Global Spread of Infectious Diseases

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Abstract

We develop simple models for the global spread of infectious diseases, emphasizing human mobility via air travel and the variation of public health infrastructure from region to region. We derive formulas relating the total and peak number of infections in two countries to the rate of travel between them and their respective epidemiological parameters.

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1 Introduction and linear model

Recent outbreaks of atypical pneumonia (SARS) [1] as well as likely future epidemics and pandemics of influenza [2] provide ample motivation for the study of the global propagation of infectious diseases. (For an overview of modelling of infectious diseases in humans, see [3]). In this letter we construct a class of simple models of this phenomena, with particular attention to human mobility and the variation of public health capabilities across national and regional boundaries. Spatial dynamics involving the diffusion equation, of the type studied in [4] (as in, e.g., the spread of rabies in fox populations), is of less interest to us than regional or national variation of parameters. We treat each region as spatially homogenous and focus on mobility (e.g., via air travel) as the mechanism by which disease is transmitted.

The population variables in our model: $S =$ susceptibles, $I =$ infected, $R =$ recovered and $D =$ deceased, are functions of time $t$ and of discrete geographical location labelled by an index $i = 1, \ldots, N$. Thus our equations describe the time evolution of a $4N$ dimensional vector:

$$\vec{x} = \begin{pmatrix} S_1 \\ I_1 \\ R_1 \\ D_1 \\ S_2 \\ I_2 \\ \vdots \\ \vdots \end{pmatrix}$$

In the simplest linear model, the dynamics of $\vec{x}$ are characterized by a $4N \times 4N$ matrix whose entries are probabilities per unit time: $t_i =$ probability of transmission of disease from an infected to susceptible individual in region $i$, $r_i =$ probability of recovery of infected individual in region $i$, $d_i =$ probability of death of infected individual in region $i$, $m_{i\to j} =$ probability of movement of an infected individual from country $i$ to country $j$. Each of these probabilities incorporates several additional parameters that would appear in a more complicated model. For example, $t_i$ depends on other factors such as the probability and effectiveness of quarantine, the length of time an infected individual remains asymptomatic, the population density, etc. A very simple modification would be to include asymptomatic as well as symptomatic carriers of the infection by expanding our matrix to $5N \times 5N$ dimensions. Contagious asymptomatics would have a large transmission probability, as they are difficult to quarantine. We will return later to enhancements of the basic model.
The basic parameters $r_i, t_i, d_i, m_{i\rightarrow j}$ vary from region to region, and can be estimated from epidemiological data. Our organizing principle for dividing the world into regions is the relative homogeneity of these parameters within each region. This division may or may not follow national boundaries, as the parameters may vary significantly (e.g., from urban to rural regions) within a given country.

The basic reproductive rate [3], commonly denoted $\mathcal{R}_0$, is defined as the average number of secondary cases caused by a single infected individual. A simple computation (neglecting migration) for region $i$ yields

$$\mathcal{R}_0^i = t_i + (1-r_i-d_i)t_i + (1-r_i-d_i)^2t_i + \cdots = \left(\frac{t_i}{r_i+d_i}\right)^2.$$  \hspace{1cm} (2)

When $\mathcal{R}_0 > 1$ the infected population grows exponentially.

The system of equations governing the time evolution of $\vec{x}$ is

$$\frac{d\vec{x}}{dt} = M\vec{x} + \vec{J},$$  \hspace{1cm} (3)

where $\vec{J}$ is a possible source of infected individuals coming from zoonosis, an animal reservoir of disease. All elements of $\vec{J}$ are zero except the $(4i-2)$ and $(4i-3)$ entries corresponding to an animal reservoir in region $i$ which contributes to $dI_i/dt$ and $-dS_i/dt$. Note that, unlike the well-known SIR model [4], equation (3) is linear. The transmission rate per unit time is given by $t_iI_i$ rather than $t_iS_iI_i$. This makes our model slightly less realistic, as the transmission rate per infected individual does not drop as the number of susceptibles goes to zero. The SIR model predicts some fraction of uninfected susceptibles $S(t \rightarrow \infty)$ even when $\mathcal{R}_0 > 1$, whereas our model would predict that each individual in the entire population is eventually be infected. This leads to an overestimate relative to the SIR model of the total number of infected in countries with $\mathcal{R}_0 > 1$. However, the difference is only numerically significant when $\mathcal{R}_0$ is close to 1. (We do not expect the input parameters to be sufficiently well-determined that, e.g., a factor of two in the predicted number of infections is very significant.) Another method for cutting off the exponential growth is to add (nonlinear) logistic terms of the form $-k_iI_i^2$ to the right hand side of the equation, at the cost of adding additional parameters.

Equation (3) can be solved analytically:

$$\vec{x} = -M^{-1}J + e^{Mt} \left(\vec{x}_0 + M^{-1}J\right),$$  \hspace{1cm} (4)

where $\vec{x}_0$ is the initial condition. The importance of the variables $S_i, R_i, D_i$ is to impose the overall conservation of humans, which is a consequence of the form of $M$, and the constraint that $S, I, R, D$ be positive semi-definite at all times. Although equations (3) and (4) appear simple, the constraints lead to a nontrivial system.

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Below we exhibit the matrix $M$ for the case of two countries, $i = 1, 2$.

$$M = \begin{pmatrix}
0 & -t_1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -r_1 - d_1 - m_{1\rightarrow 2} + t_1 & 0 & 0 & 0 & m_{2\rightarrow 1} & 0 & 0 \\
0 & r_1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & d_1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & -t_2 & 0 & 0 \\
0 & m_{1\rightarrow 2} & 0 & 0 & 0 & -r_2 - d_2 - m_{2\rightarrow 1} + t_2 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & r_2 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & d_2 & 0 & 0 \\
\end{pmatrix}.$$

(5)

Note the sum rule implicit in this matrix: $\sum_i^{4N} x_i = \text{constant}$, which reflects conservation of humans.

Despite the simplicity of these models, they may be useful tools for public health policy. For example, the economic impacts on developed country economies from diseases in developing nations can be estimated. This data can be used in cost-benefit assessments of improvements in public health infrastructure in both developed and developing nations.

2 Linear model: analytics and simulations

We now discuss some of the analytic properties of our linear models. First, we note that the system of $4N$ equations can be reduced to a smaller number of equations, due to the large number of zeroes in $M$. In essence, the dynamics involves only the infected individuals $I_i$: the evolution of the $S_i, R_i$ and $D_i$ variables are dependent on $I_i$. Thus there are really only $N$ equations (but subject to constraints; see below), as can be seen from the fact that $M$ has only $N$ non-zero eigenvalues. The matrix $M$, restricted to the $N \times N$ subspace of infected populations $I_i$, is diagonal up to the (small) off-diagonal mobility entries $m_{i\rightarrow j}$. If the mobility matrix were symmetric, we could diagonalize $M$ via an orthogonal change of basis. However, in general $m_{i\rightarrow j} \neq m_{j\rightarrow i}$, so we need to use a bi-linear transformation. That is, we can obtain a diagonal matrix $M_D$

$$M_D = LMR,$$

(6)

where $L = R^{-1} = R^T$ up to corrections which vanish for symmetric $m_{i\rightarrow j}$. In the basis $\vec{y} = R^{-1}\vec{x}$, equation (3) becomes

$$LR\frac{d\vec{y}}{dt} = M_D \vec{y} + L\vec{f}.$$

(7)
While the eigenvalues $\lambda_i$ tell us a great deal - essentially, what would happen in each region if it were isolated - there is additional information in the $L, R$ matrices which relate the original regional basis to the diagonal basis. Below we investigate explicit scenarios involving a developing country $i$ with positive eigenvalue $\lambda_i$, and a developed country $j$ with eigenvalue $\lambda_j$ which is either negative, or, if positive, smaller than $\lambda_i$. In these scenarios the $m_{i\rightarrow j}$ mobility is much more important than the reverse migration $m_{j\rightarrow i}$, since the spread of disease is mainly unidirectional. Hence, we could simply assume $m_{i\rightarrow j} = m_{j\rightarrow i}$ without changing the results appreciably. In that case, $L = R^{-1}$, so equation (7) becomes uncoupled.

In the $N = 2$ case, the non-zero eigenvalues are

$$\begin{align*}
\lambda_1 &= -r_1 - d_1 - m_{1\rightarrow 2} + t_1 \\
\lambda_2 &= -r_2 - d_2 - m_{2\rightarrow 1} + t_2.
\end{align*}$$

(8)

Note that a positive eigenvalue $\lambda_i$ corresponds to $R^i_0 > 1$.

Two generic implications can be stated, depending on the sign of $\lambda_i$. Here we assume that the entries of the off-diagonal mobility matrix $m_{i\rightarrow j}$ are small compared to the other probabilities, so that we can discuss the eigenvalue associated an individual region $i$. This is likely to be the case in any realistic scenario where the mobility matrix reflects air travel.

A country with positive eigenvalue $\lambda_i$ will experience exponential growth in the number of infecteds $I_i$. This growth is only limited by the constraint of total population: eventually roughly the entire susceptible population has been infected and after a long period of time there are only recovered and dead individuals. (This situation is familiar in the case of the common cold or influenza.) There are two important timescales involved: $\lambda_i^{-1}$, which determines the rate of exponential growth, and $|\lambda_i - t_i|^{-1}$, ($\lambda_i - t_i$ is negative) which gives the rate of decline of $I_i$ after saturation occurs and there are no more susceptibles to be infected ($S_i = 0$, so effectively the transmission probability $t_i$ can be set to zero in the corresponding eigenvalue). The outbreak in a highly susceptible country cannot last much longer than the sum of these timescales.

A country with a negative eigenvalue is capable of suppressing any outbreaks of the disease. Nevertheless, there may be a steady state number of infections

$$I_j \sim \frac{J_j}{|\lambda_j|} + \sum_{i \neq j} \frac{m_{i\rightarrow j} I_i}{|\lambda_j - \lambda_i|}$$

(9)

due to the animal reservoir $J$ and/or the migration of infected individuals from other regions. This equation is valid for $m_{i\rightarrow j}$ small compared to $|\lambda_j - \lambda_i|$. (The difference in eigenvalues results from the diagonalization of $M$, and is analogous to the result in quantum mechanics for the change in energy eigenstate under a small perturbation to the Hamiltonian.) The
most dangerous sources of disease migration are countries $i$ with positive eigenvalue $\lambda_i$. The total flux of migration is roughly determined by the mobility $m_{i\rightarrow j}$, the population $S_i(0)$ and the timescales $\lambda_i^{-1}$ and $|\lambda_i - t_i|^{-1}$.

Consider a plausible worst case scenario involving a developing country $i$ with positive $\lambda_i$ and much larger population than developed country $j$ which has negative $\lambda_j$. The developing country is the main source of infection for the developed country. In this case, we obtain the simple relation

$$I_j \sim \frac{m_{i\rightarrow j} I_i}{|\lambda_j - \lambda_i|}$$

relating the number of infected in the two countries at any particular time. The total number of infections in country $j$ (during the entire epidemic) is related to $I_j(t)$ in a complicated way, depending on recovery and death rates. However, by solving equation (4) we can obtain a simple expression for the ratio of total number of infections $N_i$ in the two countries

$$\frac{N_j}{N_i} = \frac{m_{i\rightarrow j}}{|\lambda_j|} \left( \frac{d_j + r_j}{d_i + r_i} \right)$$

(11)

to leading order in $m_{i\rightarrow j}$. The first ratio in this result can be interpreted as the fraction of infected individuals who travel from country $i$ to $j$ in the timescale $|\lambda_j|^{-1}$, which is roughly the “halving” time in country $j$. As long as the death and recovery rates in the two countries are not too different, this can be used as a rule of thumb to estimate the ratio of total number of infections. Obviously it behooves country $j$ to make $|\lambda_j|^{-1}$ as small as possible.

We can also obtain simple expressions for the peak number of infected individuals in both countries (neglecting animal reservoirs):

$$I_i^{\text{peak}} = \frac{\lambda_i}{t_i} \left( P_i - I_i(0) \left( 1 + \frac{t_i}{\lambda_i} \right) \right) \sim \frac{\lambda_i}{t_i} P_i$$

(12)

and

$$I_j^{\text{peak}} = \frac{m_{i\rightarrow j}}{|\lambda_i - \lambda_j|} \left( \frac{\lambda_i}{t_i} \left( P_i - I_i(0) \left( 1 + \frac{t_i}{\lambda_i} \right) \right) \right) + I_i(0) \left( \frac{\lambda_i}{I_i(0)t_i} \left( P_i - I_i(0) \left( 1 + \frac{t_i}{\lambda_i} \right) \right) \right)$$

\[ \sim \frac{m_{i\rightarrow j}}{|\lambda_i - \lambda_j|} \frac{\lambda_i}{t_i} P_i \]

(13)

where $I_i(0)$ is the initial number of infecteds, and $P_i$ is the total population, in country $i$. This gives the maximum capacity required of the medical system during the epidemic. Again, our result is likely to be an overestimate relative to a more realistic SIR or logistic model.

Below we describe the results of two illustrative simulations of the linear model. The parameters are chosen to be realistic average probabilities per week of transmission, recovery,
death and international travel. We integrate equation (3) forward numerically, discretizing
time in units of weeks, and starting with a random number of infecteds between 1 and 10.
Country 1 has population $10^9$ and country 2 has population $10^8$. Note that the figures display
the infected population $I_i(t)$ as a function of time, not the total number of individuals who
have ever been infected. The latter quantity, although not displayed, agrees precisely with
the result given in equation (11). The peak infected results in equations (12) and (13) are
also confirmed.

1) One positive and one negative eigenvalue. The epidemic infects the entire population
of country 1 (figure (1)), but infects only a small fraction of the population of country 2
(figure (2)). The parameter values used are $t_1 = 1; r_1 = 0.7; d_1 = 0.2; t_2 = 0.85; r_2 =
0.9; d_2 = 0.05; m_{12} = 0.00001; m_{21} = 0$, eigenvalues $\lambda_1 = 0.09999, \lambda_2 = -0.1$. The overall
results are consistent with our result (11).

2) Two positive eigenvalues. The epidemic sweeping through country 1 (figure (3)) drives
rapid growth in country 2 (figures (4),(5)) until it has completed its course. At this point
slower growth characterized by $\lambda_2$ (which is very small) resumes. In the end all susceptible
individuals in both countries are infected. The falloff of $I_2$ appears abrupt in figure (5)
because $|\lambda_2 - t_2|$ is much larger than $\lambda_2$. $t_1 = 1; r_1 = 0.75; d_1 = 0.2; t_2 = 0.851; r_2 =
0.8; d_2 = 0.05; m_{12} = 0.00001; m_{21} = 0$, eigenvalues $\lambda_1 = 0.04999, \lambda_2 = 0.001$.

The numerical values of parameters have been varied only slightly between the two ex-
amples, but the resulting behaviors are very different, largely because the eigenvalue $\lambda_2$ has
changed sign.

3  Nonlinear models

To make the models more realistic, we can let the parameters $t_i, r_i, d_i$ depend on local quantities $x_i$. The resulting equations are nonlinear, although still straightforward to simulate numerically. For example, it is possible that a region’s medical capabilities are overwhelmed as the number of infected individuals increases. Indeed, in both the SARS outbreak and the influenza of 1918 (Spanish flu) medical personnel were disproportionately affected.

As a simple example, we take the parameters from simulation 1 in the previous section,
and let the recovery rate $r_2$ of country 2 (which had a negative eigenvalue) interpolate
between the initial value $r_2$ when $I_2 = 0$ and $r_2^*$ when $I_2$ is large, according to the formula

$$r_2(I_2) = r_2 + (r_2^* - r_2) \left( \frac{I_2}{I_2 + I_2^*} \right).$$

(14)
This reflects a saturation of medical treatment capabilities after some characteristic number of infections. When $I_2$ is much larger than $I_2^*$ the recovery probability per unit time is reduced from its initial value of $r_2$ to $r_2^*$, and the eigenvalue $\lambda_2$ may become positive. We take $I_2^* = 2000$, $r_2 = .9$ and $r_2^* = .7$. The results are shown in figures (6) and (7). Figure (7) reveals the onset of the nonlinear behavior when $I_2$ is a few thousand (compare to figure (2)).

4 Internet viruses and worms

These models can be modified to describe the propagation of computer viruses and worms. (From the point of view of our models, there is no essential difference between the two.) A virus commonly inserts itself into other program files, in the same manner that a virus in nature takes over the workings of normal cells. When the infected program runs, the virus code gets a chance to inspect its environment and look for and infect new carriers in the form of other program files. A worm is a self-replicating program that does not alter files but resides in active memory and duplicates itself by means of computer networks. Worms use facilities of an operating system that are meant to be automatic and invisible to the user. It is common for worms to be noticed only when their uncontrolled replication consumes system resources, slowing or halting other tasks.

The variation of parameters by region in our model would be a consequence of different levels of security administration in home, small business, educational and corporate networks.

Mobility $m_{i\rightarrow j}$ has no analog here, as the infected computer does not hop from network to network. Rather, an infected machine can infect other machines connected to the Internet, leading to a non-local (off-diagonal) transmission matrix $t_{i\rightarrow j}$. Machines on local networks $k$ with strong firewalls and virus scanning would be difficult to infect, leading to correspondingly small entries $t_{i\rightarrow k}$. However, once a virus or worm has penetrated the firewall, spread within a local network can be quite rapid, so the diagonal elements $t_{k\rightarrow k}$ may be quite large. Often, the only factor limiting the rate of infection is saturation of available bandwidth by worm scanning activity.

“Slammer”, the most successful worm to date, exploited a security hole in Microsoft’s SQL Server (a database server), and infected 75,000 machines around the world in less than a half hour on January 25, 2003 [5]. The initial doubling time of the infected population was 8.5 seconds, and the growth curve displayed a typical logistic shape.
5 Discussion

We have attempted to model the spread of infectious diseases in a global environment, taking into account geographical variation of public health capabilities as well as human mobility (i.e., via air travel). We believe our models capture a large range of possible behaviors using a minimal set of parameters, each of which can be roughly estimated from data.

One interesting conclusion from our models is that typical international mobility – the probability per unit time of international travel for a given infected individual, estimated at $m_{i\rightarrow j} \sim 10^{-5}$ per week – is still sufficiently small that a country with well-developed public health infrastructure (effectively, a negative eigenvalue $\lambda$) can resist an epidemic even when other more populous countries experience complete saturation. In the quasi-realistic simulation 1 (figures (1),(2)), of order $10^5$ infections occur in country 2, even though the disease has swept completely through country 1. In reaching this conclusion, we kept the mobility parameter fixed during the outbreak, and did not assume any draconian quarantine on international travellers arriving in country 2. Such measures would reduce the number of infections in country 2 considerably. Of course, this conclusion assumes that the public health infrastructure in country 2 remains robust during the outbreak. In the nonlinear simulation 3 (figures (6), (7)), we see that a breakdown in the medical system can lead to grave consequences.

In the case of two countries, one of which is a “reservoir” with positive eigenvalue $\lambda_i$ and the other with negative eigenvalue $\lambda_j$, a good rule of thumb arising from equation (11) is that the ratio of total number of infections in the two countries is given by the fraction of infected individuals who migrate in a timescale $|\lambda_j|^{-1}$, which is the “halving” time for the epidemic in country $j$. In our simulation 1, this timescale is about two months, and the fractional mobility over that period is $\sim 10^{-4}$, leading to $10^5$ infections in country 2 if the entire $10^9$ population of country 1 is infected. The maximum number of infections at any given time in the simulation is $5 \cdot 10^3$ (figure (2)). If the medical system of country 2 can treat this number of patients without breaking down (entering the nonlinear regime), it can prevent a larger outbreak.

Our formula (11) is not applicable to early SARS data since the eigenvalues have clearly been time-dependent during the early stages of the epidemic (estimates of $\mathcal{R}_0$ vary widely during different time periods [1]). Even developed countries like Canada and Taiwan exhibited $\mathcal{R}_0 > 1$ during the first months (positive eigenvalues), although as of this writing eigenvalues appear to be negative for all countries.
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References

[1] For analysis of recent SARS epidemiological data, see C. Dye and N. Gay, 10.1126/science.1086925 (Science Express Perspectives); M. Lipsitch et al., 10.1126/science.1086616 (Science Express Reports); S. Riley et al., 10.1126/science.1086478 (Science Express Reports)

[2] See, e.g., the World Health Organization Influenza Pandemic Preparedness Plan, http://www.who.int/emc-documents/influenza/docs/index.htm

[3] R.M. Anderson and R.M. May, Infectious Diseases of Humans, Oxford University Press (1991), ISBN 0-19-854599-1

[4] J.D. Murray, Mathematical Biology, Springer-Verlag (2003), ISBN 0387952284.

[5] See, e.g., http://www.caida.org/analysis/security/sapphire/
Figure 1: Number of infected in country 1, simulation 1. Note saturation and cutoff.

Figure 2: Number of infected in country 2 (negative eigenvalue), simulation 1.

Figure 3: Number of infected in country 1, simulation 2. Note saturation and cutoff.
Figure 4: Number of infected in country 2 (small positive eigenvalue), simulation 2. Rapid growth driven by migration from country 1 levels off after epidemic subsides in country 1. Subsequent growth in country 2 is much slower.

Figure 5: Number of infected in country 2 (small positive eigenvalue), simulation 2. This graph extends over a longer period of time, exhibiting eventual saturation.

Figure 6: Number of infected in country 2, simulation 3. Initially negative eigenvalue becomes positive as number of infected increases, leading to saturation in country 2.
Figure 7: Number of infected in country 2, simulation 3. Detail of non-linear region in which recovery probability per week falls from .9 to .7. Compare to figure (2).