MODELING THE GEOGRAPHICAL SPREAD OF INFLUENZA PANDEMIC A (H1N1)

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The 2009 A H1N1 is the first pandemic of the XXI century.

In the 20th century, three pandemics were caused by the emergence of different influenza A subtypes that were antigenically divergent from human viruses:

1. The 1918 H1N1 (Spanish flu)
2. The 1957 H2N2 (Asian flu)
3. The 1968 H3N2 (Honh Kong flu)

Since April 2009, the outbreak of a novel influenza A (H1N1) virus (2009 H1N1 Mexican swine flu) has spread globally and developed into a human influenza pandemic after 40 years.
As of February 2010 the 2009 A (H1N1) has caused at least 16,000 deaths.

At the beginning of a flu pandemic, preexisting immunity to the hemagglutinin (HA) of the newly emerging virus is generally low (antigenic shift), guaranteeing a large pool of susceptible hosts for rapid spread and infection of 10 to 40% of the population worldwide.
After a new HA becomes fixed in circulating human viruses, it undergoes gradual changes in its antigenic structure in a process called antigenic drift, so as to escape recognition by the human immune system. Such drift leads to loss of immunity and is associated with the frequent seasonal flu epidemics that occur during inter-pandemic periods.

THE ESTIMATE OF THE BASIC REPRODUCTIVE NUMBER (Ro) OF THE INFLUENZA A(H1N1) EPIDEMIC IN MEXICO

We first consider a very simple mathematical framework which mirrors the dynamics of influenza A(H1N1).
Even with this oversimplified model, we will show that there is a relationship between the basic reproductive number (Ro) and the exponential phase of the epidemic.

Let us consider a population of fixed size N in which the densities of susceptibles, infectious and recovered at time t are denoted by $S, I,$ and R, respectively; then the total population size is $N = S + I + R.$

The model is

$$\frac{dS}{dt} = -\lambda S \qquad (1)$$

$$\frac{dI}{dt} = \lambda S - \gamma I \qquad (2)$$

$$\frac{dR}{dt} = \gamma I \qquad (3)$$

Here, λ is the so-called force of infection and it is the probability that infection is acquired from and infectious individual; then λ is defined as

$$\lambda = \beta \frac{I}{N} \qquad (4)$$

THE CONCEPT OF THE BASIC REPRODUCTION NUMBER Ro

A disease will be established in a population provided the total population exceeds a certain critical number of susceptibles equal to γ/β , this is,

$$Ro = \frac{N}{N_t} = \frac{N}{\gamma/\beta} = N\,\frac{\beta}{\gamma} > 1$$

Since the removal rate from the infective class is γ $\left(|\gamma| = \frac{1}{time}\right)$, then $\gamma^{-1} = D =$ average period of infectivity $\approx$ duration of the disease.
Thus,

$$Ro = \frac{N}{N_t},$$

is the fraction of the population that comes into contact with an infective individual during the period of infectiousness.

The threshold value Ro is also expressed as:

$$Ro\hat{x} = 1$$

The available data we have is about the initial rise (approximately exponential) of the incidence of confirmed diagnosed cases of influenza A(H1N1). Thus in the early stages of the epidemic the number of susceptibles is approximately equal to N , this is, $S \approx N$, and equations (2) and (4) give:

$$\frac{dI}{dt} = \left[\beta - \gamma \right] I = \frac{dI}{dt} = [Ro\gamma - \gamma]I = [\frac{(Ro-1)}{D}]I \qquad (5)$$

where $D^{-1} = \gamma$ and it is the duration of the infectiousness.
That is, the incidence of the infection, and thence the incidence of diagnosed influenza cases (i. e. γI), is expressed as:

$$I(T) = I(0)Exp\left[\frac{(Ro-1)}{D}t\right] \qquad (6)$$

Similarly, in the early stages of the epidemic, if there are $c(t)$ cases at time t , there will be $(Ro-1)c(t)$ cases an interval of time D later and therefore,

$$\frac{dc(t)}{dt} = \frac{(Ro-1)}{D}c(t) \qquad (7)$$

Integrating equation (7) gives

$$c(t) = c(0)Exp\left[\frac{(Ro-1)}{D}t\right] \qquad (8)$$

Another way of calculating Ro is to considered the compound interest rate of increase in the number of diagnosed cases in the initial phases in which as we have seen is roughly exponential, then

$$\Lambda = \frac{\ln(2)}{t_d} \qquad (9)$$

where t_d is the doubling time and the constant $\ln(2) = a \approx 0.7$. Thus we can identify either from equations (6) or (8) the exponential growth rate, Λ, as being related to Ro by

$$\Lambda = \frac{(Ro-1)}{D} \qquad (10)$$

Therefore the initial doubling time, t_d, either for infection (as revealed by seropositivity) or for diagnosed cases of influenza A(H1N1) is approximately

$$t_d = \frac{aD}{Ro-1} \qquad (11)$$

Alternatively from equation (10) we can write

$$Ro = 1 + D\Lambda \qquad (11)$$

Estimates of Ro during the influenza A(H1N1) epidemic in Mexico in 2009

DATE OF REPORT	RATE OF GROWTH (Λ)	DOUBLING TIME (t_d) (days)	Ro
May 13	0.3249	2.15	2.29
May 28	0.3001	2.2	2.2
June 8	0.2918	2.39	2.17
August 5	0.2651	2.64	2.06

Some estimates of Ro during the influenza A(H1N1) epidemic in Mexico in 2009 as reported in the literature

$Ro = 1.4$	Secretaría de Salud, INDRE, México May 6, 2009
$Ro = [1.4 - 1.6]$	Rambaut et al. Science 324: 1557-1561 (2009)
$Ro = [2.2 - 3.1]$	Boëlle et al. Eurosurveillance 14: 1- 4 (2009)
$Ro = 2.06 \pm 0.01$	This work

Exponential incidence in homogeneous and uniformly mixing populations

If a person has a total of k contacts per day, then among these there are kI/N contacts with infectives, where N is the population size and I is the number of infectives.

Let c be the probability that a given susceptible becomes infective in one contact with one infective.

Assume that c is a constant for the disease under investigation. Then $1-c$ is the probability that a given susceptible does not become infective in one contact with one infective.

Thus, assuming that each contact is independent of other contacts, the probability that a given susceptible does not become infective during a day (that is in kI/N contacts with infectives) equals $(1-c)^{kI/N}$.

Hence, the probability that a given susceptible becomes infective in one day is $1-(1-c)^{kI/N}$, or equivalently, $1-e^{\beta I}$, where $-\beta = -k\ln(1-c)/N$.
Thus, the transmission coefficient β is a parameter that summarizes both population and disease spread characteristics.

Now, we may express the incidence as the number of susceptibles, S, times the probability to become infective, i.e.,

$$G(S,I) = S(1-e^{-\beta I}) \qquad (1)$$

If $s, i,$ and g denote the proportions of susceptibles, infectives and new infectives, respectively, we can write equation (1) in the form

$$g(s,i) = s(1-e^{\gamma i}), \qquad (2)$$

where $\gamma = \beta N = -k\ln(1-c)$.

Lara-Sagahón A., Khartchenko V., José M. V. Stability analysis of a delay-difference SIS epidemiological model. ***Applied Mathematical Sciences***. **1** (26): 1277-1298 (2007).

Delay-Difference SIR Epidemiological Model

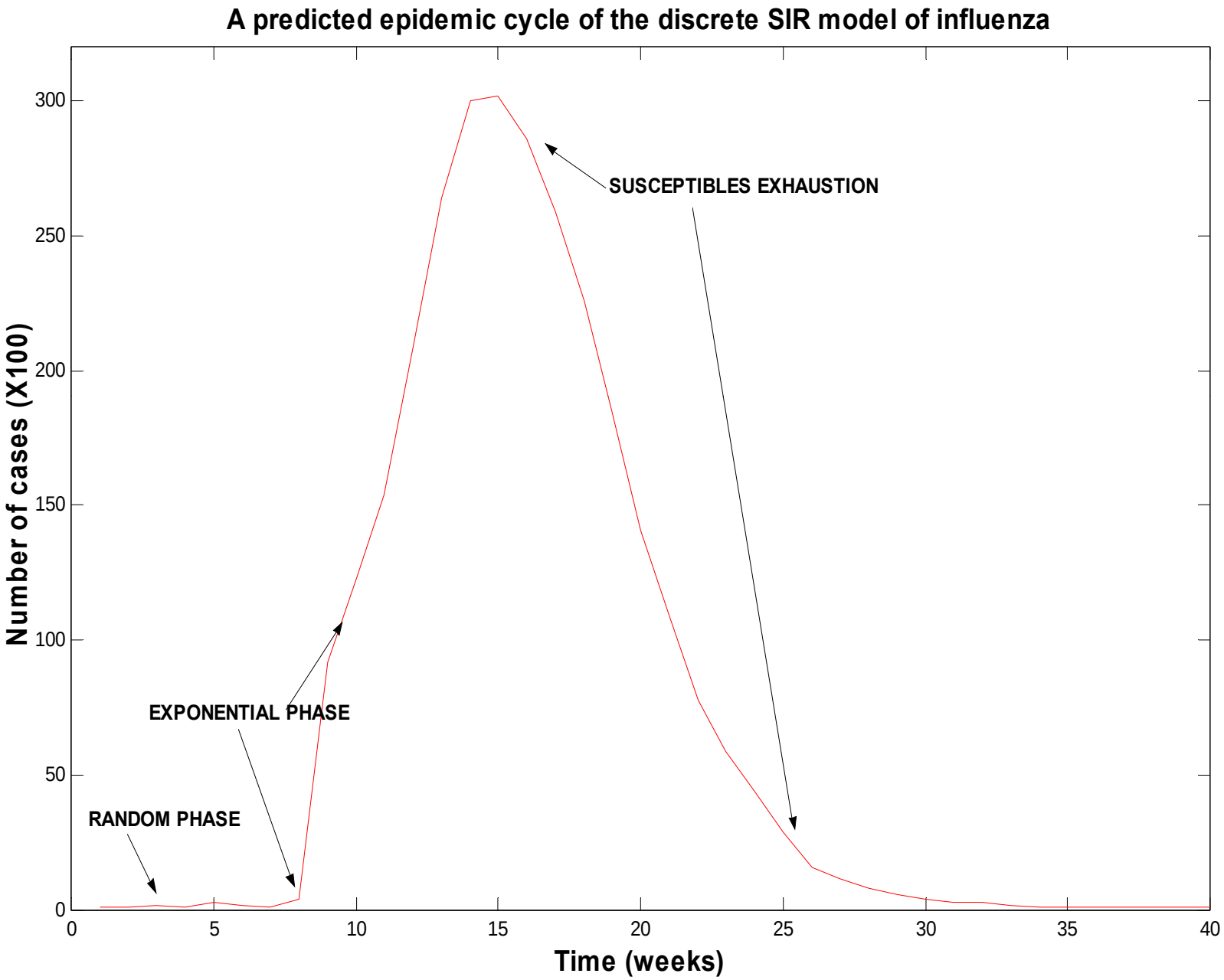
If we assume a constant period of infectiousness, the difference equations of the model are:

$$
\begin{aligned}
S_{t+1} &= S_t - [S_t(1-e^{-\gamma I_t})] + [S_{t-\gamma}(1-e^{-\gamma I_{t-\sigma}})] \\
I_{t+1} &= I_t + [S_t(1-e^{-\gamma I_t})] - [S_{t-\sigma-\varepsilon}(1-e^{-\gamma I_t})] \\
Z_{t+1} &= Z_t + [S_{t-\sigma-\varepsilon}(1-e^{-\gamma I_{t-\sigma-\varepsilon}})] \\
N_t &= S_t + I_t + Z_t
\end{aligned}
$$

The intrinsic reproductive number, Ro, is:

$$
Ro = \gamma\sigma = \beta N\sigma \begin{cases} \leq 1 \Rightarrow \text{no epidemic} \\ > 1 \Rightarrow \text{endemic equilibrium} \\ \text{globally asimptotically stable} \end{cases}
$$

Lara-Sagahón A., Khartchenko V., José M. V. Stability analysis of a delay-difference SIS epidemiological model. ***Applied Mathematical Sciences***. **1** (26): 1277-1298 (2007).


A predicted epidemic cycle of the discrete SIR model of influenza
Number of cases (X100)
Time (weeks)
SUSCEPTIBLES EXHAUSTION
EXPONENTIAL PHASE
RANDOM PHASE
0
50
100
150
200
250
300
0
5
10
15
20
25
30
35
40

SIMPLE MODEL FOR THE SPATIAL SPREAD OF THE INFLUENZA EPIDEMIC

Assumptions

- **The populations consists of susceptibles $S(x,t)$ and infectives $I(x,t)$ which interact.**
- **The susceptibles and infectives have the same diffusion coefficient D .**
- **The basic reproductive number is $Ro = 1/\lambda$.**
- **We want to model the spatial spread of an epidemic wave of infectiousness into a uniform population of susceptibles.**
- **We look for traveling wave solutions by setting:**

$$I(x,t) = I(z), \qquad S(x,t) = S(z), \qquad z = x - wt$$

where w is the wave speed. This represents a wave of constant shape traveling in the positive $x-$ direction.

The non-dimensional model can be expressed as:

$$\frac{\partial S}{\partial t} = -IS + \frac{\partial^2 S}{\partial x^2}$$

$$\frac{\partial I}{\partial t} = IS - \lambda I + \frac{\partial^2 I}{\partial x^2}$$

STOCHASTIC SYSTEM OF DELAY-DIFFERENCE EQUATIONS FOR A SEIRS EPIDEMIOLOGICAL MODEL

Considering all the foregoing assumptions, we can now express the flow rates of the variables X , E , Y and Z per day by the following system of delay-difference equations:

$$X_{t+1} = (1-\mu)(X_t - G_t + (1-\mu)^{\varepsilon+\sigma+\omega} G_{t-\varepsilon-\sigma-\omega-1}) + \mu N \quad (1.1)$$

$$E_{t+1} = (1-\mu)(E_t - G_t + (1-\mu)^{\varepsilon} G_{t-\varepsilon}) \quad (1.2)$$

$$Y_{t+1} = (1-\mu)(Y_t + (1-\mu)^{\varepsilon} G_{t-\varepsilon} - (1-\mu)^{\varepsilon+\sigma} G_{t-\varepsilon-\sigma}) \quad (1.3)$$

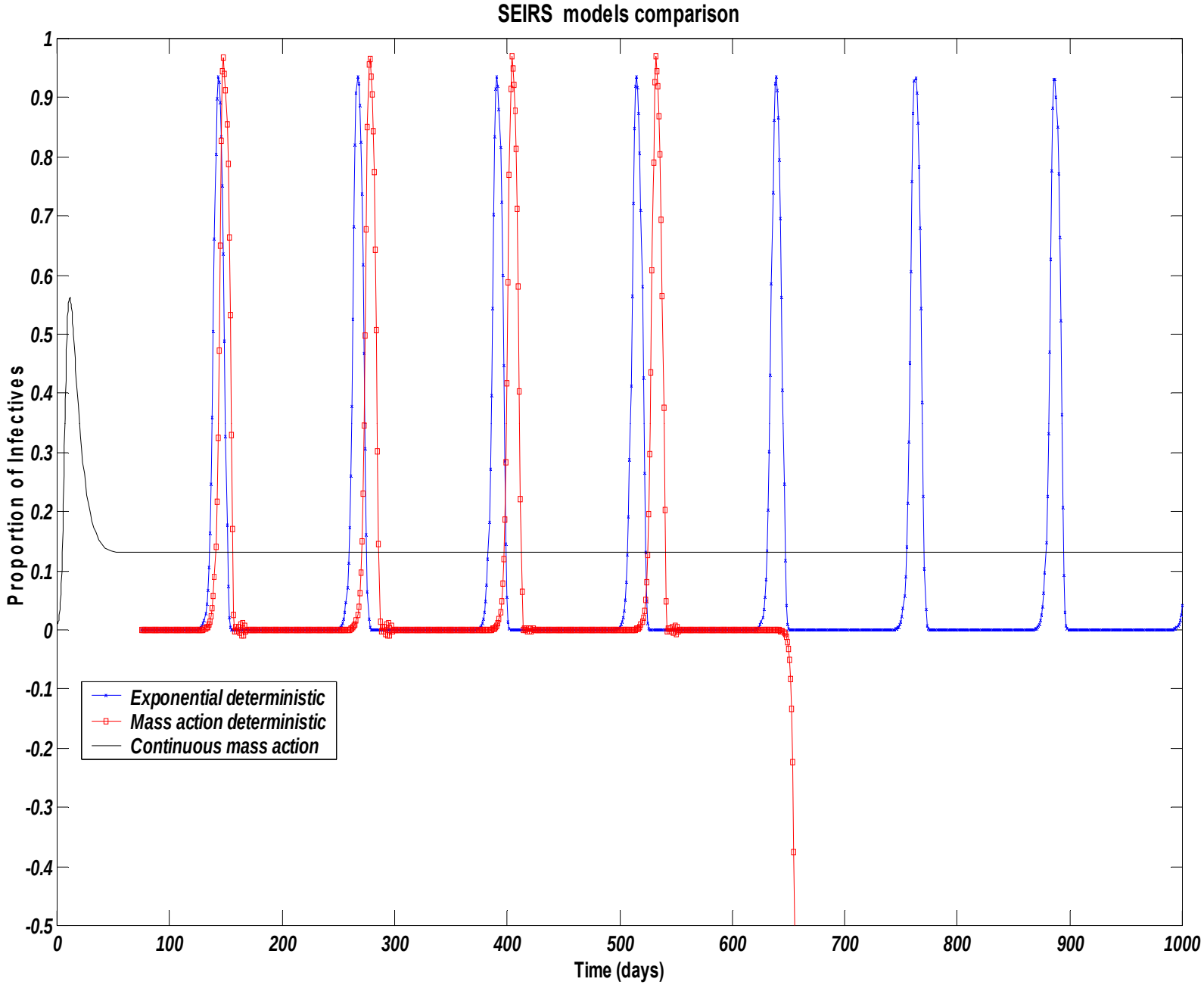
$$Z_{t+1} = (1-\mu)(Z_t + (1-\mu)^{\varepsilon+\sigma} G_{t-\varepsilon-\sigma} + (1-\mu)^{\varepsilon+\sigma+\omega} G_{t-\varepsilon-\sigma-\omega-1}) \quad (1.4)$$

$$N_t = X_t + E_t + Y_t + Z_t , \quad (1.5)$$

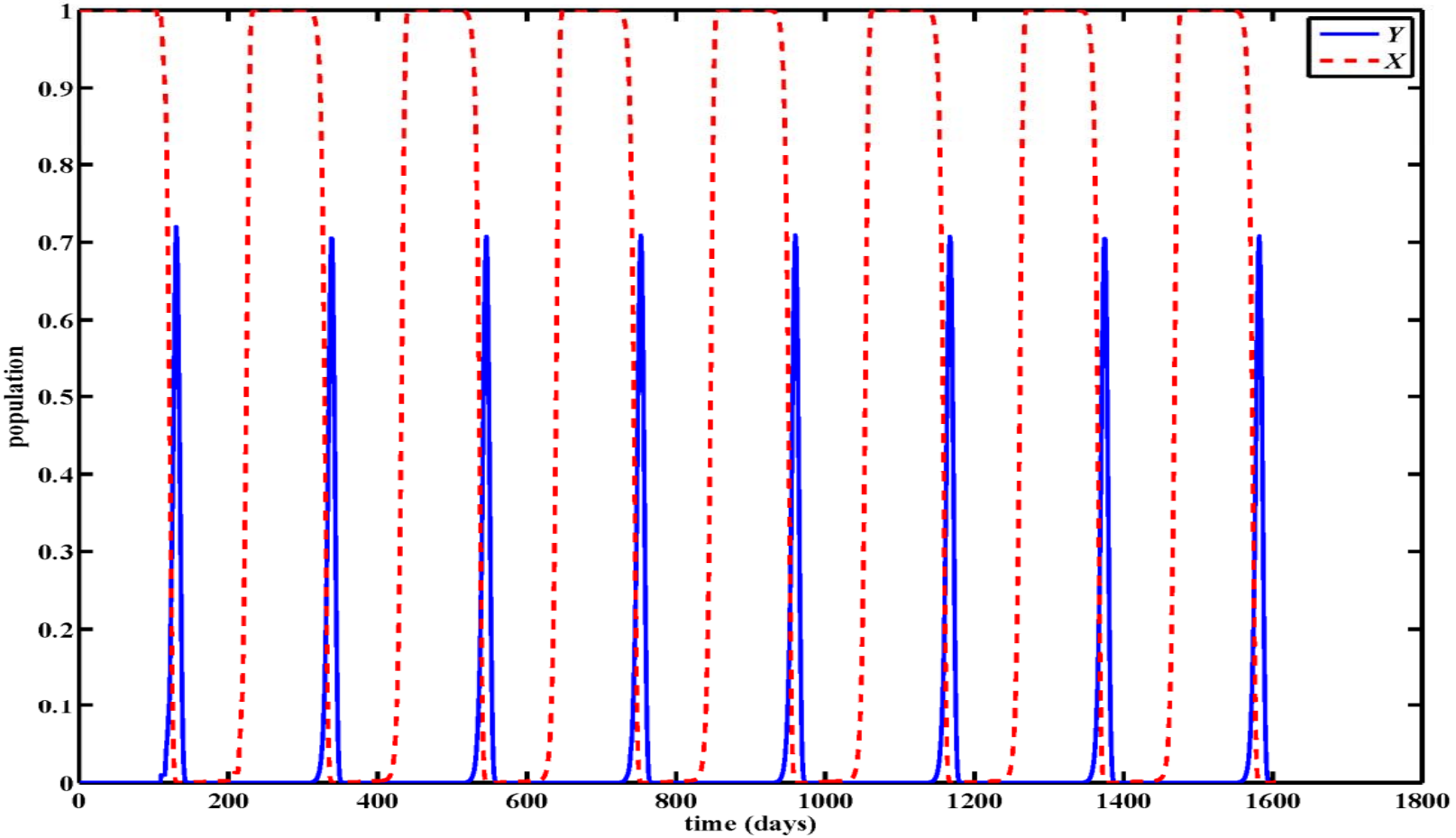
where,

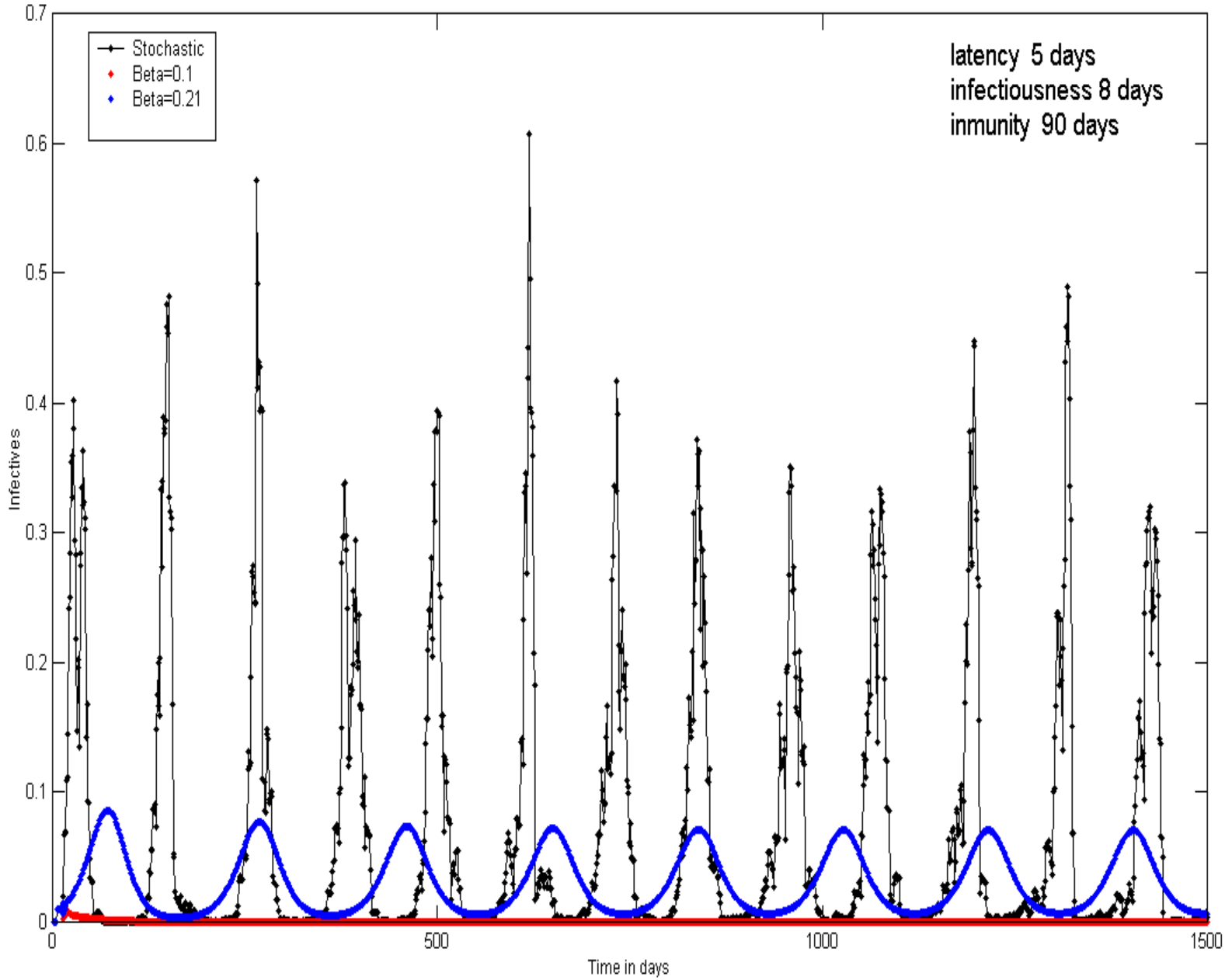
$$G_t = X_t(1-\exp(-\beta Y_t)) + < \xi(t,t') > , \quad (1.6)$$

where ξ represents uncorrelated Gaussian noise.


SEIRS models comparison
Proportion of Infectives
Time (days)
Exponential deterministic
Mass action deterministic
Continuous mass action
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
0
100
200
300
400
500
600
700
800
900
1000

Dynamics of the SEIR model. Population of susceptible (X) and of infectious (Y) individuals as a function of time. The parameter values of the model are: transmission parameter $\beta = 1.91$, latent period $\varepsilon = 5$ days, infectious period $\sigma = 8$ days, immunity period $\omega = 90$ days, mortality rate $\mu = 1/(365 \times 70) = 4 \times 10^{-5}$, and the population has been conveniently normalised to $N = 1$.




Stochastic
Beta=0.1
Beta=0.21
latency 5 days
infectiousness 8 days
inmunity 90 days
Infectives
Time in days
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
500
1000
1500

The most astonishing thing about the pandemic was the complete mystery which surrounded it.

…the pandemic spread rapidly, and no more so, than people traveled from point to point.

Soper GA (1919). The lessons of the pandemic. *Science* **49**: 501–506.

GOAL OF THE MODEL

The goal is to develop a general model for viral pandemics in order to reproduce the geographical spread of the infection.
In this manner we can improve our ability to predict and control epidemics- but that may first require new sociological models that are both predictive and quantitative.
The interdisciplinary approach remains vital, this time at the interface of epidemiology, sociology, and evolution

In this model the fitting of the influenza data is just an example

This approach is different from other works in which an excruciating amount of details are included. The model minimizes the number of parameters to be fitted. The merit of the model is to point out relevant parameters.
We made a coarse-graining typical of Statistical Mechanics.

The model is given in fractions, dimensionless, and we acknowledge that we do not have all actual data.

Justification of the Model

We live in an ever more connected, mobile and interdependent world, where small perturbations can have unpredictable and sometimes far-reaching effects. The paradox is that we increasingly demand predictability.

We expect the future to be anticipated, risks assessed and solutions to be rational. We have to be ahead of everything - including threats from infectious diseases or bioterrorism.

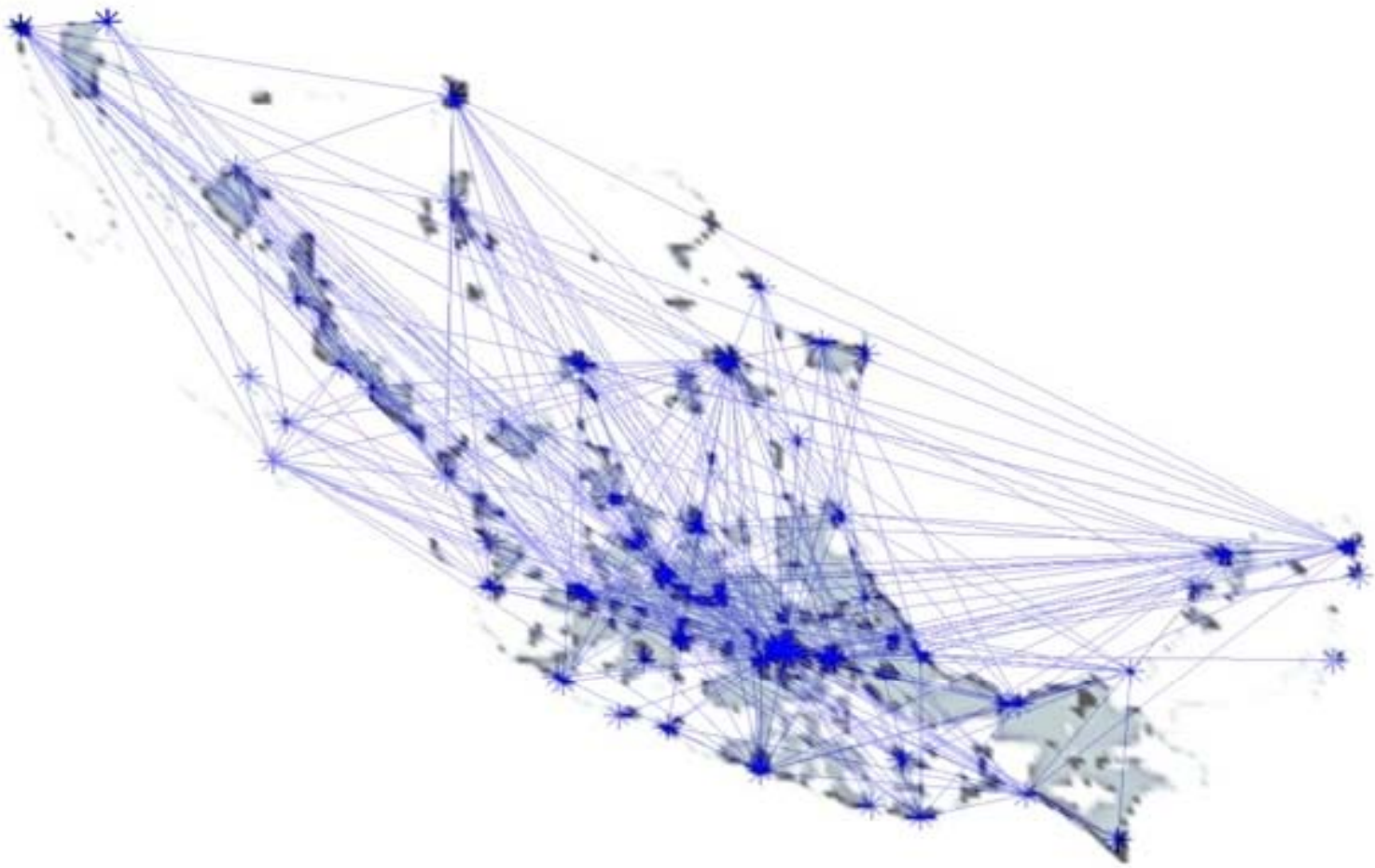
Sometimes an overwhelming amount of data, significantly boosted computer power and theoretical advances - network theory and social sciences - have endowed models with a new realism. Yet fundamental limitations remain in how well they capture key social parameters: population mobility, human behavior.

Faced with lethal or novel pathogens, people change their behaviour to try to reduce their risk.

Global communications mean that a novel lethal disease outbreak could trigger potentially drastic social and economic consequences across the world within days. The opportunity for mathematical modellers is just now.

Map showing the population density distribution used in the calculations, the population color scale was fitted well with a quadratic function to the data.
The grid is of size 224 ×152 cells.

Map of the network of airlines in Mexico. There are 55 airports.



SPATIAL MODEL

Identical systems of delay-difference equations for a new SEIR (susceptible-exposed-infectious-recovered) epidemiological model are defined in a two dimensional grid weighted with the population density, in which the cells are coupled with a network of air and terrestrial communications.

Thus, the time evolution is divided into a local deterministic dynamics, as determined by the SEIR model, and a spatial stochastic dynamics based on the mechanisms by which the infectious disease spreads.

We define a two-dimensional geographical model by considering a grid of cells (i, j). In each cell one independent epidemiological model, weighted with the population density $\rho(i, j)$ is attached, then

$$G_t(i, j) = \rho(i, j) X_t(i, j)[1 - \exp(\beta Y_t(i, j)]$$

Herein we elaborate a stochastic model of the geographical spread infectious diseases using Monte Carlo simulations.

Terrestrial and Aerial Communications by Monte Carlo

£1 Att each time step one finds the cells in which $Y_t(i,j) \geq \eta$, where η is a parameter that measures the contagiousness of the illness.

£2 Selects a random number $p \in [0,1]$ from a flat distribution and compare it with v_t and $v_a \propto$ number of passengers per day.

£3 One leaves the system unchanged if $p > v_t$, otherwise one sets $X_t(\alpha) = 1 - \eta$ and $Y_t(\alpha) = \eta$, where α stands for the indexes of a neighboring cell.

£4 If a is a cell connected by air traveling network and $p < v_a$ then start infection in a.

Introducing noise into the dynamics…

£ Noise 1 Choose $X_t(i,j) < \eta$ at random

£ Noise 2 Select a random number $p \in [0,1]$ and compare it with $w = e^{-1/kt}$

£ Noise 2 If $p \leq w$ then start the infection

RESULTS I

Movie I: Terrestrial – No aerial – No Noise – S=1

Movie II: Terrestrial – No aerial – Noise – S=1

Movie III: Terrestrial – Aerial – No noise – S=1

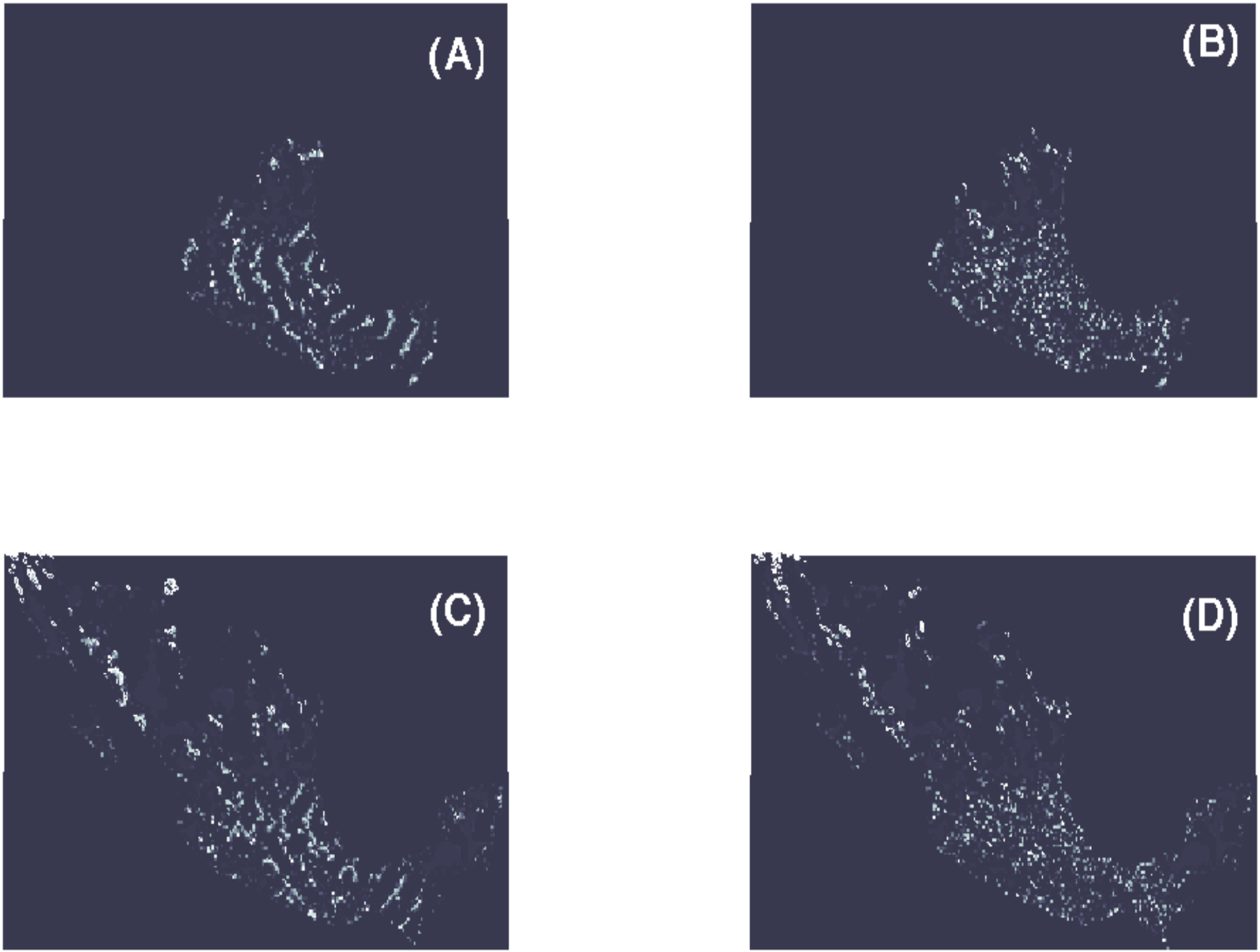
Movie IV: Terrestrial – Aerial – Noise – S=1

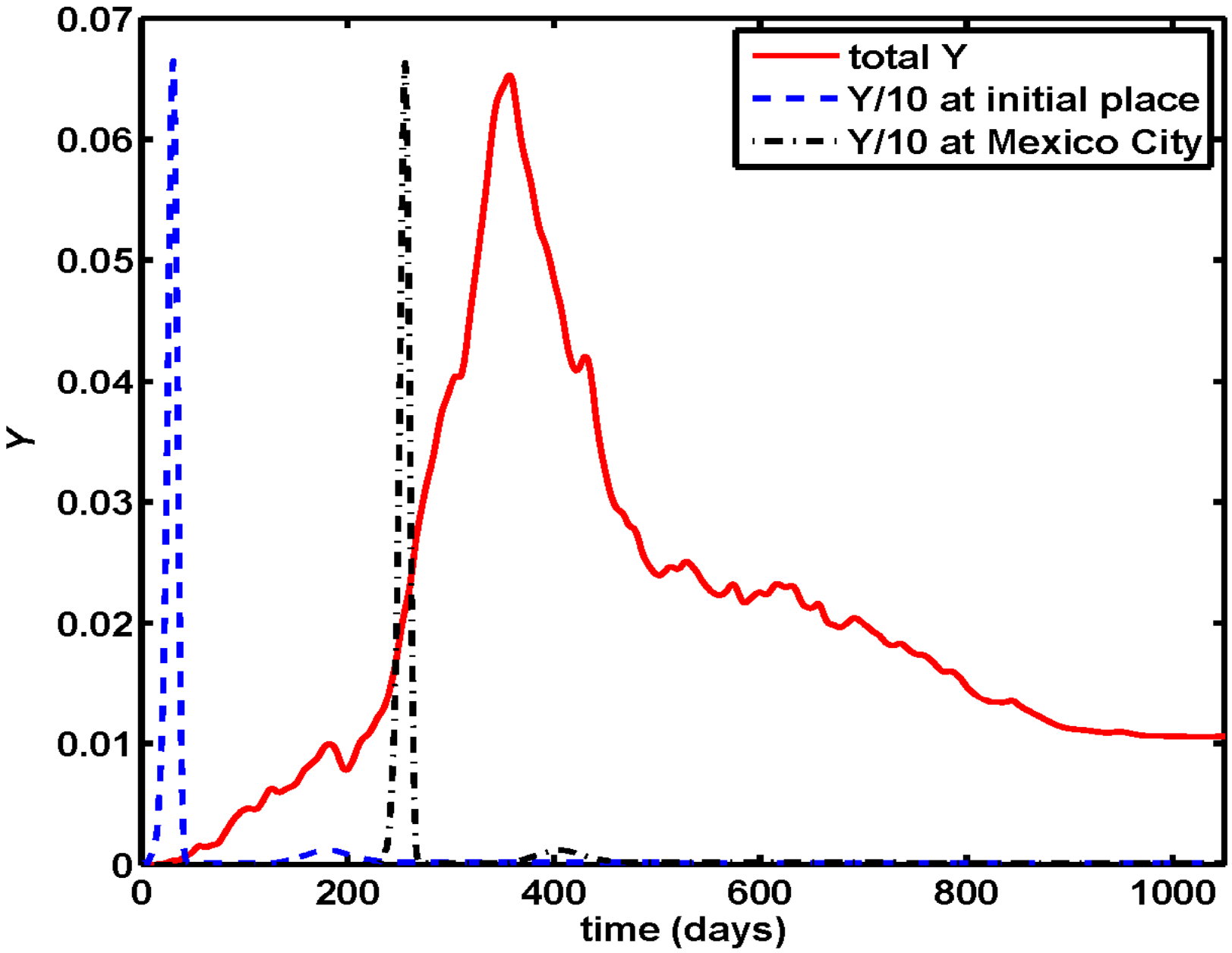
Movie V: Terrestrial – Aerial – No Noise – S=0.1

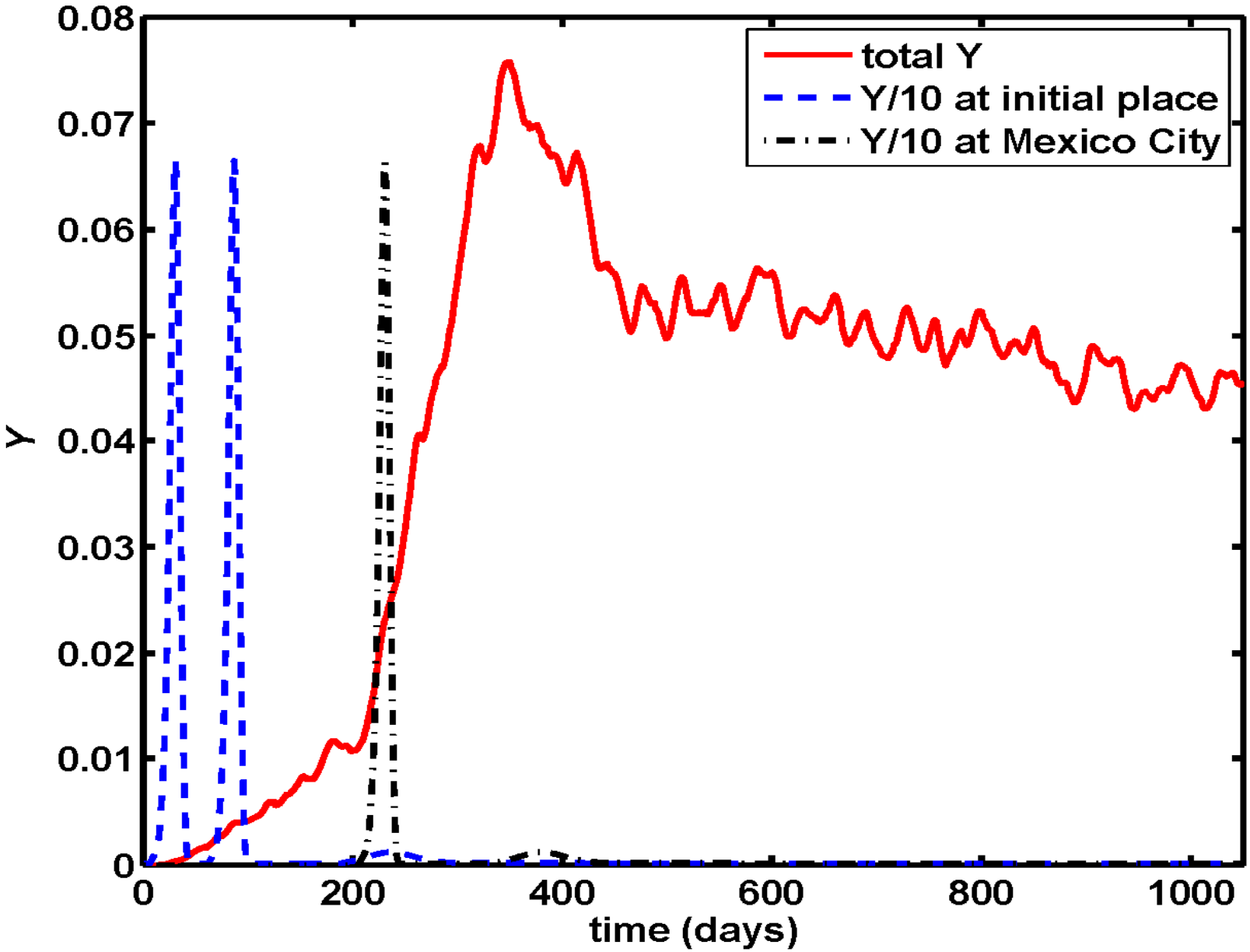
Movie VI: Terrestrial – Aerial – Noise – S=0.1

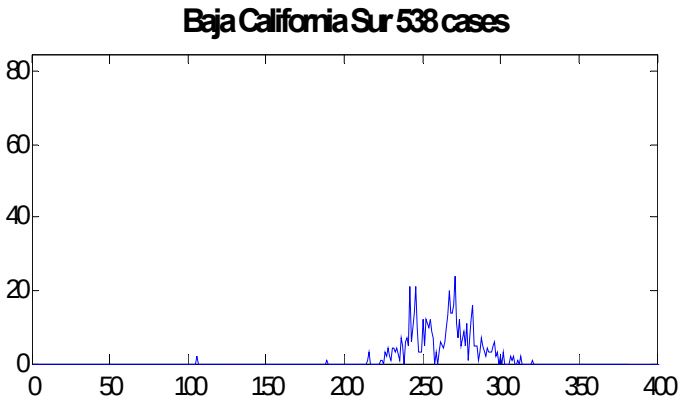
Movie VII: Actual data of the geographical spread of influenza in Mexico

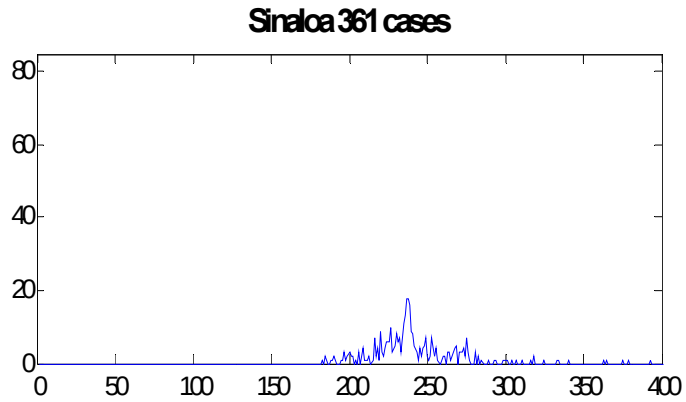
Movie VIII: Fitting simulation of the geographical spread of influenza in Mexico

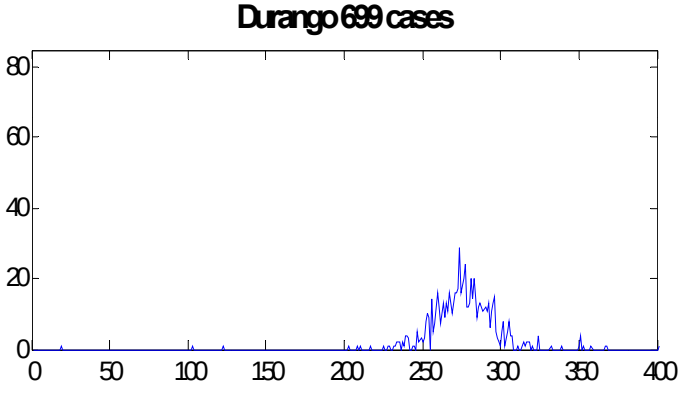

(A)
(B)
(C)
(D)

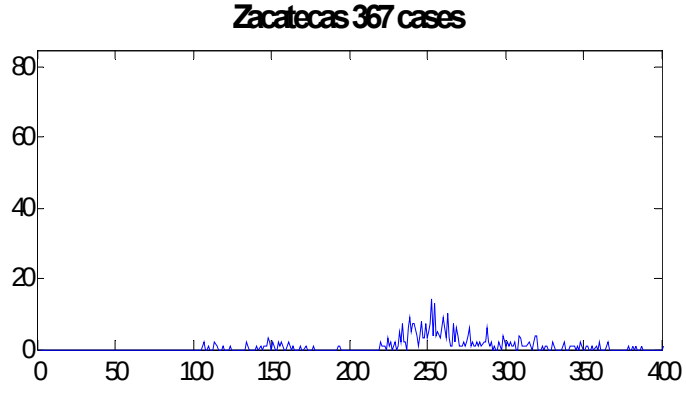

total Y
Y/10 at initial place
Y/10 at Mexico City
Y
time (days)
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0
200
400
600
800
1000

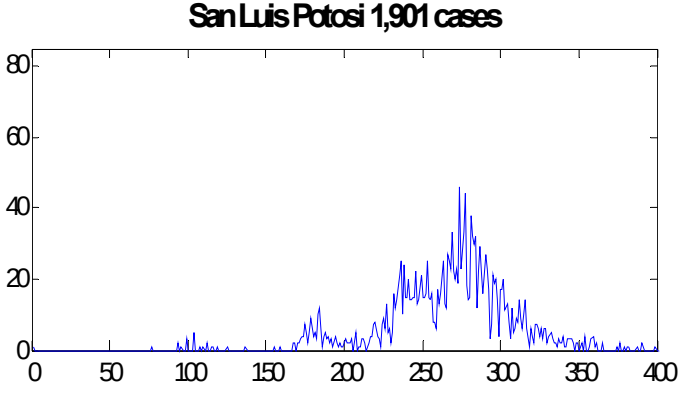

total Y
Y/10 at initial place
Y/10 at Mexico City
Y
time (days)
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0
200
400
600
800
1000

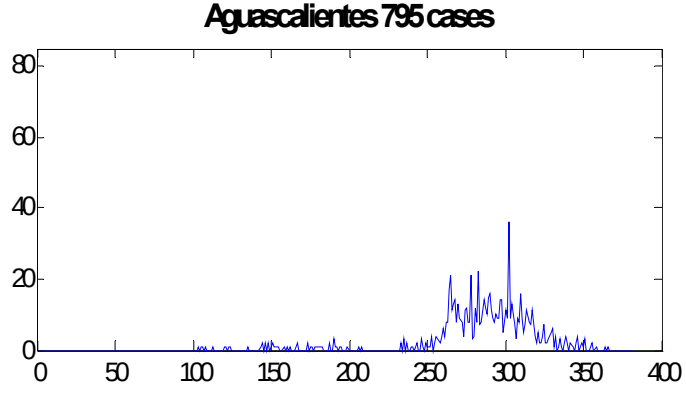

Baja California Sur 538 cases
0
20
40
60
80
0
50
100
150
200
250
300
350
400

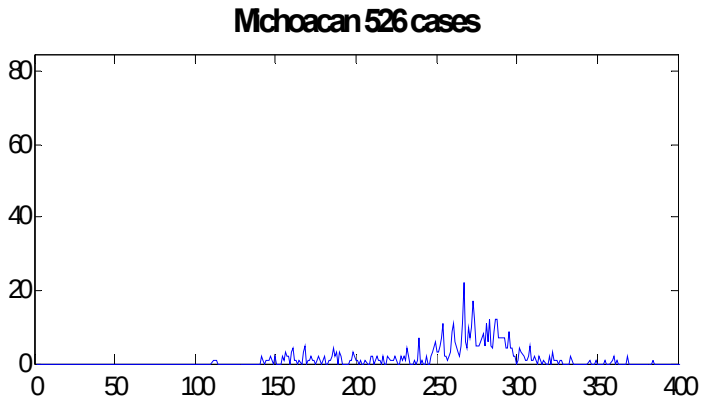

Sinaloa 361 cases
0
20
40
60
80
0
50
100
150
200
250
300
350
400

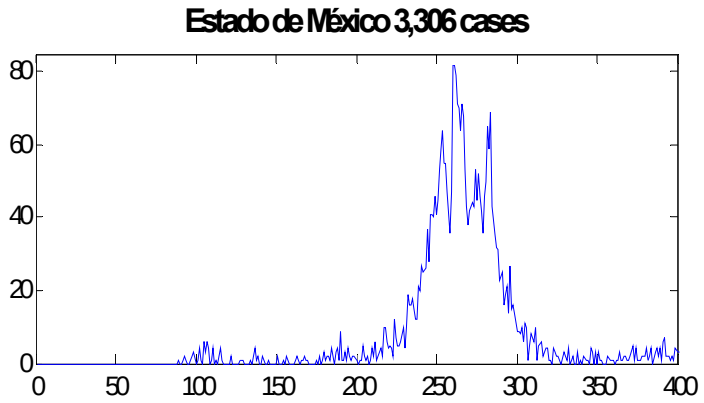

Durango 699 cases
0
20
40
60
80
0
50
100
150
200
250
300
350
400

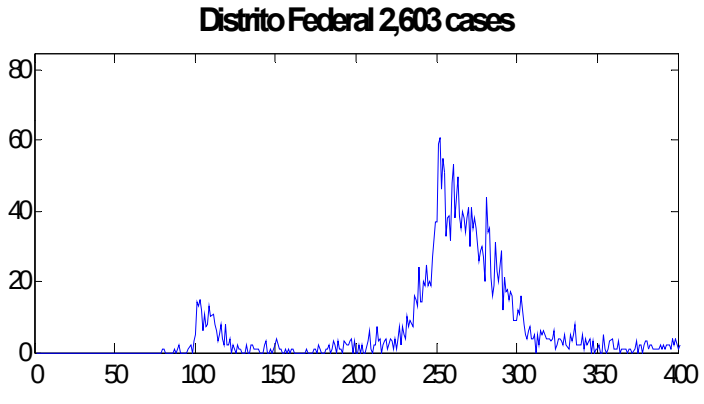

Zacatecas 367 cases
0
20
40
60
80
0
50
100
150
200
250
300
350
400

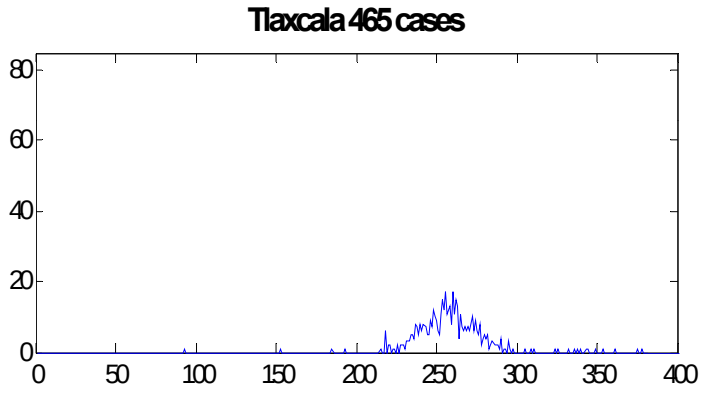

San Luis Potosi 1,901 cases
0
20
40
60
80
0
50
100
150
200
250
300
350
400

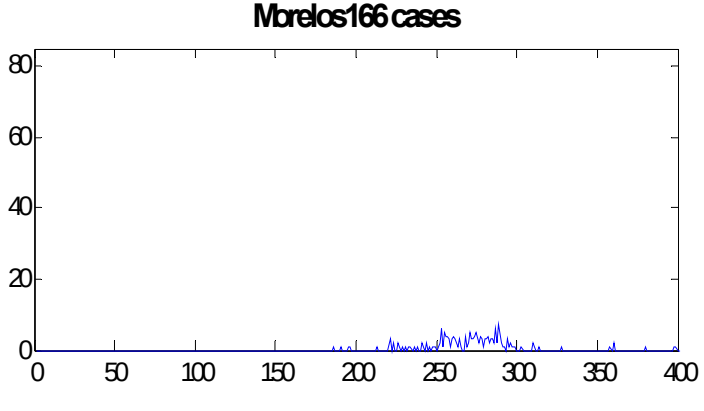

Aguascalientes 795 cases
0
20
40
60
80
0
50
100
150
200
250
300
350
400

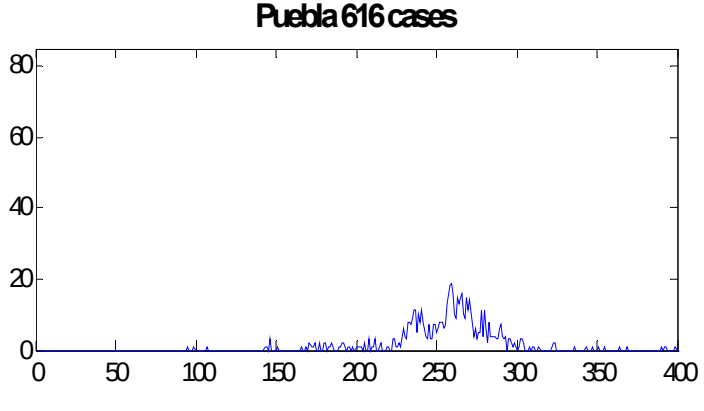

Michoacan 526 cases
80
60
40
20
0
0 50 100 150 200 250 300 350 400


Estado de México 3,306 cases
80
60
40
20
0
0 50 100 150 200 250 300 350 400

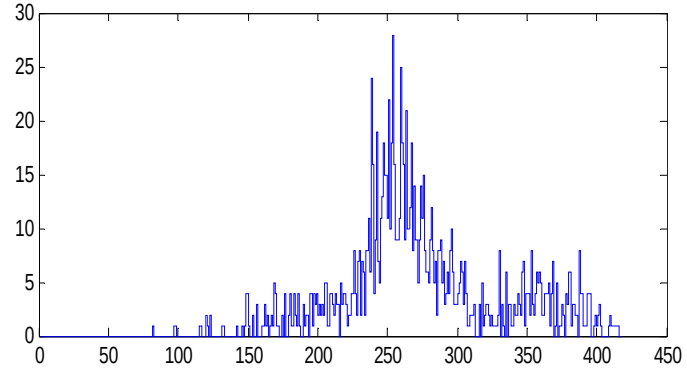

Distrito Federal 2,603 cases
80
60
40
20
0
0 50 100 150 200 250 300 350 400

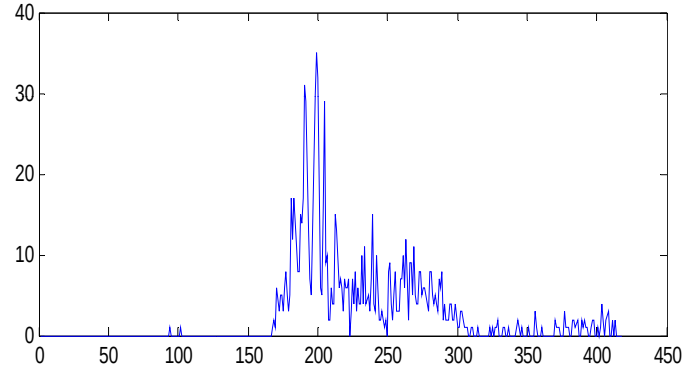

Tlaxcala 465 cases
80
60
40
20
0
0 50 100 150 200 250 300 350 400

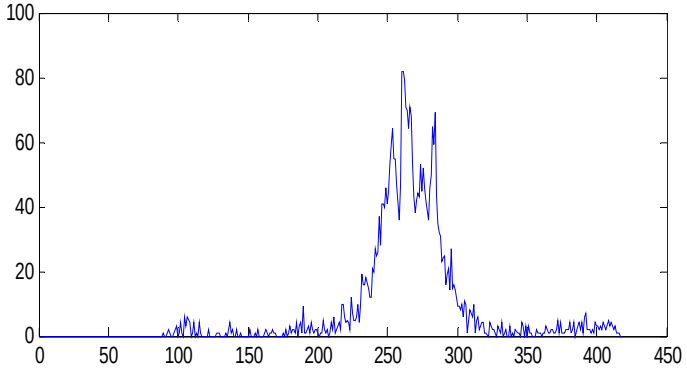

Morelos166 cases
80
60
40
20
0
0 50 100 150 200 250 300 350 400


Puebla 616 cases
80
60
40
20
0
0 50 100 150 200 250 300 350 400

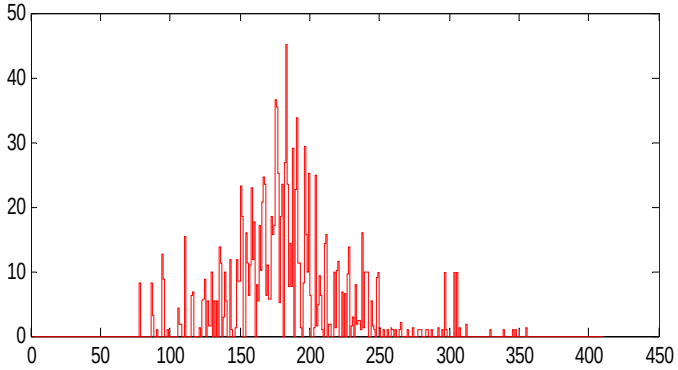
Actual data of influenza incidence

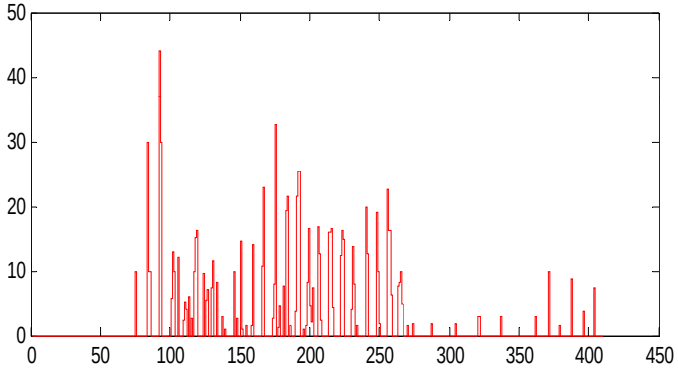


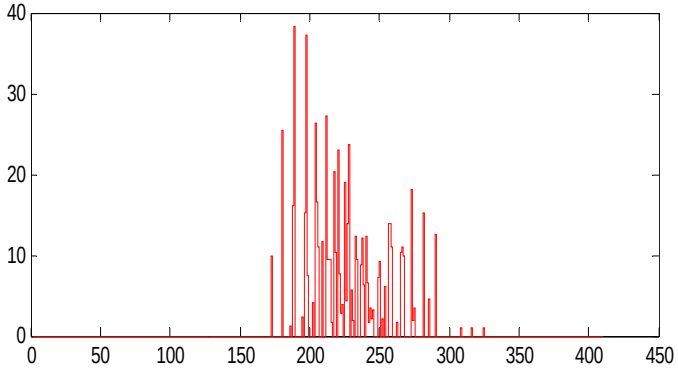


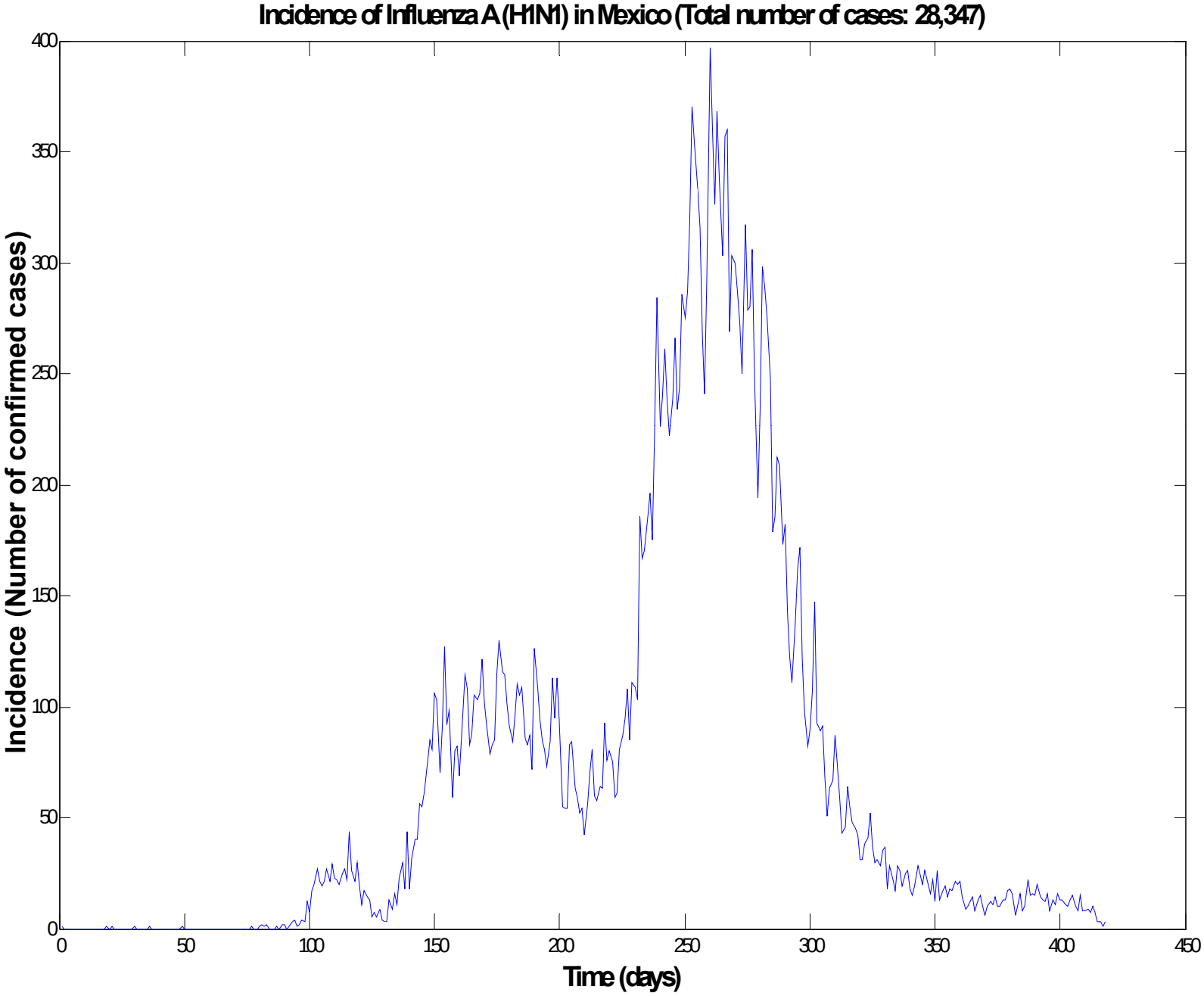


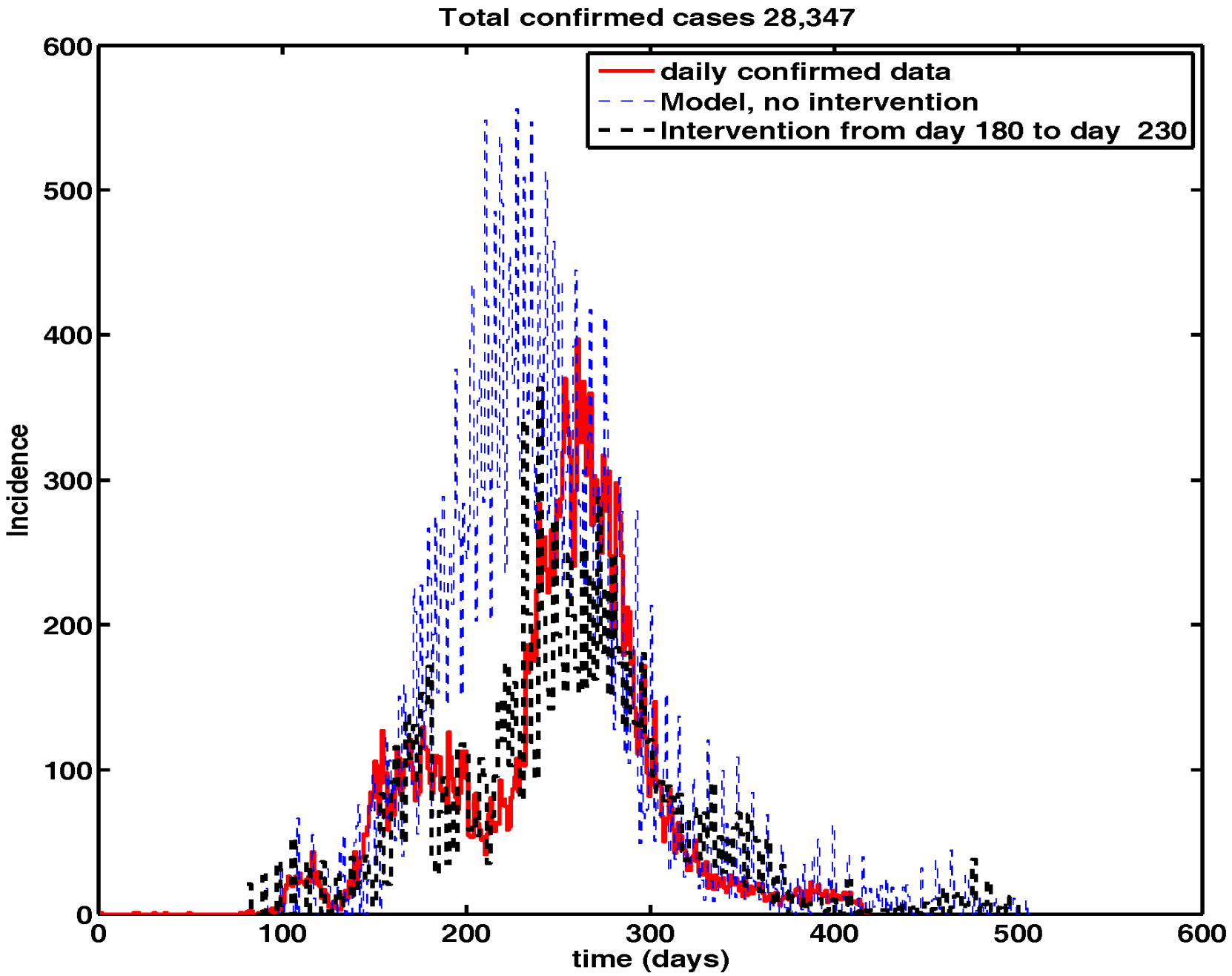
Simulation data of influenza incidence

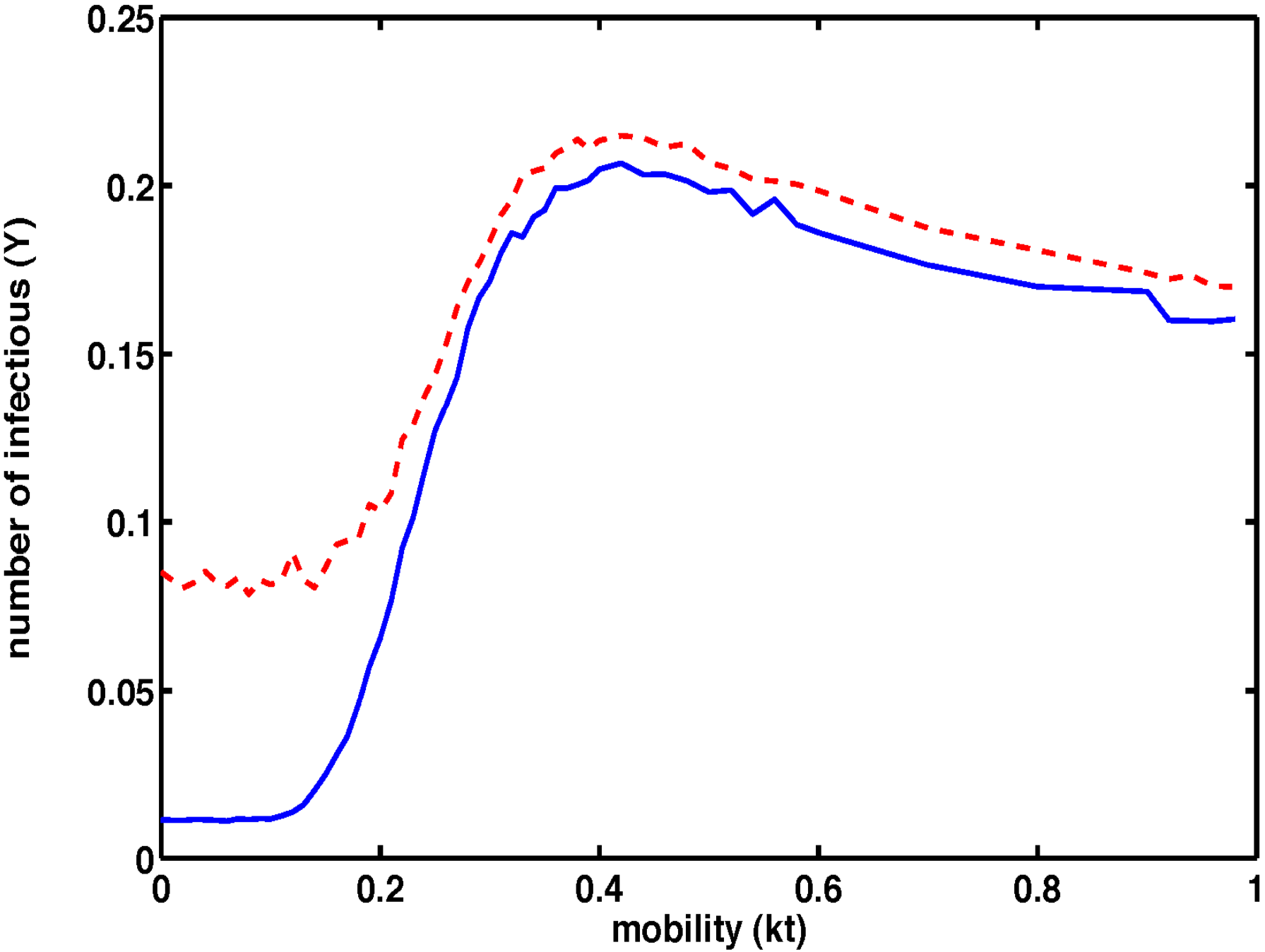






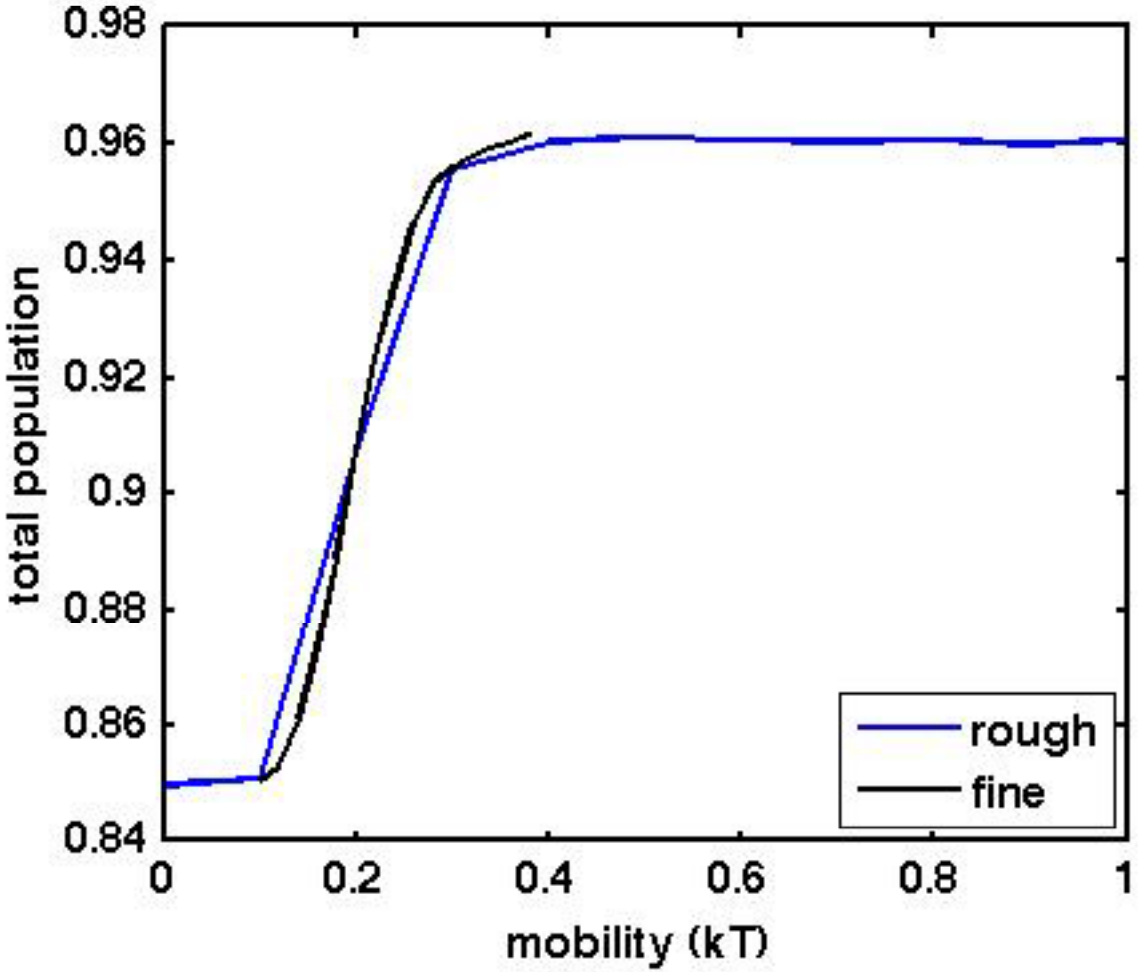

Incidence of Influenza A (H1N1) in Mexico (Total number of cases: 28,347)
Incidence (Number of confirmed cases)
Time (days)
0
50
100
150
200
250
300
350
400
450


Total confirmed cases 28,347
daily confirmed data
Model, no intervention
Intervention from day 180 to day 230
Incidence
time (days)
0
100
200
300
400
500
600

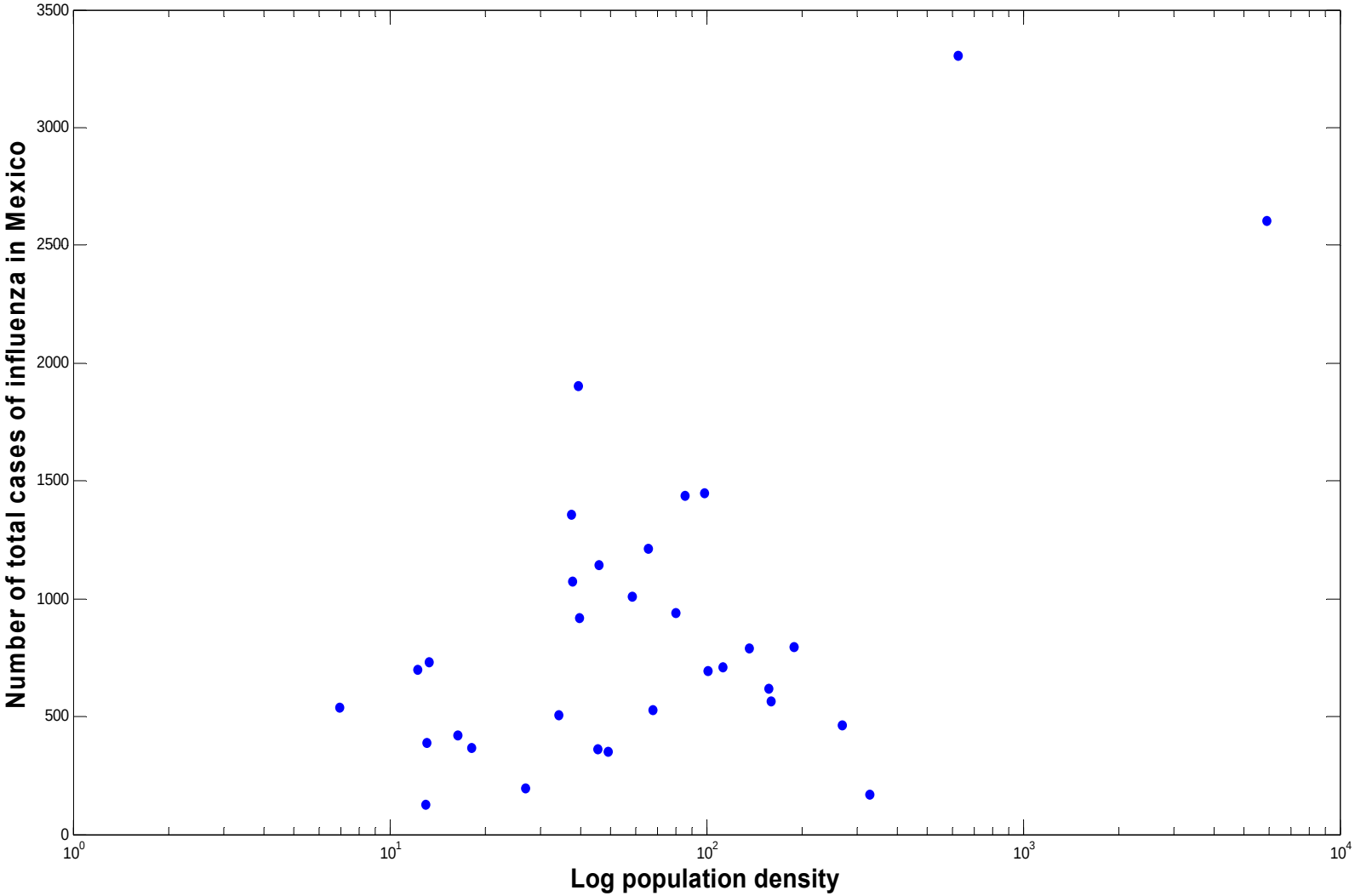

0.25
0.2
0.15
0.1
0.05
0
number of infectious (Y)
0
0.2
0.4
0.6
0.8
1
mobility (kt)

Phase transition

- S=0.1



Relationship between epidemic sizes with population density. Note that there is not an apparent correlation as it would be expected from the law of mass action.



SOME CONCLUSIONS

When we use actual data from the influenza pandemics in Mexico in 2009, the model is able to reproduce both, the local dynamics of the epidemics and the stochastic global path of the pandemic, including the effect of social distancing measures.

The local dynamics is able to reproduce a wide variety of behaviors, including sustained oscillations, and when it is combined with a stochastic spatial spread, the system becomes noise-driven, and the complete model is able to reproduce fade outs and a great variability in epidemic sizes.

We have neatly separated the parameters that regulate the specific natural history of an infectious viral disease, from the parameters that simulate demographic and social conditions of the domain where the disease is spread.

By doing so the dynamics can be regarded as the result of the interplay between the progress of the disease and the changes in the network by which it is scattered, so we can use this model to predict the effects of taking 4 kinds of measures to manage the pandemic, namely,
1) Social measures that reduce people mobility
2) Reduce the number of flights, or even cancel them altogether and,
3) Administering mass vaccination, either compulsory or not. If one associates a cost to each one of these measures, one could use this model to decide the best cost/benefit strategy to combat a future outbreak.
4) Antiviral administration

We found that pandemics can be driven solely by noise, which is a new unexpected result. Therefore, one can infer that vaccines are only very efficient if applied timely.

The basic reproduction number, R_0, depends on the stochastic nature of the infection spread.

Movies

Movie S1. No aerial-No Thermal noise-Terrestrial- $S = 1$
At the onset of the spread of the infection there are waves that form concentric circles and they are influenced by the population density and terrestrial mobility v_f but the front waves remain during the propagation.

Movie S2. No aerial-Thermal noise-Terrestrial- $S = 1$
Initially propagating concentric waves can be observed but noise has a blurring effect. The front waves persist at the boundaries of new infected areas. After a while a pulsatile-like sustained dynamics is attained. Notice that in the absence of air traveling after two years, the infection does not cover the entire Mexican territory.

Movie S3. Terrestrial-Aerial-No thermal Noise- $S = 1$
At the onset of the spread of the infection there are waves that form concentric circles but given aerial transport the infection spreads quickly to other parts of the country. Once the spread of the infection reaches other places the local spread is due to terrestrial movement manifested by waves that form transient concentric circles. There is a clash of front waves and a pulsatile-like behavior is soon apparent and the spread is sustained both in space and time.

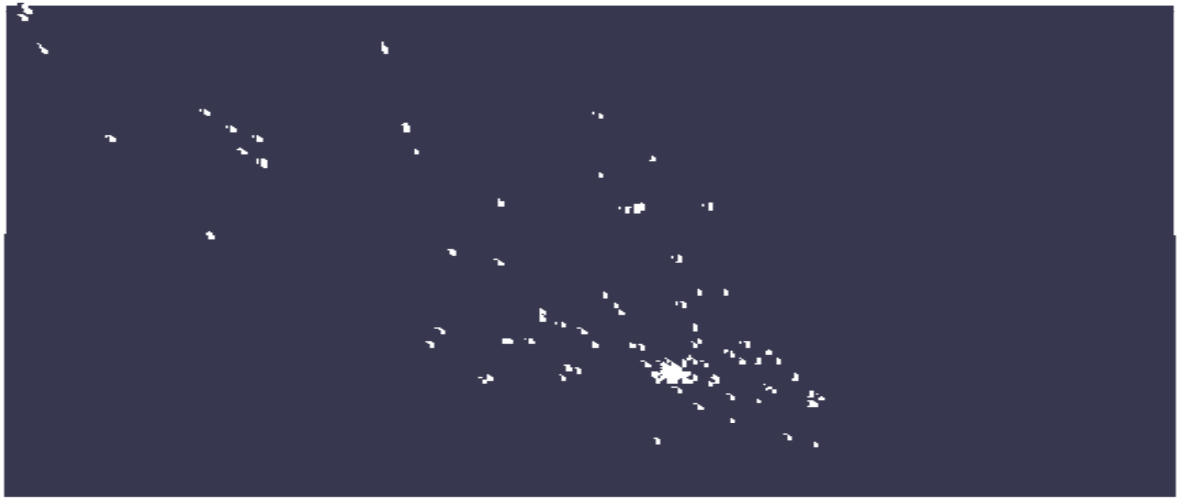
Movie S4. Terrestrial-Aerial-Thermal noise- $S = 1$
The infection spreads quickly to all over the country and it immediately shows a sustained and pulsatile-like behavior. The presence of noise makes wave fronts not discernible. The infection exhibits a regular behavior in the major cities of the country from which it spreads locally via terrestrial mobility.

Movie S5. Terrestrial-Aerial-No Noise- $S = 0.1$
The infection spreads quickly to all over the country but the front waves are not renewed and they eventually fade-out. Hence, the lack of noise does not maintain the pandemic.

Movie S6. Terrestrial-Aerial-Noise- $S = 0.1$
The infection spreads quickly to all over the country but there are not apparent front waves. The presence of noise leads to an endemic state of the pandemic.

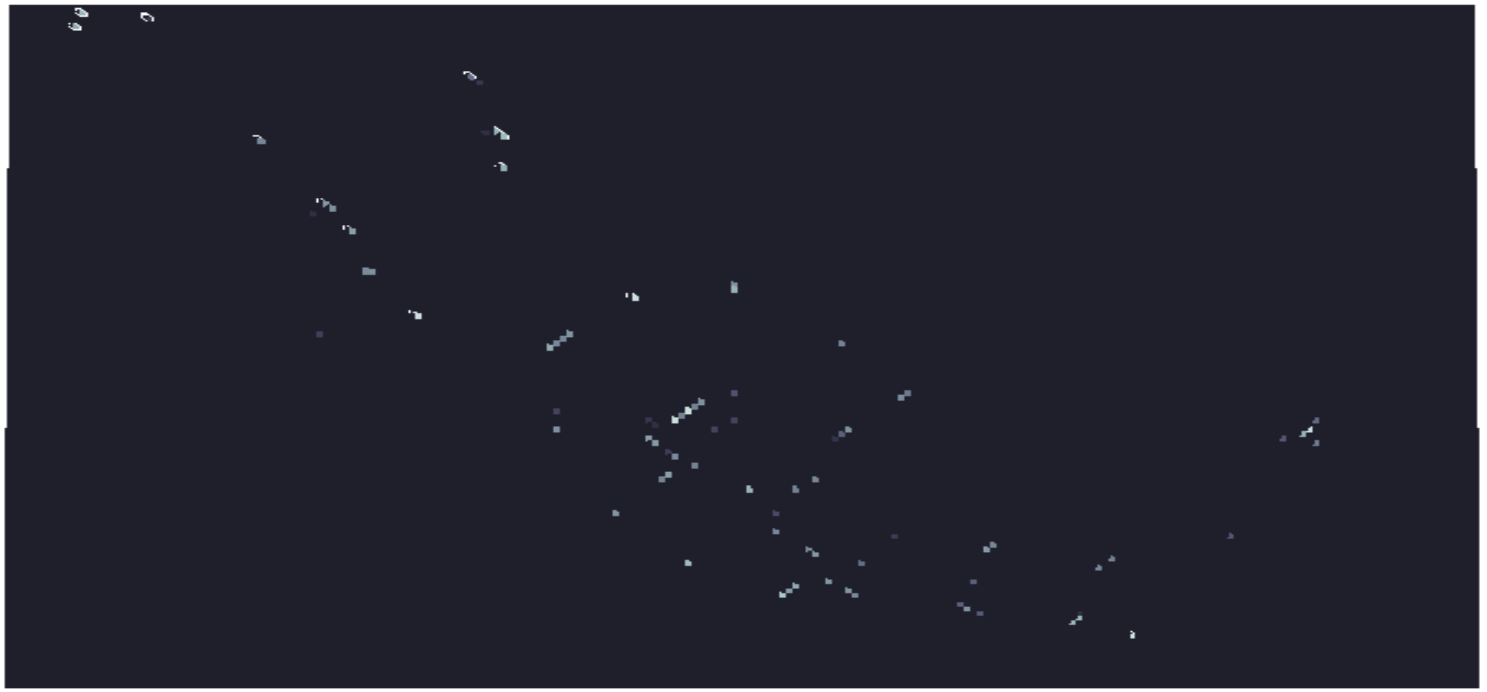
Still-Image of Movie S7 Actual Data

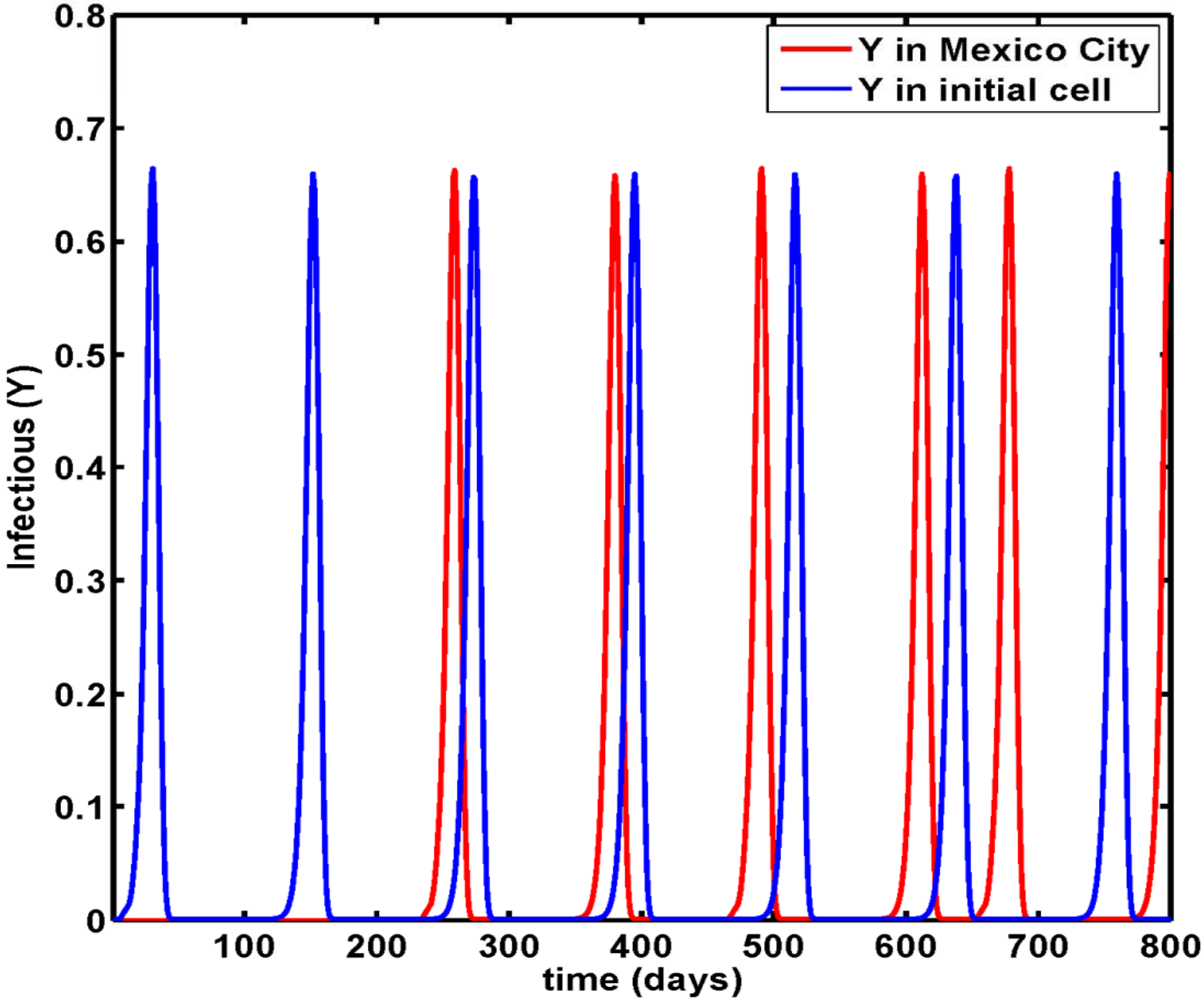
The infection starts at a small Village in the state of Veracruz. It rapidly spreads to the major cities of the country. No waves are observed because the movie considers the incidence of infection, i.e., new cases per day. The infection appears in the most populated areas of Mexico which can be considered as hubs from air traveling. The pandemic persists for some time until it completely disappears.

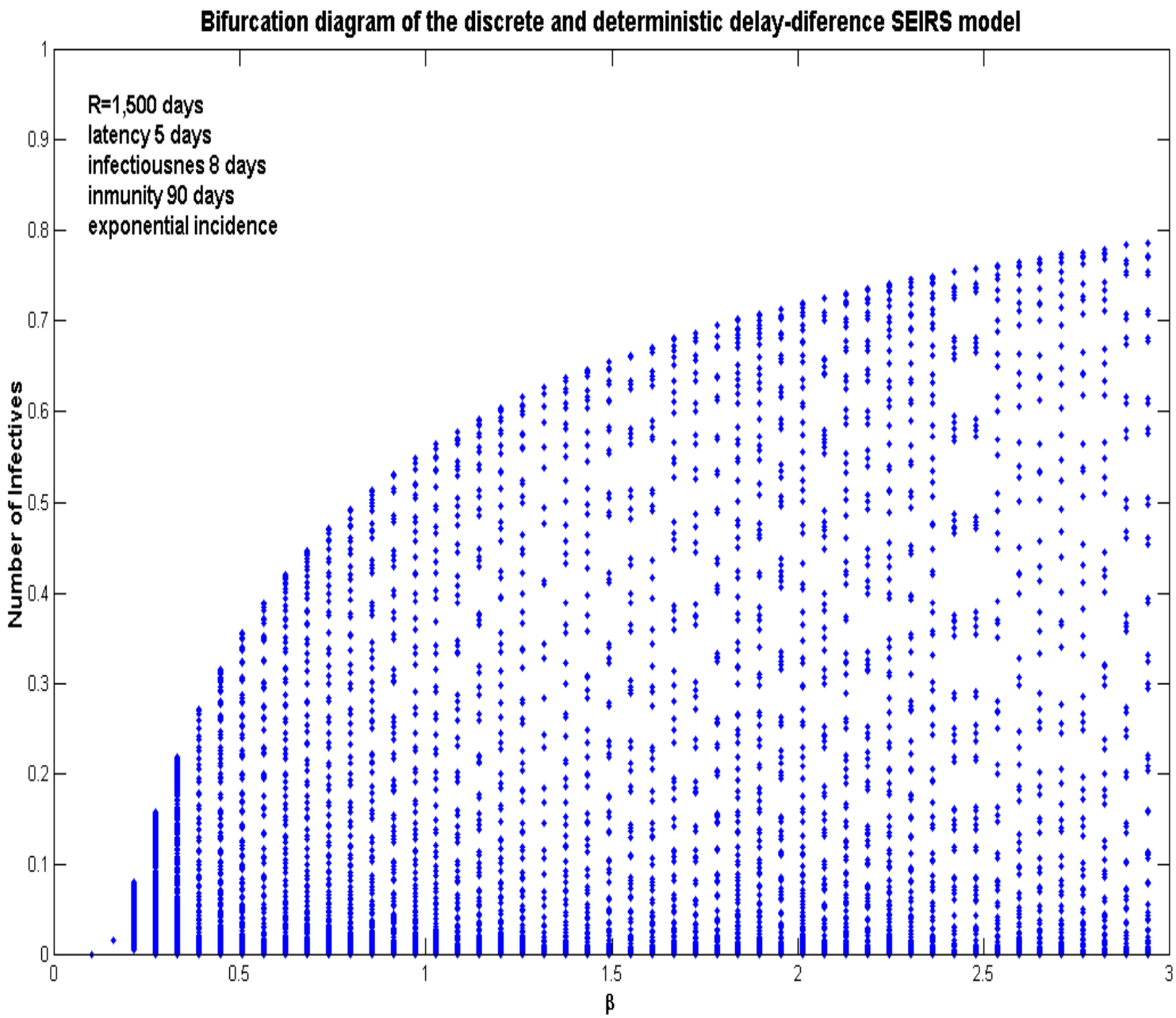


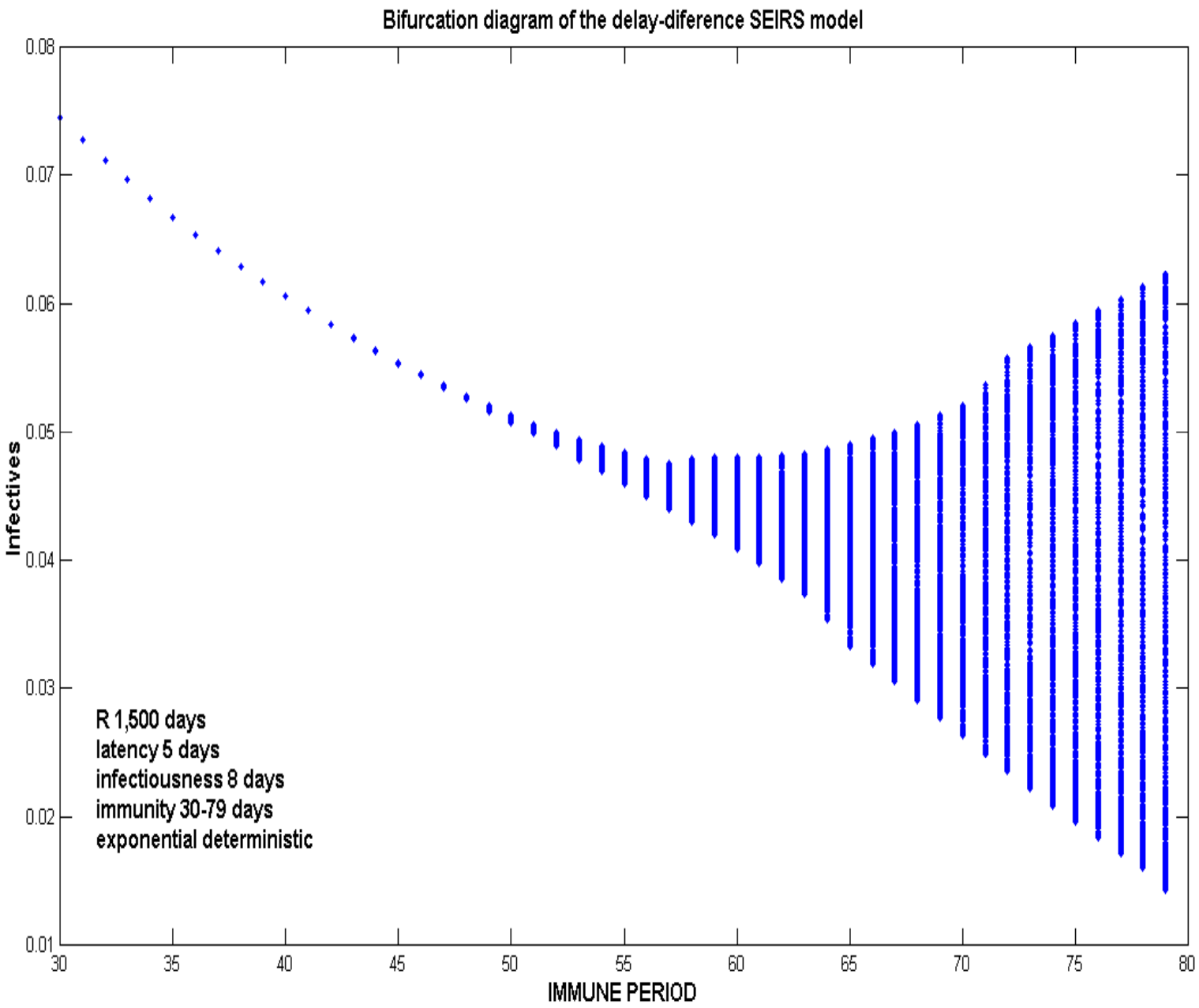
Still-Image of Movie S8 Fitting of the Model

The infection starts at a small Village in the state of Veracruz. It rapidly spreads to the major cities of the country. No apparent waves are formed because in this simulation we also took into account the daily incidence of the infection. The infection persists cyclically in the most populated areas of Mexico until the pandemic disappears. Small waves of propagation are hardly noticed.




Y in Mexico City
Y in initial cell
Infectious (Y)
time (days)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
100
200
300
400
500
600
700
800


Bifurcation diagram of the discrete and deterministic delay-diference SEIRS model
R=1,500 days
latency 5 days
infectiousnes 8 days
inmunity 90 days
exponential incidence
Number of Infectives
β
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
0.5
1
1.5
2
2.5
3


Bifurcation diagram of the delay-diference SEIRS model
Infectives
IMMUNE PERIOD
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
30
35
40
45
50
55
60
65
70
75
80
R 1,500 days
latency 5 days
infectiousness 8 days
immunity 30-79 days
exponential deterministic