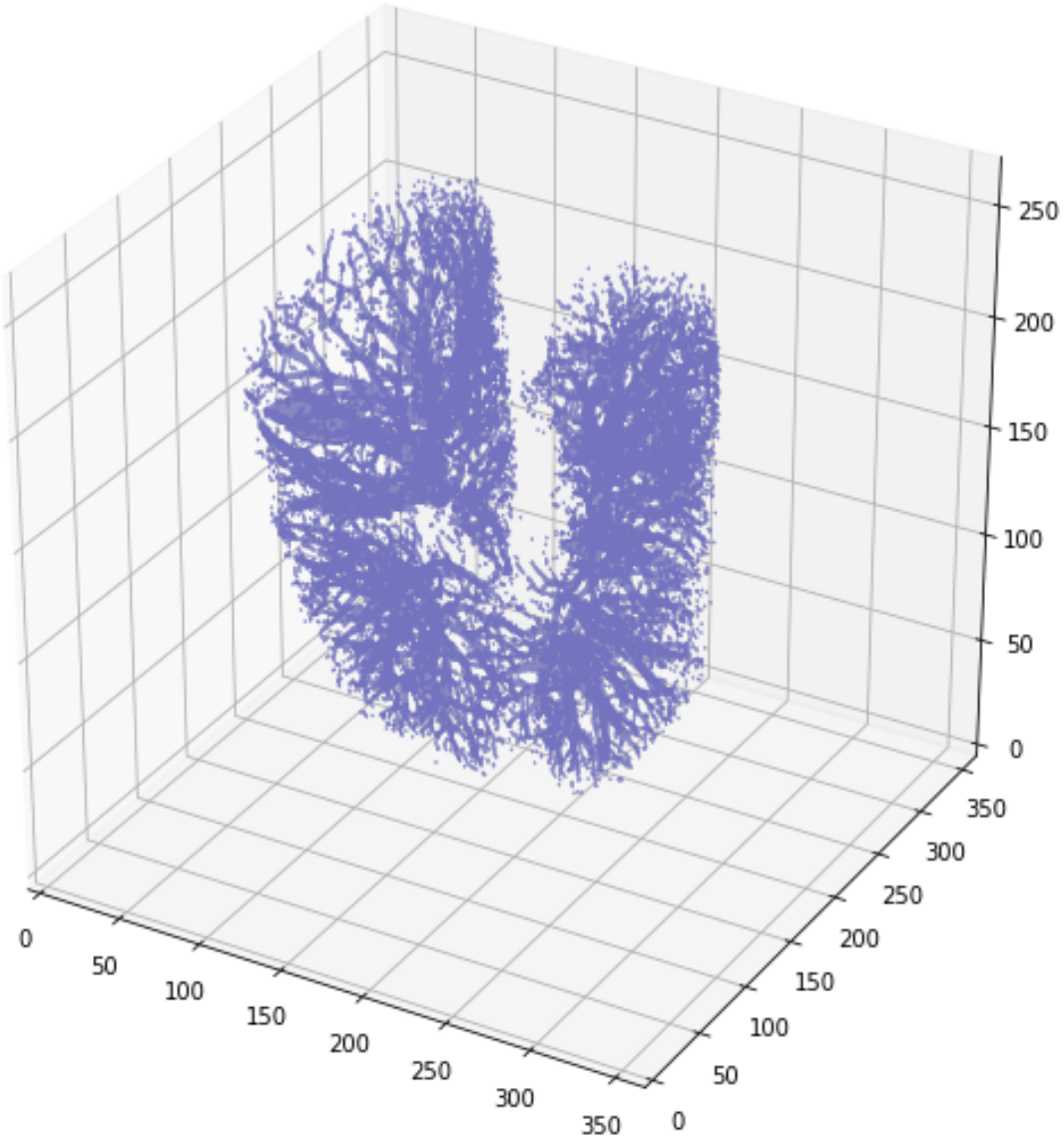
Predict lung function decline (pulmonary fibrosis)



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1. Introduction

1.1 What is Pulmonary fibrosis

Pulmonary fibrosis is a lung disease that occurs when lung tissue becomes damaged and scarred. The word “pulmonary” means lung and the word “fibrosis” means scar tissue— similar to scars that you may have on your skin from an old injury or surgery.The scar tissue thickened, stiff tissue makes it more difficult for the lungs to work properly as shown in Fig 1. As pulmonary fibrosis worsens, it becomes progressively more short of breath. As of now pulmonary fibrosis has no treatment but some medications and therapies help to improve quality of life.

No one is certain how many people are affected by PF. One recent study estimated that idiopathic pulmonary fibrosis (or IPF, which is just one of more than 200 types of PF) affects 1 out of 200 adults over the age of 60 in the United States—that translates to more than 200,000 people living with PF today. Approximately 50,000 new cases are diagnosed each year and as many as 40,000 Americans die from IPF each year.

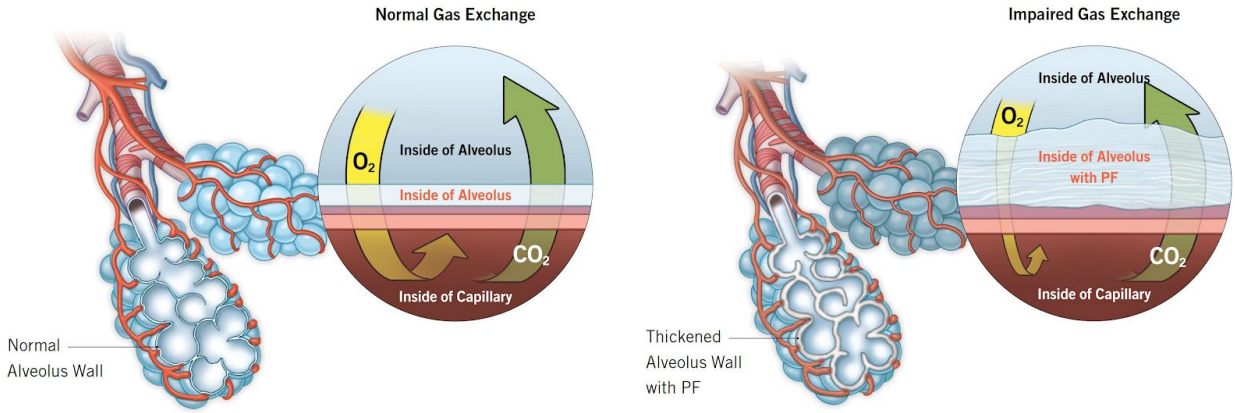


Figure 1 Illustration of lugs with and without PF (www.pulmonaryfibrosis.org/)

1.2 Problem Statement

According to research; the respiratory system undergoes various anatomical, physiological and immunological changes with age. The structural changes include chest wall and thoracic spine deformities which impairs the total respiratory system compliance leading to increase work of breathing.The lung parenchyma loses its supporting structure causing dilation of air spaces: “senile emphysema”. Respiratory muscle strength decreases with age and can impair effective cough, which is important for airway clearance. The lung matures by age 20–25 years, and thereafter aging is associated with progressive decline in lung function.

1.3 Dataset

The dataset used in this project is acquired from kaggle where uploaded for competition by OSIC (Open Source Imaging Consortium) dataset. The dataset contains a baseline chest CT scan and associated clinical information for a set of patients. A patient has an image acquired at time Week = 0 and has numerous follow up visits over the course of approximately 1-2 years, at which time their FVC is measured.

Files: there are five files in the dataset including the training and testing csv and dicom files and the submission format of csv file.

Attribute Description: the attributes of training data includes: Patient, Weeks, FVC, Percent, Age, Sex amd SmokingStatus. Now let's see the detail of some of the attributes that are ambiguous and not so common.

Patient: a unique identifier of each patient

Weeks: the relative number of weeks pre/post the baseline CT

FVC: is a measurement of lung size (in liters) and represents the volume of air in the lungs that can be exhaled following a deep inhalation measured by Spirometry. Spirometry is performed by deeply inhaling and forcefully exhaling into a spirometer (the device that records the various measurements of lung function). In addition to FVC, expiratory volume-one second (FEV1) is crucial in the interpretation of spirometry measurement results. This is a measure of how much air can be exhaled in one second following a deep inhalation.

Percent: a computed field which approximates the patient's FVC as a percent of the typical FVC for a person of similar characteristics. The person of similar characteristics means, the reference FVC of healthy individual with normal lung function and of the same age, sex and height. The percent value greater or equal to 80% is considered as NORMAL, 70-79% MILD, 60-69% MODERATE and less than 60% is considered SEVERE.

1.4 Target

The aim of the project is to predict a patient's severity of decline in lung function based on a CT scan of their lungs and determine lung function based on output from a spirometer, which measures the volume of air inhaled and exhaled. Using machine learning techniques to make a prediction with the image, metadata, and baseline FVC as input.

1.5 Stakeholders

The stakeholders are the patients and their families by better understanding their prognosis when they are first diagnosed with this incurable lung disease. Improved severity detection would also positively impact treatment trial design and accelerate the clinical development of novel treatments. Health care providers and insurance companies are also possible stakeholders

1.6 Evaluation Metrics

The evaluation metric of this competition is a modified version of Laplace Log Likelihood, presented in Fig. 2. Predictions are evaluated with a modified version of the Laplace Log Likelihood. For each sample in the test set, an FVC and a Confidence measure (standard deviation σ) has to be predicted.

Confidence: values smaller than 70 are clipped

$$\sigma_{clipped} = max(\sigma, 70)$$

Error greater than 1000 are also clipped in order to avoid large errors

$$\Delta = min(|FVC_{true} - FVC_{predicted}|,\ 1000)$$

The metrics is defined as:

$$metric = -\frac{\sqrt{2}\Delta}{\sigma_{clipped}} - ln(\sqrt{2}\sigma_{clipped})$$

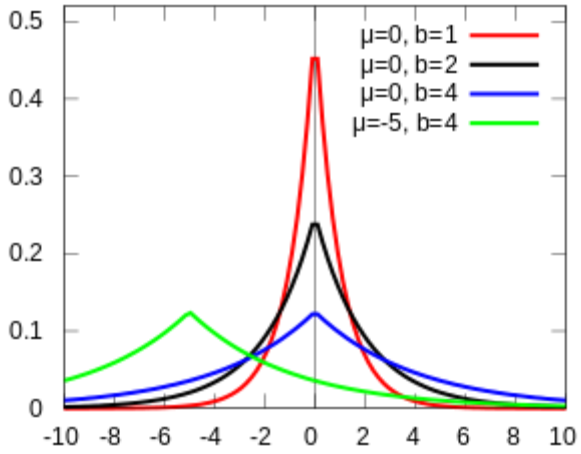


Figure 2. Laplace distribution (wikipedia.org)

1.7 DICOM File

DICOM was developed to make medical images and associated data standardized for easier interchange. Besides that, DICOM defines network oriented services for transfer or printing of the images, media formats for data exchange, work-flow management, consistency and quality of presentation and requirements of conformance of devices and programs. Information Object Definitions (IODs) are introduced in the standard to define attributes that describe a certain characteristic of the image. IODs have a well-defined meaning and their attributes precisely describe the type of the object, data of the patient, performed procedures or reports as well as the technical information about the medical imaging device used in the procedure. Technical information includes the name of the imaging device manufacturer, device serial number and other details about the device. These attributes vary when comparing devices from different manufacturers and different modalities (CT, MRI, mammography, etc.). DICOM Standard also defines network services that are used for information transfer. To make a transfer both stations have to support the same service and objects. Two stations that support the same services and objects are called Service-Object Pair Class (SOP Class).

2. Exploratory data analysis(EDA)

There are a total of 176 patients and they have a minimum of 6 and maximum of 10 records as shown in Fig. 3. The average number of records the patient has is approximately 9. Both the train and test csv dataset are clean, there are no outliers, all features are useful, all well structured, there are no missing values in both train and test as well. Hence, the dataset is well structured and cleaned and ready to use for analytics processes.

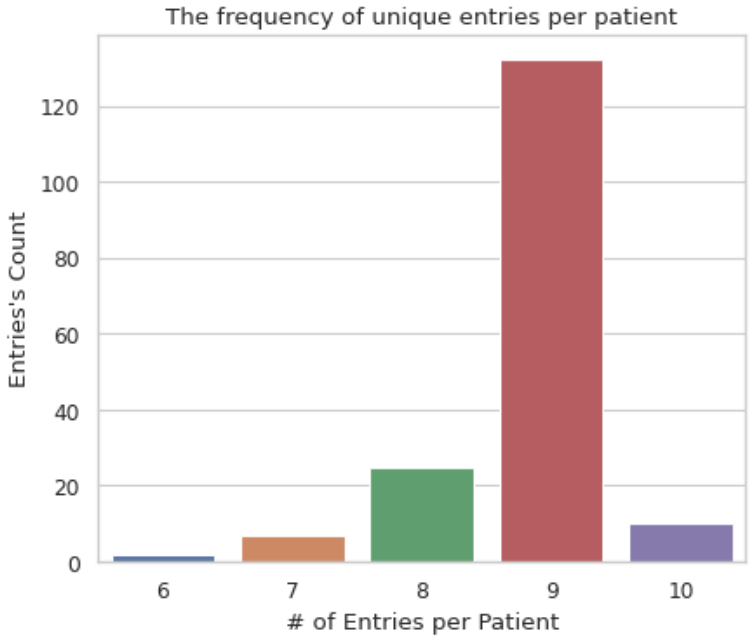


Figure 3. The frequency of unique entries per patient

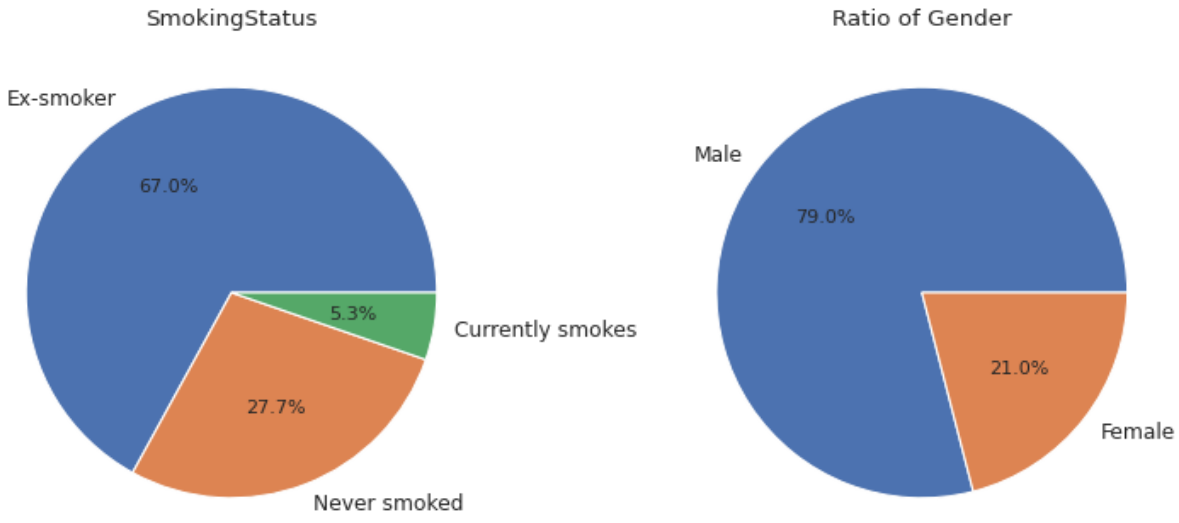


Figure 4. Smoking Status and Gender proportion

The majority of the patients are male with 79% of total patients. Current smoking patients are only 5.3% where the majority ex-smokers with 67% as shown in Fig. 4 above. FVC ranges from 827 to 6399 and seems to have a (visually) normal distribution with mean 2690 and standard deviation 833. The FVC distribution skewed to the right so as the distribution curve of percent and weeks. The Age distribution looks normal compared to others without any skewness which lies between 49 and 88 with mean age of 67. One can also note that the distribution of FVC, Percent and Age has bimodal as well as shown in Fig. 5.

The distribution of FVC, Percent, Weeks and Age, look normal with some skewness.

To see the correlation between each feature, the scatter plot is presented in Fig. 6. Generally FVC of men is higher than that of females and it looks uniformly distributed between male and female patients for Percent and Age with respect to Weeks. It is logical that if the FVC of men is higher, the FVC with the respective Age of Men is also higher compared to Female. A clear correlation is observed between FVC and Percent,

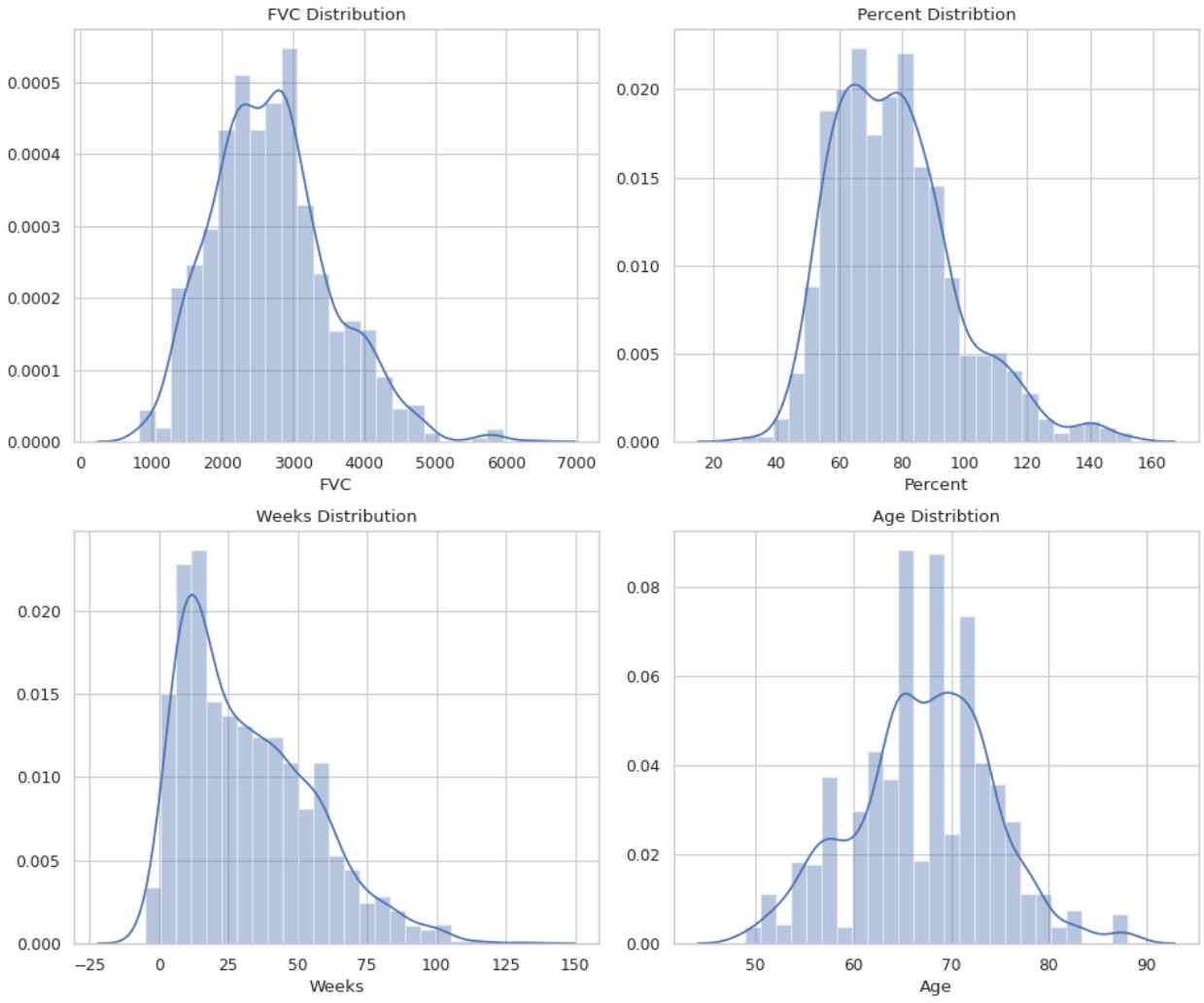


Figure 5. Distribution of FVC, Percent, Weeks and Age

Figure 6. Relationship between numerical features

The effect of smoking on the relationship between these features is also analysed and FVC are higher for ex-smoke patients then for people that still smoke and the lowest for people that never smoked. The Percent is highest for current smokers and lowest for non-smokers. But it is hard to decide or conclude that if a person smokes it is likely to have high FVC or Percent.

In order to check further the correlation among the features, we plot the correlation matrix as a heatmap as shown in Fig 7. As we have already noticed in the scatter plot, Percent and FVC have strong correlation and other features have less correlation from approximately zero negative for FVC vs Weeks, FVC vs Age, Percent vs Weeks, Age vs Weeks and approximately zero positive correlation for Percent vs Age.

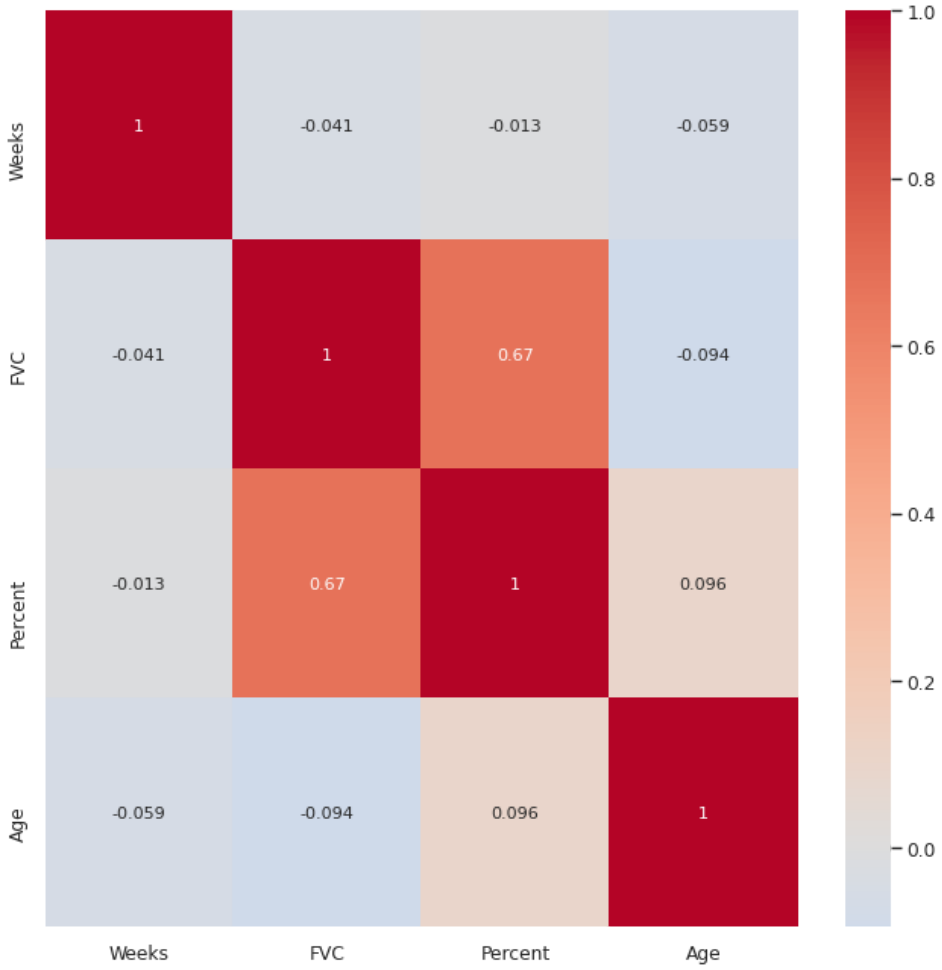


Figure 7. Correlation heatmap

3. DICOM Preprocessing

DICOM differs from other image formats in that it groups information into data sets. A DICOM file consists of a header and image data sets packed into a single file. The information within the header is organized as a constant and standardized series of tags. By extracting data from these tags one can access important information regarding the patient demographics, study parameters, etc. Fig 8 below shows the information extracted from a single dicom file of patient ID00423637202312137826377. As shown in Fig 8, a single dicom has a bunch of information tagged to it, hence after loading or reading dicom there should be a series of processes to make the file ready for machine learning. These steps are: converting the raw voxel values in the image to Hounsfield Units, Resampling, 3D plotting, Segmentation (masking), Normalization and Zero centering.

3.1 Hounsfield Units

In order to manipulate the dicom images first we need to load all DICOM images from a folder into a list. The voxel values in the dicom image lists are raw and we need to convert these raw values into Hounsfield Units. The Hounsfield unit (HU) is a relative quantitative measurement of radio density used by radiologists in the interpretation of computed tomography (CT) images. Density is measured in the Hounsfield unit (HU) scale, defined (approximately) as –1,000 HU for air, 0 HU for water, and 1,000 HU for bone. The Hounsfield Units for Human Body is summarized in Table 3.

HU are obtained from a linear transformation of the measured attenuation coefficients. The absorption/attenuation coefficient of radiation within a tissue is used during CT reconstruction to produce a grayscale image. The physical density of tissue is proportional to the absorption/attenuation of the X-ray beam. From these DICOM attributes we can have the linear correlation between the voxel value in the image and HU. As long as we have the 'Rescale Slope' and an 'Rescale Intercept', we can have the HU.

$$H\_Units(x,y) = voxel\_value(x,y) * RescaleSlope + RescaleIntercept$$

Both the rescale intercept and rescale slope are stored in the DICOM header at the time of image acquisition (these values are scanner-dependent, so we need external information). The distribution of Hounsfield Units converted from the first dicom of patient ID00423637202312137826377 is shown in Fig 10 along with the original and HU images. From the HU histogram (distribution) one can observe that:

- There is a lot of air, the peak around -1000
- At around -500 there are some pixels classified as Lung;
- The smaller gaussian-shaped peak at 0 indicates soft tissues;
- The distribution tail from 700 onward shows the presence of bones.

Display an image of patient ID00423637202312137826377 thirty six of every 10 slices is shown in Fig 11. I wish I could tell you about the images of every slice but one can easily note that as the number slices increase the lung tissue is clearly seen.

```
Dataset.file_meta -------------------------------
(0002, 0000) File Meta Information Group Length  UL: 200
(0002, 0001) File Meta Information Version       OB: b'\x00\x01'
(0002, 0002) Media Storage SOP Class UID         UI: CT Image Storage
(0002, 0003) Media Storage SOP Instance UID      UI: 2.25.122976501513298718954405079383491607 34
(0002, 0010) Transfer Syntax UID                 UI: Explicit VR Little Endian
(0002, 0012) Implementation Class UID            UI: 1.2.276.0.7230010.3.0.3.6.1
(0002, 0013) Implementation Version Name         SH: 'OSIRIX_361'
(0002, 0016) Source Application Entity Title     AE: 'ANONYMOUS'
-------------------------------------------------
(0008, 0005) Specific Character Set              CS: 'ISO_IR 100'
(0008, 0008) Image Type                          CS: ['ORIGINAL', 'PRIMARY', 'AXIAL']
(0008, 0018) SOP Instance UID                    UI: 2.25.122976501513298718954405079383491607 34
(0008, 0060) Modality                            CS: 'CT'
(0008, 0070) Manufacturer                        LO: 'GE MEDICAL SYSTEMS'
(0008, 1090) Manufacturer's Model Name           LO: 'LightSpeed VCT'
(0010, 0010) Patient's Name                      PN: 'ID000076372021774119564 30'
(0010, 0020) Patient ID                          LO: 'ID000076372021774119564 30'
(0010, 0040) Patient's Sex                       CS: ''
(0012, 0063) De-identification Method            LO: 'Table;'
(0018, 0015) Body Part Examined                  CS: 'Chest'
(0018, 0050) Slice Thickness                     DS: "1.25"
(0018, 0060) KVP                                 DS: "120.0"
(0018, 1110) Distance Source to Detector         DS: "949.075012"
(0018, 1111) Distance Source to Patient          DS: "541.0"
(0018, 1120) Gantry/Detector Tilt                DS: "0.0"
(0018, 1130) Table Height                        DS: "130.0"
(0018, 1140) Rotation Direction                  CS: 'CW'
(0018, 1151) X-Ray Tube Current                  IS: "79"
(0018, 1170) Generator Power                     IS: "9600"
(0018, 1190) Focal Spot(s)                       DS: "0.7"
(0018, 1210) Convolution Kernel                  SH: 'BONE'
(0018, 5100) Patient Position                    CS: 'FFS'
(0020, 000d) Study Instance UID                  UI: 2.25.808966718627260998884618059530129887 90
(0020, 000e) Series Instance UID                 UI: 2.25.517696004658745999017234969461934543 21
(0020, 0010) Study ID                            SH: ''
(0020, 0013) Instance Number                     IS: "1"
(0020, 0032) Image Position (Patient)            DS: [-158.700, -153.500, -69.750]
(0020, 0037) Image Orientation (Patient)         DS: [1.000000, 0.000000, 0.000000, 0.000000, 1.000000, 0.000000]
(0020, 0052) Frame of Reference UID              UI: 2.25.640580193257842357741057183393674031 44
(0020, 1040) Position Reference Indicator        LO: 'SN'
(0020, 1041) Slice Location                      DS: "-69.75"
(0028, 0002) Samples per Pixel                   US: 1
(0028, 0004) Photometric Interpretation          CS: 'MONOCHROME2'
(0028, 0010) Rows                                US: 512
(0028, 0011) Columns                             US: 512
(0028, 0030) Pixel Spacing                       DS: [0.652344, 0.652344]
(0028, 0100) Bits Allocated                      US: 16
(0028, 0101) Bits Stored                         US: 16
(0028, 0102) High Bit                            US: 15
(0028, 0103) Pixel Representation                US: 1
(0028, 0120) Pixel Padding Value                 SS: -2000
(0028, 1050) Window Center                       DS: "-500.0"
(0028, 1051) Window Width                        DS: "-1500.0"
(0028, 1052) Rescale Intercept                   DS: "-1024.0"
(0028, 1053) Rescale Slope                       DS: "1.0"
(0028, 1054) Rescale Type                        LO: 'HU'
(7fe0, 0010) Pixel Data                          OW: Array of 524288 elements
```

Figure 8. Information retracted from a single dicom

Table 3 Hounsfield Units for Human Body

Air	*-1000*
Lung	*-500*
Fat	*-50 to -100*
Water	*0*
Cerebrospinal Fluid	*15*
Kidney	*30*
Muscle	*10 to 40*
Blood	*40*
Grey Matter	*43*
White Matter	*46*
Liver	*40 to 60*
Bone	*1000*

3.2 Resampling

There are a total of 176 patients with a total 33035 dicom files. Each patient has a different number of dicom files. The distribution of DICOM counts per the patient is plotted as shown in fig 9. The minimum DICOM the patient has is 12, average is 187 and the maximum is 1018 files. There are ten different sizes of rows(width) [512, 1100, 768, 632, 752, 734, 1302 , 788, 733, 843] and fie different sizes of columns (height) [512, 888, 768, 632, 1302]. The images are too big and need to be resized. The problem here is not only the sizes are too big to analyze but they are non-uniform at the same time. The distance between slices are also different. This can be problematic for automatic analysis (e.g. using ConvNets). A common method of dealing with this kind of problem is resampling the full dataset to a certain isotropic resolution. If we choose to resample everything to 1mm1mm1mm pixels we can use 3D convnets without worrying about learning zoom/slice thickness invariance.

```
def resample(image, scan, new_spacing=[1,1,1]):
  spacing = map(float, ([scan[0].SliceThickness] + list(scan[0].PixelSpacing)))
  spacing = np.array(list(spacing))
    # Determine current pixel spacing
  resize_factor = spacing / new_spacing
  new_real_shape = image.shape * resize_factor
  new_shape = np.round(new_real_shape)
  real_resize_factor = new_shape / image.shape
  new_spacing = spacing / real_resize_factor
  image = scipy.ndimage.interpolation.zoom(image, real_resize_factor, mode='nearest')
  return image, new_spacing
```

Figure 9 Resampling function

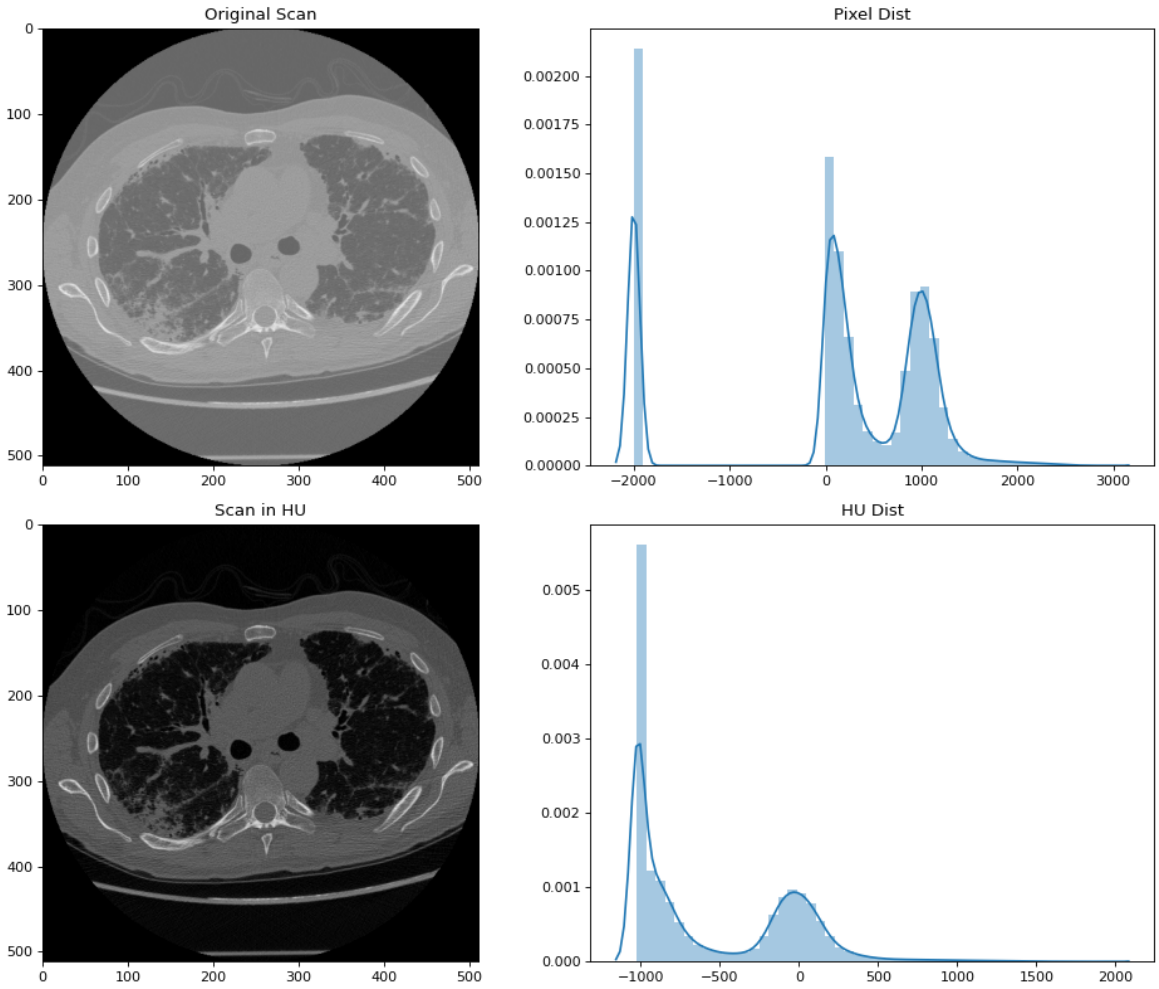


Figure 10. Comparison of original scan and converted HU scan image and pixel distribution

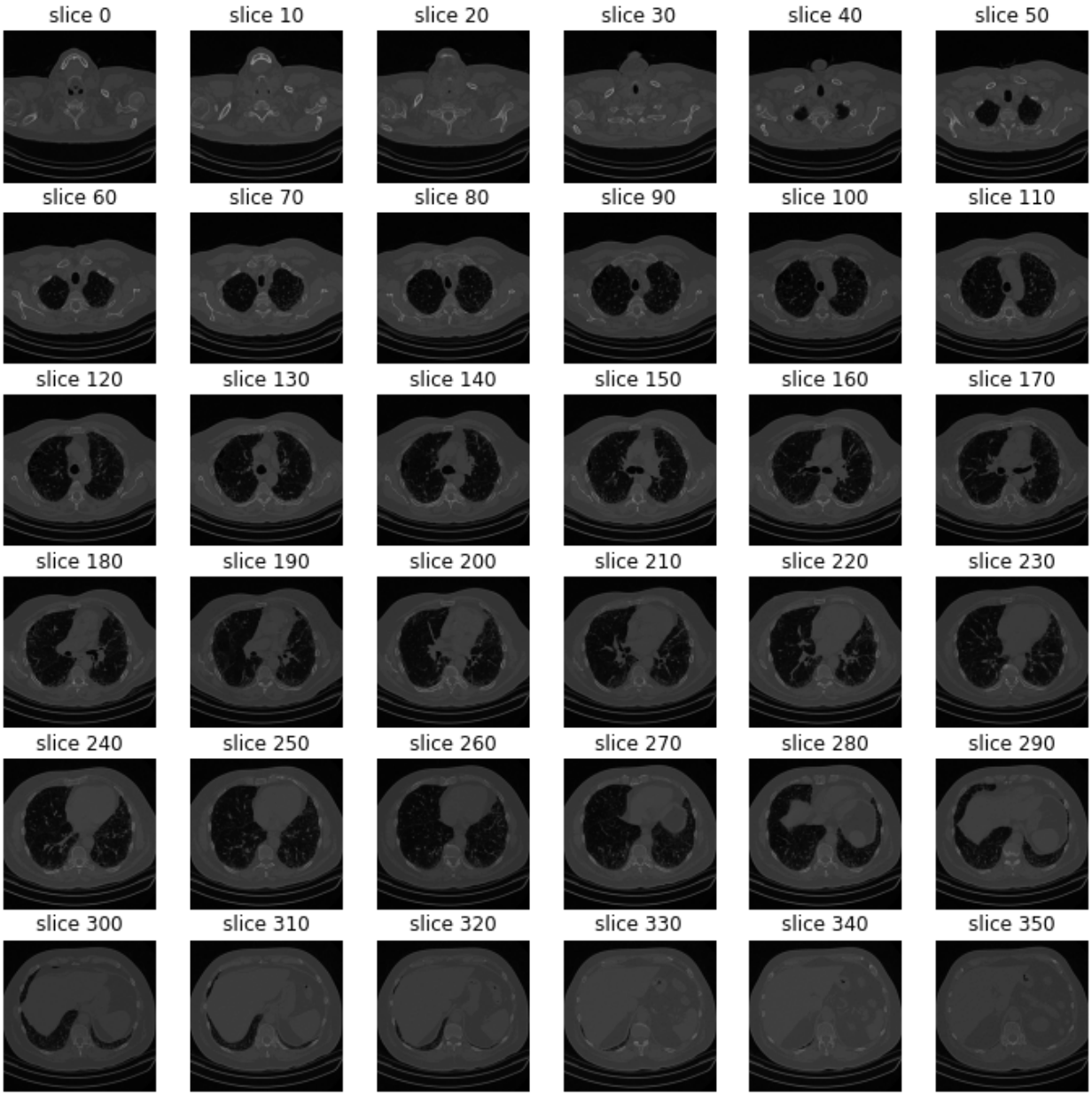
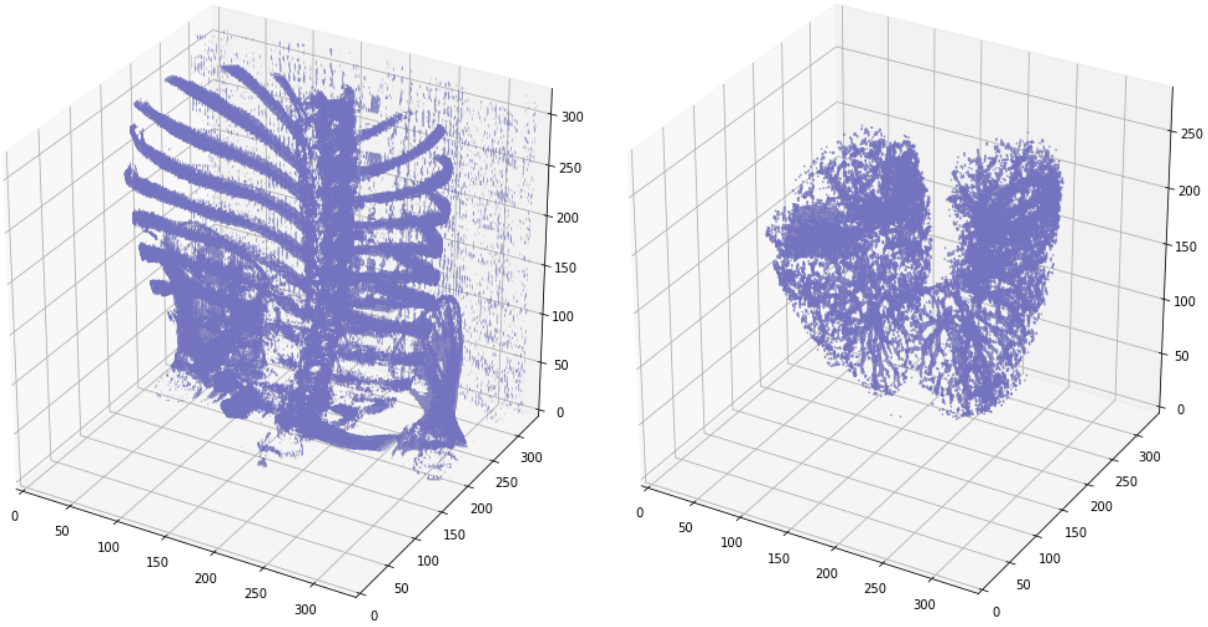


Figure 11. Displaying image every ten slices for patient (ID00009637202177434476278)

3.3 Segmentation (Masking)

Machine learning algorithms work a lot better when we narrowly define what it is looking at. One way to do this is by segmenting the lungs (and usually some tissue around it) or by applying a mask onto the original image to erase voxels outside of the lung fields. The purpose of segmenting or masking is to auto-detect the boundaries surrounding a volume of interest (our case is the lungs). The 3D plot of unmasked and masked dicom is presented in Fig 12a and 12b respectively. As shown in Fig 12b, all the surrounding tissues including bones and soft tissues are eliminated, only the vortex of lung tissue is plotted.



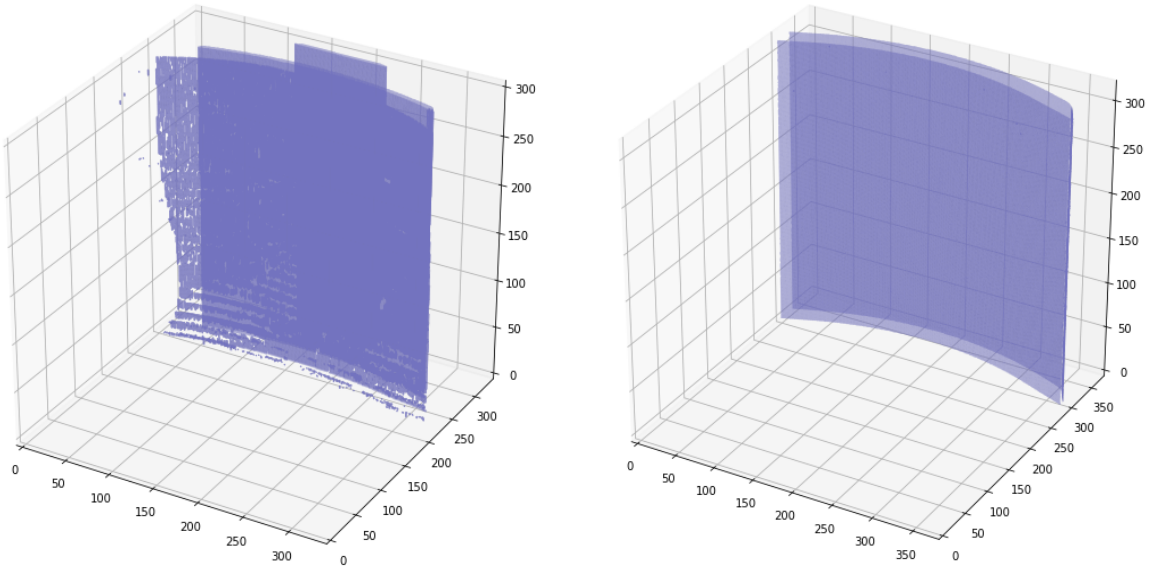
a b

Figure 12. Comparison of 3D plot of original image and segmented image of patient (ID000096372021774344762 78)

3.4 Wrangling of DICOM

Looking at the Figure above, Fig 12 (b), the segmented 3D plot, the lung part is extracted perfectly. But that is not the case for some scans. For instance, Fig. 13 below shows the segmented images of patient ID00173637202238329754031 and ID00027637202179689871102 respectively. As shown in the plot, the function used to segment a part of lungs leaving the rest up for grabs doesn't seem to work. So in order to identify the images, we counted the pixels of the binary image and see the sum of the unique pixel ratio (pr) using the following code shown in screenshot Fig 14.

After calculating the sum of the unique pixel ratio, we found that for a pixel ratio greater than approximately 100, the segmented plot works perfect. The images with less than 100 pixel ratio have no clear lung separated from other tissues. Not only some of the pixels have less than 100 pixel ratio, but only have a single binary value either zero or one. Therefore we just go ahead and drop any records where the pixels are fewer than 100 and those with a single binary value.



A ID00173637202238329754031 B ID00027637202179689871102

Figure 13. 3D plot of segmented image

```
#calculate the unique counts of the first segmented images
unique, counts = np.unique(dict_dicom['Imgs'][0], return_counts=True)
pr=dict(zip(unique, counts))
pr[0]/pr[1]
```

```
67.30670130972815
```

Figure 14. Screenshot of code used to calculate the ratio of the sum of the unique pixels in an image

4. Modeling

4.1 Feature Engineering

Machine learning models can only work with numerical values. For this reason, it is necessary to transform the categorical values of the relevant features into numerical ones by encoding categorical features into numerical features. The sex of the patient and the Smoking status of the patient are the only caterical featiures in the dataset so we will encode these two features. There are different input data is pre-processing technique of feature encoding in Data frame analytics. These are: Label-Encoder and One-Hot-Encoder, DictVectorizer and Pandas get_dummies. In this research we used simple encoding using for loops as in Fig 15.

```
#vectorize the categorical features and normilize
def get_tab(df):
    vector = [(df.Age.values[0] - 30) / 30]
    if df.Sex.values[0] == 'male':
       vector.append(0)
    else:
       vector.append(1)
    if df.SmokingStatus.values[0] == 'Never smoked':
        vector.extend([0,0])
    elif df.SmokingStatus.values[0] == 'Ex-smoker':
        vector.extend([1,1])
    elif df.SmokingStatus.values[0] == 'Currently smokes':
        vector.extend([0,1])
    else:
        vector.extend([1,0])
    return np.array(vector)
```

Figure 15 Screenshot of feature encoding

4.2 Setting-up the Evaluation Metrics

As explained in chapter 1 of section 1.6, the evaluation metric of this competition is a modified version of Laplace Log Likelihood. Where the confidence values smaller than 70 are clipped and FVC errors greater than 1000 are also clipped. The test set consists of Three_Patient_Week(s) per patient. You need to predict the Forced vital capacity(FVC) i.e. volume of air exhaled and the confidence value in our prediction.

The criterion function set to satisfy the evaluation metrics and used in the machine learning process as shown in Fig. 16. The function we want to minimize or maximize is called the objective function or criterion. When we are minimizing it, we may also call it the cost function, loss function, or error function.

```
#Define the evaluation metrics
def score(fvc_true, fvc_pred, sigma):
    sigma_clip = np.maximum(sigma, 70)
    delta = np.abs(fvc_true - fvc_pred)
    delta = np.minimum(delta, 1000)
    sq2 = np.sqrt(2)
    metric = (delta / sigma_clip)*sq2 + np.log(sigma_clip* sq2)
    return np.mean(metric)
```

Figure 16 Evaluation metric function

4.3 CNN Model

The dataset is composed of mixed data types. Which includes numerical, categorical and computerized tomography (CT) Scan images. Therefore, the convolutional neural network (CNN) model should handle all mixed inputs or we need a model that accepts multiple inputs.

4.3.1 Modeling Process

Figure 17 below shows the summary of mixed input CNN models. In one branch the model takes all the standardized numerical features and encoded categorical features as an input and the other branch takes the image data as input. The inputs that are returned contain information about the shape and dtype of the input data that you feed to your model.

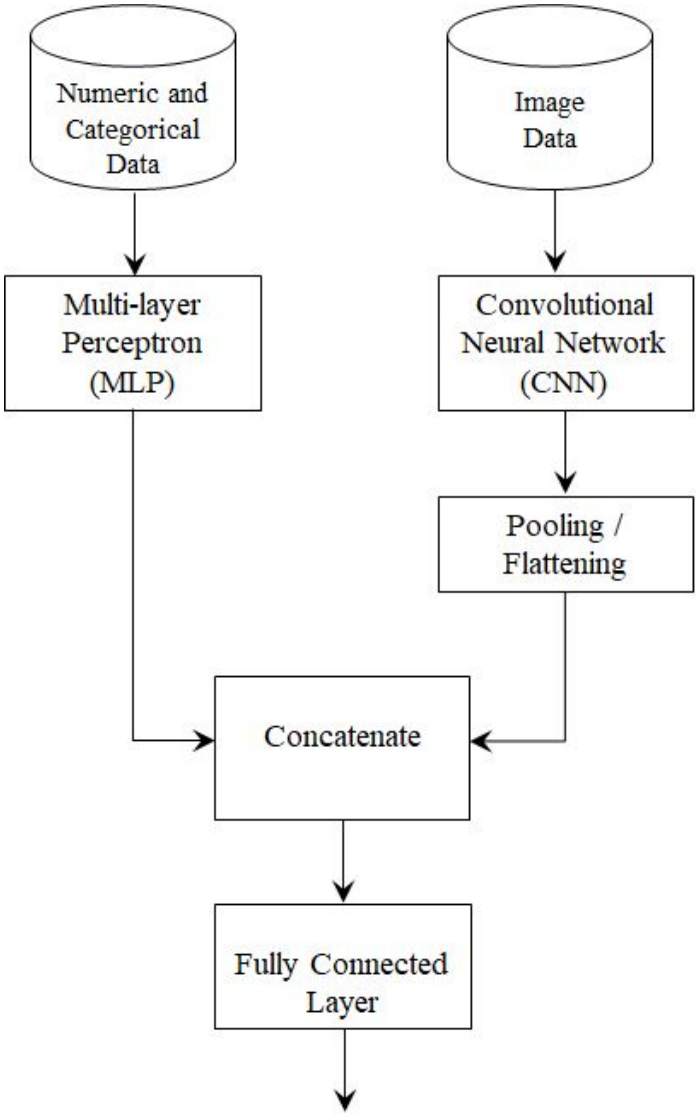


Figure 17 Keras multi-input (mixed) data model

First we created a sequence class because sequences are a safer way to do multiprocessing. Its structure guarantees that the network will only train once on each sample per epoch which is not the case with generators. Every Sequence must implement the getitem and the len methods. If we want to modify our dataset between epochs we may implement on_epoch_end. The method getitem should return a complete batch. We used a batch size of 32 which means the number of samples that will be propagated through the network is 32.

The image size was standardized to 512x512 and the ResNet convolutional neural network is designed with 8layes. It is known that neural networks are universal function approximators and that the accuracy increases with increasing number of layers. But there is a limit to the number of layers added that result in accuracy improvement. That means if we keep increasing the layer to improve the accuracy, we will see that the accuracy will start to saturate at one point and eventually degrade. In the degradation problem, we know that shallower networks perform better than the deeper counterparts that have a few more layers added to them. So, we can skip the

training of a few layers using skip-connections or residual connections. That is why we used res_block in each layer in our model design. We used advanced activation in Keras LeakyReLu. After applying GlobalAveragePooling2D on the final layer. For categorical and numeric features , we created a parallel layer. The fully connected layers of both pathways were concatenated, and were followed by an additional fully connected layer.

4.3.2 Modeling Training

Leaving the test dataset for testing to produce the final predicted files, we split the training for training and validation. Using the splited dataset, we train the model for steps_per_epoch 50 and for a total of 30 epochs. We implemented a callback object to limit the number epochs. Otherwise, too many epochs can lead to overfitting of the training dataset, whereas too few may result in an underfit model. Early stopping is a method that allows us to specify an arbitrary large number of training epochs and stop training once the model performance stops improving on a hold out validation dataset.

4.4 Model Evaluation

The loss of training and validation versus number epochs, for the first two steps the validation loss is less than the training loss, as shown in Fig. 18. This has two possible scenarios: first the training set had many hard cases to learn or second scenario would be the validation set has mostly easy cases to predict. But after the second step, the trend is very smooth for validation but with some noise for training. Looking at the loss versus epoch curve, it is smooth. This is because of the ResNet as ResNet drastically improves the loss function surface. Without ResNets, the loss function has lots of bumps, and with ResNet, it turned down to smooth. Generally, it is fair to say that the model continuously learnt.

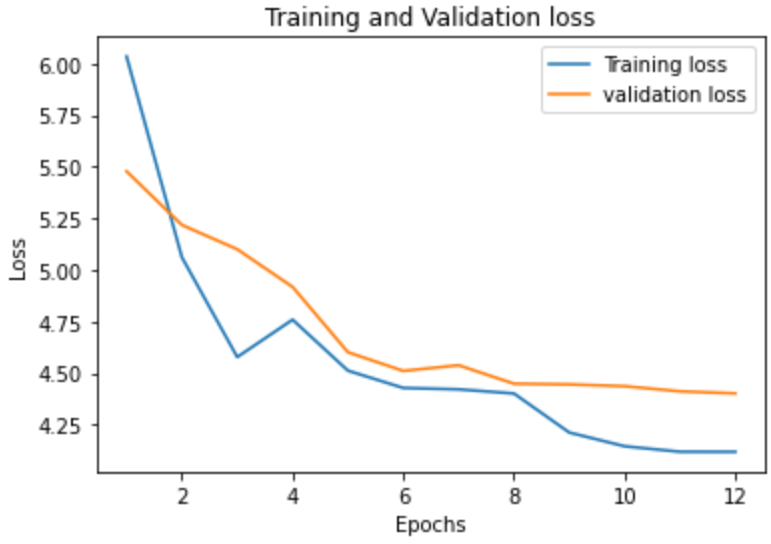


Figure 18 Training and validation loss versus epoch curve

5. Conclusion

In this project, we implemented a mixed input Keras, convolutional neural network to predict the patient's severity of decline in lung function based on a CT scan of their lungs and the details of the patient, and determine lung function based on the output from a spirometer. The Spirometer measures the volume of air inhaled and exhaled. The developed model predicts the forced vital capacity (FVC) along with its uncertainty (confidence). The confidence in this case is used in the metric calculation is basically the uncertainty of the model predictions in terms of its standard deviation. The performance of the model evaluated in terms of training and validation loss indicates that the model continuously learnt the

This kind of research helps to predict the patient's severity of decline in lung function based on a CT scan of their lungs and determine lung function based on output from a spirometer, which measures the volume of air inhaled and exhaled. Hence, the model developed in this study will give valuable information on the patient's lung function.

6. References

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