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CONTENT

The Appendix

In honor of the first Doctor of Mathematical Sciences Acad. Blagoj Popov, a mathematician dedicated to differential equations, the idea of holding the "Day of DifferentialEquations" was born, prompted by Prof. Ph.D. Boro Piperevski, Prof. Ph.D. Borko Ilievski, and Prof. Ph.D. Lazo Dimov. Acad. Blagoj Popov presented his doctoral dissertation on 05.05.1952 in the field of differential equations. This is the main reason for holding the "Day of Differential Equations" at the beginning of May.

This year on May 5th, the "Day of Differential Equations" was held for the seventh time under the auspices of the Faculty of Computer Sciences at "Goce Delcev" University in Stip and Dean Prof. Ph.D. Saso Koceski, organized by Prof. Ph.D. Biljana Zlatanovska, Prof. Ph.D. Marija Miteva and Prof. Ph.D. Limonka Koceva Lazarova.

The participants of this event were:

1. Prof. Ph.D. Aleksa Malcheski from the Faculty of Mechanical engineering at Ss.Cyril and Methodius University in Skopje;
2. Prof. Ph.D. Slagjana Brsakoska from the Faculty of Natural Sciences and Mathematics at Ss.Cyril and Methodius University in Skopje;
3. Prof. Ph.D. Natasa Koceska, Prof. Ph.D. Limonka Koceva Lazarova, Prof. Ph.D. Marija Miteva and Prof. Ph.D. BiljanaZlatanovska from the Faculty of Computer Sciences at Goce Delcev University in Stip;
4. Ass. Prof. Ph.D. Biljana Citkuseva Dimitrovska and Ass. M.Sc. Maja Kukuseva Panova from the Faculty of Electrical Engineering at Goce Delcev University in Stip.

Acknowledgments to Prof. Ph.D. Boro Piperevski, Prof. Ph.D. Borko Ilievski and Prof.Ph.D. Lazo Dimov for the wonderful idea and the successful realization of the event this year and in previous years.

Acknowledgments to the Dean of the Faculty of Computer Sciences, Prof. Ph.D. Saso Koceski for her overall support of the organization and implementation of the "Day of Differential Equations".

The papers that emerged from the "Day of Differential Equations" are in the appendixto this issue of BJAMI.

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SEIR+D MODEL OF TUBERCULOSIS

NATASHA STOJKOVIC, MAJA KUKUSEVA PANEVA, ALEKSANDRA STOJANOVA ILIEVSKA AND CVETA MARTINOVSKA BANDE

Abstract. Tuberculosis (TB) is a highly contagious infectious disease caused by the bacterium Mycobacterium tuberculosis. It primarily affects the lungs but can also affect other parts of the body. TB poses a significant global health burden, with millions of new cases and deaths reported each year. Understanding the spread of tuberculosis and evaluating control measures are crucial for effective disease management. The SEIR model is a commonly used mathematical framework for studying the spread of infectious diseases. It divides the population into four compartments: Susceptible (S), Exposed (E), Infectious (I), and Recovered (R). In the case of tuberculosis, an additional compartment for the number of deaths (D) is included. The model tracks the flow of individuals between these compartments over time. In the paper SEIR+D model is used to study and simulate the spread of tuberculosis. The simulation of the model on the sample of 10000 individuals is performed. The result of the simulation shows that the number of infected and dead individuals is high. These results are obtained, because in the model it is assumed that the population is not vaccinated. Future research will be focused on the development of the model for tuberculosis with vaccination compartment.

1. Introduction

Tuberculosis is an infectious disease caused by Mycobacteria tuberculosis [1] that attacks the lungs. The disease is characterized by the formation of tubercles on the lungs and other tissues that develop after the initial infection. Tuberculosis has a high mortality rate in underdeveloped and developing countries. The bacteria can survive for a long period in an external environment that is protected from sun and cannot be destroyed by freezing, but can be destroyed at temperature above +65°C.

Epidemic models are defined as mathematical models used to understand how infectious diseases spread through a given population. By using mathematical techniques, the spread of an infectious disease is determined and the number of infected individuals during a given time interval (weeks, months, years) can be estimated. When modeling these models, the characteristics of a specific infectious disease, such as incubation period, recovery rate, transmission and contact rate etc., must be considered as input data. Some of these inputs are taken directly from real data and others are assumed or estimated. Therefore, when examining the model, many assumptions are considered and their effect on the course of the disease are examined.

Depending on the type of the infectious disease, several mathematical models have been developed such as SIR, SIER, SVEIR etc., [2]. The SIR model [3] is the basic epidemiology model where the total population is divided into three compartments: susceptible, infected, and recovered. This model applies only to those infectious diseases

Keywords. Tuberculosis, SEIR model, simulation, differential equations

in which the infected individual can immediately infect other individuals. However, many diseases have a latent (exposed) period during which the individual is infected but is not contagious and cannot transmit the disease to other individuals.

The model involving exposed population is the SEIR model [4] and it is used to describe the dynamics of diseases such as tuberculosis, Covid-19, or a certain type of flu. SVEIR\model [5] is an extension of the SEIR model that includes vaccination compartment to study the impact of vaccination on disease transmission such as measles and tuberculosis.

2. Model description

Mathematical models are a useful tool to describe infectious diseases such as tuberculosis, N1H1, Covid-19 etc. These models are developed by Kermack and McKendrick, [6]. In this paper, the SIER +D model for tuberculosis is explained.

The total population at any given time is divided into 5 compartments: susceptible, infected, exposed, recovered and dead.

$$N(t) = S(t) + E(t) + I(t) + R(t) + D(t) \tag{2.1}$$

where time t is in days.

The tuberculosis SEIR model in AnyLogic consists of several key components:

1. **Population (*N*)**: The total number of individuals in the population. This parameter represents the size of the population under consideration.
2. **Susceptible (*S*)**: The number of individuals who are susceptible to contracting tuberculosis. It is calculated as the difference between the population size and the sum of individuals in the other compartments (E, I, R, and D).
3. **Exposed (*E*)**: The number of individuals who have been exposed to tuberculosis but are not yet infectious. Exposed individuals are in the latent stage of the disease and can potentially infect others. The flow into the exposed compartment is determined by the exposure rate (exposureRateAlpha) and the interaction between susceptible and infectious individuals.
4. **Infectious (*I*)**: The number of individuals who are currently infectious and can transmit the disease to susceptible individuals. The flow into the infectious compartment is determined by the transmission rate (transmissionRateBeta) and the number of exposed individuals.
5. **Recovered (*R*)**: The number of individuals who have recovered from tuberculosis and have developed immunity to reinfection. They are no longer infectious and cannot transmit the disease. The flow into the recovered compartment is determined by the recovery rate (recoveryRateGamma) and the number of infectious individuals.
6. **Dead (*D*)**: The number of individuals who have succumbed to tuberculosis and have died. The flow into the dead compartment is determined by the mortality rate (mortalityRateDelta) and the number of infectious individuals.

The deployed model is shown in Figure 1.

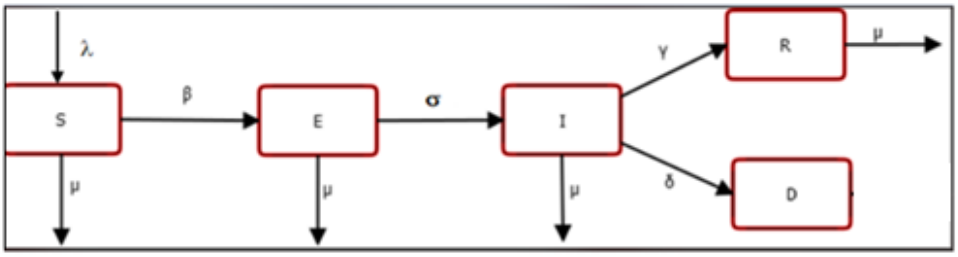

Figure 1. *Flow chart of tuberculosis*

In this model, the parameters are given in Table 1:

Table 1. *Parameters for the SEIR+D model*

λ	natural birth rate
μ	natural mortality rate
β	transmission rate
σ	rate at which exposed individuals become infectious
γ	recovery rate (where recovery time $\tau_{recovery} = \frac{1}{\gamma}$)
δ	mortality rate of tuberculosis

The SEIR+D model is given with the following system of differential equations:

$$\begin{aligned}
\frac{dS(t)}{dt} &= \lambda - \frac{\beta S(t) I(t)}{N} - \mu S(t) \\
\frac{dE(t)}{dt} &= \frac{\beta S(t) I(t)}{N} - \sigma E(t) - \mu E(t) \\
\frac{dI(t)}{dt} &= \sigma E(t) - \gamma I(t) - \delta I(t) - \mu I(t) \\
\frac{dR(t)}{dt} &= \gamma I(t) - \mu R(t) \\
\frac{dD(t)}{dt} &= \delta I(t)
\end{aligned} \tag{2.2}$$

With the initial non-negative conditions:

$$S(0) = S_0 \geq 0, E(0) = E_0 \geq 0, I(0) = I_0 > 0, R(0) = R_0 \geq 0, D(0) = D_0 \geq 0. \tag{2.3}$$

Theorem 2.1. *Let us suppose that the system of differential equation holds, then a feasible solution set for initial conditions (2.3)*

$$\Omega = \left\{ x = (S, E, I, R, D) \in \mathbb{R}^5 : 0 \le N \le \frac{\Lambda}{\mu} \right\}$$

is a bounded region.

Proof. For this model, the total population is given by $N(t) = S(t) + E(t) + I(t) + R(t) + D(t)$ then:

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dR}{dt} + \frac{dD}{dt} = \lambda - \mu(S + E + I + R) = \lambda - \mu(N - D). \quad (2.4)$$

$D \approx N$, from equation (2.4) the following is obtained:

$$\frac{dN}{dt} \approx \lambda - \mu N. \quad (2.5)$$

Then:

$$\frac{dN}{dt} \le \lambda - \mu N\,. \quad (2.6)$$

Solving the ordinary differential equation led to

$$N \le \frac{\lambda}{\mu}. \quad (2.7)$$

The bounded region is

$$\Omega = \left\{ x = (S, E, I, R, D) \in \mathbb{R}^5 : 0 \le N \le \frac{\lambda}{\mu} \right\} \quad (2.8)$$

□

Theorem 2.2. *If the initial values are* $\{(S(0), E(0), I(0), R(0), D(0)) \ge 0\} \in \Omega$, *then the solution set* $\{(S(t), E(t), I(t), R(t), D(t))\}$ *of the proposed model is non-negative for all* $t \ge 0$.

Proof. First, all the compartments of the model (2.2) are continuously differentiable and, as such, if all compartments have non-negative initial conditions and if any of the compartments is zero at time $t = t_i \ge 0$, its derivative is non-negative by inspection. If $S(0) \ge 0, S(t_1) = 0$ and $N(t_1) \ne 0$, the first equation in (2.2) can be rewritten as:

$$\frac{dS(t_1)}{dt} = \lambda - \frac{\beta S(t_1) I(t_1)}{N} - \mu S(t_1) = \lambda \ge 0 \quad (2.9)$$

Where it can be established that $S(t_1^+) \ge 0$ and $S(t)$ is non-negative for all time $t \ge 0$. Next, if $E(0) \ge 0, E(t_2) = 0$ and $I(t_2) \ne 0$, the second equation of model (2.2) can be rewritten as:

$$\frac{dE(t_2)}{dt} = \frac{\beta S(t_2) I(t_2)}{N} - \sigma E(t_2) - \mu E(t_2) \ge 0 \quad (2.10)$$

So that $E(t_2^+) \geq 0$ and hence $E(t)$ is non-negative for all time $t \geq 0$. Assuming that $I(0) \geq 0, I(t_3) = 0$ and $E(t_3) \neq 0$, then the third equation of model (2.2) can be rewritten as:

$$\frac{dI(t_3)}{dt} = \sigma E(t_3) - \gamma I(t_3) - \delta I(t_3) - \mu I(t_3) \geq 0 \tag{2.11}$$

Where it can be established that $I(t_3^+) \geq 0$ and hence $I(t)$ is non-negative for all time $t \geq 0$. Next if we assume that $R(0) \geq 0, R(t_4) = 0$ and $I(t_4) \neq 0$, then the fourth equation of model (2.2) can be rewritten as follows:

$$\frac{dR(t_4)}{dt} = \gamma I(t_4) - \mu R(t_4) \tag{2.12}$$

So that $R(t_4^+) \geq 0$ and hence $R(t)$ is non-negative for all time $t \geq 0$. Finally, assuming that $D(0) \geq 0, D(t_5) = 0$ and $I(t_5) \neq 0$. The fifth equation of the model (2.5) can be rewritten as:

$$\frac{dD(t_5)}{dt} = \delta I(t_5) \geq 0 \tag{2.13}$$

So that $D(t_5^+) \geq 0$ and hence $D(t)$ is non-negative for all time $t \geq 0$.

From this it can be concluded that since none of the compartments would have negative derivative at time $t = t_i$ when all other compartments are non-negative, than all compartments are non-negative for all time $t \geq 0$. As a result of this, the total population is also non-negative for all time $t \geq 0$, since the total population is $N(t) = S(t) + E(t) + I(t) + R(t) + D(t)$. Hence the proof is completed. □

Theorem 2.3. *The equilibrium point for the system of ordinary differential equations is:*

$$X^* = (S^*, E^*, I^*, R^*, D^*) = \left(\frac{\lambda}{\mu}, 0, 0, 0, 0 \right). \tag{2.14}$$

Proof. All the equations from system (2.2) are equal to zero.

$$\frac{dS}{dt} = \frac{dE}{dt} = \frac{dI}{dt} = \frac{dR}{dt} = \frac{dD}{dt} = 0.$$

$$\begin{aligned}
&\lambda - \frac{\beta SI}{N} - \mu S = 0 \\
&\frac{\beta SI}{N} - \sigma E - \mu E = 0 \\
&\sigma E - \gamma I - \delta I - \mu I = 0 \\
&\gamma I - \mu R = 0 \\
&\delta I = 0
\end{aligned} \tag{2.15}$$

With Consecutive solving of the set of equations (2.9) the disease- free equilibrium point is obtained:

$$X^* = (S^*, E^*, I^*, R^*, D^*) = \left(\frac{\lambda}{\mu}, 0, 0, 0, 0 \right). \quad \square$$

The fundamental concept in epidemiology is the basic reproduction number $\Re_0$. With the following theorem, the basic reproduction number $\Re_0$ for this model is obtained.

The basic reproduction number of the system is derived and proven in [7], from where:

$$\Re_0 = \frac{\beta\sigma}{(\sigma + \mu)(\gamma + \delta + \mu)}$$

3. Case study

The simulation is performed in AnyLogic® software, [8]. The simulation software AnyLogic has been chosen because of its availability and simplicity for using. Also, this software is free simulation software. AnyLogic can be used to simulate healthcare, markets and competition, manufacturing, supply chain and logistics, retail, business processes, social and ecosystem dynamics, defense, asset management, pedestrian dynamics, road traffic etc.

The models in AnyLogic are based on any of the three simulation models: discrete events, system dynamics or agent-based systems.[9]

The sample of population on which the simulation is performed is equal to 10000. The incubation period of tuberculosis is between 3-10 weeks [10], in the paper it is taken to be 30 days so the incubation rate is 0,033. The recovery time for tuberculosis is between 6 and 12 months [11], so for recovery rate we will take 0.0037. According to [12], the current birth rate for World in 2023 is 17.464 births per 1000 people, so the birth rate is 0.0174. The death rate is 7.71 per 1000 people, so the mortality rate is 0.0071,[13].

The other parameters are hypothetically estimated for the purpose of the research. All parameters are given in Table 2.

Table 2. *Parameters in the tuberculosis model*

λ	0.0174
μ	0.0071
β	0.1
σ	0.033
γ	0.0037
δ	0.03

The result of the simulation is given in Figure 1. For this scenario, the value from the transmission rate is given from Table 2.

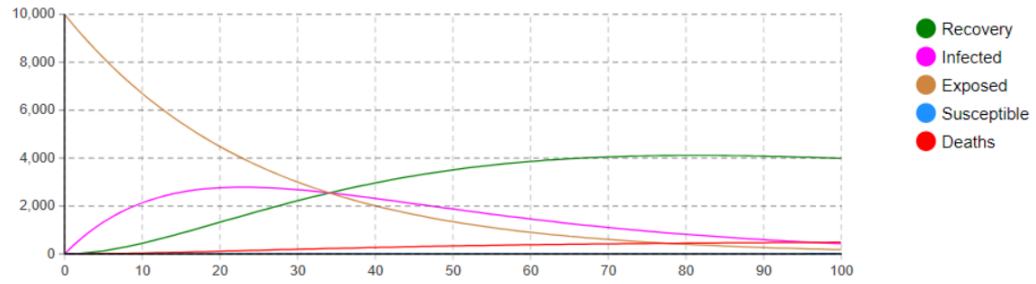

Figure 2. *Simulation results for parameters from Table 2*

The simulation results are shown in Figure 2. The simulations results show that the number of infected individuals from tuberculosis raises to a maximum value of 3000 and then starts to decrease. The number of exposed individuals decreases over time, while the number of recovered individuals rises over time. The number of dead individuals from tuberculosis is around 300. This number is high because the population is not vaccinated.

4. Results and discussion

Epidemiological models of infectious diseases are described with ordinary differential equations that can help study how infectious diseases evolve over time in the population. These models are widely used by Public Health workers to predict the course of infectious diseases and possible outbreaks.

In this paper, the classical SEIR model was modified by adding the dead compartment that accounts fatalities due to tuberculosis. The SEIR+D model is used to study and simulate the spread of tuberculosis and account both recovered individuals and unfortunate outcomes of death due to tuberculosis. The simulation results show that the number of infected individuals is high. This result is expected because the population is not vaccinated. Future research by the authors will focus on deploying a model for tuberculosis with a vaccination compartment.

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