Machine Learning for Applications in Medical Physics

Alessandra Retico Istituto Nazionale di Fisica Nucleare Sezione di Pisa



alessandra.retico@pi.infn.it



Alessandra Retico Artificial Intelligence applications in Healthcare



Legend: HER, Electronic Health Records; NIPT, noninvasive prenatal test

[J. He et al., The practical implementation of artificial intelligence technologies in medicine, Nature Medicine 25, 30–36 (2019)]

Medical Imaging: there are many techniques based on different physical principles



Medical images are more than pictures!!!

INFN

Alessandra Retico



Decision Support Systems (DSS) for Detection/Diagnosis

Image processing and analysis techniques can help:

- to improve image visualization
- to detect abnormalities in diagnostic images (lesions, etc.)
- to follow up pathological conditions (growth rate of lesions)
- to evaluate the efficacy of treatment



Computer Aided Detection/Diagnosis (CAD) systems or Decision Support Systems (DSS) are developed to assist clinicians in their tasks, not to replace them!

Historical overview

Artificial Intelligence (AI) methods used in the development of DSS:

- In the 90s Old-fashion systems (rule-based)
 - Since the 2000s Hand-crafted feature and Machine Learning classification (Radiomics and ML)

• Since 2015 – Deep-Learning image classification



Old-fashion CAD systems



Alessandra Retico

Alessandra Retico Hand-crafted feature + Machine Learning classification



- Semiautomated lesion segmentation of mass lesions in 0 mammograms
- Automated classification into benign/malignant category

0.756213

0.430173

0.834195

542495 0.111326 0.940627

0 95874

0.326646 0.946453 0.317354 0.386372 0.021095 0.702353 0.085369 0.840329

Feature

extraction

Artificial Neural Network (ANN) classifier







Alessandra Retico

CAD system for lung nodule detection



INFN

Alessandra Retico



Example: voxel-based nodule characterization

- Each voxel v of a nodule candidate is described in terms of a vector of features
 - voxel v slice z-1 slice z-1 slice z+1 + other features computed on the voxel neighborhood



Each vector of features is analyzed by an Artificial Neural Network/Support Vector Machine which assigns the class membership to each voxel

A majority criterion is adopted to assign candidates to either the "nodule" or the "healthy tissue" class

- Voxels classified as nodule
- Voxels classified as normal tissue

normal

tissue

Alessandra Retico



Combining different CAD methods increases the performance in the identification of pulmonary nodules

Train + validation sets:

• 69 CTs with 138 nodules (96 internal and 42 juxtapleural)

Independent Test set:

• 69 CTs with 114 nodules (95 internal and 19 juxtapleural)



Alessandra Retico

ÎNFŇ

12

[Camarlinghi et al, Int. Journal of Computer Assisted Radiology and Surgery, IJCARS (2011)]

Alessandra Retico

M5L lung CAD on-demand

Lung nodule detection SW developed by INFN MAGIC-5 and M5L projects

→ laboratory performance: 80% sensitivity to nodules @ 5 FP/exam

 \rightarrow clinical validation

Assisted reading improves nodule detection by +7% in the per-patient analysis

MAGIC-5 and M5L project leader: P. Cerello, INFN, Turin

Collaboration with Candiolo Cancer Institute-FPO, IRCCS and Univ. of Turin





Human Neuroimaging: a "Big Data Challenge"



Predictive models based on multimodal and multidimensional data can be used to characterize the pathologyspecific brain correlates (neuroimaging-based *biomarker* of a disease/condition), and then to *predict* the single subject's group membership

INFN

Alessandra Retico

Characterization of subjects with Autism Spectrum Disorders

INFN

Research in

IRCCS FONDAZIONE

collaboration with







Evaluation of Altered Functional Connections in Male Children With Autism Spectrum Disorders on Multiple-Site Data Optimized With Machine Learning

Giovanna Spera', Alessandra Retico'*, Paolo Bosco², Elisa Ferrari¹², Letizia Palumbo¹, Piernicola Oliva45, Filippo Muratori².6 and Sara Calderoni².6



 Abstract
 Abstract

 Transport Instances and Social Xaron
 The intermethod agreement, between automated algorithms for brainstem segmentation in investigates, focular on the posterial involvement of this instances in A studies, Sectiona Diose of Social Advances and Social Xarons, and

Open issue: *stratification of the heterogeneous ASD population?*





The Artificial Intelligence in Medicine (AIM) INFN-CSN5 Project



Project coordinator: A. Retico

Bari (S. Tangaro) Bologna (D. Remondini) Cagliari (P. Oliva) Catania (M. Marrale) Firenze (C. Talamonti) Genova (A. Chincarini) Lab. Naz. Sud (G. Russo) Milano (C. Lenardi) Napoli (G. Mettivier) Pavia (A. Lascialfari) Pisa (M.E. Fantacci) Artificial Intelligence to become the next revolution in medical diagnostics and therapy.

 New image processing and data analysis strategies, including radiomics approaches, need to be developed and extensively validated.



Long-standing collaboration with Italian & European centers (Hospitals / IRCCS) and with international consortia for data sharing

Harmonization of multicenter data in the study of Autism Spectrum disorders (ASD)



mprage.nii

Data gathered by different scanner and/or acquisition systems encode the site "signature", which can confound ML algorithms and hide subtle information of interest.

NYU-1

NYU-2 OHSU

OHSU USM USM UM-1 UM-2

ABIDE1

0.98

0.98

1.00

ABIDE2 ABIDE1

1.00 1.00

1.00 0.99

1.00 0.99

0.99 1.00

0.96

0.96 0.98 0.98

0.75 0 99





Caltech 51463 mprage.nii



AUC ABIDE1 ABIDE2 ABIDE2 ABIDE1 ABIDE2 ABIDE1 NYU 0.78 0.89 0.99 1.00 0.99 ABIDE1 ABIDE NYU-1 0.70 0.99 1.00 1.00 ABIDE2 Autism Brain Imaging NYU-2 1.00 0.98 0.99 ABIDE2 Data Exchange OHSU 0.63 0.97 (2200 MRI scans, 40 ABIDE1 OHSU 0.99 acquisition sites) ABIDE2 USM

NYU



mprage.nii

KKI_5077

mprage.nii

ML classifiers can easily distinguish brain features of subjects from site A vs. site B (AUC ~1), whereas barely distinguish ASD vs. controls (AUC~0.6).

	Artificial Intelligence In Medicine 108 (2020) 101926				
		Contents lists available at ScienceDirect	H A		
8_mprage.		Artificial Intelligence In Medicine	REDICINE		
ווו	ELSEVIER	journal homepage: www.elsevier.com/locate/artmed	10.000		
50957_	n confounders and outliers in classification medical studies: The trum Disorders case study	Check for updates			
age.nii	Elisa Ferrari ^{a,*} , Giovanna Spera	Paolo Bosco ⁰ , Sara Calderoni ^{0,c} , Piernicola Oliva ^{0,e} , Letizia Palumbo ¹ , ¹ , Maria Evelina Fantacci ^{6,g} , Alessandra Retico ^f			

How to mitigate site effects?

The site contribution to can be modelled and discarded, while keeping interesting data dependencies (e.g. on age and sex)

Alessandra Retico



NYU mpra

Deep residual CNN for breast density classification

Automated identification of tissue density class (A, B, C, D) with a residual CNN (R-CNN)

Goal: To contribute to the development of a new personalized **dose index** (depending on breast density) for each patient and each mammographic exam.



Dataset: about **2000 digital mammographic exams** collected by Azienda Ospedaliero-Universitaria Pisana (AOUP).

Dense/Non-dense	Left $(\%)$	Right (%)	All (%)	BI-RADS	Left $(\%)$	Right (%)	All (%)
Accuracy	84.4	88.8	89.4	Accuracy	73.3	76.7	77.3
Recall	82.3	89.9	90.0	Recall	72.1	79.2	77.1
Precision	85.5	87.7	88.9	Precision	76.6	75.2	78.6

[Lizzi F. et al., Residual convolutional neural networks to automatically extract significant breast density features. vol. 1089. Springer International Publishing; 2019]









Alessandra Retico Radiomics and Machine Learning to predict patients' outcome

- Radiomic features are analyzed with Machine Learning methods to develop predictive models of diagnosis, prognosis or treatment outcome.
- For example: Predictive models of outcome of Radiotherapy Treatment (RT) based on Radiomics and Dosiomic features



Alessandra Retico The AIM working group on lung CT analysis (AIM-Covid19-WG)

Objective: Automatic quantification of lung involvement on CT scans. An index of severity of lung involvement has been defined [Yang, Radiology, 2020]: **CT-Severity Score (CT-SS)** ______CT-SS= 1 (<5%), 2 (5%-25%), 3 (25%-50%), 4 (50%-75%), 5 (>75%)









Steps for the automatic quantification of lung involvement in CT scans



Radiomics

21

Alessandra Retico

Alessandra Retico

U-Net: Convolutional Networks for Biomedical Image Segmentation

[O. Ronneberger et al., U-Net: Convolutional Networks for Biomedical Image Segmentation, Medical Image Computing and Computer-Assisted Intervention (MICCAI), Springer, LNCS, Vol.9351: 234--241, 2015]



https://lmb.informatik.uni-freiburg.de/people/ronneber/u-net/

https://github.com/MIC-DKFZ/nnUNet

Network architecture and available datasets

Target: 200x150x100

arrays; 2-bit data

Input (3D, 16-bit data): CT data resampled to 200x150x100 arrays



about 17 M trainable parameters

We used only **public datasets** with annotations (in part collected for other clinical purposes)

Alessandra Retico

INFN

DATASETS	Clinical motivation	Number of cases	Lung mask	Lesion mask	CT-SS
COVID-19- Challenge [1]	COVID-19 pandemic	199	No	Yes	No
MosMed [2]	COVID-19 pandemic	1110	Yes, only for 91 CTs (made in house)	Yes, only for 50 CTs	Yes
TCIA-Plethora [3]	Lung/pleura diseases	402	Yes	No	No
TCIA-LCTSC Lung segmentation [3]	Lung cancer	60	Yes	No	No
COVID-19-CT-Seg Benchmark [4]	COVID-19 pandemic	10	Yes	Yes	Yes

[1] https://covid-segmentation.grand-challenge.org/

- [2] https://mosmed.ai/
- [3] https://www.cancerimagingarchive.net/
- [4] https://zenodo.org/record/3757476

LungQuant1.0: a sequence of two U-nets to segment lungs and COVID-19 lesions on CT scans



[Lizzi, F. *et al* (2021). Making data big for a deep-learning analysis: Aggregation of public COVID-19 datasets of lung computed tomography scans. *Proceedings of the 10th International Conference on Data Science, Technology and Applications, DATA 2021*, (Data), 316–321. https://doi.org/10.5220/0010584403160321] [Lizzi, F., Agosti, A., Brero, F., Cabini, R. F., Fantacci, M. E., Figini, S., ... Retico, A. (2021). Quantification of pulmonary involvement in COVID-19 pneumonia by means of a cascade of two U-nets: training and assessment on multiple datasets using different annotation criteria. *IJCARS*, https://link.springer.com/article/10.1007/s11548-021-02501-2]

Alessandra Retico

Alessandra Retico

INFN

LungQuant: training details and cross-validation scheme

Loss functions:

Unet_1: Dice_{loss} =
$$1 - \frac{2 \cdot |M_{true} \cap M_{pred}|}{|M_{true}| + |M_{pred}|}$$

$$L = Dice_{loss} + CE_{weighted}$$

Jnet_2:
$$CE_{weighted} = w(x) \sum_{x \in \Omega} log(M_{true}(x) \cdot M_{pred}(x)$$

Evaluation metric: $Dice_{metric} = \frac{2 \cdot |M_{true} \cap M_{predict}|}{|M_{true}| + |M_{pred}|}$

Computing resources available at INFN-Pisa, CINECA and Univ. of Pavia have been exploited:

- $\circ~$ GPUs with at least 16 GB of RAM
- Each run required ~12h to complete 100 epochs

Train-validation-test data split (hold out)



We trained both the U-net for 300 epochs and we chose the epoch with the best metric on the validation set to evaluate the performance on the test set.

U-net₁	train	val	test
Plethora	319	40	40
MosMed (91 CT-0)	55	18	18
LCTSC	36	12	12
U-net ₂ ^{60%}	train	val	test
COVID-19 challenge	119	40	40
MosMed (50 CT-1)	30	10	10

U-net ₂ ^{90%}	train	val	test
COVID-19 challenge	179	20	/
MosMed (50 CT-1)	45	5	/

COVID-19-CT-Seg (indipendent test)	/	/	10
---------------------------------------	---	---	----

The LungQuant system performance



F. Lizzi et al. IJCARS, doi: 10.1007/s11548-021-02501-2

Test on the COVID-19-CT-Seg benchmark set of 10 fully annotated CT scans

Blue: U-net lung mask Red: U-net lesion mask Green: reference lesion segmentation

Dice coefficients: 0.95 ± 0.01 for lung segmentation 0.66 ± 0.13 for lesion segmentation



International Journal of Computer Assisted Radiology and Surgery https://doi.org/10.1007/s11548-021-02501-2

ORIGINAL ARTICLE

Quantification of pulmonary involvement in COVID-19 pneumonia by means of a cascade of two U-nets: training and assessment on multiple datasets using different annotation criteria

Francesca Lizzi^{1,2} · Abramo Agosti⁶ · Francesca Brero^{4,5} · Raffaella Fiamma Cabini^{4,6} · Maria Evelina Fantacci^{2,3} · Silvia Figini^{4,11} · Alessandro Lascialfari^{4,5} · Francesco Laruina^{1,2} · Piernicola Oliva^{8,9} · Stefano Piffer^{7,10} · Ian Postuma⁴ · Lisa Rinaldi^{4,5} · Cinzia Talamonti^{7,10} · Alessandra Retico²



Alessandra Retico

Clinical validation of the SW with radiologists from 5 Italian Hospitals (PI, PV, FI, PA, MI), *in progress*



Deep Learning vs. traditional Machine Learning approaches

- Deep Neural Networks are replacing traditional handcrafted feature extraction + ML approaches in many Medical Physics applications, thus fostering *data driven decision making*
 - Pros:
 - No prior selection of problem-related features ⇒ no loss of information
 - Cons:
 - Larger and larger samples of annotated data are needed to train the models
 - Deep Neural Networks are black boxes: which image features are relevant for making a decision?

Data augmentation (flip, rotate, scale images to augment data sets)

Model interpretability, explainable AI

Mandatory in medical

applications



Conclusions

- Medical imaging daily produces an incredible amount of digital information which is not fully exploited neither for diagnosis/therapy nor for research!
- Clinicians need to be supported by reliable, effective and easy-to-use DSS for diagnosing and monitoring a wide range of diseases
- The development of AI-based clinical DSS has multiple levels of complexity, thus it requires multidisciplinary skills

→ There is still lot of room to make original contributions in this field of research!



Contact: alessandra.retico@pi.infn.it INFN, Sezione di Pisa