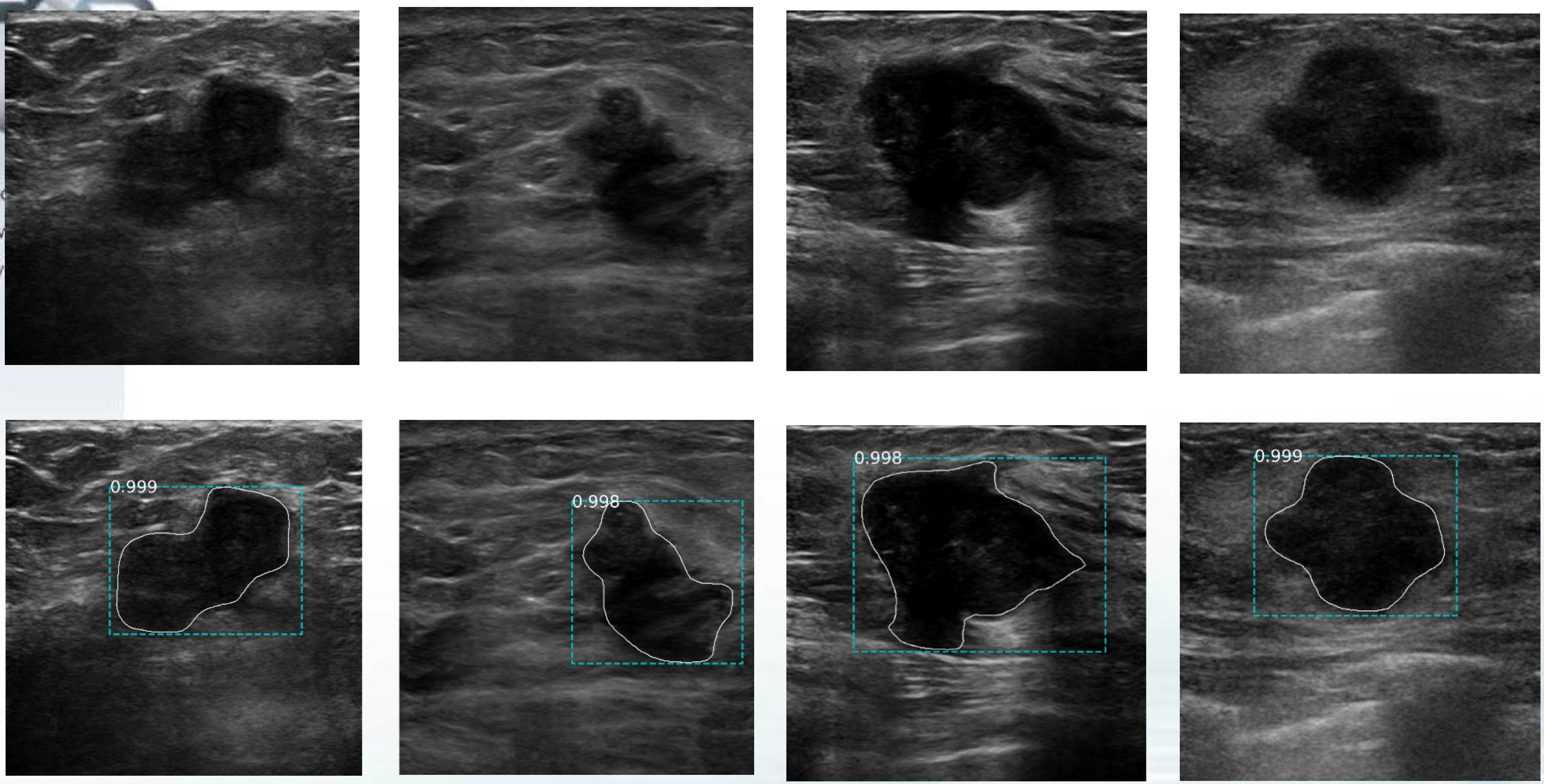
Distant Metastasis Prediction

- Distant metastasis: 147 cases
- Control group: 147 cases

15 pixels 20 pixels

	Accuracy [%]	Sensitivity [%]	Specificity [%]
Tumor	78.8 ± 4.2	89.6 ± 10	69.6 ± 11.2
Peritumor 20 px	84.4 ± 5.7	**91.2 ± 5.2**	78.6 ± 8.9
Peritumor 15 px	**84.8 ± 3.5**	88.8 ± 5.2	81.3 ± 7.1

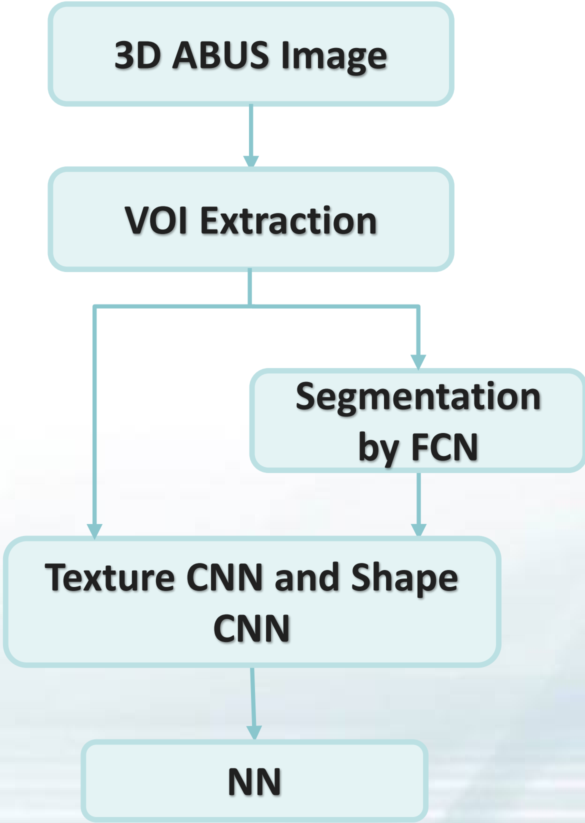
Tumor Detection and Segmentation



Average dice coefficient = 0.851

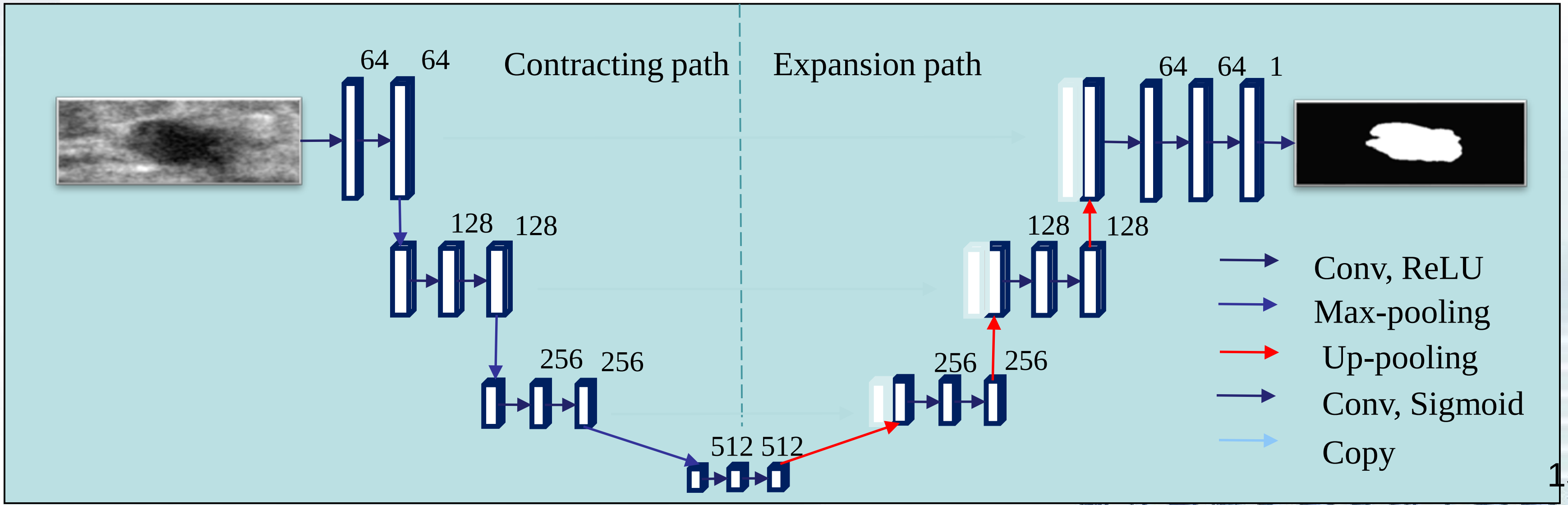
ABUS Deep Learning CADx

- Two 3-D CNNs, texture CNN and shape CNN, with different architecture were used to obtain the texture and the morphology features.
- The input of the shape CNN was the mask image of the VOI generated from the fully convolutional network (FCN).
- Then, the features extracted from the two CNNs were concatenated as the input of an artificial neural network (NN) for classification.



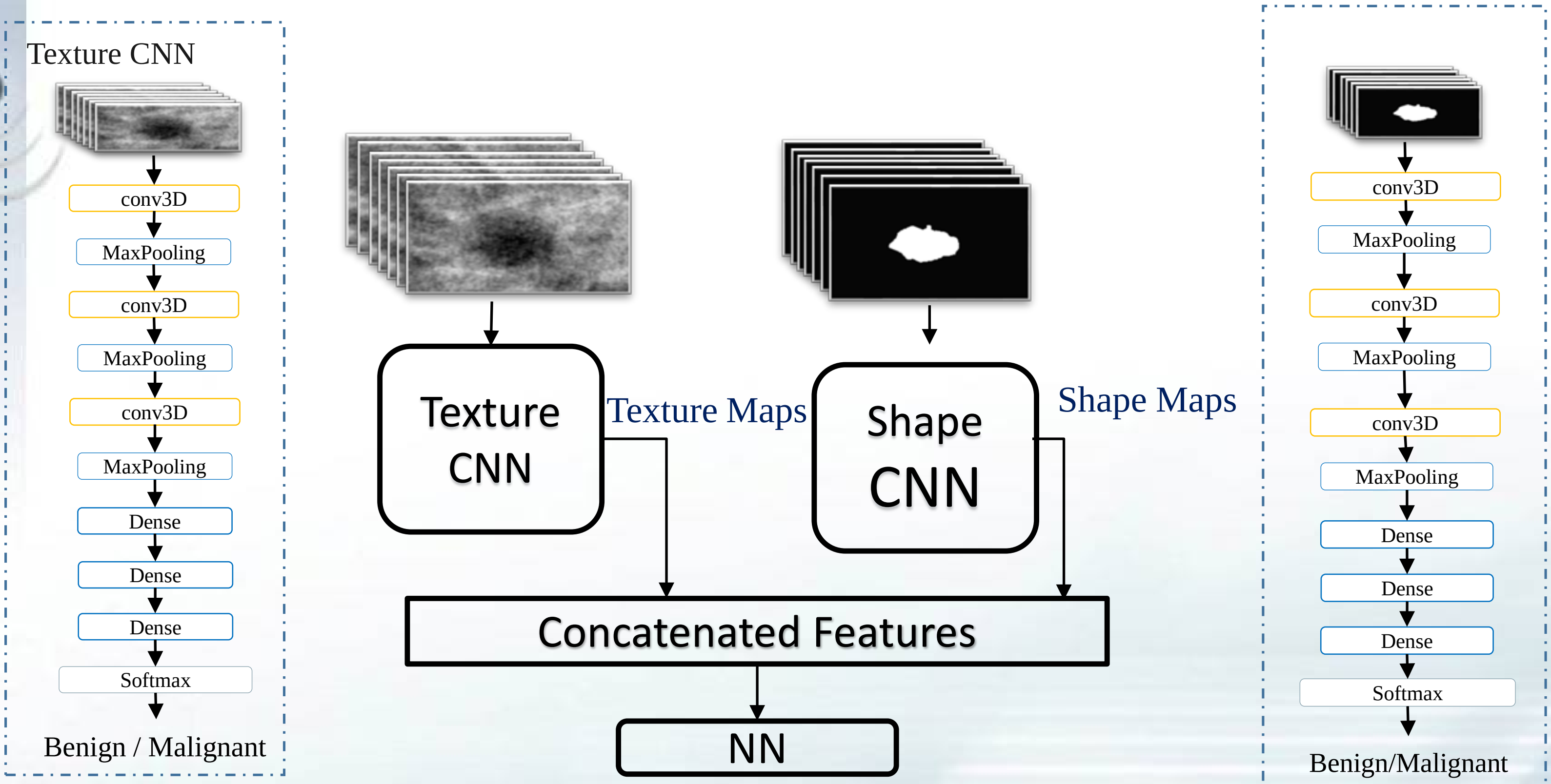
Tumor Segmentation

- FCN contains contracting path and expansion path.
  - **Contracting path** is the typical architecture of a convolution network.
  - **Expansion path** is for increasing the resolution of the feature maps from contracting path.



CNN Feature Extraction

- Two different structured CNN models with Texture CNN and Shape CNN



Experiments

- A total of 77 tumors from 74 patients (age: 50.06±13.9)
  - 35 benign tumors (size: 12.1±8.92 mm)
  - 42 malignant tumors (size: 13.0±7.4 mm)
- Compared with the previous **handcrafted** features using the proposed classification NN model.

	Accuracy(%)	Sensitivity(%)	Specificity(%)	PPV(%)	NPV(%)
GLCM + Ranklet + Ellipse	75.32 (58/77)	83.33 (35/42)	65.71 (23/35)	74.46 (35/47)	76.66 (23/30)
Texture CNN + Shape CNN	85.71 (66/77)	92.85 (39/42)	77.14 (27/35)	82.97 (39/47)	90.00 (27/30

Our Previous IEEE TMI ABUS Works

- **Computer-Aided Tumor Detection Based on Multi-Scale Blob Detection Algorithm in Automated Breast Ultrasound Images**
  - **IEEE Transactions on Medical Imaging, vol. 32, no. 7, pp. 1191-1200, July 2013.**

- **Multi-dimensional tumor detection in automated whole breast ultrasound using topographic watershed**
  - **IEEE Transactions on Medical Imaging, vol. 33, no. 7, pp. 1503-1511, July 2014.**

- **Tumor Detection in Automated Breast Ultrasound Using 3-D CNN and Prioritized Candidate Aggregation**
  - **IEEE Transactions on Medical Imaging, vol. 38, no. 1, pp. 240-249, Jan 2019.**

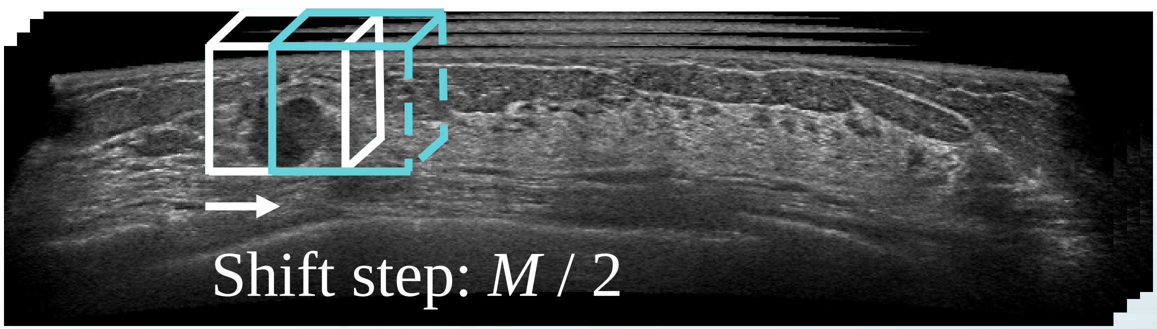
2016 IF=3.942 => 2018 7.816

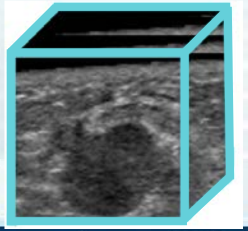
7.816

Impact Factor

VOI Extraction

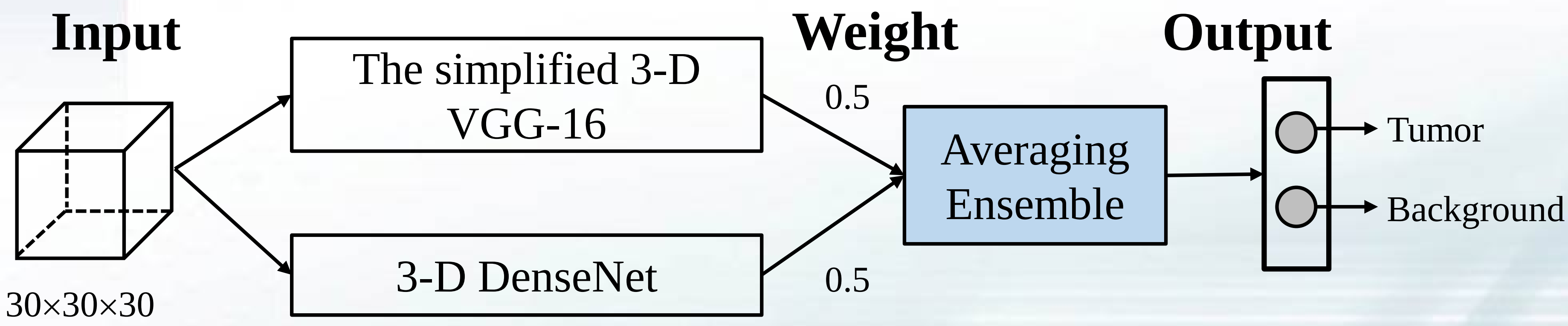
- The sliding window approach with a fixed size **window *M*** and the **shift step *M*/2** is employed for VOI extraction.
- In order to detect tumors with different sizes, **three different window sizes** {*M* = 20, 25, 35 mm} are used.





3-D Tumor Detection CNN

- The **ensemble method** is proposed for combining
  - The simplified 3-D VGG-16
  - The 3-D densely connected convolutional network (DenseNet)



National Taiwan University

Focal Loss for Data Imbalance

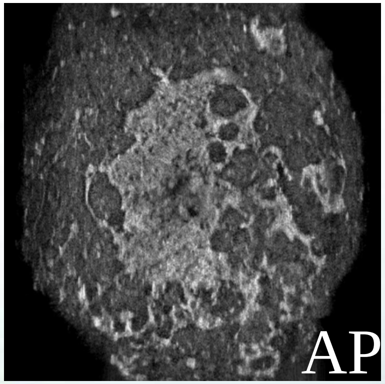
- There are 3,000-4,500 VOIs generated from an ABUS image, but only 3-5 VOIs covers or overlaps with the tumor volumes.
  - That is, compared to the **background** samples, the number of **tumor** samples is too small.
- This **data imbalance problem** will be encountered during training and cause inefficient training and model degeneration.
- Therefore, the **focal loss** is adopted as the loss function in our networks.

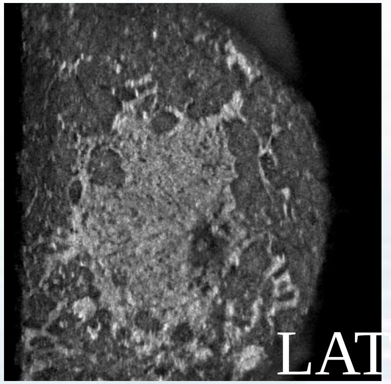
$$\mathrm{FL}(p_t) = -\alpha_t \times (1 - p_t)^{\gamma} \log(p_t)$$

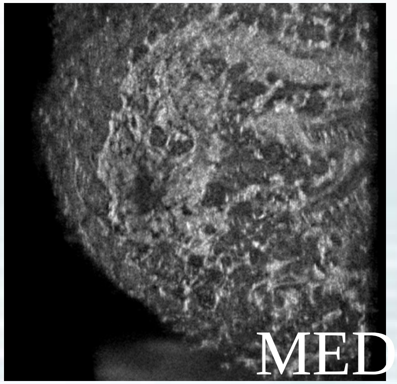
  - During training, the focal loss with $\gamma = 2$ and $\alpha_t = 0.25$ is adopted in both the simplified 3-D VGG-16 and 3-D DenseNet.

Experimental Results

- GE ABUS images from **Seoul National University Hospital** are used in this study
  - 246 cases
    - Each case consists of 4-6 passes
  - 333 pathology-proven tumors
    - 254 malignant and 79 benign tumors.







Focal Loss Results

- Comparison of tumor detection with or without **focal loss** function at various sensitivity
  - 3-D DenseNet is better than 3-D simplified VGG-16
  - Focus Loss can reduce the FP numbers
  - Ensemble of two CNNs can reduce the FP numbers

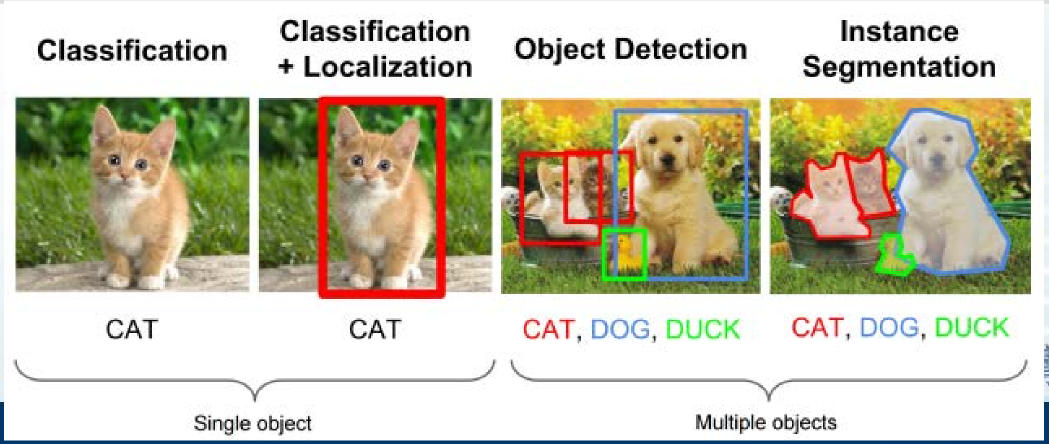
2019 IEEE TMI paper

Sensitivity (%)	FPs per pass (case)				
	3-D simplified VGG-16		3-D DenseNet		Proposed Ensemble
	Cross Entropy	Focal Loss	Cross Entropy	Focal Loss	
84.8	12.7 (74.7)	9.4 (54.8)	4.9 (28.9)	4.2 (24.6)	3.7 (21.7)
90.9	19.6 (114.8)	15.6 (91.2)	9.8 (57.4)	5.5 (32.4)	4.6 (27.1)
95.3	36.4 (214)	34.3 (201.4)	16.3 (95.6)	13.9 (81.2)	6.0 (34.8)
98.1	69.8 (410.3)	42.3 (248.4)	32.7 (192.2)	19.9 (116.8)	15.7 (91.4)
100.0	-	-	-	-	21.6 (126.2)

Deeping Learning for ABUS One-stage CADe

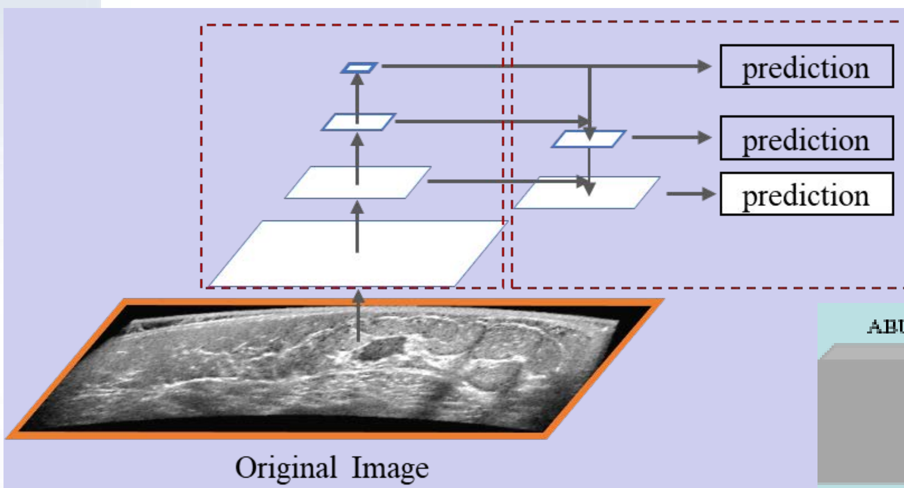
Object Detection

- Object Detection
  =**Object Localization** + **Feature Extraction** +**Image Classification**
- Two-stage vs One-stage
  - Two-stage = **Region Proposal** + **Recognition**
    - R-CNN, fast R-CNN, faster R-CNN
  - One-stage: **YOLO** (You only look once), Single Shot Detector (**SSD**)

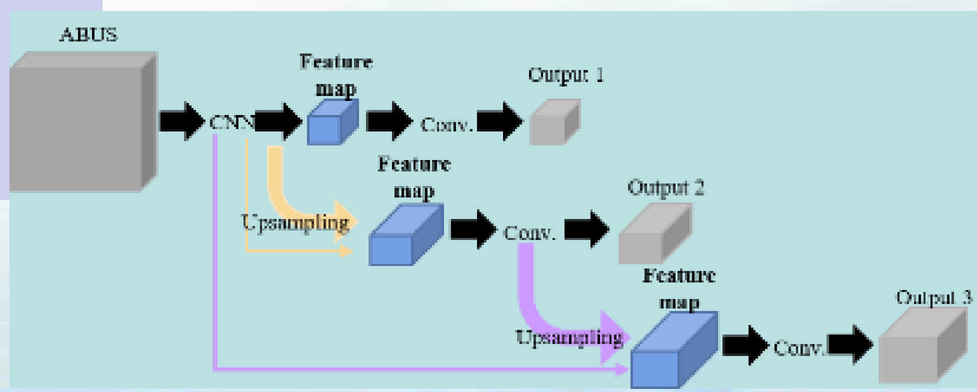


ABUS One-stage CADe

- YOLOv3
- Feature pyramid network (FPN)
  - Multi scale for different tumor sizes
- The execution time is **extremely fast** (<1 second)
  - Predicts with **one take (640×160×640)**, instead of sliding window method
  - GeForce RTX 2080 Ti graphic card



YOLOv3 FPN



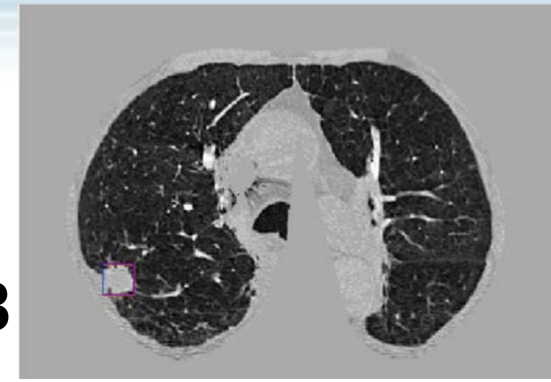
Result

- Sun Yat-sen University Cancer Center, Guangzhou, China, 523 tumors from 258 patients
- Sensitivity: 95%, FPs/Pass: 2.6

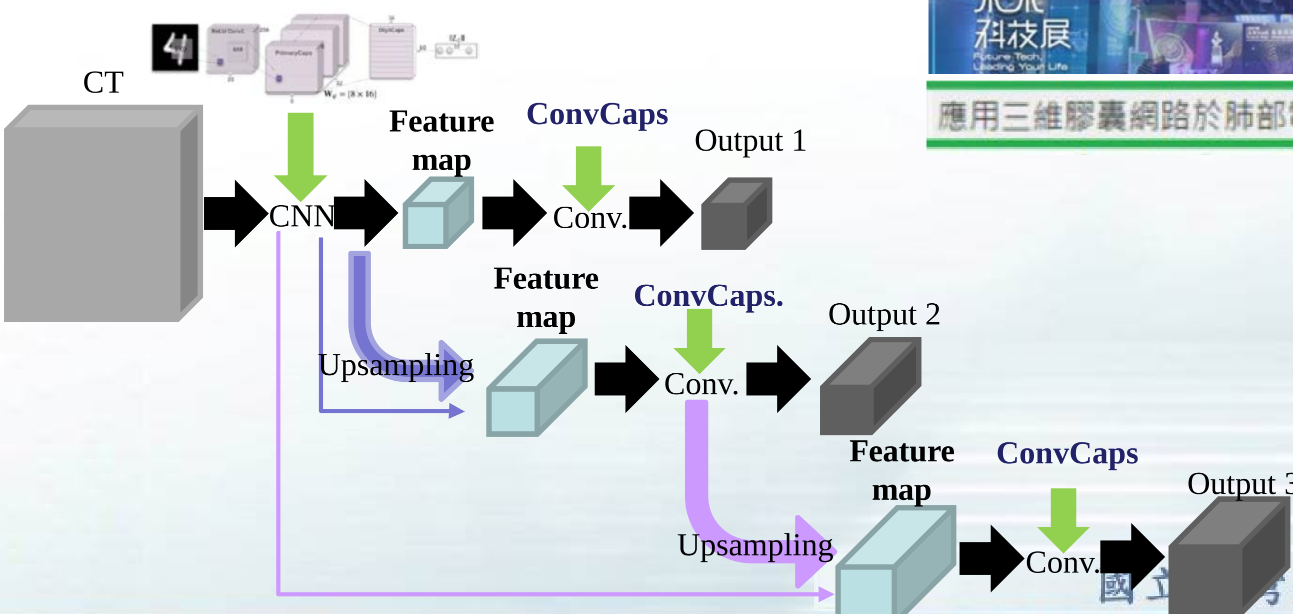
Sensitivity (%)	False positives per pass							
	Proposed				Chiang *et al*			
	Overall	*S*	*M*	*L*	Overall	*S*	*M*	*L*
70	0.3	0.4	0.2	0.3	22.5	-	27.4	6.6
76	0.4	0.6	0.3	0.4	38.2	88.8	-	9.7
81	0.5	0.8	0.8	0.5	59.1	-	59.1	13.6
85	0.7	1.5	0.5	0.6	-	176.1	88.8	20.2
90	1.3	2.4	1.1	1.1	127.0	243.7	127.1	30.7
95	2.6	3.9	1.8	2.9	176.1	-	176.1	88.8
98	21.6	34.3	3.8	34.3	-	-	-	176.1
100	-	46.7	29.4	-	-	-	-	-
Execution time per pass	0.8 s				11 s			

3D Lung CT CAD

- **YOLO and Capsule networks**
- **1186 nodules from 888 CT scans**
- **Sensitivity: 96.1%, FPs/Scan: 8**
- **即將在彰基試用**
- **資拓宏宇即將產學合作**



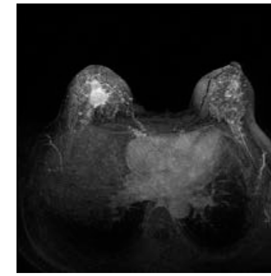
**Ground truth of tumor in red, detected tumors in blue.*



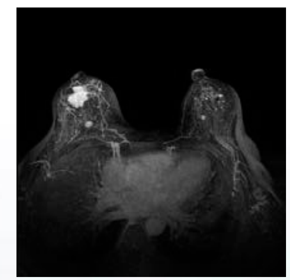
Other Deep Learning Studies

Breast Tumor Biomarker Analysis for DCE-MRI

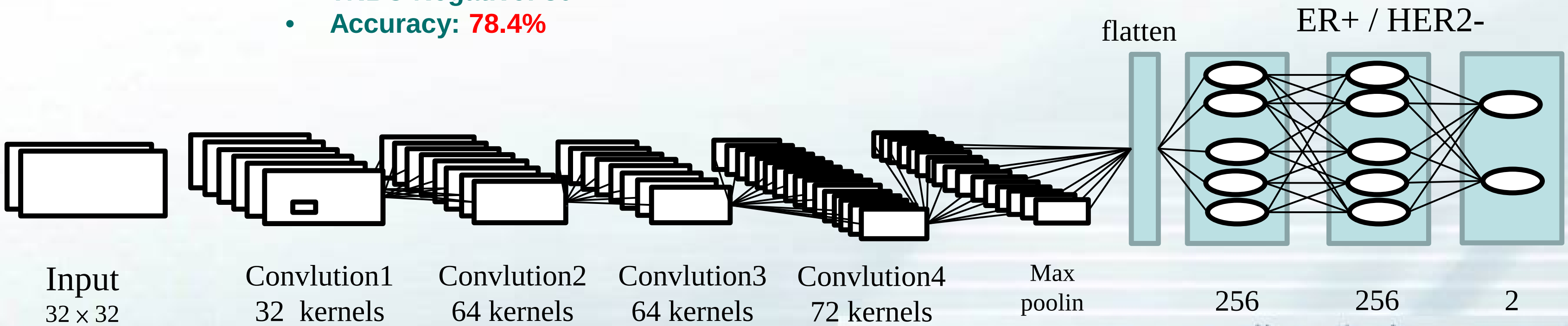
- 102 cases from National Taiwan University Hospital
  - ER:
    - ER Positive: 59
    - ER Negative: 43
    - Accuracy: 74.5%
  - PR:
    - PR Positive: 38
    - PR Negative: 64
    - Accuracy: 72.5%
  - HER2:
    - HER2 Positive: 47
    - HER2 Negative: 55
    - Accuracy: 84.3%
  - TNBC: (ER- /PR- / HER2-)
    - TNBC Positive: 22
    - TNBC Negative: 80
    - Accuracy: 78.4%



ER- / HER2+

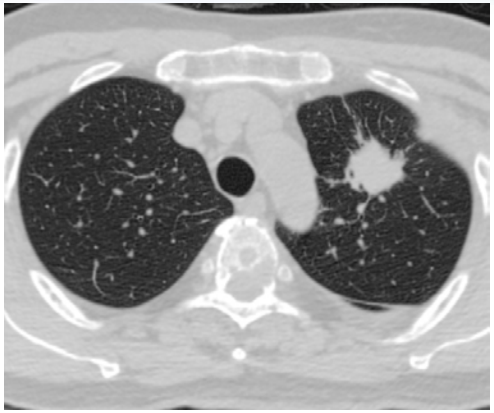


ER+ / HER2-



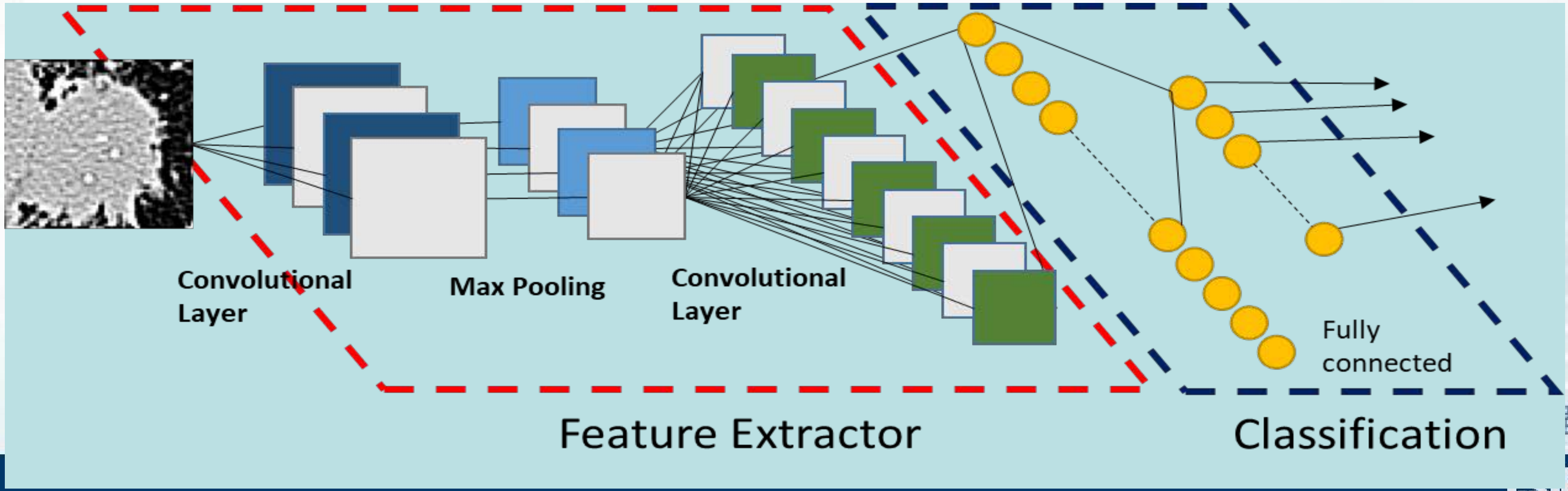
EGFR Gene Mutation in Lung CT

CT image with **EGFR+**

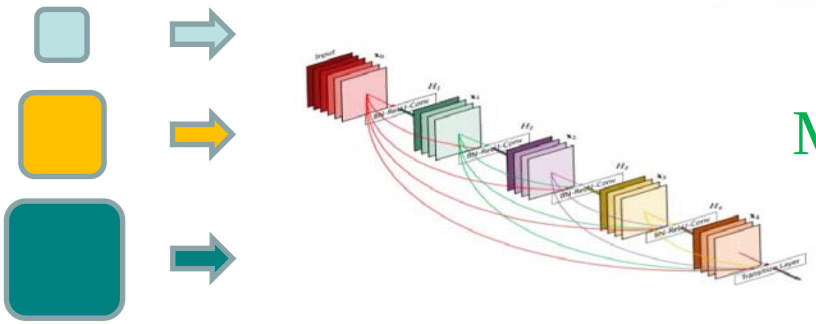


CT image with **EGFR-**

	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
DL Method	78.5	77.6	79.4	78.8	78.3

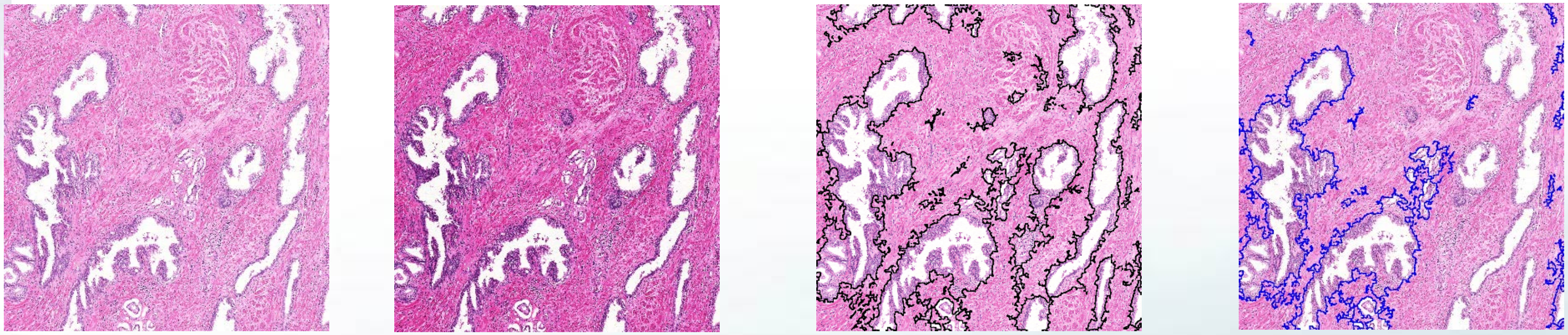


Prostate Cancer Regions Detection in Whole-slide Pathology Image



Multi-resolution DenseNet

H&E Image → Color Normalization → Tissue Segmentation → ⊕ → Malignant region



	Accuracy	Sensitivity	Specificity	PPV	NPV	Az
Proposed System	**95.5**	**96.6**	**90.0**	**97.8**	**83.9**	**0.980**

Thanks for Your Attention !