

Artículo especial

From epidemic outbreaks to pandemics: the critical time of percolation

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Summary

One transcendental aspect of epidemiology is to predict the evolution of infectious diseases, especially in cases of pandemic outbreaks. In the last decade the emphasis has been placed in the spatial progression of epidemics. Percolation models have been proposed that describe the progress of parasitic infestations and epidemics. In this study, we propose a model that connects the temporal and spatial progress of a global epidemic, determining the time at which an epidemic outbreak becomes a pandemic based on the percolation threshold.

First, we propose a simple model of the temporal progression of the geographic progress of epidemics. By means of simulation, we estimate the percolation threshold of epidemics at two scales: global and local. Then, we connect both approaches, determining the time at which this threshold is reached (the critical time of percolation).

The advanced model yields a logistic progress of infected localities over time. The estimated percolation thresholds were approximately 59% of the infected localities at local and global scales, and these were not different from the theoretical percolation threshold of square grids.

We propose an easy method for following and predicting the geographical progression of infectious disease over time at several scales. Another remarkable aspect of the advanced model is that it allows us to define a pandemic in a more precise form, such as the state of and epidemics in which the percolation threshold is reached, changing the current definition of epidemics in phase 6 (the pandemic phase).

Keywords: epidemics, model, percolation

Introducción

A number of viruses have pandemic potential. For example, the coronavirus, which is responsible for the severe acute respiratory syndrome (SARS), caused more than 8000 cases in 2003 (Fineberg 2014). The outbreak of EBOLA threatened to spread to the entire world in 2014 and now counts more than 12,000 cases (CDC 2015). More classic examples are the Influenza viruses, which are characterized by their persistence, versatility, potential severity, and speed of spread. These viruses are endemic in a number of species, including humans, birds, and pigs. The influenza virus causes annual outbreaks that are punctuated by occasional worldwide pandemics, which are characterized by sustained community spread in multiple regions of the world. For example, 1918–19 A(H1N1) affected 50 million of persons (all viral segments of avian origin); 1957–69 A (H2N2) affected 2–4 million persons (five segments of A(H1N1) + (PBI;HA;NA) of avian origin); 1968–70 A (H3N2) affected 1–2 million persons (six segments of H2N2 + (PBI and HA) of avian origin); 1977–79

A (H1N1) affected 0.7 million (identical with 1918–19 virus) (Ebrahim et al. 2010), and the recent 2009 A(H1N1), which combined viral parts from three viral lineages (triple reassortant, classical and Eurasian swine), had millions of cases all over the world (Garten et al. 2009, Shrestha et al. 2011).

Additionally, several cases and deaths in humans have been caused by a number of avian influenza A viruses, such as A(H5N1), A(H7N9) and A(H10N8), as recently reported in 2013. Such cases could be harbingers of a pandemic, which is difficult to assess without knowing the history of the disease in the past. The 2009 A(H1N1) pandemic presented a public health emergency of uncertain scope, duration, and effect. The experience exposed a number of deficiencies and defects at the local and global levels. These included limitations of scientific knowledge, difficulties in decision making and complexities in international cooperation. Additionally, beyond spread, the degree to which a pandemic is defined according to the severity of the disease or whether it could be simply described as often producing many illnesses and deaths remains ambiguous (Fineberg 2014).

One of the transcendental aspects of epidemiology is to predict the evolution of infectious diseases, especially in cases of pandemic outbreaks. This attempt is usually conducted using mathematical models that consider the progress of cases over time at a certain location and relevant parameters such as the reproductive number, doubling time, and transmissibility (Bailey 1975, Anderson & May 1979, May & Anderson 1979, Canals et al. 1989a,b, Canals 1992, Heesterbeek et al. 2015, Canals 2010, Heffernan et al. 2005). However, these models do not include the spatial dimension of the disease progression or the conditions of connectivity that have been established between distant regions, factors which are currently very relevant in ecology, epidemiology and other areas such as physics (Grassberger 1983, 1991, Miller 2009, Hanski 1998). In recent decades it has placed special emphasis on the role of population mobility and networks connection by transport airlines in the spread of epidemics (Colizza et al. 2006, 2007a, 2007b, Vespignani 2009, Balcan et al. 2009, 2011, 2012, Ajelli et al. 2010, Gonçalves et al. 2013, Gomez et al. 2014, Merler et al. 2015, Schum et al. 2015). These models have been explored agent based stochastic spatially explicit discrete-time simulation models and stochastic metapopulation models (GLEaM) simulating the global spread of epidemics and determining the threshold below the disease vanishes.

In the field of physics, percolation models study the connectivity between cells. Hammersley and Broadbent introduced the concept in 1956 for studying the obstruction of gas filters (Grassberger 1983). The basic task was to determine the proportion of small obstructed channels that are required to attain a complete obstruction of the filter. This idea has been used to study the spatial continuity of fire spread, the spread of parasites in orchards and the spread of epidemics (Grassberger 1983, 1991, Miller 2009, Canals 2010, Canals & Canals 2010). Basically, the model studies the connectivity that occurs in a grid of square cells when each cell can be in two stages ("on" and "off"), asking for the proportion of cells in state "on" that are necessary for spatial continuity and allowing the crossing from one side to another through cells in the "on" state. In the case of infectious diseases, the "on" state represents an infected spatial area. If an infected cell can infect its neighboring cells, then a system of propagation of an infection is established. Percolation is a threshold

phenomenon independent of the path, and for the specific case of square grids, the percolation threshold $p_c = 0.5927$; i.e., over this proportion of infected cells, the infection crosses the entire grid. In the vicinity of p_c ($p - p_c \ll 1$), the critical functions $P(p) = k_1(p - p_c)^b$, $S(p) = k_2(p - p_c)^{-g}$ and $L(p) = k_3(p - p_c)^{-v}$ are universal (i.e., not dependent on the geometry of the grid), where $P(p)$ is the probability of a cell belonging to the percolating group, $S(p)$ is the average size of the percolating group, and $L(p)$ is the probability of a percolating group being formed (Grassberger 1983, 1991, Canals & Canals 2010). The percolation threshold is dependent on the shape of the grid cells.

Based on empirical studies, it has been proposed that independent of the path or configuration of infected countries the percolation threshold is also valid in the progress of an epidemic, such as A(H1N1)-2009 (Canals & Canals 2010).

In this study, we propose a simple model that describes numerically the temporal progress of an epidemic that connected with the spatial percolation threshold, determines the time at which an epidemic outbreak becomes a pandemic.

Materials and Methods

First, a simple model that relates the proportion of countries infected (p) in the world and time was proposed. Second, the percolation threshold for the grid that constitutes the countries of the world (global scale) and also the states of the U.S.A. (local scale) was estimated by means of simulation. Finally, the percolation threshold (p_c) was introduced in the first model, determining thereby the critical time for percolation (t_c).

To estimate the threshold at a global scale, a grid constituted by 147 non-insular countries was considered, which account for the entire continental surface of North, Central and South America, Europe, Asia and Oceania. Small countries whose inclusion would not have an effect on the result of this study, such as Andorra or Vatican City, were considered to be part of the neighboring countries. The cells were the countries, and their form was determined by their boundaries. At a local scale, a grid would include all of the states of the U.S.A., excluding Alaska and Hawaii. To establish a working definition of percolation at global scale an "ocean" criteria was considered; an epidemic percolates if

geographical continuity from infected countries is observed both in the north - south, as one east - west. The North-South continuity will be obtained if the infection spreads from at least a Eurasian country with coastlines on the Arctic Ocean, to at least one country that has coastlines on the Indian Ocean. The continuity East- West will be obtained if the infection spreads from at least one Asian country with coasts on the Pacific Ocean to at least a country belonging to the bloc Eurasia - Africa possessing coasts on the Atlantic Ocean and also extends through the American continent from a country bordering the Atlantic Ocean to a country bordering the Pacific Ocean.

A random variable is defined such that $X = 1$ if the locality is infected and $X = 0$ if not. A program that assigned these possible states for each locality (country or state): infected ($X = 1$; black) and not infected ($X = 0$; white) was built, and the resulting map was painted. At a global scale, the following operative definition was adopted: an epidemic percolates if it has geographic continuity of infected countries from the glacial Arctic ocean to the Indian ocean (North-South axis) and from the Pacific ocean to the Atlantic ocean, crossing by the Eurasia-Africa block and the block constituted by the American continent (East-West axis). At a local scale, the definition was the existence of geographic continuity of infected states from the Atlantic to Pacific ocean (East-West axis) and from Canada to Mexico and/or the Gulf of Mexico (North-South axis).

Defining $p = P(X = 1)$, the program generated a random number for each locality "j" of the grid, with a uniform distribution ($0 \leq n_j \leq 1$). If $n_j \leq p$, then the locality was considered to be infected ($X = 1$) and the locality was painted black. For example, if $p = 0.3$, then we obtained a map with approximately 30% of the countries (Fig. 1) or states (Fig. 2) infected. The value of p varied from 0 to 1, repeating the procedure 100 times for each value. Then, 100 maps of infected localities were obtained for each value of p . Each map was carefully examined to determine whether percolation had occurred. The percolation probability (ψ) for each value of p was calculated with $\psi = \text{number of percolation events}/100$.



Figura 1. Example of the map obtained with a proportion of infected localities $p = 0.3$ at a global scale. Countries in black and white represent infected and non-infected countries, respectively.

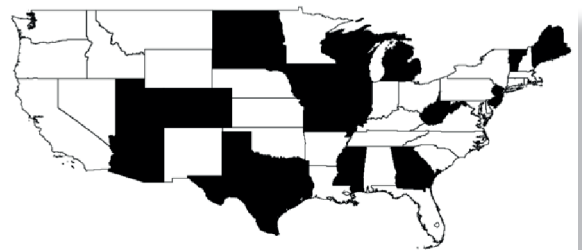


Figura 2. Example of the map obtained with a proportion of infected localities $p = 0.3$ at a local scale for EEUU. States in black and white represent infected and non-infected countries, respectively.

Graphics between p and ψ were obtained, and a probit regression was performed: $\text{probit}(\psi) = \beta_1 p + \beta_0$, where $\text{probit}(\psi) = Z\psi + 5$, and $Z\psi$ is the value Z in an cumulative normal distribution (i.e., $Z_\psi = \int_0^{Z_\psi} \frac{1}{\sqrt{2\pi}} e^{-\frac{z^2}{2}} dz = \psi$).

When the model was fitted, the value of p to obtain 50% of the percolation events (p_{50}) was calculated. As in a standardized normal distribution, $\text{probit}(0.5) = 0 + 5$; then, p_{50} will satisfy the following: $5 = \beta_1 p_{50} + \beta_0$, which yields $p_{50} = (5 - \beta_0) / \beta_1$. Furthermore, because the variance of Z is 1, the standard deviation of p_{50} is $= 1 / \beta_1$ (McCullagh & Nelder 1989). In this study, we used p_{50} as a proxy for the percolation threshold (p_c).

Results

Model

Consider a proportion p ($0 \leq p \leq 1$) of infected countries (or states) at time t . The epidemic outbreak can take different time scales to progress, from weeks to decades. Thus, we use a non-dimensional differential of t : $d\tau = dt/t$.

We propose that the variation in time of p will follow a logistic model:

$$\frac{dp}{d\tau} = p(r - bp), \quad \text{with } r \text{ a constant}$$

that represents the intrinsic rate of increment of the proportion of infected countries, and b a parameter that represents the dense dependent effect.

Considering that when $\frac{dp}{p d\tau} = 0$, then $p = r/b = 1$.

This model can be as $\varepsilon = \frac{dp/p}{dt/t} = (r - bp)$ expressed as

[Eq. 1], where ε is the time elasticity of p . Considering that $u = \ln t$, this model has an explicit solution:

$$\ln\left(\frac{p}{1-p}\right) = \alpha_1 u + \alpha_0, \text{ or } \text{logit}(p) = [\text{Eq. 2}],$$

Equation 1 describes, in an easy way, the numerical progression of the proportion of localities infected in an epidemic over time. The time-elasticity corresponds to the percentage variation of the proportion of infected localities with an infinitesimal change in time, independent of the temporal scale used. The function p can be expressed as

$$p = \frac{t^{\alpha_1} e^{\alpha_0}}{1 + t^{\alpha_1} e^{\alpha_0}} = \frac{1}{1 + (t^{\alpha_1} e^{\alpha_0})^{-1}} \quad [\text{Eq. 3}], \text{ and analogously}$$

$$\varepsilon = \frac{\alpha_1}{1 + t^{\alpha_1} e^{\alpha_0}} = \frac{r}{1 + t^{\alpha_1} e^{\alpha_0}} \quad [\text{Eq. 4}]. \text{ In this model,}$$

the proportion of infected localities increases to an asymptotic value of $p = 1$ (i.e., 100% of the countries were infected), and the elasticity decreases linearly with the proportion of infected localities and decreases non-linearly with time (Fig. 3).

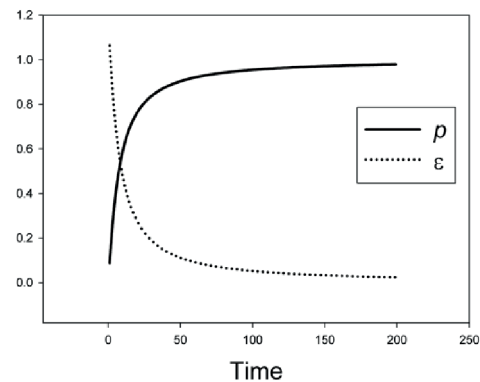
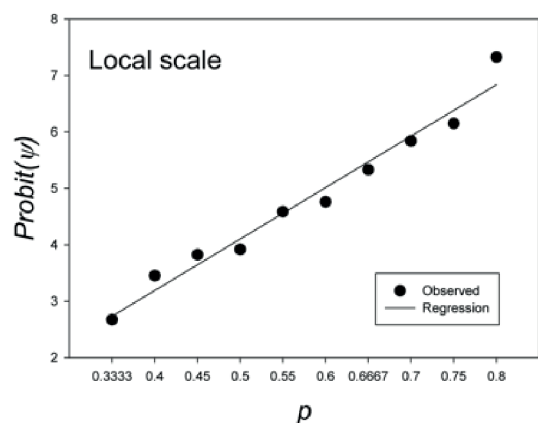


Figure 3. Progression of the proportion of infected localities (p) and the elasticity (ε) in the model (Eq[3] and Eq[4].

Determining the percolation threshold (p_c)

The probit model had a good fit without significant distortions along the different values of p at the two scales. At a global scale, the regression between $\text{probit}(\psi)$ and p was $\text{probit}(\psi) = 4.327p + 2.449$ ($R^2 = 0.984$, $F_{1,17} = 1049.60$, $p < 0.001$). The percolation threshold ($p_c \approx p_{50}$) was $p_c = 0.590 \pm 0.231$ ($\pm$ standard deviation). At a local scale, for USA, the regression was $\text{probit}(\psi) = 8.881p - 0.319$ ($R^2 = 0.967$, $F_{1,8} = 236.47$, $p < 0.001$), with a $p_c = 0.599 \pm 0.113$ (Fig. 4).



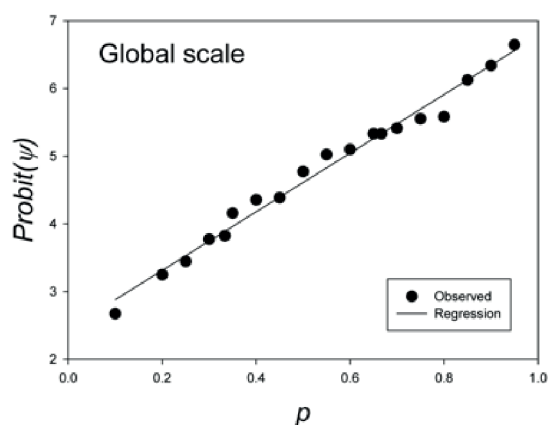


Figura 4. Probit transformation of the probability of percolation ($\text{probit}(\psi)$) as a function of the proportion of infected localities (p) at local and global scales. The solid line is the regression line, and the points are those obtained by the simulations.

The critical time of percolation

At the two different scales, we obtained percolation thresholds p_c that were not different from the percolation threshold of a square grid ($= 0.5927..$) ($t_{17} = 0.05$, $p > 0.05$ and $t_8 = 0.15$, $p > 0.05$ for the global and local scale, respectively). Then, substituting into [Eq. 2], we obtain

$$\ln\left(\frac{p_c}{1-p_c}\right) = \alpha_1 \ln t_c + \alpha_0 \quad \text{or} \quad t_c = \frac{\left(\frac{p_c}{1-p_c}\right)^{\frac{1}{\alpha_1}}}{e^{\frac{\alpha_0}{\alpha_1}}}$$

[Eq. 5]. As an example, if we approximate $p_c \approx 0.5$,

then t_c would simply be $t_c = e^{-\frac{\alpha_0}{\alpha_1}}$.

Discussion

One of the transcendental aspects of epidemiology is attempting to predict the progression of infectious diseases. This attempt is usually realized by using mathematical models that predict the progression of cases over time and deriving some relevant parameters, such as the reproductive number (R_0),

doubling time, and transmissibility (β) (6-14). However, these models do not include the spatial dimension of this progress (although others, such as diffusion and network models, do (Liu & Xiao 2013, Pellis et al. 2015); additionally, they do not include the connectivity conditions that can be established between distant regions—these factors are very relevant today in ecology, epidemiology and other scientific fields (Grassberger 1983, 1991, Miller 2009).

In recent decades it has placed special emphasis on the role of population mobility and networks connection by transport airlines in the spread of epidemics (Colizza et al. 2005, 2007^a, 2007^b, Vespignani 2009, Balcan et al. 2009, 2011, 2012, Ajelli et al. 2010, Gonçalves et al. 2013, Gomez et al. 2014, Merler et al. 2015, Schum et al. 2015). These models have been explored agent based stochastic spatially explicit discrete-time simulation models and stochastic metapopulation models (GLEaM) simulating the global spread of epidemics and determining the threshold below the disease vanish and also a second threshold defines the criteria that permit an epidemic to move out of the giant strongly connected component and to invade the populations of the sink nodes (Schumm et al. 2015). These models have shown a good fit to the propagation of different diseases such as Influenza AH1N1, AH5N1, SARS and Ebola (Colizza et al. 2006, 2007, Gomes et al. 2014, Merler et al. 2015). The focus of these models is the spatial spread in time, while our model only uses the number of infected localities and wondered when this number becomes uncontrollable as a result of having crossed the threshold established by the percolation of the geographic space.

Percolation, being a threshold phenomenon, allows for an explanation of abrupt changes in the propagation of water, gases, parasites, fire and other materials, and it is relevant in the spread of epidemics.

Our model of epidemic progression is an easy model that relates the increase in the proportion of infected localities over time. It not proposes a continuous spatial progress of the epidemic like other percolation models that are useful at local scale, only uses the percolation threshold to determine the time in which this occurs, and agrees with previous empirical studies of the propagation of the AH1N1-2009 Influenza realized in Chile and Argentina (Canals & Canals 2010, Canals 2010, Cuestas et al. 2011). For example, the empirical fit

using probit models and relating the proportion of infected countries and time showed a relatively good fit at the beginning of this epidemic (Canals 2009); later, logistic regression between the proportion of countries infected and time had a better fit. Moreover, when the proportion of infected countries was related to the logarithm of time ($\ln t$), the determination coefficients (R^2) increased from approximately 0.7 to values that were higher than 0.94 (Canals & Canals 2010). Other later studies in Argentina showed a good fit at the local scale (Cuestas et al. 2011).

Considering countries at a global scale and states at a local scale to be geographic unities, we obtained the percolation threshold that was closest to the expected value ($p_u = 0,5927$) for a grid of square cells (Feng et al. 2008). Despite the irregular form of the cells of countries and states, the contour of the grid in our case is geographic; in addition, inside the grid, there are zones that cannot be occupied because they do not correspond to areas of land.

In previous studies (Canals & Canals 2010), we see that the percolation thresholds vary depending on the geometric forms of the cells. In the case of the states of the USA, the form is similar to squares in several states, and then, a threshold value that is similar to that of a square grid was expected. However, in the case of countries at a global scale, we obtain also a similar value, which suggests that in the case of irregular forms of cells, the threshold value converges to an average value that is similar to that of square grids.

The random changes of localities from not infected to infected established a theoretical continuity among distant localities when really there is not; for example, between Chile and the USA. However, this agrees with the role of transport network in epidemics progression, geographic continuity is established by means of global transport networks (Tatem et al. 2006). Moreover, this random change does not introduce distortions in the percolation threshold because percolation is precisely a threshold phenomenon that is independent of the path. This attribute means that regardless of the previous configurations of the infected cells, when the threshold is reached, the system will percolate.

This model is different from the classic epidemiologic models that use differential or difference equations, such as SEIR models, to estimate the number of cases over time, and more sophisticated spatial models, such as those based

on diffusion processes (Liu & Xiao 2013), to model the continuous propagation of epidemics. Also, it is different from stochastic approaches such as agent-based or GLEaM models. The advanced model is based on a spatial progression (contamination of cells) and introduces time as a variable, which allows us to estimate when the percolation will happen. At a global scale, this choice allows us to determine the instant at which the geographic barriers that contain the epidemic disappear as the epidemic changes from an epidemic outbreak to pandemics. This threshold is different to that proposed by other models. While in other models the threshold for the spread of an epidemics (ie R_0) or the threshold for the spatial spread (Balcan et al. 2012), in our model the threshold of interest is the instant in which a disease cross the entire geographic space without barriers (percolation of the system).

Our model allows us to predict the propagation but does not report the number of cases in each locality. Our model intent to predict the number of infected localities and the time of percolation, but not predicts the spatial trajectory of the spread such as GLEaM models. In this sense, these models would be complementary to propose epidemics mitigation measures. The good fit and predictive capacity of our model allows us to propose an easy method to follow and predict the spatial progression of the proportion of infected localities over time, adapting the sizes of the cells to local situations, such as cities or communities. The proposed method comprises the following steps:

- i) Obtain information on the proportion of localities infected (P) at time (t) at the beginning of the epidemic,
- ii) To perform a logistic regression between P and $\ln(t)$ [Eq 2]
- iii) To estimate the critical time of percolation t_c by [Eq 3]
- iv) To repeat steps i), ii) and iii) as the epidemic progresses

Following the curve of P vs $\ln(t)$ allows us to study the behavior of the progression of the epidemics while looking for efficient and effective mitigation and control measures. If the curve follows linear

progress (in the logit regression) without changes, the estimation of t_c will not vary, while if there are effective control measures, the curve will change, and the estimation of t_c will increase progressively (Fig. 5).

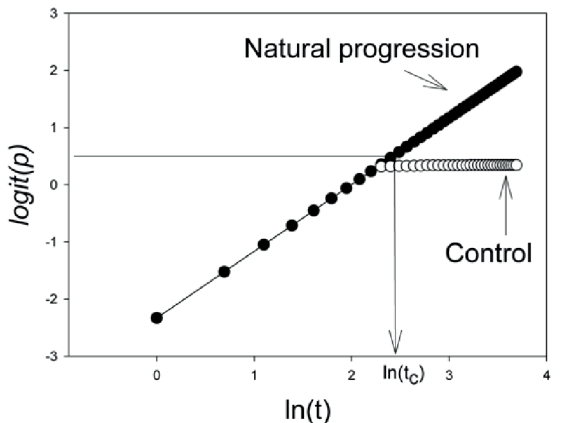


Figura 5. Hypothetical progression of an epidemic over time. $\text{Logit}(p)$ is $\ln(p/(1-p))$, with p the proportion of infected localities, and $\ln(t)$ is the natural logarithm of the time in arbitrary units. The black circles represent the natural increments in the number of localities infected; the solid line is the regression line based on only 9 points; the horizontal line and vertical arrow show the coordinates of the logit of the percolation threshold and the time at which it is reached (critical time of percolation t_c); and the white circles represent a situation in which control and mitigation measures have been successful, without reaching the percolation threshold.

Another remarkable aspect of the advanced model is that it allows us to define pandemics in a more precise form, as “the state of and epidemics in which the percolation threshold is reached (i.e., $P = 0.59$)” because it is the moment at which there is geographic continuity worldwide. It is very interesting that in the AH1N1-2009 epidemics, the WHO declared it as phase 6 (pandemic phase) on June 11, 2009, based on the human-to-human spread of the virus in at least three countries in one WHO region, and the percolation occurred on June 7, 2009 (Canals & Canals, 2010).

Acknowledgements

The present study was funded by the FONDECYT 1150514 grant to M.C. The funder had no role in devising, conducting, analyzing or reporting this study.

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