CONSTRAINED OPTIMAL CONTROL FOR A MULTI-GROUP DISCRETE TIME INFLUENZA MODEL

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In April of 2009 the World Health Organization (WHO) announced the emergence of a novel strain of A-H1N1 influenza.

Continuous time models have been used to study influenza outbreaks and the impact of different control policies.

There is a recent interest in the study of discrete disease transmission models.

We introduce a novel discrete time influenza model, and formulate a discrete optimal control problem including social distancing and antiviral treatment as control policies.
Motivation

- In April of 2009 the World Health Organization (WHO) announced the emergence of a novel strain of A-H1N1 influenza.
- Continuous time models have been used to study influenza outbreaks and the impact of different control policies.
- There is a recent interest in the study of discrete disease transmission models.
- We introduce a novel discrete time influenza model, and formulate a discrete optimal control problem including social distancing and antiviral treatment as control policies.
We propose the following discrete model:

\[
S_{t+1} = S_t (1 - G_t) \\
I_{t+1} = S_t G_t + (1 - \tau_t) (1 - \sigma_1) (1 - \delta) I_t \\
T_{t+1} = (1 - \sigma_2) T_t + \tau_t (1 - \sigma_1) (1 - \delta) I_t \\
R_{t+1} = R_t + \sigma_1 (1 - \delta) I_t + \sigma_2 T_t
\]  

(1)

where

\[
G_t = \rho (1 - x_t) \frac{I_t + \epsilon T_t}{N_t},
\]  

(2)
We propose the following discrete model:

\begin{align*}
S_{t+1} & = S_t (1 - G_t) \\
I_{t+1} & = S_t G_t + (1 - \tau_t) (1 - \sigma_1) (1 - \delta) I_t \\
T_{t+1} & = (1 - \sigma_2) T_t + \tau_t (1 - \sigma_1) (1 - \delta) I_t \\
R_{t+1} & = R_t + \sigma_1 (1 - \delta) I_t + \sigma_2 T_t
\end{align*} \tag{1}

where

\[ G_t = \rho (1 - x_t) \frac{I_t + \epsilon T_t}{N_t}, \tag{2} \]
Optimal Control Problem

- Our goal is to minimize the number of infected individuals over a finite time interval $[0, n]$ by using a minimal effort on treatment and social distancing.

- The problem can be written as:

$$\text{minimize } \frac{1}{2} \sum_{t=0}^{n-1} (B_1 I_t^2 + B_2 x_t^2 + B_3 \tau_t^2)$$

subject to Model (1)

where Model (1) is given by

$$S_{t+1} = S_t (1 - G_t)$$

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Group-Structured Model

Age-Group 1

\[ S_1 \rightarrow I_1 \rightarrow R_1 \]
\[ T_1 \]

Age-Group 2

\[ S_2 \rightarrow I_2 \rightarrow R_2 \]
\[ T_2 \]

Age-Group 3

\[ S_3 \rightarrow I_3 \rightarrow R_3 \]
\[ T_3 \]
Group-Structured Model

Age-Group 1

\[ S_1 \rightarrow I_1 \rightarrow R_1 \]
\[ T_1 \]

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\[ T_1 \]

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\[ T_3 \]
Model Formulation

- The model is given by the following system of difference equations:

\[
\begin{align*}
S_i(t + 1) &= S_i(t)(1 - G_i(t)) \\
I_i(t + 1) &= S_i(t)G_i(t) + (1 - \tau_i(t))(1 - \sigma_i)l_i(t) \\
T_i(t + 1) &= (1 - \sigma) T_i(t) + \tau_i(t)(1 - \sigma_i)I_i(t) \\
R_i(t + 1) &= R_i(t) + \sigma_i I_i(t) + \sigma T_i(t).
\end{align*}
\]

where

\[
G_i = \rho_i \sum_{j=1}^{m} \left( q_j(1 - x_j(t)) \left( \frac{l_j(t) + \epsilon_j T_j(t)}{N_j} \right) \right),
\]

and \( q_i \) (proportionate mixing) is given by:

\[
q_{ij} = q_j = \frac{C_j N_j}{\sum_{k=1}^{m} C_k N_k}.
\]
If \( n \) denotes the final time, the optimal control problem is formulated as:

\[
\min \frac{1}{2} \sum_{i=1}^{m} \sum_{t=0}^{n-1} (B_{li}l_i(t)^2 + B_{xi}x_i(t)^2 + B_{\tau_i}\tau_i(t)^2)
\]

s.t. Model (4).
If \( n \) denotes the final time, the optimal control problem is formulated as:

\[
\text{minimize} \quad \frac{1}{2} \sum_{t=0}^{n-1} \left( B_1 l_t^2 + B_2 x_t^2 + B_3 \tau_t^2 \right)
\]

subject to Model (1)
If $n$ denotes the final time, the **optimal control problem** is formulated as:

$$
\min \frac{1}{2} \sum_{i=1}^{m} \sum_{t=0}^{n-1} \left( B_{l_i} l_i(t)^2 + B_{x_i} x_i(t)^2 + B_{\tau_i} \tau_i(t)^2 \right)
$$

s.t. Model (4).
We want to consider the case of **limited resources**.

An isoperimetric constraint is included:

\[
\sum_{t=0}^{n-1} (\tau_i(t) l_i(t)) = k
\]  

(6)
When Resources are Limited

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Methodology

Pontryagin’s Maximum Principle

- Classical result that provides the necessary conditions for finding an optimal solution (1961).
- There are many applications to optimal control problems in epidemiology.

Interior Point Methods

- IPM were introduced by Karmarkar in 1984 for solving linear programming problems.
- There is few evidence of interior-point methods applied to epidemiological problems.
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- IPM were introduced by Karmarkar in 1984 for solving linear programming problems.
- There is few evidence of interior-point methods applied to epidemiological problems.
The Hamiltonian at time $t$ is defined as:

$$H_t = \frac{1}{2} \left( B_1 I_t^2 + B_2 x_t^2 + B_3 \tau_t^2 \right) + \sum_{i=1}^{4} \lambda_{t+1}^i y_{t+1}^i .$$

The necessary conditions are given by:

- The adjoint equation:
  $$\lambda_t^i = \frac{\partial H_t}{\partial y_t^i} ,$$

- The transversality condition:
  $$\lambda_{n}^i = 0 ,$$

- The optimality condition:
  $$\frac{\partial H_t}{\partial x_t} = 0 \quad \text{and} \quad \frac{\partial H_t}{\partial \tau_t} = 0 .$$
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$$n-1 \sum_{t=0}^{n-1} \frac{1}{2} \left( B_1 l_t^2 + B_2 x_t^2 + B_3 \tau_t^2 \right)$$

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- The necessary conditions are given by:
  - The adjoint equation:
    
    $$\lambda_t^i = \frac{\partial H_t}{\partial y_t^i},$$
    
    $$\lambda_t^1 = \frac{\partial H_t}{\partial S_t}, \quad \lambda_t^2 = \frac{\partial H_t}{\partial I_t}, \quad \lambda_t^3 = \frac{\partial H_t}{\partial T_t},$$
  
  - The transversality condition:
    
    $$\lambda_n^i = 0,$$
  
  - The optimality condition:
    
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The Optimal Control Problem is posed as a non-linear programming problem:

$$\min f(y)$$
$$\text{s.t. } E(y) = 0, \quad 0 \leq y \leq y_{\text{max}}.$$  \hfill (7)

Where

$$y = (S_1(1), I_1(1), T_1(1), \tau_1(0), x_1(0), \ldots, S_1(n), I_1(n), T_1(n), \tau_1(n-1), x_1(n-1), \ldots, S_m(1), I_m(1), T_m(1), \tau_m(0), x_m(0), \ldots, S_m(n), I_m(n), T_m(n), \tau_m(n-1), x_m(n-1)))_{5 \cdot n \cdot m}$$

$m$ is the number of groups and $n$ is the final time.
The Optimal Control Problem is posed as a non-linear programming problem:

\[
\begin{align*}
\min & \quad f(y) \\
\text{s.t} & \quad E(y) = 0, \\
& \quad 0 \leq y \leq y_{\text{max}}.
\end{align*}
\]

(7)

Where

\[
y = (S_1(1), l_1(1), T_1(1), \tau_1(0), x_1(0), \ldots, \\
S_1(n), l_1(n), T_1(n), \tau_1(n-1), x_1(n-1), \ldots, \\
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S_m(n), l_m(n), T_m(n), \tau_m(n-1), x_m(n-1))_{5 \cdot n \cdot m}
\]

\(m\) is the number of groups and \(n\) is the final time.
The objective functional is given by:

\[ f(y) = \frac{1}{2} \sum_{i=1}^{m} \sum_{t=0}^{n-1} (B_{li} l_i(t)^2 + B_{xi} x_i(t)^2 + B_{\tau_i} \tau_i(t)^2) \]

The objective functional can be written as:

\[ f(y) = \frac{1}{2} \sum_{i=1}^{m} (B_{li} \| \tilde{l}_i \|^2 + B_{\tau_i} \| \tau_i \|^2 + B_{x_i} \| x_i \|^2) , \]

The equality constraint is given by:

\[ E(y) = \begin{pmatrix} E_1 \\ E_2 \\ \vdots \\ E_m \end{pmatrix}_{3 \times n \times m} \]
The objective functional can be written as:

\[ f(y) = \frac{1}{2} \sum_{i=1}^{m} \left( B_l \| \tilde{I}_i \|^2 + B_{\tau_i} \| \tau_i \|^2 + B_x \| x_i \|^2 \right), \]

The equality constraint is given by:

\[
E(y) = \begin{pmatrix}
E_1 \\
E_2 \\
\vdots \\
E_m
\end{pmatrix}_{3 \cdot n \cdot m}
\]
The objective functional can be written as:

\[ f(y) = \frac{1}{2} \sum_{i=1}^{m} \left( B_{l_i} \| \tilde{l}_i \|^2 + B_{\tau_i} \| \tau_i \|^2 + B_{x_i} \| x_i \|^2 \right), \]

\[ l_i = (l_i(1), l_i(2), \ldots, l_i(n)) \]

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\[
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\]

\[
\tilde{I}_i = (I_i(0), I_i(2), \ldots, I_i(n - 1))
\]

The equality constraint is given by:

\[
E(y) = \begin{pmatrix}
E_1 \\
E_2 \\
\vdots \\
E_m
\end{pmatrix}
\]

\[
E(y)_{3 \cdot n \cdot m}
\]
The objective functional can be written as:

\[ f(y) = \frac{1}{2} \sum_{i=1}^{m} \left( B_{I_i} \| \tilde{I}_i \|^2 + B_{\tau_i} \| \tau_i \|^2 + B_{x_i} \| x_i \|^2 \right) , \]

The equality constraint is given by:

\[ E(y) = \begin{pmatrix} E_1 \\ E_2 \\ \vdots \\ E_m \end{pmatrix} \in \mathbb{R}^{3 \cdot n \cdot m} \]
Equality constraint

Where $E_i \in \mathbb{R}^{3 \cdot n \cdot m}$ is given by:

$$E_i(y) = \begin{pmatrix}
S_i(1) - S_i(0)(1 - G_i(0)) \\
I_i(1) - S_i(0)G_i(0) - (1 - \tau_i(0))(1 - \sigma_1)I_i(0) \\
T_i(1) - (1 - \sigma)T_i(0) - \tau_i(0)(1 - \sigma_1)I_i(0) \\
\vdots \\
S_i(n) - S_i(n - 1)(1 - G_i(n - 1)) \\
I_i(n) - S_i(n - 1)G_i(n - 1) - (1 - \tau_i(n - 1))(1 - \sigma_n)I_i(n - 1) \\
T_i(n) - (1 - \sigma)T_i(n - 1) - \tau_i(n - 1)(1 - \sigma_n)I_i(n - 1)
\end{pmatrix} = 0$$
For the isoperimetric constraint

\[
\sum_{i=1}^{m} \left( \sum_{t=0}^{n-1} (\tau_i(t) l_i(t)) \right) = k,
\]

By using Pontryagin’s Maximum Principle, we define a new state variable:

\[
z_{t+1} = z_t + \sum_{i=1}^{m} \left( \sum_{t=0}^{n-1} (\tau_i(t) l_i(t)) \right)
\]

with \( z_0 = 0 \) and \( z_n = k \)
For the isoperimetric constraint

\[ \sum_{i=1}^{m} \left( \sum_{t=0}^{n-1} (\tau_i(t) l_i(t)) \right) = k \iff \tau_1^T \tilde{I}_1 + \cdots + \tau_m^T \tilde{I}_m - k = 0. \]

By using Pontryagin’s Maximum Principle, we define a new state variable:

\[ z_{t+1} = z_t + \sum_{i=1}^{m} \left( \sum_{t=0}^{n-1} (\tau_i(t) l_i(t)) \right) \]

with \( z_0 = 0 \) and \( z_n = k \)
Isoperimetric Constraint using Interior Point Methods

By using Pontryagin’s Maximum Principle, we define a new state variable:

\[ z_{t+1} = z_t + \sum_{i=1}^{m} \left( \sum_{t=0}^{n-1} (\tau_i(t)l_i(t)) \right) \]

with \( z_0 = 0 \) and \( z_n = k \)

For Interior Point Methods the equality constraint was:

\[ E(y) = \begin{pmatrix} E_1 \\ E_2 \\ \vdots \\ E_m \end{pmatrix}_{3 \cdot n \cdot m} \]
By using Pontryagin’s Maximum Principle, we define a new state variable:

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For Interior Point Methods we modify the Equality Constraint as:

\[
E(y) = \begin{pmatrix}
E_1 \\
E_2 \\
\vdots \\
E_m \\
\tau_1^T\tilde{I}_1 + \cdots + \tau_m^T\tilde{I}_m - k
\end{pmatrix}
\]
Numerical Results

Core Problem

- Comparison Between FB and IPM.
- Implication of Strategies.

Group-Structured Model

- Pandemic Influenza.
- Seasonal Influenza.

Limited Resources
Numerical Results

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Limited Resources
We compare three different strategies for solving our optimal control problem:

- **Strategy 1**: Only social distancing.
- **Strategy 2**: Only treatment.
- **Strategy 3**: Social distancing and treatment.

Comparison between **Forward-Backward** and **Interior-Point methods**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>FB # of iterations</th>
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<th>IPM # of iterations</th>
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<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>0.67997</td>
<td>15</td>
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<td>2</td>
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<td>12</td>
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<td>0.30423</td>
<td>23</td>
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where

$$f = \frac{1}{2} \left( B_1 \| \tilde{I} \|^2 + B_2 \| \tau \|^2 + B_3 \| x \|^2 \right).$$
Numerical Solution: Comparison between FB and IPM

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<td>12</td>
<td>0.33016</td>
</tr>
<tr>
<td>3</td>
<td>87</td>
<td>0.30423</td>
<td>23</td>
<td>0.30092</td>
</tr>
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where

$$f = \frac{1}{2} \left( B_1 \| \tilde{I} \|^2 + B_2 \| \tau \|^2 + B_3 \| x \|^2 \right).$$
Basic Reproductive Number $R_0$

Number of secondary cases produced by a single infected individual in a population of susceptible individuals.

In our model

$$R_0 = \sum_{i=1}^{m} \frac{\rho_i q_i}{1 - (1 - \sigma_i)}.$$
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- Strategy 3 yields the highest reduction of the final epidemic size.
- For single policies Strategy 1 has more impact in the reduction of the final epidemic size than Strategy 2.
The final epidemic size is reduced under the implementation of each strategy.

For Strategy 3 we get a reduction of 32%.

The reduction for Strategies 1 and 2 are 28% and 25%, respectively.
- The total Population is divided into three subgroups.
- We consider two scenarios:
  - Influenza H1N1.
  - Seasonal Influenza.
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Population Characteristics

Characteristics of each group in the case of H1N1 influenza:

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<td>0 – 19</td>
<td>27%</td>
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<td>3</td>
<td>65 and more</td>
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Characteristics of each group in the case of seasonal influenza:

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- The biggest effort both in treatment and social distancing has to be implemented in the highest risk Group 2.
- The final epidemic size is reduced by 7%, 6% and 8% in Groups 1, 2 and 3 respectively.
The biggest effort has to be applied both in the highest activity level Group 1 and the larger population size Group 2.

The implementation of policies reduce the final epidemic size by 13%, 14%, and 11% in Groups 1, 2 and 3 respectively.
A high number of doses has to be used in Group 2.
This number is higher in the case of influenza H1N1 than in the case of seasonal influenza.
For Groups 1 and 3 the number of doses is higher for seasonal influenza than for H1N1.
Numerical Results for Limited resources

For different values of $k$ (treatment doses):

- Low value of $R_0$
- High value of $R_0$
For small values of \( k \), the optimal control solution requires the implementation of highest values of treatment at the beginning of the epidemic until the resources are expended.
The optimal control solution requires the implementation of higher values of treatment than the ones for an small value of $R_0$. The final epidemic size is reduced by 11%, 7%, 5%, and 1% in each case.
We formulated discrete group-structured influenza model. Previous research on influenza models including group structure have been done only in the continuous case.

We introduced treatment and social distancing as control policies and we formulated optimal control problems.

The optimal control problems was posed as a non-linear programming problem.

We solved the problems by using primal-dual interior-point method for different strategies and considering different scenarios.

In the case of limited resources, IPM allowed to include isoperimetric constraint in a very simple way.
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  - Generalized Least Squares (GLS)
- Parameter Estimation Using Real Data
  - Influenza Outbreak in a Border School, United Kingdom
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Parameter values may be estimated in order to have a more realistic approach and to compare the model predictions with real data.

The parameters in the model can be represented as a vector $\theta \in \mathbb{R}^m$ and the real data can be expressed as a vector $y \in \mathbb{R}^n$.

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Ordinary Least Squares (OLS)

We want to find

\[ \theta_{\text{OLS}} = \min \sum_{i=1}^{n} (Y_i - f(t_i, \theta_0))^2 = \min \sum_{i=1}^{n} R_i^2. \]

therefore we solve:

\[ \sum_{i=1}^{n} [(Y_i - f(t_i, \theta_0)) \nabla f(t_i, \theta_0)] = 0. \]
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By using the Gauss-Newton method, let $J$ be the Jacobian of $f$, the procedure is summarized in Algorithm 1:

**Algorithm 1 OLS Algorithm**

1: Given an initial point $\theta_{init}$.
2: for $k = 0, 1, 2 \ldots$ until convergence do
3:   Gauss-Newton step
      $$J_k^T J_k \Delta \theta = -J_k^T R_k$$
4:   Update $\theta = \theta + \Delta \theta$.
5:   Check convergence, if $||J_k^T R_k|| < \epsilon$, break,
6:   end for
We need to solve the equation:

\[ \sum_{i=1}^{n} w_i \left( Y_i - f(t_i, \theta_{GLS}) \right) \nabla f(t_i, \theta_{GLS}) = 0 \]

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We also use the Gauss-Newton method. Let be $W = \text{diag}(w_1, w_2, \ldots, w_n)$ then by changing Step 3 in the OLS Algorithm, we obtain the GLS Algorithm:

**Algorithm 2 GLS Algorithm**

1. Given an initial point $\theta_{\text{init}}$.  
2. for $k = 1, 2, \ldots$ until convergence do  
3. Gauss-Newton step  
   \[ J_k^T W_k J_k \Delta \theta = -J_k^T W_k R_k. \]  
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We apply the methodology on two different problems:
- Influenza outbreak in a border school United Kingdom.
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In 1978 an influenza outbreak was reported in a border school in the United Kingdom.

We use a discrete SIR model to describe this outbreak:

\[
\begin{align*}
S_{t+1} &= S_t G_t \\
I_{t+1} &= S_t (1 - G_t) + (1 - \sigma) I_t \\
R_{t+1} &= R_t + \sigma I_t
\end{align*}
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where

\[
G_t = e^{-\beta \frac{I_t}{N}}
\]
In 1978 an influenza outbreak was reported in a border school in the United Kingdom. The number of infected individuals was recorded daily.

We use a discrete SIR model to describe this outbreak:

\[
\begin{align*}
S_{t+1} &= S_t - G_t I_t + \left(1 - \sigma\right) I_t \\
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where

\[ G_t = e^{-\beta \frac{I_t}{N}} \]  \hspace{0.5cm} (10)
The total population \((N)\) is 763 individuals and the final time is 14 days.

By using OLS and GLS we estimate the susceptibility \((\beta)\) and the probability that an infectious individual get recovered \((\sigma)\).

The function \(f\) is given by the daily number of infected individuals, From the previous model:

\[
f_i = S_i (1 - G_i) + (1 - \sigma) l_i
\]

for \(i = 1, 2, ..., n\), and \(G_i\) given by \((10)\).
As an estimate we take an average of the values that we obtain by using OLS and GLS; hence, $\beta = 3.0771 \pm 0.1429$ and $\sigma = 0.27 \pm 0.05$. 

![Graph showing numerical results using OLS and GLS](image-url)
As an estimate we take an average of the values that we obtain by using OLS and GLS; hence, \( \beta = 3.0771 \pm 0.1429 \) and \( \sigma = 0.27 \pm 0.05 \).
the model is given by the system of difference equations:

\[
\begin{align*}
S_{t+1} &= S_t (1 - G_t) \\
A_{t+1} &= q S_t G_t + (1 - \sigma_1) (1 - \delta) A_t \\
I_{t+1} &= (1 - q) S_t G_t + (1 - \tau_t) (1 - \sigma_1) (1 - \delta) I_t \\
T_{t+1} &= (1 - \sigma_2) T_t + \tau_t (1 - \sigma_1) (1 - \delta) I_t \\
R_{t+1} &= R_t + \sigma_1 (1 - \delta) I_t + \sigma_1 (1 - \delta) A_t + \sigma_2 T_t.
\end{align*}
\]

where

\[
G_t = \rho \frac{I_t + \epsilon T_t + mA_t}{N_t};
\]
The figure shows the data and model fit for estimate values of susceptibility $\rho = 0.8996$ and effectiveness of the treatment $\epsilon = 0.9115$. 
We adjusted the methodology presented by Banks\(^1\) for a discrete time epidemiological model.

- We used a discrete time model to estimate parameters from a influenza outbreak in a border school in United Kingdom.
- We estimated parameters by using data from the influenza pandemic in San Francisco (1918) by introducing a class of asymptomatic individuals in our original model.
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Future Work

- We want to use a better globalization strategy in order to have a solution with less sensitivity to initial conditions.
- We claim that by improving the algorithm, more realistic values for the weight constants can be used.
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*This work is dedicated to my family and to the memory of my aunt Blanca Ines.*
Questions?
Thanks!!

Thank you!!