SIMULATION OPTIMIZATION FOR A VACCINE DISTRIBUTION STRATEGY AGAINST THE SPREAD OF A(H1N1) EPIDEMIC.

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ABSTRACT
An optimal strategy in order to contain the epidemiological risk of the A(H1N1) disease is analyzed. We scope two different epidemic propagation models, the epidemiological SIR model proposed by Kermack and McKendrick (Kermack and McKendrick 1927) and a small-world network model, assuming that the second one shows a better performance since it considers the interactions between agents and also presents a more realistically dynamic (Moore and Newman 2000) than with the SIR model. To verify our assumption, establishing the proper disease parameters, a simulation is done for different epidemiological scenarios with both models. Furthermore, the results of simulation runs are employed for an optimal containment model based on a vaccination or self-isolation strategy. Additionally, other simulation were performed in order to obtain an optimal policy using our previous results from the spreading models simulation, getting a better insight of the diseases behavior during an outbreak.

Keywords: complex network, epidemiology, spreading models, small world networks

1. INTRODUCTION

In 2009 the human flu A(H1N1) epidemics expanded rapidly all over the five continents, with a predominance of America by the current connectivity conditions, becoming a pandemic in just a few weeks. Public Health Institutions showed a lot of concern because the lack of knowledge about this new subtype of influenza virus, which showed a high spreading factor and transmissibility in a short elapse of time. Governments, the whole society and the World Health Organization (WHO) considered this matter as a high priority issue. This motivated to search strategies needed to design adequate containment policies at the proper moment of the outbreak in order to save, not only lives, but expenses as well. But before carrying out any analysis of cost-effectiveness, it is desirable to understand the dynamic of the epidemic propagation. It is necessary to understand the disease behavior as a mathematical model of the epidemic. We implemented spatial agent-based and real time situation simulations to provide pandemic risk assessments and also we proposed optimal intervention and prevention strategies as well as to estimate costs due to the planned policy. The most common ways to control an outbreak are vaccination and isolation, each one represents a corresponding cost and benefit. An optimal intervention should consider these factors in the scheme of the epidemic containment policy, resulting on a "cost-effectiveness" analysis. The A(H1N1) disease is characterized by pre-symptomatic, infectious and recovery stages that makes detection and control cases more difficult (Kuperman et al. 2001). Therefore we explore some outgoing features of spreading dynamics utilizing the epidemiological SIR model in order to evaluate their parameters of contagious conditions, applying on a dynamically changing small-world-like network (Kuperman et al. 2001). Interactions within a population is studied by means of different kind of social networks, mathematically based on the structure of the population, which in our case presents three subpopulations that interact in proportion to their sizes. With these zero dimensional models, it has been possible to study the epidemic features, the asymptotic solution for the density of infected people, the effect on stochastic fluctuations on the modulation of an epidemic situation as well as the thresholds values. Another classical approach to the epidemic spread describes spatially extended subpopulations, such as elements on a lattice. We consider a population rarely falls into either of these categories, being neither well mixed nor lattices. Watts and Strogatz (Watts and Strogatz, 1998) introduced small world network analysis in order to study the dynamic of many social processes such as disease spreading, formation of public opinion, distribution of wealth, transmission of cultural traits, etc. In the case of epidemiological models, it has been shown that small world networks present a much faster epidemic propagation than other studied epidemic models, such as reaction-diffusion models, or discrete models based on regular lattices of a social network (Kuperman et al., 2001). In this paper we use the epidemiological SIR-Kermack-McKendrick model (KMK) to acquire the epidemic features which are well studied, later, with these parameters we simulate the spread by means of a small-world network which, as mentioned before, presents a much faster epidemic propagation. Therefore we will be able to compare our

results obtained with the KMK model. Understanding these patterns will help direct the allocation of scarce resources, thus facilitating appropriate community preparation; furthermore it will help to design an optimal containment strategy, which is the scope of this work. With this study we are able to examine the relative importance of vaccination and self-isolation, two common measures for controlling the spread of infectious diseases (Yarmand et al. 2010). Since our epidemic propagation models, either the epidemiological SIR model and the small world network model, require realistic parameters to estimate appropriate behaviors of the threshold and propagation of the disease, we focused on a specific mostly homogenous population from the Mexico´s City metropolitan zone in the range of ages form 20 – 64 years, which represents numerically the biggest social group, moreover, it seems to be the most susceptible population among the other age groups. Besides, having more realistic data of the targeted population supports the validation of our results. Additionally, simulation results validation is also sustained on the corresponding literature (Córdova et al. 2010).

Once we have obtained results from both epidemic propagation models (epidemiological SIR model and small world network model), by means of simulating with different parameters, we focused on an optimal cost-effectiveness intervention. (Yarmand et. al., 2010), proposed a linear model considering two control measures: vaccination and self-isolation, having as decision variables the proportion of the targeted population under vaccination intervention and the fraction of the population being self-isolated. We considered this optimal model as adequate to scope the effectiveness of either of both models inasmuch as it presents a very useful simplicity for comparing our results. Accordingly, thus we find that the objective function is the linear summation of the relative costs of vaccination and self-isolation by considering the relative marginal costs, associated with each of the decision variables. Constrains are related to the number of individuals under treatment and to the percentage of total infective individuals (attack rate). Hence the present work seeks a strategy for mitigating the severity of the A(H1N1) influenza pandemic based on the threshold number Ro..

2. LITERATURE REVIEW

In this section we present an overview of the literature pertaining to contributions related to the disease spreading through a social network, especially on a small work network. Also a review is done on references about epidemiological containment strategies.

D. Watts and Strogatz (Watts, Strogatz 1998) designed in 1998 a model of dynamic networks for collective phenomena called “Small world”, which differences the homogeneous agents as it had been treated before in heterogeneous agents, whose interactions are random, producing an intermediate between regular networks and completely disordered ones, being better its approximation for social networks, neuronal networks, electricity transmission networks, and even for diseases’ spread networks. Their work was related with the model realized by L. Sattenspiel and C. Simon in 1987 (Sattenspiel and Simon, 1998), which defined mathematically the spread and prevalence of an infection inside a heterogeneous population, considering the possible interactions within the population. Their work is the main reference for the construction of the diseases spread. M. Kuperman and G. Abramson (Kupermann and Abramson, 2001) used in the year 2001 this approach to networks in order to build the spread of an epidemic, in like manner, Matt J. Keeling and Ken T. D. Eames (Keeling and Eames, 2001) proposed epidemiologic models related with networks. Meanwhile, Cristopher Moore and M. E. J. Newman (Moore and Newman, 2000) presented a model that approached the spread of an epidemic using a model of percolation and networks like the “Small world”. Alexei Vázquez (Vázquez, 2006) came up with a work that supported the idea of analyzing the topology of an infection spread based on the analysis of a network with homogeneous nodes with a correlation with the measures of the K network, concluding that the rate of contagion between an infected node and a susceptive node is proportional to the average measures of the K network, therefore suggesting that the spread of an epidemic can be researched with the model of the networks “Small world”. Eduardo Cuestas, Mario Vilaró, and Pablo Serra (Cuestas et al., 2011) proposed a model of predictability of the spatial and temporal spread of the epidemic of the influenza H1N1 in Argentina with the method of percolation. The researchers Mauricio Canals and Andrea Canals (Canals and Canals, 2010) also designed a model based on a model of percolation for the epidemic of the influenza H1N1, and the obtained data would be compared geographically by the WHO (World Health Organization), indicating with this the validity of this kind of approach. Dionne M. Aleman, Theodorus G. Wibisono, and Brian Schwartz (Aleman et al., 2011) made a simulation of the spread of a disease during a “pandemic” outbreak based on non-homogeneous agents. In regard to the works that have been realized in Mexico, the most notorious one is the one made by Córdova Villalobos, et al, (Córdova et al., 2010), in which a compilation of 42 experts of many fields in health sciences is done. These studies are about epidemics from several points of view, allowing the comprehension and planning against the influenza A (H1N1). At the National University of México (UNAM) there is a project that studies collective phenomena called FENOMEC, and in this project G. Cruz-Pacheco, L. Esteva, A. A. Minzonil, P. Panayotaros, and N. F. Smyth (Cruz-Pacheco 2005) proposed a mathematical model for the spread of an epidemic.

Thus once that the spread of an outbreak has been studied, many projects have been based on these

models and proposed strategies to contain it. Kleczkowski A., Olés K., Gudowska-Nowak E. and Giññigan C.A. (Kleczkowski et al., 2011), designed a strategy based on a small world network that would reduce the costs of controlling the spread. Meantime, Pinar Keskinocak, Ali EkiciJulie, and L. Swann (Keskionacak et al., 2013) designed a plan for food distribution during an influenza spread. Sean Carr and Stephen Roberts (Carr and Roberts, 2010) developed a simulation to locate clinics and hospitals, and the distribution of resources during the spread of the epidemic of the influenza H1N1. Yarmand, Ivy, Roberts, Bengtson and Bengtson (Yarmand et al., 2010) studied and analyzed the cost vs. the effectiveness between vaccination and isolation related to the epidemic of the H1N1. Another research about the distribution and optimization of vaccines during an outbreak of H1N1, was made by Yarmand, Julie S. Ivy, Brian Denton, Alun L. and Lloyd (Yarmand et al. 2014), this research considered the optimal location of the vaccination in two phases in different geographical regions that are under uncertainty.

3. EPIDEMIC SPREADING MODELS

3.1. SIR kinetic model

Traditionally the process of disease spreading relied on differential equations whose solutions describe the time propagation of the disease within uniformly mixed populations which means that all individuals in the population are equally likely, hence any infected person is equally likely to infect any other person. The spreading process itself is modeled using rate equations, describing population flows between epidemiological classes of individuals, such as susceptible (S), exposed (E), infective (I), and recovered (R). The simplest of these types of models is the widely-utilized Susceptible-Infected-Removed (SIR) model, in which susceptible individuals (S) may become infected (I) and continue to infect others until finally removed (R) from the population due to recovery, death, or self-containment. This compartmental model, however, doesn´t consider heterogeneity nor the spatially or the contact patterns between individuals effects, but only that an infected agent transmits the disease to a susceptible agent with a time rate *t*. The total population is given by $S(t)+I(t)+R(t) = N(t)$. This model assumes a closed population, meaning there are no births, deaths or travel into or out of the population. Between S and I stages, the transition rate is β I, where β is the contact rate, which takes into account the probability of getting the disease in a contact between a susceptible and an infectious subject. Stages I and R interact with the transition rate of recovery or death γ. If the duration of the infection is denoted τ, then $\gamma = 1/\tau$, since an individual experiences one recovery in τ units of time.

The SIR system described above can be expressed by the following set of ordinary differential equations:

$$\frac{dS}{dt} = -\beta IS$$

$$\frac{dI}{dt} = \beta IS - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

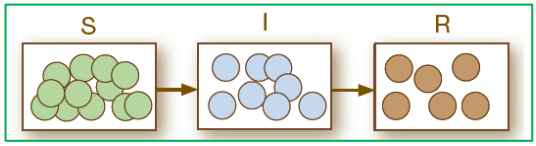

fig.1 SIR compartmental model

A key term in the study of epidemics is the basic reproduction number $\mathbf{R_0}$ (also called basic reproduction ratio). This ratio is derived as the expected number of new secondary infections from a single infection in a population where all subjects are susceptible. This quantity describes the epidemic threshold such that when $R_0 > 1$, the population is vulnerable to a large scale epidemic, although not guaranteed to experience one. Conversely when $R_0 < 1$, the population only experiences small local outbreaks. Hence R_0 serves as an order parameter for the phase transition. In the SIR model the R_0 number is calculated by:

$$\text{Ro} = \beta\frac{N}{\gamma} = N * \frac{\ln\left(\frac{S(0)}{S(t)}\right)}{(N - S(t))}$$

For setting up the parameters for the simulation, R_0 was set to R_0=1.4.

3.2 SIR model on dynamic Small-World network

As mentioned in the previous sections a population rarely shows a well- mixed behavior, nonetheless a population shows spatiality between individuals, heterogeneity. Therefore an outlook on social contacts arises for describing the spread of a disease. Instead of relying on this kind of mean-filed models we used an epidemic propagation model based on the effects of contacts patterns between individuals, described by contact networks, where the vertices correspond to individuals and the edges to contacts between them (Chen, 2005), resulting on much insight in the context of spreading processes obtaining a more realistic network topologies such as small-world networks. For developing the model we capture some outlining features of the A(H1N1) epidemic spreading dynamics by utilizing the SIR mechanism on a dynamically changing small-world contact network (Saramäki and Kaski, 2005). For a formulation of our spreading model, we consider a social network, such as various networks, displays the small world property, which means that long-range contacts between individuals result in short average distances along the edges of the network. In epidemiology these long-range contacts can be considered either infrequent contacts or random encounters taking place in an underlying regular short-range network structure, which in turn can be interpreted as groups of people having regular or frequent contacts. Therefore, we define our network as a regular one-dimensional ring-shaped lattice of N

vertices with fixed coordination number $2z = 4$, with additional temporary long-range links, a clustering coefficient $C(k)$ between $0 < C(k) < 1$, and changing their configuration at random with a rewiring probability P. The rewiring mechanism is equivalent to link exchanging method [13], at each time step, we randomly select a pair of edges A–B and C–D. These two edges are then rewired to be A–D and B–C. To prevent multiple edges connecting the same pair of nodes, if A–D or B–C already exists in the network, this step is aborted and a new pair of edges is randomly selected. (Figure 2).

For the spread dynamic we use the SIR mechanism, such as any node is labeled as susceptible S, or as infected I or as recovered R. Initially, the number of susceptible individuals is N – I, where I corresponds to the initial outbreak size. The dynamics of the model is such that at every discrete time step of the network with lenght Δt, it is randomly rewired and each infected individual in the network infects its new nearest neighbors, if susceptible, so that each infection occurs with an attack rate transmission (ART) determined by the own features of the A(H1N1). We established this ART = 5% and 10%. Once a vertex becomes infected, after some virus check frequency it becomes recovered R with a random gain resistance chance. At this stage the individual recovers and can no longer be infected or infect others (the individual is resistant to the virus). The process ends until any individual is no longer infected.

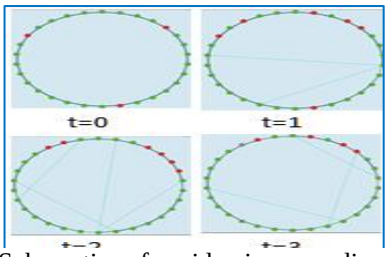

Figure 2: Schematic of epidemic spreading on a dynamic small-world contact network with coordination number $2z = 4$. At times $t = 0,2,3,4$ three vertex are infected (solid red circle). Then the infection spreads to neighboring vertices as well as randomly chosen far-off vertices with a rewiring probability P. Recovered vertices are shown as solid grey circles.

3.3. Optimization model

Additionally to the propagation model we needed to prepare an optimization model in order to obtain the optimal strategy based on a cost-effectiveness scope (Ferguson et al. 2005). As mentioned above, a linear model was used being decision variables vaccination fraction and self-isolation fraction among infected population denoted by $\boldsymbol{p_1}$ and $\boldsymbol{p_2}$ respectively. Constrains are the number of individuals under treatment, percentage of total infective individuals, and the threshold number R_0, those data were previously estimated by means of the epidemic spread model simulation. And the objective function is related to relative costs of the considered interventions, c1 for vaccination and c2 for self-isolation, obtaining an optimization model as the following:

$$\boldsymbol{min\ Z = c1p_1 + c2p_2}$$

Subject to:

Max number of people under treatment (related to surge capacity) ≤ V1

% of infected people among the population ≤V2

$$\boldsymbol{Susceptible \leq R}$$

Since c1 and c2 are relative costs, then we have

$$\boldsymbol{c1 + c2 = 1}$$

$$\boldsymbol{0 \leq V1 \leq total\ population}$$

$$\boldsymbol{0 \leq V2 \leq 1}$$

$$\mathrm{R} = \boldsymbol{(1\text{-}\%\ susceptible\ population) * R_0}$$

Where V1, V2, c1 and c2, are determined by the modeler based on our results of the prior epidemic models simulation. We also assumed costs c1 and c2 being both 0.5 (Yarmand, 2010).

4. SIMULATION

As mentioned, we prepared two simulation models for the spread of the A(N1H1) epidemics, one using the KMK epidemiological SIR model (Kuperman and Abramson 2005; Kermack and McKendrick, 1927) and the other uses the SIR model mechanical on the small-world network dynamic, as in the Watts and Strogatz model (Moore and Newmann 2000; Kuperman and Abramson 2005; Saramäki J, Kaski 2005; Xiao et al. 2003). Once we established the parameters, NetLogo 5.0.4 software was used to perform the simulation for different scenarios of propagations disease. This software was employed, mainly, because of its agent-based framework, which was of great relevance for the scope of this research, also the versatility of this software was proven, and given that it contains several libraries in which it is possible to develop different kind of models with remarkable simplicity without loss of generality. Besides, it has not been enough employed in the epidemic spread simulation field. Thereby we were able to perform our simulation, to obtain the needed scenarios for a later searching of the optimal epidemical mitigation strategy. The KMK virus spread model included in the model libraries was used for the search of features for the A(H1N1) epidemic. As mentioned, the NetLogo agent-based framework was useful to develop our small-world network virus spread model.

For the optimization model Lingo software was employed to optimize the simulation results.

4.2. Model parameters

A simulation was made considering the A(H1N1) disease parameters based on the WHO assumptions for our targeted Mexico city´s population and on the gathered data during the 2009 outbreak. Definitions and values of the corresponding parameters needed for the KMK disease spread model dynamic as well as for the small-world network model are depicted in Table 1

Table 1: Definitions and values of parameters for KMK model

Parameters	Definition	Estimated value
$1/\gamma$	Infectious period	1.5 days
$1/\kappa$	Latency period	1.9 days
Average recovery time	Total time since the contagious moment	3.4 days (84 hours)
Recovery chance	Inverse of mortality rate	98%
Attack Rate Transmission ART	Is the infection chance	7.5%
Transmission risk	Corresponds to the infection chance. This parameter affects directly the transmission rate β	is adjusted during the simulation process to acquire the corresponding R_0 threshold value

4.3. Simulation runs

Once we established the parameters, NetLogo 5.0.4 software was used to perform the simulation for different scenarios of propagations disease. We used the NetLogo epiDEM-Basic model which is structured on the KMK model (Yang and Wilensky, 2011). We performed the simulation for an ART= 5%, and a population size of 100 people with the following adjustments: (see Figure 3.). In order to average the R_0's outcomes, 30 replications were run.

Figure 3. Adjustments for the KMK model to

With the previously Ro distribution with KMK model results we setup our small-world network model to fit with these results. (Figure 4)

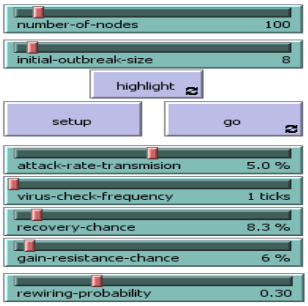

Figure 4. Adjustment controls for the Small-world network model

5. RESULTS AND ANALYSIS

The results obtained from our epidemic spread models show a scope of the different scenarios during the A(H1N1) epidemic outbreak using the disease parameters and focused on a specific population. For adjusting the Ro threshold 30 experiments were performed with the established parameters.

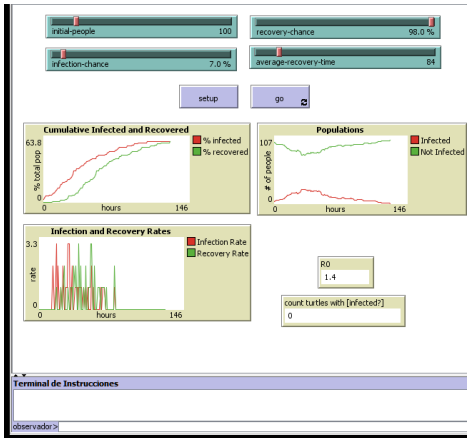

Figure 5. NetLogo Interface simulating KMK SIR model

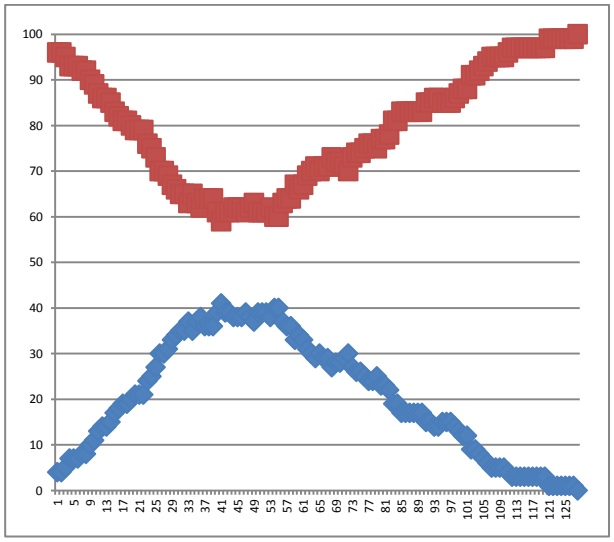

Figure 6. Averaged dynamic of KMK model with ART 5% and Rho=1.4. Blue series corresponds to the averaged proportion of infected people. Red series corresponds to averaged not infected people. The averaged dynamics last about 127 hours.

Next we performed our SIR adapted to a small-world network model with a population of 100 nodes, an outbreak size of 5 an ART of 5%.

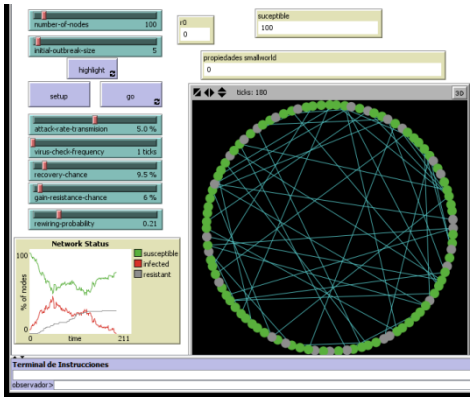

Figure 6. NetLogo Interface simulating small-world network model

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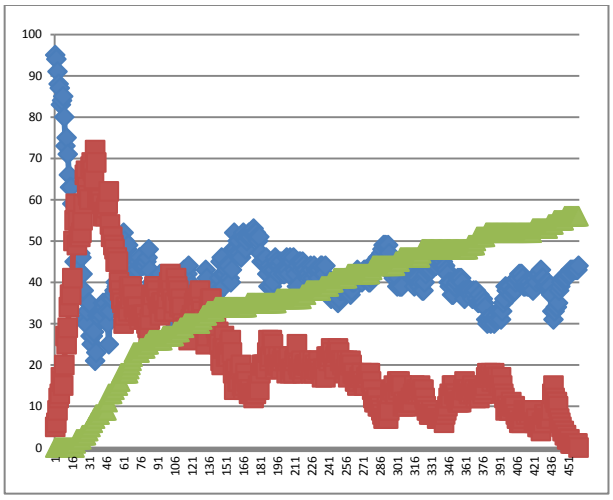

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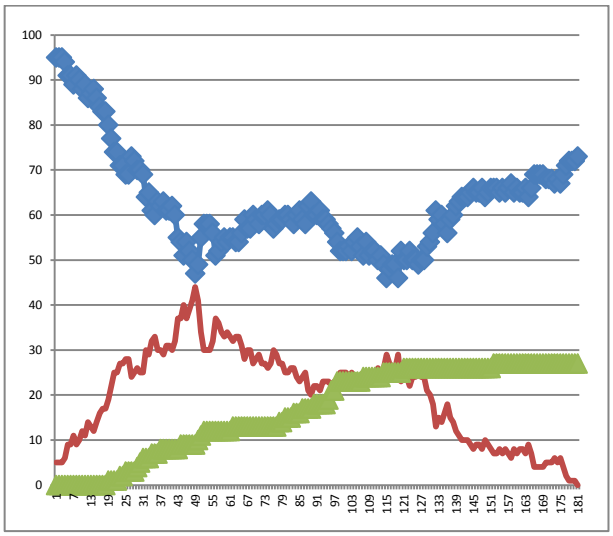

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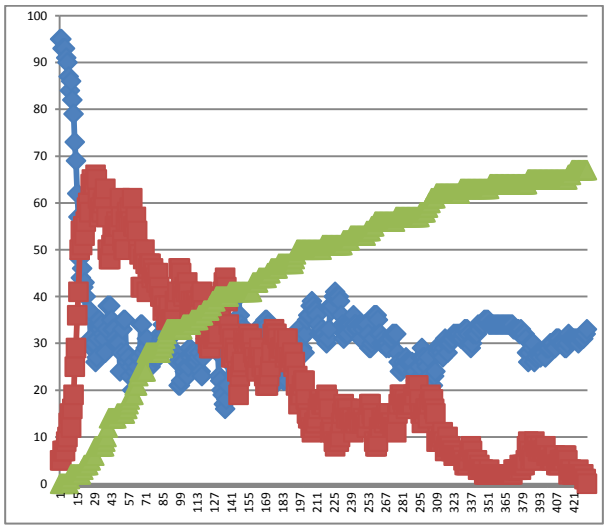

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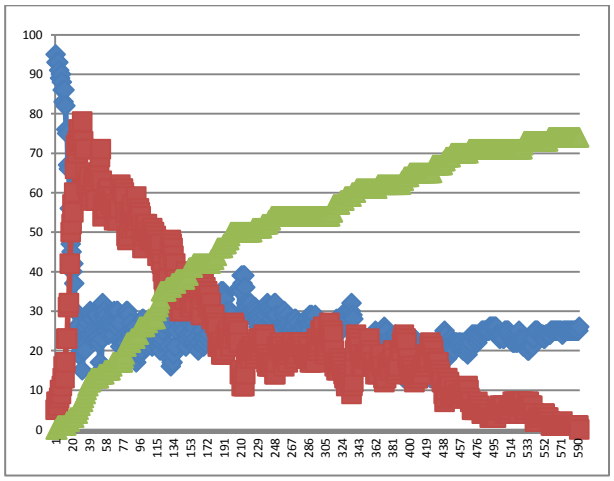

Figure 7. Plots of averaged dynamic. 30 experiments were performed for each rewiring probability. Red series corresponds to the dynamic of infected nodes. Blue series corresponds to susceptible. Plot A corresponds to a rewiring probability P=0.5 with Rho=1.4. Plot B corresponds to a rewiring probability P=0.3 with Rho= 1.25. Plot C corresponds to a rewiring probability P=0.6 with Rho =1.57. Plot D corresponds to a rewiring probability P=0.7 with Rho =1.75

After our parameterization of the simulation, several runs were performed in order to obtain the corresponding A(H1N1) Rho threshold of 1.4. While with the heterogeneous mean-field modeling many parameters needed to be set to acquire the Rho, also s the dynamical behavior of the spread didn´t show a regularity in the outcomes, as much as about 30 experiments should be developed in order to average Rho =1.4 (±0.2) (Córdova et al, 2010).

Conversely, the small-world network model to keep the averaged Rho at the range of 1.4, just the rewiring probability should be adjusted, obtaining a suitable outcomes at the range of P=0.5 with less than 10 repetitions and with an error of less than 0.07, also

the disease parameters were maintained at its initial values established as mentioned above.

Once we have a good method to estimate the threshold number Rho, it is possible to design a containment strategy with an optimization model considering that Rho depends on the susceptible population. Fraser (Fraser, 2007) recommends that to develop a vaccine distribution strategy, the susceptible population for the A(H1N1) outbreak occurred in 2009 should be of 70%, which corresponds to a Rho =1.4.

Some remarkable results emerge from the corresponding plots; When the rewiring probability increases, outbreak duration lasts longer, as well as the threshold Rho increases. About the behavior of the population stages, one can notice that the susceptible population behaves asymptotically proportional to the rewiring probability.

Comparing with the literature, it has a proper fit with the with real data obtained from the A(H1N1) outbreak occurred from March to September 2009. (Cordova et. al., 2010)

6. CONCLUSIONS

Significant difference should be appreciated for both spread models, thus the "small-world" network model shows a better performance and a more accurate estimation than SIR KMK model. Although the small-world model doesn´t consider the disease features, it shows a good performance in the epidemic dynamics The present work pretends to be a good issue in order to collaborate with a better estimation of the dynamics during a new outbreak of A(H1N1); also to generate more realistic scenarios in order to develop a more accurate proper planning on containment strategies.

We suggest for a future research to use the simulation of our model, to build an optimization model with the objective the amount or fraction of the population should be vaccinated and how many should be self-isolated and especially in any time.

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