Global Travel and Severe Acute Respiratory Syndrome (SARS)

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1 Introduction

Severe Acute Respiratory Syndrome (SARS) first appeared in November 2002 in the Guangdong province of China. First reported in Asia in February 2003, the illness spread to more than two dozen countries in Asia, North America, South America and Europe within months. By the time the disease had been declared 'eradicated' in May 2005 by the World Health Organization (WHO), a total of 8098 people in 28 countries world wide had been infected, and of those, 774 had died.

The advance of commercial air traffic plays an ever increasing role in the spread of infectious diseases and in the potential for these diseases to reach pandemic proportions. Despite the significance of commercial air traffic and its role in the worldwide dissemination of infectious diseases, our understanding of global air traffic dynamics remains limited. It is the goal of this paper to give insight into the nature of air traffic as it pertains to the spread of diseases.

The models developed are specifically related to the SARS disease. They can be further generalized to fit other similar (in terms of transmission) diseases, but modifications are necessary in order to take into account diseases with latency periods that are short relative to the flight time.

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Questions. The problem presenter posed the following questions:

Q1. Is it possible to develop a mathematical model to forecast the movement of disease from a given point source location?

Q2. Can these models be developed such that their predictions agree with the SARS data provided?

Q3. Was the movement of SARS random in nature or did the cases travel in a systematic fashion?

Q4. Were these movements predictable?

2 The data

The data that was provided by Khan was abundant. It allowed us to get a good idea of three important aspects:

1. infrastructure,
2. connections,
3. disease.

Infrastructure. The data details the busiest 802 airports worldwide. Due to a data sharing agreement, each airport had been assigned a random number, while their names had been deleted from the database. Below, we refer to these airports as A_i, $i = 1, \ldots, 802$. Only Hong Kong International airport was identified, which was the point of origin of SARS once it left mainland China. In the random ordering chosen for the airports, Hong Kong International has number 7. The total number per year of inbound and outbound passengers for each airport is included in the database. Also, information is provided that localizes these airports within 12 major geographical zones.

Connections. We are given a 802×802 table, detailing, for any pair $i, j = 1, \ldots, 802$, the number of seats on flights between airports A_i and A_j. This is different from the actual number of passengers between A_i and A_j, but the latter information is sensitive commercial data and is not available. Also provided in the table is the distance between A_i and A_j, computed by taking the distance between them on a sphere.

Disease importation. For each of the airports, the number of imported cases into that airport is provided. A case is defined as imported in the airport if, following a careful epidemiological enquiry, it is identified as having arrived into the airport while either in the latent or the active stage of the disease. A case identified in the city that the airport serves, and for which the transmission was clearly local, is not counted. Not available is the time course of the cases: we are given the total number of imported cases over the course of the SARS epidemic, with no finer temporal detail.

3 Dynamics in the airports

3.1 Choice of modelling paradigm. We elaborate two different models. One uses ordinary differential equations both for the population and the movement. The other uses ordinary differential equations at the population level, and a stochastic process for movement of individuals between locations.

Because of the nature of the data, and in particular, the absence of geographical information about the airports (and in particular, about the urban centers they are close to), we choose to consider airports as the units of analysis. Two airports are then considered as directly connected one to another if the number of seats between them is nonzero in the database.

3.2 The model within each airport. From now on, we denote by n the total number of airports. (Here, $n = 802$). The model in each airport $i = 1, \ldots, n$ is based on the classical SEIR model, which has individuals in one of the epidemiological states: susceptible, exposed, infectious and recovered, with numbers at time t denoted $S_i(t)$, $E_i(t)$, $I_i(t)$ and $R_i(t)$, respectively.

The following are remarks concerning these epidemiological states, in the present context. This discussion will allow us to greatly simplify the model.

Susceptibles represent almost all the population. They are potentially affected by the disease, if subject to an infecting contact.

Exposed (or latent) individuals are susceptibles who have become carriers of the disease. In the case of SARS, estimates of the incubation period (the length of time between infection and the onset of symptoms) vary between 2-10 and 7-10 days, meaning that in any case, the inclusion of a class of exposed individuals is necessary in our model. It is generally assumed that patients in this stage of infection do not transmit the disease.

Infectious individuals actively spread the infection, through contacts with susceptible individuals. Several functions are used to model this transmission, but in the case of large populations such as those traveling through airports, it is generally assumed that *incidence*, the rate of apparition of new cases, takes the form

$$\beta_i \frac{S_i I_i}{N_i}$$

in airport A_i, where $N_i = S_i + E_i + I_i + R_i$ is the population in the airport and β_i is the disease transmission coefficient in airport i. This type of incidence is called *mass action* incidence. The disease transmission coefficient β_i represents the probability that infection occurs, given contact. We allow it to vary from location to location, because factors such as hygiene or social distance play a role in the transmission of the disease.

Recovered individuals are individuals who, having recovered from infection, are immune to reinfection (permanently in the case of an SEIR model, temporarily in the case of an SEIRS model).

Simplifications. Because we are interested in the course of the epidemic over a short time interval of about one year, and that our focus is on the appearance of new cases in new airports rather than the global course of the epidemic, we make a certain number of simplifying assumptions.

First, we suppose that the total population in each airport is large and roughly constant, and that $N_i \approx S_i$, that is, the total number $E_i + I_i + R_i$ is negligible compared to N_i (or S_i). This implies that proportional incidence takes the form

$$\beta_i I_i.$$

Note that this implies that the incidence function, which is typically the only nonlinearity in basic epidemiological models, is linear here; this may not be true for other diseases. It is also not true if the disease is considered on a longer time period, because in this case, $E_i + I_i + R_i$ might increase to such a point that S_i is no longer approximately equal to N_i. Finally, we interpret the class of recovered individuals as in the first meaning it was given [4], in terms of *removed* individuals. Individuals are removed from the I class either by recovery or by death. Individuals in the R class play no role in the short term transmission of the disease, and thus we neglect this class from now on.

These assumptions imply that the only epidemiological states of interest in our model are the E and I classes. Independent of transport between locations, the equations in a

given airport i are

$$\frac{d}{dt}E_i(t) = \beta_i I_i(t) - \alpha E_i(t),$$
$$\frac{d}{dt}I_i(t) = \alpha E_i(t) - \gamma_i I_i(t),$$

where $1/\alpha$ is the mean duration of the latent period, and $1/\gamma_i$ is the mean duration of infection before removal by either death or recovery. (Implicit in this formulation is the assumption that the duration of the latent stage and the infectious stage are both exponentially distributed random variables.) The parameter α is the same in all airports, as it represents a pre-diagnosis disease-specific aspect, and is thus independent of location. On the other hand, the parameter γ_i is influenced by treatment, and thus depends on the location.

Accounting for travel. The model we have described thus far accounts for disease transmission in each location, but does not implement movement between locations. To do this, we consider each airport as a vertex in an undirected graph, and set an edge in the graph between airports A_i and A_j if the database shows a nonzero number of seats between airports A_i and A_j. In airport i and for individuals in epidemiological state X (where X is E or I), we then use an operator

$$\mathbf{T}_i^X(t, \mathbf{X}(t))$$

to describe the travel of individuals, where $\mathbf{X} = (X_1, \ldots, X_n)^T$ is the vector of individuals in state X. These operators depend on the type of modelling paradigm used, and are detailed later.

Model equations. In each of the $i = 1, \ldots, n$ airports, we use the following equations:

$$\frac{d}{dt}E_i(t) = \beta_i I_i(t) - \alpha_i E_i(t) + \mathbf{T}_i^E(t, \mathbf{E}(t)) \tag{3.1a}$$
$$\frac{d}{dt}I_i(t) = \alpha_i E_i(t) - \gamma_i I_i(t) + \mathbf{T}_i^I(t, \mathbf{I}(t)). \tag{3.1b}$$

4 Deterministic modelling of transport

4.1 The transport operator. In the deterministic model, it is assumed that movement between airports occurs continuously, with the rate of transport of individuals for airport i to airport j equal to $p_{ji}^X X_i$, for individuals in epidemiological state $X = \{E, I\}$. Individuals inbound to airport i arrive at the rate

$$\sum_{j=1}^{n} p_{ij}^X X_j,$$

where it is assumed for simplicity of notations that $p_{ii} = 0$ for all i. Thus,

$$\mathbf{T}_i^X(t, \mathbf{X}(t)) = \sum_{j=1}^{n} p_{ij}^X X_j - p_{ji}^X X_i. \tag{4.1}$$

Note that in this case, the transport operator is autonomous. Also, we assume (and this is satisfied by the data provided) that the transport graph is strongly connected, i.e., that any airport can be reached from any other airport in a finite number of steps (flights).

4.2 Model equations. The model equations are thus given, for $i = 1, \ldots, n$, by

$$\frac{d}{dt}E_i(t) = \beta_i I_i(t) - \alpha_i E_i(t) + \sum_{j=1}^{n} p_{ij}^E E_j - p_{ji}^E E_i, \tag{4.2a}$$

$$\frac{d}{dt}I_i(t) = \alpha_i E_i(t) - \gamma_i I_i(t) + \sum_{j=1}^{n} p_{ij}^I I_j - p_{ji}^I I_i. \tag{4.2b}$$

Non-dimensionalizing time so that $t = \tilde{t}/\alpha$ leads to

$$\frac{d}{dt}E_i(t) = \frac{\beta}{\alpha}I_i(t) - \left[1 + \sum_{j=1}^{n} \frac{p_{ji}^E}{\alpha}\right] E_i(t) + \sum_{j=1}^{n} \frac{p_{ij}^E}{\alpha} E_j(t), \tag{4.3a}$$

$$\frac{d}{dt}I_i(t) = E_i(t) - \left[\frac{\gamma}{\alpha} + \sum_{j=1}^{n} \frac{p_{ji}^I}{\alpha}\right] I_i(t) + \sum_{j=1}^{n} \frac{p_{ij}^I}{\alpha} I_j(t). \tag{4.3b}$$

Depending on the purpose, we use one of these systems: (4.2) is easier to interpret, making the mathematical analysis easier, while (4.3) is more robust numerically.

4.3 Mathematical analysis. The model (4.2) is a particular case of the models of [1, 2, 3]. Therefore, we do not go into details of the analysis, referring to these papers for precisions.

Grouping disease dependent terms and transportation-dependent terms and writing $\tilde{I} = [I_1\ I_2\ \ldots I_n\ E_1\ E_2 \ldots E_n]^T$, we can write the above system of $2n$ equations in matrix notation as

$$\frac{d}{dt}\tilde{I} = (D + C)\,\tilde{I}, \tag{4.4}$$

where the disease dependent matrix D is given by

$$D = \begin{bmatrix} -\dfrac{\gamma}{\alpha}\mathbb{I}_n & \mathbb{I}_n \\ \\ \dfrac{\beta}{\alpha}\mathbb{I}_n & -\mathbb{I}_n \end{bmatrix}, \tag{4.5}$$

and the connectivity matrix C is given by

$$C = \begin{bmatrix} P_n^I & \mathbb{O}_n \\ \mathbb{O}_n & P_n^E \end{bmatrix}, \tag{4.6}$$

where $\mathbb{I}_n$ denotes the $n \times n$ identity matrix, and $\mathbb{O}_n$ denotes the $n \times n$ zero matrix. The matrix P_n^I is the $n \times n$ matrix given by

$$P_n^I = \frac{1}{\alpha}\begin{bmatrix} -\sum\limits_j p_{j1}^I & p_{12}^I & \cdots & p_{1n}^I \\ p_{21}^I & -\sum\limits_j p_{j2}^I & \cdots & \vdots \\ \vdots & \vdots & \ddots & \vdots \\ p_{n1}^I & \cdots & \cdots & -\sum\limits_j p_{jn}^I \end{bmatrix}. \tag{4.7}$$

The matrix P_n^E is similar to P_n^I with the superscript I replaced with E.

The first result concerns the asymptotic behavior of the movement problem. A matrix such as (4.7) is singular. However, the analysis can be conducted as explained in [3], by considering the augmented matrix incorporating the total population. This allows us to state the following:

Theorem 4.1 *Assume that there are initially individuals in the system, and that each of the travel matrices is irreducible. Then*

$$\lim_{t\to\infty} N(t) = N^* \gg 0.$$

Note that it was assumed earlier that the connection graph is strongly connected. The assumption of irreducibility of P_n^E and P_n^I simply translates this fact in matrix terms.

The next step in the analysis is to establish the existence of disease free equilibria (DFE), that is, of equilibria for which $E_i = I_i = 0$ for all $i = 1, \ldots, n$. Clearly, setting $E_i = I_i = 0$ for $i = 1, \ldots, n$ in (4.2) implies that $E_i = I_i = 0$ remain zero. Thus the DFE of (4.2) is unique and equal to N^*.

Finally, we conclude this brief analysis with considerations on the *basic reproduction number*, $\mathcal{R}_0$. The basic reproduction number represents the average number of secondary cases generated in a wholly susceptible population by the introduction of one infective individual. This is a measure of the ability of the disease to spread.

To compute $\mathcal{R}_0$, we proceed as in [3], using the method of [5]. We consider only the infected classes E and I, and form the matrices F and V representing new infections and other movements within the infected classes, respectively. Then F takes the form

$$F = \begin{pmatrix} 0 & F_{12} \\ 0 & 0 \end{pmatrix},$$

with

$$F_{12} = \text{diag } (\beta_1, \ldots, \beta_n).$$

The matrix V is the block matrix

$$V = \begin{pmatrix} V_{11} & 0 \\ -V_{21} & V_{22} \end{pmatrix},$$

with

$$V_{11} = -P_n^E + \text{diag } \left(\alpha_i + \sum_{j=1}^{n} p_{ji}^E \right), \qquad V_{21} = \text{diag } (\alpha_i),$$

and

$$V_{22} = -P_n^I + \text{diag } \left(\gamma_i + \sum_{j=1}^{n} p_{ji}^I \right).$$

It can be established as in [3] that V_{11} and V_{22} are $n \times n$ irreducible M-matrices, giving the *next generation* matrix

$$FV^{-1} = \begin{pmatrix} F_{12}V_{22}^{-1}V_{21}V_{11}^{-1} & F_{12}V_{22}^{-1} \\ 0 & 0 \end{pmatrix},$$

and the following result holds.

Theorem 4.2 ([3]) *Let $\mathcal{R}_0 = \rho(FV^{-1}) = \rho(F_{12}V_{22}^{-1}V_{21}V_{11}^{-1})$, with $\rho(\cdot)$ the spectral radius. If $\mathcal{R}_0 < 1$, then the DFE is globally asymptotically stable, whereas if $\mathcal{R}_0 > 1$, the DFE is globally asymptotically unstable.*

4.4 Numerical simulations. For the disease related parameters, we use the following values:

- transmission coefficient $\beta = 0.5$,
- mean incubation period $1/\alpha = 7$ days,
- mean sojourn time in the infectious stage $1/\gamma = 21$ days.

The latter two values are obtained from the literature on SARS. Estimating β is probably one of the hardest tasks in epidemiological modeling, and the value we use is deduced from running the simulation several times and observing realistic spread times. In the case of system (4.2), the p_{ij} represent the strength of the connection between airports i and j. To estimate values, we use the following formula:

$$p_{ij} = \frac{\text{Number of seats between } i \text{ and } j}{\text{Total number of seats (between all airports)}} \tag{4.8}$$

$$= \frac{N_{ij}}{\sum_{i,j}^{802} N_{ij}}. \tag{4.9}$$

For example, consider the link from airport 7 to airport 9. The number of available seats is 4,364,182. The total number of seats between all airports is 920,641,841. Therefore, $p_{7,9} = 0.0047404$.

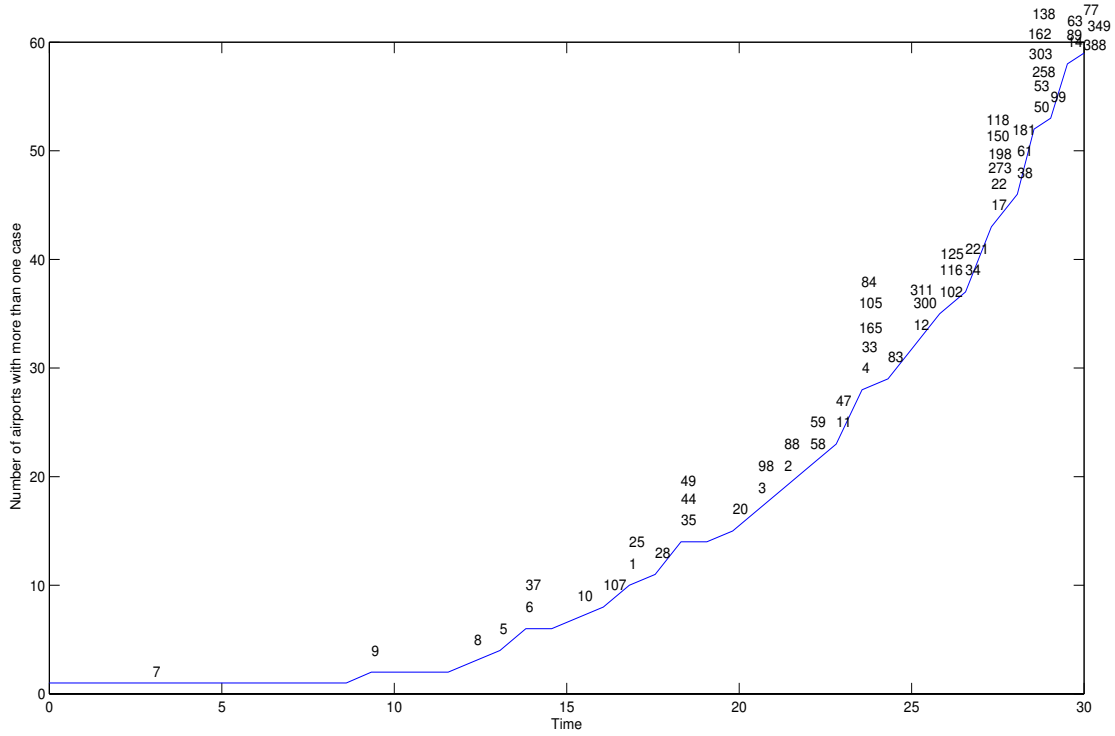

Figure 1 Time of onset of cases in airports for an epidemic initiated in airport 7 (Hong Kong), where the numbers above the curve represent the airports that report their first case at the corresponding time.

Here, we assume that travelers restrain from going to airports where there are known cases. Inbound flows, in airport i, takes the form

$$\sum_{k=1}^{802} p_{ik}^{E} e^{-cI_i} E_k$$

for exposed, and

$$\sum_{k=1}^{802} p_{ik}^{I} e^{-cI_i} I_k$$

for infectious. Figure 1 then shows the time of activation of some airports, following an epidemic initiated in airport 7 (Hong Kong). In this figure, we assume that an airport becomes active once the number of cases in that airport becomes larger than 1. For example, we see that after about 10 days, airport 9 becomes active, followed by airports 8, 5, 6 and 37 (the latter two becoming active at the same time).

Comparing the results shown on Figure 1 with the data, we see that over 70% of the airports that become active within the first 30 days of simulation had SARS cases in the data. We also observe that the agreement between simulations and data is better during the initial phase of the simulation (the first 20 days) than later. Indeed, most of the airports becoming active in the simulation, during the first phase, had SARS cases. This proportion then decreases, and most of the airports becoming active in the simulations during the second phase did not have SARS cases in the data. This is easy to understand: the model assumes instantaneous travel between sites. Therefore, a very small time after the simulation is initiated, there are infectives in all patches (since the connection graph is strongly connected), albeit in very small numbers. The initial spread is then governed by the strength of the connections, while the process homogenizes for larger times, with the number of infectives becoming larger (and larger than 1) in most patches.

5 Stochastic modelling of transport

Consider that the travel of individuals is described by the operator

$$\mathbf{T}_i^X(t, \mathbf{X}(t)) = \Delta_T(t) \times \text{a dispersion kernel},$$

where $\Delta_T(t) = \sum_{k=0}^{\infty} \delta(t - kT)$ is a Dirac comb for the Dirac delta function δ, and T is the period of the movements, e.g., $T = 1$ day if the movement phase is assumed to take place every day. The dispersion kernel then takes the exposed and infective individuals to other patches. An example is the kernel resulting from drawing, at random, a destination among the airports to which an airport has access, with uniform probability density weighted by the volume of the route relative to all routes out of that airport, i.e., with probabilities p_{ij} given as in (4.8).

Preliminary results (not presented here) that were obtained with this model are also quite promising, although they are of course more prone to variability, and thus a larger number of simulations is required in order to deduce some general trends. This will be an area of future study.

6 Conclusions

Due to the limited time imparted to this exercise, it is of course difficult to produce detailed results. However, we are able to draw some positive conclusions. The models developed give remarkably good indications on the future spread of the disease, when it is initiated in the same point of origin as SARS. Thus, even though our approach was extremely simplified, it seems that we can answer questions **Q1** and **Q2** of the introduction by the affirmative. To answer **Q3** is harder: even the deterministic model uses an average approach, because the rates of movement from one airport to another describe the movement of "average individuals". Further investigations of the stochastic model would probably allow for a more definitive answer to this question. Finally, to answer **Q4** is also difficult; to do so would require the ability to more precisely compare the predictions of our models with the time course of the epidemic, which was not available in our data.

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