# Prognosing Idiopathic Pulmonary Fibrosis with Machine Learning

Arnav Kumar

April 20, 2021

## 1 Introduction

**Idiopathic Pulmonary Fibrosis.** Idiopathic Pulmonary Fibrosis (IPF) or Cryptogenic Fibrosing Alveolitis is a disease affecting the lung base and leads to lung function decline with little to no therapies available other than lung transplant (Gross and Hunninghake, 2001; Mason et al., 1999). Although it was previously believed that the disease affects only 5 out of every 100,000 individuals, the disease is now known to be much more prevalent (Coultas et al., 1994; Mason et al., 1999; Raghu et al., 2018). While age-related, with a median diagnosis age of 66, there is no known cause (King Jr et al., 2011; Raghu et al., 2018). Recently, there have been claims that IPF occurs as a result of abnormally activated alveolar epithelial cells (King Jr et al., 2011).

Patients of IPF experience a shortness of breath, and some features of the disease include diffuse pulmonary infiltrates recognizable by radiography and varying degrees of inflammation or fibrosis (Gross and Hunninghake, 2001). Affected lung areas alternate with unaffected areas in the lung (Gross and Hunninghake, 2001). Affected areas are characterized by the differences in cell age and due to a honeycomb fibrosis pattern (Gross and Hunninghake, 2001).

The outcome of Pulmonary Fibrosis can range from rapid health declination to a healthy stability, but doctors are unable to easily diagnose the severity of the disease. There exist methods to diagnose severity, but these can be complicated and are not standardized (Robbie et al., 2017). An example of such a method is a cough scale questionnaire or a shortness of breath questionnaire (King Jr et al., 2014; Robbie et al., 2017; van Manen et al., 2016). Another method of diagnosing severity is through a functionality test known as the 6 month 6 minute Walk Distance or 6MWD test, but as the name suggests, this test is not instantaneous, and still requires the effort of trained professionals (du Bois et al., 2014; Robbie et al., 2017). On the other hand, Machine learning has

been used with data from different points in time to provide a prognosis by using a software tool called CALIPER that uses radiological changes to predict IPF severity (Maldonado et al., 2014). Another case of using machine learning used computed tomography (CT) scans of the lung region and obtained an accuracy of around 76.4% or 70.7%, only outperformed 66% of doctors and only classified the severity rather than providing numerical estimates (Walsh, Calandriello, et al., 2018). An accurate prognosis of the disease will put patients at more ease, and may pave the path for any treatments that will come in the future. For this reason, it is essential that a consistent and easy method for diagnosing the severity of the disease is found.

**Deep Learning Methods.** Machine learning is a good fit for the task at hand because doctors can let the program run given the data, and it has been used in the past to diagnose other diseases and make predictions (Wang et al., 2010). Although machine learning has been used before for this task (du Bois et al., 2014; Maldonado et al., 2014; Robbie et al., 2017), the accuracy of the models can be improved on. Furthermore, a machine learning model could make it easier to get a prognosis.

For a disease such as IPF which is a fibrosing disease within the lungs, imaging the lungs through CT scans yields enough insight to accurately evaluate the patient's prognosis (Walsh, Devaraj, et al., 2018).

Furthermore, for injuries like neck fractures, machine learning has proven to be an improvement to the prediction performance using a method of bayesian classification (Kukar et al., 1996). For diseases like cancer, machine learning has also been used to give a prognosis and modern machine learning methods have been shown to outperform more classical methods including decision trees (Cruz and Wishart, 2006). On another note, machine learning has already been used with images of leafs to determine plant diseases and their severity, showing the ability to handle and diagnose disease severity based on a CT scan input using machine learning (Mwebaze and Owomugisha, 2016).

**Question.** This study aims to create a model that uses one baseline CT scan, as well as the forced vital capacity (FVC) of the lungs over the time period of one to two years. The model then predicts the FVC of the lungs for the next 3 checkups, and hence predicting the rate at which the lung

condition degrades. The main questions of interest are: what is the greatest accuracy a machine learning model can attain in predicting the FVC of a IPF patient on their next 3 checkups, and which method produces this accuracy?

# 2 Procedure

This study employs the use of many machine learning models. These models are coded in python (Van Rossum and Drake, 2009) with the packages Tensorflow2 (Martin Abadi et al., 2015), Scikit-learn (Pedregosa et al., 2011), and Pandas (McKinney et al., 2010). Many of these models are modified and influenced from the work of kaggle notebooks (Consortium, 2020). These models include a linear regression, simple neural network, linear regression with auto-encoder generated features, simple neural network with auto-encoder generated features, bayesian, quantile regression, and linear decay. Exploratory data analysis was performed, and the data was preprocessed for use by the models. The data was split into two categories, training data, and testing data. The models all trained on the training data, and would then be tested on the testing data which they had never seen before.

**Laplace Log Likelihood Metric.** The use of percent accuracy cannot be employed as the model is not given a categorization task, but rather a regression task. Using percent accuracy requires the model output to be discrete, not continuous. For this reason, the use of the Laplace Log Likelihood (LLL) metric is employed to measure the model accuracy. The model's FVC prediction, the true FVC, and the model's confidence are required to calculate the LLL. (Actually, confidence is a misnomer. A higher confidence score corresponds to a greater model uncertainty.)

A LLL closer to 0 represents a model which is more accurate, but the score 0 itself is unattainable for all practical purposes (due to the nature of the metric). An example of an outstanding score would be around -6.5.

The worst score a model should get is -8.023. This score is attained as a result of always guesses the mean FVC, and always has a confidence of the standard deviation of the FVCs. Any model with a LLL lower than -8.023 is useless.

The following graph shows an example of how the model's confidence affects the metric. A

confidence which is too high or too low is punished with a worse score. The local minimum describes the best metric obtainable when the predicted FVC is 2800mL, and the true FVC is 2500mL.

**Linear Regression.** The linear regression (LR) method relies on the assumption that the FVC can be expressed as a linear combination of the input features.

The linear regression model required the formatting of data by including `weeks_passed` and `first_FVC` features obtained from the patient's first checkup. After the data formatting, the Scikit-learn package was used to create a linear regressor which was then trained on the training data. This model was used to predict the FVC for the testing data, and the model accuracy was measured.

**Dense Neural Network.** The data was first formatted in the same way used for linear regression, then several dense neural networks were made, each with a different architecture. The models were then trained on the training data, and used to predict the forced vital capacity from the testing data. Then, the model with the most accurate predictions was chosen, and the model accuracy was calculated.

**Auto-encoder.** The base auto-encoder used in the study to modify the previous methods was created by Kaggle user Welf Crozzo (Crozzo, 2020a). The tabular data created by the encoder was then be used as input data for another model such as the linear regression and dense neural network models.

The encoder was loaded from Welf Crozzo's notebook, and was used to stride over the data, adding 2000 extra features based on the patient's CT scan DICOMS. Using this new input data, a linear regression and many simple neural network models were created. All these models were then trained on the training data, and used to predict the FVC for the testing data. The best simple neural network was selected and the model accuracies were calculated for the linear regression and simple neural network models.

**Bayesian Partial Pooling.** The bayesian method was modified from Kaggle user Carlos Souza and used partial pooling (Souza, 2020). The slope and $y$-intercept of the models are distributed according to a normal distribution, and the deviance of the model from the average model helped

determine confidence. Each patient has their own $\alpha_i$ and $\beta_i$ derived from a common normal distribution. FVC is predicted for the patient using the linear model $y = \alpha_i x + \beta_i$, and the confidence was found based on the amount of data known for the patient for that time range.

Features were removed from the data, and the data was reformatted into a matrix completion task. The partial pooling bayesian hierarchical model was created and trained. The testing data was similarly converted into a matrix completion task, and the model was used to predict the FVC for the testing data. Finally, the model accuracy was calculated.

**Multiple Quantile Regression.** The multiple bayesian regression method was taken from Kaggle user Ulrich G (G, 2020). The method uses convolutional neural networks and quantile regression to determine the model confidence. The quantile regression give the first and third quantiles of the FVC, which can be used to find a spread, and hence a measure of confidence.

The multiple quantile regression required the initial formatting of data by creating base information similarly to the linear regression model. The convolutional neural network was made and trained on the tabular data. The quartile difference from the ground truth was then used to calculate the model confidence. Finally, the model predicts the FVC of the patients in the testing data, and the accuracy of the model was calculated.

**Linear Decay Theory.** The linear decay method used here originates from Welf Crozzo's kaggle notebook (Crozzo, 2020b). The model assumes that the FVC of the patient decays according to the formula $FVC = a.quantile(0.75)(week - week_{test}) + FVC_{test}$, and that the confidence decays according to the formula $Confidence = Percent + a.quantile(0.75)|week - week_{test}|$. A convolutional network (CNN) was then used to predict the coefficient $a$.

Similar to the other models, the data was first formatted. A linear decay model was then created, and a convolutional neural network was made to predict the coefficients of the model. The convolutional neural network was trained with the training data, and was then used to predict the FVC and confidence for the testing data. Following the prediction, the model accuracy was calculated.

| Model | Training data | Private testing data | Public testing data |
|---|---|---|---|
| Linear Regression | -6.671 | -6.867 | -6.902 |
| Dense Neural Network | -6.763 | -6.888 | -6.953 |
| LR with Auto-encoder | -6.348 | | |
| DNN with Auto-encoder | -11.623 | | |
| Bayesian Partial Pooling | -6.146 | -6.868 | -6.909 |
| Multiple Quantile Regression | | -6.922 | -6.845 |
| Linear Decay Theory | -6.723 | -6.877 | -6.918 |

Figure 1: Laplace Log Likelihood of different models organized by dataset

# 3 Results

Figure 1 displays the model performance of the models analysed using the model's Laplace Log Likelihood. Training data is the same data that the model was trained on, whereas testing data is data the model has never seen before. Out of the testing data, there is the public testing data, which is only around 15% of the total testing data, and there is private testing data, which consists of the other 85% of the testing data.

The two models with the auto-encoders do not have matric values for the private and public testing data due to Kaggle's time limit for submissions. Both models take a lot of time to run, and hence could not be submitted to the Kaggle competition.

Figure 2 shows the accuracy of the predictions of several models. The true patient FVC is graphed against the model prediction, so a scatterplot closer to the line $y = x$ means the model is more accurate. In addition, figure 3 is a histogram of the errors of the models. For this reason, we desire an error which has low spread, is unimodal, and is centered at 0.

# 4 Conclusions

**Analysis** The results of the project clearly demonstrate that the DNN with Auto-encoder, DNN, and Multiple Quantile Regression models performed the worst. On the other hand, the best models were either purely or partly statistical. Figure 4 shows the LLL of the models as

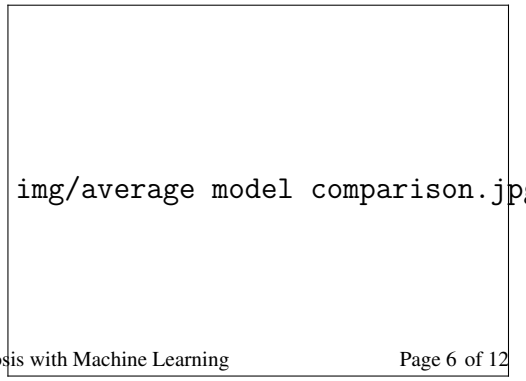
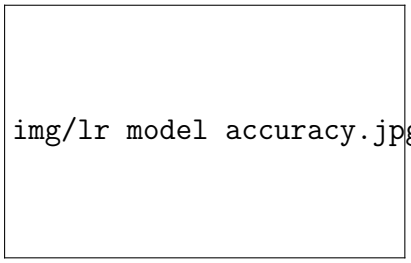
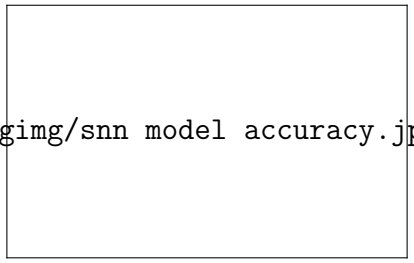


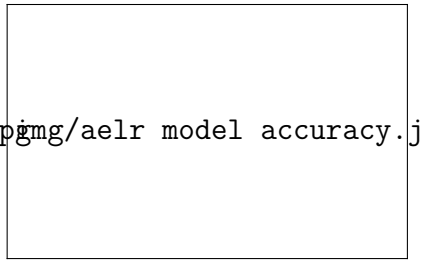

Figure 4: Comparison of Average Model LLL



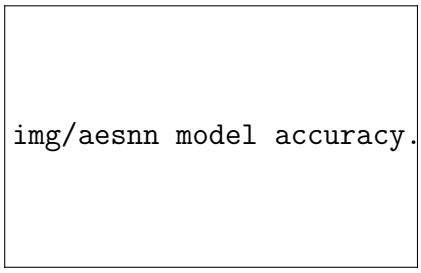

(a) Linear Regression



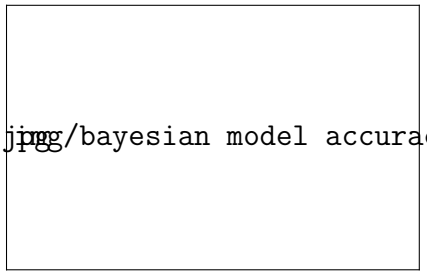

(b) dense neural network




(c) LR with Auto-encoder

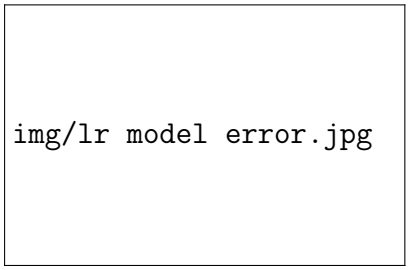



(d) DNN with Auto-encoder

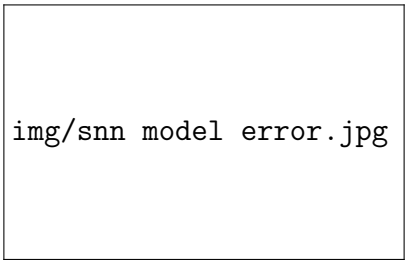



(e) Bayesian Partial Pooling

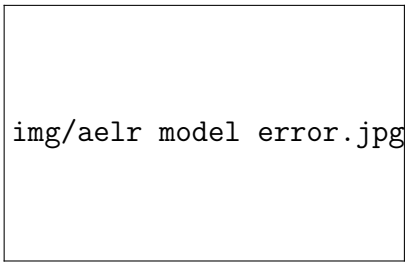
Figure 2: Plots of True FVC vs Model Prediction



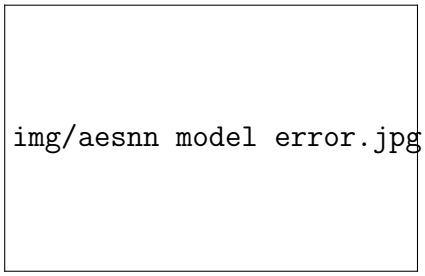

(a) Linear Regression



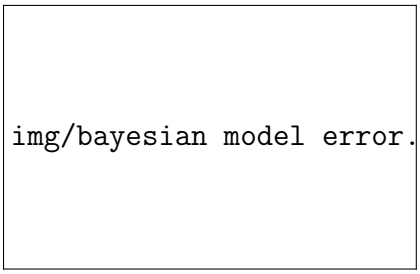

(b) dense neural network




(c) LR with Auto-encoder




(d) DNN with Auto-encoder




(e) Bayesian Partial Pooling

Figure 3: Plots of True FVC vs Model Prediction

a graph, verifying that statistical models performed the most consistently, and with greatest accuracy.

Overall, models which use neural networks perform poorly because a linear model is sufficient to represent

the data. By introducing extra layers which means a lot or more tunable variables, there is a lower chance that the model will find the best combinations of weights. Instead, the model will likely end up with a suboptimal set of weights and biases, and will have reached a 'local minimum' rather than a 'global minimum'.

This is displayed prominently in the Dense Neural Network with Auto-encoder features which has a LLL score worse than. Figure 1 demonstrates that this model has a LLL worse than the baseline score of -8.023. Additionally, figure 3(d) supports the idea that this model is inaccurate due to it's high error. The reason for it's poor performance can be attributed to the high number of input features of the model. These input features each create more weights and biases for the model to train, and there is a higher chance of reaching an nonoptimal local minimum.

Another interesting find is that the Bayesian Partial Pooling method seemed to overfit the training data. Its performance on the training data was much better than the testing data, but this model still outperformed many others.

There are several other factors that make the statistical models a better choice. For the field of medicine, having a method which is well understood is prefered, and statistical methods are guaranteed to always perform as expected. Additionally, these methods provide a useful measure of confidence to doctors.

Overall, use of the Bayesian Partial Pooling or Linear Decay Theory methods are advised for their accuracy, consistency, and confidence values.

**Significance** The results of this project allowed the accurate and successful prognosis of IPF. The use of the Linear Decay Theory Model or the Bayesian Partial Pooling Model would not only eliminate human bias in the prognosis, but it would give patients enough time to come to terms with their disease and look into what lifestyle changes they can make to slow the progression.

Additionally, the lessons learnt from this project can be applied to the diagnosis and prognosis of their diseases. Namely, the lesson of not overcomplicating the model can be applied to other projects and has a similar conclusion has been made before in many other projects. This phenomina has been described by Occam's razor, which states that when there are multiple competing

hypothesis (the multiple models being compared), the hypothesis with the simplest assumption (the assumption that FVC is a linear function of features) is the best hypothesis.

# 5 Acknowledgements

Thank you to Dr. Christian Jacob for supporting and guiding me through the project. Additionally, I would like to thank my teachers, Dr. Beatriz-Garcia Diaz and Ms. Bogusia Gierus for their continued support. Finally, I would like to thank Mr. Chuck Buckley for providing invaluable feedback.

# References


Consortium, O. S. I. (2020). Osic pulmonary fibrosis progression. Kaggle. Retrieved, from https://www.kaggle.com/c/osic-pulmonary-fibrosis-progression

Coultas, D. B., Zumwalt, R. E., Black, W. C., & Sobonya, R. E. (1994). The epidemiology of interstitial lung diseases. *American journal of respiratory and critical care medicine*, *150*(4), 967–972. https://doi.org/10.1164/ajrccm.150.4.7921471

Crozzo, W. (2020a). Image2vec: Autoencoder. https://www.kaggle.com/miklgr500/image2vec-autoencoder

Crozzo, W. (2020b). Linear decay (based on resnet cnn). https://www.kaggle.com/miklgr500/linear-decay-based-on-resnet-cnn

Cruz, J. A., & Wishart, D. S. (2006). Applications of machine learning in cancer prediction and prognosis. *Cancer informatics*, *2*. https://doi.org/10.1177/117693510600200030

du Bois, R. M., Albera, C., Bradford, W. Z., Costabel, U., Leff, J. A., Noble, P. W., Sahn, S. A., Valeyre, D., Weycker, D., & King, T. E. (2014). 6-minute walk distance is an independent predictor of mortality in patients with idiopathic pulmonary fibrosis. *European Respiratory Journal*, *43*(5), 1421–1429. https://doi.org/10.1183/09031936.00131813

G, U. (2020). Osic-multiple-quantile-regression-starter. https://www.kaggle.com/ulrich07/osic-multiple-quantile-regression-starter

Gross, T. J., & Hunninghake, G. W. (2001). Idiopathic pulmonary fibrosis. *New England Journal of Medicine*, *345*(7), 517–525. https://doi.org/10.1056/NEJMra003200

King Jr, T. E., Bradford, W. Z., Castro-Bernardini, S., Fagan, E. A., Glaspole, I., Glassberg, M. K., Gorina, E., Hopkins, P. M., Kardatzke, D., Lancaster, L., Et al. (2014). A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *New England Journal of Medicine*, *370*(22), 2083–2092. https://doi.org/10.1056/NEJMoa1402582

King Jr, T. E., Pardo, A., & Selman, M. (2011). Idiopathic pulmonary fibrosis. *The Lancet*, *378*(9807), 1949–1961. https://doi.org/10.1016/S0140-6736(11)60052-4

Kukar, M., Kononenko, I., & Silvester, T. (1996). Machine learning in prognosis of the femoral neck fracture recovery. *Artificial intelligence in medicine*, *8*(5), 431–451. https://doi.org/10.1016/S0933-3657(96)00351-X

Maldonado, F., Moua, T., Rajagopalan, S., Karwoski, R. A., Raghunath, S., Decker, P. A., Hartman, T. E., Bartholmai, B. J., Robb, R. A., & Ryu, J. H. (2014). Automated quantification of radiological patterns predicts survival in idiopathic pulmonary fibrosis. *European Respiratory Journal*, *43*(1), 204–212. https://doi.org/10.1183/09031936.00071812

Martin Abadi, Ashish Agarwal, Paul Barham, Eugene Brevdo, Zhifeng Chen, Craig Citro, Greg S. Corrado, Andy Davis, Jeffrey Dean, Matthieu Devin, Sanjay Ghemawat, Ian Goodfellow, Andrew Harp, Geoffrey Irving, Michael Isard, Jia, Y., Rafal Jozefowicz, Lukasz Kaiser, Manjunath Kudlur, ... Xiaoqiang Zheng. (2015). TensorFlow: Large-scale machine learning on heterogeneous systems [Software available from tensorflow.org]. https://www.tensorflow.org/

Mason, R. J., Schwarz, M. I., Hunninghake, G. W., & Musson, R. A. (1999). Pharmacological therapy for idiopathic pulmonary fibrosis: Past, present, and future. *American Journal of Respiratory and Critical Care Medicine*, *160*(5), 1771–1777. https://doi.org/10.1164/ajrccm.160.5.9903009

McKinney, W. Et al. (2010). Data structures for statistical computing in python, In *Proceedings of the 9th python in science conference*. Austin, TX.

Mwebaze, E., & Owomugisha, G. (2016). Machine learning for plant disease incidence and severity measurements from leaf images, In *2016 15th ieee international conference on machine learning and applications (icmla)*. IEEE. https://doi.org/10.1109/ICMLA.2016.0034

Pedregosa, F., Varoquaux, G., Gramfort, A., Michel, V., Thirion, B., Grisel, O., Blondel, M., Prettenhofer, P., Weiss, R., Dubourg, V., Vanderplas, J., Passos, A., Cournapeau, D., Brucher, M., Perrot, M., & Duchesnay, E. (2011). Scikit-learn: Machine learning in Python. *Journal of Machine Learning Research*, *12*, 2825–2830.

Raghu, G., Remy-Jardin, M., Myers, J. L., Richeldi, L., Ryerson, C. J., Lederer, D. J., Behr, J., Cottin, V., Danoff, S. K., Morell, F., Et al. (2018). Diagnosis of idiopathic pulmonary fibrosis. an official ats/ers/jrs/alat clinical practice guideline. *American journal of respiratory and critical care medicine*, *198*(5), e44–e68. https://doi.org/10.1164/rccm.201807-1255ST

Robbie, H., Daccord, C., Chua, F., & Devaraj, A. (2017). Evaluating disease severity in idiopathic pulmonary fibrosis. *European Respiratory Review*, *26*(145). https://doi.org/10.1183/16000617.0051-2017

Souza, C. (2020). Bayesian experiments. https://www.kaggle.com/carlossouza/bayesian-experiments

Van Rossum, G., & Drake, F. L. (2009). *Python 3 reference manual*. Scotts Valley, CA, CreateSpace.

van Manen, M. J., Birring, S. S., Vancheri, C., Cottin, V., Renzoni, E. A., Russell, A.-M., & Wijsenbeek, M. S. (2016). Cough in idiopathic pulmonary fibrosis. *European Respiratory Review*, *25*(141), 278–286. https://doi.org/10.1183/16000617.0090-2015

Walsh, S. L., Calandriello, L., Silva, M., & Sverzellati, N. (2018). Deep learning for classifying fibrotic lung disease on high-resolution computed tomography: A case-cohort study. *The Lancet Respiratory Medicine*, *6*(11), 837–845. https://doi.org/10.1016/S2213-2600(18)30286-8

Walsh, S. L., Devaraj, A., Enghelmayer, J. I., Kishi, K., Silva, R. S., Patel, N., Rossman, M. D., Valenzuela, C., & Vancheri, C. (2018). Role of imaging in progressive-fibrosing interstitial lung diseases. *European Respiratory Review*, *27*(150). https://doi.org/10.1183/16000617.0073-2018

Wang, Y., Fan, Y., Bhatt, P., & Davatzikos, C. (2010). High-dimensional pattern regression using machine learning: From medical images to continuous clinical variables. *Neuroimage*, *50*(4), 1519–1535. https://doi.org/10.1016/j.neuroimage.2009.12.092