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A probabilistic Model for COPD Diagnosis and Phenotyping Using Bayesian Networks

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ABSTRACT

Introduction: This research was meant to provide a model for COPD diagnosis and to classify the cases into phenotypes; General COPD, Chronic bronchitis, Emphysema, and the Asthmatic COPD using a Bayesian Network (BN).

Methods: The model was constructed through developing the Bayesian Network structure and instantiating the parameters for each of the variables. In order to validate the achieved results, the same data set was applied to a neural network application using the Levenberge- Marquardt algorithm. Furthermore, a card Diag, a C++ application that enables graphical classification of COPD into phenotypes and depicts the relationships of COPD phenotypes was developed.

Results: The results showed that a Bayesian Network can be successfully applied to develop a probabilistic model for diagnosis and classification of COPD cases into the corresponding phenotypes.

Conclusions: A model that classifies COPD cases into phenotypes of general COPD, Chronic bronchitis, Emphysema, and Asthmatic COPD was successfully developed. Moreover, the achieved results also helped to represent graphical representations of COPD phenotypes and explained how the phenotypes relate to each other. It was also observed that COPD is mostly associated with people aged 40 years or older. Overall, smoking is the major cause of COPD.

Keywords: Bayesian networks, COPD Diagnosis, COPD Phenotypes, Noisy-OR CPD

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is caused by inflammation and obstruction of the small airways in the lungs [1, 2]. The development of COPD may be assumed as a result of procedures in which the airways and alveoli lose elasticity, alveoli walls are destroyed, the airway walls become thick, the airways secrete a lot of mucus which leads to their blockage.

The World Health Organization (WHO) points COPD as the fourth leading cause of death worldwide. Yet, it is a both treatable and preventable disease [1, 3, 4]. Smoking of tobacco products, alpha-1-antitrypsin (A1At), and air pollution are the main risk factors associated with the development and progression of COPD [5, 6]. COPD is usually either undiagnosed or under-diagnosed due to a number of factors, including slow progression of COPD symptoms development [7]. In addition, differentiating COPD patients and those with chronic asthma may not be so easy [1, 4].

A number of researchers have conducted some commendable works on COPD diagnosis. However, most of such studies have been mainly based on the results of pulmonary test using a spirometry [7-9]. Moreover, such studies have also classified COPD cases using the GOLD initiative staging criteria; stage I – IV that is based on the severity of the disease [1, 4]. Regardless the fact that the first step towards managing the effects of disease in a patient starts by determining the disease type, there is a lack of research purposed to identify the type of COPD phenotype (General COPD, Chronic bronchitis, Emphysema, and the Asthmatic COPD) the patient may be suffering from. For instance, given an asthmatic COPD case, if the diagnosis ends up with COPD positive, asthma would be left unattended. Therefore, it is very essential for a diagnosis to not only determine the severity but also the COPD phenotype.

1.1 COPD Phenotypes

1.1.1 Asthma

Asthma is a disorder characterized by chronic airway obstruction, hypersensitivity, and airway inflammation due to an encounter with some stimuli [1, 4, 10]. Airflow obstruction in Asthma could be partially or completely reversible. Moreover, Asthma effects are experienced both during exhalation and inhalation by different patients. Asthma has different magnitudes from a simple nuisance to a life-threatening effect [2, 10]. Asthma symptoms include chest tightness, shortness of breath, sputum production, coughing, and wheezing.

1.1.1 Chronic Bronchitis

Chronic bronchitis is characterized by a constant irritation and/or inflammation of the lining walls of bronchial tube [2, 5]. Chronic bronchitis develops from its acute form and is usually caused by smoking or exposure to irritants. Chronic bronchitis symptoms include a cough that becomes chronic over time and sputum production which changes coloration to yellowish-brown and bloody with progression of the disease.

1.1.2 Emphysema

Emphysema is characterized by destruction of air sacs leading to shortness of breath [2, 5, 10]. Emphysema is usually associated with heavy smoking or exposure to irritants and as Emphysema progresses, the patient tends to avoid activities that lead to shortness of breath.

1.2 Probabilistic graphical modelling: Bayesian Networks (BNs)

Methods of knowledge modelling are very important for succession of designed intelligent systems and software [11-13]. Probabilistic Graphical Modelling (PGM) is strengthened by probability theory which offers a declarative representation of the vague events that offer great reasoning capabilities. Therefore, an amalgamation of graphical models and probability theory is more intuitive, hence it is served as a great tool for probabilistic reasoning. There are two types of graphical models; the Bayesian Networks (BNs) and Markov Networks (MNs) [14].

However, this study only focused on modelling and reasoning with Bayesian networks for COPD disease diagnosis given the fact that Bayesian networks give a clear representation of cause(s) and effect(s) as experienced in the case of diseases,

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risk factors, and symptoms. A Bayesian network is a type of a probabilistic graphical model composed of random variables connected with the caused effect form [15]. That is, a variable in the Bayesian network may have one or many parents, but all variables do not have parents. Also, the connection between the variables is in such a way that cannot be traversed through the network and end up where stated. Therefore, a Bayesian network is said to be a Directed Acyclic Graph (DAG) [5]. Each variable in a BN has a Conditional Probability Table (CPT) and each parent-child relationship in a BN is associated with a Conditional Probability Distribution (CPD) that defines such joint probability distributions.

Methods

This study was a cross sectional study. The dataset used in this study was obtained through conducting interviews with patients at the location where this study was conducted. Patients were instructed on the goals of this research and importance of their support. The interview questions were organized in a structured linguistic form so that patients could describe their health conditions. For example, a question about shortness of breath was categorized as: High, Moderate, Low or None. In addition, to ensure about accuracy of patients' choices, they were expected to state the time period over which they have experienced such a condition and assert a number value in the range 0f 0 to 10.

Since this study was conducted under a highly experienced respiratory system specialist, it can adequately be said that whether a patient was genuinely answering the survey questions. As a matter of fact, there were a number of patients who would deny telling the truth about their social and health histories. However, as a part of interview training, researchers were made aware that such a social behaviour is possible in medical practices.

The data set used in this study had 200 cases; 100 COPD and 100 Asthma, respectively. A total of 200 cases were collected from interviews which were then randomly divided to 60 % training data set and 40 % testing data sets. There were cases of chronic bronchitis, emphysema, asthma, acute asthma, and the general COPD in the data set. To ensure about an even distribution and random assignment of each patient case to the training or testing sets, the data set was categorized by the type of disease and assigned each case an identification number. Thereafter, random numbers were generated in each group and fractions were obtained for training and testing groups based on the percentages as specified above.

1.2 Bayesian Networks in Medical Diagnosis

Medical diagnosis is both a science and art involving decision making that sometimes may be performed with much uncertainty. Therefore, medical diagnosis is not different from human reasoning in which decision making is mainly performed based on the known facts and underlying assumptions. The use of facts and assumptions in reasoning is usually based on the degree of belief assigned to each of the variables. Thus, it's the degree of belief that qualifies some information as either a fact or an assumption.

A Bayesian network is a modelling tool used for reasoning which uses degrees of belief as probabilities [0, 1]. Bayesian networks fit in medical diagnosis because events in the network are not only handled as true or false, but also as present or absent to a certain degree. In a Bayesian network, the variables usually include risk factors, constituent diseases, and symptoms. For example, consider a symptom X and parameters $x_1 \ldots x_n$, with x_1 being the lowest level of symptom X and x_n being the highest level of symptom X. Therefore, a given patient may only experience a given symptom to some x_1 level but not at x_n level. Such a representation can only be simplified using BNs.

So, modelling with a BN is using a set of tools and techniques aimed to create a complex system which attempts to depict the relationships between network variables and causations of certain events and their corresponding outcomes. Thus, variables in a BN are random variables and their goal is to determine the relationships that maximize or

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explain certain outcomes of events.

A Bayesian network fits in modelling medical diagnosis problems because it offers a consistent and complete representation of variables in the network. This network is a composition of subunits that fit together into a coherent whole system. Also, a Bayesian network offers a complete illustration to specify a probability distribution assuming that the number of direct causes of events remains minimal [14, 15]. A combination of the above characteristics makes BN a consistent tool fitting for modelling in medical diagnosis.

1.3 Building the Bayesian Network

The process of developing this model was iterative and started by consulting with experts and also studying through the relevant literature. Interviews were necessary for the COPD patients to collect data. This involved developing a structured questionnaire based on network representation.

So, we ended up with a questionnaire of ten questions in addition to patient age and a Bayesian network of five risk factors (Smoking, Exposure, Age, Allergy, and Family History of either Asthma or COPD), four diseases (COPD, Asthma, Chronic bronchitis, and Emphysema), and lastly six symptoms (Dyspnea, Cough, Sputum, Chest pain, Body Activity, and Wheezing). Also, each of the variables has constituent parameters distributed in a representation based on degrees of belief.

1.4 Micro Models

One of the major challenges in encountering with Bayesian networks involves dealing with large probability distributions. The first solution to such a problem lies in the use of micro model techniques which include the Noisy-Or model, deterministic CPDs, tree CPDs, and sigmoid CPDs among others [14].

One of the micro models that stands out in medical diagnostic problems is the Noisy-Or model for its simplicity [13]. Using the Noisy-Or, an X number of diseases can give rise to some symptom y provided that at least one of the diseases is present. Therefore, a conditional probability P (e|C1, C2… Cn) can be built as [1]:

$$P(e|C) = 1 - \prod 1 - P(e|C_i) \qquad (1)$$

Figure 1 represents an example of the Noisy-Or design.

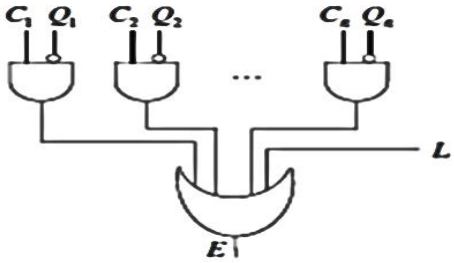


Figure 1. An example sketch diagram showing the Noisy-Or micro model design

In a Noisy-Or CPD, each Ci parent is capable of establishing an effect on the effect E except under some unusual circumstances by the suppressor Qi. In addition, the leak variable is meant to represent all other causes of effect E not included in the model. However, the Noisy-Or model can be simplified by eliminating all the network variables that have single children as long as their absence will not compromise network accuracy [14, 16].

The act of eliminating such variables is known as bypassing and leaves a simplified design as shown in Figure 2.

1.5 Levenberg-Marquardt algorithm

To verify test results from the Bayesian network, a neural network application was developed using the Levenberg-Marquardt (LM) algorithm as the training algorithm. The LM algorithm was designed to serve as an intermediate optimization algorithm between the Gauss-Newton method and gradient descent algorithm and address the limitation of each of those techniques [17]. The mathematical description of the LM neural network training algorithm has been presented by Hagan and Menhaj (1994) [18].

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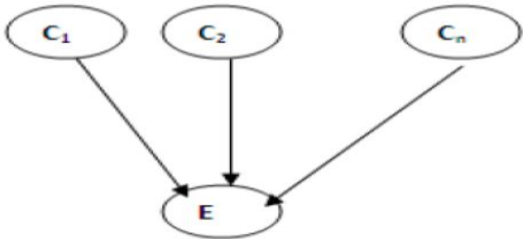


Figure 2. An example sketch diagram showing the relationships of variables in a pruned Bayesian network after bypassing non- essential variables.

1.6 Model evaluation

Accuracy, precision, recall, and F-Score were applied to evaluate the model, where precision was defined as (2), recall as (3), and F-Score was defined as (4).

Precision = (# correct) / (# Guessed) (2)

Recall = (# correct) / (# actual) (3)

F-score = (2 × precision × recall) / (precision + recall) (4)

Precision is a measure of a classification system's ability to present only relevant items. Recall is the measure of a system's ability to correctly classify all relevant items. Precision and recall results of classification systems are usually inversely proportional. That is, the higher the precision, the lower the recall and vice versa. However, the main objective of determining precision and recall was to achieve a compromise of the two measures to avoid presenting results that may be biased. F measure, also known as F-score or F1-score is used to get a trade-off, i.e., the harmonic mean of precision and recall. F1 score of 0 is said to be very low and so performs poorly, further, an F1 score of 1 as well achieves the maximum performance. Therefore, an F1 score of precision and recall attempts to achieve an acceptable average for the system performance regarding to data classification. In other words, with precision and recall, a balance is sought through which a classification algorithm achieves a balance of both true positive and negative results.

Results

The test data set used in this study comprised of 40 COPD and 40 Asthma cases. We applied each of the test cases to the Bayesian network and achieved impressive results. In order to validate our results, we also developed a neural network application using the Levenberg-Marquardt (LM) algorithm and the results clearly showed that the Bayesian network results reflect a true representation of our physician expert's diagnosis for each of the patient cases. In addition to validating the test results using a neural network representation, we developed a C++ application that enables us to visually see the distribution of the various COPD phenotypes and asthma diseases by generating an integer value based on a combination of the specifications of the patient's risk factor and symptoms. We have discussed each of our solutions in the sections below.

1.7 Results using the Bayesian Network

We applied the test data set to our Bayesian network and achieved very impressive results. The Bayesian network managed to classify all 40 Asthma cases correctly. In addition, the Bayesian network singled out 6 Asthma cases to be of the asthmatic COPD phenotype. This classification acknowledges the presence of both Asthma and COPD in a given patient at the same time. As a result, we can comfortably claim a 100 % classification of the Asthma test cases. Moreover, for the 40 COPD cases, the Bayesian network also managed to classify 39 of the 40 cases amongst the various COPD phenotypes. The Bayesian network classified 1 COPD test case as Asthma. What's more, the network also identified 5 COPD cases to be of the asthmatic phenotype. Consequently, the Bayesian network achieved a ((39 / 40) * 100) 97.5 % classification of the COPD test cases. Tables 1 and 2 below give a summary of the results as achieved by the Bayesian network.

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Table 1. Bayesian Network Classification results of 40 Asthma test cases

Disease Classification	Number of Cases
Asthma	34
Asthmatic COPD	6

Table 2. Bayesian Network Classification results of 40 COPD test cases

COPD Phenotype	Number of Cases
Asthma	1
Asthmatic COPD	13
Bronchitis	5
General COPD	21

1.8 Results using Neural Networks

Furthermore, to validate the model, the same data set was applied to a neural network application on MatLab using the Levenberg-Marquardt (LM) as the training algorithm, results were reasonable compared to those achieved by Bayesian network. Tables 3 and 4 give a summary of our results using Levenberg-Marquardt algorithm.

Firstly, the neural network classification of the Asthma disease test cases closely matches the Bayesian network results as we were able to achieve 100 % classification of the Asthma test cases. The neural network classified 34 cases as Asthma and 6 cases as asthmatic COPD cases. Table 3 below shows the summaries of the results from the neural network application for the Asthma test cases.

Table 3. Neural Network Classification results of 40 Asthma test cases

Disease Classification	Number of Cases
Asthma	34
Asthmatic COPD	6

Secondly, the neural network classifications of the COPD test cases were as well impressive. We had the neural network application classify 10 cases as general COPD, 25 as chronic bronchitis, and 2 as the asthmatic COPD phenotypes. However, we had 2 COPD test cases classified as Asthma and 1 COPD test case classified as neither Asthma nor COPD diseases. Table 4 below gives a summary of the results we achieved from the classification of COPD test cases using neural networks.

Table 4. Neural Network Classification results of 40 COPD test cases

COPD Phenotype	Number of Cases
Asthma	2
Asthmatic COPD	2
Bronchitis	25
General COPD	10
None	1

1.9 CardDiag Application

Additionally, a C++ application named cardDiag was developed that assigned a numerical value between negative infinity to positive infinity to each of the patient cases. Thereafter, a scatter plot and a group plot of the test dataset values were created by the cardDiag application as shown in the figures below.

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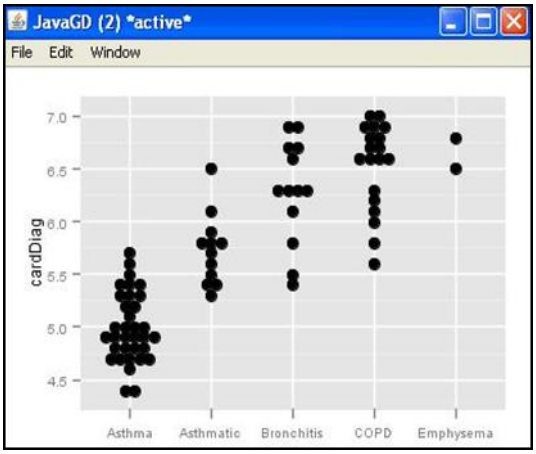


Figure 3. A screen snapshot of the CardDiag Application results' scatter plot. It shows classification and distribution of COPD phenotypes. This scatter plot was developed using R statistical software.

As it can be seen in Figure 3, Asthma, asthmatic COPD, and Chronic bronchitis are the most common. This is because advanced cases of COPD tend to be an amalgamation of chronic bronchitis and Emphysema diseases.

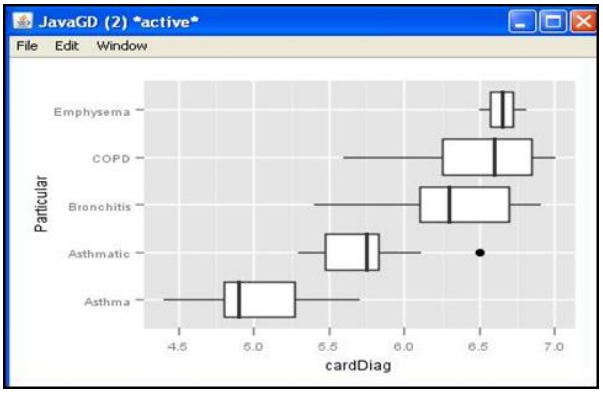


Figure 4. A screen snapshot of the cardDiag Application results' group plot. It shows the classification and distribution of COPD phenotypes. This scatter plot was developed using R statistical software.

Precision and recall were used to calculate F1 score used as metric to evaluate classification algorithms with the results as shown in Table 5 below. F1 score values from 0 to 1 and higher scores were better.

Table 5. Calculated values for the precision, recall, and F1 score in Bayesian network

Model	Accuracy	Precision	Recall	F1 Score
Bayesian network	0.9625	1	0.9875	0.9937
Neural network using LM algorithm	0.9625	1	0.9625	0.9809

Both techniques achieved the same accuracy and precision results and had high F1 scores. However, recall and F1 score for the Bayesian network show better result than for the LM algorithm.

Discussion

Diagnosis and phenotyping of COPD is a difficult task; without experience and personally acquired skills a physician may end up with wrong results for dealing with other COPD cases. By application of Bayesian networks, as one of the probabilistic graphical modelling techniques, it can provide a better model for medical diagnosis cases that require differential diagnosis. To conduct a

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diagnosis of COPD, a differential diagnosis of Asthma is required.

Several studies have attempted to diagnose, classify, and predict COPD [19-22]. This study is the first research that has attempted to classify COPD cases into phenotypes. The present study illustrates that BN is a robust tool for modelling medical diagnosis (especially, the COPD). Results of the study showed a successive relation and overlap of Asthma and COPD phenotypes. Both the Bayesian network and the LM algorithm (used to verify the model) had a 100 % classification of 40 Asthma test cases as shown in Tables 1 and 3. However, the Bayesian networks classified the 40 COPD test cases as 39 COPD and 1 Asthma. On the other hand, the LM algorithm classified 37 out of 40 test cases as COPD, 2 as Asthma, and 1 as neither Asthma nor COPD.

Actually, the little variation in the classification using the two techniques above is related to the reasoning approach. For instance, a probability of 0.20 was used as the threshold. That is for a given case with the Bayesian networks a probability of 0.87 for COPD, Chronic bronchitis with a probability of 0.77, and Asthma with a probability of 0.18 are declared, using threshold of a probability of 0.20, it can be said that this case belongs to the chronic bronchitis phenotype. However, the LM algorithm classified some cases to be asthmatic COPD with probabilities as low as 0.12. For example, one of the cases classified as asthmatic COPD by the LM algorithm is a case with ID of 200.

According to the BN, for this case, COPD has a probability of 0.845 with chronic bronchitis and Asthma equal to 0.685 and 0.124, respectively. Therefore, use such results should be applied to adopt an acceptable threshold when using the Bayesian network. However, from the achieved results, the Bayesian network has proven to be a better tool for classifying cases for COPD diagnosis.

Conclusions

There are a number of observations and conclusions from this research. First and foremost, the Bayesian network has proven that computational techniques can be employed not only to diagnose COPD and Asthma, but also to classify COPD cases based on phenotypes; general COPD, chronic bronchitis, emphysema, and asthmatic COPD. Second, the results from our cardDiag application also confirm that one can go beyond classifying COPD cases to also observe the overlaps in COPD cases. Figure 4 above represents the overlap between Asthma, Asthmatic COPD, and chronic bronchitis. In addition, the same figure also shows an overlap between chronic bronchitis and emphysema. Hence, the middle point between asthma and chronic bronchitis is asthmatic COPD and the middle point between chronic bronchitis and emphysema is general COPD.

1.10 General Observations

Some of the general observations made include; 94 out of 100 COPD cases were associated with cigarette smoking. Also, 93 of 100 COPD cases were associated with patients of 40 years or older. For the COPD cases with patients younger than 40, heavy smoking or a high exposure to any of the risk factors was observed. Finally, the essential variables for consideration of COPD diagnosis are as follows.

Risk factor:

- smoking of tobacco products or exposure to their second hand smoke
- exposure to other irritants such as chemical, metal fumes, etc.
- Age –COPD symptoms may be experienced anywhere between early 30s and 40 years of age.
- Asthma
- Symptoms:
- Cough – starts scantily and worsens with the progression of the disease. The cough is most likely associated with chronic bronchitis cases and may not be observed in patients with emphysema.
- Sputum (phlegm or mucus) – people with COPD cough out sputum that starts colorless, becomes yellowish-brown, and then bloody which is based on the severity of the disease. Sputum is most likely associated with chronic bronchitis cases and may not be observed in patients with

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emphysema.

- Body activity – COPD patients may feel no significant change in their bodies in the early stages of the disease. However, as COPD progresses, such patients may feel from slightly weak to very weak depending on their physical activity.
- Dyspnea – commonly known as shortness of breath is the main reason for body inactiveness and worsens over time. Dyspnea is common in all COPD cases. However, dyspnea severity is usually the highest in patients with emphysema.

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Conflict of interest

The authors declare that there is no conflict of interests.

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