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# A REAL TURKEY DATA APPLICATION TO THE SEIR MODEL FOR TUBERCULOSIS DISEASE

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**Abstract**

*The SEIR mathematical model in the literature is applied to analyze the tuberculosis transmission dynamics in Turkey. It consists of four classes: susceptible (S), exposed (E), infected (I) and recovered (R). The equilibrium points and the basic reproduction number of the SEIR model are given. The structural identifiability analysis of the model is conducted in the Maple program and also with the differential algebra method. As a result of the structural identifiability analysis, all parameters in the model are found as locally structurally identifiable, but aren't found to be globally identifiable. In addition, if an additional parameter is known, all other parameters are obtained to be globally identifiable. The number of tuberculosis cases in Turkey from 2005 to 2016 is used to solve the parameter estimation problem. The practical identifiability of the model is examined using Monte Carlo simulations. Sensitivity analysis of the model is also studied. Matlab program is used to estimate the model parameters and perform practical identifiability analysis. It is concluded that three parameters $\mu, \beta$ and $\gamma$, except for the parameter $\varepsilon$, are all practically identifiable. As a result, the basic reproduction number calculated with the obtained values shows that tuberculosis disease will continue in Turkey.*

**Keywords: Parameter estimation, Tuberculosis, Epidemic model, Structural identifiability, Practical identifiability, Sensitivity analysis**

# TÜBERKÜLOZ HASTALIĞI İÇİN SEIR MODELİNE GERÇEK TÜRKİYE VERİ UYGULAMASI

**Özet**

*Türkiye'de tüberküloz iletim dinamiklerini belirlemek için literatürdeki SEIR matematiksel model uygulanmıştır. SEIR matematiksel model, duyarlı (S), maruz kalmış (E), enfekte (I) ve iyileşmiş (R) olmak üzere dört sınıftan oluşmaktadır. SEIR matematiksel modelin denge noktaları ve temel üreme sayısı verilmiştir. Modelin yapısal tanımlanabilirlik analizi Maple programında ve ayrıca diferansiyel cebir yöntemi ile belirlenmiştir. Yapısal tanımlanabilirlik analizi sonucunda, modeldeki tüm parametreler local yapısal tanımlanabilir olarak bulunmuş, fakat, global tanımlanabilir bulunmamıştır. Ek olarak, ek bir parametrenin bilinmesi durumunda tüm diğer parametreler global tanımlanabilir olarak elde edilmiştir. Parametre tahmin probleminin çözümü için Türkiye'de 2005'den 2016 yılına kadar tüberküloz vaka sayıları kullanılmıştır. Modelin pratik tanımlanabilirliği Monte Carlo simülasyonları kullanılarak incelenmiştir. Modelin duyarlılık analizi de incelenmiştir. Modelin parametre tahmini ve pratik tanımlanabilirlik analizi için Matlab programı kullanılmıştır. $\varepsilon$ parametresi hariç $\mu$, $\beta$ ve $\gamma$ parametrelerinin hepsi pratik tanımlanabilir olduğu sonucuna ulaşılmıştır. Sonuç olarak, elde edilen değerlerle hesaplanan temel üreme sayısı Türkiye'de tüberküloz hastalığının devam edeceğini göstermektedir.*

**Anahtar Kelimeler: Parametre belirleme, Tüberküloz, Epidemik model, Yapısal tanımlanabilirlik, Pratik tanımlanabilirlik, Duyarlılık analizi**

**Cite**

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## 1. Introduction

The infectious disease known as Tuberculosis (TB) is an infectious disease caused by the pathogenic bacterium Mycobacterium tuberculosis, which primarily affects the lungs. It has the potential to cause global pandemics. It spreads from person to person through airborne particles expelled by coughing, sneezing or spitting. TB is a preventable and treatable infectious disease making early diagnosis and treatment critically important. It is treated with drugs [1,2]. Because many people can carry TB bacteria in their bodies throughout their lives, it is necessary to distinguish between TB infection and the active form of the disease. Following infection, the likelihood of disease progression is higher during the period called primary disease. After this stage, the rate of disease development decreases significantly during a period called endogenous reactivation. This suggests that the lifetime risk of developing TB is approximately 10% [3].

In the first quarter of the 20th century, Kermack and McKendrick modeled infectious diseases with differential equation systems [4,5]. Especially in the past two decades, many studies have been performed to determine the disease transmission mechanism of many epidemiological diseases using mathematical modeling. The first study on the spread and treatment of tuberculosis was made by Frost in 1937 [6]. Tamhaji and Hamdan [7] studied the transmission process for TB spread including the vertical transmission process derived from the system of nonlinear differential equations via mycobacterial virus using the Susceptible-Infected-Recovered (SIR) model, which is more realistic and suitable for the local situation when added to (or compared with) the theoretical model.

The models developed subsequently were constructed by considering disease transmission dynamics such as transmission, treatment, geographic and demographic conditions. Kabunga, Doungmo Goufo and Tuong [8] proposed an eight-compartment mathematical model for TB. They analyzed the model and computed the basic reproduction number for the Democratic Republic of the Congo. Both deterministic and stochastic SEIR models were used to understand the TB transmission dynamics in the Ashanti Region of Ghana [9]. Fundamental analyses of the models and the stability analysis of equilibrium points were performed. Das et al. [10] proposed a SEIR model to understand the disease transmission mechanism of TB and the stability of disease-free endemic equilibrium points investigated. An SVEITR model was studied for TB data in the United States from 1988 to 2019 [11]. Waaler et al. [12] investigated the sensitivity analysis of changes in the appropriate population compartment of BCG vaccination and TB chemotherapy. In a subsequent study, Waaler et al. [13] evaluated the effect of different combinations of BCG vaccination levels and treatment strategies considering the secret time preference parameter.

A five-compartment mathematical model [14] and parameter estimation were performed using tuberculosis disease cases in China between January 2005 and December 2012. In the study [15], a BSEIR model including BCG vaccinated, susceptible, exposed, infected and recovered individuals was developed to examine tuberculosis infection in Malaysia region, taking into account the migration effect. Dontwi and colleagues [16] used the SEIR model to determine the tuberculosis transmission process in the Amansie West district of the Ashanti Region. Ergen, Çilli and Yahnıoğlu [17] used the SIR model to estimate the effects of the TB epidemic, AIDS and Crimean-Congo Hemorrhagic Fever (CCHF) in terms of the number of infected people, including HIV-positive patients in Turkey. In [18], SIR, SEIR and BSEIR models were constructed with the reported data of TB in Turkey and the parameters were obtained using the least squares method. The stability analysis and the sensitivity analysis of the models were performed.

The success of an epidemiological model depends on the ability to accurately estimate the parameters in such models, which often contain multiple unknown parameters and cover processes that cannot be directly observed, with limited observations obtained from the system defined by differential equations [19]. Before solving a parameter estimation problem, it is important to verify its well-defined nature; only well-defined models can uniquely extract specific parameters from the data. Otherwise, the resulting parameter estimates will be unreliable. The ability to uniquely determine the model's parameters from the available data indicates that the parameter estimation problem is a well-posed. This occurs when the parameters are structurally identifiable. Practical identifiability analysis investigates the extent to which a model performs well with real data and how reliably its parameters can be estimated using these data. In this context, structural identifiability assesses whether a model can produce unique solutions at the theoretical level, while practical identifiability reveals the extent to which this theoretical adequacy can be implemented with real data [20].

In this study, a SEIR model [18] is used to determine and understand the spread dynamics of TB in Turkey. In Section 2, some properties and definitions of the model are given. The structural and the practical identifiability of the model is examined in Section 3. While the structural analysis examines whether the model's parameter values are uniquely determined by observations in error-free data sets, the practical identifiability analysis investigates the fit of the model with the data. Here, we deal the parameter estimation problem and also assess the sensitivity analysis of the model. At the end of the study, we provide an overall summary of the findings.

## 2. Mathematical Model Description

We use the model of [18], which formulates the spread of tuberculosis as a deterministic model divided into four population at any time $t$. $S(t)$ is the susceptible population. $E(t)$ represents the population that is infected but not showing symptoms of disease. $I(t)$ class represents the infected individuals, and $R(t)$ represents the population that has recovered from the disease. Their relations are given with a schematic diagram in Fig.1. The model is given in (1)-(4).

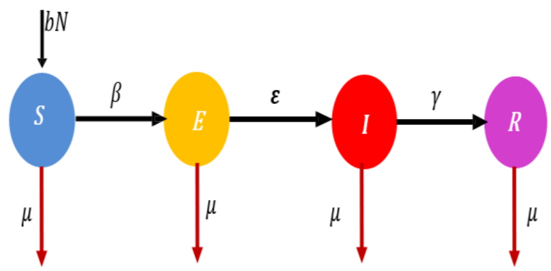


Figure 1. Schematic diagram of the Tuberculosis Transmission Model.

Table 1. Description of variables in the model.

| Variables of Model | Description (at time t) |
|---|---|
| $S$ | The number of susceptible people |
| $E$ | The number of exposed people |
| $I$ | The number of infected people |
| $R$ | The number of recovered people |

Table 2. Description of parameters in the model.

| Parameters of Model | Description |
|---|---|
| $\mu$ | The death rate |
| $\beta$ | The transmission rate |
| $\frac{1}{\varepsilon}$ | The latent period |
| $\gamma$ | The recovery rate |
| $b$ | The birth rate |

$$\frac{dS(t)}{dt} = bN - \beta\frac{SI}{N} - \mu S, \tag{1}$$

$$\frac{dE(t)}{dt} = \beta\frac{SI}{N} - \varepsilon E - \mu E, \tag{2}$$

$$\frac{dI(t)}{dt} = \varepsilon E - \gamma I - \mu I, \tag{3}$$

$$\frac{dR(t)}{dt} = \gamma I - \mu R. \tag{4}$$

Here $\beta$ is the transmission rate, $\varepsilon$ is the incubation period, $\gamma$ is the recovery rate, $\mu$ is the birth rate and $b$ is the death rate which is selected to be equal to $\mu$. Description of parameters and variables used in the model are given in Table 1 and Table 2. Summing Equations (1)-(4) yields

$$\frac{d(S(t)+E(t)+I(t)+R(t))}{dt} = 0, \tag{5}$$

which means that total population $(N)$ is constant in case of $\mu = b$. We write each class as a proportion of the total population to make dimensionless of the model equations by attaining

$$s = \frac{S}{N},\ e = \frac{E}{N},\ i = \frac{I}{N},\ r = \frac{R}{N},\ n = \frac{N}{N} = 1. \tag{6}$$

The purpose of nondimensionalization is to simplify equations, facilitate analysis and comparison, and make basic epidemiological parameters such as $R_0$ clear. Thus, the normalized system is obtained as:

$$\dot{s} = \mu - \beta si - \mu s, \tag{7}$$

$$\dot{e} = \beta si - \varepsilon e - \mu e, \tag{8}$$

$$\dot{i} = \varepsilon e - \gamma i - \mu i, \tag{9}$$

$$\dot{r} = \gamma i - \mu r. \tag{10}$$

The equilibrium points are obtained by solving the following system:

$$0 = \mu - \beta\bar{s}\bar{\imath} - \mu\bar{s}, \tag{11}$$

$$0 = \beta\bar{s}\bar{\imath} - \varepsilon\bar{e} - \mu\bar{e}, \tag{12}$$

$$0 = \varepsilon\bar{e} - \gamma\bar{\imath} - \mu\bar{\imath}, \tag{13}$$

$$0 = \gamma\bar{\imath} - \mu\bar{r}. \tag{14}$$

For the disease-free equilibrium (no spread) point, the number of infected people is zero since there is no virus in the population. Considering that $r = 0, e = 0$ and $i = 0$; we can find $\bar{s}$ as follows [18, 21]:

$$0 = \mu - \beta\bar{s}\bar{\imath} - \mu\bar{s} \tag{15}$$

$$\mu\bar{s} = \mu \tag{16}$$

$$\bar{s} = \frac{\mu}{\mu} = 1. \tag{17}$$

In other words, $E_0 = (\bar{s}, \bar{e}, \bar{\imath}, \bar{r}) = (1,0,0,0)$ is obtained. However, the endemic equilibrium point is as follows [21]:

$$E_* = (\bar{s}, \bar{e}, \bar{\imath}, \bar{r}) = \begin{pmatrix} \frac{(\varepsilon+\mu)}{\beta}\frac{(\gamma+\mu)}{\varepsilon}, \\ \frac{\mu}{(\varepsilon+\mu)} - \left(\frac{\mu}{\beta}\right)\frac{(\gamma+\mu)}{\varepsilon}, \\ \frac{\mu\varepsilon}{(\varepsilon+\mu)(\gamma+\mu)} - \frac{\mu}{\beta}, \\ \frac{\gamma\varepsilon}{(\varepsilon+\mu)(\gamma+\mu)} - \frac{\gamma}{\beta} \end{pmatrix}. \tag{18}$$

$R_0$ is the basic reproduction number, which shows the number of people who can be infected by an infected person.

The $R_0$ number for the model is found as follows [18, 22-24]:

$$R_0 = \frac{\varepsilon\beta}{(\varepsilon+\mu)(\gamma+\mu)}. \tag{19}$$

## 3. Parameter Estimation Problem for Tuberculosis Cases for Turkey

We specify both the structural identifiability and the practical identifiability of the model for the contain and removal of the TB disease transmission mechanism. First, we obtain the structural identifiability for the model by using differential algebraic method and also the Structural Identifiability ANalyser (SIAN) program [25].

Following this, we assess the parameters using real data from Turkey and hence test the practical identifiability for the model parameters. The algorithm written for the parameter estimation problem has been solved in Matlab 2021a.

### 3.1. Structural Identifiability Analysis

Modeling the dynamics of a biological systems is expressing the information that explains the behavior of this system with differential equations. The state variables and parameters of a biological system constitute the basis of a dynamic model; the parameters are usually unknown and are determined using experimental data. This process is called parameter identification and its main purpose is to minimize the difference between the values predicted by the model and the observed data [26].

Various statistical techniques, such as maximum likelihood, are used to determine model parameters. However, even when the data is continuous and noise-free, some parameters may be difficult to determine with the available data. This creates uncertainty about whether the correct parameters can be determined with the available data, regardless of the data fitting method chosen. Therefore, it is necessary to check whether the parameters in the model have structural identifiability [25]. Structural identifiability determines whether a unique optimum value for the parameters can be obtained using measurements of continuous noiseless data. Structural identifiability analysis depends on the mathematical structure of the model and is independent of the available data [26].

A useful model has three basic characteristics. First, the model should accurately reflect the main effects of the problem and ignore unnecessary details. Second, it should make predictions that can be tested. Models that have these two characteristics are good. Third, the model should help understand the biological system. Together, a good model should provide biological insights. This makes the model truly useful. The goal of mathematical modeling is to formulate a model that can be used to understand biological data, not just the model itself [20].

The parameters required to model the spread of infectious diseases cannot be determined directly from clinical studies. For this reason, the estimated of these parameters is based on periodic case reports in health institutions. As a result, the parameters of the model are determined by structural identifiability from the provided data set. Here, it should be stated whether the parameter is effective and whether the data comes from a unique parameter set. If the parameter values can be uniquely determined by observations in error- free data sets, the model is theoretically called "structural identifiable". Conversely, if multiple parameter combinations can produce the same data set, the model is defined as "parameter sets yielding the same output," and such models are considered locally identifiable. If the model lacks structural identifiability, it is impossible to determine the true values of the parameters [27].

Definition 1:

$$\boldsymbol{x}' = \boldsymbol{f}(\boldsymbol{x}(t), \boldsymbol{p}), \qquad \boldsymbol{x}(0) = \boldsymbol{x}_0 \tag{20}$$

is the compact form of the biological system (of the model). Here, $\boldsymbol{p}$ is the parameter set. The system variable is $\boldsymbol{x}(t)$. $\boldsymbol{x}(0)$ are the initial values [27].

The measurable system output function is

$$\boldsymbol{g}(\boldsymbol{x}(t), \boldsymbol{p}). \tag{21}$$

It expresses the number of TB virus infections.

Definition 2: Here, $\boldsymbol{p}$ denotes the set of parameters. If, for every value of $\boldsymbol{q}$ in (within) the parameter space, equation [28] is as follows, then it is said to be structurally globally (or uniquely) identifiable:

$$\boldsymbol{g}(\boldsymbol{x}(t), \boldsymbol{p}) = \boldsymbol{g}(\boldsymbol{x}(t), \boldsymbol{q}) \Leftrightarrow \boldsymbol{p} = \boldsymbol{q}. \tag{22}$$

There are several methods to evaluate the structural identifiability of dynamic models, such as differential algebra approach [28], the differential algebra based method [29], Taylor series [29]. For local identifiability, software packages such as Observability Test [30], EAR [31] and STRIKE GOLD [32] are used. However, there may be parameters that cannot be defined globally, but only locally [33, 34]. The identifiability of the system is specified by packages such as Differential Algebra [35], Comboss [36] and GENSSI 2.0 [37] for structural identifiability [25].

The SIAN software developed in Maple evaluates the local and the global identifiability of the ordinary differential equation model based on the following input-output property [25, 38]; we will use this software to determine the local identifiability [25].

Input:

$$\dot{\boldsymbol{x}}(t) = \boldsymbol{f}\big(\boldsymbol{x}(t), \mu, \boldsymbol{u}(t)\big), \tag{23}$$

$$\boldsymbol{y}(t) = \boldsymbol{g}\big(\boldsymbol{x}(t), \mu, \boldsymbol{u}(t)\big), \tag{24}$$

$$\boldsymbol{x}(0) = \boldsymbol{x}^*. \tag{25}$$

Here, the state variables, the input variables, the output variables, the unknown parameters and the initial conditions are denoted by $\boldsymbol{x}, \boldsymbol{u}, \boldsymbol{y}, \mu$ and $\boldsymbol{x}^*$ respectively, and the vectors of rational functions with complex coefficients are denoted by $\boldsymbol{f}$ and $\mathbf{g}$, SIAN assings (expresses) the identifiability of each parameter and initial condition as global, only local, or unidentifiable.

There is no control variable for the SEIR model. The output variable is $\beta\frac{SI}{N}, N$. If we use the SIAN program to determine the structural identifiability of the model, we obtain that all parameters are locally identifiable with known data $\beta\frac{SI}{N}$ and $N$. The SIAN results are given in Table 3.

As a second approach, we will use the differential algebra approach to determine the structural identifiability of our model, which distinguishes between local and global identifiability and additionally allows the display of parameter correlations that cause non-identifiability. When the model cannot be identified, we can reparameterize the displayed parameters with this approach and obtain a structurally identifiable model. While examining structural identifiability with differential algebra approach, we assume that there are the data for the variables $I$ and $N$. The results obtained are the same as those obtained with SIAN. Detailed calculations are given in the Appendix A.

Table 3. SIAN gets for the model parameters.

| Output | Locally identifiable parameters | Globally identifiable parameters |
|---|---|---|
| $\beta\frac{SI}{N}, N$ | $\mu, \beta, \gamma, \varepsilon, S(0), E(0), I(0), R(0)$ | $\mu, S(0)$ |
| $\beta\frac{SI}{N}, N, \mu$ | $\mu, \beta, \gamma, \varepsilon, S(0), E(0), I(0), R(0)$ | $\mu, S(0)$ |
| $\beta\frac{SI}{N}, N, \beta$ | $\mu, \beta, \gamma, \varepsilon, S(0), E(0), I(0), R(0)$ | $\mu, \beta, \gamma, \varepsilon, S(0), E(0), I(0),$ |
| $\beta\frac{SI}{N}, N, \gamma$ | $\mu, \beta, \gamma, \varepsilon, S(0), E(0), I(0), R(0)$ | $\mu, \beta, \gamma, \varepsilon, S(0), E(0), I(0),$ |
| $\beta\frac{SI}{N}, N, \varepsilon$ | $\mu, \beta, \gamma, \varepsilon, S(0), E(0), I(0), R(0)$ | $\mu, \beta, \gamma, \varepsilon, S(0), E(0), I(0),$ |

### 3.2. Parameter Estimation

The annual number of tuberculosis patients in Turkey between 2005 and 2016 is given in Table 4 [39]. The initial condition is set as $t_0 = 2005$. For parameter estimation, assuming that $y_i, \{y_1, y_2, \dots, y_n\}$, represents the number of tuberculosis cases for year $t_i, \{t_1, t_2, \dots, t_n\}$, the statistical model can be expressed as follows [40]:

$$y_i = g(\boldsymbol{x}(t_i), \widehat{\boldsymbol{p}}) + E_{\mathrm{i}}, \tag{26}$$

$\widehat{\boldsymbol{p}}$ is real parameter set. The random variable $E_{\mathrm{i}}$, which represents the observation and the measurement errors, is expressed as follows:

$$E_{\mathrm{i}} = g(\boldsymbol{x}(t_i), \widehat{\boldsymbol{p}})^{\xi}_{\epsilon_i}. \tag{27}$$

Here $\xi \geq 0$ and constant value, and $\epsilon_i, i = 1, \dots, n$ , denote independent and identically distributed random variable with zero mean and constant variance ${\sigma_0}^2$.

Therefore, the expected value of $y_i$ is $E(y_i) = g(\boldsymbol{x}(t_i), \widehat{\boldsymbol{p}})$ and its variance is $Var(y_i) = g(\boldsymbol{x}(t_i), \widehat{\boldsymbol{p}})^{2\xi}\sigma_0^2$ here, different $\xi$ values express the varying error scales in the measurements. If $\xi = 1$, the equation expresses the relative error model. The ordinary least squares method is used as the basis for calculating the parameters in question [27].

When solving the optimization problem, Matlab's fminsearchbnd is used for the parameters used with the lower and the upper limits lb and ub. Since the units of the obtained data are annual data, the parameter units are arranged to be annual. The lower and the upper limits for the parameters were chosen to be compatible with the literature. Therefore, since the average life expectancy in Turkey is 50-80 years [41], the lower and the upper limits for the $\mu$ mortality rate were taken as $\mu = \frac{1}{80}$ and $\frac{1}{50}$. The optimization problem to obtain the parameters was solved using Matlab2019a and the fminsearchbnd program [42-43].

The initial values of $I(0)$ and $N(0)$ are chosen as real data [39]. The other initial values are estimated values. So the inditional conditions of variables are given in Table 6.

The model was fitted to the data by running the algorithm until the error reduction stops and optimization tolerances were met. The results of parameter estimation are shown in Table 5.

Table 4. Annual Tuberculosis case numbers in Turkey between 2005-2016 [39].

| Years | Tuberculosis Cases |
|---|---|
| 2005 | 20535 |
| 2006 | 20526 |
| 2007 | 19694 |
| 2008 | 18452 |
| 2009 | 17402 |
| 2010 | 16551 |
| 2011 | 15679 |
| 2012 | 14691 |
| 2013 | 13409 |
| 2014 | 13378 |
| 2015 | 12772 |
| 2016 | 12417 |

Figure 3 shows the residual errors. This means that the error distribution is random and the model's predictions are highly consistent with the real data set dynamics; however, the number of cases in 2013 is less than the data and more than the data in 2016. Considering the data set covering a 12-year period, it can be stated that the residual errors are within the acceptable limits.

Table 5. Parameter values obtained with case numbers for TB in the 2005-2016 optimization results.

| Parameter | Value |
|---|---|
| $\mu$ | 0.02 |
| $\beta$ | 1.23593 |
| $\varepsilon$ | 0.50067 |
| $\gamma$ | 1.14599 |

If we write the obtained parameters into $R_0$, the basic reproduction number is found as:

$$R_0 = 1.02. \tag{28}$$

This means [44] that the disease will continue in Turkey.

Table 6. The initial condition of variables in the model.

| Variables | The Initial Condition |
|---|---|
| $S(0)$ | 55754470 |
| $E(0)$ | 50000 |
| $I(0)$ | 20535 [39] |
| $R(0)$ | 13035535 |

### 3.3. Sensitivity Analysis

The sensitivity of the model to changes in parameters and the structure is examined and investigated with sensitivity analysis. Sensitivity analysis evaluates the uncertainties associated with the model parameters and quantitatively measures the effect of changes in these parameters on the state variables. This analysis is especially used to evaluate the effect of parameter errors on the model reliability during the data collection process. It determines the parameter that significantly affects the targeted interventions. The value's absolute magnitude illustrates how strong the relationship is. That is, the larger the absolute value, the more significantly that variable affects the other [43].

The normalized forward sensitivity index for each parameter of the basic reproduction number $R_0$ [45] is obtained as follows:

$$\frac{\partial R_0}{\partial p} \cdot \frac{p}{R_0} \tag{29}$$

where $p$ is a parameter. The sensitivity analysis results of the parameters are given in Table 7. From Table 7, we can say that $\mu, \beta$ and $\gamma$ are the most effective parameters on $R_0$, respectively. Reducing $\beta$, increasing $\gamma$ and decreasing $\mu$ will reduce the patient contact rate, increase the recovery rate of sick individuals and reducing the natural mortality rate can help prevent possible epidemics.

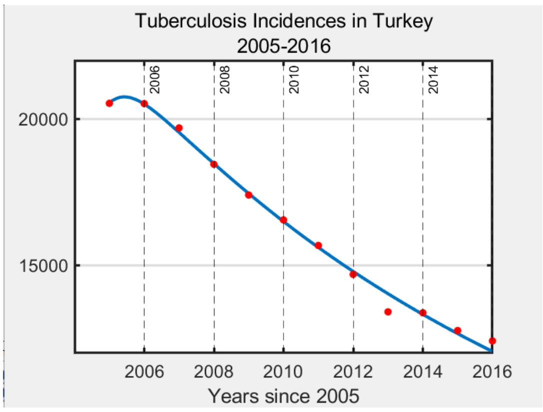


Figure 2. Tuberculosis incidences and its estimation.

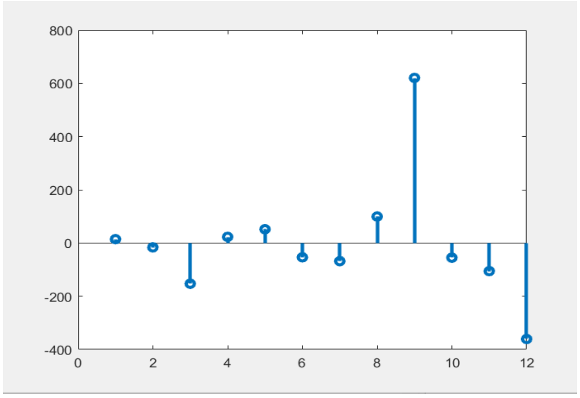


Figure 3. Residual errors.

Table 7. Sensitivity analysis of parameters.

| Parameter | Sensitivity Value |
|---|---|
| $\mu$ | $-2.77677929$ |
| $\beta$ | 1 |
| $\varepsilon$ | 0.038382 |
| $\gamma$ | $-0.982847194$ |

### 3.4. Practical Identifiability Analysis

Practical identifiability is an effective technique has been used recently in model-based research [20, 46-48]. There is heterogeneity in parameter estimates due to the structure of the model and experimental conditions. The meaningful quantification of the parameter is provided by practical identifiability. Practical identifiability, which has many definitions in the literature, generally calculates whether the specified parameter distribution, which is most likely to be obtained from a given data set, is within practically acceptable limits by iterating over various measurement errors. Structural identifiability is necessary for practical identifiability. If structural analysis reveals that a model is structurally undefinable, then practical analysis is not required. In the other words, structurally identifiable models benefit from practical identifiability. The measurements are highly precise and have a low margin of error. The model structures are considered 100% accurate, which are the assumptions underlying the structural analysis. Model uncertainty is exploited in areas where measurement errors are high [20, 28].

The Monte Carlo simulation method was applied to evaluate the performance of statistical estimation methods. This method can be used in practical identifiability analyses to test the reliability of the parameters on observation data produced with varying measurement errors in different experimental designs [28].

In this study, we will use Monte Carlo simulations for practical identifiability analysis. Monte Carlo simulations allow us to examine many hypothetical situations with varying numbers of observations and levels of error;

however, such scenarios may not always be suitable for real-world applications [28]. For this purpose, 1001 synthetic data were generated by adding and fitting increasing levels of measurement error the $\boldsymbol{p}$ parameter set.

The Monte Carlo simulation procedure [27, 49], which is a sampling method using random numbers with probability distributions, can be summarized as follows:

1. $\widehat{\boldsymbol{p}}$ is the actual parameter set. The epidemiological model is solved numerically with $\widehat{\boldsymbol{p}}$. The resulting output vector is $\boldsymbol{g}(\boldsymbol{x}(t),\widehat{\boldsymbol{p}})$, which is the vector at discrete time points $t_i, i = 1, \dots, n$.
2. The statical model $y_i = g(\boldsymbol{x}(t_i),\widehat{\boldsymbol{p}}) + E_\text{i}$ where $E_\text{i}$ are the random variables with a given measurement error is generated $M = 1000$ data sets. The output vector obtained as a result of the first step represents the mean value. The standard deviation is $\sigma_0$% of the mean drawn by the normal distribution. We set $\xi = 1$ in the statical model $y_i = g(\boldsymbol{x}(t_i),\widehat{\boldsymbol{p}}) + E_\text{i}$ , and attaining $E(\epsilon_i) = 0,\ Var(\epsilon_i) = {\sigma_0}^2$ . We get

$$y_i = g(\boldsymbol{x}(t_i),\widehat{\boldsymbol{p}}) + g(\boldsymbol{x}(t_i),\widehat{\boldsymbol{p}})_{\epsilon_i}\ \ i = 1,2,\dots,n$$

and $E(y_i) = g(\boldsymbol{x}(t_i),\widehat{\boldsymbol{p}})$ with

$$Var(y_i) = \big(g(\boldsymbol{x}(t_i),\widehat{\boldsymbol{p}})\big){\sigma_0}^2.$$

3. We fit the model

$$\boldsymbol{x}' = f(\boldsymbol{x},t,\boldsymbol{p})$$
$$\boldsymbol{x}(0) = \boldsymbol{x}_0$$

to estimated parameter set $p_j,\ j = 1,2,\dots,M$ ,thus,

$$p_j = min\sum_{i=1}^{n}\big(y_i - g(\boldsymbol{x}(t_i),\boldsymbol{p})\big)^2,\ j = 1,2,\dots,M,$$

for each set of the $M$ generated data sets.

4. The average relative error of estimate (ARE) for each element of the parameter set $\boldsymbol{p}$ is calculated as follows:

$$ARE\big(p^{(k)}\big) = 100\% \times \frac{1}{M}\sum_{j=1}^{M}\frac{\left|\hat{p}^{(k)} - {p_j}^{(k)}\right|}{\hat{p}^{(k)}} \qquad (30)$$

where is the kth element of $p^{(k)}, \hat{p}^{(k)}$ and ${p_j}^{(k)}$ is $k^{th}$ parameter in the set $p$ , in the true parameter set $\hat{p}$ and in the set $p_j$, respectively. The AREs were introduced in the study [28]. The ARE results are given in Table 8. As a result, from Table 8 it can be concluded that $\mu, \beta$ and $\gamma$ are practically identifiable, while $\varepsilon$ is not practically identifiable.

Table 8. ARE calculation for different noise level.

| $\sigma_0$ | $\mu$ | $\beta$ | $\varepsilon$ | $\gamma$ |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 1 | 14.2725 | 0.7205 | 0.9731 | 0.8547 |
| 5 | 17.3654 | 3.5992 | 4.8468 | 3.8185 |
| 10 | 17.5192 | 7.1819 | 9.9245 | 7.6252 |
| 20 | 17.8037 | 14.2500 | 26.9404 | 15.2033 |
| 30 | 18.1834 | 21.0303 | 79.1745 | 22.5245 |

## 4. Conclusion

Tuberculosis is a heterogeneous disease. Although attempts are made to express this heterogeneity correctly with mathematical models and to improve existing models, it is unlikely that this heterogeneity will be defined correctly. It is a disease that requires careful treatment and does not have immunity. Necessary health measures should be taken to prevent the disease. Considering the heterogeneity of this disease, mathematical models that correctly define heterogeneity should be developed.

The main objective of this study is to create a reliable model with structural and practical identifiability analyses to understand the spread dynamics of tuberculosis in Turkey. SEIR deterministic model [18] is used for the model, identifiability analyses are performed and the basic reproduction number is obtained as 1.02 and the structural and the practical identifiability analyses are performed. In solving the parameter estimation problem, Turkey tuberculosis cases between 2005 and 2016 [39] were used. The structural identifiability of the model was considered both using the differential algebra method and the SIAN program in the Maple. As a result of the analysis performed with the SIAN program, it was seen that the model was locally structurally identifiable. The same results were obtained with the differential algebra method. It was seen that all parameters except one were practically identifiable. With the parameters obtained at the end of the parameter determination process, the basic reproduction number was calculated as 1.02. This value indicates that TB disease will continue in Turkey. According to the results of the sensitivity analysis for the model parameters reducing $\beta$, increasing $\gamma$ and decreasing $\mu$ are to increase the recovery rate and reduce contact with infected people in order to prevent TB disease.

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## Appendix A

Given that data for $I$ and $N$ are available, we present below the proof of the model's structural identifiability for Equations (1)-(4). By manipulating the model equations, an input-output relationship is derived. While this resulting polynomial-expressed in terms of $I$ and its derivatives- is not unique, it encapsulates all the necessary information for assessing structural identifiability [49].

Adding the Equations (1)-(4) yields the following:

$$S' + E' + I' + R' = \mu N - \beta\frac{SI}{N} - \mu S + \beta\frac{SI}{N} - \varepsilon E \tag{31}$$

$$-\mu E + \varepsilon E - \gamma I - \mu I + \gamma I - \mu, \quad \mathrm{N}' = 0. \tag{32}$$

Taking the derivative of the both sides of (1) yields the following:

$$S'' = \mu N' - \left(\frac{(\beta S'I + I'S\beta)N - \beta SIN'}{(N^2)}\right) - \mu S'. \tag{33}$$

By multiplying (3) by $\left(\frac{\varepsilon+\mu}{\varepsilon}\right)$ and adding with (4), we obtain as:

$$\left(\frac{\varepsilon+\mu}{\varepsilon}\right) \tag{34}$$

$$I' = \varepsilon E - (\gamma+\mu)I \tag{35}$$

$$\left(\frac{\varepsilon+\mu}{\varepsilon}\right)I' = \left(\frac{\varepsilon+\mu}{\varepsilon}\right)\varepsilon E - \left(\frac{\varepsilon+\mu}{\varepsilon}\right)(\gamma+\mu)I \tag{36}$$

$$\left(\frac{\varepsilon+\mu}{\varepsilon}\right)I' = (\varepsilon+\mu)E - \frac{(\varepsilon+\mu)(\gamma+\mu)I}{\varepsilon} \quad (37)$$

$$E' = \beta\frac{SI}{N} - (\varepsilon+\mu)E \quad (38)$$

$$\left(\frac{\varepsilon+\mu}{\varepsilon}\right)I' = (\varepsilon+\mu)E - \frac{(\varepsilon+\mu)(\gamma+\mu)I}{\varepsilon} \quad (39)$$

$$E' + \left(\frac{\varepsilon+\mu}{\varepsilon}\right)I' = \beta\frac{SI}{N} - \frac{(\varepsilon+\mu)(\gamma+\mu)I}{\varepsilon} \quad (40)$$

$$\varepsilon E' + (\varepsilon+\mu)I' = \varepsilon\beta\frac{SI}{N} - \big((\varepsilon+\mu)(\gamma+\mu)\big)I \quad (41)$$

Taking the derivative of the both sides of (35) yields as

$$I'' = \varepsilon E' - (\gamma+\mu)I' \quad (42)$$

$$\varepsilon E' = I'' + (\gamma+\mu)I'. \quad (43)$$

By putting this into (42), we get

$$I'' + (\gamma+\mu)I' + (\varepsilon+\mu)I' = \varepsilon\beta\frac{SI}{N} - \big((\varepsilon+\mu)(\gamma+\mu)\big)I \quad (44)$$

$$\varepsilon\beta\frac{SI}{N} = I'' + (\gamma+\mu+\varepsilon+\mu)I' + \big((\varepsilon+\mu)(\gamma+\mu)\big) \quad (45)$$

$$S = \frac{N}{\varepsilon\beta I}I'' + \frac{(\gamma+\mu+\varepsilon+\mu)}{\varepsilon\beta}\frac{NI'}{I} + \frac{\big((\varepsilon+\mu)(\gamma+\mu)\big)}{\varepsilon\beta}\frac{NI}{I} \quad (46)$$

$$S = \frac{N}{\varepsilon\beta I}I'' + \left(\frac{\gamma+2\mu+\varepsilon}{\varepsilon\beta}\right)\frac{NI'}{I} + \frac{\big((\varepsilon+\mu)(\gamma+\mu)\big)}{\varepsilon\beta}N. \quad (47)$$

Taking the derivative of the both sides of (48) yields as.

$$S = \frac{N}{\varepsilon\beta I}I'' + \left(\frac{\gamma+2\mu+\varepsilon}{\varepsilon\beta}\right)\frac{NI'}{I} + \frac{\big((\varepsilon+\mu)(\gamma+\mu)\big)}{\varepsilon\beta}N \quad (48)$$

$$S' = \frac{1}{\varepsilon\beta}\frac{\big((N'I'' + I'''N)I - I'N\,I''\big)}{I^2} + \left(\frac{\gamma+2\mu+\varepsilon}{\varepsilon\beta}\right)\frac{(N'I' + I''N)I - I'(NI')}{I^2} + \frac{\big((\varepsilon+\mu)(\gamma+\mu)\big)}{\varepsilon\beta}N' \quad (49)$$

$$\frac{1}{\varepsilon\beta} = a_1 \quad (50)$$

$$\left(\frac{\gamma+2\mu+\varepsilon}{\varepsilon\beta}\right) = a_2 \quad (51)$$

$$\frac{\big((\varepsilon+\mu)(\gamma+\mu)\big)}{\varepsilon\beta} = a_3 \quad (52)$$

$$S' = a_1\frac{\big((N'I'' + I'''N)I - I'N\,I''\big)}{I^2} + a_2\frac{(N'I' + I''N)I - I'(NI')}{I^2} + a_3N' \quad (53)$$

$$S' = \frac{a_1N'I''I}{I^2} + \frac{a_1I'''NI}{I^2} - \frac{a_1I'N\,I''}{I^2} + \frac{a_2N'I'I}{I^2} + \frac{a_2NI''I}{I^2} - \frac{a_2(I')^2N}{I^2} + a_3N'. \quad (54)$$

$$\begin{aligned} S'' &= a_1\left(\frac{(N''I''I + N'I'''I + N'I''I')I^2 - (2II'N'I''I}{I^4}\right) \\ &+a_1\left(\frac{(I^{IV}NI + I'''N'I + I'''NI')I^2 - (2II'I'''NI)}{I^4}\right) \\ &-a_1\left(\frac{(I''NI'' + N'I'I'' + NI'I''')I^2 - (2II'I'NI'')}{I^4}\right) \\ &+a_2\left(\frac{N''I'I + N'I''I + N'I'I')I^2 - (2II'I'IN')}{I^4}\right) \\ &+a_2\left(\frac{I'''NI + N'I''I + NI''I')I^2 - (2II'NI''I)}{I^4}\right) \\ &-a_2\left(\frac{(2(I')I''N + (I')^2N')I^2 - (2II'(I')^2N)}{I^4}\right) \\ &+ a_3N''. \end{aligned} \quad (55)$$

By substituting 48, 50, 51, 52, 54 and 55, the following is obtained.

$$\frac{1}{\varepsilon} = \frac{1}{\bar{\varepsilon}} \quad (56)$$

$$\frac{1}{\varepsilon\beta} = \frac{1}{\bar{\varepsilon}\bar{\beta}} \quad (57)$$

$$\left(\frac{\gamma+2\mu+\varepsilon}{\varepsilon\beta}\right) = \left(\frac{\bar{\gamma}+2\bar{\mu}+\bar{\varepsilon}}{\bar{\varepsilon}\bar{\beta}}\right) \quad (58)$$

$$-\frac{\mu}{\varepsilon\beta} = -\frac{\bar{\mu}}{\bar{\varepsilon}\bar{\beta}} \quad (59)$$

Thus, we have from (56), $\varepsilon = \bar{\varepsilon}$, from (57), $\beta = \bar{\beta}$, from (59), $\mu = \bar{\mu}$, and from (58),$\gamma = \bar{\gamma}$ are obtained. Thus, the model is structurally identifiable.