International Journal of Bifurcation and Chaos

DYNAMICS OF PERSISTENT INFECTIONS IN HOMOGENEOUS POPULATIONS

JOAQUÍN SANZ[1,2], LUIS MARIO FLORÍA[1,2], and YAMIR MORENO[1,3*]
[1]*Institute for Biocomputation and Physics of Complex Systems (BIFI), University of Zaragoza, C/ Mariano Esquillor, Edificio I + D, Campus Ro Ebro, 50018 Zaragoza, Spain*

[2]*Department of Physics of Condensed Matter, Faculty of Sciences, University of Zaragoza, C/ Pedro Cerbuna 12, 50009 Zaragoza, Spain*

[3]*Department of Theoretical Physics, Faculty of Sciences, University of Zaragoza, C/ Pedro Cerbuna 12, 50009 Zaragoza, Spain*

Received (to be inserted by publisher)

Modeling the dynamics of persistent infections presents several challenges. These diseases are characterized by long latency periods, which makes it compulsory to consider populations of varying sizes. In this paper, we discuss a model for the spreading of persistent infections in homogeneous, well-mixed, populations. We first derive the equations describing the system's dynamics and find the epidemic threshold by means of a stability analysis. Analytical solutions are then shown to agree with results obtained with numerical simulations. The present model, although simple, open the path to more complex approaches to the spreading of persistent infections.

Keywords: Epidemiology, tuberculosis, persistent infections

1. Introduction

Epidemic spreading processes constitute a vast field of intense research since nearly a century [Anderson & May, 1992; Daley & Gani, 1999; Murray, 2002]. The mathematical models developed in this period to describe disease dynamics have become invaluable tools for health authorities. These theoretical tools have been at the root of many of their decisions about strategies of vaccination, prevention and profilaxis [Anderson & May, 1992; Daley & Gani, 1999; Murray, 2002; Strogatz, 2001]. As time goes by, these models have suffered a gradual process of sophistication, incorporating the influence of new parameters of the substrate populations on top of which the epidemics take place [Hufnagel *et al.*, 2004; Guimerá *et al.*, 2005; Colizza *et al.*, 2006] and considering each time more subtle and precise dynamics [Li *et al.*, 1999; Gómez-Gardeñes et al., 2008]. The improvement of computational platforms with ever-increasing complexity aimed at providing models with high accuracy and predictive power necessary implies the gathering of

*Correspondig author: Dr. Yamir Moreno, Institute for Biocomputation and Physics of Complex Systems (BIFI), University of Zaragoza, Edificio I + D, C/ Mariano Esquillor s/n, Campus Rio Ebro, Zaragoza 50018, Spain. phone: +34 976762993 fax: + 34 976 762990 e-mail: yamir.moreno@gmail.com

information regarding both population structure and disease specificities. The task of improving the quality and accessibility of the actual information required for an optimal description of epidemic processes is challenging, but in the last few years, the topological characterization of contact networks on top of which epidemics take place has actually stirred up the discipline [Boccaletti et al., 2006; Eubank et al., 2004; Colizza et al., 2007; Gómez-Gardeñes et al., 2008; Colizza & Vespignani, 2008; Meloni et al., 2009]. This has been feasible thanks to the use of new computational methods, and the incorporation of data coming from such diverse sources as simple statistical surveys [Liljeros et al., 2001], mobile phone calls registers [González et al., 2008], bank note mobility patterns [Brockmann et al., 2006], global transport networks [Colizza & Vespignani, 2008] and geo-demographical distribution of population [Ferguson et al., 2005].

Despite of all the progresses made, epidemic modeling has not gained in accuracy for all diseases. In fact, as a consequence of its greater -and grateful- mathematical simplicity, the SIR (susceptible-infected-recovered) and SIS (susceptible-infected-susceptible) models are the frameworks for which highest levels of accuracy and sophistication have been achieved, both at a theoretical, general level [Pastor-Satorras & Vespignani, 2001; Lloyd & May, 2001; Moreno et al., 2002, 2003] or within more precise, applied scenarios [Meloni et al., 2009; Gómez-Gardeñes et al., 2008; Ferguson et al., 2005]. Moreover, the current degree of modeling sophistication corresponds to short-cycle diseases, whose main feature consists in that individuals become infectious suddenly after becoming infected [Murray, 2002]. These are the cases of diseases that typically transmit from one person to another like respiratory virus and influenzas, two highly topical examples being SARS and H1N1 (influenza A). The fact that the cycle of infection is short-lived allows a most efficient reconstruction of the contact maps between infectious and susceptible individuals and a key theoretical and computational approximation, common to most of current models: the total population size can be assumed to be constant during the outbreak.

Persistent diseases −for which infected individuals can enter into asymptomatic, latent states for a not negligible periods before developing clinical symptoms− are the paradigmatic, opposite scheme to short cycle diseases, both regarding the mathematical and computational challenges that its modeling represents, and the relative less sophisticated models currently available [Li *et al.*, 1999; Murphy et al., 2002; Sanz et al., 2010]. However, the global impact of persistent diseases -mostly in underdeveloped countries- is everything but a small problem, evidencing the need for a global research effort. Specifically, the most threatening persistent pathogen is the tuberculosis (TB) bacillus. Mycobacterium tuberculosis ($M.tb$) is an extraordinarily successful pathogen that currently infects approximately one-third of the global population, causes 8 million new cases of tuberculosis annually and is the responsible of more than 2 million deaths per year [Bleed et al., 2001]. TB prevalence was diminishing for decades [Wilson, 1990; Styblo et al., 1969; Daniel et al., 1994], but the tendency was alarmingly inverted in the last years due to the proliferation of multi-drug resistant strains, the coexistence with other deadly diseases such as AIDS and the progressive lack of effectiveness of the main preventive tool since 1921: the BCG vaccine.

In this work, we present a new model adequately designed for describing the transmission of tuberculosis on a well mixed population, −i.e. in which all the individuals have the same probability of contacting each other per unit time− whose total volume can vary in time. The extremely long typical periods that characterize latency in tuberculosis disease [Murphy et al., 2002] force us to consider open populations, and so, a SEIR-like (susceptible-exposed-infectious-recovered) approach [Hethcote, 2000] results more adapted to the TB case. Within this context, proportions of susceptible, latent and sick individuals with respect to the varying population size appear in the model as more suitable variables from a mathematical point of view, rather than numbers of individuals of each type -the most abundant approach commonly found in the literature [Li *et al.*, 1999; Murphy et al., 2002; Blower et al., 1995]-. On the other hand, and contrary to other persistent diseases, in tuberculosis infection, latency is not a necessary step in the infection cycle. In a non vanishing proportion of cases, infected individuals become infectious suddenly after contagious, just as for a SIR-like process. This phenomenology, -called primoinfection- is not usually taken into account in pure SEIR models, which nevertheless have been mathematically characterized into great detail, also for varying population sizes [Hethcote, 2000; Li *et al.*, 1999]. Our model is therefore a SEIR epidemiological model with primoinfection formulated in terms of densities and assuming a well mixed population. The model so derived can be understood as a lineal combination of a somehow generalized variable-population SIR model plus a classical SEIR model similar to that studied in [Li *et al.*, 1999]. In what follows, we focus on the

analytical characterization of the epidemic threshold of the model, that adequately reduces to those of the SIR and SEIR cases when the adequate parameters are turned off. We also perform numerical simulations on randomly rewired networks simulating the aerial spreading of the disease within a demographically homogeneous area and show that they agree with the stationary proportions of susceptible, latent and sick individuals analytically predicted by the model.

2. The model

As we have already pointed out, the main feature of the tuberculosis' infection cycle is its long latency period. In this sense, after entering the organism, the pathogen reaches the bloodstream, and it is phagocyted −but not killed− by the macrophages of the human immune system. At this point, the bacillus is forced by the phage to interrupt its growth process and to sporulate, maintaining its metabolism in a basal state that traduces in a latency state for the host, who neither suffer any clinical symptom, nor is infectious. This latency period lasts in average as much as 500 years [Murphy et al., 2002], a time that obviously exceeds human life expectancy. This means that most tuberculosis carriers die because of reasons not related with the disease, even without being aware of their infected condition.

The active phase of the illness arrives when the bacillus enters in the reproductive phase. This can occur suddenly after the contagious as a consequence of the macrophages incapacity to force the bacillus' sporulation. This situation leads to primoinfection and occurs in a 5% to 10% of cases [Comstock, 1982; Styblo, 1986]. The other possibility consists of the rupture of the dynamical equilibrium between the pathogen and the host that ultimately defines the latency state. When this occurs, −usually related to suppressive episodes of the immune system such as AIDS infection or chemotherapy in cancer patients− the bacillus leaves out its spores and reproduces up to the lysis of the phage. In both cases, actively reproductive bacteria freely flow into the bloodstream and migrate, typically to the lungs, where their uncontrolled growth cause the tubercle lesions from which the disease takes its name. At this point, the pathogens reach the sputum, making the host infectious. Although other tissues are susceptible of becoming the pathogen' substrate −mostly nervous and osseous tissues− pulmonary tuberculosis is not only the statistically most relevant variety, but also the unique responsible of the aerial spreading of the bacillus.

Taking into account the above features of TB, we have constructed our model by dividing the population into three subsets, depending on the state of the individuals in relation to the disease: uninfected −class U−, latent carriers −class L− and tuberculosis patients −class T− who are simultaneously infected and infectious. For simplicity, we assume that all individuals that enter into the active phase of the disease are infectious, hypothesis that is equivalent to neglect the proportion of extra-pulmonary tuberculosis. Let β be the number of contacts per unit time. In a population made up of N individuals, with U healthy individuals and T tuberculosis patients, the closure relationship $N = U + L + T$ is complete when the latent carriers L, who neither can transmit the bacillus nor can suffer a contagious, are also taken into account. So, we have that the number of contacts per unit time between healthy and infectious individuals is $\beta T \frac{U}{N}$. Denoting by λ the probability that a healthy individual gets infected after contacting an infectious subject, the number of new contagions per unit time in our population reads as $\lambda\beta T \frac{U}{N}$.

As noted before, for the tuberculosis case, once an individual catch the bacillus there are two possibilities: either the newly infected subject get sick (and therefore infectious as well) or he enters into latency. We assume that the former transition occurs with probability p and therefore the latter takes place with probability p. In terms of our model, this amounts to consider a flux from the healthy to the latent state $U \to L$ of volume $(1-p)\lambda\beta T \frac{U}{N}$ per unit time, and the complementary primoinfection flux $U \to T$ that corresponds to $p\lambda\beta T \frac{U}{N}$ individuals per unit time.

Once the contagion dynamics is defined, we also consider that the population size varies concurrent to the disease spreading. To take this variation into account, we add to the model demographical fluxes −births and deaths not related with the disease−. Hence, bN new individuals per unit time are added to the population −all of them healthy− and μN are removed (i.e., deceased individuals are homogeneously distributed among the three classes). According to this scheme, b represents the birth rate of the population and μ its natural death rate. Finally, latent individuals go to the active phase at a relapse rate r that represents, essentially, the inverse of the mean latency period. This implies a flux of rL individuals per

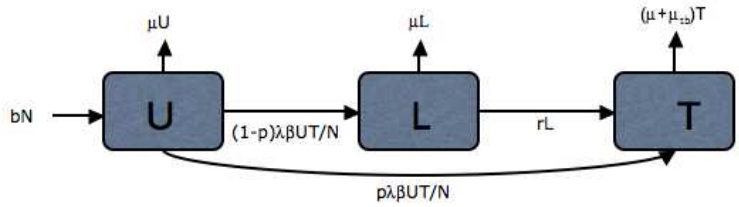


Fig. 1. Flux diagram of our model for TB spreading. Labels represent the possible transitions between the compartments in which the whole population is divided according to the individuals' state. The model assumes a well mixed population of varying size. Parameters are introduced in the main text.

unit time abandoning the latency class and entering into the active phase. Moreover, sick individuals die at a rate μ_{tb}. Figure 1 shows the flux diagram of the different transitions that define our epidemic model. The corresponding mathematical description is given by the following system of ODEs, in which the last equation corresponds to the temporal evolution of the whole population:

$$\begin{aligned}
\frac{dU(t)}{dt} &= bN(t) - \lambda\beta U(t)\frac{T(t)}{N(t)} - \mu U(t),\\
\frac{dL(t)}{dt} &= (1-p)\lambda\beta U(t)\frac{T(t)}{N(t)} - (\mu + r)L(t),\\
\frac{dT(t)}{dt} &= p\lambda\beta U(t)\frac{T(t)}{N(t)} + rL(t) - (\mu + \mu_{tb})T(t),\\
\frac{dN(t)}{dt} &= (b-\mu)N(t) - \mu_{tb}T(t).
\end{aligned} \tag{1}$$

2.1. *Reformulation in terms of densities*

The description of the dynamical system in terms of the number of individuals is nevertheless not an optimal choice. To evaluate the impact of the spreading process on a population of varying size, it is more reasonable -and mathematically kinder- to study the temporal evolution of the densities of healthy, latent and sick individuals, rather than the number of individuals of each type. In order to do that, we define the respective densities as:

$$\begin{aligned}
u(t) &= \frac{U(t)}{N(t)},\\
l(t) &= \frac{L(t)}{N(t)},\\
t(t) &= \frac{T(t)}{N(t)}.
\end{aligned} \tag{2}$$

In this way, we recover a non-dimensional closure relationship $u + l + t = 1$. Taking into account that

$$\begin{aligned}
\frac{du(t)}{dt} &= \frac{1}{N(t)}\left(\frac{dU(t)}{dt} - u\frac{dN(t)}{dt}\right),\\
\frac{dl(t)}{dt} &= \frac{1}{N(t)}\left(\frac{dL(t)}{dt} - l\frac{dN(t)}{dt}\right),\\
\frac{dt(t)}{dt} &= \frac{1}{N(t)}\left(\frac{dT(t)}{dt} - t\frac{dN(t)}{dt}\right),
\end{aligned} \tag{3}$$

the temporal evolution of the system in terms of densities is finally given by:

$$\begin{aligned}\frac{du}{dt} &= b - (\lambda\beta - \mu_{tb})ut - bu,\\ \frac{dl}{dt} &= (1-p)\lambda\beta ut + \mu_{tb}lt - (b+r)l,\\ \frac{dt}{dt} &= p\lambda\beta ut + \mu_{tb}t^2 - (b+\mu_{tb})t + rl.\end{aligned} \tag{4}$$

This kind of approach is specially suitable for open populations [Li *et al.*, 1999; Sanz et al., 2010], though it is not the only possible choice [Murphy et al., 2002; Hethcote, 2000]. Note that in the previous equations the natural death rate does not appear anymore.

2.2. *Epidemic threshold*

State-of-the-art epidemiological models are aimed at reproducing actual epidemic outbreaks as accurately as possible. Their final goal is to anticipate the course of an outbreak or even make predictions in real time, which will provide health authorities with new means to fight disease contagion. However, compartmental models in epidemiology share, despite of particularities of each model, a common dynamical outcome [Anderson & May, 1992; Daley & Gani, 1999; Murray, 2002]. Typically, in these kind of models the parameter (phase) space is divided in two regions. In one of them, an initially healthy population remains macroscopically unaffected after the addition of a small fraction of infectious individuals, while, in the other, the disease is able to spread to affect a macroscopic fraction of the population. That is, there are two asymptotic, absorbing states: the disease-free regime and an active phase. The critical epidemic point or epidemic threshold divides the two regions of the phase space. The determination of the epidemic threshold is one of the key goals of epidemiology, for this would allow designing efficient vaccination campaigns and other countermeasures [Hethcote, 2000]. This will also be our main objective. To this end, let us first characterize the fixed points of the dynamics described in (2), which have to verify:

$$\begin{aligned}\frac{du^*}{dt} &= 0 = b - (\lambda\beta - \mu_{tb})u^*t^* - bu^*,\\ \frac{dl^*}{dt} &= 0 = (1-p)\lambda\beta u^*t^* + \mu_{tb}l^*t^* - (b+r)l^*,\\ \frac{dt^*}{dt} &= 0 = p\lambda\beta u^*t^* + \mu_{tb}t^{*2} - (b+\mu_{tb})t^* + rl^*.\end{aligned} \tag{5}$$

In Eq. (5). only two the equations are independent due to the closure relationship $u + l + t = 1$. The trivial solution for the system (5) is the fixed point corresponding to a disease free population: $(u^*, l^*, t^*) = (1, 0, 0)$. In order to look for not trivial fixed points, we can work out u^* from the first equation in (5) to obtain:

$$u^* = \frac{b}{(\lambda - \mu_{tb})t^* + b}, \tag{6}$$

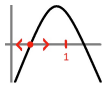
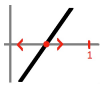
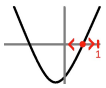
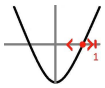
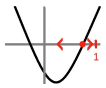
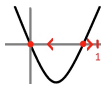
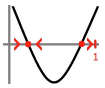
which, after substitution in the third equation in (5) gives

$$\frac{dt^*}{dt} = 0 = t^*\left[\mu_{tb}(\lambda\beta - \mu_{tb})t^{*2} + [\mu_{tb}b - (\mu_{tb} + b + r)(\lambda\beta - \mu_{tb})]t^* + [\lambda\beta(pb + r) - (r + b)(\mu_{tb} + b)]\right]. \tag{7}$$

This equation is quadratic except for the common factor t^*, which in turns guarantees stationarity of the disease free fixed point. So, we could write down explicitly the analytical expressions of the additional two solutions t_1^* and t_2^* of the quadratic trinomial. However, if we call:

$$\mu_{tb}(\lambda\beta - \mu_{tb})t^{*2} + [\mu_{tb}b - (\mu_{tb} + b + r)(\lambda\beta - \mu_{tb})]t^* + [\lambda\beta(pb + r) - (r + b)(\mu_{tb} + b)] = \zeta t^{*2} + \eta t^* + \Theta, \tag{8}$$

we can more easily determine the sign of the three coefficients ζ, η and θ depending on the possible values of $\lambda\beta$:

	Region 1: $\lambda\beta < \lambda\beta_1$	$1 \to 2$ $\lambda\beta = \lambda\beta_1$	Region 2: $\lambda\beta_1 < \lambda\beta < \lambda\beta_2$	$2 \to 3$ $\lambda\beta = \lambda\beta_2$	Region 3: $\lambda\beta_2 < \lambda\beta < \lambda\beta_3$	$3 \to 4$ $\lambda\beta = \lambda\beta_3$	Region 4: $\lambda\beta_3 < \lambda\beta$
ζ	-	0	+	+	+	+	+
η	+	+	+	0	-	-	
θ	-	-	-	-	-	0	+
ζ	-	0	+	+	+	+	+
$t_1^* + t_2^* = -\eta/\zeta$	+	N.d.	-	0	+	+	+
$t_1^* t_2^* = \theta/\zeta$	+	N.d.	-	-	-	0	+
Phase portrait							

- Main term $\zeta = 0 \longleftrightarrow \lambda\beta = (\lambda\beta)_1 = \mu_{tb}$.
- First order term $\eta = 0 \longleftrightarrow \lambda\beta = (\lambda\beta)_2 = \mu_{tb}\frac{\mu_{tb}+2b+r}{\mu_{tb}+b+r}$.
- Independent term $\Theta = 0 \longleftrightarrow \lambda\beta = (\lambda\beta)_3 = \frac{(r+b)(\mu_{tb}+b)}{pb+r}$.

which, noting that for any parameter combination, it is verified that

$$(\lambda\beta)_1 < (\lambda\beta)_2 < (\lambda\beta)_3, \tag{9}$$

allows us to construct the following sign table for the phase portrait description of the model's dynamics:

Let us focus firstly on the point $t^* = 1$, that apparently can appear as a dynamical attractor for the physically meaningful range $0 \leq t \leq 1$ in all the regions, with a basin of attraction that corresponds, for regions 2 to 4, to values of t that are greater than the largest solution of Eq. (7), that is, when $\zeta > 0$ (i.e. $\lambda\beta > \mu_{tb}$):

$$t^*_{max} = \frac{-\eta + \sqrt{\eta^2 - 4\zeta\theta}}{2\zeta}, \tag{10}$$

or with minus sign before the root, when $\zeta < 0$. In region 1, the basin of this hypothetical disease free attractor corresponds to the values of $t > t^*_{min}$, where we denote by t^*_{min} the smallest solution of (7). Note that, provided that $t < 1$, entering the basin of attraction leads to $\dot{t} > 0$ until $t = 1$. However, we should also consider the temporal evolution of N. More precisely, it is easy to see that, when proportion of infectious individuals exceeds the threshold:

$$t_{limit} = \frac{b - \mu}{\mu_{tb}}, \tag{11}$$

the spreading process is able to cause a demographical decay in the population, i.e., $\dot{N} < 0$. This behavior continues to be so until the annihilation of the whole population. Therefore, as it can be seen from Table 1, when the proportion of sick individuals is greater than t^*_{min} −in region 1− or t^*_{max} −in regions 2 to 4−, the proportion of sick individuals grows up indefinitely. This growth of the density of infectious individuals eventually causes that the whole population dies out. Therefore, the point $t = 1$ is everything but an stable point of the dynamics, as it leads to population's extinction. So, at least in regions 1 to 3, the only −also stable− possible fixed point corresponds to the disease free state, i.e., to $t^* = l^* = 0$.

The situation is different in region four, where there exist an additional stable stationary value for $t^* > 0$. Hence, in this region, the previous fixed point $t^* = l^* = 0$ is unstable and the transition between regions three and four defines the epidemic threshold, which is given by the condition:

$$(\lambda\beta) = (\lambda\beta)_c = \frac{(r + b)(\mu_{tb} + b)}{pb + r}. \tag{12}$$

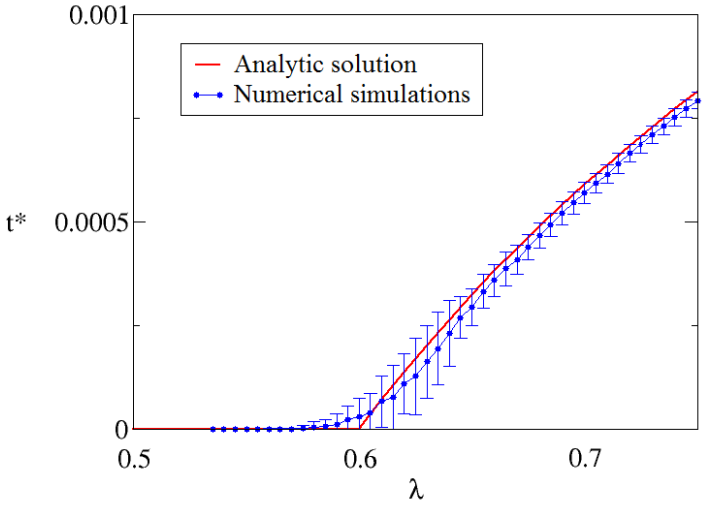


Fig. 2. t^* values at stationarity vs the spreading rate. The figure shows the predicted values of t^* from the model and those obtained from MC simulations. Error bars correspond to two times the standard deviations for the 100 realizations carried out for each numerical point. Results were obtained for an initial population of $N_o = 1000$ individuals distributed as $(u_o, l_o, t_o) = (0.5, 0.4, 0.1)$. The rest of parameters are those discussed in the main text.

As a matter of fact, there is a simpler way to obtain the threshold Eq. 12. The condition for the singularity of the Jacobian matrix in the vicinity of the disease-free fixed point reduces to:

$$\begin{vmatrix} -b & 0 & -(\lambda\beta - \mu_{tb}) \\ 0 & -(b+r) & (1-p)\lambda\beta \\ 0 & r & -(b+\mu_{tb}) + p\lambda\beta \end{vmatrix} = 0, \tag{13}$$

that leads to the same threshold in Eq. 12., or expressed as it is usually found in the literature:

$$(\lambda)_c = \frac{1}{\beta}\frac{(r+b)(\mu_{tb}+b)}{pb+r}. \tag{14}$$

Finally, it is worth noticing that the result Eq. 14 reduces to the well-known threshold for the SIR model [Murray, 2002] when we take $b = \mu = 0$ and $p = 1$. In turn, when taking $p = 1$.

2.3. *Numerical simulations.*

In this section, we compare the analytical, stationary proportions predicted by the model −those that constitute the solution of the system Eq. (5) and that can be easily derived by explicitly working out t^* at (7) and substituting it into (6)− with the results of numerical Montecarlo (MC) simulations.

We consider an initial population of N_o individuals distributed in the different classes. At each time step, each sick individual contacts β randomly chosen individuals. When one of these contacts is a healthy node −i.e., an individual belonging to U class− the contagion is produced with a probability equal to the spreading rate λ. In the case that contagion takes place, the newly infected node goes directly to the T class with probability p. In the complementary case (with probability $1 - p$), the contagion causes the individual to enter into latency. The results that follow have been obtained using an initial population of $N_o = 1000$ individuals and we have taken $\beta = 6$. In addition to the contagion dynamics, at each time step individuals of classes U and L leaves the system with probability μ, while sick individuals die with a higher probability equal to $\mu + \mu_{tb}$. Births are also simulated by introducing bN individuals −all of them into class U−. Finally, the transition from latency to the infectious phase takes place with probability r.

Regarding the parameter values, for birth and natural death rates $-b$ and $\mu-$ we have taken as a reference the typical values of a developed country like Spain: $b = 0.01$ and $\mu = 0.009$ events per capita

and year. The rest parameters −those directly related to the disease spreading− are not easily measurable on real populations. In spite of this, plausible approximations can be made, and usually, typical validity ranges are accepted in the literature [Murphy et al., 2002]: $r = 0.002$, $p = 0.07$ and, finally $\mu_{tb} = 0.8$ deaths due to tuberculosis per capita and year. Therefore, the spreading rate will be our free, control parameter (in part because it is the most harder to obtain). In particular, we explore the region between $\lambda = 0.5$ and $\lambda = 1$.

Given the previous selection of parameters, it can be easily shown that we are between regions 3 and 4. So, taken into account the analytical characterization of the dynamics of the model made in the previous section, the only caution one should have in mind is that the initial proportion of sick individuals should not be bigger than t^*_{max}. This will guarantee that the state $t = 1$ will not become an attractor of the system dynamics. In this sense, it can be easily calculated that, for our set of parameters, the largest solution of (7) is always greater than unity and thus the eventual state $t^* = 1$ will never be an attractor for the dynamics. Moreover, substituting the chosen model parameters in Eq. 14 predicts $\lambda_c = 0.6$.

Figure 2 compares the results derived from the analytical solution of the model to those obtained from MC simulations. As it can be seen, although the analytical curve is systematically above the numerical values, it lies within the limits of the error bars, and therefore both are in agreement. Regarding the epidemic threshold, MC results predict a somewhat smaller value for λ_c. Although the differences are not large and the agreement can also be considered good, it is likely that these deviations come from finite size effects and that working with larger system sizes will reduce the gap.

3. Conclusions

We have discussed a model for the spreading of persistent infections in homogeneous populations. The model complements the epidemiological framework previously discussed for complex heterogeneous populations [Sanz et al., 2010]. This kind of approach is particularly suited for diseases like Tuberculosis, where one can have at the same time new ingredients such as long latency periods and primoinfections. Finally, it is also worth mentioning that the model discussed here is probably the simplest one may devise for the spreading of persistent infections in homogeneous populations. As it has been shown before for the SIR model, the results obtained for well-mixed populations are equivalent (for instance, in what concerns the existence of a critical pint) to those one would obtain if the population were considered homogeneous, i.e., a random network with a bounded second moment of the degree distribution [Boccaletti et al., 2006]. Future works should consider the implementation of models that explicitly takes into account the concurrent interaction of persistent infections with other diseases, which is known to drastically change the dynamics of the disease being modeled.

Acknowledgments

We acknowledge financial support from the Government of Aragón through the Grant PI038/08. This work has also been partially supported by MICINN through Grants FIS2008-01240 and FIS2009-13364-C02-01.

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