COMPUTER SIMULATION MODELS – DIAGNOSIS, TREATMENT AND CONTROL MEASURES FOR TUBERCULOSIS

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خلاصہ

تپ دق، انٹراسیلولر پیتھوجن بیکٹیریا "مائیکوبیکٹیریم" کی وجہ سے ہوتی ہے۔ تپ دق بیس سے تیس لاکھ سالانہ اموات کی وجہ بنتی ہے۔ اس بیماری کی وجہ بننے والا بیکٹیریا لف نوڈز میں پایا جاتا ہے اور آسانی سے کنٹرول نہیں کیا جا سکتا۔ اس ریویو کا مقصد ہیلتھ کیئر سسٹم میں کمپیوٹر سائمولیشن ماڈلنگ کی بطور سکریننگ ٹول تشخیصی ایکیوریسی کو چیک کرنا ہے۔ تپ دق کو کنٹرول کرنے کے لیے دوائیوں کا دائرہ کار بہت محدود ہوتا ہے کیونکہ وہ "مائیکوبیکٹیریم" کے اندر موجود سیلولر پاتھ ویز کو روک کر تپ دق کو ختم کرتی ہیں۔ کمپیوٹر سائمولیشن ماڈلز اس معاملے میں بہتر اور موثر علاج دریافت کرنے میں مددگار ثابت ہوتے ہیں۔ بیماری کی شروعات، بیماری کی مختلف حالتیں، بیماری کی روک تھام، اور بیماری کی ابتدا کے بارے میں یہ کمپیوٹر ماڈلز بہت بہتر طریقے سے ڈاکٹرز کی راہنمائی کر سکتے ہیں۔ کیڈ سافٹویئر (کمپیوٹر ایڈڈ ڈیزائن) پھیپھڑوں کی سیگمنٹیشن کرتے ہیں۔ میٹاڈسک ہوموجینیئٹی کو دیکھنے لیے استعمال ہوتی ہے۔ آرٹیفیشل نیورل نیٹورک تین پرتوں پہ مشتمل ایک بیک پروگریشن نیٹورک ہے جس میں بنیادی سافٹویر متلب 7.0 ہے اور اس کا فنکشن بالکل دماغ کی طرح کا ہے سمیر نیگیٹو سیمپلز کو چیک کرنے میں مدد کرتا ہے۔ قابو پانے پہ مبنی ماڈلنگ بیکٹیریا کے نظام انہضام کے بارے میں معلومات مہیا کرتی ہے لیکن اس قسم کے طریقے کو ابھی تک "مائیکوبیکٹیریم" کے جینوم کو اسٹڈی کرنے کے لیے اور اس کی ماڈلنگ کے لیے استعمال نہیں کیا گیا۔ ایک اور ٹول جس میں ابھی تک فعال کیسز کو اسٹڈی کیا جاتا ہے اس کا سمولیشن بنایا جاتا ہے جو دو کیسز کے بیچ میں موجود فرق کو کم کرنے کے لیے استعمال کیا جاتا ہے۔

Abstract

Tuberculosis, a bacterial disease caused by the intracellular pathogen. *Mycobacterium tuberculosis* and it is accounted for two to three million deaths per year. Causative agents are mostly localized in lymph nodes and are not easily controlled. The basic purpose of this review was to assess the diagnostic accuracy of computer simulation modeling as a screening tool for implementation in health care sectors. Therapeutics have limited scope for the treatment of Tuberculosis because they are composed of multiple drugs that retard the essential cellular pathways in *Mycobacterium tuberculosis*. Modeling Tools are effectual and widely used for designing control strategies. Onset of disease, epidemiological conditions, prophylactic, and genesis of disease is analyzed by simulation modeling. CAD software is used in lung segmentation. Meta-Disc is used for the exploration of heterogeneity. Artificial neural network is a three-layered back progression network having Matlab 7.0 version and it works like a brain for the detection of smear-negative samples. Constraint-based modeling provides a narrative approach to examine microbial metabolism but has not yet been applied to genome-scale modeling of *Mycobacterium tuberculosis*. Active case finding simulation tools are remarkably used to minimize the case detection-gap.

Keywords: Tuberculosis, SimulationModel, Epidemiology, Matlab, Neural network, *Mycobacterium tuberculosis*

Introduction

Computer simulation methods are used to control the spread of infectious diseases and it helps as resource outcome of alternative strategies for analysis.Simulation modeling is used for *in vivo* and *in vitro* study. Infectious diseases such as AIDS, tuberculosis,influenza are studied through simulation models (Panchanathan*et al*., 2010). Epidemiological characteristics are analyzed by using computer simulation modeling.Many processes are optimized and evaluated by such a powerful research engine. In healthcare, research simulation is rooted for three decades but the usage of simulation in non-academic practitioners has increased in the past five to ten years. Simulation modeling proliferation is evident in health care centers (Brenner*et al*., 2010).Model usage is specified by the availability of tools, parameters, and research questions.Deterministic,stochastic,and agent-based systems are widely used (Saxena*et al*., 2018).

Materials and Methods

Review of literature was undertaken to summarize the role of computer simulation models used in diagnosis, progression tendency and treatment predictions of tuberculosis.

PubMed, Google Scholar, and academic research databases like Web of Science, IEEE Xplore and Science Direct were used from October, 2019 to March, 2020. Keywords used to compare and contrast these models were artificial neural network, python, machine learning, artificial intelligence, chest x rays scores, and infections.

Results and Discussion

Tuberculosis: Tuberculosis (TB) is a bacterial disease caused by *Mycobacterium tuberculosis*. It is considered as a serious health consequence because bacterium attacks the lungs and other parts of the body. *Bacterium* infected about one-third of the world's population and about three million deaths are reported each year(Okuonghae, 2013).*Mycobacterium tuberculosis* is transmitted through close contact between people by cough,sneeze, and air currents(Blower*et al*., 2002). In China, TB epidemic isseasonal and mostly occurs in winter and spring season(Rao *et al.,* 2016).New cases of TB estimated in 2016 by world health organization are 10.4 million(Glaziuo*et al*.,2018).All over the world, 80% of cases are seen in 22 densely populated countries. Per 10,000 people the incidence rate of TB is 59 to 1063(Zhao *et al.,* 2017).

After exposure to *Mycobacterium tuberculosis*, infection passes to the early latent stage. TB agents are mostly located in lymph nodes.Later on, active form is transferred toadvanced latent form.Organs and tissues are invaded by inactive forms.Active pulmonary tuberculosis involves the formation of inflammatory tissues in the lungs and respiratory tracts.High mortality rate leads to bacteria excretion.Although, *Mycobacterium tuberculosis* is not destroyed and overall recovery is impossible (Melnichenko and Romanyukha, 2009).

Infectious diseases spread mainly due to the interconnection of the world. Aspects of geographics highlghts that the speed of the spread of infectious disease is faster nowadays.TBinfection is not easily controlled.Due to improper treatments,no usage of medicines as prescribed by physicians and low quality of medicines may develop multidrug resistance TB (MDR TB) (O'Brien,1994).The incidence of tuberculosis is more among HIV positive people.In 2013 among HIV positive people 320,000 death cases were recorded (Glaziou*et al*., 2018).Besides using antiretroviral therapy,antimicrobial chemotherapy, WHO short-course chemotherapy strategy, and applying control measures TB is still a major cause of death. InChina, the tuber culosis incidence rate is declined by ≤ 0.1 % in the year 2005 (Dowdy and Chaisson, 2009).Pakistanhaving 179.2 million cases is ranked 5^{th} among highly burdened TB countries.According to the National TB control program, 413,450 TB cases are reported every year in Pakistan (Khan, 2017).

Computer Simulation models: Tuberculin test, fluorography, and septum tests are used for the detection of tuberculosis infection. Among children, TB is detected by using a tuberculin test.It is done once a year.Inadults, TBis done by fluorography. It is mostly done once in a duration of six months during visits to clinicians. It is a preventive method usually done at an earlier stage of infection even at that time bacterial excretion is not started. Persons who are not diagnosed by flurogram and in those whom changes are reported after treatment, bacteriological tests are applied (Melnichenko and Romanyukha, 2009).

Global Funds to Fight AIDS, Tuberculosis and Malaria(GFATM) are aided and strengthened by simulation tools. HIV resources in past are mobilized by AIM and Goal tools i.e. spectrum software suite models (Stover *et al.,* 2010). Transmission modes of tuberculosis are studied by using different models including Disease Transmission Kernel (DTK) model (Huynh *et al*., 2015). Infectious diseases are simulated by deterministic, stochastic, and agent-based models (Lee *et al*., 2008). Type of model to be used is determined by the availability of tools and parameters. Stochastic models are useful to cure disease. Due to the low prevalence of clinical courses in the community,stochastic courses outcome impact is high (Walensky *et al*., 2002). Due to relative simplicity, deterministic models are mostly used (Arenas *et al*., 2009). Non-homogeneous spread of infection in the community is overcome by agent-based models. Clinical facts of infection must be considered for using any variability in models. Clinical features such as resistance sate, expose state and passive maternal immunity are considered. Infectivity and contagiousness are evolving parameters for any infectious disease. Any unique model is developed for every disease by accounting its evolving parameters. Validity is a continuous process and validity of the model must be taken into account.Many studies mostly rely on conclusions without checking the validity of its use (Musgrave and Watmough, 2009).

A study was conducted to analyze tuberculosis by using computer-simulated methods. Simulations models stability was checked by using software packages like Matlab and Simulink software.Mathematical biology TB and its developmental procedures were studied by using computer simulation methods (Chung *et al*., 2013). Simulation is rooted in healthcare systems. According to Robert and English, (1981) emergency and non-emergency admissions are studied by using simulation.In healthcare sectors, the use of simulation has been

increased throughout the 1980s and 1990s.In past simulation methods are used for hospital bed planning,emergency medical systems,scheduling and patient flow (Benneyan,1997).

Melnichenko and Romanyukha, (2009) applied computer modelto analyze the onset of disease, epidemiological conditions, prophylactic, and genesis of disease. Basic mechanisms were included and development of a simulation model was based on birth rate, death rate, and migration because demographics play a vital role in the emergence of disease. They concluded that incidence, prevalence of infection, and mortality can be assessed with the help of computer simulations models.

Computer- aided detection (CAD) of TB: Chest x-rays (CXR) is used as a screening tool for tuberculosis (Kranzer *et al*., 2013). Verbal screening done for TB is less sensitive than CXR (Ellis *et al.*, 2006). The role of CXR in the diagnostic field is limited due to the non-availability of trained personnel, cost, and limitations of x-rays facilities (Onozaki *et al.*, 2015). The advantage of digital chest radiography is that software is capable of automated interpretation such as the "Computer Assisted Diagnosis for TB" (CAD4TB) software. Diagnostic Image Analysis Group of the Radboud University Medical Centre, Netherland introduced a low source Computer Assisted Diagnosis For TB (CAD4TB). CAD4TB is a digital chest radiography used with the aid of software for automation (Pinto *et al.*, 2013). In programmatic settings, CAD4TB 5 is the automatic CXR reading software used for diagnosis (Fig.1).CAD4TB 5 has two main components i.e. quality check and TB analysis (Melendez *et al*., 2017).

Chest x-ray scoring procedure for pulmonary tuberculosis:CAD4TB is a machine learning methodology based on software used to differentiate between normal and abnormal x-ray images.Textural abnormality and shape abnormality are identified in the lungs with cumulative abnormality score (Range 0 - 95). A higher score is indicative of more serious tuberculosis(Ginneken*et al*.,2006). Radiologists and clinicians can use cloud-based software for TB diagnosis purposes. However, CXR abnormalities are not differentiated in persons suffering from pneumonia and lung cancer using CAD4TB (Fig.1). It is used as a screening tool but has certain limitations (Zaidi *et al*., 2018).

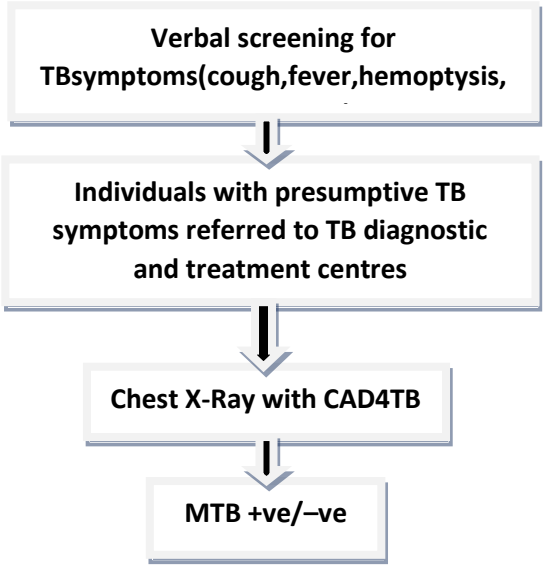

Fig. 1. Screening and diagnostic algorithm - CAD4TB

Computed tomography scan - diagnosis of spinal tuberculosis: Spinal tuberculosis also known as Plott's disease is a form of skeletal tuberculosis. Its incidence is high in areas having pulmonary TB affecting about 1 to 2% of cases of tuberculosis. Infection mostly occurs in the anterior portion of the vertebral body.Anterior vertebral body destruction can be seen through a computed tomography (CT) scan. Cloaca is visualized, thick and irregular wall shown on CT scan is due to paraspinal abscesses (Boushab *et al*., 2019).

MATLAB Based Neural Artificial Network: Pulmonary tuberculosis is diagnosed using MATLAB based neural artificial network. Artificial Neural Network is a mathematical model work like a brain and manages information.Diagnosis of Pulmonary Tuberculosis using accurate methodology is important to control its prevalence.In the past due to lack of standard tuberculosis diagnosis is not satisfactory. Earlier used methods performance is not good. So there is a need to use accurate methods to overcome tuberculosis complex problems. Even a less experienced person can handle artificial neural networks easily due to easy labeling.

Artificial neural is a three-layered back progression network. Model designing is based on the detection of tuberculosis and the interpretation of results. Matlab 7.0 version is used for such systematic designing. A graphical based approach is known as the GUI program and its easy to handle.Artificial neural network training involves shape features and symptoms. The Dicom formatted x-rays reading is taken by converting it into Matrix format. Morphological features are extracted by viewing these images (Fig.2). To the neural network extracted features are fed. Tuberculosis detection is done based on reading images shape features and symptoms. Graphical user interface(GUI) development involves image processing, reading, histogram plotting, and result interpretation either person has TB or not (Chandrika *et al* .,2012).

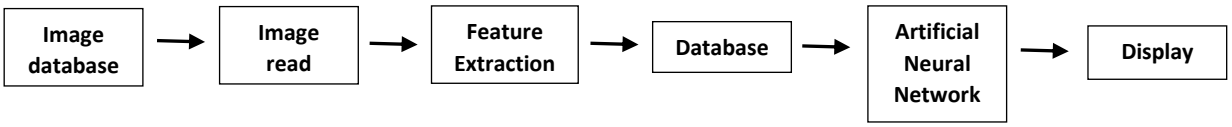

Fig. 2. Dependency diagram for diagnosis of tuberculosis using MATLAB neural netwrok

In the past calculation of the number of hidden layers is a major issue due to lack of analytical formula. Hidden layers determination is done according to trainee experience and repeating procedures. In present, a Back progression(BP) with variable neurons having hidden neuron information is introduced. Artificial neural networks (ANN) overcome the limitations of the regression model.ANN is a cost-effective, satisfactory network having 73.68% sensitivity and 69.05% specificity. ANN has remarkable applications in signaling, pattern identification, diagnosis, and forecast predictions (Fig.3). While training databases for artificial neural network following steps are taken into account: TB and Non-TB images readout,noise removal, and shape features calculations. In the end, vector values are fed to the network and same process is repeated for all images (Chandrika *et al.*, 2012).

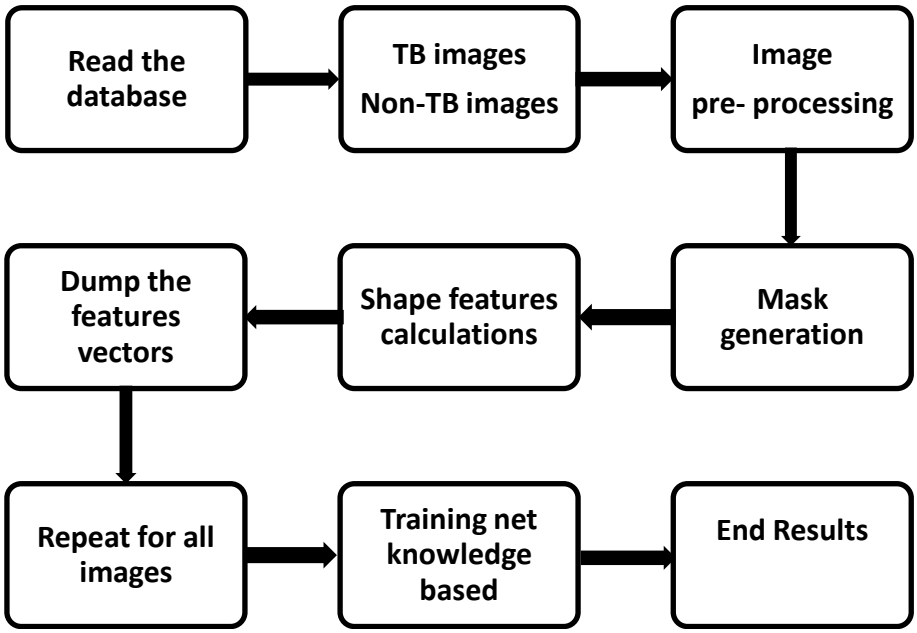

Fig.3. Application of ANNfor TB (Chandrika*et al*., 2012)

Tuberculosis pleurisy - Meta Disc1.4 software: Tuberculosis pleurisy is classified as extrapulmonary tuberculosis (EPTB)(Gui and Xiao, 2014).In the past Tuberculosis pleurisy effusion (TPE) diagnosis was done through pleural tissue biopsy. The success rate of pleural fluid mycobacterium culture is 36% (Tay and Tee, 2013).Distinction between malignant pleural effusion and TPE is difficult due to poor laboratory findings.Accurate diagnosis of TPE needs a reliable biomarker. A denosine deaminase (ADA),C-reactive protein (CRP), interleukin-6(IL-6), and lactate dehydrogenase (LDH) are widely used biomarkers. ADA an enzyme and involved in catalysis of adenosine to inosine and its level increases in TB because mycobacterial antigens stimulate T cells lymphocytes (Barua and Hossain, 2014).ADA1 and ADA2 are two isoenzymes (Tay and Tee, 2013). In Tuberculosis pleural effusion, level of ADA is high due to higher activity of ADA2. Lymphoid cell differentiation is based on the level of ADA and correlation between ADA level and lymphocytes count is examined. A comparison of TPE and overall study population showed that weak

correlation exists between age and ADA level. Immunity affects the pleural fluid ADA level. ADA activity is not based on the amount of lymphocytes rather it is based on TB and rapid proliferation rate of lymphocytes (Tay and Tee, 2013).

Meta Disc 1.4 software is created in Microsoft visual basic 6 and is an accurate meta-analysis software include dialog boxes, roll down menus, and online helping facilities (Zamora *et al*., 2006). Meta Disc1.4 software is used for checking the sensitivity, specificity,positive likelihood ratio (LR+) and negative likelihood ratio(LR-) of ADA in the diagnosis of TB. Data is analyzed. Sensitivity and specificity are determined by Forest plots. Accuracy of ADA in diagnosing TB is checked by calculating summary receiver operating characteristic(SROC) curve. The results show that the non-threshold effect is the cause of heterogeneity and the source of the non-threshold effect is cut off value of ADA. When ADA is higher than 50U/L it acts as a reliable biomarker. ADA test is simple and affordable,its range value is important to assess the diagnostic pattern of TB. There is no proper standard in the ADA cut off value while diagnosing tuberculosis. The disadvantage of this software is that it can not distinguish between bacteria meningitis and TBM (Tuon *et al.,* 2010).

(Mycobacterium tuberculosis-) **Artificial Intelligence:**In the 1990s computer-aided diagnosis system was introduced to detect stained *bacilli*. Chromatic structural patterns are identified with these computer programs. Although it's easy for an experienced pathologist to identify a *bacilli* because each has its specific morphology. But the main problem is that morphological features range in which they vary is not precisely recorded.Artificial intelligence(AI)-assisted detection method was used. Total 201 test samples (108 positive cases and 93 negative cases) were set. Classification model training is done on the CIFAR-10 dataset. As target is small i.e. 20×4 pixels so CIFAR-10 is designed to deal with micro-images.Mini-batch stochastic gradient descent algorithm is an optimal method. The initial learning rate is set to 0.05 and after every five epochs, it is multiplied by 0.1. Model trial is done for twenty-five epochs. The sliding window method generates 32×32 pixel patches.These patches are fed into TB-AI.A map of each slide is generated. The first run of machine learning methodology is error-prone.The second run is necessary.However, in the second run, two positive cases are missed and seventeen negative cases are misdiagnosed (Table 1).TB-AI is 97.94% sensitive and 83.65% specific.It has certain limitations in distinguishing contaminant bacilli from pathogenic bacilli. Pathologists have to confirm the positive results given by TB-AI(Xiong*et al.,* 2018).

Table 1. Diagnosis of test cases by TB-AI and pathologists

First run	151 cases are similar to pathologists	93 cases are positive	61 cases are negative
	47 cases differ from pathologists	15 cases are positive(pathologists) but negative by TB-AI	32 negative by pathologists but positive by TB-AI
Second run	28 samples are diagnosed accurately	20 positive cases	8 negative cases

Progression of tuberculosis and computer simulation models: Granulomas are the main site of *Mycobacterium tuberculosis* infection. Granulomas are dense structures having immune cells. Inhaled *mycobacterium*are transported across the alveolar epithelium and lymph nodes involves a series of events leading to the production of anti-inflammatory chemokines.As a result of an immune response, additional mononuclear leukocytes are accumulated at the site of infection. Macrophage rich cell mass known as granuloma is formed.When a person is infected, primary granulomas start to progress at an early stage and in latent stage granulomas reactivate (Guirado *et al*., 2013).

Vitamin D deficiency also leads to the progression of TB. Vitamin D is an important immunomodulator of innate immune response act as a cofactor and induces antimicrobial activity. The serum level of vitamin D is low in TB patients. Females have a higher progression rate as compared to males due to such deficiency. Vitamin D association with TB progression is checked through Kaplan-Meier analysis and result is supported by meta-analysis(Talat *et al*., 2010). Besides genetic,sex and ethnicity, ecological conditions are also TB prevailing factors. TB incidence is also related to temperature, wind speed, and precipitation. Spatiotemporal data analysis is aided with the help of spatial autocorrelation and spatial penal data tools. OpenGeoDa software is used for conducting spatial-temporal data (Rao *et al.,* 2016).

All TB states are modeled individually. Even a healthy person has a greater risk of developing a disease like tuberculosis. First state ELTB (early latent TB), persists for a period of five years during which a person has a greater chance of active TB (ATB). Later on patient enters the latent state which can last for many years and have a slow progression rate. Mortality rate increases in symptomatic patients (Kasaie *et al.,* 2013). New TB drugs can be marketed by understanding the pathophysiology of granulomas (Guirado *et al.,* 2013).

Agent-based simulation methods describe the natural epidemic history of tuberculosis. Infection modeling is done as a linear function of time in the case of active TB patients.Infectiousness increases from zero to a maximum infectiousness *Imax* during the first nine months of the disease and remains unchanged for the rest of the disease.Upon diagnosis and treatment, active cases can be recovered but multiple reinfections are required for latently infected people to return to ELTB (Kasaie *et al.,* 2013). A brief epidemiological trends of TB are provided in table 2.

Table 2. Epidemic trends of Tuberculosis

Parameter	Duration	Study
ATB - mortality rate	0.12 per year	Tiemersma*et al.*,(2011)
Early latency TB (ELTB) duration	5 years	Dowdy *et al*., (2012)
Fast progression rate	0.03 per year	Vynnycky and Fine, (1997)
Slow progression rate	0.005 per year	Horsburgh, (2004)
Recovery rate	0.12 per year	Tiemersma*et al.*,(2011)
Diagnosis and treatment rate	0.74 per year	WHO, (2013)
Latent immunity toward re-infection	0.8	Andrews *et al*., (2012)

Significance of computer simulation models: Matlab based simulation platforms can be used to analyze results and simulate molecular dynamics of epidemiological conditions. Ancillary, Simulink toolbox, and Matlab softwares are used in the computer simulations model. Theory, modeling, evaluation, and accuracy of the model are crucial steps of computer simulations.Computer simulation models as compared to mathematical models can deal frequently with complex random events and different health policies (Chung *et al*., 2013). Simulation models predict that the effectiveness of strategies based on the combination of treatments and prevention is more than a strategy based on treatment only (Brewer and Heymen, 2004).

Artificial neural network detection method based on adaptive resonance theory is the most reliable model for the detection of smear-negative samples (Mithra *et al.,* 2018). The artificial immune system(AISs) is a new part of computational science that uses genetic algorithms to simulate biological behaviors. AISs are used for diagnostic purposes (Shamshirband *et al.,* 2014). Disease simulation is a complex process including random nature, uncertainty, and a lot of information needed to be compiled. Software operations and computer simulations play a key role as a research and teaching tool.Software is cost-effective, fast and appropriate tool for diagnosing tuberculosis (Chung *et al*., 2011).

Limitations Of Computer Simulation Models: To make use of whole-genome sequence data for routine uses software tools are developed.While developing software tools developers centered on technical aspects morethan a practical one.In clinical cases to provide full data packages, more improvements may be needed in software tools i.e user-friendliness, privacy, version control, data management, and Laboratory Information Management System connectivity. For the development of software tools mycobacterium field expert collaboration must be needed (Beek *et al*., 2019).In the 1960s when the computer was used as a research tool,bioinformatics was introduced.In scientific community biological data is interpreted with the help of various tools. Biological data from high throughput techniques, scientific experiments, and literatureis organized, visualized, and analyzed with the help of computational tools. All of these tools are available online (Machado *et al*., 2018). Table 3 summerizes various tools used for TB.

Table 3. Computer simulation models for Tuberculosis

Reference	Study	Tool
Jacques *et al*., (2005)	Analysis of transcriptional regulation in bacterium	MTBRegList
Catanho*et al.*, (2006)	Genomics comparative analysis	GenoMycDB Mycobacterium tuberculosis comparative database
Steingart *et al.,* (2007)	Serological antibody detection tests for diagnosis of pulmonary tuberculosis	Meta-Disc 1.4 software
Zhu *et al.,*(2009)	Functional and genomic study of genus *Mycobacterium*	MyBASE
Kapopoulou*et al.*,(2011)	Insilico generated information on genus Mycobacterium and essential genes	The Mycobrowser Portal
Lew *et al*., (2011)	System supporting functional annotation including protein analysis	MycoMemSVM

Conclusion

Tuberculosis is a widespread infectious disease that affects millions of people worldwide every year. Due to the alarming rate of the spread of Tuberculosis particularly in developing countries, medical experts are implementing new strategies for the diagnosis, treatment of this disease. In the past Tuberculin test;flurographywas used for the detection of TB. Currently Deterministic, Stochastic, and Agent-based models are used. More research is needed to develop new diagnostic tools that will treat the most resistant strains of Tuberculosis. Simulation model stability is checked by using software packages like Matlab and Simulink.

In terms of aims reported at the start of this paper, it can be acquired that the computer simulation model is essential although development and implementation are a communal and complicated issue. Besides developmental stages, modeling has certain limitations. The model focuses on the individual who is susceptible to TB and failed out to predict the persistence of TB in subpopulations.

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References

Andrews, J. R., Noubary, F., Walensky, R. P.,Cerda, R., Losina, E. And Horsburgh S, C. R. (2012). Risk of progression to active tuberculosis following reinfection with *Mycobacterium tuberculosis*. *Clinical Infectious Diseases*. 54: 784-791.

Arenas, A. J., González-Parra, G. and Moraño, J. A. (2009). Stochastic modeling of the transmission of respiratory syncytial virus (RSV) in the region of Valencia, Spain. *Biosystems*. 96: 206-212.

Barua, R. and Hossain, M. A. (2014). Adenosine deaminase in diagnosis of tuberculosis: a review. *Anwer Khan Modern Medical College Journal*. 5: 43-48.

Benneyan, J. C. (1997). An introduction to using computer simulation in healthcare: patient wait case study. *Journal of the Society for Health Systems*. 5: 1-15.

Blower, S. M. and Daley, C. L. (2002). Problems and solutions for the Stop TB partnership. *The Lancet Iinfectious Disease*. 2: 374-376.

Boushab, B. M., Kone, N. and Basco, L. K. (2019). Contribution of Computed Tomography Scan to the Diagnosis of Spinal Tuberculosis in 14 Cases in Assaba, Mauritania. *Radiology Research and Practice*, 2019.

Brenner, S., Zeng, Z., Liu, Y.,Wang, J., Li, J. and Howard. P. K. (2010). Modeling and analysis of the emergency department at University of Kentucky Chandler Hospital using simulations. *Journal of Emergency Nursing*. 36: 303-310.

Brewer, T. F. and Heymann, S. J. (2004). To control and beyond: moving towards eliminating the global tuberculosis threat. *Journal of Epidemiology & Community Health*. 58: 822-825.

Catanho, M., Mascarenhas, D., Degrave, W. and Miranda, A. B. D. (2006). GenoMycDB: a database for comparative analysis of mycobacterial genes and genomes.5:115-12.

Chandrika, V., Parvathi,C. S. And Bhaskar, P. (2012). Diagnosis of tuberculosis using MATLAB based artificial neural network. *IJIPA*, 3(1), 37-42.

Chung, C. Y., Chung, H. Y. and Sung. W. T. (2013). Mathematical Models for the Dynamics Simulation of Tuberculosis. *In Applied Mechanics and Materials*. 418: 265-268.

Chung, C. Y., Chung, H. Y. and Ou, S. C. (2011). Computer Simulation Applied to a Bio-mathematic Model for Tuberculosis. *Procedia Engineering*. 15: 3626-3631.

Demay, C., Liens, B., Burguière, T., Hill, V., Couvin, D., Millet, J. and Rastogi, N. (2012). SITVITWEB–a publicly available international multimarker database for studying *Mycobacterium tuberculosis* genetic diversity and molecular epidemiology. *Infection, Genetics and Evolution*. 12: 755-766

Ding, C., Yuan, L. F., Guo, S. H., Lin, L. and Chen, W. (2012). Identification of mycobacterial membrane proteins and their types using over-represented tripeptide compositions. *Journal of proteomics*. 77: 321-328

Dowdy, D. W. and Chaisson, R. E. (2009). The persistence of tuberculosis in the age of DOTS: reassessing the effect of case detection. *Bulletin of the World Health Organization*. 87: 296-304.

Dowdy, D. W.,Golub, J. E., Chaisson, R. E. and Saraceni,V. (2012). Heterogeneity in tuberculosis transmission and the role of geographic hotspots in propagating epidemics. *Proceedings of the National Academy of Sciences*. 109: 9557-9562.

Ellis, S. M. and Flower, C. (2006). The WHO manual of diagnostic imaging: radiographic anatomy and interpretation of the chest and the pulmonary system. World Health Organization.

Feuerriegel, S., Schleusener, V., Beckert, P., Kohl, T. A., Miotto, P., Cirillo, D. M. and Fellenberg, K. (2015). PhyResSE: a web tool delineating *Mycobacterium tuberculosis* antibiotic resistance and lineage from whole-genome sequencing data. *Journal of Clinical Microbiology*. 53: 1908-1914.

Floyd, K., Glaziou, P., Zumla, A. and Raviglione, M. (2018). The global tuberculosis epidemic and progress in care, prevention, and research: an overview in year 3 of the End TB era. *Lancet Respiratory Medicine*. 6(4):299-2314.

Glaziou, P., Floyd, K. and Raviglione, M.C. (2018). Global epidemiology of tuberculosis. In Seminars in Respiratory and Critical Care Medicine. *Thieme Medical Publishers*. 39: 271-285

Gui, X. and Xiao, H. (2014). Diagnosis of tuberculosis pleurisy with adenosine deaminase (ADA): a systematic review and meta-analysis. *International Journal of Clinical and Experimental Medicine*. 7: 3126

Guirado, E. and Schlesinger, L. (2013). Modeling the *Mycobacterium tuberculosis* granuloma–the critical battlefield in host immunity and disease. *Frontiers in Immunology*. 4: 98.

Harris, M., Qi, A., Jeagal, L., Torabi, N., Menzies, D., Korobitsyn, A. and Khan, F. A. (2019). A systematic review of the diagnostic accuracy of artificial intelligence-based computer programs to analyze chest x-rays for pulmonary tuberculosis. *PloS One*.,14 (9).

HorsburghJr, C. R. (2004). Priorities for the treatment of latent tuberculosis infection in the United States. *New England Journal of Medicine*. 350: 2060-2067.

Huynh, G. H., Klein, D. J., Chin, D. P., Wagner, B.G., Eckhoff, P. A., Liu, R. and Wang, L. (2015). Tuberculosis control strategies to reach the 2035 global targets in China: the role of changing demographics and reactivation disease. *BMC Medicine*. 13: 88.

Iwai, H.,Kato-Miyazawa, M., Kirikae, T. and Miyoshi-Akiyama, T. (2015). CASTB (the comprehensive analysis server for the *Mycobacterium tuberculosis* complex): A publicly accessible web server for epidemiological analyses, drug-resistance prediction and phylogenetic comparison of clinical isolates. Tuberculosis (Edinburgh, Scotland). 95: 843-844.

Jacques, P. É., Gervais, A. L., Cantin, M., Lucier, J. F. O., Dallaire, G., Drouin, G. and Brzezinski, R. (2005).MtbRegList, a database dedicated to the analysis of transcriptional regulation in *Mycobacterium tuberculosis*. *Bioinformatics*. 21: 2563-2565.

Kapopoulou, A., Lew, J. M. and Cole, S. T. (2011). The Myco Browser portal: a comprehensive and manually annotated resource for mycobacterial genomes. *Tuberculosis*. 91: 8-13.

Kasaie, P., Dowdy, D.W. and Kelton, W.D. (2013). An agent-based simulation of a tuberculosis epidemic: understanding the timing of transmission. In *2013 Winter Simulations Conference (WSC)* (pp. 2227-2238). IEEE.

Khan, A. H. (2017). Tuberculosis control in Sindh, Pakistan: Critical analysis of its implementation. *Journal of Infection and Public Health*.10: 1-7.

Korzeniewska- Koseła, M. (2019). Tuberculosis in Poland in 2017. *Przegl Epidemiology*. 73(2): 211-226.

Kranzer, K., Afnan-Holmes, H., Tomlin, K., Golub, J.E., Shapiro, A. E., Schaap, A. and Glynn, J. R. (2013). The benefits to communities and individuals of screening for active tuberculosis disease. *The International Journal of Tuberculosis and Lung Disease*. 17: 432-446

Lange, C., Chesov, D., Heyckendorf, J., Leung, C. C., Udwadia, Z. and Dheda, K. (2018). Drug-resistant tuberculosis: An update on disease burden, diagnosis and treatment. *Respirology*. 23(7): 656-673.

Lee, B. Y., Bedford, V. L., Roberts, M. S. and Carley, K. M. (2008). Virtual epidemic in a virtual city: simulating the spread of influenza in a US metropolitan area. *Translational Research*. 151: 275-287.

Lew, J. M., Kapopoulou, A., Jones, L. M. and Cole, S. T. (2011). TubercuList–10 years after. *Tuberculosis*. 91: 1-7.

Machado, E., Cerdeira, C., de Miranda, A. B. and Catanho, M. (2018). Web Resources on Tuberculosis: Information, Research, and Data Analysis. Mycobacterium: Research and Development (2018): 159. DOI: 10.5772/intechopen.73549

Malhotra, S., Mugumbate, G., Blundell, T. L. and Higueruelo, A.P. (2017). TIBLE: a web-based, freely accessible resource for small-molecule binding data for mycobacterial species. Database (2017): 1-7

Manjelievskaia, J., Erck, D., Piracha, S. and Schrager, L. (2016). Drug-resistant TB: deadly, costly and in need of a vaccine. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 110(3): 186-191.

Melendez, J., Philipsen, R. H. H. M., Chanda-Kapata, P., Sunkutu, V., Kapata, N. and van Ginneken, B. (2017). Automatic versus human reading of chest X-rays in the Zambia National Tuberculosis Prevalence Survey. *The International Journal of Tuberculosis and Lung Disease*. 21: 880-886.

Melnichenko, A. and Romanyukha, A. A. (2009). A model of tuberculosis epidemiology: Data analysis and estimation of parameters. *Mathematical Models and Computer Simulations*. 1: 428-444.

Metri, R., Hariharaputran, S., Ramakrishnan, G., Anand, P., Raghavender, U. S., Ochoa-Montaño, B. and Srinivasan, N. (2015). SInCRe—structural interactome computational resource for *Mycobacterium tuberculosis*. Database (2015).1-10

Mithra, K. S. and Emmanuel, W. S. (2018). Gaussian model based hybrid technique for infection level identification in TB diagnosis. *Journal of King Saud University-Computer and Information Sciences*.

Murphy, K., Habib, S. S., Zaidi, S. M. A., Khowaja, S., Khan, A., Melendez, J. and Philipsen, R.H.H. (2020). Computer aided detection of tuberculosis on chest radiographs: An evaluation of the CAD4TB v6 system. *Scientific Reports*. 10: 1-11.

Musgrave, J. and Watmough, J. (2009). Examination of a simple model of condom usage and individual withdrawal for the HIV epidemic. *Mathematical, Biosciences and Engineering*. 6: 363-376.

O'Brien, R. J. (1994). Drug-resistant tuberculosis: etiology, management and prevention. *In Seminars in Respiratory Infections*. 9: 104-112).

Ochoa-Montaño, B., Mohan, N. and Blundell, T. L. (2015). CHOPIN: a web resource for the structural and functional proteome of *Mycobacterium tuberculosis*. Database,2015. 1-10

Okuonghae, D. (2013). A mathematical model of tuberculosis transmission with heterogeneity in disease susceptibility and progression under a treatment regime for infectious cases. *Applied Mathematical Modelling*. 37: 6786-6808.

Onozaki, I., Law, I., Sismanidis, C., Zignol, M., Glaziou, P. and Floyd, K. (2015). National tuberculosis prevalence surveys in Asia, 1990–2012: an overview of results and lessons learned. *Tropical Medicine & International Health*. 20: 1128-1145.

Panchanathan, S. S., Petitti, D. B. and Fridsma, D. B. (2010). The development and validation of a simulation tool for health policy decision making. *Journal of Biomedical Informatics*. 43: 602-607.

Pinto, L. M., Pai, M., Dheda, K., Schwartzman, K., Menzies, D. and Steingart, K.R. (2013). Scoring systems using chest radiographic features for the diagnosis of pulmonary tuberculosis in adults: a systematic review. *European Respiratory Journal*. 42: 480-494.

Radusky, L., Defelipe, L.A., Lanzarotti, E., Luque, J., Barril, X., Marti, M.A. and Turjanski, A.G. (2014). TuberQ: a *Mycobacterium tuberculosis* protein druggability database. Database ,2014. 1-10

Ragonnet, R., Trauer, J.M., Denholm, J. T., Marais, B. J. and McBryde, E. S. (2017). A user-friendly mathematical modelling web interface to assist local decision making in the fight against drug-resistant tuberculosis. *BMC Infectious Diseases*. 17: 374.

Rao, H. X., Zhang, X., Zhao, L., Yu, J., Ren, W., Zhang, X. L. and Wei, Z. (2016). Spatial transmission and meteorological determinants of tuberculosis incidence in Qinghai Province, China: a spatial clustering panel analysis. *Infectious Diseases of Poverty*. 5: 45.

Salazar-Austin, N., Dowdy, D.W., Chaisson, R.E. and Golub, J.E. 2019. Seventy years of tuberculosis prevention: Efficacy, effectiveness, toxicity, durability, and duration. *American Journal of Epidemiology*. 188(12): 2078-2085.

Saxena, S., Abdullah, M., Sriram, D. and Guruprasad, L. (2018). Discovery of novel inhibitors of *Mycobacterium tuberculosis*MurG: homology modelling, structure based pharmacophore, molecular docking, and molecular dynamics simulations. Journal of Biomolecular Structure Dynamics.*36*(12):3184-3198. http://doi: 10.1080/07391102.2017.1384398.

Shabbeer, A., Ozcaglar, C., Yener, B. and Bennett, K.P. (2012). Web tools for molecular epidemiology of tuberculosis. *Infection, Genetics and Evolution*. 12: 767-781

Shamshirband, S., Hessam, S., Javidnia, H., Amiribesheli, M., Vahdat, S., Petković, D. and Kiah, M.L.M. (2014). Tuberculosis disease diagnosis using artificial immune recognition system. *International Journal of Medical Sciences*. 11: 508.

Steingart, K. R., Henry, M., Laal, S., Hopewell, P.C., Ramsay, A., Menzies, D. and Pai, M. (2007). Commercial serological antibody detection tests for the diagnosis of pulmonary tuberculosis: a systematic review. *PLoSMedicine*.4(8).

Stover, J., Johnson, P., Hallett, T., Marston, M., Becquet, R. and Timaeus, I.M. (2010). The Spectrum projection package: improvements in estimating incidence by age and sex, mother-to-child transmission, HIV progression in children and double orphans. *Sexually Transmitted Infection*. 86(2): ii16-ii21

Talat, N., Perry, S., Parsonnet, J., Dawood, G. and Hussain, R. (2010). Vitamin D deficiency and tuberculosis progression. *Emerging Infectious Diseases*. 16: 853.

Tay, T. R. and Tee, A. (2013). Factors affecting pleural fluid adenosine deaminase level and the implication on the diagnosis of tuberculous pleural effusion: a retrospective cohort study. *BMC Infectious Diseases*. 13: 546.

Tiemersma, E. W.,van der Werf, M. J., Borgdorff, M. W., Williams, B. G. and Nagelkerke, N. J. (2011). Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. *PloS One*. 6(4).

Tuon, F. F., Higashino, H. R., Lopes, M.I.B.F., Litvoc, M. N., Atomiya, A. N., Antonangelo, L. and Leite, O.M. (2010). Adenosine deaminase and tuberculous meningitis—a systematic review with meta-analysis. *Scandinavian Journal of Infectious Diseases*. 42: 198-207.

vanBeek, J., Haanperä, M., Smit, P.W., Mentula, S. and Soini, H. (2019). Evaluation of whole genome sequencing and software tools for drug susceptibility testing of *Mycobacterium tuberculosis*. *Clinical Microbiology and Infection*. 25: 82-86.

Vynnycky, E. and Fine, P.E.M. (1997). The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. *Epidemiology and Infection*.119: 183-201.

Walensky, R. P., Goldie, S. J. Sax, P. E., Weinstein, M. C., Paltiel, A. D., Kimmel, A. D. and Freedberg, K. A. (2002). Treatment for primary HIV infection: projecting outcomes of immediate, interrupted, or delayed therapy. *Journal of Acquired Immune Deficiency Syndromes*.31: 27-37.

World Health Organization. (2013). Global tuberculosis report 2013. World Health Organization.

Xiong, Y., Ba, X., Hou, A., Zhang, K., Chen, L. and Li, T. (2018). Automatic detection of *Mycobacterium tuberculosis* using artificial intelligence. *Journal of Thoracic Disease*. 10: 1936

Zaidi, S. M. A., Habib, S. S., Van Ginneken, B., Ferrand, R. A., Creswell, J., Khowaja, S. and Khan, A. (2018). Evaluation of the diagnostic accuracy of Computer-Aided Detection of tuberculosis on Chest radiography among private sector patients in Pakistan. *Scientific Reports*. 8:1-9. Zamora, J., Abraira, V., Muriel, A., Khan, K. and Coomarasamy, A. (2006). Meta-DiSc: a software for meta-analysis of test accuracy data. *BMC Medical Research Methodology*. 6: 31.

Zhao, Y., Li, M. and Yuan, S. (2017). Analysis of transmission and control of tuberculosis in mainland China, 2005–2016, based on the age-structure mathematical model. *International Journal of Environmental Research and Public Health*. 14: 1192.

Zhu, P. P., Li, W. C., Zhong, Z. J., Deng, E. Z., Ding, H., Chen, W. and Lin, H. (2015). Predicting the subcellular localization of mycobacterial proteins by incorporating the optimal tripeptides into the general form of pseudo amino acid composition. *Molecular BioSystems*. 11: 558-563.

Zhu, X., Chang, S., Fang, K., Cui, S., Liu, J., Wu, Z. and Wang, J. (2009). MyBASE: a database for genome polymorphism and gene function studies of Mycobacterium. *BMC Microbiology*. 9: 40.