CoViD-19: Inflammation and Molecular Imaging

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Remote

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Prognostic methods to predict the evolution of the COVID-19 disease can be decisive to address the most suitable therapeutic approach. We propose an AI algorithm to make predictions of the patient respiratory condition and functional response, by merging information from CT scans, blood

gas analysis and biomechanical simulations of air ventilation in the lung tissues performed by the software developed at MedLea Srls. Our work is based on a COVID-19 dataset of about 60 patients and on publicly available datasets. A deep segmentation network is used to segment COVID-19 lesions on the CT that are subsequently correlated with clinical parameters. A preliminary study on diagnostic accuracy and perspectives on prognostic capabilities are presented.

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Spike Proteins in MERS-CoV, SARS-CoV and SARS-CoV-2 Coronaviruses: Differences in Proteic Conformation

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In recent years, three different coronaviruses (MERS-CoV, SARS-CoV and SARS-CoV-2), posed a grave threat to the global public health, security and economy. All these RNA viruses present a similar surface structure characterized by Spike Glycoproteins (S) having a key role in viral pathogenesis. The S proteins protrude from the surface of mature virion (see Fig. 1), and are responsible for anchoring the host cellular membrane though its receptors. Through biological investigations, has been proposed that the transmissibility of different CoVs viruses is strongly related to different spike protein secondary conformation.
Here, we investigate through infrared and terahertz spectroscopy, the secondary conformation of Spike glycoproteins for MERS-CoV, SARS-CoV and SARS-CoV-2. We experimentally prove that the three viruses present Spike glycoproteins with different secondary conformations. In particular, SARS-CoV-2 has a secondary conformation characterized by the formation of intermolecular β-sheet structures, more able to anchoring the virus to human receptors.
Moreover, we also proved that the conformation of SARS-CoV-2 strongly change by passing from an alkaline environment (characterizing the bats ambient) to physiological one (characteristic of human physiology). All these information, strongly indicate the huge capability of the SARS-CoV-2 virus to adapt to different external conditions and paves the way to use vibrational spectroscopy as an alternative monitoring approach (in particular in open spaces), overcoming the limitations of conventional bio-chemical ones.

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Automatic Lung Analysis for COVID-19 Patients

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Objectives: Coronavirus disease 2019 (COVID-19) is an infectious lung disease affecting more than 124 million individuals worldwide as of Mar 28, 2021, and still significantly impacts our daily life. In 2020, we presented an automatic lung analysis workflow to analyze lung function quantitatively at the lung lobe level [1]. To further support and contribute to COVID-19 analysis, we extended our work and developed a fully automatic research prototype analysis workflow for lung fissure delineation and opacity detection.
Methods: The deep learning system consists of deep reinforcement learning landmark detection, deep image to image network work for lung fissure delineation, and a Dense-UNet for opacity feature extraction and detection for COVID-19 cases. The algorithm was trained with over 8000 chest CT image volumes, including 1400 COVID-19 cases. The algorithm was validated using both an in-house testing dataset of 200 cases, and a completely unseen dataset, the first batch of 120 cases from the RSNA International COVID-19 Open Radiology Database (RICORD). Two types of correlations, Pearson's Coefficient and Kendall's Tau, were used in statistical analysis for datasets with adequate image quality. The lung lobe mask and opacity mask were then overlapped with PET/SPECT images for automatic quantifications to produce quantitative results in each lung lobe and opacity region in the respective lobe for both CT and PET/SPECT images.
Results: The automatic lung analysis workflow completed successfully for all patient datasets. For the in-house testing dataset, the Pearson Coefficient between the percentage of opacity predicted and the ground truth is 0.95. For the 104 datasets with adequate image quality in RICORD, the mean and standard deviation of the percentage of infectious opacity in the whole lung (segmented in our workflow) is 31.8±26% for our segmentation and 33.5±30% for the annotation. The Pearson's Coefficient is 0.765 ($p<.0001$), and Kendall's Tau is 0.720 ($p<.0001$). RICORD dataset consists of

annotations from 3 different teams, therefore, we further investigated the inter-team variability of annotation. The Pearson's Coefficients are 0.765(p<.0001) for team 1, 0.670(p<.0001) for team 2, and 0.827(p<.0001) for team 3. The percentages of volume (CT) and activity (PET/SPECT) of opacity region in each lung lobe are provided for functional analysis.
Conclusion: The image quality plays a critical role in the accuracy of segmentation. Our automatic segmentation shows reasonable and acceptable results with the completely unseen RICORD public dataset of relatively suboptimal reconstruction quality from multiple vendors. The quantification of both anatomical and functional information provides the ability to (1) analyze lung lobe level function and opacity infection for COVID patients and (2) monitor treatment effectiveness by comparing the functional change before and after treatment.
[1] Gao, Fei, et al. "Evaluation of Automatic Lung Lobe Segmentation for SPECT/CT LungVQ Image Analysis." Journal of Nuclear Medicine 61.supplement 1 (2020): 1489-1489.

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The potential of the EuPRAXIA photon beams for CoViD-19 research

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The advent of Free Electron Lasers (FELs) opened up the way for an unprecedented, wide class of experiments exploiting the peculiar features of these radiation sources. Key elements of FEL beams are the high peak brilliance, the short pulse duration, which is of the order of tens of femtoseconds, and the high degree of coherence of the radiation.
EuPRAXIA is the first European project that develops a dedicated particle accelerator research infrastructure based on novel plasma acceleration concepts and laser technology. It focuses on the development of electron accelerators and underlying technologies, their user communities, and the exploitation of existing accelerator infrastructures in Europe.
Within this framework, the Laboratori Nazionali di Frascati (LNF) will be equipped with a unique combination of a high brightness GeV-range electron beam generated in a state-of-the-art X-band RF linac, a 0.5 PW-class laser system and the first 5th generation light source driven by a plasma accelerator. These features will enable at LNF new promising synergies between fundamental physics oriented research and applied physics experiments with high social impact applications. Among these, there are research lines which will exploit the photon beams generated by the EuPRAXIA facility to perform experiments and contribute to the development of techniques aimed at understanding the mechanisms of CoViD-19 infection and at evaluating its consequences.
The facility will indeed produce two beams in the X-ray region. It will exploit plasma acceleration to produce ultra-bright photon pulses with durations of few femtoseconds in the soft X-ray regime, down to a wavelength between 2 and 4 nm, in the so called "water window". Since the plasma source also accelerates and wiggles electrons, it will give rise to a brilliant keV X-ray emission referred to as betatron source.
These two photon beams produced by EuPRAXIA can be exploited to perform a variety of experiments on condensed and biological matter. Among these, in this presentation we highlight three classes of experiments that are relevant for CoViD-19 related studies:

1- Coherent imaging experiments that exploit the soft X-ray FEL pulses to determine the 3D shape of viral particles in native conditions (e.g. in a fully hydrated environment) and/or in complex with cells, cells nuclei and cells membranes.
2- Hard X-ray absorption and serial crystallography test experiments aimed at exploring the potential application of betatron radiation to obtain information on metal binding and atomic resolution electron density maps of viral proteins.
3- Hard X-ray phase-contrast imaging that exploit betatron radiation to perform high-resolution microtomographic imaging on samples of tissues affected by CoViD-19.

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COVID-19 in 2021: Lessons Learned and Remaining Challenges

Registered talk courtesy provided by Accademia Nazionale del Lincei and Ospedale Pediatrico Bambino Gesù

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The role of AI in COVID-19 management: quantification of lung involvement using CT scans

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Purpose: The World Health Organization (WHO) fixed as the gold standard for COVID-19 diagnosis the positive tested RT-PCR while the use of Computed Tomography (CT) images and Artificial Intelligence (AI) for this purpose is still under evaluation since differential diagnosis for other kinds of pneumonia is not reliable. However, AI and CT may be useful to follow up patients and to evaluate the severity of the lung infection allowing the workload reduction in radiology departments. As Artificial Intelligence in Medicine (AIM) INFN project, we worked on this topic developing a system, called LungQuant, based on a cascade of two U-nets using only publicly available data.

Method: The system is made of two U-nets: the first one is trained to segment the lung, while the second one is trained to segment the lung infection due to COVID-19. The output of the first U-Net is then refined using a connected-component labeling strategy, which helps to remove small regions of the segmented mask not connected with the main objects identified as the lungs. The second U-Net for the COVID-19 lesions segmentation is trained on a bounding-box enclosing the morphologically refined segmented lungs. The LungQuant algorithm processes CT images and returns as output the lung segmentation, the lung infection segmentation and the CT-Severity Score (CT-SS), which is defined as the ratio between infected volume and total lung volume. The system has been trained and tested on publicly available datasets to ensure reproducibility. It has been evaluated also in a

cross-dataset scheme to study the transferability of its performances. 551 lung CTs have been used to train and evaluate the first U-net for lung segmentation. Three different datasets, containing both COVID-19 and non COVID-19 patients, have been aggregated to obtain a consistent number of samples. To train the second U-net, devoted to the infection segmentation, 249 CTs scans have been used taken from two different datasets. We also applied data augmentation to increase the amount of training data by applying rotations, elastic transformations, zooming and by adding gaussian noise to the original CTs. Finally, the whole system has been tested also on a completely independent public dataset (COVID-19-CT-Seg) to evaluate the LungQuant generalization capability. Both the lung and the infection segmentation masks have been evaluated with the DICE index and CT-SS assessment has been evaluated with accuracy and Mean Absolute Error (MAE).

Results: The LungQuant system has been evaluated on different test sets and we found that the performance strongly depends on the quality of labeling and on how much similar both the test image selection criteria and test image labels are with respect to the training set's one. The DICE indices obtained on the completely independent test set are 0.95 ± 0.01 for lung segmentation and 0.66 ± 0.13 for the infection segmentation. The system is able to classify the CTs in terms of CT Severity Score with an accuracy equal to 90% on the independent test set with a MAE equal to 4.2% on COVID-19-CT-Seg.

Discussion and conclusions: We developed a fully automated quantification pipeline, the LungQuant system, for the identification and segmentation of the lungs and the pulmonary lesions related to COVID-19 pneumonia in CT scans. The system returns the COVID-19 related lesions, the lung mask and the ratio between their volumes, which is converted into a CT-SS. The LungQuant system achieved a Dice index of 0.95 ± 0.01 in the lung segmentation task and of 0.66 ± 0.13 in segmenting the COVID-19 related lesions on the fully annotated publicly available benchmark COVID-19-CT-Seg dataset of 10 CT scans. The system is able to classify the CTs in terms of CT-SS with an accuracy equal to 90% on the independent test set with a MAE equal to 4.2%. Despite this result is encouraging, it was obtained on a rather small dataset, constituted by COVID-19-CT-Seg and MosMed CT scans, which involves most subjects with low disease severity. Therefore, a broader validation of a larger data sample with more heterogeneous composition in terms of disease severity is required.

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On Resonant Ablation of CoViD Virus in Public Places

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According to the latest US CDC declarations, Covid infection is largely transmitted by air and not -as previously supposed- by touching objects "polluted"by others. Thus, at least in public gatherings, we should focus more on cleaning the air surrounding participants rather than on disinfecting objects in contact with them. A low-cost method to accomplish it consists in beaming signals at frequencies that are resonant with the intrinsic frequency of the Covid virus. Resonance condition reduces the intensity of the external (ultrasound/microwave) beam to be well below the IEEE standard of safety. The applied frequency bands are easy to cover the known mutant variants of the virus. As we have emphasized in our previous publication(1) , similar techniques have been effective in various flu infections (including their variant avatars) and have also been studied in efforts to ablate cancer cells (without damaging normal cells). Parenthetically, it should be noted that non virus specific methods such as UV light &/or thermal ablation methods pose problems with input power and thus safety.

(1) https://doi.org/10.1080/15368378.2020.1803081; Non-chemical signatures of biological materials: Radio signals from Covid19?, by Y. Srivastava, E. Sassaroli , J. Swain , A. Widom , M. Narain & G. de Montmollin.

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Zn-induced interactions between SARS-CoV-2 orf7a and BST2/tetherin

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In this talk I will present a first X-ray Absorption Spectroscopy study of the interactions of Zn with human BST2/tetherin and SARS- CoV-2 orf7a proteins as well as with some of their complexes. The analysis of the XANES region of the measured spectra shows that Zn can bind to BST2, as well as to orf7a and that BST2-orf7a complexes get formed. These structural information confirm the conjecture, recently published by some of the present Author, according to which the accessory orf7a (and possibly also orf8) viral protein is (are) capable of interfering with the BST2 antiviral activity. Our tentative explanation for this interesting conjectured behaviour is that when BST2 gets in contact with Zn, bound to the orf7a Cys15 ligand, it has the ability of displacing the metal owing to the creation of a new disulfide bridge across the two proteins. The formation of this BST2-orf7a complex may prevent BST2 to adopt the proper functional conformation thus impairing its antiviral activity.

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Multimodal X-ray Imaging with Darkfield Contrast: Improved COVID-19 Detection with Chest X-rays

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Diseases of the respiratory system are leading global causes of chronic morbidity and mortality. While advanced medical imaging technologies of today deliver detailed diagnostic information, a low-dose, fast, and inexpensive option for early detection and/or follow-ups is still lacking.
Here, we report on the first human application of a novel modality, namely X-ray dark-field chest imaging, which might fill this gap. Enabling the assessment of microstructural changes in lung parenchyma, this technique presents a more sensitive alternative to conventional chest X-rays, and yet requires only a fraction of the dose applied in computed tomography (CT).
For this first clinical evaluation, we have built a novel dark-field chest X-ray system, which is also capable of simultaneously acquiring a conventional thorax radiograph. With this first system world-wide, we are presently conducting two patient studies. The first is devoted to chronic obstructive pulmonary disease (COPD), the second to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
First results look very promising and show that X-ray dark-field chest imaging allows the diagnosis of COPD and COVID-19 more effectively than conventional chest X-ray does.

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Round Table

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