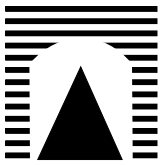

UNIVERSITÀ DEGLI STUDI ROMA TRE
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REACTION-DIFFUSION MODELS FOR EPIDEMICS WITH INFORMATION

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Parole chiave: Reaction-diffusion models, Epidemiology, SIR Models, Information, Finite difference methods, Explicit methods

This following work illustrates several mathematical models useful in analysing the phenomenology of the development of epidemics in a population.
The emphasis will be placed on the mathematical analysis and on the numeric treatment of the phases of the development of epidemics, in which the inhabitants can be exposed, with a specific application to the measles disease in hypothetical inhabitants, in a predetermined interval of time and in a specific geographical area. A mathematical model where the $''force\ of\ infection''$ is present will be particularly analyzed along with the effect the $''information''$ contains.

The term epidemic comes from the Greek words $''epi''$, meaning on, and $''dêmos''$, meaning people/population. Therefore epidemic means the diffusion of an infectious disease in a population, in an elevated number of cases, in a limited period of time. In order for a disease to develop, it's necessary that the process of contagiousness between people is relatively easy. What essentially characterises an epidemic is the duration of the specific disease, the period of contagiousness, and the quantity of people infected.
An epidemic is different than an endemic, which derives from the Greek words $''en''$, meaning in, and , $''dêmos''$ meaning people/population. An endemic, therefore, designates the existence of an infectious disease that is constantly present in a specific population or in a particular geographic area and that can disappear by eliminating the cause (for example by drying up the swamps and thus eliminating malaria).
An epidemic is also different than a pandemic, from the Greek words $''pan''$, meaning all, and $''dêmos''$, meaning people/population, which is an epidemic that strikes several geographic areas in the world, with an elevated number of serious cases and a high death rate (for example the Spanish influenza in 1918, the Asian influenza in 1957, the Hong Kong influenza, the HIV of 1969, and the SARS of 2003).

An epidemics originates with the presence of a pathogenic agent, like a fungus,

a virus, a bacteria, or a living thing.
The principal factors that influence the differences between risk of infection in different situations are: the characteristics of the population, which are the major or minor susceptibilities to infections depending on age, the presence of concomitant pathologies, the strength of the immune system or the presence of an infectious disease in the community.
The determining factor of the diffusion of an epidemic is the contact, which can be direct, when it happens between individuals of the same species (such as measles), or indirect, when there is an interposition of an intermediate guest (such as malaria).

Epidemics can be transmitted as follows:

- beginning with one source of infection, in general represented by products or contaminating devises;

- from an environmental cistern of infection. For example a common source can be the city water system;

- associated with carriers: the most frequent mechanism of transmission happens due to the hands of carriers that contain microbes or are infected;

- from person to person, depending on the common modality of transmission of the infections: through the airways, through microscopic drops of saliva, or simply by direct contact between an infected and a healthy person, or indirect contact through objects that are easily exposed to contamination(bathroom, door handles, handrails, etc.)

A particular epidemic that we have analized in the numerical programs in the Appendix is the epidemic of measles disease. Measles is a highly contagious infectious viral and exanthematic disease, that strikes children during their school or preschool years, is at its peak at the end of winter and during spring, and generally gives immunity to the disease. If adequately treated, measles are benign

and only in rare cases do serious complications occur. Measles have an articulated evolution that can be divided into 4 phases: incubation, invasion, eruption, and resolution.

1. Incubation: This phase lasts an average of 9 to 11 days without symptoms.

2. Invasion: This is known as the catarrhal phase with uneasiness, irritability, high fever, dry and a peevish cough, red eyes, tearing, intolerance to light, nasal secretion, and sneezing. Right before the exanthema phase, signs of Koplik appear (small white spots on the mucous membrane inside the cheeks). At the end of the catarrhal phase, the fever disappears for 6-12 hours.

3. Skin eruption or exanthema: it begins after the 14th day of contact. It is characterized by a rash with round shaped spots, barely protruding, of a pale pink colour. It always begins on the cheeks, behind the ears and on the face. The following day the spots invade the neck, the chest and the upper extremities. The third day the rash spreads to the abdomen and lower extremities, travelling downward and becoming more apparent. During the rash, temperature goes up and remains high, up to 39°- 40°, for two or three days.

4. Resolution phase: The rash disappears after 5-6 days starting from the top to the bottom of the body, from the head to the feet, travelling as it did during the appearance, and thinning and flaking of the skin occurs. The cough can last for a long time and the fever drops when the rash covers the whole body.

The contagious phase starts during incubation, two or three days before the catarrhal phase and ends 2-5 days after the rash appears.
The disease is especially contagious when the symptoms are not yet apparent.
To limit the diffusion, isolation of the patient is necessary during the contagious phase until the 5th day after the appearance of the rash.

The following figure represents the tendency of measles epidemic in Italy from 1996 to 2007:

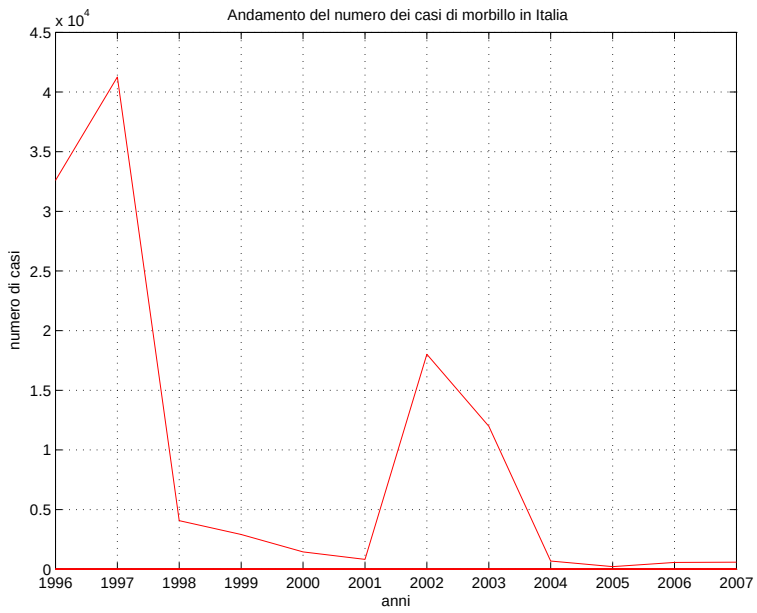

Figura 1: The run on of the number of measles cases in Italy from 1996 to 2007 (source: Minister of Health)

The best model to describe the evolution of an epidemic through a mathematical point of view is the Kermack-McKendrick model (1927), also called SIR model: SIR model is made up of a system of linear or non-linear ordinary differential equations, in which an equation describes the evolution of all of the three classes previously defined and presents, in its interior, the dependence or not, of the three classes (coupled differential system). Also we assume that the population struck by the epidemic is homogeneous (individuals are all the same, and their age difference, sex, and residence do not count), that it is closed, that it is in a specific city or geographical area without neither immigration nor emigration, and that it is demographically motionless (there are no births or death). We also assume that the disease is a type that gives immunity, so a person from the REMOVED group cannot re-enter the SUSCEPTIBLE group and therefore can't get re-infected. The

number of individuals that belong to the three classes at time t, are respectively indicated with $S(t)$, $I(t)$, e $R(t)$, and such that they satisfy the following relations

$$S(t) + I(t) + R(t) = P(t)$$

$$S(0) + I(0) + R(0) = P(0)$$

The passagge of single individuals from one class to another is governed by the following two processes :

1. The process of healing the disease, that governs the passage from INFECTED to the REMOVED;

2. The process of infection that describes the passage from SUSCEPTIBLES to INFECTED.

The process of healing, described in general terms, is represented from the following differential equation:

$$R' = R_{tomorrow} - R_{today} = \gamma(t)I \tag{1}$$

where $\gamma(t) = \gamma$ represent the removal rate, or the rate with which the infected leave their class to enter the removed class, intrinsic to the disease and to its progression among the infected individuals, having form $\gamma(t) = \gamma = \frac{1}{t}$, where t is the duration of the infection. Such an equation is called equation of velocity where R varies and describes how to calculate every 24 hours the value of R based on the number of infected I and type of disease.

The process of infection is characterized by two important parameters: the rate of contact $''c''$ and the degree of infectiousness of the disease $''\phi''$. These represent the fraction of people infected with whom on average a susceptible comes into contact ia period of one day and the infectiousness,that is the probability that a contact with an infected individual transmits the disease, respectively. Therefore we get that the quantity of people who infected daily is given by kSI, with $k := \frac{c\phi}{P}$,

where P is the population. In conclusion we have that the variation of S, from *today* to *tomorrow* is given by

$$S' = S_{domani} - S_{oggi} = -kSI \tag{2}$$

and the variation of $''I''$ in the time is given by

$$I' = I_{domani} - I_{oggi} = kSI - \gamma I \tag{3}$$

Reuniting the equations (1), (2), (2), we obtain the SIR model, described by the following coupled differential equations:

$$\begin{cases} S' = S_{domani} - S_{oggi} = -kSI \\ I' = I_{domani} - I_{oggi} = kSI - \gamma I \\ R' = R_{domani} - R_{oggi} = \gamma I \end{cases} \tag{4}$$

and if we add others important factors, we obtain the following SIR model with vital dynamics:

$$\begin{cases} \frac{dS}{dt} = -kSI - \mu S + \mu \\ \frac{dI}{dt} = kSI - \mu I - \gamma I \\ \frac{dR}{dt} = \gamma I - \mu R \end{cases} \tag{5}$$

with initial values $S(0) = S_0 > 0, \quad I(0) = I_0 > 0, \quad R(0) = R_0 > 0$ and suc that $S(0) + I(0) + R(0) = 1$, where $k, \mu > 0$ and where

- Birth and death rates are equal;
- The population $P = S + I + R$ is constant and sufficiently ample so that the dimensions of each class can be considered continuous variables instead of discrete, and in which the newborns are susceptible;
- The individuals are removed from every class with a proportional rate to the dimension of each group with a constant of proportionality μ, called mortality rate. The average duration of life is $\frac{1}{\mu}$.

- The population is distributed evenly. We express with k the average number of daily contacts with one individual infected kS. This way the average daily number of healthy individuals is kS. This quantity is considered fixed and does not vary with the seasons. The type of contact, direct or indirect, to favour transmission, depends on the specific disease.

- The individuals heal and are removed from the class of infected with a proportional rate to the number of infected with constant of proportionality γ, called the dayly rate of recovery. The average period of infectiousness is equal to $\frac{1}{\gamma}$.

The model, described above, is known as endemic classic model or SIR model with vital dynamics.

A key problem in shaping the dynamic evolution of an infective disease is the mathematical representation of the mechanism of transmission as well as the mechanism of progression.
The mechanism of transmission has to do with the process of infection for which an individual exits from the susceptible class and enters the infected one.
The mechanism of progression has to do with the process of recovery for which an individual exits from the infected class and enters the removed one.
The mechanism of transmission is measured at the rate $''\lambda(t)''$ with which susceptible individuals become infected; while the mechanism of progression is measured at the rate $''\gamma(t)''$ with which infected individuals become removed.

Therefore there are two parameters identified as follows::

1. $\lambda(t)$: represents the probability that in a unit of time a susceptible gets infected;

2. $\gamma(t)$: represents the probability that in a unit of time an infected recovers and becomes removed;

The parameter $\lambda(t)$ is also known as $''force\ of\ infection''$, and has to do with the mechanism of infectiousness. The force of infection is characterized by the way in which individuals come into contact with each other and by the pathogenic agent produced by the infected population.
Instead the parameter $\gamma(t)$ has to do with the progression of the disease, precisely its development and result for an individual.
In general the force of infection is a function of time and of the quantity of the infected at time t. Therefore it's represented by the formula:

$$\lambda(t) = [g(I(\cdot))](t)$$

that acts on each individual in the susceptible class.
Therefore the measure of the force of infection is given by the rate of incidence

$$\sigma(t) = \lambda(t)S(t)$$

that represents the number of new cases at time t.

The $''force\ of\ infection''$ FoI, introduced, assumes different forms according to the current and remote anamnesis of the wide diffusion of the disease that we will represent with the parameter $''M''$, called $''information\ index''$
The mathematical relation that ties the force of infection FoI to the index of information M is given by the following formula:

$$FoI(M) = \beta(M)I \tag{6}$$

with $\beta(M)$ such that $\beta'(M) < 0$.

Introducing the relation (6), the system (5) becomes

$$\begin{cases} S' = -\beta(M)SI - \mu S + \mu \\ I' = \beta(M)SI - \mu I - \gamma I \\ R' = \gamma I - \mu R \\ S(0) = S_0 > 0, \quad I(0) = I_0 > 0, \quad R(0) = R_0 > 0 \\ S(t) + I(t) + R(t) = 1 \end{cases} \tag{7}$$

where the peak indicates the first derivative compared to time, and

- β is a function of M and such that $\beta'(M) < 0$;
- M is the index of information, parameter that reassumes the available information on the current and remote anamnesis;
- μ is the rate of mortality, referred to the quantity of the removed with fatal results;
- γ is the rate of recovery from the disease, referred to the quantity of removed with a positive result.

The model I've analyzed from numerical point of view is a SIR model with vital dynamic with a particular choice of the information index of form $M = kI$, with $k > 0$: namely M is a linear function of the current prevalence of the disease, represented by, for example the current standardized incidence of serious cases of the disease. This model is calles model P, where P stands for punctual /local. Now in order to formulate the mathematical model, it is necessary to define first of all in mathematical terms the following quantities:

- the spatial density of susceptible individuals $''s(x,t)''$;
- the spatial density of infected individuals $''i(x,t)''$
- the index of information $M(x,t)$;
- the rate of mortality and the rate of recovery, in general spatially non-uniform $\mu(x)$ and $\nu(x)$ respectively;

The densities s and i are conveniently normalized, so that in absence of disease the distribution of the susceptible is $s(x,t) = 1$.
The random motion of the susceptible individuals can be modelled through a classic equation of the diffusion with coefficient $''D_s''$, expressed in $\frac{km^2}{day}$.
The random motion of the infected individuals can be modelled through a classic

equation of the diffusion with coefficient $''D_i''$, expressed in $\frac{km^2}{day}$, with $0 \leq D_i << D_s$, since it's biologically reasonable to hypostasize that the infected individuals have limitations in their daily activity, namely being infected. Therefore we can formulate the model P using coupled parabolic differential equations:

$$\begin{cases} \frac{\partial s(t)}{\partial t} = D_s \Delta s + \mu(x) - \mu(x)s(x,t) - \beta(M)s(x,t)i(x,t) \\ \frac{\partial i(t)}{\partial t} = D_i \Delta i - (\mu(x) + \nu(x))i(x,t) + \beta(M)s(x,t)i(x,t) \\ \beta(M) = \frac{\beta(0)}{1+\alpha(\frac{M}{I*})} \end{cases} \tag{8}$$

where

- $\beta(0) = \beta_0$ is the rate in which it's possible to obtain a *''basic reproductive number''* or a *''basic reproductive ratio''* of infection, denoted by $\Re_0$ or BRN, is the mean number of secondary cases a typical single infected case will cause in a population with no immunity to the disease in the absence on intervantions to control the infection. This parameter is defined by the mathematical relation

$$\Re_0 = \frac{\beta_0}{\mu + \nu}$$

- I^* is the value of endemic prevalence, a simple value of reference;

- α is the relative rate of decline of the contact rate for an infinitesimal increase in the infective prevalence.

to which we add the initial conditions

$$\begin{cases} s(x,0) = s_0(x) \\ i(x,0) = i_0(x) \end{cases} \tag{9}$$

and Neumann boundary condition

$$\begin{cases} \frac{\partial s}{\partial \nu} = 0 \\ \frac{\partial i}{\partial \nu} = 0 \end{cases} \tag{10}$$

where $\frac{\partial}{\partial \nu}$ is the outward normal derivative on baundary of domain.

To discretize the system (8) that represents the model P, we used finite forward differences for the time and central differences in space. Using this, the system (8), in one dimension, becomes

$$\begin{cases} s_j^{n+1} = \frac{\Delta t}{\Delta x^2} D_s s_{j+1}^n + (1 - 2\frac{\Delta t}{\Delta x^2} D_s - \mu\Delta t) s_j^n + \frac{\Delta t}{\Delta x^2} D_s s_{j-1}^n + \mu\Delta t - \Delta t \frac{\beta_0 I^*}{I^* + \alpha k i_j^n} s_j^n i_j^n \\ i_j^{n+1} = \frac{\Delta t}{\Delta x^2} D_i i_{j+1}^n + (1 - 2\frac{\Delta t}{\Delta x^2} D_i - \Delta t(\mu + \nu)) i_j^n + \frac{\Delta t}{\Delta x^2} D_i i_{j-1}^n + \Delta t \frac{\beta_0 I^*}{I^* + \alpha k i_j^n} s_j^n i_j^n \end{cases} \tag{11}$$

while in two dimensions, the system (8) becomes

$$\begin{cases} s_{j,h}^{n+1} = \frac{\Delta t}{\Delta y^2} D_s s_{j,h+1}^n + \frac{\Delta t}{\Delta x^2} D_s s_{j+1,h}^n + \\ +(1 - 2\frac{\Delta t}{\Delta x^2} D_s - 2\frac{\Delta t}{\Delta y^2} D_s - \mu\Delta t) s_{j,h}^n + \\ + \frac{\Delta t}{\Delta x^2} D_s s_{j-1,h}^n + \frac{\Delta t}{\Delta y^2} D_s s_{j,h-1}^n + \\ +\mu\Delta t - \Delta t \frac{\beta_0 I^*}{I^* + \alpha k i_{j,h}^n} s_{j,h}^n i_{j,h}^n \\ i_{j,h}^{n+1} = \frac{\Delta t}{\Delta y^2} D_i i_{j,h+1}^n + \frac{\Delta t}{\Delta x^2} D_i i_{j+1,h}^n + \\ +(1 - 2\frac{\Delta t}{\Delta x^2} D_i - 2\frac{\Delta t}{\Delta y^2} D_i - \Delta t(\mu + \nu)) i_{j,h}^n + \\ + \frac{\Delta t}{\Delta x^2} D_i i_{j-1,h}^n + \frac{\Delta t}{\Delta y^2} D_i i_{j,h-1}^n + \\ +\Delta t \frac{\beta_0 I^*}{I^* + \alpha k i_{j,h}^n} s_{j,h}^n i_{j,h}^n \end{cases} \tag{12}$$

In the simulation of the model P in one dimension, the steps of discretizzation Δx and Δt are given by respectively

$$\Delta x = \frac{L}{M - 1}$$

$$\Delta t = \frac{maxt}{N - 1}$$

where L=length intervall, M=number of points, $maxt$=simulated maximum time ed N=nembre of temporal iterations.

In this case we take in consideration the following parameters:

```
DeltaX=0.5;   % space step
DeltaT=0.01;  % time step
L=15;  % Interval length
maxt=365;  % Final time
x=0:DeltaX:L;
```

```
M=length(x); % number of points
t=0:DeltaT:maxt;
N=length(t);  % number of iterations

Ds=6;  % diffusion coefficients
Di=0.01;
nu=1/7;  % removal rate from the disease
mi=1/(75*365);   % general mortality rate from the disease
beta0=20*(mi+nu);  % contact rate
Istar=(0.9*mi)/(mi+nu);  % endemic prevalence in the classical SIR model
alpha=0.5;  % relative rate of decline of the contact rate
            % for an infinitesimal increase in the infective prevalence
k=0.02; % actually reported incidence of serious cases of the disease
```

and as initial data

$$s_0(j) = 1 \quad \text{per} \quad j = 1, ..., M$$

$$i_0(j) = \begin{cases} 0 & \text{for} \quad j = 1, ..., 14, 18, ..., M \\ 1 & \text{for} \quad j = 15, 16, 17 \end{cases}$$

Based on the simulation, based on the programs in the appendix and referring to the system (11) in one spatial dimension, the following graphics have been elaborated, that represent the evolution of the epidemic of measles in the population referred to during 365 days, taking into consideration the fact that the disease in an individual lasts an average of 24 days.

Every graphic below represents the state of the disease in the population at intervals of 10 days starting from the first to the eightieth day.

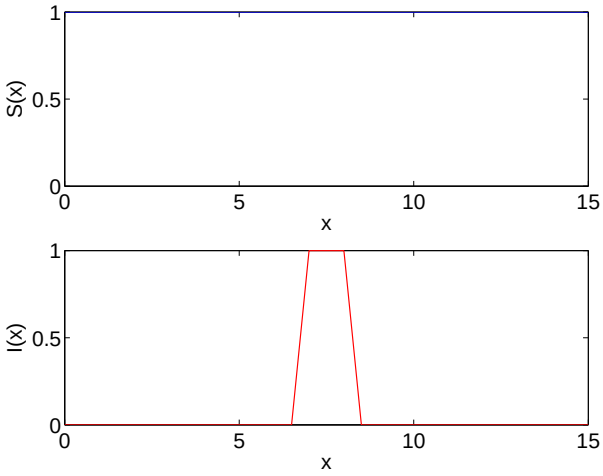

Figura 2: Initial data

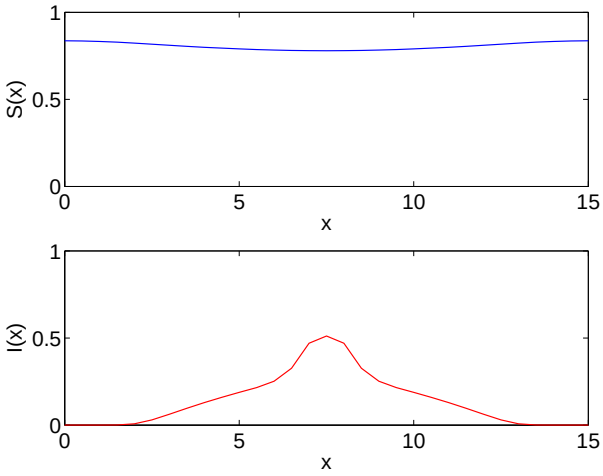

Figura 3: Maesles after 10 days

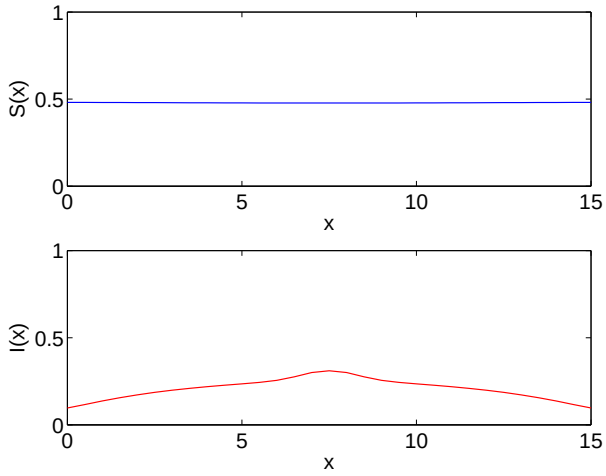

Figura 4: Maesles after 20 days

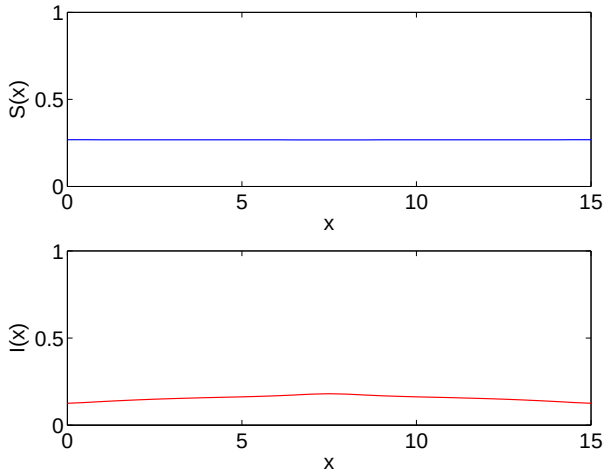

Figura 5: Maesles after 30 days

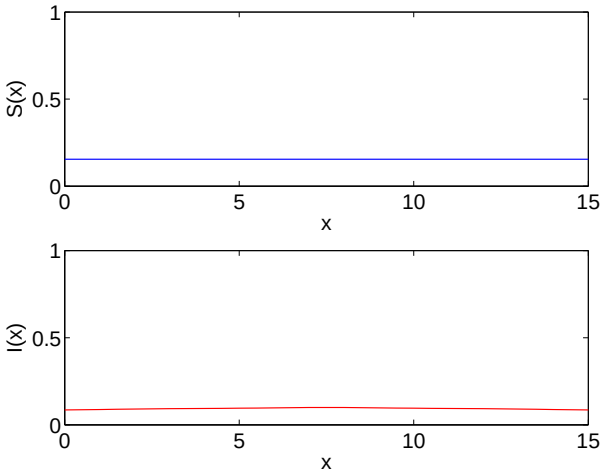

Figura 6: Maesles after 40 days

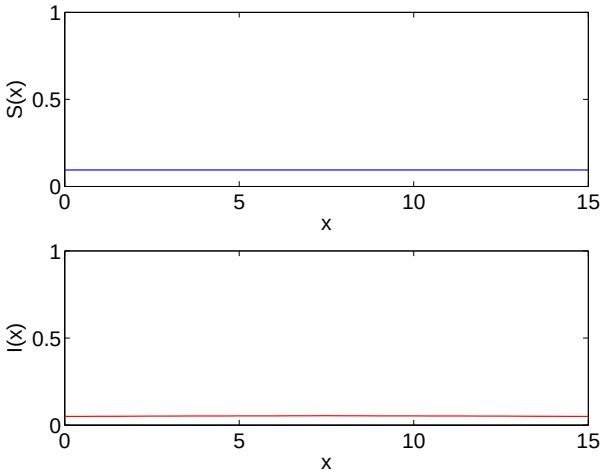

Figura 7: Maesles after 50 days

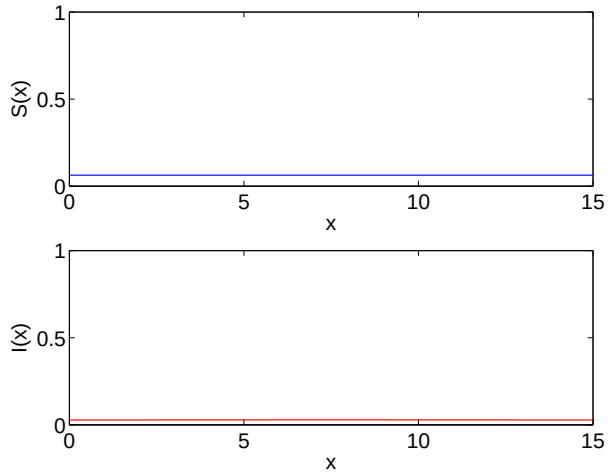

Figura 8: Maesles after 60 days

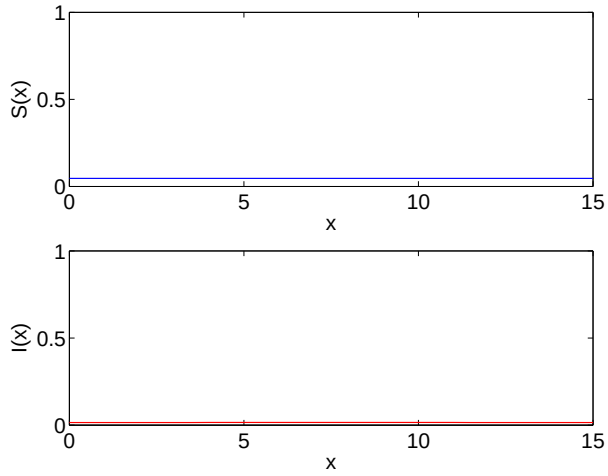

Figura 9: Maesles after 70 days

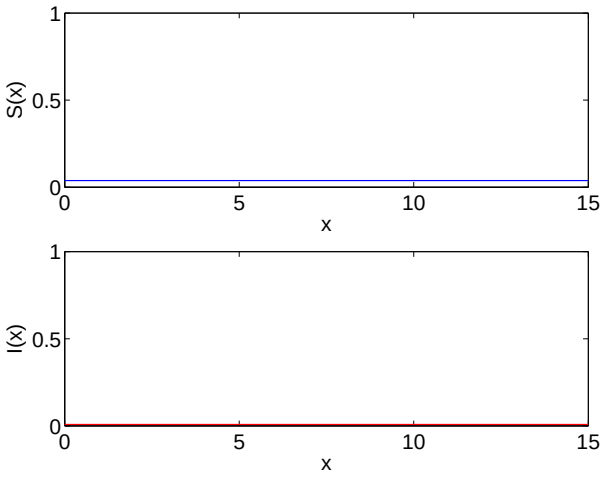

Figura 10: Maesles after 80 days

In the simulation of the model P in two dimensions, steps of discretization Δx, Δy and Δt are given by respectively

$$\Delta x = \frac{L}{M-1}$$

$$\Delta y = \frac{L1}{M-1}$$

$$\Delta t = \frac{maxt}{N-1}$$

where L=shorter side of rectangle, $L1$=longer side of rectangular, M=number of points, $maxt$=simulated maximum time and N=number of temporal iterations. In this other case we take in consideration the following parameters::

```
DeltaX=0.2;  % space step
DeltaY=0.6; % space step
DeltaT=0.001; % time step
L=5; % shorter side of the rectangle
L1=15;  % longer side of rectangle
maxt=365;  % final time
x=0:DeltaX:L;
M=length(x);   % number of points on the x-axis
```

```
y=0:DeltaY:L1;
M=length(y);   % numebr of points on the y-axis
[X,Y]=meshgrid(x,y);
t=0:DeltaT:maxt;
N=length(t);  % number of iterations

Ds=6;  % diffusion coefficients
Di=0.01;
nu=1/7;  % removal rate from the disease
mi=1/(75*365);   % general mortality rate from the disease
beta0=20*(mi+nu);  % contact rate
Istar=(0.9*mi)/(mi+nu);  % endemic prevalence in the classical SIR model
alpha=0.5;  % relative rate of decline of the contact rate
            % for an infinitesimal increase in the infective prevalence
k=0.02; % actually reported incidence of serious cases of the disease
```

and as initial data

$$s_0(j,h) = \begin{cases} 1 & \text{for} \quad j,h = 1,....,14,18,...,M \\ 0 & \text{for} \quad j,h = 15,16,17 \end{cases}$$

$$i_0(j,h) = \begin{cases} 0 & \text{for} \quad j,h = 1,....,14,18,...,M \\ 1 & \text{for} \quad j,h = 15,16,17 \end{cases}$$

Based on the simulation, based on the programs in the appendix and referring to the system (12) in two spatial dimensions, the following graphics have been elaborated, that represent the evolution of the epidemic of measles in the population referred to during 365 days, taking into consideration the fact that the disease in an individual lasts an average of 24 days.

Every graphic below represents the state of the disease in the total population at intervals of 10 days starting from the first to the eightieth day.

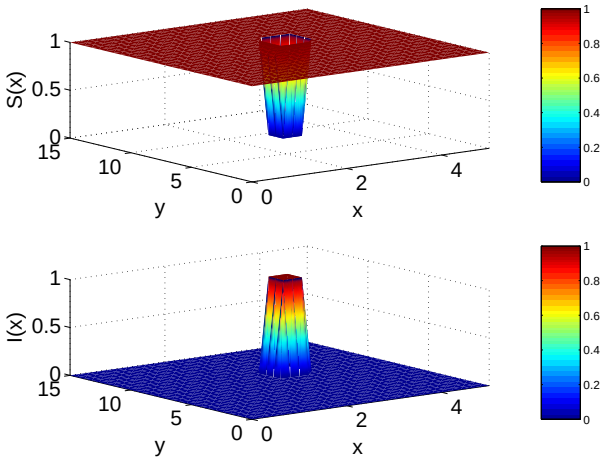

Figura 11: Initial data

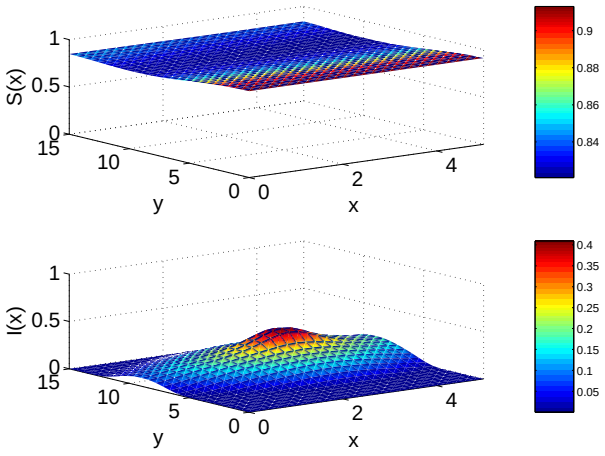

Figura 12: Maesles after 10 days

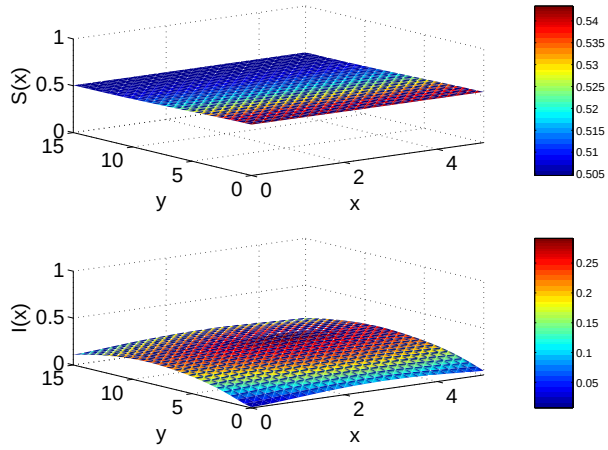

Figura 13: Maesles after 20 days

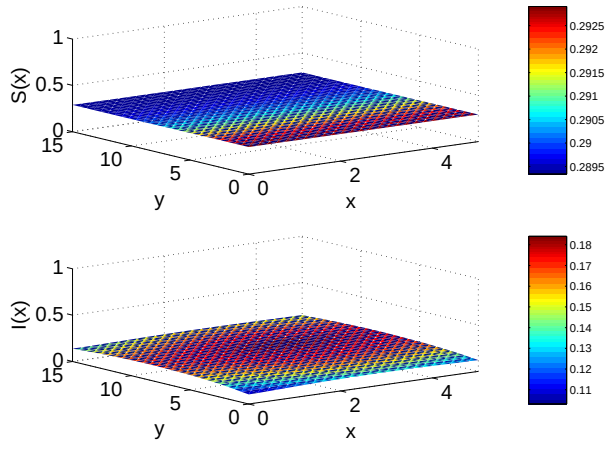

Figura 14: Maesles after 30 days

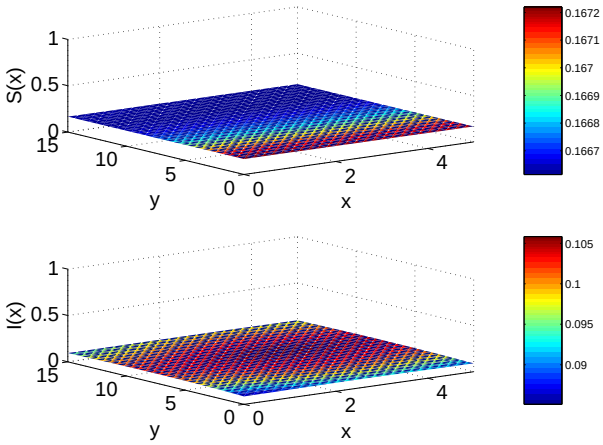

Figura 15: Maesles after 40 days

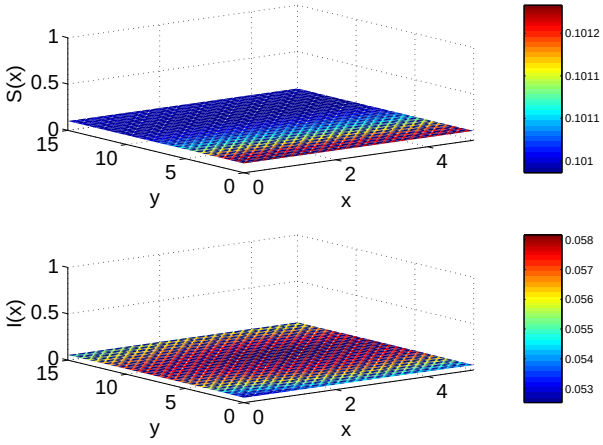

Figura 16: Maesles after 50 days

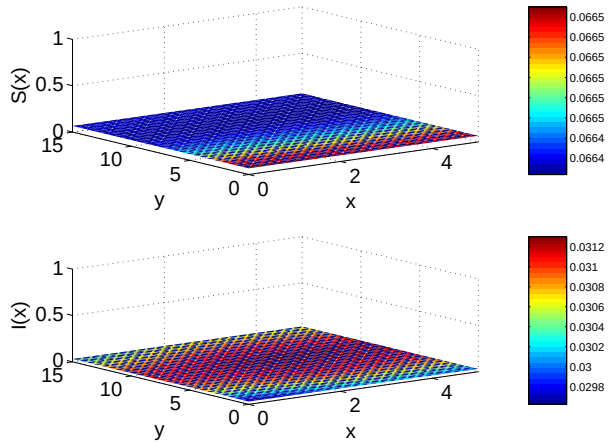

Figura 17: Maesles after 60 days

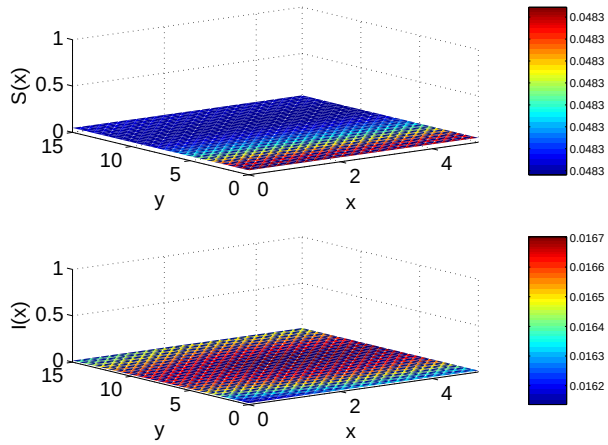

Figura 18: Maesles after 70 days

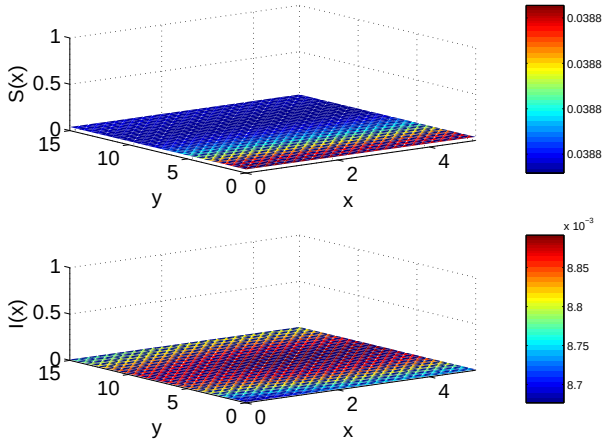

Figura 19: Maesles after 80 days

CONCLUSION:

The system of partial differential equations, denominated the model P discretized through with Euler explicit method, implemented and simulated with MATLAB language, consented us to show with opposing analytic-numeric calculus and with the relative graphic representation, that the system mentioned above is able to furnish models of representation of the progression of epidemics provoked by infective diseases.

In particular the data relative to measles has been taken as reference for the mathematical implementation in this work and the implementative calculus and graphics exposed in Chapter 3, for the model P are refered to these data.

In fact the graphics are able to visualize the spreading of the measles epidemic, in a homogeneous population, spatially structured, closed, and demographically immobile, that causes a progressive diminution of the classes of susceptible until it reaches levels that tend towards zero and a corresponding increase of the classes of infected.

Even though the work done here on the model $"P"$ is affected by all the simplifications derived from the assumed limited hypothesis, we were able to show that this establishes a work base for the management of epidemics.

Further developing the model and adding constant and appropriate boudary conditions, costantly updated, you can reach an even more complete system, that provides indications based on scientific presumptions for the government knowingly and non-random phenomena epidemic, always more possible in a globalized world and characterized by continuous intercontinental exchanges.

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