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Review Article

Review of Mathematical Modeling of Hansen's (Leprosy) Disease: Questions Unanswered - The Road Ahead

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In this article, we have surveyed the research done with respect to mathematical modeling of leprosy. We also briefly deal with some of the clinical studies done on leprosy. We have classified these studies and discussed some of the key findings of both these studies. In our survey/analysis it has been observed that little research involving mathematical modeling has been done dealing with the in vivo dynamics of leprosy. Based on these facts, we have identified few possible unanswered research questions and have also suggested few pointers for mathematical modeling studies that can help us to better understand the *in vivo* dynamics, which can play a crucial role in the control and eradication of leprosy. Modelling studies on bio-markers leading to lepra Type - I and Type - II reactions; factors leading to G1D and G2D deformities in leprosy; genetic studies to predict the risk and prognosis; optimum regimens; optimum regimens to treat nerve damage and health care system to improve the access to services are likely to have useful in marching towards this goal.

Keywords : Mathematical Modelling, Leprosy, Tuberculosis, Mycobacterium, Cross Immunity, Lepra Reaction, Schwann Cells, Heterogeneity, *In Vivo*

Introduction

Hansen's disease (commonly known as leprosy) is caused by *Mycobacterium leprae*, due to transmission between infectious and healthy people. The main outcome pathway of the pathogen is the nasal secretions of untreated cases that often enter the sensitive body through skin ruptures or nasal membranes. Even though leprosy is not inherited, it can be transmitted to infants via breast milk, and the infection happens through the placenta. In order to contract the disease, closer proximity to an infected person seems necessary. Armadillos, a mammal found in the South and North American continent, is only the animal known to date, which can be a carrier for leprosy.

For most people who are exposed to *M. leprae*, the infection dies quietly. Leprosy affects the neurotic neurons, eyes, skin and upper respiratory tract mucosa for those who are developing the disease. The immunity of the patient depends on various clinical signs of leprosy. The disease

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becomes apparent in two extremes, tuberculosis and lepromatous leprosy, as the infection progresses. The tuberculoid form grows when there is adequate power of the cellular immune response to maintain the infection located. But if cellular responses are not enough or absent, lepratic leprosy causes the bacterium, which has far greater bacteria than tuberculoid intake in lesions. For clinical purposes, leprosy cases are categorized as paucibacillary (PB) and multibacillary (MB) leprosy based upon the bacterial load magnitude of the disease and the amount of parts of the skin. The infection may cause nerve function impairments which can result in secondary complications, such as untreated wound infection and soil and palm ulcers. Impairment of nerve function may develop the responses of Lepra reactions slowly or during periods of inflammation. There are two main kinds of reactions: (i) type II reactions occurring predominantly in patients at the lepromatous end of the spectrum; and (ii) reversal reactions (RR) (type I reactions) occurring especially in patients with borderline leprosy, particularly during treatments.

It is hard for leprosy, owing to the absence of appropriate immunological instruments and due to the slow onset of the disease, to identify both the reference points for evaluating the Incubation period and times of infected disease. The different leprosy grading introduced by WHO includes :

1. Grade 0 : No noticeable deformity or harm, no anaesthesia.
2. Eyes-Grade 0 : No visual impairment due to leprosy ;
3. Grade 1 : There is anaesthesia, but no deformity or harm is noticeable.
4. Grade 2 : Deformity or harm that is visible.

Dapsone, an anti *M. leprae* was the most significant leprosy treatment until widespread resistance was developed. Combining therapy was crucial to slow or stop the growth of resistance. Rifampicin is combined with dapsone to treat preventive leprosy. Rifampicin and clofazimin are now merged in multibacillary leprosy with the dapsone known as multi-drug treatment (MDT).

In terms of both worldwide and domestic programmes, leprosy has now achieved a critical point. The very lengthy incubation period leads to issues in assessing the effect of instant modifications of policy – which react to transmission changes occurring a decade earlier and the effects of modifications now almost a decade away.

Mathematical modeling has always been a powerful tool to help us conceptualize the disease transmission dynamics as well as the spread patterns in a quantitative way. It also helps us to test and compare different intervention and control strategies that will help in control and eradication. Using mathematical modeling we can qualitatively test different hypotheses to understand their importance. Owing to this modeling can play a key role in managing leprosy to zero disability and transmission: a world free of leprosy.

In this survey, we conduct a study on mathematical modeling in Leprosy. Some of leprosy related clinical studies are also briefly dealt. We later discuss the key findings of both these studies and give pointers to some of the possible unanswered questions and the road ahead for future research in mathematical modeling for this disease.

Mathematical Modeling in Leprosy

In this section, we discuss most of the research works done for leprosy with respect to mathematical modeling. To the best of our knowledge, we tried to obtain all the research papers dealing with mathematical modeling related to leprosy from various search engines with multiple/

combination keywords. Based on the research papers obtained, we classify them into the following five categories. We will now discuss these works with respect to each category.

Deterministic Modeling in Leprosy

The paper (Chiyaka et al 2013) discusses three models to deal with the deterministic approach towards the modeling of leprosy. The first model is a proposition of the deterministic SEIR and SEI models for paucibacillary leprosy (PB) and multibacillary leprosy (MB), respectively. The population is divided into five time-dependent categories:

- Individuals yet to be infected,
- Infected but no sign of any symptoms shown,
- Infected manifesting as paucibacillary leprosy,
- Infected manifesting as multibacillary leprosy,
- Non-infectious group (successfully recovered and immune to being infected again).

The second deterministic model (Chiyaka et al 2013) was a compartmental model for a community with access to MDT, assuming that treatment perfectly worked for compliant patients. The third deterministic model in the paper (Chiyaka et al 2013) was for a community where MDT was accessible, assuming that the treatment failed to completely cure the non-compliant patients.

Analysis of $R0$ for all three models showed that for the first model, successful infection during interaction with infected was directly proportional to transmission and the rate of progression towards clinical infections. With the wide spread use of multidrug treatment (MDT) recommended by WHO (WHO 1982), there is reduction in number of source cases, and resultant decreased rate of transmission. Non-compliant behaviour of patients, as well as inadequacy in the treatment, resulted in the increase in value of $R0$ and slower elimination of the disease (Chiyaka et al 2013).

In the study of Sousa et al (2012), estimation of the risk of infection with Leprosy in Brazil has been done where the results showed that it would take a minimum of 44-45 years for the elimination of the disease in the endemic areas of the country.

Mushayabasa & Bhunu (2012) carried out a comprehensive and qualitative mathematical analysis and showed that the disease-free equilibrium was globally, asymptotically stable whenever the reproductive number was less than unity. The disease-free equilibrium was globally asymptotically stable whenever the reproductive number was less than unity and using Centre manifold theory; it was shown that the model had a locally asymptotically stable endemic equilibrium when the reproductive number was greater but close to unity.

Stochastic Modeling in Leprosy

In the study of Joshua et al (2008), data were gathered for four periods between January 1991 and March 2003 from 148 endemic region panchayats in South India. Bayesian space-cohort and space-period models with and without interactions were contrasted for the research. The variation in leprosy incidence was obtained using Bayesian methods over 20 rolling cohorts and four-time periods of a South India vaccine trial. Developments in the incidence of leprosy in period impacts continued to decline over four-time points. There was a slight decrease in the projected period impacts of leprosy as a consequence of environmental factors, such as urbanization and overcrowding due to insufficient accommodation. It was noted that almost 37% of the individuals in this pocket belong to the economically poorer strata as they live in close proximity to each other, leading to a greater danger of disease contracting.

Varella et al (2018) studied the spread of leprosy in Juiz de Fora using the SIR model, and it involves some of the computationally resolved pathological elements using the Gillespie algorithm as a stochastic strategy. The equations scheme has been converted into a collection of stochastic equivalent procedures performed using the Gillespie algorithm (Gillespie 1976). A steady 20-year population set of 441,816 inhabitants, which according to the census (Varella et al (2018) was approximately the number of people living in Juiz de Fora in 1996 was considered. The research resulted in the likelihood of eradication of leprosy in the town before 2,045 being 99.21% if the assumptions of the model are maintained constant.

Cross Immunity in Leprosy and Tuberculosis

In the paper by Lietman et al (1997) the interdependence between leprosy and tuberculosis is discussed. Individuals infected with *M. leprae* can be infected with *M. tuberculosis* or vice versa, but the degree of cross-immunity because of previous decreases the incidence rate. The cross-immunity degree ranges from zero (when no protection is provided by earlier exposure to other species) to 1. Results obtained in the presence of tuberculosis, eradication of leprosy will take place only if the Ro (corresponding to leprosy) is less than 1. However, tuberculosis could not eliminate leprosy if the endemicity of the latter was severe - for example, if *R*0 (corresponding to leprosy) is approximately equal to or greater than 4.

A computer simulation program was used by Meima et al (2004) to understand these scenarios to study the impact of the elimination strategies. The study considered the two policies - no vaccination with BCG and the other was the vaccination of infants starting in the year 1975 with initial coverage of approximately 5%. The vaccination was then gradually increased it to 80% in 1990, and then 95% after the year 1999.

Scenarios without BCG vaccination - The incidence rate of Leprosy stayed fixed until 1995, but the fall in incidence was predicted between 2000 and 2020 that averaged to be 1.6% per year. The study projected the average annual decline in incidence rate during the period 2000-2020 to be 8.3%.

Scenarios with BCG vaccination - Since vaccination was done to infants, there was negligible impact till 2000, and net coverage of the vaccination was also low. The vaccination was projected to improve the annual decline of the incidence of leprosy during 2000–20 by very few per cent. The annual decrease in the incidence rate was in the range from 4.90% to 10.00%.

Approaching Leprosy Using Computer Simulation

SIMCOLEP is an individual model used by Blok et al (2015), predicting the potential incidence of leprosy in India, Brazil and Indonesia, the three most significant endemic nations. The population of each nation has been adapted to the simulation of the general population and family structure derived from a range of sources, including country censuses, population and health (DHS) and WHO. In India and Indonesia, the elimination target of fewer than 10 out of 100,000 was already met and will be achieved in Brazil by 2016. In Brazil, the majority of the cases are in larger families, whereas in Indonesia, the majorities are in lower families.

The models in the study of Blok et al (2017) based on areas in Brazil clearly showed that the NCDR in Amazonas, Cear´a and Tocantins remains above 10 per 100,000 by 2020, indicating that the goal will not be met. The Amazonas will most likely achieve the objective before 2040, while the NCDR is (far) above 10 per 100,000 in the modeled time frame for Cear´a and Tocantins.

de Matos et al (2016) used the SIMCOLEP to evaluate future NCDR tendencies in Par´a State (endemic region of Brazil). The model was quantified for the period from 1990 to 2014. Two scenarios consisting of the discontinuation of contact tracing and present control measure with chemoprophylaxis were examined. If systematic contact tracing were discontinued, it would not lead to higher NCDR over the long term. Two years before 2028, systemic contact tracking for contacts would cut NCDR by 40 % in conjunction with chemoprophylaxis and result in the elimination goal being achieved. With the present control programme, leprosy elimination as an issue of public health could probably be accomplished around 2030. The provision of chemoprophylaxis would further reduce the NCDR and bring about two years of elimination.

Heterogeneity in Projected Leprosy

The extent to which specific heterogeneity processes can explain the clustering of households is investigated using a model of microsimulation (Fischer et al 2010), where information from more than 20,000 patient contacts in Bangladesh was gathered. Six mechanisms of random susceptibility, household and genetic factors and half a household and genetic factors were regarded to produce heterogeneity. Furthermore, it was assumed that a proportion of 5%, 10%, and 20% of the population is sensitive, leading to a total of 18 instances. The system of the household outcomes in a high incidence among spouses and the genetic mechanisms underestimate the incidence among spouses. In the incidence of siblings, kids, and parents, the genetic mechanisms vary. Genetic mechanisms tend to underestimate the incidence found between spouses but prevails more in moderately large households. The present decline in new case identification of leprosy is forecast to continue over the next decades for all six processes. Reduction is slowest and quickest for both genetic mechanisms and family and random. Mechanisms that combine household and genetic processes take an intermediate position.

The assessment of accessible information from the Indian Ministry of Health and Family Welfare was conducted, and linear mixed-effect regression models were included to detect trends in leprosy reported at the district level (Brook et al 2015). Around 5% of the population in some endemic areas, most of them without any symptoms carry *M. lepra*e in nasal passages (Lockwood & Suneetha 2005, Beyene et al 2003). Respiratory inhalation of aerosolized *M. leprae* particles and frequent contact with nasal mucous membranes and/or skin excretions are believed to play a part (Davey & Rees 1974, Job et al 2008, McDougall et al 1975). The GADM administrative boundaries were used in the spatial analysis, supplemented with a revised version for selected jurisdictions (Brook et al 2015). The report also highlights the connection between leprosy and tuberculosis. Leprosy trends at the domestic, state and district level in India show a slow decline, with the frequency of new cases decreasing by less than 2% per year at district level over the 2008- 2015 period.

Clinical Studies in Leprosy

In this section, we discuss few clinical studies that can lead to research questions that mathematical modelling studies can deal with.

Type I and Type II Reactions in Leprosy

In the report by Vieira et al (2016) the development of type 2 lepra reaction has been discussed. In this study all patients were recruited from the leprosy outpatient unit of the Clinics, Hospital, Sao Paulo, Brazil. All the patients were given MDT and underwent various investigations. The results obtained from this study are as follows:

The frequency of circulating regulatory T cells in patients with type 1 reaction (T1R) and type 2 reaction (T2R) was studied. T2R patients showed a remarkably lower number of circulating and in situ Tregs than T1R patients and controls. This decrease was paralleled by increased in situ IL-17 expression but decreased TGF-β expression.

Biopsies from T1R and T2R patients before the reaction episodes showed a similar number of forkhead box protein P3 + (FoxP3+) and IL-17+ cells. However, in biopsies that were taken during the reaction, T2R patients showed a fall in Tregs and a rise in IL-17+ cells, whereas T1R patients showed the opposite result.

A nested case-control study was used to evaluate T1R (n = 10) and TR2 (n = 10) in comparison to the leprosy patients without reactions (n = 29), matched by factors like age-group (+/- 5 years), gender and histopathological classification was done in (Stefani et al 2009). Increase of plasma CXCL10 (P=0.004) and IL6 (p=0.013) were observed in T1R patients in comparison to controls without reaction. IL6 (p = 0.05), IL7 (p = 0.039), and PDGF-BB (p = 0.041) were elevated in T2R. In (Sousa et al 2012), the use of IL-6 as a biomarker in several diseases has been widely discussed based on the various effects of cytokines on the control of innate and adaptive immunity. In (Fisman & Tenenbaum 2010), genetic variants of IL-6 as possible bio-markers for T2R in leprosy has been proposed. The results presented here add up to a solid body of evidence implicating IL-6 in the pathogenesis of leprosy T2R and point to these cytokines as a possible valuable predictive marker for this aggressive leprosy phenotype.

M. leprae and Schwann Cells

Article by Hagge et al (2002) describes a new model (method) for studying the effects of *M. leprae* on Schwann cells. It is observed in (Hagge et al 2002) through experiments that the viability of *M. leprae* in Schwann Cells reduces at 37 degrees compared to 33 degrees Celsius.

A mathematical model was developed to study the interactions between *M. leprae* on Schwann cells and Schwann cell–neuron interactions in (Hagge et al 2002). This model determined the effect of *M. leprae* infection on Schwann cells and Schwann cell–axon interactions and the effect of incubation temperature on the viability of *M. leprae* in Schwann cells. Following are some of the results (Hagge et al 2002).

Schwann cells cultivated at 33 degrees Celsius appeared to survive and form typical “swirled” monolayers in a manner similar to those cultivated at 37 degrees Celsius. These cells maintained their viability and survived for several weeks in culture. In contrast, Schwann cells infected with viable *M. leprae* at 33 degrees Celsius appeared to retract from the surface of the flask and form large cellular aggregates, resulting in the loss of the typical “swirled” monolayers appearance.

When the expression of Schwann cell markers was evaluated in cells infected with *M. leprae* and held at 33 degrees Celsius, results indicated that the expression of several Schwann cell genes was altered in some cultures.

Significantly higher levels of NCAM mRNA and lower levels of N-cadherinm RNA were found in cultures infected with viable *M. leprae* than in uninfected cultures and cultures infected with irradiated *M. leprae.*

Damage to peripheral nerves is the major complication of reversal (type I) reactions in leprosy. The underlying mechanism of nerve damage remains largely unresolved; however, an important role for type-I T cells has been suggested (Spierings et al 2000). Because reversal reactions in leprosy are often accompanied by

severe and irreversible nerve destruction and are associated with increased cellular immune reactivity against *M. leprae*, a likely immune-pathogenic mechanism of damage to Schwann cells and peripheral nerves in leprosy is that infected Schwann cells process and present antigens of *M. leprae* to antigen-specific, inflammatory, type- l T cells, and that these T cells subsequently damage and lyse infected Schwann cells (Spierings et al 2000).

Nerve Damage in Leprosy

Kumar (2017) examined several important aspects in understanding the feasible and most common pathway of entry of *M. leprae* into the nerve, the localization of *M. leprae* in the nerve & reactions to Schwann cell infection, still unknown injury mechanisms, axonal atrophy, and lastly demyelination. Inflammation is described not only by its chemical mediators such as cytokines and chemokines, but also by one of the inflammation's most fundamental phenomena – edema. An inflammation of and around the nerves, in part caused by the immunological responses of each portion of the leprous immune spectrum, can certainly lead to non-specific inflammation associated with infection and foreign substances (i.e. mycobacterium elements).

In the paper of Scollard et al (2015), the nervous harm mechanism in leprosy is described. Even after MDT, a large number of dead bacterial cells tend to remain within a nerve which continue to evoke acute and chronic neuritis as well as immunological responses.

Key Findings from Mathematical Modeling and Clinical Studies

Over the last few decades, there have been many useful tools that have helped the world to reduce the occurrence rate of leprosy disease drastically. One such tool has been mathematical modeling which can be approached through many ways – deterministic modeling, stochastic modeling, etc. In this work, we have briefly discussed and summarized works on mathematical modelling and few clinical works in leprosy. Some of the key findings from the mathematical modeling studies and clinical observations include the following :

Deterministic Modeling

Deterministic modeling helped to arrive at a solution based conclusions using the collected data for years. Basic reproductive ratio ($R0$) values for the base model have been shown to be directly proportional to the rate of transmission and progression to clinical diseases during interactions. Adequate therapy reduced transmission directly with the implementation of MDT. Non-compliant behaviour of patients, as well as inadequacy in the treatment, resulted in the increase in value of $R0$ and hence slower elimination of the disease.

Stochastic Modeling

Using a Bayesian model, it was shown that in India, people from economically poorer strata are more susceptible to leprosy because they live in close proximity to each other, leading to a greater danger of disease contraction. Factors such as urbanization and overpopulation due to insufficient accommodation have also been discovered to have led to more often close contact with the infection source.

Cross Immunity

It has been experimentally proven that exposure to one species of *Mycobacterium* (*M. tuberculosis*) provides a degree of protection against infection by another infection (*M. leprae*). *M. leprae* can also infect people already infected with *M. tuberculosis*, but the level of incidence is decreased by the degree of cross-immunity. In the presence of tuberculosis, leprosy will surely be eradicated if the $R0$ (corresponding to leprosy) is less than one. The degree of cross-immunity between these species of *Mycobacterium* was

found to be in the range of 0.5018 - 0.75. However, the endemicity of leprosy cannot be eliminated by *M. tuberculosis*.

Computer Simulation

A computer simulation program SIMLEP is effective to predict new case detection rate (NCDR) trends in the future. The scenarios in the endemic areas of India, Brazil and Indonesia have been studied using SIMLEP and the continuation of current strategy of using MDT, BCG and chemoprophylaxis to eliminate leprosy was reported to be fruitful. In Par´a State of Brazil, the NCDR of leprosy is still declining. With the present control programme, the elimination of leprosy as an issue of public health could probably be accomplished around 2030. The provision of the chemoprophylaxis would further reduce the NCDR and bring about two years of elimination.

Heterogeneity

Considering heterogeneity in susceptibility (Fisher et al 2010), the mechanism of the household causes elevated spousal incidence, while genetic arrangements underestimated these incidences. In terms of siblings, kids, and parents, the genetic mechanisms vary. Prevalence of leprosy has a higher chance for a family with many members. Genetic mechanisms tend to underestimate the incidence found between spouses but prevails more in moderately large households.

Vaccination

Vaccination using BCG was also found out to be important tool in the elimination of leprosy. It is provided only to children so the impact of vaccination was shown over the passage of decades and the results were positive. Another heat killed Indian vaccine (*Mycobacterium indicus pranii,* Mw) has been found to be effective in reducing the incidence of leprosy in household contacts of leprosy cases (Talwar & Gupta 2017). Its use as a public health intervention is yet to be realized in leprosy.

Clinical Findings

M. leprae prefers to multiply in the cooler regions of the body and mainly affect trunk nerve sections that are in close contact with the skin. The sequence of nervous injury mechanisms in leprosy is difficult to identify because of the bacteria's dormancy and long incubation period before producing any nerve damage. Reverse leprosy reactions are often correlated with serious and irreversible destruction of the nerves and associated with increasing cell reactivity against *M. leprae*. In Schwann Cells, *M. leprae's* viability decreases at 37 degrees Celsius.

National sample survey to assess the new case disease burden of leprosy in India

With the objectives of estimating the new leprosy case load; record both Grade 1 and Grade 2 disabilities in the new cases a national sample survey of leprosy in partnership with Indian Council of Medical Research (ICMR) institutions, National Leprosy Eradication Programme (NLEP), Panchayati Raj members, and treated leprosy patients to detect new cases of leprosy in India was undertaken (Katoch et al 2017). The key findings are: Out of 14,725,525 (10,302,443 rural; 4,423,082 urban) population screened and 2161 new cases - 1300 paucibacillary (PB) and 861 multibacillary (MB) were detected. New case estimates for leprosy was 330,346 (95% Confidence limits, 287,445-380,851). Disabilities observed in these cases were 2.05/100,000 population and 13.9 per cent (302/2161) in new cases. Self-stigma in patients with disabilities was reduced, and the patients were well accepted by the spouse, neighbour, workplace, and social functions.

Questions Unanswered - The Road Ahead

From the above discussions in the previous sections, it can be seen that certain modeling studies involving both deterministic and stochastic are done at the population level, and also behaviour/spread pattern of the disease are studied. Few computer simulations and cross-immunity studies have also been done. But to the best of our knowledge, little research involving mathematical modeling is done dealing with the *in vivo* dynamics of leprosy. As discussed in section 3, some of the clinical studies for the *in vivo* dynamics are in progress. These can lead to and be possible pointers for mathematical models that can help us better understand the in vivo dynamics, which can play a crucial role in the control and eradication of leprosy.

We have identified and listed some of the possible research questions/ priority areas for research in which mathematical modeling can play a crucial role in understanding the underlying mechanism and thereby helping the clinicians, public health workers and doctors in developing and implementing better treatment and control measures :

(i) Modeling studies on bio-markers leading to Lepra Type - I and Type - II reactions may assist in the diagnosis and clinical management of immune pathologies of leprosy reactions.

(ii) Modeling studies on factors leading to G1D and G2D deformities in leprosy can be helpful.

(iii) Modeling studies on genetics can help to identify patients at risk for leprosy related nerve injury responses.

(iv) Modeling studies on the best possible drug regimen in treating leprosy are needed.

(v) Nerve damage can be effectively treated with steroids, but the chances of recurrence are high. So research is required from modeling perspective for the best steroid regimen(s).

(vi) Modeling studies on health care are required to enhance the identification and treatment of patients.

Conclusions

In this survey, we have done a review of the literature available on leprosy with respect to mathematical modelling. It has been observed that the available literature can be broadly classified in deterministic and stochastic modelling, which deal with the disease at the population level, and also some of the research works deal with the behaviour/spread pattern of the disease. Few computer simulations and cross-immunity studies have also been done. But from our survey, it has been observed, and it can be concluded that very little research involving mathematical modelling is done dealing with the *in vivo* dynamics of leprosy. Some of the clinical studies for the *in vivo* dynamics of leprosy are in progress. Motivated by the above-mentioned facts, we conclude this work by discussing few possible unanswered research questions and also have given few pointers for mathematical models that can help us in better understanding the *in vivo* dynamics which can play a crucial role in control and eradication of leprosy.

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