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Modeling Pulmonary Tuberculosis for Optimal Control Including Prevention

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Authors' contributions

This work was carried out in collaboration between all authors. Author FAB carried out the system simulations as well as wrote part of the first draft. The remaining authors finished the draft writing and reviewed the simulations and corrected application of the theory. Authors DMMP and AML proposed the model and reviewed the last version of the draft before submitting it. All authors agreed with the revisions and submission of the paper's final version.

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Abstract

It is formulated and analyzed an optimal control problem for the transmission dynamics of the SEIS-like pulmonary tuberculosis (TB) including prevention by means of non-linear differential equations, which are linked to a functional cost. Also, it is established and analyzed the use of optimal control to reduce the latent and infectious populations by using the Pontryaguin's maximum principle (a Hamiltonian function which establishes a problem with numerical limits). After that, simulations of the problem are done. Finally, with an analysis of the viability of strategies to control the disease, we have concluded that the application of effective control measures in the prevention generates a significant decrease in the infected population as well as affects directly the propagation of the infection.

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1 Introduction

Tuberculosis is an infectious disease, transmissible, curable, and usually chronic, with a variable clinical manifestation. It is produced by *Mycobacterium tuberculosis* (*M. tuberculosis*), which has a wide distribution around the world. This disease is considered a public health care problem, and together with the human immunodeficiency virus (HIV), are the main causes of death around the world. In 2014 were estimated 9.6 million of new TB cases, being 5.4 million men, 3.2 women, and 1.0 million children. Also, 1.5 million deaths were caused by TB, from where: 1.1 million persons being HIV negative and 0.4 million HIV positive (~890,000 men, 480,000 women, and 140 children). Using this information (from 2014) and previously reported diagnostics, we are able to estimate that around 9 million cases are produced by tuberculosis and ~1.7 million people die because of it [1].

This disease can affect all organs but the lungs are the most susceptible [2]. In medical terms, TB can be acquired through inhalation of water drops generated by a cough or sneeze of an infectious person. The resulting pulmonary infection is the so called primary TB. Most of the people recover from primary tuberculosis without evidence of the disease. The infection can remain latent for several years.

Lung tuberculosis may be the first signal of an immune dysfunction associated to human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS). Co-infection with this disease may be the first cause of death in infected persons. For instance, one of each ten persons will develop active tuberculosis within the second year after being diagnosed with HIV [3].

On the other hand, control can be understood as the process through which the influence on the behavior of a dynamical system is exerted, namely, a system which changes in time to achieve a previous stage [4]. Some studies about mathematical modeling using optimal control theory have appeared. Thereby, Nanda, Moore, and Lenhart [5] have considered a mathematical model to simulate drug therapy for myelogenous leukemia in patients over a fixed time horizon. The dynamics of the infection is analyzed with an ordinary differential equations system which describe the interaction between virgin-T cells, effector-T cells and cancer cells in a hypothetical patient. Yan, Zou [6] discussed the applications of optimal and suboptimal controls to a SEQIJR SARS model through the Pontryaguin's maximum principle. Also, results show that the proposed suboptimal control can drive to interpretations near the optimal control, but with easier strategies for long periods. Additionally, Rodrigues, Monteiro, and Torres [7] have proposed that the functional cost depends not only on the medical treatment of the infected persons, but also in the cost related to education campaigns and sanitation. They refer that computational tools allow to obtain solutions to this kind of problems in a short time and low cost. Sadiq, Khan, Islam, Zaman, and Jung have considered a model for leptospirosis epidemic with nonlinear saturated incidence through the application of optimal control techniques to eradicate the infection in humans [8].

Moreover, Trauer, Denholm, and McBryde proposed a model for the tuberculosis transmission in highly endemic regions of the Asia-Pacific, identifying that without reinfection during the latent stage, the model could not be calibrated to the estimated incidence rate, moderate costs and lower value of R_0. MDR-TB is transformed in the dominant strain at equilibrium [9]. Taufik, Lestari, and Septiarini, have studied a mathematical model for tuberculosis disease including vaccination in a VEIT model, demonstrating the equilibrium point and stability an endemic model taking into account exogenous reinfection [10].

2 Model

The implemented SEIS model interprets the TB transmission dynamics considering the following assumptions: persons which enter into the susceptible group (S) at a proportional rate of the population by birth or loss of immunity, after they turn into carriers. In latent stage (E), they do not show any symptoms and can not infect anybody. Also, the infected persons can not be immune to that disease.

The variables and parameters are: $x(t)$: average number of susceptible people to TB, $w(t)$: average number of people in latent stage with TB, $y(t)$: average number of infected people, $N(t)$: total population, β: TB transmission probability, θ: rate of people which develops infection, ω: rate of infectious people coming back to the susceptible stage, $l = \frac{1}{\mu+\theta}$: latent period, $i = \frac{1}{\mu+\omega}$: PTB infectious period, $p = \frac{1}{\mu}$: life expectancy. Due to the constant increase of new TB cases (latent and infected), it is considered an extension of the initial model (with control) to decrease the new infections, see Fig. 1.

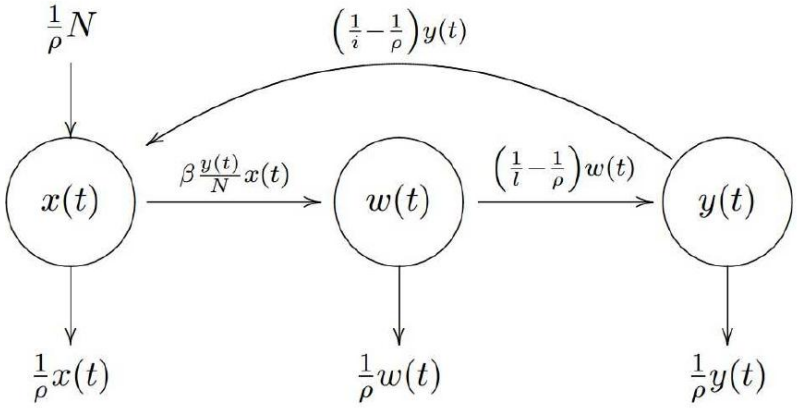

Fig. 1. Transmission dynamics of the PTB

The dynamics is interpreted with the following differential equations system:

$$\frac{dx(t)}{dt} = \frac{1}{\rho}N + \left(\frac{1}{i}-\frac{1}{\rho}\right)y(t) - \beta\frac{y(t)}{N}x(t) - \frac{1}{\rho}x(t) \quad (1)$$

$$\frac{dw(t)}{dt} = \beta\frac{y(t)}{N}x(t) - \frac{1}{l}w(t) \quad (2)$$

$$\frac{dy(t)}{dt} = \left(\frac{1}{i}-\frac{1}{\rho}\right)w(t) - \frac{1}{i}y(t) \quad (3)$$

where $i, l, \rho > 1, 0 < \beta < 1$ and $N(t) = x(t) + w(t) + y(t)$ constant, taking into account $\frac{dN}{dt} = \frac{dx}{dt} + \frac{dw}{dt} + \frac{dy}{dt}$ and initial conditions $x(0) = x_0, w(0) = w_0, y(0) = y_0$. The epidemiological sense regions of the disease is:

$$\Omega = \{(x, y, w) \in R_+^3 : 0 < x \leq N, 0 \leq w, y < N\}$$

To add the optimal control in infected people and the relationship with the cost functional, we propose:

$$J(x(t), \boldsymbol{u}(t)) = \frac{1}{2}\int_0^\tau [\gamma_1 w^2(t) + \gamma_2 u^2(t)]dt$$

where

$u = u(t)$: control of the latent population w(t)
γ: 1, 2 cost (Colombian pesos)
τ: final fixed time
$x = [x(t), w(t), y(t)]$: state variables.

Now we look for an optimal control $\bar{u}$, such that

$$J(x, \bar{u}) = \min_{\Omega} J(x, u)$$

where $\Omega = \{u | u$ u an optimal is measurable in $[0, \tau]$ and $0 \leq u \leq 1\}$

3 Application of the Pontryaguin's Maximum

First we define G corresponding to the integral of the functional

$$G(w, u) = \frac{1}{2}[\gamma_1 w^2 + \gamma_2 u^2]$$

which drives to the cost problem

$$J(u) = \psi(x(\tau))$$

For fixed τ, x is the state variables vector and u is the control vector.

The Hamiltonian function is

$$H = \varphi^t F + \epsilon G(w, u)$$

where φ is an adjunct vector and F is the vector function of the state variables and $\epsilon > 0$

$$F = \begin{pmatrix} \beta\frac{1}{\rho}N + \left(\frac{1}{i} - \frac{1}{\rho}\right)y(t) - \beta(1-u)\frac{y(t)}{N}x(t) - \frac{1}{\rho}x(t) \\ \beta(1-u)\frac{y(t)}{N}x(t) - \frac{1}{l}w(t) \\ \left(\frac{1}{i} - \frac{1}{\rho}\right)w(t) + \frac{1}{i}y(t) \end{pmatrix}, \quad \varphi = \begin{pmatrix} \varphi_1 \\ \varphi_2 \\ \varphi_3 \end{pmatrix}$$

For $\bar{u}$, x have sense, and $0 \leq \bar{u} \leq 1$ is required. Accordingly, the Hamitonian function is:

$$\begin{aligned} H(x, u, \varphi) = \varphi_1 &\left[\frac{1}{\rho}N + \left(\frac{1}{i} - \frac{1}{\rho}\right)y(t) - \beta(1-u)\frac{y(t)}{N}x(t) - \frac{1}{\rho}x(t)\right] \\ &+ \varphi_2\left(\beta(1-u)\frac{y(t)}{N}x(t) - \frac{1}{l}w(t)\right) + \varphi_3\left[\left(\frac{1}{i} - \frac{1}{\rho}\right)w(t) + \frac{1}{i}y(t)\right] \\ &+ \frac{1}{2}\epsilon(\gamma_1 w^2 + \gamma_2 u^2) + v_1 u + v_2(1-u) \end{aligned}$$

with $v_i(t), i = 1,2$ penalization multipliers, such that $v_i(t) > 0$ and

$$v_1(t)u = 0, \quad v_2(t)(1-u) = 0 \tag{4}$$

Applying the first order condition $\frac{dH}{du} = 0$ we obtain

$$\frac{dH}{du} = \frac{\beta \frac{y(t)}{N} x(t) \varphi_2 - \beta \frac{y(t)}{N} x(t) \varphi_1 - v_1 + v_2}{\epsilon \gamma_2}$$

where

$$u(t) = \frac{\beta \frac{y(t)}{N} x(t)(\varphi_2 - \varphi_1)}{\epsilon \gamma_2} \quad . \tag{5}$$

If $0 < u(t) < 1$ and taking into account (4), we have $v_1 = 0$ and $v_1 = 0$

Similarly, if $u = 0$, then $v_1 = 0$ and $v_2 = 0$, therefore

$$0 = \frac{\beta \frac{y(t)}{N} x(t)(\varphi_2 - \varphi_1) v_1}{\epsilon \gamma_2}$$

namely, $v_1(t) = \beta \frac{y(t)}{N} x(t)(\varphi_2 - \varphi_1)$.

Finally, if $u = 1$ so $v_1 = 0$ and $v_2 \geq 0$, for that reason

$$1 = \frac{\beta \frac{y(t)}{N} x(t)(\varphi_2 - \varphi_1) + v_2}{\epsilon \gamma_2}$$

after that, $v_2(t) = \epsilon \gamma_2 + \beta \frac{y(t)}{N} x(t)(\varphi_2 - \varphi_1)$

then we obtain

$$\bar{u}(t) = \begin{cases} 0 \quad si \quad \frac{\beta \frac{y(t)}{N} x(t)(\varphi_2 - \varphi_1)}{\epsilon \gamma_2} < 0 \\ \frac{\beta \frac{y(t)}{N} x(t)(\varphi_2 - \varphi_1)}{\epsilon \gamma_2} \quad si \quad 0 < u(t) < 1 \\ 1 \quad si \quad \frac{\beta \frac{y(t)}{N} x(t)(\varphi_2 - \varphi_1)}{\epsilon \gamma_2} > 1 \end{cases} \tag{6}$$

So, the control can be characterized by

$$\bar{u}(t) = min\left(max\left(0, \frac{\beta \frac{y(t)}{N} x(t)(\varphi_2 - \varphi_1)}{\epsilon \gamma_2} \right), 1 \right)$$

and the conjugated system (adjunct) is

$$\frac{d\varphi}{dt} = -H_x(x, u, \varphi)$$

with the terminal condition $\varphi(\tau) = \phi(\boldsymbol{x}(\tau))$, with

$$\frac{d\varphi_1}{dt} = -H_x, \quad \frac{d\varphi_2}{dt} = -H_w, \quad \frac{d\varphi_3}{dt} = -H_s$$

so, the system is as follows

$$\frac{d\varphi_1}{dt} = -\beta(1-u)\frac{y(t)}{N}\varphi_1 - \frac{1}{\rho}\varphi_1 + \beta(1-u)\frac{y(t)}{N}\varphi_2 \equiv g_1(x,\varphi,u) \tag{7}$$

$$\frac{d\varphi_2}{dt} = \frac{1}{l}\varphi_2 - \left(\frac{1}{l}-\frac{1}{\rho}\right)\varphi_3 - \epsilon\gamma_1 w(t) \equiv g_2(x,\varphi,u) \tag{8}$$

$$\frac{d\varphi_3}{dt} = -\left(\frac{1}{i}-\frac{1}{\rho}\right)\varphi_1 - \frac{1}{i}\varphi_3 \equiv g_3(x,\varphi,u) \tag{9}$$

and terminal conditions $\varphi_1(\tau) = 0, \varphi_2(\tau) = 0, \varphi_3(\tau) = 0$.

4 Boundary Problem

It is formed by the state variables of the PTB dynamics, their respective initial conditions, conjugated system, terminal conditions and control:

$$\begin{cases}
\frac{dx(t)}{dt} = \frac{1}{\rho}N + \left(\frac{1}{i}-\frac{1}{\rho}\right)y(t) - \beta(1-u)\frac{y(t)}{N}x(t) - \frac{1}{\rho}x(t) \\
\frac{dw(t)}{dt} = \beta\frac{y(t)}{N}x(t) - \frac{1}{l}w(t) \\
\frac{dy(t)}{dt} = \left(\frac{1}{i}-\frac{1}{\rho}\right)w(t) - \frac{1}{i}y(t) \\
\frac{d\varphi_1}{dt} = -\beta(1-u)\frac{y(t)}{N}\varphi_1 - \frac{1}{\rho}\varphi_1 + \beta(1-u)\frac{y(t)}{N}\varphi_2 \\
\frac{d\varphi_2}{dt} = \frac{1}{l}\varphi_2 - \left(\frac{1}{l}-\frac{1}{\rho}\right)\varphi_3 - \epsilon\gamma_1 w(t) \\
\frac{d\varphi_3}{dt} = -\left(\frac{1}{i}-\frac{1}{\rho}\right)\varphi_1 - \frac{1}{i}\varphi_3 \equiv g_3(x,\varphi,u) \\
x(0) = x_0, \quad w(0) = w_0, \quad y(0) = y_0 \\
\varphi_1(\tau) = \varphi_t, \quad \varphi_2(\tau) = \varphi_{2t}, \quad \varphi_3(\tau) = \varphi_{3t} \\
\bar{u}(t) = min\left(max\left(0, \frac{\beta\frac{y(t)}{N}x(t)(\varphi_2-\varphi_1)}{\epsilon\gamma_2}\right), 1\right)
\end{cases}$$

5 Numerical Solution to the Boundary Problem

It is well known that the solution to the boundary problem for a nonlinear equations system with high dimensions is not easy. Then, the objective is to find an approximate solution to the system in the range $[0,\tau]$ by solving the problem for $\tau = 1$ and using this solution as an initial approximation to resolve $\tau = \tau + \epsilon$ with ϵ being small enough.

The simulation of the boundary problem was carried out using the MATLAB software. The parameters values used for the simulation were estimated previously and with initial conditions, $x(0) = 400,\ w(0) = 300$and $y(0) = 35$, indicating that the infectious outbreak begins with the introduction of at least one infected person to the system.

Figs. 2 and 3 show the values for $\gamma_i, i = 1,2$ used in the simulation. The state variables behavior without and with control are depicted with a dotted and continuous line, respectively. Additionally, controls are shown for each infected population and the basic reproduction number as function of time (in weeks).

In Fig. 2, it is possible to see that applying an optimal control to the prevention of the susceptible and latent populations induces a great change to the controls, mainly to the susceptible population, which stabilizes in around 60 weeks. For the latent population, it can be observed that control has variability, while in the infected population, control is shown since week 30. From these results, it is concluded that applying campaigns to the susceptible population inhibits the occurrence of latent and new infection cases due to stabilization.

In Fig. 3 can be observed that using optimal control does not present significant changes in the susceptible and latent populations. For the latent population a change occurs at week 40, while, the infected population changes due to control remain relatively stable. Therefore, control applied to PTB is necessary.

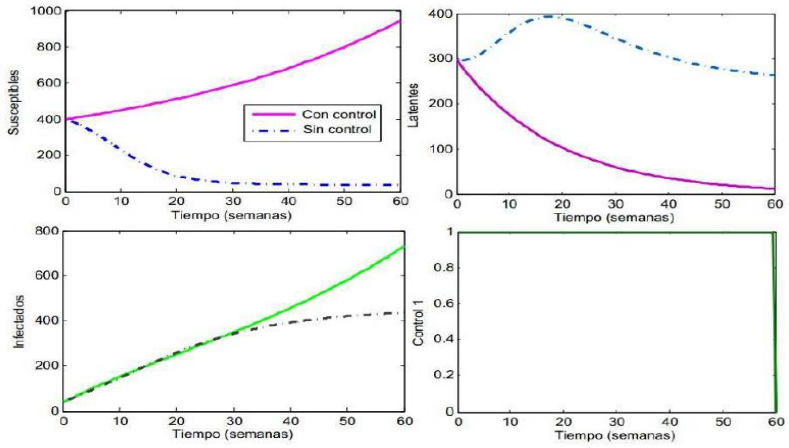

Fig. 2. Optimal control problem with intermediate costs in the control $u, \gamma_1 = 1, \gamma_2 = 1$

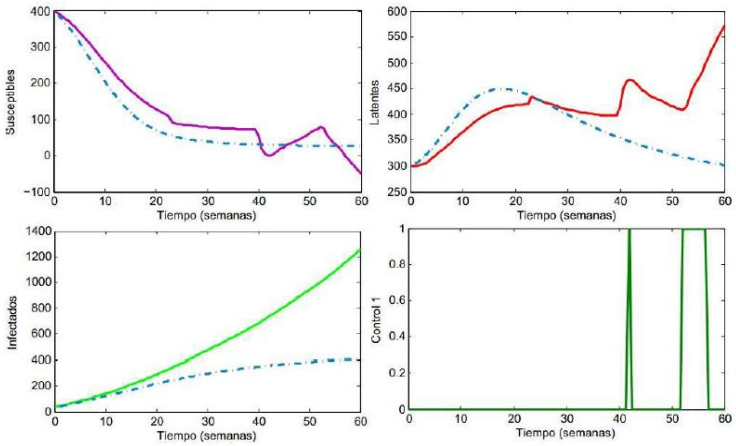

Fig. 3. Optimal control problem with intermediate costs in the control $u, \gamma_1 = 1, \gamma_2 = 0.1$

6 Conclusions

The application of effective control measures for TB prevention generates a significant decrease of the infected cases and directly impact the spread of the infection. Then, the introduction of control by prevention is a valuable measure for health care institutions to reduce the spread of PTB in the population. Through specific campaigns for the susceptible population, such as, vaccination BCG, epidemiologic surveillance, and attention to priority groups, drives to a constant decrease of the PTB spread. The effectiveness of the control will be reflected in the infected population. In this context, the optimal control problem with the exposed considerations contributes to the comprehension and understanding of the TB incidence.

Competing Interests

Authors have declared that no competing interests exist.

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