TB Or Not TB?

by

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Abstract

This report studies the epidemiology of Tuberculosis (TB) with emphasis on the evolution of TB within a population exposed to TB in the Middle East. American troops fighting overseas have been exposed to this disease and could potentially spread it to the general population. A dynamical system was used to model the evolution of TB. The epidemiology of TB was modeled with existing disease parameters for an idealized problem representing the population in the region surrounding Santa Fe, New Mexico. The epidemiology simulations imply that increased troop exposure could lead to a few thousand more cases of TB in New Mexico over the next 150 years.

1 Introduction

This report explores the epidemiology of Tuberculosis (TB). The spread of Tuberculosis has always been an issue in America, and is especially a problem now because of American troops fighting overseas in the Middle East acquiring it, and then returning home with this disease and possibly spreading it throughout the general population. Many of these soldiers have an antibiotic-resistant strain of TB, making this problem even more alarming in our society today.

In this project, a dynamical system with five ordinary differential equations was used to model the evolution of TB in time. A program was developed to integrate the equations modeling the evolution of the disease. We modeled the spread of the disease with existing disease parameters for an idealized problem representing the population in the region surrounding Santa Fe, New Mexico. We then doubled the proportion of new infections of the disease to estimate the long term effects of the TB epidemiology associated with the increased exposure to our troops. The results for the model of the existing disease were compared to that with the increased exposure and the differences in the time history of TB was analyzed.

A seventh-order Runge-Kutta-Fehlberg scheme was implemented to numerically integrate the epidemiology model. This numerical method was applied to study the stability for both linear and nonlinear cases. Mathematica was also applied to construct analytical solutions to check the numerical results for a simplified case. The solutions were found to be stable and approach equilibrium states. The numerical scheme was coded using the language C. All plots for this project were generated using the software program Gnuplot. All analytical estimates were performed using Mathematica. The computer that performed all calculations is a Mac with a 10.6.8 operating system. The C and Mathematica programs developed for the project are listed in the Appendices.

2 Background Information and the Epidemiology of Tuberculosis

Tuberculosis is an urgent health issue today, because a new antibiotic-resistant strain has emerged in the Middle East among other places, and is currently coming home with American troops. There has been an ongoing effort in developing a new TB vaccine, with no successful results yet. Our own University of New Mexico was awarded a grant from the Bill and Melinda Gates Foundation for developing this vaccine by pharmacy professor Dr. Pavan Muttil, Jetty [1], because of the threat seen here in the United States and worldwide from a new, untreated TB strain. The study is still ongoing. There was another, larger study out of the University of Oxford for a vaccine called MVA85A that replaced the Bacille Calmette-Guerin (or BCG) that was developed ninety years ago and only works for a few years. This new MVA85A vaccine, however, failed substantially and hopes are now pinned on other pending vaccines.

Mycobacterium TB has plagued human kind since antiquity, Blower and Chou [2]. Blower's definition of multi-drug-resistant TB (MDRTB) is defined as TB that is resistant to two of the best anti-tuberculosis drugs, which are Isoniazid and Rifampicin. Right now, MDRTB is only showing up in localized areas, but the threat of the fast spreading disease is urgent. The modern global TB epidemic affects nine million people annually and kills 1.4 million each year, Steenhuysen [3]. Tuberculosis, which was known in history as consumption or the white plague, has been found as far back as the ancient Egyptian mummies of 3000 B.C. and is thought to have been in modern human remains in the Neolithic Era dating from 9000 years ago in the Mediterranean. It was only recently in 1944 that scientists came up with the first antibiotic of streptomycin that was effective against these mycobacterium and it was generally thought to be on its' way to eradication once the last patients were treated and cured especially in the 1980s. However,

with the rise of drug resistant strains from previous levels of 5000 cases in 1987, has now gone up to 7600 cases in 2005 in Great Britain, for example. New York currently has more than 20,000 TB patients that have multi-drug resistant strains, and have to be quarantined in hospitals.

Latest figures show that 45.7 percent of US troops that work in the public of Afghanistan are showing up with TB exposure, Mitchell et al. [4]. However, since TB scratch tests are notoriously false-positive, the real figure is probably somewhat lower. According to Mitchell et al., in the United States, the percentage of MDRTB cases has increased slowly, from 0.9 percent of the total number of reported TB cases in 2008 to 1.3 percent of cases in 2011. In the rest of the world, however, particularly in the Middle Eastern countries Iraq and Afghanistan, this figure in American troops coming down with MDRTB is 2.9 percent to 10 percent in certain crowded public areas of Afghanistan. In addition, there is a long-term threat of active TB cases developing later since latent TB can change into active or contagious TB if a patient's immune system fails, as with AIDS patients. Coupled with rising rates of MDRTB, the computer model in this project below shows a real threat not only to the US but worldwide. According to this model, this could turn into a real epidemic. American troops today in active duty are now being routinely checked for TB infection before and after they go on their tours of duty, Aronson et al. [5].

3 Mathematical Modeling

3.1 The Dynamical System

The dynamical system modeling the evolution of TB is based on the work of Blower et al. [6]. The Blower description may be expressed as a system of five ordinary differential equations. The equations and their stability properties have been analyzed by Tucker [7]. The basic mathematical model is given

by the following five equations:

$$\frac{dX}{dt} = \Pi - \lambda X - \mu X, \tag{1}$$

$$\frac{dL}{dt} = (1-p)\lambda X - (\nu + \mu)L, \tag{2}$$

$$\frac{dT_i}{dt} = pf\lambda X + q\nu L + \omega R - (\mu + \mu_T + c)T_i, \tag{3}$$

$$\frac{dT_n}{dt} = p(1-f)\lambda X + (1-q)\nu L + \omega R - (\mu + \mu_T + c)T_n, \tag{4}$$

and

$$\frac{dR}{dt} = c(T_i + T_n) - (2\omega + \mu)R. \tag{5}$$

In Equations (1) to (5), the independent variables are: the susceptible cases X, the latently infected cases L, the infectious cases T_i, the non-infectious cases T_n, and the recovered cases R. The parameters in Equations (1) to (5) are defined in Blower et al. [6], as follows: the average life expectancy $1/\mu$, the recruitment rate Π, the proportion of new infections that develop TB within a year p, the progression rate to TB v, the probability of developing infectious TB (fast TB) f, the probability of developing infectious TB (slow TB) q, the mortality rate due to TB μ_T, the rate of relapse to active TB 2ω, and the natural cure rate c. The last parameter is λ the per-susceptible risk of becoming infected. This term is modeled both as a constant $\lambda = 1$ and as a feed-back term $\lambda = \beta T_i$ in this study. Moreover, a transmission coefficient β is defined so that $\beta\Pi/\mu =$ constant. The application of a constant λ linearizes the dynamical system and allows the construction of exact analytical solutions in specific cases.

For the special case of λ being constant, Equations (1) to (5) may be written as a linear matrix equation of the following form:

$$\begin{bmatrix} X \\ L \\ T_i \\ T_n \\ R \end{bmatrix}'$$

$$= \begin{bmatrix} -(\lambda+\mu) & 0 & 0 & 0 & 0 \\ (1-p)\lambda & -(\nu+\mu) & 0 & 0 & 0 \\ pf\lambda & q\nu & -(\mu+\mu_T+c) & 0 & \omega \\ p(1-f)\lambda & (1-q)\nu & 0 & -(\mu+\mu_T+c) & \omega \\ 0 & 0 & c & c & -(2\omega+\mu) \end{bmatrix} \times \begin{bmatrix} X \\ L \\ T_i \\ T_n \\ R \end{bmatrix} + \begin{bmatrix} \Pi \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}. \quad (6)$$

3.2 Analytical Solutions of the Dynamical System

The system of ordinary differential equations of Equation (6) may also be written as a matrix operator equation of the form:

$$\mathbf{X}' = \mathbb{A}\mathbf{X} + \mathbf{F}(t) \quad \text{with} \quad \mathbf{X}(t_0) = \mathbf{X}_0 \quad (7)$$

where $\mathbb{A}$ is the matrix, $\mathbf{X}$ is the solution vector, and $\mathbf{F}(t)$ is the non-homogeneous term. The general solution for the system of ODEs of Equation (7) is given

by the matrix equation:

$$\mathbf{X}(t) = \exp[\mathbb{A}(t - t_0)]\mathbf{X}_0 + \exp[\mathbb{A}(t)] \int_{t_0}^{t} \exp[-\mathbb{A}(s)]\mathbf{F}(s)\, ds. \tag{8}$$

The solution given by Equation (8) for the system of ODES of Equation (7) is computed by determining the eigenvalues $\{\mathrm{E}_i\}$ and eigenvectors $\{\mathbf{x}_i\}$ of the matrix $\mathbb{A}$ ($i = 1, 2, 3, 4, 5$). Recall that the eigenvalues and eigenvectors satisfy the relationship $\mathbb{A}\mathbf{x} = \mathrm{E}\mathbf{x}$. If the matrix $\mathbb{A}$ has 5 distinct real-valued eigenvalues, then the matrix exponential, $\exp[\mathbb{A}(t)]$, is computed using the matrix formula:

$$\exp[\mathbb{A}(t)] = \Big[\exp[E_1 t]\mathbf{x}_1 \;\; \exp[E_2 t]\mathbf{x}_2 \;\; \exp[E_3 t]\mathbf{x}_3 \;\; \exp[E_4 t]\mathbf{x}_4 \;\; \exp[E_5 t]\mathbf{x}_5\Big] \times \Big[\mathbf{x}_1 \;\mathbf{x}_2 \;\mathbf{x}_3 \;\mathbf{x}_4 \;\mathbf{x}_5\Big]^{-1}. \tag{9}$$

where $\{\mathbf{x}_i\}$ are column vectors. For a derivation of Equation (9), see Braun [8]. If the matrix $\mathbb{A}$ has repeated or complex-valued eigenvalues, the representation of the matrix exponential of Equation (9) is more complex and is beyond the scope of the present study.

3.3 Numerical Method

In this study a seventh-order Runge-Kutta-Fehlberg (RKF) scheme was implemented to integrate the threshold of collapse problems. This scheme employed variable stepsize control. High-order Runge-Kutta schemes were developed in astrodynamics, for example see the textbook of Battin [9].

The scheme applied in this study was developed by Fehlberg [10], and is defined by the following equations:

$$f_0 = f(x_0, y_0), \tag{10}$$

$$f_\kappa = f(x_0 + \alpha_\kappa h, y_0 + h\sum_{\lambda=0}^{\kappa-1}\beta_{\kappa\lambda} f_\lambda), \tag{11}$$

$$y = y_0 + h\sum_{\kappa=0}^{10} c_\kappa f_\kappa + 0(h^8), \tag{12}$$

and

$$\hat{y} = y_0 + h\sum_{\kappa=0}^{12} \hat{c}_\kappa f_\kappa + 0(h^9), \tag{13}$$

where h is the step size. In Equation (11), $\kappa = 1, 2, 3, ..., 12$. An ordinary differential equation is integrated numerically by applying Equations (10), (11), and (12) in an iterative fashion. Equation (10) represents the system of equations to be integrated at the initial data point, (x_0, y_0). Equations (12) and (13) are the seventh and eighth-order RKF schemes, respectively. Equation (12) is used to calculate the solution. Equation (13) is used to compute the stepsize update. In Equations (11), (12), and (13), there are quadrature constants, $\alpha_\kappa, \beta_{\kappa\lambda}, c_\kappa, \hat{c}_\kappa$, required by the numerical method, Fehlberg [10] (see page 65).

The seventh-order Runge-Kutta-Fehlberg scheme is used in this study because the solutions may have highly nonlinear characteristics. For example, nonlinear problems may have solutions that become very sensitive to the initial conditions. The RKF numerical method allows the accurate calculation of data when the rate of change of the solution is very small and very large.

In addition to the analytical solutions constructed with Mathematica, the RKF code developed for this project was checked against known solutions to a linear vibration problem. For an outline of the validation problem and its solution, see Baty and Armijo [11].

3.4 The Stability of Dynamical Systems

The qualitative theory of ordinary differential equations is the study of the global behavior of solutions to ODEs including their stability. Stability, in the context of this project, was defined as the long-time behavior of a solution of a dynamical system, Sanchez [12]. A stable system in an epidemiology model approaches an equilibrium set. The characteristics of a non-stable system would include the rate of change of the solution growing without bound, or the system suddenly exploding around a fixed value. In this study numerical experiments were used to determine whether or not the model problems are stable.

The analysis of all of the numerical experiments was done by plotting components of the solutions of the system in phase space. Phase space is defined as a five-dimensional representation of the solutions to the given ODEs, Arnold [13]. The goal of the analysis was to discover the solutions that reach equilibrium points. A given system of ODEs represents a slope field in the region of phase space where the equations are defined. A solution of the system is a curve in phase space that is tangent to the slope field defined by the differential equations for each point on the curve.

4 Epidemiology of Tuberculosis

4.1 Analytical Example

To begin studying the TB model given by Equation (6), an analytical solution to this system is built for a simple case. The parameters in the model are defined as follows:

$$\Pi = 25.00, \lambda = 1.00, \mu = 0.02, p = 0.175, c = 0.058, \mu_T = 0.139, \qquad (14)$$

and

$$\omega = 0.005, f = 0.70, q = 0.50, \nu = 0.003915. \tag{15}$$

The values from Equations (14) and (15) are substituted into Equations (1) to (5) and the eigenvalues are eigenvectors are computed using Mathematica. The eigenvalues for this problem are real-valued and distinct. The calculation of the eigenvalues and eigenvectors the resulting matrix, $\mathbb{A}$, is shown in Appendix B.

Using the eigenvalues and eigenvectors, the exponential of the matrix $\exp[\mathbb{A}(t)]$ may be computed using:

$$\begin{aligned}\exp[\mathbb{A}(t)] &= \exp[-1.02t]\mathbb{M}_1 + \exp[-0.220052t]\mathbb{M}_2 \\ &+ \exp[-0.217t]\mathbb{M}_3 + \exp[-0.0269482t]\mathbb{M}_4 + \exp[-0.023915t]\mathbb{M}_5,\end{aligned} \tag{16}$$

where

$$\mathbb{M}_1 = \begin{bmatrix} 1.0 & 0 & 0 & 0 & 0 \\ -0.828243 & 0 & 0 & 0 & 0 \\ -0.150612 & 0 & 0 & 0 & 0 \\ -0.0634389 & 0 & 0 & 0 & 0 \\ 0.0125404 & 0 & 0 & 0 & 0 \end{bmatrix}, \tag{17}$$

$$\mathbb{M}_2 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0.0975233 & -0.00982255 & 0.492098 & 0.492098 & -0.0258928 \\ 0.0975233 & -0.00982255 & 0.492098 & 0.492098 & -0.0258928 \\ -0.0595243 & 0.00599529 & -0.300357 & -0.300357 & 0.0158039 \end{bmatrix}, \tag{18}$$

$$\mathbb{M}_3 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0.0435866 & 0 & 0.5 & -0.5 & 0 \\ -0.0435866 & 0 & -0.5 & 0.5 & 0 \\ -7.25862 & 0 & -83.2667 & 83.2667 & 0 \end{bmatrix}, \tag{19}$$

$$\mathbb{M}_4 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ -0.0070807 & -0.0101992 & 0.00790197 & 0.00790197 & 0.0258928 \\ -0.0070807 & -0.0101992 & 0.00790197 & 0.00790197 & 0.0258928 \\ -0.26914 & -0.387675 & 0.300357 & 0.300357 & 0.984196 \end{bmatrix}, \tag{20}$$

and

$$\mathbb{M}_5 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0.828243 & 1.0 & 0 & 0 & 0 \\ 0.0165829 & 0.0200218 & 0 & 0 & 0 \\ 0.0165829 & 0.0200218 & 0 & 0 & 0 \\ 0.316124 & 0.38168 & 0 & 0 & 0 \end{bmatrix}. \tag{21}$$

Moreover, the non-homogeneous term of Equation (8) may be computed using

$$\int_{t_0}^{t} \exp[-\mathbb{A}(s)]\mathbf{F}(s)\, ds = \Big[\exp[1.02t]\mathbf{w}_1 + \exp[0.220052t]\mathbf{w}_2 + \exp[0.217t]\mathbf{w}_3 + \exp[0.0269482t]\mathbf{w}_4 + \exp[0.023915t]\mathbf{w}_5\Big], \tag{22}$$

where

$$\mathbf{w}_1 = \begin{bmatrix} 24.5098039 \\ -20.3000735 \\ -3.6914705 \\ -1.554875 \\ 0.3073627 \end{bmatrix}, \tag{23}$$

$$\mathbf{w}_2 = \begin{bmatrix} 0 \\ 0 \\ 11.0795743 \\ 11.0795743 \\ -6.7625265 \end{bmatrix}, \tag{24}$$

$$\mathbf{w}_3 = \begin{bmatrix} 0 \\ 0 \\ 5.0214976 \\ -5.0214976 \\ -836.246544 \end{bmatrix}, \tag{25}$$

$$\mathbf{w}_4 = \begin{bmatrix} 0 \\ 0 \\ -6.5688061 \\ -6.5688061 \\ -249.682724 \end{bmatrix}, \tag{26}$$

and

$$\mathbf{w}_5 = \begin{bmatrix} 0 \\ 865.8195693 \\ 17.3352498 \\ 17.3352498 \\ 330.4662345 \end{bmatrix}. \tag{27}$$

Next, applying the initial condition $\mathbf{X}_0 = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 \end{bmatrix}^{\mathrm{T}}$ in Equation (8) and combining the result with Equation (22) produces:

$$\begin{aligned} \mathbf{X}(t) = {} & \exp[-1.02t]\mathbf{v}_1 + \exp[-0.220052t]\mathbf{v}_2 \\ & + \exp[-0.217t]\mathbf{v}_3 + \exp[-0.0269482t]\mathbf{v}_4 + \exp[-0.023915t]\mathbf{v}_5 \\ & + \Big\{ \exp[-1.02t]\mathbb{M}_1 + \exp[-0.220052t]\mathbb{M}_2 + \exp[-0.217t]\mathbb{M}_3 \\ & \quad + \exp[-0.0269482t]\mathbb{M}_4 + \exp[-0.023915t]\mathbb{M}_5 \Big\} \\ & \times \Big[\exp[1.02t]\mathbf{w}_1 + \exp[0.220052t]\mathbf{w}_2 + \exp[0.217t]\mathbf{w}_3 \\ & \quad + \exp[0.0269482t]\mathbf{w}_4 + \exp[0.023915t]\mathbf{w}_5 \Big], \end{aligned} \tag{28}$$

where

$$\mathbf{v}_1 = [\text{Column One of } \mathbb{M}_1], \tag{29}$$

$$\mathbf{v}_2 = [\text{Column One of } \mathbb{M}_2]\,, \tag{30}$$

$$\mathbf{v}_3 = [\text{Column One of } \mathbb{M}_3]\,, \tag{31}$$

$$\mathbf{v}_4 = [\text{Column One of } \mathbb{M}_4]\,, \tag{32}$$

and

$$\mathbf{v}_5 = [\text{Column One of } \mathbb{M}_5]\,. \tag{33}$$

Equation (28) is the analytical solution of the linear problem defined by Equations (6) with the parameters of Equations (14) and (15) and the initial condition $\mathbf{X}_0 = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 \end{bmatrix}^{\mathrm{T}}$.

Equation (28) has been used to check the C code developed to solve the dynamical system used to model the evolution of TB. For example, Equation (28) may be used to show that the solution to the first variable approaches $X(t) \to 24.5098039$ as $t \to \infty$, which is in agreement with the computational result.

4.2 Numerical Example: A Linear Model for Northern New Mexico

In this section a simple model is described and applied to study the effects on the evolution of TB in New Mexico caused by troop exposure in the Middle East. Parameters from a published model are used to represent a baseline or unperturbed evolution of TB. The effects of troop exposure are then modeled by changing the proportional constant p associated with new infections. From Mitchell et al. [4], the number of new infections is assumed to approximately double because of the troop exposure. The war (troop exposure) is assumed to last for 20 years. To estimate the behavior of the disease in a community

surrounding Santa Fe, New Mexico, the following initial data is assumed:

$$\mathbf{X}_0 = \begin{bmatrix} X \\ L \\ T_i \\ T_n \\ R \end{bmatrix} = \begin{bmatrix} 120,000 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}, \tag{34}$$

where the initial data implies that at the beginning of the disease time history that there are 120,000 susceptible individuals and one infectious case. It is assumed that there are approximately 120,000 individuals in the region surrounding Santa Fe that are susceptible to TB. The model consists of the initial data of Equation (34) and Equations (1) to (5) with the following parameters:

$$\Pi = 4400, \mu = 0.0222, c = 0.058, \mu_T = 0.139, \tag{35}$$

and

$$\omega = 0.005, f = 0.70, q = 0.85, \nu = 0.00256, \tag{36}$$

Blower, et al [6]. The proportional constant associated with new infections is assumed to be given by:

$$p = \begin{cases} 0.10 & \text{if } t < 20 \\ 0.05 & \text{if } t \geq 20 \end{cases}, \tag{37}$$

which is used to represent the increased exposure to TB of the troops in the Middle East. The per-susceptible risk of becoming infected is modeled as

$$\lambda = 1.0, \tag{38}$$

for the first example. Equation (38) guarantees that the governing dynamical system, Equation (6), will be linear.

Figures 1 through 5 show the results for the linear epidemiology model of Tuberculosis. Figure 1 shows the number of susceptible cases of TB for the constant values of $p = 0.1$, $p = 0.05$, and the values of Equation (37). In figure the number of susceptible cases is the same for each value of p, however this number occurs at different times in evolution of the disease.

Figures 2 through 4 show the latent, infectious and non-infectious cases, respectively. Each figure shows the transition of the linear evolution of TB at 20 years from the $p = 0.1$ solution to the $p = 0.05$ solution. Figure 5 shows the number of recovered cases for the two constants.

For this example, the matrix $\mathbb{A}$ associated with the dynamical system of Equation (6) has five, distinct, real-valued eigenvalues. The eigenvalues are all negative, which implies the solution will be stable in time. Figures 2 through 5 show the asymptotic values to which the independent variables X, L, T_i, T_n, and R converge. The solution of the dynamical system suggests that the disease approaches the equilibrium values after about 120 years. Hence the time-scale associated with a perturbation in TB is on the order of several decades.

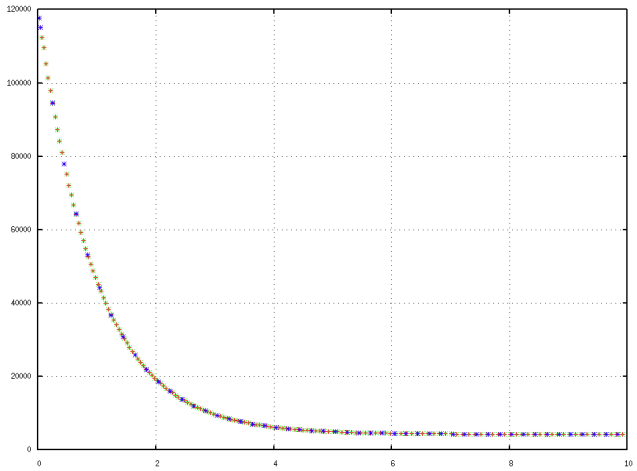

Figure 1: Solutions for the simple linear model for X, the susceptible cases. The vertical axis is number of cases and the horizontal axis is time in years. The red and blue curves assume the constant values of $p = 0.1$ and $p = 0.05$ for all time respectively, while the green curve assumes $p = 0.1$ if $t < 20$ years and $p = 0.05$ if $t \geq 20$ years.

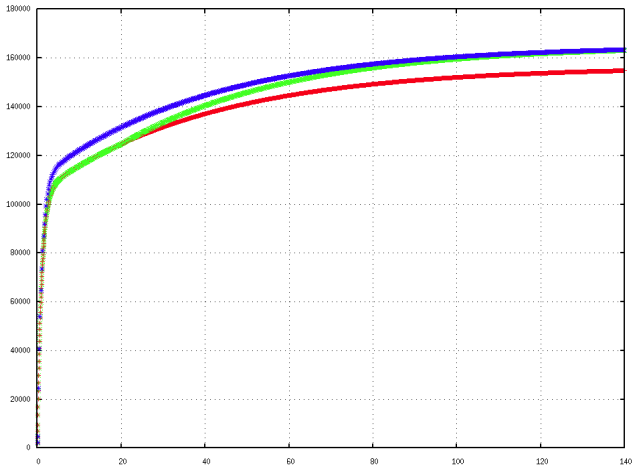

Figure 2: Solutions for the simple linear model for L, the latent cases. The vertical axis is number of cases and the horizontal axis is time in years. The red and blue curves assume the constant values of $p = 0.1$ and $p = 0.05$ for all time respectively, while the green curve assumes $p = 0.1$ if $t < 20$ years and $p = 0.05$ if $t \geq 20$ years.

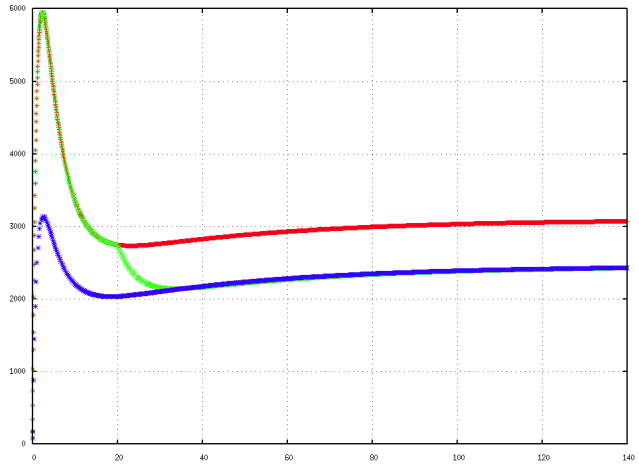

Figure 3: Solutions for the simple linear model for T_i, the infectious cases. The vertical axis is number of cases and the horizontal axis is time in years. The red and blue curves assume the constant values of $p = 0.1$ and $p = 0.05$ for all time respectively, while the green curve assumes $p = 0.1$ if $t < 20$ years and $p = 0.05$ if $t \geq 20$ years.

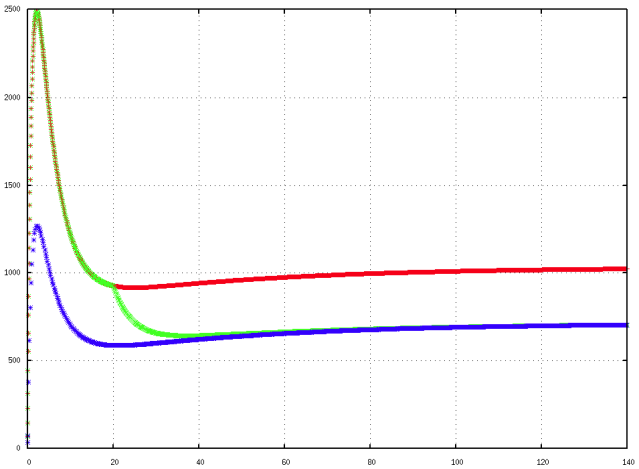

Figure 4: Solutions for the simple linear model for T_n, the non-infectious cases. The vertical axis is number of cases and the horizontal axis is time in years. The red and blue curves assume the constant values of $p = 0.1$ and $p = 0.05$ for all time respectively, while the green curve assumes $p = 0.1$ if $t < 20$ years and $p = 0.05$ if $t \geq 20$ years.

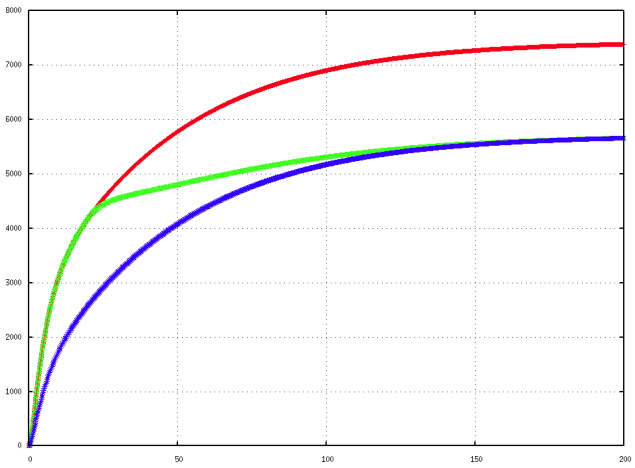

Figure 5: Solutions for the simple linear model for R, the recovered cases. The vertical axis is number of cases and the horizontal axis is time in years. The red and blue curves assume the constant values of $p = 0.1$ and $p = 0.05$ for all time respectively, while the green curve assumes $p = 0.1$ if $t < 20$ years and $p = 0.05$ if $t \geq 20$ years.

4.3 Numerical Example: A Nonlinear Model for Northern New Mexico

For the second numerical example, the same problem of Section 4.2 is studied with the nonlinear feed-back term:

$$\lambda = 0.00005 \cdot T_i, \tag{39}$$

following Blower et al. [6]. In this case the epidemiology model for TB is defined by Equations (1) through (5), (34) through (37), and (39). Again, the initial susceptible population is assumed to be 120,000 individuals, and at time zero one infectious case is present. The effect of the troop exposure is modeled by Equation (37), which reduces the new infection population constant by a factor of two after 20 years.

Figures 6 through 10 show the effect of the war (troop exposure) by comparing the variable new infection constant, Equation (37), with the constant new infection value $p = 0.05$. In Figure 6 the effect of the change in p is shown. By increasing p the number of susceptible cases decreases during the war. Figure 7 then shows that the change in p causes the number of latent cases to increase sooner than the baseline disease model. Figure 7 also shows that TB converges back to the baseline model around 200 years after the troop exposure is over. This figure implies that the disease changes a lot about 50 years after the war and then converges back to the baseline case over the next 100 years. The characteristic time-scale of the disease is approximately 150 years.

Figures 8 and 9 show the change in infectious and non-infectious cases caused by the war. The solutions are similar to the latent case in that the numbers of infectious and non-infectious cases increase sooner than the baseline disease model. Figures 8 and 9 also show that both of these populations have localized peaks around 50 years. Figure 10 shows the number of recovered cases associated with the troop exposure.

To understand the effect of the troop exposure with respect to the baseline TB model, Figures 11 through 15 show the differences of the TB war and the TB baseline models. Figure 11 shows that the war causes an increase of about 85,000 latent cases of TB at 45 years after the beginning of the war (25 years after the war is over). This figure also shows a minor decrease in the number of latent cases 75 years after the beginning of the war. Figures 12 and 13 show the infectious and non-infectious cases caused by the war. Both of these plots have peaks around 45 years after the beginning of the war. Figure 12 shows an increase of about 1500 cases of TB 45 years after the war. Moreover, Figure 13 shows an increase of about 500 cases of TB 45 years after the war. Both Figures 12 and 13 show a decrease in the number of cases of TB with respect to the baseline model 75 years after the war. Figure 14 shows the sum of the infectious and non-infectious cases due to the war. This plot exhibits a peak of 2000 cases approximately 45 years after the beginning of the war. Figure 15 shows the recovered cases associated with the war. The recovered cases peak about 60 years after the beginning of the war and converge back to the baseline model at about 200 years. It is interesting to note that the recovered cases is strictly positive, because recovered cases only occur as a result of troop exposure.

The baseline and war TB models show that the evolution of Tuberculosis lasts on the order of 150 years. Notice that the effect of Equation (37) may be seen in the infectious and non-infectious cases. For these independent variables, the solutions show a kink at 20 years, the end of the war. Also notice, the solutions of the TB epidemiology model are all stable in time and converge to equilibrium solutions around 200 years.

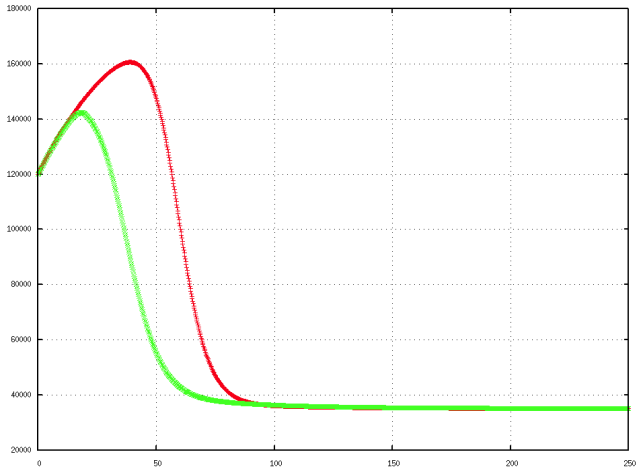

Figure 6: Solutions for the nonlinear model for X, the susceptible cases. The vertical axis is number of cases and the horizontal axis is time in years. The red curve is the number of susceptible cases without the war, and the green curve is the number of susceptible cases with the war.

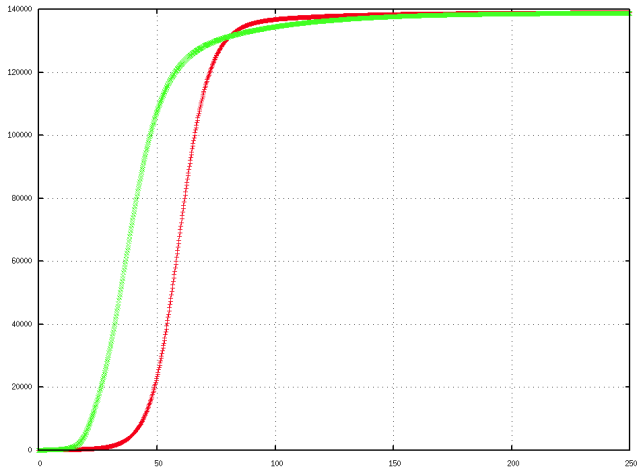

Figure 7: Solutions for the nonlinear model for L, the latent cases. The vertical axis is number of cases and the horizontal axis is time in years. The red curve is the number of latent cases without the war, and the green curve is the number of latent cases with the war.

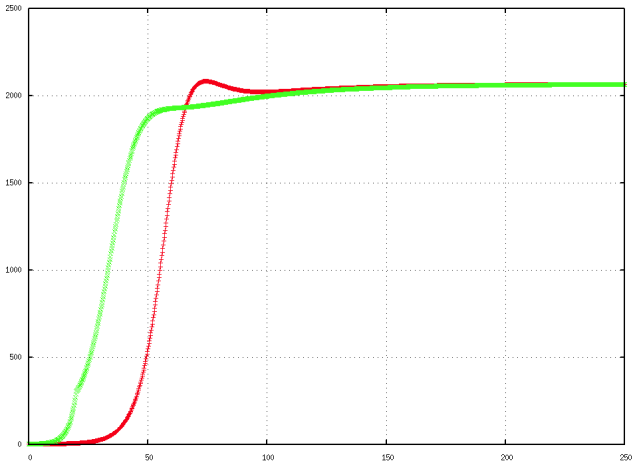

Figure 8: Solutions for the nonlinear model for T_i, the infectious cases. The vertical axis is number of cases and the horizontal axis is time in years. The red curve is the number of infectious cases without the war, and the green curve is the number of infectious cases with the war.

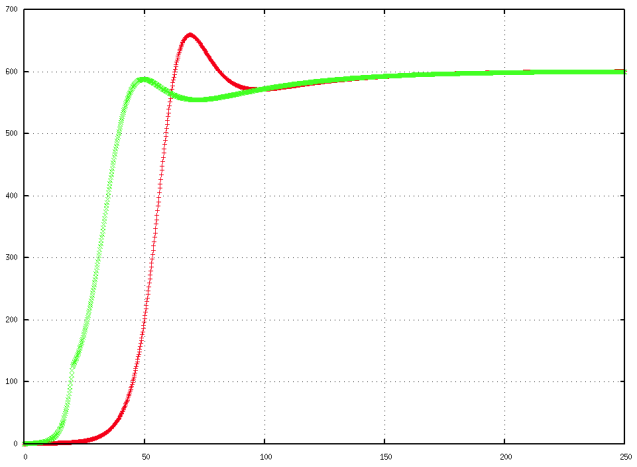

Figure 9: Solutions for the nonlinear model for T_n, the non-infectious cases. The vertical axis is number of cases and the horizontal axis is time in years. The red curve is the number of non-infectious cases without the war, and the green curve is the number of non-infectious cases with the war.

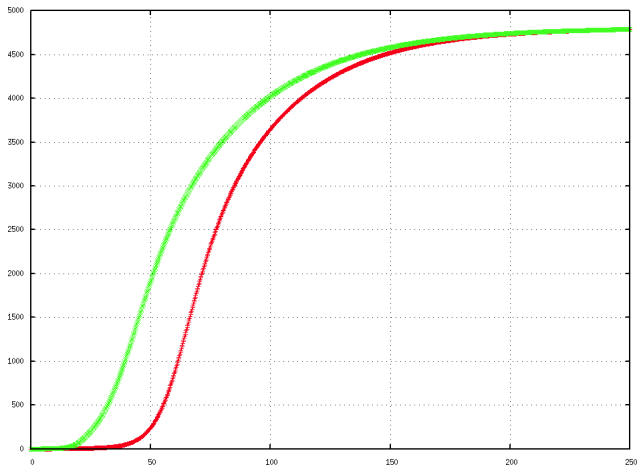

Figure 10: Solutions for the nonlinear model for R, the recovered cases. The vertical axis is number of cases and the horizontal axis is time in years. The red curve is the number of recovered cases without the war, and the green curve is the number of recovered cases with the war.

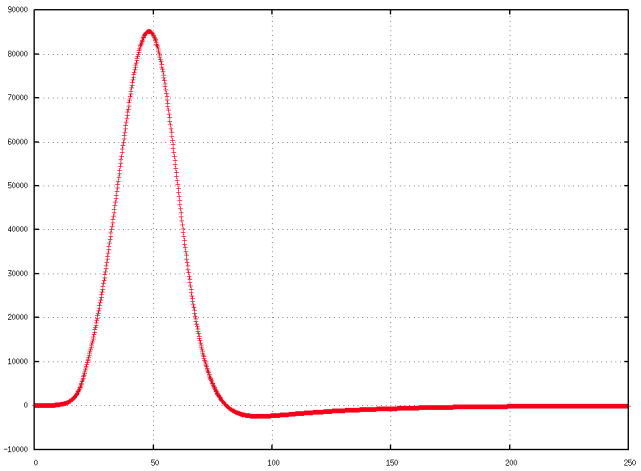

Figure 11: Latent cases caused by the war. The vertical axis is number of cases and the horizontal axis is time in years. Compare with Figure 7.

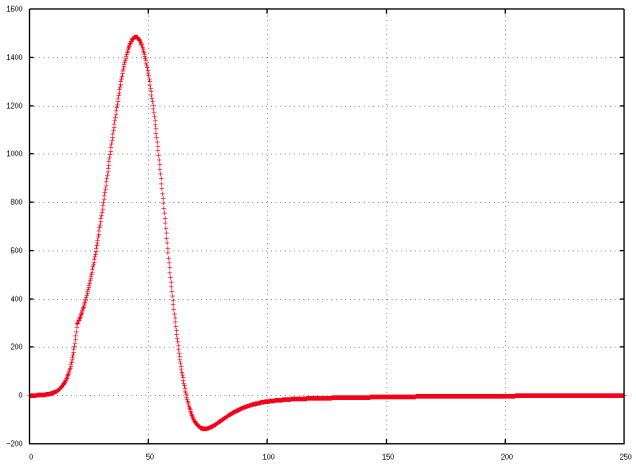

Figure 12: Infectious cases caused by the war. The vertical axis is number of cases and the horizontal axis is time in years. Compare with Figure 8.

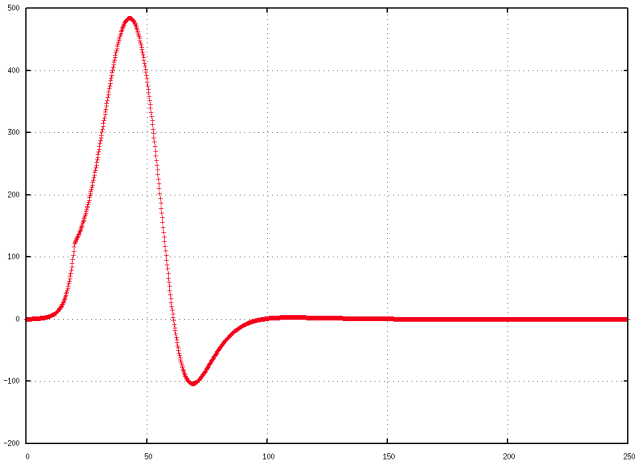

Figure 13: Non-infectious cases cause by the war. The vertical axis is number of cases and the horizontal axis is time in years. Compare with Figure 9.

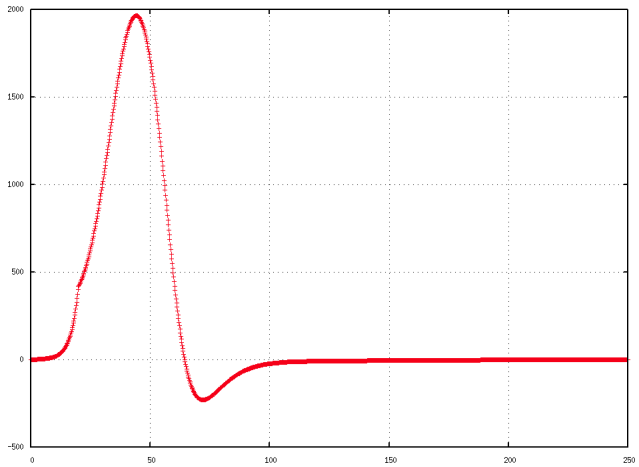

Figure 14: The sum of infectious and non-infectious cases caused by the war. The vertical axis is number of cases and the horizontal axis is time in years. Compare with Figures 12 and 13.

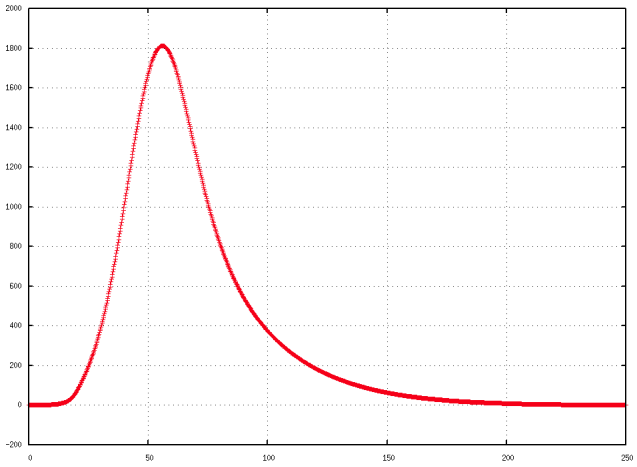

Figure 15: Recovered cases resulting from the war. The vertical axis is number of cases and the horizontal axis is time in years. Compare with Figure 10.

5 Summary and Conclusions

This project studied the epidemiology of Tuberculosis (TB) with emphasis on the evolution of TB within a population exposed to TB in the Middle East. American troops fighting overseas have been exposed to this disease and could potentially spread it to the general population.

In our project, a dynamical system was used to model the evolution of TB in time. A C program was developed to integrate the equations modeling the evolution of the disease. The epidemiology of TB was modeled with existing disease parameters for an idealized problem representing the population in the region surrounding Santa Fe, New Mexico. The proportion of new infections of the disease was doubled on a 20 year time interval to estimate the long term effects of the TB epidemiology associated with the increased exposure to our troops.

Our computational simulations involved both a simplified linear model and a more realistic nonlinear model. An analytical solution was constructed for the linear model problem. The eigenvalues and eigenvectors were computed with Mathematica to construct an analytical solution. The analysis of the linear problem and computational results of the nonlinear problem show that the solutions of our model of TB epidemiology are stable in time. The following results are implied from the nonlinear model:

1. The time-scale of the disease is on the order of 100 to 150 years. The major fluctuations in the number of disease cases occur within 50 years of the end of the war (troop exposure).

2. The peak number of latent cases of TB associated with the war occurs 25 years after the war, and is approximately 85,000 cases.

3. The peak number of infectious and noninfectious cases is approximately 2,000 and occurs 45 years after the beginning of the war (25 years after the end of the war).

4. The peak number of recovered cases is 1,800 and occurs approximately 60 years after the war begins (40 years after the end of the war).

The basic result of the simulations is that increased troop exposure could possibly lead to a few thousand more cases of TB in New Mexico over the next 150 years.

The TB epidemiology models were developed and analyzed by Don Tucker, based on research by Blower et al. Peter, Claire, and Sarah worked with Joanne Baty to visit the University of New Mexico Medical Hospital to obtain the background information on TB in New Mexico and the United States. Sam, Peter, Claire, and Sarah, along with help from Roy Baty, developed a computer model and code to perform the calculations. Sam and Peter developed Mathematica scripts to study analytical solutions to a linear TB model. The entire team worked on developing the report.

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Appendix A: C Code Listing

```c
/*  Epidemiology Model for Tuberculosis */
/*  Supercomputing Challenge 2013 */
/*  By Sam Baty, Peter Armijo, Claire Armijo, and Sarah Baty */
/*  Seventh Order Variable Step Size Runge-Kutta-Felhberg Scheme */

#include <stdio.h>
#include <math.h>

double fctn(int j, double t, double dt0, double y[]);

int main()
{
    int i, j, k, its;
    double err, tol;
    double alfa[13], c[11], chat[13], error[100];
    double beta0[13], beta1[13], beta2[13], beta3[13], beta4[13], beta5[13], beta6[13];
    double beta7[13], beta8[13], beta9[13], beta10[13], beta11[13], beta12[13];
    double f0[6], f1[6], f2[6], f3[6], f4[6], f5[6], f6[6];
    double f7[6], f8[6], f9[6], f10[6], f11[6], f12[6];
    double y0[100], y[100], ya1[100], ya2[100], yhat[100];
    double dt, dt0, t, t0;
    double delta, order, errY, errN;

    /* Initialize Parameters for Seventh Order Runge-Kutta-Fehlberg Scheme */

    alfa[0]=0.0;
    alfa[1]=2.0/27.0;
    alfa[2]=1.0/9.0;
    alfa[3]=1.0/6.0;
    alfa[4]=5.0/12.0;
    alfa[5]=1.0/2.0;
    alfa[6]=5.0/6.0;
    alfa[7]=1.0/6.0;
    alfa[8]=2.0/3.0;
    alfa[9]=1.0/3.0;
    alfa[10]=1.0;
    alfa[11]=0.0;
    alfa[12]=1.0;
```

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```
c[0]=41.0/840.0;
c[1]=0.0;
c[2]=0.0;
c[3]=0.0;
c[4]=0.0;
c[5]=34.0/105.0;
c[6]=9.0/35.0;
c[7]=9.0/35.0;
c[8]=9.0/280.0;
c[9]=9.0/280.0;
c[10]=41.0/840.0;

chat[0]=0.0;
chat[1]=0.0;
chat[2]=0.0;
chat[3]=0.0;
chat[4]=0.0;
chat[5]=34.0/105.0;
chat[6]=9.0/35.0;
chat[7]=9.0/35.0;
chat[8]=9.0/280.0;
chat[9]=9.0/280.0;
chat[10]=0.0;
chat[11]=41.0/840.0;
chat[12]=41.0/840.0;

for(i=0;i<=12;i++){
    beta0[i]=0.0;
    beta1[i]=0.0;
    beta2[i]=0.0;
    beta3[i]=0.0;
    beta4[i]=0.0;
    beta5[i]=0.0;
    beta6[i]=0.0;
    beta7[i]=0.0;
    beta8[i]=0.0;
    beta9[i]=0.0;
    beta10[i]=0.0;
    beta11[i]=0.0;
    beta12[i]=0.0;
}
```

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```
beta0[0]=0.0;

beta1[0]=2.0/27.0;

beta2[0]=1.0/36.0;
beta2[1]=1.0/12.0;

beta3[0]=1.0/24.0;
beta3[1]=0.0;
beta3[2]=1.0/8.0;

beta4[0]=5.0/12.0;
beta4[1]=0.0;
beta4[2]=-25.0/16.0;
beta4[3]=25.0/16.0;

beta5[0]=1.0/20.0;
beta5[1]=0.0;
beta5[2]=0.0;
beta5[3]=1.0/4.0;
beta5[4]=1.0/5.0;

beta6[0]=-25.0/108.0;
beta6[1]=0.0;
beta6[2]=0.0;
beta6[3]=125.0/108.0;
beta6[4]=-65.0/27.0;
beta6[5]=125.0/54.0;

beta7[0]=31.0/300.0;
beta7[1]=0.0;
beta7[2]=0.0;
beta7[3]=0.0;
beta7[4]=61.0/225.0;
beta7[5]=-2.0/9.0;
beta7[6]=13.0/900.0;

beta8[0]=2.0;
beta8[1]=0.0;
beta8[2]=0.0;
beta8[3]=-53.0/6.0;
beta8[4]=704.0/45.0;
beta8[5]=-107.0/9.0;
beta8[6]=67.0/90.0;
beta8[7]=3.0;

beta9[0]=-91.0/108.0;
beta9[1]=0.0;
beta9[2]=0.0;
beta9[3]=23.0/108.0;
beta9[4]=-976.0/135.0;
beta9[5]=311.0/54.0;
beta9[6]=-19.0/60.0;
beta9[7]=17.0/6.0;
beta9[8]=-1.0/12.0;
```

```
beta10[0]=2383.0/4100.0;
beta10[1]=0.0;
beta10[2]=0.0;
beta10[3]=-341.0/164.0;
beta10[4]=4496.0/1025.0;
beta10[5]=-301.0/82.0;
beta10[6]=2133.0/4100.0;
beta10[7]=45.0/82.0;
beta10[8]=45.0/164.0;
beta10[9]=18.0/41.0;

beta11[0]=3.0/205;
beta11[1]=0.0;
beta11[2]=0.0;
beta11[3]=0.0;
beta11[4]=0.0;
beta11[5]=-6.0/41.0;
beta11[6]=-3.0/205.0;
beta11[7]=-3.0/41.0;
beta11[8]=3.0/41.0;
beta11[9]=6.0/41.0;
beta11[10]=0.0;

beta12[0]=-1777.0/4100.0;
beta12[1]=0.0;
beta12[2]=0.0;
beta12[3]=-341.0/164.0;
beta12[4]=4496.0/1025.0;
beta12[5]=-289.0/82.0;
beta12[6]=2193.0/4100.0;
beta12[7]=51.0/82.0;
beta12[8]=33.0/164.0;
beta12[9]=12.0/41.0;
beta12[10]=0.0;
beta12[11]=1.0;

/* Perform Integration */
/* Integration Parameters */

t=0.0;
dt=0.02;
dt0=dt;

tol=0.0000000001;
delta=0.0;
```

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```
its=2500;

for(i=1;i<=5;i++){
    f0[i]=0.0;
    f1[i]=0.0;
    f2[i]=0.0;
    f3[i]=0.0;
    f4[i]=0.0;
    f5[i]=0.0;
    f6[i]=0.0;
    f7[i]=0.0;
    f8[i]=0.0;
    f9[i]=0.0;
    f10[i]=0.0;
    f11[i]=0.0;
    f12[i]=0.0;
}

/* Define Initial Data */

y0[0]=0.0;

/* Input Initial Data Here */

y0[1]=120000.0;
y0[2]=0.0;
y0[3]=1.0;
y0[4]=0.0;
y0[5]=0.0;

for(i=1;i<=5;i++){
y[i]=y0[i];
}

t=t0;

/* Integration Loop Here */

for(j=1;j<=its;j++){

/* Compute F0 */

t=t0+alfa[0]*dt;

for(i=1;i<=5;i++){y[i]=y0[i];}
for(i=1;i<=5;i++){f0[i]=fctn(i, t, dt0, y);}


/* Compute F1 */

t=t0+alfa[1]*dt;

for(i=1;i<=5;i++){y[i]=y0[i]+dt*beta1[0]*f0[i];}
for(i=1;i<=5;i++){f1[i]=fctn(i, t, dt0, y);}


/* Compute F2 */

t=t0+alfa[2]*dt;

for(i=1;i<=5;i++){y[i]=y0[i]+dt*(beta2[0]*f0[i]+beta2[1]*f1[i]);}
for(i=1;i<=5;i++){f2[i]=fctn(i, t, dt0, y);}
```

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```
/* Compute F3 */

t=t0+alfa[3]*dt;

for(i=1;i<=5;i++){y[i]=y0[i]+dt*(beta3[0]*f0[i]+beta3[1]*f1[i]+beta3[2]*f2[i]);}
for(i=1;i<=5;i++){f3[i]=fctn(i, t, dt0, y);}


/* Compute F4 */

t=t0+alfa[4]*dt;

for(i=1;i<=5;i++){y[i]=y0[i]+dt*(beta4[0]*f0[i]+beta4[1]*f1[i]+beta4[2]*f2[i]+beta4[3]*f3[i]);}
for(i=1;i<=5;i++){f4[i]=fctn(i, t, dt0, y);}


/* Compute F5 */

t=t0+alfa[5]*dt;

for(i=1;i<=5;i++){y[i]=y0[i]+dt*(beta5[0]*f0[i]+beta5[1]*f1[i]+beta5[2]*f2[i]+beta5[3]*f3[i]+beta5[4]*f4[i]);}
for(i=1;i<=5;i++){f5[i]=fctn(i, t, dt0, y);}


/* Compute F6 */

t=t0+alfa[6]*dt;

for(i=1;i<=5;i++){y[i]=y0[i]+dt*(beta6[0]*f0[i]+beta6[1]*f1[i]+beta6[2]*f2[i]+beta6[3]*f3[i]+beta6[4]*f4[i]+beta6[5]*f5[i]);}
for(i=1;i<=5;i++){f6[i]=fctn(i, t, dt0, y);}


/* Compute F7 */

t=t0+alfa[7]*dt;

for(i=1;i<=5;i++){y[i]=y0[i]+dt*(beta7[0]*f0[i]+beta7[1]*f1[i]+beta7[2]*f2[i]+beta7[3]*f3[i]+beta7[4]*f4[i]+beta7[5]*f5[i]+beta7[6]*f6[i]);}
for(i=1;i<=5;i++){f7[i]=fctn(i, t, dt0, y);}


/* Compute F8 */

t=t0+alfa[8]*dt;

for(i=1;i<=5;i++){
ya1[i]=beta8[0]*f0[i]+beta8[1]*f1[i]+beta8[2]*f2[i]+beta8[3]*f3[i]+beta8[4]*f4[i]+beta8[5]*f5[i]+beta8[6]*f6[i];
ya2[i]=beta8[7]*f7[i];}

for(i=1;i<=5;i++){y[i]=y0[i]+dt*(ya1[i]+ya2[i]);}
for(i=1;i<=5;i++){f8[i]=fctn(i, t, dt0, y);}
```

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```
  /* Compute F9 */

  t=t0+alfa[9]*dt;

  for(i=1;i<=5;i++){
  ya1[i]=beta9[0]*f0[i]+beta9[1]*f1[i]+beta9[2]*f2[i]+beta9[3]*f3[i]+beta9[4]*f4[i]+beta9[5]*f5[i]+beta9[6]*f6[i];
  ya2[i]=beta9[7]*f7[i]+beta9[8]*f8[i];}

  for(i=1;i<=5;i++){y[i]=y0[i]+dt*(ya1[i]+ya2[i]);}
  for(i=1;i<=5;i++){f9[i]=fctn(i, t, dt0, y);}


  /* Compute F10 */

  t=t0+alfa[10]*dt;

  for(i=1;i<=5;i++){
  ya1[i]=beta10[0]*f0[i]+beta10[1]*f1[i]+beta10[2]*f2[i]+beta10[3]*f3[i]+beta10[4]*f4[i]+beta10[5]*f5[i]+beta10[6]*f6[i];
  ya2[i]=beta10[7]*f7[i]+beta10[8]*f8[i]+beta10[9]*f9[i];}

  for(i=1;i<=5;i++){y[i]=y0[i]+dt*(ya1[i]+ya2[i]);}
  for(i=1;i<=5;i++){f10[i]=fctn(i, t, dt0, y);}


  /* Compute F11 */

  t=t0+alfa[11]*dt;

  for(i=1;i<=5;i++){
  ya1[i]=beta11[0]*f0[i]+beta11[1]*f1[i]+beta11[2]*f2[i]+beta11[3]*f3[i]+beta11[4]*f4[i]+beta11[5]*f5[i]+beta11[6]*f6[i];
  ya2[i]=beta11[7]*f7[i]+beta11[8]*f8[i]+beta11[9]*f9[i]+beta11[10]*f10[i];}

  for(i=1;i<=5;i++){y[i]=y0[i]+dt*(ya1[i]+ya2[i]);}
  for(i=1;i<=5;i++){f11[i]=fctn(i, t, dt0, y);}


  /* Compute F12 */

  t=t0+alfa[12]*dt;

  for(i=1;i<=5;i++){
  ya1[i]=beta12[0]*f0[i]+beta12[1]*f1[i]+beta12[2]*f2[i]+beta12[3]*f3[i]+beta12[4]*f4[i]+beta12[5]*f5[i]+beta12[6]*f6[i];
  ya2[i]=beta12[7]*f7[i]+beta12[8]*f8[i]+beta12[9]*f9[i]+beta12[10]*f10[i]+beta12[11]*f11[i];}

  for(i=1;i<=5;i++){y[i]=y0[i]+dt*(ya1[i]+ya2[i]);}
  for(i=1;i<=5;i++){f12[i]=fctn(i, t, dt0, y);}


  /* Advance Solution in Time by dt */

  for(i=1;i<=5;i++){
  ya1[i]=c[0]*f0[i]+c[1]*f1[i]+c[2]*f2[i]+c[3]*f3[i]+c[4]*f4[i]+c[5]*f5[i];
  ya2[i]=c[6]*f6[i]+c[7]*f7[i]+c[8]*f8[i]+c[9]*f9[i]+c[10]*f10[i];}

  for(i=1;i<=5;i++){y[i]=ya1[i]+ya2[i];}
```

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```
    /* Compute Solution +1 Order for Variable Step */

    for(i=1;i<=5;i++){
    ya1[i]=chat[0]*f0[i]+chat[1]*f1[i]+chat[2]*f2[i]+chat[3]*f3[i]+chat[4]*f4[i]+chat[5]*f5[i];
    ya2[i]=chat[6]*f6[i]+chat[7]*f7[i]+chat[8]*f8[i]+chat[9]*f9[i]+chat[10]*f10[i]+chat[11]*f11[i]+chat[12]*f12[i];}

    for(i=1;i<=5;i++){yhat[i]=ya1[i]+ya2[i];}

    /* Error for Step Size Update */

    for(i=1;i<=5;i++){error[i]=y[i]-yhat[i];}

    err=0.0;
    for(i=1;i<=5;i++){err+=error[i]*error[i];}
    err=sqrt(err);

    /* Solution Time Advance */

    for(i=1;i<=5;i++){y[i]=y0[i]+dt*y[i];}

    /* Solution for Next Time Step */

    t0=t0+dt;

    for(i=1;i<=5;i++){y0[i]=y[i];}

    /* Error for Simple Oscillator */

     /* errY=y[1]-cos(t0);
     errN=y[2]-sin(t0); */


    /* Print Output */

    /* printf("%12u %14.6e %14.6e %14.6e %14.6e %14.6e %14.6e %14.6e\n", j, t0, err, dt, y[1], y[2], errY, errN); */

    printf("%12u %14.6e %14.6e %14.6e %14.6e %14.6e %14.6e %14.6e %14.6e\n", j, t0, err, dt, y[1], y[2], y[3], y[4], y[5]);


    /* Update Step Size */

    if(err != 0.0){delta=tol/err;}
    if(err == 0.0){delta=1.0;}
    order=1.0/7.0;
    delta=0.84*pow(delta,order);

    if(dt <= 0.1){
    dt=delta*dt;
    if(delta <= 0.01) {dt=0.01*dt;}
    if(delta >= 4.00) {dt=4.00*dt;}}
    if(dt > 10.0*dt0){dt=10.0*dt0;}
    }

    return 0;
}
```

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```
double fctn(int j, double t, double dt0, double y[])
{
    double a, b, f;
    double b1, kr, lr, l0, nr, mr1, mr2;
    double p1, l1, m1, p2, c1, m2, o1, z1, q1, v1;


    /* Listing of Linear Model */

    /* if (t <= 20.0) {p1=4400.00;}     /* Recruitment Rate
    if (t >= 20.0) {p1=4400.00;}        /* Recruitment Rate

    l1=1.000;       /* Multiplicative Factor
    m1=0.0222;      /* Inverse of Life Expectancy

    if (t <= 20.0) {p2=2.0*0.050;}         /* Proportation of New Infections
    if (t >= 20.0) {p2=0.050;}             /* Proportation of New Infections

    c1=0.058;       /* Natural Cure Rate
    m2=0.139;       /* Morality Rate Due to TB
    o1=0.005;       /* Rate of Relapse to TB
    z1=0.70;        /* Probability of Developing Infectious TB
    q1=0.85;        /* Probability of Developing Infections TB
    v1=0.00256;     /* Progression Rate

    if (j == 1) {f=p1-l1*y[1]-m1*y[1];}
    if (j == 2) {f=(1.0-p2)*l1*y[1]-(v1+m1)*y[2];}
    if (j == 3) {f=p2*z1*l1*y[1]+q1*v1*y[2]+o1*y[5]-(m1+m2+c1)*y[3];}
    if (j == 4) {f=p2*(1.0-z1)*l1*y[1]+(1.0-q1)*v1*y[2]+o1*y[5]-(m1+m2+c1)*y[4];}
    if (j == 5) {f=c1*(y[3]+y[4])-(2.0*o1+m1)*y[5];}  */

    /* Listing of Nonlinear Model */

    if (t <= 20.0) {p1=4400.00;}     /* Recruitment Rate */
    if (t >= 20.0) {p1=4400.00;}     /* Recruitment Rate */

    l1=1.000;       /* Multiplicative Factor -- Linear Model -- Not used in the Nonlinear Model */
    m1=0.0222;      /* Inverse of Life Expectancy */

    if (t <= 20.0) {p2=0.0*0.050;}     /* Proportation of New Infections */
    if (t >= 20.0) {p2=0.0*0.050;}         /* Proportation of New Infections */

    c1=0.058;       /* Natural Cure Rate */
    m2=0.139;       /* Morality Rate Due to TB */
    o1=0.005;       /* Rate of Relapse to TB */
    z1=0.70;        /* Probability of Developing Infectious TB */
    q1=0.85;        /* Probability of Developing Infections TB */
    v1=0.00256;     /* Progression Rate */
    b1=0.00005;     /* Mutiplication Factor for Feedback Term -- Nonlinear Model */

    if (j == 1) {f=p1-b1*y[3]*y[1]-m1*y[1];}
    if (j == 2) {f=(1.0-p2)*b1*y[3]*y[1]-(v1+m1)*y[2];}
    if (j == 3) {f=p2*z1*b1*y[3]*y[1]+q1*v1*y[2]+o1*y[5]-(m1+m2+c1)*y[3];}
    if (j == 4) {f=p2*(1.0-z1)*b1*y[3]*y[1]+(1.0-q1)*v1*y[2]+o1*y[5]-(m1+m2+c1)*y[4];}
    if (j == 5) {f=c1*(y[3]+y[4])-(2.0*o1+m1)*y[5];}


    return f;
}
```

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Appendix B: Mathematica Script Listing

```
In[71]:= p1 = 25.00;
         l1 = 1.000;
         m1 = 0.020;
         p2 = 0.175;
         c1 = 0.058;
         m2 = 0.139;
         o1 = 0.005;
         z1 = 0.70;
         q1 = 0.50;
         v1 = 0.003915;
         A = {{-(l1 + m1), 0, 0, 0, 0}, {(1.0 - p2) * l1, -(v1 + m1), 0, 0, 0}, {p2 * z1 * l1, q1 * v1, -(m1 + m2 + c1), 0, o1},
           {p2 * (1.0 - z1) * l1, (1.0 - q1) * v1, 0, -(m1 + m2 + c1), o1}, {0, 0, c1, c1, -(2 * o1 + m1)}}
         MatrixForm[A]
         Eigenvalues[A]
         ev = Eigenvectors[A]
         ew = Transpose[ev]
         e0 = Inverse[ew]
         MatrixForm[ew]
         MatrixForm[e0]
         ef = {Exp[-1.02 t] * {0.7640823139190684, -0.6328454991122558, -0.11507994732250712, -0.04847252269693451, 0.009581861879926873},
           Exp[-0.2200517995689359 t] * {0., 0., -0.6492221064140331, -0.6492221064140331, 0.3962591488996208},
           Exp[-0.2169999999999997 t] * {0., 0., 0.7071067811865349, -0.7071067811865601, 7.850462293419218 * -15},
           Exp[-0.02694820043106394 t] * {0., 0., 0.0262904265233252 26, 0.0262904265233252 22, 0.9993085744385682},
           Exp[-0.023915 t] * {0., 0.9339346306306942, 0.018699011093612425, 0.018699011093612 56, 0.3564643035101139}}
         eT = Transpose[ef]
         MatrixForm[eT]
         eA = eT.e0

Out[81]= {{-1.02, 0, 0, 0, 0}, {0.825, -0.023915, 0, 0, 0}, {0.1225, 0.0019575, -0.217, 0, 0.005},
          {0.0525, 0.0019575, 0, -0.217, 0.005}, {0, 0, 0.058, 0.058, -0.03}}

Out[82]//MatrixForm=
⎛ -1.02       0          0       0       0    ⎞
⎜  0.825   -0.023915     0       0       0    ⎟
⎜ 0.1225   0.0019575   -0.217    0     0.005  ⎟
⎜ 0.0525   0.0019575     0     -0.217  0.005  ⎟
⎝    0         0        0.058   0.058  -0.03 ⎠

Out[83]= {-1.02, -0.220052, -0.217, -0.0269482, -0.023915}

Out[84]= {{0.764082, -0.632845, -0.11508, -0.0484725, 0.00958186},
          {0., 0., -0.649222, -0.649222, 0.396259}, {0., 0., 0.707107, -0.707107, 7.85046 × 10^-15},
          {0., 0., 0.0262904, 0.0262904, 0.999309}, {0., 0.933935, 0.018699, 0.018699, 0.356464}}
```

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Out[85]= {{0.764082, 0., 0., 0., 0.}, {−0.632845, 0., 0., 0., 0.933935}, {−0.11508, −0.649222, 0.707107, 0.0262904, 0.018699}, {−0.0484725, −0.649222, −0.707107, 0.0262904, 0.018699}, {0.00958186, 0.396259, 7.85046 × 10^−15, 0.999309, 0.356464}}

Out[86]= {{1.30876, 0., 0., 0., 0.}, {−0.150216, 0.0151297, −0.757981, −0.757981, 0.0398829}, {0.0616407, 0., 0.707107, −0.707107, 0.}, {−0.269326, −0.387944, 0.300565, 0.300565, 0.984877}, {0.886831, 1.07074, 0., 0., 0.}}

Out[87]//MatrixForm=

$$\begin{pmatrix} 0.764082 & 0. & 0. & 0. & 0. \\ -0.632845 & 0. & 0. & 0. & 0.933935 \\ -0.11508 & -0.649222 & 0.707107 & 0.0262904 & 0.018699 \\ -0.0484725 & -0.649222 & -0.707107 & 0.0262904 & 0.018699 \\ 0.00958186 & 0.396259 & 7.85046\times10^{-15} & 0.999309 & 0.356464 \end{pmatrix}$$

Out[88]//MatrixForm=

$$\begin{pmatrix} 1.30876 & 0. & 0. & 0. & 0. \\ -0.150216 & 0.0151297 & -0.757981 & -0.757981 & 0.0398829 \\ 0.0616407 & 0. & 0.707107 & -0.707107 & 0. \\ -0.269326 & -0.387944 & 0.300565 & 0.300565 & 0.984877 \\ 0.886831 & 1.07074 & 0. & 0. & 0. \end{pmatrix}$$

Out[89]= {{0.764082 e^−1.02 t, −0.632845 e^−1.02 t, −0.11508 e^−1.02 t, −0.0484725 e^−1.02 t, 0.00958186 e^−1.02 t}, {0. e^−0.220052 t, 0. e^−0.220052 t, −0.649222 e^−0.220052 t, −0.649222 e^−0.220052 t, 0.396259 e^−0.220052 t}, {0. e^−0.217 t, 0. e^−0.217 t, 0.707107 e^−0.217 t, −0.707107 e^−0.217 t, −117.757 e^−0.217 t}, {0. e^−0.0269482 t, 0. e^−0.0269482 t, 0.0262904 e^−0.0269482 t, 0.0262904 e^−0.0269482 t, 0.999309 e^−0.0269482 t}, {0. e^−0.023915 t, 0.933935 e^−0.023915 t, 0.018699 e^−0.023915 t, 0.018699 e^−0.023915 t, 0.356464 e^−0.023915 t}}

Out[90]= {{0.764082 e^−1.02 t, 0. e^−0.220052 t, 0. e^−0.217 t, 0. e^−0.0269482 t, 0. e^−0.023915 t}, {−0.632845 e^−1.02 t, 0. e^−0.220052 t, 0. e^−0.217 t, 0. e^−0.0269482 t, 0.933935 e^−0.023915 t}, {−0.11508 e^−1.02 t, −0.649222 e^−0.220052 t, 0.707107 e^−0.217 t, 0.0262904 e^−0.0269482 t, 0.018699 e^−0.023915 t}, {−0.0484725 e^−1.02 t, −0.649222 e^−0.220052 t, −0.707107 e^−0.217 t, 0.0262904 e^−0.0269482 t, 0.018699 e^−0.023915 t}, {0.00958186 e^−1.02 t, 0.396259 e^−0.220052 t, −117.757 e^−0.217 t, 0.999309 e^−0.0269482 t, 0.356464 e^−0.023915 t}}

Out[91]//MatrixForm=

$$\begin{pmatrix} 0.764082\, e^{-1.02\,t} & 0.\, e^{-0.220052\,t} & 0.\, e^{-0.217\,t} & 0.\, e^{-0.0269482\,t} & 0.\, e^{-0.023915\,t} \\ -0.632845\, e^{-1.02\,t} & 0.\, e^{-0.220052\,t} & 0.\, e^{-0.217\,t} & 0.\, e^{-0.0269482\,t} & 0.933935\, e^{-0.023915\,t} \\ -0.11508\, e^{-1.02\,t} & -0.649222\, e^{-0.220052\,t} & 0.707107\, e^{-0.217\,t} & 0.0262904\, e^{-0.0269482\,t} & 0.018699\, e^{-0.023915\,t} \\ -0.0484725\, e^{-1.02\,t} & -0.649222\, e^{-0.220052\,t} & -0.707107\, e^{-0.217\,t} & 0.0262904\, e^{-0.0269482\,t} & 0.018699\, e^{-0.023915\,t} \\ 0.00958186\, e^{-1.02\,t} & 0.396259\, e^{-0.220052\,t} & -117.757\, e^{-0.217\,t} & 0.999309\, e^{-0.0269482\,t} & 0.356464\, e^{-0.023915\,t} \end{pmatrix}$$

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Out[92]= {{1. e^−1.02 t + 0. e^−0.220052 t + 0. e^−0.217 t + 0. e^−0.0269482 t + 0. e^−0.023915 t, 0. e^−1.02 t + 0. e^−0.220052 t + 0. e^−0.217 t + 0. e^−0.0269482 t + 0. e^−0.023915 t, 0. e^−1.02 t + 0. e^−0.220052 t + 0. e^−0.217 t + 0. e^−0.0269482 t + 0. e^−0.023915 t, 0. e^−1.02 t + 0. e^−0.220052 t + 0. e^−0.217 t + 0. e^−0.0269482 t + 0. e^−0.023915 t, 0. e^−1.02 t + 0. e^−0.220052 t + 0. e^−0.217 t + 0. e^−0.0269482 t + 0. e^−0.023915 t}, {−0.828243 e^−1.02 t + 0. e^−0.220052 t + 0. e^−0.217 t + 0. e^−0.0269482 t + 0.828243 e^−0.023915 t, 0. e^−1.02 t + 0. e^−0.220052 t + 0. e^−0.217 t + 0. e^−0.0269482 t + 1. e^−0.023915 t, 0. e^−1.02 t + 0. e^−0.220052 t + 0. e^−0.217 t + 0. e^−0.0269482 t + 0. e^−0.023915 t, 0. e^−1.02 t + 0. e^−0.220052 t + 0. e^−0.217 t + 0. e^−0.0269482 t + 0. e^−0.023915 t, 0. e^−1.02 t + 0. e^−0.220052 t + 0. e^−0.217 t + 0. e^−0.0269482 t + 0. e^−0.023915 t}, {−0.150612 e^−1.02 t + 0.0975233 e^−0.220052 t + 0.0435866 e^−0.217 t − 0.0070807 e^−0.0269482 t + 0.0165829 e^−0.023915 t, 0. e^−1.02 t − 0.00982255 e^−0.220052 t + 0. e^−0.217 t − 0.0101992 e^−0.0269482 t + 0.0200218 e^−0.023915 t, 0. e^−1.02 t + 0.492098 e^−0.220052 t + 0.5 e^−0.217 t + 0.00790197 e^−0.0269482 t + 0. e^−0.023915 t, 0. e^−1.02 t + 0.492098 e^−0.220052 t − 0.5 e^−0.217 t + 0.00790197 e^−0.0269482 t + 0. e^−0.023915 t, 0. e^−1.02 t − 0.0258928 e^−0.220052 t + 0. e^−0.217 t + 0.0258928 e^−0.0269482 t + 0. e^−0.023915 t}, {−0.0634389 e^−1.02 t + 0.0975233 e^−0.220052 t − 0.0435866 e^−0.217 t − 0.0070807 e^−0.0269482 t + 0.0165829 e^−0.023915 t, 0. e^−1.02 t − 0.00982255 e^−0.220052 t + 0. e^−0.217 t − 0.0101992 e^−0.0269482 t + 0.0200218 e^−0.023915 t, 0. e^−1.02 t + 0.492098 e^−0.220052 t − 0.5 e^−0.217 t + 0.00790197 e^−0.0269482 t + 0. e^−0.023915 t, 0. e^−1.02 t + 0.492098 e^−0.220052 t + 0.5 e^−0.217 t + 0.00790197 e^−0.0269482 t + 0. e^−0.023915 t, 0. e^−1.02 t − 0.0258928 e^−0.220052 t + 0. e^−0.217 t + 0.0258928 e^−0.0269482 t + 0. e^−0.023915 t}, {0.0125404 e^−1.02 t − 0.0595243 e^−0.220052 t − 7.25862 e^−0.217 t − 0.26914 e^−0.0269482 t + 0.316124 e^−0.023915 t, 0. e^−1.02 t + 0.00599529 e^−0.220052 t + 0. e^−0.217 t − 0.387675 e^−0.0269482 t + 0.38168 e^−0.023915 t, 0. e^−1.02 t − 0.300357 e^−0.220052 t − 83.2667 e^−0.217 t + 0.300357 e^−0.0269482 t + 0. e^−0.023915 t, 0. e^−1.02 t − 0.300357 e^−0.220052 t + 83.2667 e^−0.217 t + 0.300357 e^−0.0269482 t + 0. e^−0.023915 t, 0. e^−1.02 t + 0.0158039 e^−0.220052 t + 0. e^−0.217 t + 0.984196 e^−0.0269482 t + 0. e^−0.023915 t}}

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