MAT^2

MATerials MATemàtics
Volum 2013, treball no. 3, 17 pp. ISSN: 1887-1097
Publicació electrònica de divulgació del Departament de Matemàtiques
de la Universitat Autònoma de Barcelona
www.mat.uab.cat/matmat

The SIR model and the Foundations of Public Health

Howard (Howie) Weiss

We introduce and analyze a basic transmission model for a directly transmitted infectious disease. The model consists of a system of three coupled non-linear ordinary differential equations which does not possess an explicit formula solution. However, simple tools from calculus allow us to extract a great deal of information about the solutions. Along the way we illustrate how this simple model helps to lay a theoretical foundation for public health interventions and how several cornerstones of public health required such a model to illuminate.

Sir Ronald Ross

1 Introduction

"As a matter of fact, all epidemiology, concerned as it is with the variation of disease from time to time or from place to place, must be considered mathematically, however many variables as implicated, if it is to be considered scientifically at all."

Sir Ronald Ross, MD

We introduce and analyze the most basic transmission model for a directly transmitted infectious disease caused by bacteria, viruses, or fungi. Direct transmission occurs through individual-to-individual contact: through a sneeze or cough, through skin-skin contact, or through exchange of body

fluids. Examples in the American media this week are the H7N9 flu, whooping cough, mumps, tuberculosis, and MERS-CoV.

The SIR (susceptible-infected-removed) model, developed by Ronald Ross[1], William Hamer, and others in the early twentieth century [4], consists of a system of three coupled non-linear ordinary differential equations, which does not possess an explicit formula solution. However, simple tools from calculus allow us to extract a great deal of information about the solutions. Along the way we illustrate how this simple model helps to lay a theoretical foundation for public health interventions and how several cornerstones of public health required a similar model to discover.

The SIR disease transmission model is derived assuming several strong assumptions. There are hundreds of papers (and some books) where the authors extend this basic model in many directions by relaxing some assumptions. The mathematical analysis quickly becomes significantly more sophisticated and in this article we focus on one of the simplest models.

We begin with a population that can consist of humans (e.g., a school, hospital, or city), animals (e.g., a pig farm, bat colony, or deer in a forest), or plants (e.g., spruce forest, sod farm, or wheat field). We then partition the population into three groups or compartments: susceptible individuals, infected individuals, and removed individuals. We denote the sizes of these subpopulations at time t by $S(t)$, $I(t)$, and $R(t)$. There are many assumptions behind the model, including a large and closed population, the outbreak is short lived; no natural births or natural deaths occur, the infection has zero latent period (an individual becomes infectious as soon as they become infected), recovering from infection confers lifetime immunity, and mass-action mixing of individuals. Mass action mixing assumes that the rate of encounter between susceptible and infected individuals is proportional to the product of the population sizes. Doubling the size of either population results in twice as many new infections per unit time. This requires that the members of both populations are homogeneously distributed in space and thus do not mix mostly in any smaller subgroups. Intuitively, every person will encounter every other person per unit time with equal probability. But keep in mind that the SIR model is deterministic and there are no probabilities[2].

Is the mass action mixing assumption reasonable? Most humans have contacts with only a small fraction of individuals in their community, and are more likely to have contacts with family members, neighbors, and classmates. Children typically have many more contacts than seniors. A common and

[1] Sir Ronald Ross received the second Noble Prize in Medicine and Physiology for his discovery of the transmission of malaria by the mosquito. He was also a closet Mathematician and published papers in several areas of pure and applied mathematics.

[2] One can formulate a stochastic analog of the SIR model as a Markov chain.

pragmatic view is that one should begin modeling with the simplest model and latter add more complexity, if required. The next step is sometimes to use multiple classes of susceptible and infected individuals and assume well mixing between these sub-classes with different rates. Models with well-mixing can serve as null models against the influence of more detailed mechanisms. The well-mixing hypothesis also allows the use of ordinary differential equations (ODEs) instead of partial differential equations or agent based models, which can be substantially more difficult to parametrize, simulate, and analyze.

2 Methods

2.1 The SIR Model

The SIR model is the following system of quadratic ODEs:

$$\frac{dS}{dt} = -\beta\, S\, I \tag{1}$$

$$\frac{dI}{dt} = \beta\, S\, I - \nu\, I \tag{2}$$

$$\frac{dR}{dt} = \nu\, I, \tag{3}$$

where the disease transmission rate $\beta > 0$ and the recovery rate $\nu > 0$ (or in other words, the duration of infection $D = 1/\nu$).

The bi-linear incidence term $\beta\, S\, I$ for the number of new infected individuals per unit time corresponds to homogeneous mixing of the infected and susceptible classes. The total population size should remain constant, and this easily follows from the SIR system: that the sum of the left hand sides of the three equations is the derivative of the total population size and the sum of the right hand sides is zero. We denote the total population size by N. Since $R(t) = N - S(t) - I(t)$, the system can be reduced to a system of two ODEs: (1) and (2).

Suppose that each infected individual has κ contacts (each sufficient for transmission) per unit time and κ is independent of the population size. Then $\kappa\, S/N$ of these contacts are with susceptible individuals. If the fraction τ of adequate contacts result in transmission, then each infected individual infects $\kappa\, \tau\, S/N$ susceptible individuals per unit time. Thus $\beta = b/N$ where $b = \kappa\, \tau$. The parameter τ is called the *transmissibility* of the infectious disease.

2.2 Analysis of the SIR Model

2.2.1 Long term limits exist

Since the right hand side of (1) is negative and the right hand side of (3) is positive, this implies that $dS/dt \leq 0$ and $dR/dt \geq 0$. Since $0 \leq S(t) \leq S(0) \leq N$ and $0 \leq R(0) \leq R(t) \leq N$, this implies that the limits $S(\infty) = \lim_{t\to\infty} S(t), R(\infty) = \lim_{t\to\infty} R(t)$, and thus $I(\infty) = \lim_{t\to\infty} I(t) = N - S(\infty) - R(\infty)$ exist.

2.2.2 The disease always dies out

It is also easy to prove that the disease always dies out, $I(\infty) = 0$ for all initial conditions, without having a formula for $I(t)$. If not, (3) implies that for t sufficiently large, $dR/dt > \nu I(\infty)/2 > 0$, and this implies that $R(\infty) = \infty$, a contradiction. □

2.2.3 Epidemic threshold theorem

We define the *effective reproductive number* $R_e = (S(0)/N)\, b/\nu$ and the *basic reproductive number* $R_0 = b/\nu$. If the entire population is initially susceptible, i.e., $S(0) = N - 1$, $I(0) = 1$, $R(0) = 0$, and large (recall this is a model assumption), then $R_e = ((N-1)/N)\, b/\nu$ is approximately equal to R_0. Henceforth, to beautify formulas involving R_0, we will assume that the quantity $(N-1)/N$ is equal to 1.

We now show that R_e is the threshold value or tipping point that determines whether an infectious disease will quickly die out or whether it will invade the population and cause an epidemic.

Theorem 2.1. 1. *If $R_e \leq 1$, then $I(t)$ decreases monotonically to zero as $t \to \infty$.*

2. *If $R_e > 1$, then $I(t)$ starts increasing, reaches its maximum, and then decreases to zero as $t \to \infty$. We call this scenario of increasing numbers of infected individuals an epidemic.*

It follows that an infection can invade and cause an epidemic in an entirely susceptible population if $R_0 > 1$ or $b > \nu$.

Proof. Equation (2) and the discussion in Section 2.2.1 imply that $dI/dt = (\beta S - \nu) I \leq (\beta S(0) - \nu) I = \nu (R_e - 1) I \leq 0$ for $R_e < 1$. This observation together with $I(\infty) = 0$ (see Section 2.2.2) proves the first statement.

Equation (2) implies $(dI/dt)(0) = \nu (R_e - 1) I(0) > 0$ for $R_e > 1$. Thus $I(t)$ is increasing at $t = 0$. Equation (2) also implies that $I(t)$ has only one

non-zero critical point. These observations, together with $I(\infty) = 0$ imply the second statement. □

Figure 1 contains solutions of the SIR system simulating a highly virulent ($R_e = 3.5$) flu epidemic in a town of $50,000$ people.

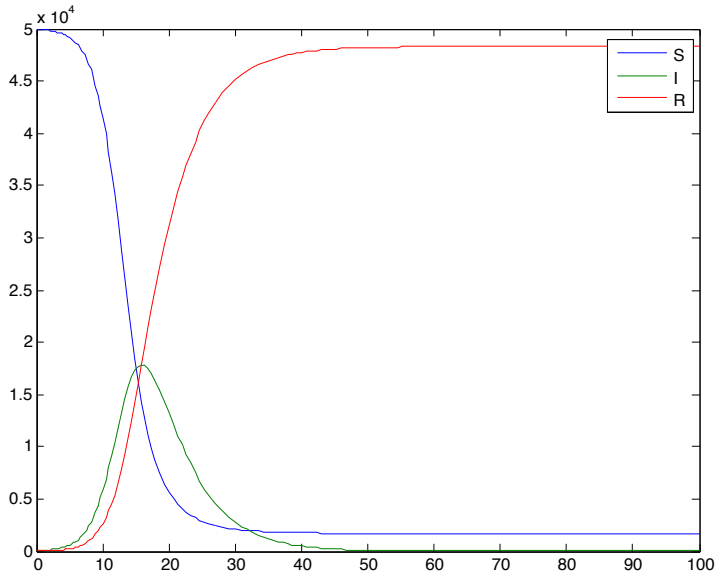


Figure 1: Solutions of SIR system of ODEs with $\beta = 0.7/50000, \nu = 1/5, S(0) = 49955, I(0) = 5, R(0) = 0$

We stress that the existence of a threshold for infection is far from obvious and was missed by many public health and infectious disease experts. The reason is that such a threshold can not be discerned from data; it requires a mathematical model to illuminate.

Above we observed that $(dI/dt)(0) = \nu\,(R_e - 1)\,I(0)$, which implies that the number of infected individuals initially starts growing/decreasing exponentially at rate $\nu\,(R_e - 1)$. The next section will provide strong intuition for the exponential growth.

2.2.4 Public Health interpretation of R_e

We defined the effective reproductive number

$$R_e = \frac{S(0)\,\beta}{\nu} = \frac{S(0)\,b}{\nu\,N} = \frac{D\,\kappa\,\tau\,S(0)}{N} \tag{4}$$

which is the product of the duration of infection, the number of contacts an infected individual has with susceptible individuals per unit time, and the transmissibility (rate of transmission). Thus R_e is the number of new infections caused by each infected individual at the beginning of the outbreak. The parameter R_e is a measure of the fitness of the pathogen. With this interpretation, the first theorem is almost obvious: if at the beginning each infected individual infects three susceptible individuals, and each of these three infected individuals infects three additional susceptible individuals, then of course the number of infections starts growing exponentially. This is schematically illustrated in the Figure 2.

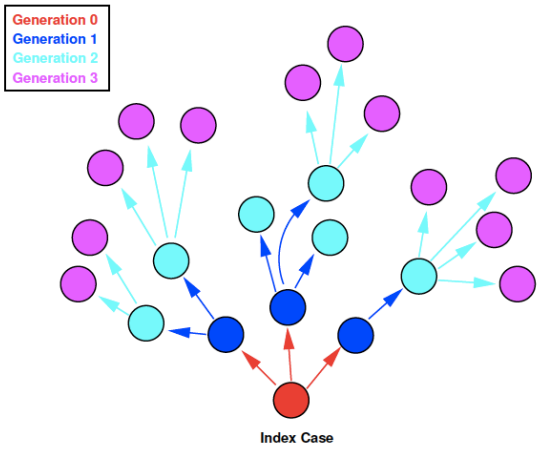


Figure 2: The exponential growth of infected individuals at the beginning of an epidemic

2.2.5 The theoretical foundation of public health interventions

Theorem 2.1 and (4) provide strategies for public health experts to prevent an epidemic by reducing R_e to less than one. For example, for the flu:

1. Reduce the duration of infection D with antivirals;
2. Reduce the contact rate κ by self-isolation of susceptible individuals (request that they stay at home and skip school or work);
3. Reduce $S(0)$ by offering flu vaccines;
4. Reduce the transmissibility τ by encouraging frequent hand washing and, in some cultures, distributing face masks.

These strategies provide a theoretical underpinning for public health interventions.

2.2.6 Vaccination and heard immunity

Vaccinating susceptible individuals removes them from the susceptible class. Even if a vaccine is 100% effective (during a year when the flu vaccine matches the circulating strains well, the annual flu vaccine is estimated to be about 60% effective), vaccinating an entire population is very expensive, and not everybody can take the vaccine. Some individuals, such as those with compromised immune systems or severe allergies, the vaccine may be worse than the disease. We ask the question, can an epidemic be prevented by vaccinating only a fraction of the susceptible class?

It easily follows from our analysis of the SIR model that the answer is yes, and the phenomenon is called *herd immunity*. Recall, to prevent an epidemic, we require that $R_e \leq 1$. Let ρ denote the fraction of the susceptible individuals who gets vaccinated (assuming that the vaccine is 100% effective). These $\rho\, S(0)$ vaccinated individuals have moved from the susceptible class to the removed class, and thus the size of the susceptible class becomes $(1-\rho)\, S(0)$.

To prevent an epidemic, we require that

$$(1-\rho)\, S(0)\, \beta/\nu \leq 1.$$

This will occur when $\rho \geq \rho_c$, where $\rho_c = 1 - 1/R_e$ denotes the critical vaccination threshold.

Thus vaccination against a disease can be completely effective without making everyone immune.

The existence of a herd immunity threshold is also far from obvious and was missed by many public health experts. A significant number of experts thought that such a threshold did not exist and thus believed that mass vaccination programs were bound to fail. The reason it was missed is that it can not be discerned from data; it requires again a mathematical model to illuminate.

Assuming a completely susceptible population, to prevent a flu outbreak with $R_0 = 1.3$, one must vaccinate "only" 23% of the population to prevent an epidemic. If the vaccine is only 60% effective then it is easy to verify (do it!) that one must vaccinate at least $23\%/.6 \approx 39\%$ of the population to prevent an epidemic.

To prevent a smallpox epidemic with $R_0 = 5$, one must vaccinate 80% of the population. Based in part on this finding, along with the belief that

humans are the only natural hosts of the smallpox virus, in 1967 the World Health Organization (WHO) mounted a successful worldwide smallpox eradication program. Smallpox is one of only a very small number of human infectious diseases that has been almost completely irradiated around the world. Even if a malaria vaccine that is 100% effective, since $R_0 > 100$, it would be necessary to vaccinate 99% of the population to prevent epidemics.

2.2.7 The maximum number of infected individuals

We now show that although we can not explicitly solve the SIR system of ODEs, we can still obtain a formula solution for $I_{\max}$.

Dividing (1) by (2) yields the ODE

$$\frac{dS}{dI} = \frac{-\beta\, S\, I}{\beta\, S\, I - \nu\, I}.$$

This ODE is separable, since for $I > 0$ it can be rewritten as

$$\int \frac{\beta\, S - \nu}{\beta\, S} dS = -\int dI.$$

Hence, $-I - S + \nu/\beta \log S = C$. In other words, for every $t \geq 0$,

$$I(t) + S(t) - \nu/\beta \log S(t) = I(0) + S(0) - \nu/\beta \log S(0). \tag{5}$$

$I_{\max}$ occurs when $dI/dt = 0$ which from (2) yields occurs when $S = \nu/\beta$. Applying (5) yields

$$I_{\max} + \nu/\beta - \nu/\beta \log \nu/\beta = I(0) + S(0) - \nu/\beta \log S(0)$$

or

$$I_{\max} = I(0) + S(0) - \nu/\beta \log S(0) - \nu/\beta + \nu/\beta \log \nu/\beta.$$

An easy exercise is to show that for an initially fully susceptible population, the maximum fraction of infected individuals is solely a function of R_0:

$$I_{\max}/N = 1 - \frac{1}{R_0}\left(1 + \log R_0\right).$$

Expression (5) has another useful application. It states that the solutions $(S(t), I(t))$ viewed in the S–I plane (orbits) are contained in the level curves of the function $F(S, I) = S + I - \nu/\beta \log S$. The level curves of this function are shown in Figure 3.

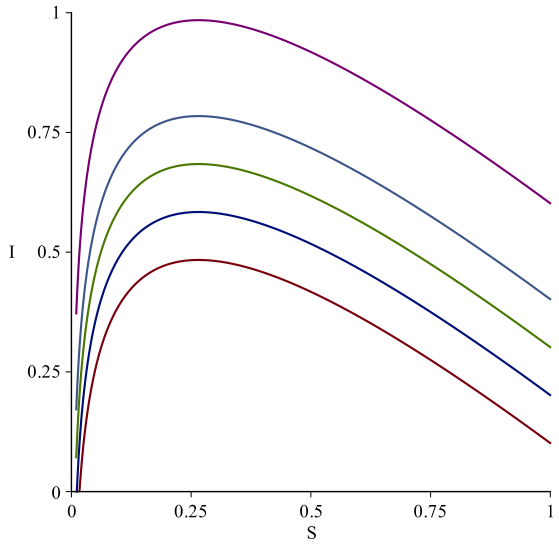


Figure 3: Parametric plots of $I(t)$ verses $S(t)$ with $\beta = 1.66$ and $\nu = 0.44$

2.2.8 Why do epidemics end?

Why do epidemics end? Do they end because there are no longer susceptible individuals in the population? This question perplexed public health experts for many years. If so, then it would be the case that $S(\infty) = 0$. We now show this is not true.

Proposition 2.2. *The limiting number of susceptible individuals*

$$S(\infty) \geq S(0)\, \exp(-R_0) > 0.$$

Proof. Dividing (1) by (3) yields the ODE

$$\frac{dS}{dR} = \frac{-\beta\, I\, S}{\nu\, I} = \frac{-\beta\, S}{\nu}.$$

This ODE is separable, since for $S > 0$ it can be rewritten as

$$\int \frac{1}{S}\, dS = \int \frac{-\beta}{\nu}\, dR.$$

Integrating both sides yields

$$S(t) = S(0)\, \exp(-\beta\, (R(t) - R(0))/\nu), \tag{6}$$

Since $0 \leq R(t) - R(0) \leq N$ it follows that $S(t) \geq S(0)\, \exp(-\beta\, N/\nu)$ and thus

$$S(\infty) \geq S(0)\, \exp(-\beta\, N/\nu) = S(0)\, \exp(-R_0) > 0.^{3}$$

□

As an epidemic proceeds, the number of susceptible individuals decreases and so the rate at which new infections arise also decreases. Eventually, $S(t)$ drops below ν/β, and the rate at which individuals recover exceeds the rate at which new infections occur. Thus, $I(t)$ starts decreasing. The epidemic ends because of the lack of new infected individuals and not because of the lack of susceptible individuals.

This is still another fundament fact can not be discerned from data; it requires a mathematical model to illuminate.

2.2.9 The size of an epidemic?

Equation (6) easily yields a transcendental equation for $S(\infty)$, which when $R(0) = 0$, reduces to

$$\begin{aligned} S(\infty)/N = (S(0)/N)\, \exp(-b\,(R(\infty)/N)/\nu) \\ = (S(0)/N)\, \exp(-b\,(1 - (S(\infty)/N))/\nu). \end{aligned} \quad (7)$$

(recall from Section 2.2.2 that $I(\infty) = 0$).

If the entire population is initially susceptible (7) has the following simple, but transcendental form solely in terms of R_0:

$$\log\left(\frac{S(\infty)}{N}\right) = R_0\left(\frac{S(\infty)}{N} - 1\right).$$

We numerically solve this equation, and Figure 4 contains a plot of $S(\infty)/N$ verses R_0.

It also follows in this case that the attack rate, the total fraction in individuals who get infected, is $1 - S(\infty)/N$.

[3] If simple models are pushed too far they may yield unreasonable results. If, for example, $R_0 = 10^3$, then for almost any population the lower bound $S(0)\exp(-R_0) < 1$. In this totally unrealistic case everybody becomes infected. However, for most infectious diseases $R_0 \leq 5$, and for large populations (recall this is a model assumption), the conclusion is meaningful.

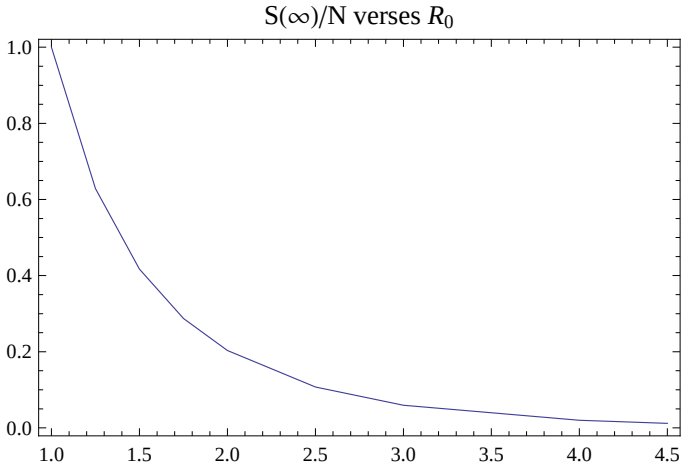


Figure 4: Plot of $S(\infty)/N$ verses R_0.

2.2.10 Five key epidemiological roles of the reproduction numbers

To recap, we have seen that R_e plays the following five key epidemiological roles:

1. R_e is a threshold value for an epidemic: an epidemic will occur if $R_e > 1$.
2. The initial exponential growth rate of an epidemic is $(R_e - 1)\nu$.
3. The critical vaccination threshold for herd immunity is $1 - 1/R_e$.
4. Assuming a fully susceptible initial population, the maximum fraction of infected individuals satisfies $I_{\max}/N = 1 - (1/R_0)\,(1 + \log R_0)$.
5. Assuming a fully susceptible initial population, the percentage of susceptible individuals $S(\infty)/N$ at the end of an epidemic is the root of the transcendental equation $\log(S(\infty)/N) = R_0\,((S(\infty)/N) - 1)$.

3 Testing the SIR model with data

We now present examples to illustrate the predictions of the SIR model. In these examples the SIR model is parametrized using actual infection data, and the $I(t)$ output of the model is compared with the time series data. By parametrizing, we mean that the parameters β and ν are estimated from the data. We note that all the fundamental facts about epidemics that we have

so far obtained were discovered *without* parametrizing the model with any data.

In practice, the transmission rate β, being a complicated function of contact rate κ and transmissibility τ, is difficult to estimate directly and usually requires data to estimate. However, the duration of infectiousness $D = 1/\nu$ can usually be estimated independently of data (e.g., by measuring the virus shedding of infected individuals over time).

The main model parametrization methods are the method of least squares, the method of maximal likelihood, and Bayesian methods. There are other statistical challenges when parametrizing models, for example, under-reporting. Not all infected individuals are officially counted. For example, most people who have the flu suffer at home and do not visit a doctor and have their diagnosis confirmed by a laboratory. One needs to estimate the underreporting rate. At the beginning of the 2009 H1N1 flu pandemic the under-reporting rate in the U.S. was estimated to be about 80 to 1 ([13]).

3.1 Dengue fever outbreaks

Dengue fever is a viral disease that is transmitted by mosquitoes. The "Dengue triad" of fever, rash, and headache is characteristic of Dengue. The disease commonly frequently found in the tropics and is endemic in about 100 countries. There are approximately 50 million cases of Dengue fever virus worldwide. Global warming is causing the range of Dengue to spread.

Figure 5 shows the number of infected individuals during outbreaks in Venezuela and Santiago de Cuba [5] along with the output of parametrized SIR models. Figure 6 illustrates an attempt to model a Dengue outbreak in Havana.

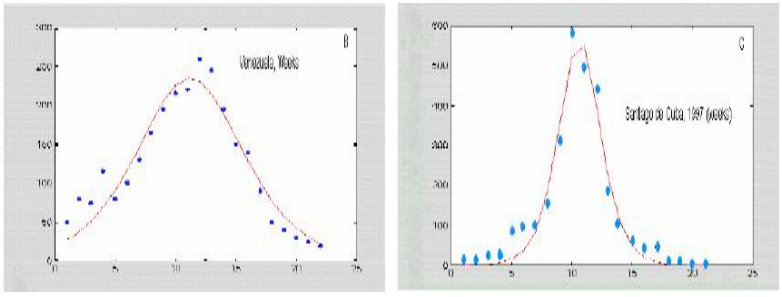


Figure 5: SIR model predictions of Dengue fever outbreaks in (a) Venezuela (2000) (b) Santiago de Cuba (1997)

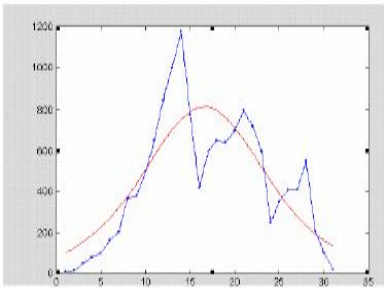


Figure 6: SIR model prediction of 2001 Dengue fever outbreak in Havana .

3.2 Classical swine fever outbreak in the Netherlands

Classical swine fever or "hog cholera" is a highly contagious viral disease of pigs and wild boar. Swine fever usually causes death within 15 days, particularly in young animals. Figure 7 shows the number of infected swine during an outbreak in the Netherlands during 1997-1998 [14] along with a parametrized SIR model.

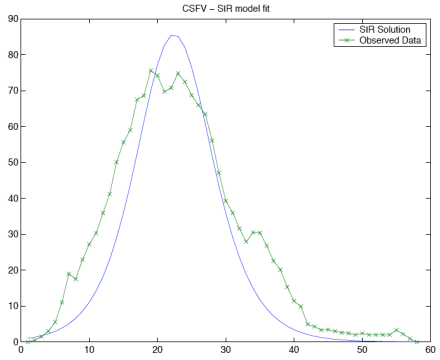


Figure 7: SIR model prediction of classical swine fever virus outbreak in the Netherlands

3.3 Norovirus in Brussels long-term care facility

Norovirus is a highly contagious viral disease and a major cause of gastrointestinal illness in closed and crowded environments, such as hospitals, nursing homes and cruise ships. Typically, people with norovirus infection develop diarrhea and abdominal pain and begin to vomit within 24 to 48 hours of

exposure. Norovirus symptoms may last a few days, but most people recover completely without treatment.

Figure 8 shows the number of norovirus infections in a Brussels long-term care facility during 2007 [16] along with a parametrized SIR model.

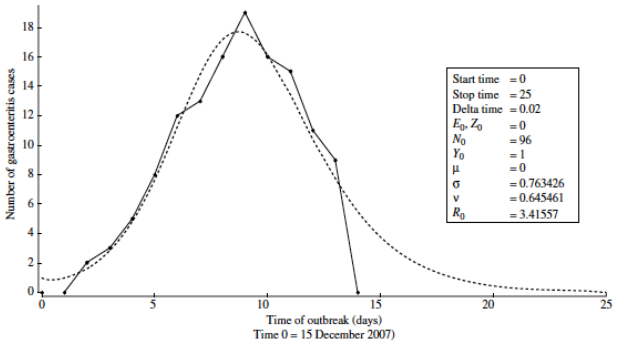


Figure 3 Closed population: number of active cases of gastroenteritis (prevalence) observed during the epidemic outbreak (left vertical axis) and fit of the number expected determined with the *SEIR* model with the Berkeley–Madonna program. Inset: force of transmission coefficient $\beta = \nu R_0$ represents the coefficient of transition from S to

Figure 8: SIR model prediction of norovirus outbreak in Brussels long-term care facility 2007

3.4 How well do the models fit the data?

All the fits except Figure 6 look pretty good. But do not to be overly impressed. The displayed data was used to parametrize the model and the parametrized model may be just regenerating the data which was used to parametrize it. More convincing would be if a parameterized model can accurately reproduce new observed data.

Furthermore, a model can achieve an excellent fit to data for reasons that have nothing to do with the model's fidelity to the underlying biological process. For an extreme example, in [12] we show that nearly any positive function is the $I(t)$ output of an SIR model with variable transmission rate $\beta(t)$. However, if the output of a model does not mimic the data (e.g., Figure 6), then the model is likely to be missing at least one important component. In this sense, a deficient model may be more helpful than a model that fits the data.

4 Concluding remarks

What have we learned? Mathematically, we learned how we can extract many useful properties of solutions of nonlinear ODEs even though the system has

no explicit formula solution. Biologically, we learned how the simple unparameterized SIR model yields several fundamental insights into outbreaks of infectious diseases and their control - insights that were nearly impossible to discern from infection data alone. Thus the analysis of the SIR model provides a theoretical framework for public health interventions.

How else could compartment models be helpful to study disease transmission? Here is a recent example from my research. The gray bars in Figure 9 represent the number of pandemic H1N1 viral isolates tested the United States during the 2009 H1N1 flu pandemic [9]. Think of this as a proxy for the number of infections.

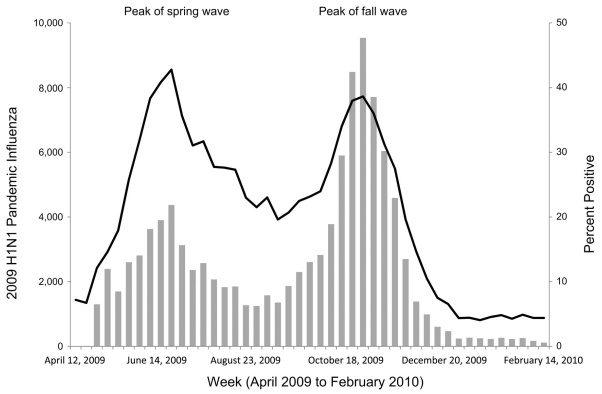


Figure 9: Number of pandemic H1N1 viral isolates tested the United States from April 2009 through March 2010.

Notice the two peaks. If all the assumptions of the SIR model held for this outbreak, Theorem 2.1 would imply there would be only one peak. Also, the US experienced one peak every year except during the pandemic years 1918, 1958, 1968, 2009, when it experienced two or more waves. What is the mechanism(s) that is generating the multiple peaks? Nobody knows. Recently in [10], we used relatively simple extensions of the SIR model to exhibit five plausible mechanisms, each of which could have generated the two peaks during 2009, both quantitatively and qualitatively.

The first two mechanisms capture changes in virus transmissibility and behavioral changes. The third mechanism involves population heterogeneity where each wave spreads through one sub-population. The fourth mechanism is virus mutation which causes delayed susceptibility of individuals. The fifth mechanism is waning immunity. We use the models to examine the effects of border control at the beginning of the outbreak and the timing of and amount of available vaccinations.

We also use the models to try to understand why China, which instituted strict border control at the onset of the outbreak, had only one peak and the US had two peaks. The models indicate that had the US also instituted strong border control at the onset of the outbreak, they would have also experienced a single peak of infections. However, the models also indicate that strong border control would not have decreased the total number of infections.

Want to learn more about infectious disease transmission models? Some references include [6, 7, 8, 11]. References for the mathematics (dynamical systems or nonlinear dynamics) required to analyze these models include [3, 15]. References [1, 2] contain introductions to stochastic transmission models.

References

[1] Linda JS Allen. *An introduction to stochastic processes with applications to biology*. Pearson Education New Jersey, 2003.

[2] Linda JS Allen. An introduction to stochastic epidemic models. In *Mathematical Epidemiology*, pages 81–130. Springer, 2008.

[3] Kathleen T Alligood, Tim D Sauer, and James A Yorke. *Chaos: an introduction to dynamical systems*. Springer, 1996.

[4] R.M. Anderson. Discussion: the Kermack-McKendrick epidemic threshold theorem. *Bulletin of mathematical biology*, 53(1):1–32, 1991.

[5] José Luis Hernández Cáceres. Extracting useful information from dengue incidence data. www.rcim.sld.cu/revista_13/articulos_htm/caceres.htm.

[6] Herbert W Hethcote. Three basic epidemiological models. *Applied Mathematical Ecology*, 18:119–144, 1989.

[7] Herbert W Hethcote. The mathematics of infectious diseases. *SIAM review*, 42(4):599–653, 2000.

[8] Herbert W Hethcote. The basic epidemiology models: Models, expressions for r0, parameter estimation, and applications. *Mathematical understanding of infectious disease dynamics*, 16:1–61, 2009.

[9] Michael A Jhung, David Swerdlow, Sonja J Olsen, Daniel Jernigan, Matthew Biggerstaff, Laurie Kamimoto, Krista Kniss, Carrie Reed, Alicia Fry, Lynnette Brammer, et al. Epidemiology of 2009 pandemic influenza a (h1n1) in the united states. *Clinical Infectious Diseases*, 52(suppl 1):S13–S26, 2011.

[10] Anna Mummert, Howard Weiss, Li-Ping Long, Jose Amigó, and Xiu-Feng Wan. A perspective on multiple waves of influenza pandemics. *PLOS ONE*, 8(4), 2013.

[11] James Dickson Murray. *Mathematical biology*, volume 2. springer, 2002.

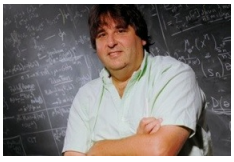
[12] Mark Pollicott, Hao Wang, and Howard (Howie) Weiss. Extracting the time-dependent transmission rate from infection data via solution of an inverse ode problem. *Journal of Biological Dynamics*, 6(2):509–523, 2012.

[13] Carrie Reed, Frederick J Angulo, David L Swerdlow, Marc Lipsitch, Martin I Meltzer, Daniel Jernigan, Lyn Finelli, et al. Estimates of the prevalence of pandemic (h1n1) 2009, united states, april–july 2009. *Emerging infectious diseases*, 15(12):2004, 2009.

[14] Arjan Stegeman, Armin RW Elbers, Jan Smak, and Mart de Jong. Quantification of the transmission of classical swine fever virus between herds during the 1997–1998 epidemic in the netherlands. *Preventive veterinary medicine*, 42(3):219–234, 1999.

[15] Steven Strogatz. *Nonlinear dynamics and chaos: with applications to physics, biology, chemistry and engineering*. Perseus Books Group, 2001.

[16] J. Vanderpas, J. Louis, M. Reynders, G. Mascart, and O. Vandenberg. Mathematical model for the control of nosocomial norovirus. *Journal of Hospital Infection*, 71(3):214–222, 2009.



Mathematics Department
Georgia Institute of Technology
Atlanta, Georgia, USA
weiss@math.gatech.edu

Publicat el 1 de juliol de 2013