## ORIGINAL RESEARCH

# Computational Models for Diagnosing Tuberculosis: A Systematic Review

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**Abstract:**

**Introduction:** Tuberculosis (TB) is an infectious disease caused by the bacterium Mycobacterium tuberculosis. It kills about 1.5 million people per year and about 95% of its victims are from Africa. A major problem of TB is the difficulty in its diagnosis due to the fact that in most cases, it is either asymptomatic or latent. This difficulty in diagnosis has motivated the development of various algorithms for TB diagnosis most of which have poor diagnosis power.

**Aim:** This research focused on systematic review and analysis of computational models for diagnosis of TB with the view to identifying their strengths and weaknesses. The overall target is to develop a standard and robust computational model with improved diagnostic power.

**Method:** Selection was from peer-reviewed articles on Google scholar assessing strictly computational TB diagnostic models. Search terms include: Diagnosis, Tuberculosis, Computational, Mathematics, Bayes, Soft computing, Fuzzy logic, Neural Network. Exclusions were made based on some criteria.

**Results:** Initial search returned 303 of which only 42 studies met the inclusion criteria. 19 were on neural network or neuro-fuzzy, 2 studies were on Expert System. 7 analysed fuzzy logic/hybrids and Bayesian/data mining appeared in 7 reports. 5 studies were on Genetic Algorithm and its hybridized forms while 2 papers were on other methods.

**Conclusion**: Results suggest that accuracy and speed need to be improved due to weaknesses in existing models. Hybridization of Genetic algorithm, Neuro-fuzzy and Bayesian techniques will most likely guarantee improved diagnosis, however, further quantitative analysis is required to confirm this.

**Keywords**: Computational Models, Diagnosis of Tuberculosis, Confusable Diseases, Africa, Nigeria, Soft Computing.

## 1. INTRODUCTION

Tuberculosis (TB) is a communicable disease that exists in Africa and the world at large. It is caused by the bacterium Mycobacterium Tuberculosis and the success and thriving nature of its pathogens has been hugely attributed to its abilities to persist in the tissues and systems of its host [1]. It is a disease that can be contracted via airborne droplets, for example when an infected person sneezes or coughs. TB mostly affects the lungs and thoracic cavity areas which lead to pulmonary tuberculosis. It can also affect other organs of the human body such as the lymphatic regions, central nervous systems and circulatory system among others, which lead to extra-pulmonary tuberculosis [2].

Over the years, TB has been more prevalent in the sub-Saharan Africa [3]. The prevalence in sub-Saharan Africa is due to the following factors: humid climates, high level of poverty, poor hygienic lifestyles, limited nutritional values in feeding and the likes [4, 5]. TB has been reported to be among neglected tropical diseases [6] due to some factors such as: unavailability of data, neglect of government officials and limited number of medical practitioners, unawareness by TB sufferers, unavailability and costliness of methods of diagnosis of the infection and others.

TB manifests in two stages, the infection stage and the disease stage. The infection stage, also known as latent phase is normally without any symptoms or ill feelings. Although some infection will develop to a disease stage, but it is also possible to have the infection for the rest of one's life without it developing to full blown TB disease.

TB can be categorised using the time or duration of infection. Cases identified within the first five years after TB infection are grouped into primary tuberculosis class while cases after five years are regarded secondary tuberculosis. Other categories of Tuberculosis infection are: Endogenous reactivation cases, where an old infection relapses and gets worse and exogenous tuberculosis, where TB disease manifests as a result of reinfection. These categories fall under the class of secondary tuberculosis [7]

TB diagnosis is carried out by medical practitioners using conventional orthodox clinical or medical methods, results were said to be achieved but with well-publicised underlying limitations in terms of speed and accuracy of diagnosis. These conventional methods in TB diagnosis include but are not limited to DNA, Nucleic acid amplification, sputum, PCR, bronchoscopy, colonoscopy, acid-fast smear, laparoscopy, Tuberculin methods [8, 9]. The speed in generating results suffers in conventional TB diagnosis as a result of the confusability of TB disease with other diseases with related symptoms as well as culture and incubation activities associated with many of the conventional examples.

The diagnosis and treatment of TB could be very difficult because of the lack of symptoms, most especially at latent stage. The difficulty could even be more complicated because the bacterium causing the infection or pathogen could linger in the face of robust immune attempt responses. Regardless of strong immune responses, there exists no effectiveness in eliminating the organism during initial infection or the latent phase of the infection [10]. This implies that one can have two instances of Tuberculosis (i.e. TB infection and then the TB disease), the former leading to the latter albeit not always.

In order to solve the problems associated with the conventional diagnosis of TB, computational methods have been proposed. Although the computational method of TB diagnosis was originally meant to tackle the challenge of speed and accuracy in conventional clinical TB diagnosis, research has shown that speed and accuracy have still not been recorded to be at the optimum that is required, though computational methods of TB diagnosis have been said to have usurped their conventional clinical counterpart in terms of speed and accuracy [11, 12] and hence a need for improvement.

In this paper, we present a systematic review of the existing computational methods of diagnosing TB. Our focus was to identify the strengths and weaknesses of the existing computational methods as these could aid in the development of a more standard and robust computational system with improved diagnostic power.

## 2. MATERIAL AND METHODS

Systematic Literature Review (SLR) method [13, 14] was adopted and the processes contained in the methodology are as follows: study design, search strategy and information sources; study selection and data collection process; and quality assessment and data synthesis.

### 2.1 Study Design, Search Strategy and Information Sources

Systematically, we reviewed interventional and observational human-based tuberculosis studies that met a priori defined inclusion and exclusion criteria. Our search strategy is composed as follows: (a) Construct search terms by identifying major keywords (b) Determine the synonyms or alternate words for the major keywords; (c) Establish exclusion criteria to make exclusion in the course of search and (d) Apply Boolean operators to construct the required search term.

Results for (a): Computational, Diagnosing, Tuberculosis.

Results for (b): Computational, Mathematical, Bayes, "Soft computing", "Fuzzy Logic", "Neural Network" OR Probability.

Results of (c): Drug, Animal, Imaging, MRI, "X ray", Radiography, Vaccines, "Computed Tomography", Financial, Autopsies

Results for (d): Diagnosis intitle: Tuberculosis Computational | Mathematics | Bayes | "Soft Computing" | "Fuzzy logic" | "Neural Network" -Drug -

Animal -imaging -MRI -"X ray" -Radiography -Vaccines -"Computed Tomography" -Financial -Autopsies.

In this research, selection was from peer-reviewed articles on Google scholar database and we accessed strictly computational TB diagnostic models using the search term constructed as "Results for (d)" and this became the final search term arrived at for this research work. Resources checked were: conference proceedings, journal articles, book chapters and books.

### 2.1.1    Study Selection and Data Collection Process

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15] was adopted to detail the study selection process that established the studies included and those excluded for this research. Studies were categorized based on the type of computational methods used. Risk of bias was assessed at the study level. Figure 1 presents the study selection process in PRISMA flow diagram.
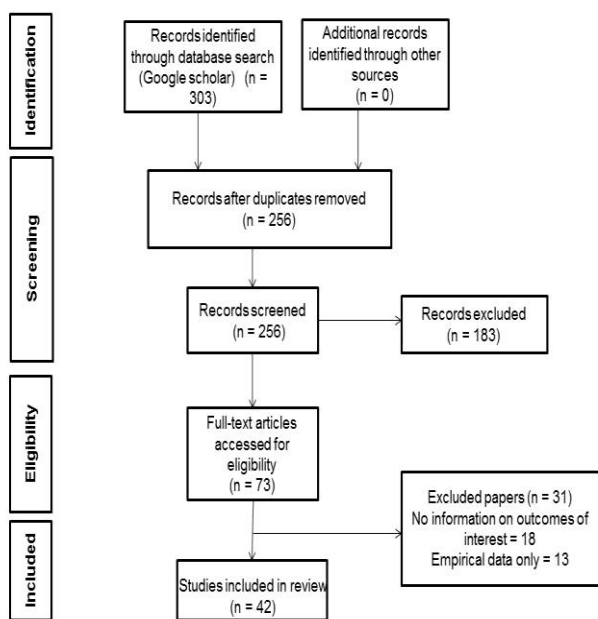


**Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of included studies.**

Studies on Tuberculosis diagnosis using computational methods of diagnosis were considered. The studies were restricted to TB diagnosis in humans. Thus the search terms include: Tuberculosis, Diagnosis, Computational, Mathematics, Bayes, Soft computing, Fuzzy logic, and neural network.

### 2.1.2    Exclusion criteria
Published articles were identified by searching Google scholar database up to year 2017. Non-English publications were not excluded. Studies were excluded if they are based on the following:
a.        Empirical data only

b.        Clinical analysis only
c.        Experiments/learning procedures
d.        Incomplete/Inappropriate study design
e.        Animal/non-human study

### 2.1.3    Selecting Primary Sources
The initial selection of primary sources was from the results of studies identified based on the search term and having any element of keywords related in any way to the work. Selection was also made based on the publication assessment quality. The assessment of publication quality was made based on the following with the view to minimizing bias: If the disease being diagnosed is TB; if the method of diagnosing TB is clearly computational; if the TB diagnosis is clearly on human only. Selection was also made based on title of the studies and abstracts.

The following data were extracted from each publication: title, author, reference, database, journal, critical success factors (i.e. factors that have a positive influence on development of a TB diagnosis tool using computational methods), methodology, target audience or population, publication quality description and year. Data categorization was based on some performance metrics from the final publication sample. A thorough review was done in order to derive a list of categories to help in the classification of the performance metrics. An initial list of 12 categories was identified and further merged to 7 factors presented in section 3.1. The final selection of primary sources from the previously selected list of papers was not based on reading the titles and abstracts only but extended to reading the full paper.

## 3. RESULTS

### 3.1 Literature Search Results
As presented in Figure 1, we identified 303 potentially relevant studies using our search term. After duplicates were removed manually, there remained 256 unique studies to review. We reviewed the titles and abstracts using the exclusion criteria and that lead to the exclusion of 183 studies. We used the same criteria to review the full texts version of the remaining 73 manuscripts. Characteristics of the 31 papers rejected at this stage are presented in Figure 1. We had 42 papers finally identified for review.

### 3.1.1    Study Characteristics
A report of the key characteristics of the 42 studies included in this systematic review is as follows: based on language of paper, twenty four (24) studies were published in English while eighteen (18) were not in English language; based on country of research, 11 publications were from Indonesia. Moreover, we identified two systematic review studies [9, 16] three case reports [1, 17, 18], and five cross sectional studies [19-23]. The remaining studies were ideas, editorials and opinion oriented in design with detailed levels of interventions. Year of publication of all relevant papers were from 1993 to 2017. Out of the 42 research papers, 11 research cases of TB diagnosis using computational method originated from Indonesia,

a total of seven research papers originated from USA and India. There were 6 research papers originating from Nigeria while 3 research papers originated from Colombia and Brazil. Three research cases of TB diagnosis using computational techniques were reported in UK while Turkey had two research papers reported and one research paper originated from China.

## 3.2 Main study results
### 3.2.1 Taxonomy of TB Computational Diagnostic Model

In this research, we identified that the computational techniques proposed for the diagnosis of Tuberculosis can be broadly grouped into five categories as listed in Table 6. These are Artificial Neural Network (ANN), Expert Systems, Fuzzy Logic, Bayesian/Data Mining and Genetic Algorithms, although some hybrid of these methods have also been proposed.

**Table 1: Taxonomy of Computational Model for TB Diagnosis**

| Computational model | Number of studies | Studies |
|---|---|---|
| Artificial Neural Network | 19 | [19], [25], [25], [7], [26], [27], [28], [29], [30], [31], [11], [32], [33], [18], [22], [12], [23], [34], [35] |
| Expert systems | 2 | [36], [21] |
| Fuzzy logic/Hybrids | 7 | [37], [38], [39], [40], [41], [42], [43] |
| Bayesian/Data mining | 7 | [17], [44], [45], [9], [16], [46], [47] |
| Genetic algorithm/Hybrids | 5 | [48], [49], [50], [51], [52] |
| Persistence and associative techniques | 2 | [1], [20] |

**[a]Persistence and associative techniques. Computational techniques for TB diagnosis involving TB persistence analysis, latency and use of associative classifiers.**

### 3.2.2 Strengths and Weaknesses of existing Computational and Soft Computing Techniques
The strengths and weaknesses of various soft computing techniques on the diagnosis of Tuberculosis are presented as follows:

### a. ANN Based Models
Diagnosis using ANN's was proposed to tackle weaknesses identified in conventional clinical methods of diagnosis. The field was founded on the premise that human intelligence can be so accurately described that a machine can be developed to simulate it. They help in detecting complex relationships that exist between dependent and independent variables. This helps in relative increase in diagnosis speed and accuracy.

**Strengths:** The strengths lie in the availability of multiple training algorithms [53, 54]. Presence of an increased number of training algorithms allows for better human emulations and knowledge transfer. ANN's also detect complex non-linear relationships between dependent and independent variables. This allows for an increased sensitivity level which ensures that ANN's become more responsive and efficient.

**Weakness:** The limitations range from how ANN training is based on reasonable amount of previous data [53]. Without relevant and adequate number of data, evaluation becomes intangible and unrealistic. Also, input of experts might be emotionally induced as humans have different reasons to give out or hold back on information. Regardless of how much ANN's have been developed to solve problems, solution interpretation could still be largely vague and is only used to induce physician's final decision [25, 55] who is ultimately responsible for critical evaluation of the diagnostic results generated by the system. The accuracy of ANN system is dependent on the choice of an initial synaptic weight for the system [53] and neural networks ability to approximate predictive output may lead to over-fitting, particularly when there is an attempt to increase the processing power of the network by adding a large number of hidden neurons which leads to poor generalization [24].

### b. Fuzzy Logic/Hybrid
**Strengths:** Fuzzy logic makes use of fuzzy sets in form of linguistic variables to approximate human reasoning. It is a computing approach based on degrees of truth rather than absolute true or absolute false values (i.e. 1 or 0). The degrees of the linguistic variables are managed by specific membership functions. Fuzzy logic has ability to deal with non-linear entities and uncertainties which make it easy to model and derive relatively efficient systems. It is easy to model human's reasoning and implement.

**Weakness:** Tuberculosis diagnostic systems using Fuzzy Logic or its hybrid work only if the knowledge about the solution is known and it is expressed using rule based format [56, 57]. The derivation of membership functions (MF) for the fuzzy sets is complex due to the subjectivity attached to it and therefore the system accuracy is a function of the MF and some other factors. Generalizing the results is also an issue, therefore fuzzy program has to run severally for each patient and fuzzy outputs would be interpreted in numerous ways. This makes the analysis difficult [38, 50]. Also, identification of the most suitable defuzzification process is complex and difficult [58] [59]. The rule based statement used in the knowledgebase could create a loop if assumptions or incidences deviate from the rules in the

knowledgebase and limited test data results might be inconclusive [39, 40, 42, 43].

#### c. Bayesian Network and Data Mining

**Strength:** The Bayesian technique is concerned with classifying data items in a data bank in order to get a probabilistic approach in solving the problem. The Bayes algorithm will calculate the probability values for all possible hypotheses. Data mining allows us use priors in regularization.

**Weakness:** The use of Bayesian Network (BN) works based on probability theory and hence approximate results are given. In this case accuracy is not always guaranteed and the need arises for increasing the accuracy level of BN based diagnostic systems. Moreover, the Data Mining (DM) models reviewed in this paper were streamlined to one type of data mining procedure and also both the BN and DM models were limited by test data [46, 47], thus the accuracy of the results is not always guaranteed.

#### d. Genetic Algorithm (GA) / Hybrid

**Strength:** Genetic Algorithm (GA) based systems work based on its internal rules, and therefore, it can be used in loosely defined problems. It follows the Darwinian principles of the survival of the fittest and more suitable for a complex, non-linear model where the global optimum is hard to locate.

**Weaknesses:** Accuracy has been said to be an issue of concern. In [49], 61% accuracy was established on completion and few data sets were used [49-52]. Results are also dependent on required requisite data.

#### e. Expert system

Any computer program that uses artificial intelligence methods in solving problems within a specialized niche ordinarily requiring human ability is an expert system. Reliance of these systems is based on 2 major components; knowledge base and inference engine. Generally expert systems are designed to mimic human characters, behaviours and knowledge.

**Strengths:** Expert systems have a very flexible knowledgebase that is extendable and updatable**.** This is in addition to the fact that they can contain and accommodate a very large amount of data as they are built with a large repository (knowledgebase) to withstand a surging barrage of knowledge and information from the expert.

**Weaknesses:** The use of Expert System (ES) for TB diagnosis is limited to information supplied by experts that are attached to the system and this might be vague and inconclusive. Inferences by experts might be emotionally induced or subject to correction due to misdiagnosis or increased strain in disease [36]. And limited test data might not generate the best return on output [21, 36].

### 3.2.2.2 Performance Metrics For Tuberculosis Diagnosis

The following seven criteria were found to be measures of performance: Accuracy, Speed, worker safety, Specificity, Sensitivity, Flexibility and Ease of use. Of these, we identified accuracy, speed and ease of use as the most common measures of performance. Results suggest that past conventional clinical methods focused on getting TB diagnosis result and system sensitivity but failed to address the speed challenge and worker safety. Our findings also indicated that ensuring the safety of workers during TB diagnosis was paramount to general acceptance of the system. Over the years, it had been documented that some traditional clinical methods of diagnosing TB could not guarantee safety of the physicians that test the patients for the disease as there is always a tendency to have contact with the pathogen and continuous exposure pose a great risk to non-sufferers where there is a likelihood to contract the disease in the process of testing and diagnosis. This made the factor very intricate in the development of computational models for TB diagnosis.

### 4. Discussion

In this study, a critical review of existing computational soft computing techniques used in diagnosis of Tuberculosis was carried out. This was done to understand the concept of these techniques, identify their strengths and weaknesses, as well as give a direction for further improvement. In consequence, these could aid in creating a pathway for developing a more functional system.

We found that most of the research works in TB diagnosis using computational techniques were conducted outside Africa. Considering the continued prevalence of TB cases in Nigeria and Africa at large, the numbers of computational soft computing TB diagnosis papers available in Africa is relatively small as Nigeria ranks 10th among the 22 high-burden TB countries in the world and the World Health Organisation estimates that 210,000 new cases of all forms of TB occurred in the country in 2013 alone [3]. This buttresses the fact that more research work is needed in Nigeria and Sub-Sahara Africa in the area of computational techniques for the diagnosis of TB.

We categorised the existing computational techniques for the diagnosis of Tuberculosis based on the computational concepts used. That yielded five categories as listed in Table 6. These are Artificial Neural Network (ANN), Expert Systems, Fuzzy Logic, Bayesian/Data Mining and Genetic Algorithms, although some hybrid of these methods have also been proposed. This categorisation help researches to identify where more work is needed.

### 5. CONCLUSION

We established from our study that accuracy and speed of TB diagnosis are major issues of concern.

Thus, existing model models for TB diagnosis are yet to attain a good level of accuracy and early diagnosis of TB is not very certain due to the confusability of TB symptoms with other communicable diseases. Our inference from this study has given direction for the development a more robust computational soft computing technique with a better level of accuracy when compared with existing models.

One of the strengths of this study is the critical review of the existing literature. We used Google scholar because it has one of the largest database for scientific articles globally. Also, the search terms were carefully and professionally defined. This was very useful in ensuring that all existing relevant articles were identified. Additionally, we used SLR (REF) and PRISMA (REF). These are internationally accepted standard for conducting and reporting systematic review. The use of these standards implies that our study is in conformity with the good practise of systematic review.

One of the limitations of this study is the use of only a single database, i.e. Google scholar. We chose Google scholar because it actually indexes many databases and it is free but it is quite possible that we might have missed out some articles which are only available in commercial databases. We were constrained by funds for subscription to some commercial databases. Future work will explore funding opportunities and include commercial databases.

This work is similar to a little extent to the work reported in [9, 16]. The works reported in [9, 16] are reviews involving related papers and comparisons in order to identify a trend; observe strengths and weaknesses of data mining models in TB diagnosis and determine ways of improving the models identified. Thus these papers focussed only on review TB diagnoses using data mining model. However, the difference between this work and the two papers [9, 16] is that, unlike the two papers, this work involves a systematic review that highlights various computational soft computing techniques used in diagnosing TB. It encompasses the following soft computing techniques (i.e. artificial neural network, Fuzzy logic, data mining/Bayesian networks, genetic algorithm and expert systems) and each of the techniques were analysed based on its strengths and weaknesses. Additionally, our study used the standard and internationally accepted methods for conducting systematics review.

In conclusion, we conducted a systematic review of existing computational methods of diagnosing Tuberculosis. We grouped the existing computational methods into 5 groups, namely: neural network, Expert System, fuzzy logic, Bayesian and Genetic Algorithm. We found out that there are a need to conduct more research in this field so as to improve the accuracy and speed of diagnosis of TB. This could lead to early diagnosis, improved quality of life and increased life expectancy, most especially in Nigeria and the Sub-Sahara Africa as a whole. Our future work will explore the development of an improved TB diagnosis using computational techniques.

## ACKNOWLEDGEMENTS

## COMPETING INTERESTS

The authors declare that there are no competing interests.

## AUTHORS' CONTRIBUTIONS

Tosin Ogunbodede conducted literature search, analysed them and wrote the first draft of the manuscript. Boluwaji Akinnuwesi and Benjamin Aribisala designed the study, revised the manuscript, wrote the final copy of the manuscript and supervised the study.

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