Mathematical Modeling of Infectious Disease

DAIDD 2013

Travis C. Porco

FI Proctor Foundation for Research in Ophthalmology

UCSF

Scope and role of modeling

In the most general sense, we may consider modeling as an effort to understand one aspect of the world by its similarity to something else. For instance, researchers may develop animal models of the pathogenesis of various disease agents. Studying the disease process in the animal model may then lead to insights that can be developed further. To be useful, the animal model must resemble the disease in humans in ways the researchers consider to be important. To be believable, the results from animal models must be tested.

Another type of model is the statistical model, which attempts to describe relevant aspects of data or a data generation process. Such models frequently do not attempt to describe the mechanism yielding the data, but rather form a basis for determining, for instance, if an estimated difference between a treatment and control group could have plausibly resulted from chance. Statistical models based on real data play an important and vital role in all areas of epidemiology and lead to essential insights. However, when such models are not based on a representation of the underlying medical or epidemiologic processes, such models may not be generalizable beyond the circumstances under which the data were collected.

While statistical models play a fundamental role in research, including research in analytical epidemiology, models based on representing the mechanism of disease transmission have played a role in epidemiology for decades. Some of the earliest mathematical models were developed by Sir Ronald Ross, who showed that mosquitoes were vectors of the malaria plasmodium. Ross wished to describe the factors responsible for spread and dissemination of the plasmodium in a quantitative way, and published papers describing what was called

a priori pathometry.

Mathematical models are attempts to gain insight into the processes of disease transmission and persistence using mathematical representations of the mechanisms of disease transmission. Models may be used to address a variety of theoretical and practical questions; these applications may include forecasting for planning, designing interventions, or simply improving our understanding. For instance, modelers may wish to estimate the number of hospital beds needed to prepare for SARS, or to estimate how many deaths of hospitalizations might result from pandemic influenza. Modelers may wish to determine whether quarantine is warranted during an influenza outbreak, or whether ring vaccination would be sufficient to control bioterrorist smallpox. As examples of improving understanding, modelers may wish to estimate the contribution of superspreaders to the invasion of a pathogen into a new region, estimate the best tradeoff of virulence and transmissibility a pathogen should seek if public health control measures change, or to determine how the mortality rate may affect the number of people who are ultimately infected by a pathogen. In general, the most important strength of mathematical models of the disease process is the ability to explore counterfactual scenarios or conditions for which no data is available, for instance, to examine the consequences of untested control strategies or the spread of a novel pathogen.

Mathematical models are most credible when the mathematical analogy which constitutes the representation are clear and plausible—when the model representation resembles the epidemic in ways the researchers consider most important. Understanding what the most important features of a disease transmission process are leads modelers at times into vigorous debate, frequently manifesting a tension between the need for insight through elegant simplicity on the one hand, and realism through increased detail on the other. Finally, note that as is the case with other types of models in science, the insights gained from modeling must ultimately be tested in some way.

In this brief lecture, we will discuss some key concepts and simple models that have been used in mathematical epidemiology, and discuss how researchers applied some of these

principles to an emerging pathogen.

The Reed-Frost Model

A classic model of infectious disease transmission was developed during the 1930s by Lowell J. Reed and Wade Hamptom Frost of Johns Hopkins. Because the model is simple to explain and provides valuable insights, we will discuss it at this time.

In the classical Reed-Frost model, we assume a fixed population of size N. At each time, there are a certain number of cases of disease, C, and a certain number of susceptibles, S. We assume each case is infectious for a fixed length of time, and ignore the latent period; when individuals recover, we assume that they are immune to further infection. During the infectious period of each case, we assume that susceptibles may be infected, so that the disease may propagate further. This constitutes an idealized, or abstract, model, exhibiting some features of an epidemic system.

Because we assume a fixed length infectious period and neglect the latent period, the generations of infection stay separate. At the beginning, we have only the generation of cases that starts the disease transmission. After the recovery of this generation, the new cases that resulted from transmission constitute the second generation of cases. These, in turn, recover, but may give rise to a third generation. Let C_1 be the number of cases in the first generation, and S_1 be the number of susceptibles that the first generation may place at risk of new infection. Similarly, let C_2 be the number of cases in the second generation, and S_2 the number of susceptibles present for the second generation of cases to potentially expose to disease; in general, the number of cases at generation t is denoted C_t and there are S_t susceptibles at that time.

The basic Reed-Frost model assumes homogeneity of risk of infection throughout the population. In particular, we assume that each susceptible has a risk p of being infected by any of the infectives in the population. In a more realistic model, we might assume that this probability depends on the population size. We might also assume that each susceptible does not have the same risk of being infected by each infective.

Assuming, however, that each susceptible has a risk p of being infected by each infective, we can then find the probability distribution of the number of cases in the second generation. In other words, we can find the probability that the number of cases in the second generation takes various values. For instance, if none of the susceptibles gets infected, we would have no cases in the second generation; we could determine the probability that C_2 is zero, i.e. $P(C_2 = 0)$.

If each susceptible has a risk p of being infected by each infective, what is the chance that a particular susceptible will be infected? Since there are C_1 infectives, a sufficient exposure from any infective would cause the susceptible to become infected. There are thus many ways to be infected—a susceptible could be infected by the first infective, or the second, or the third, etc., or may receive a sufficient exposure from more than one infective or even from all. On the other hand, there is only one way to escape infection, and that is to escape infection (to fail to receive a sufficient exposure) from all the infectives in the population.

The next assumption we will make for the basic Reed-Frost model is that the exposures are independent. Each infective constitutes an independent risk for each susceptible, and whether any susceptible is infected or not is independent of all the other susceptibles. With this assumption, we can compute the chance of escaping infection. Considering one particular susceptible individual, this susceptible has a chance $1 - p$ of escaping infection from the first case. There is also a chance $1 - p$ of escaping infection from the second case, and so on through all C_1 cases we have at the beginning. Since we must determine the chance of escaping infection from the first and from the second and so forth, we may use independence to compute this by multiplying the probabilities. The probability of escaping infection from the first and second individuals is the probability of escaping infection from the first, times the probability of escaping infection from the second, and so forth. Thus, the chance of escaping infection from all susceptibles is $(1 - p) \times (1 - p) \times \cdots \times (1 - p)$, where there are C_1 terms being multiplied. This is simply $(1 - p)^{C_1}$ for the probability of escaping infection. Thus, the probability of being infected is simply $1 - (1 - p)^{C_1}$.

As a brief digression, models of this form, known as *binomial risk models*, are frequently

used to analyze data for many real diseases. For instance, the application of binomial risk models to data from the San Francisco Men's Health Study led to the estimate that there is a 10% chance, per partnership, of the transmission of the HIV virus from an infected partner to an uninfected partner, for MSMs in San Francisco in the 1980s. Such models have been used to analyze HIV transmission data per act, rather than per partnership, to estimate potential declines in HIV infectivity due to the widespread use of antiretrovirals, or to analyze the cost-effectiveness of HIV prevention interventions in sub-Saharan Africa.

Returning to the Reed-Frost model, we have shown that the probability that any of the S_1 susceptibles will be infected is $1-(1-p)^{C_1}$. We must now determine the probability distribution of the number of new cases, C_2. Mathematically, we may consider each susceptible to be a *Bernoulli trial*, a random experiment with two outcomes, conventionally known as *success* and *failure*. Since these trials are independent of one another, and since the "success" probability is the same for each trial, we may use the *binomial distribution* to determine the probability distribution of the number of successes. For simplicity, let us denote the infection probability ("success" probability) by r; we have shown that $r = 1-(1-p)^{C_1}$. Then the binomial probability distribution gives us the probability distribution of the number of cases in the next generation:

$$P(C_2 = x) = \binom{S_1}{x} r^x (1-r)^{S_1 - x}.$$

Here, the notation $\binom{S_1}{x}$ is the number of ways to choose the supposed x new cases out of the S_1 number of susceptibles. The number of susceptibles at time 2 is simply $S_2 = S_1 - C_2$.

The same reasoning can be applied at each time. Of course, the risk r changes if the number of cases changes, so we may write the risk at time t as $r_t = 1-(1-p)^{C_t}$. Therefore, the probability distribution of the number of cases at time t is

$$P(C_t = x) = \binom{S_{t-1}}{x} r_{t-1}^x (1-r_{t-1})^{S_{t-1}-x},$$

and $S_t = S_{t-1} - C_t$.

Before exploring the behavior of this model further, observe that the number of cases over time is *random*. The randomness arises because of our assumptions about the nature

of transmission. The quantities predicted by the model, i.e. C_t and S_t, are random variables whose distribution is specified by the model. In the same way that a statistician might model the height of a randomly selected person as having a particular distribution, say a normal distribution with some specific mean and variance. Just as the statistician may consider the height of a specific person as being a realization of this random distribution (a random variate drawn from the specified distribution), we may think of a particular realization of this process as leading to a particular number of cases and susceptibles over time. In general, even if our parameters p, N, and C_1 remain the same, the number of cases may be different, just as the height of a second person drawn from the same population may be different. The Reed-Frost model is an example of a *stochastic model*, and the sequence of numbers of cases and susceptibles constitutes a *stochastic process*.

Models similar to the Reed-Frost model have been analyzed carefully by mathematicians, and these models are called *chain binomial* models. Rather than explore the formal analysis, we will explore the dynamics of the Reed-Frost model using computer simulation. The exciting open-source statistical package R `http://www.r-project.org` will provide us with an excellent platform for such exploration.

We first write a *function* in R which provides us with a simulation of the Reed-Frost model. Without going into details of the programming language, the function does three things. First, it checks that the preconditions for the computation are met. For instance, a negative transmission probability is simply meaningless, so the function checks to make sure the transmission probability is not negative. The function checks other conditions as well, such as the requirement that the number of cases not be larger than the population size. Second, the function computes the risk for each susceptible as $1-(1-p)^{C_t}$, and uses the built-in random number generator for the binomial, called `rbinom`, to compute the random number of secondary cases. Finally, the function returns the results to us.

```
reed.frost <- function(pp, nn, c1, t.end, cumul.only = FALSE) {
    if (t.end > 1000) {
```

```
        stop("t.end too big")
    }
    if (t.end <= 0) {
        stop("negative or zero ending time")
    }
    if (c1 < 0 || abs(round(c1) - c1) > 1e-07) {
        stop("invalid starting number of cases")
    }
    if (nn < 0 || abs(round(nn) - nn) > 1e-07) {
        stop("invalid population size")
    }
    if (pp > 1 || pp < 0) {
        stop("invalid transmission probability")
    }
    if (nn < c1) {
        stop("more cases than people")
    }
    ss <- rep(0, t.end)
    cc <- rep(0, t.end)
    cumul <- 0
    current.cc <- c1
    current.ss <- nn - c1
    if (!cumul.only) {
        cc[1] <- current.cc
        ss[1] <- current.ss
    }
    for (ii in 2:t.end) {
        rr <- 1 - (1 - pp)^current.cc
```

```
        current.cc.new <- rbinom(1, size = current.ss, prob = rr)
        current.ss.new <- current.ss - current.cc.new
        if (!cumul.only) {
            ss[ii] <- current.ss.new
            cc[ii] <- current.cc.new
        }
        current.ss <- current.ss.new
        current.cc <- current.cc.new
        cumul <- cumul + current.cc.new
        if (current.cc.new == 0) {
            if (!cumul.only) {
                for (jj in (ii + 1):t.end) {
                  ss[jj] <- current.ss
                }
            }
            break
        }
    }
    if (cumul.only) {
        cumul
    } else {
        list(susc = ss, cases = cc, cumul.new.cases = cumul)
    }
}
reed.frost.average <- function(pp, nn, c1, t.end, nreps = 1, cumul.only = FALSE) {
    if (cumul.only) {
        cumul <- reed.frost(pp, nn, c1, t.end, cumul.only)
        for (ii in 2:nreps) {
```

```
            cumul <- cumul + reed.frost(pp, nn, c1, t.end, cumul.only)
        }
        cumul/nreps
    } else {
        run <- reed.frost(pp, nn, c1, t.end)
        ss <- run$susc
        cc <- run$cases
        for (ii in 2:nreps) {
            run <- reed.frost(pp, nn, c1, t.end)
            ss <- ss + run$susc
            cc <- cc + run$cases
        }
        list(susc = ss/nreps, cases = cc/nreps)
    }
}
```

Let us use this function to create a random epidemic. Assume that the population size is 100, and the transmission probability is 0.02. We will run this model five times, and plot them all.

```
end.time <- 100
pp <- 0.02
sim1 <- reed.frost(pp = pp, nn = 100, c1 = 1, t.end = end.time)
sims <- list(sim1)
tot.reps <- 5
for (ii in 2:tot.reps) {
    new.sim <- reed.frost(pp = pp, nn = 100, c1 = 1, t.end = end.time)
    sims[[ii]] <- new.sim
}
```

```
times <- 1:end.time
```

As the figure illustrates, each epidemic is somewhat different.

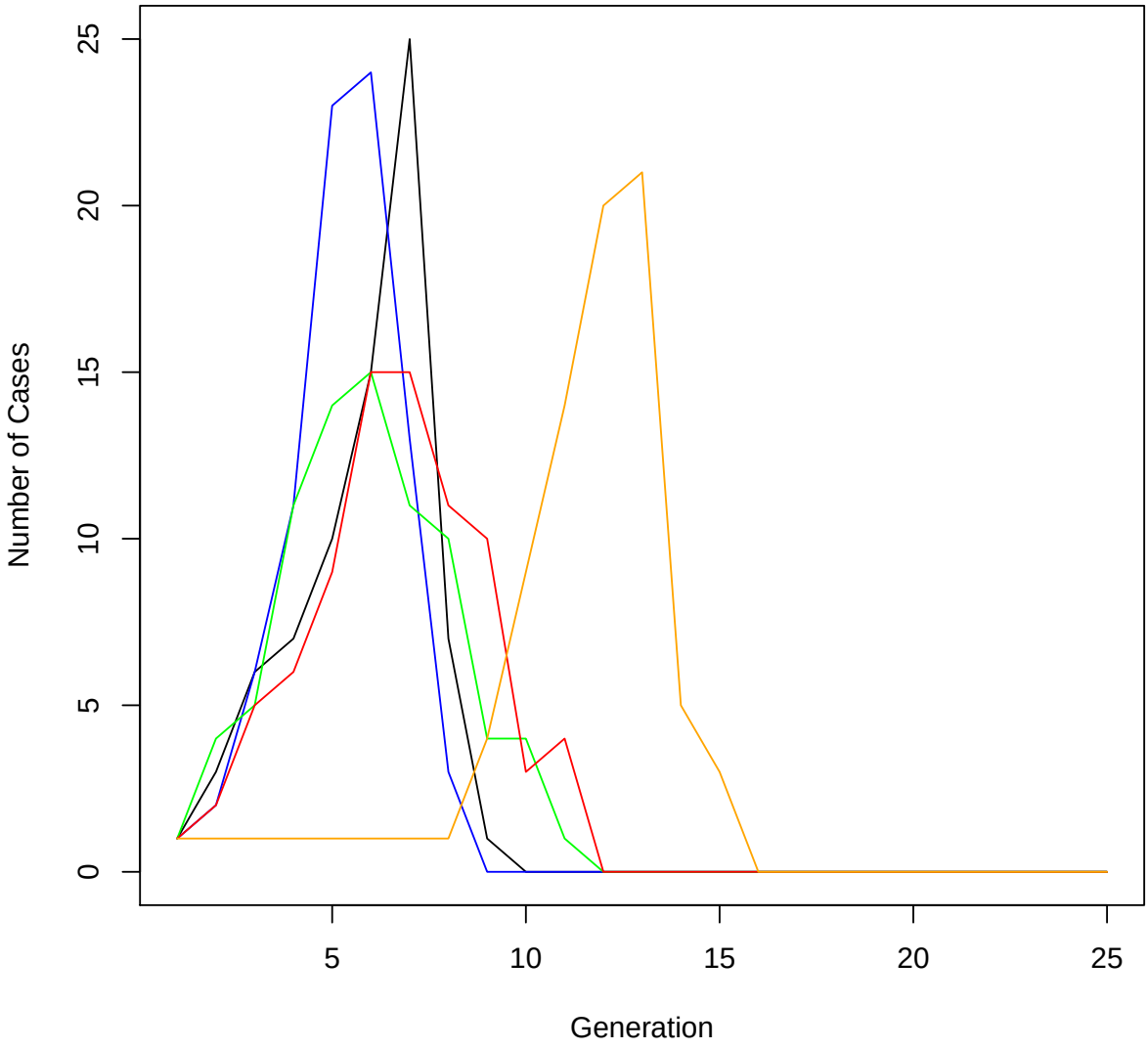
It will be interesting to plot the average number of cumulative cases for different values of the probability p. Let us begin for a small population, of size ten. We will average the results of 1000 repetitions for each value of the probability.

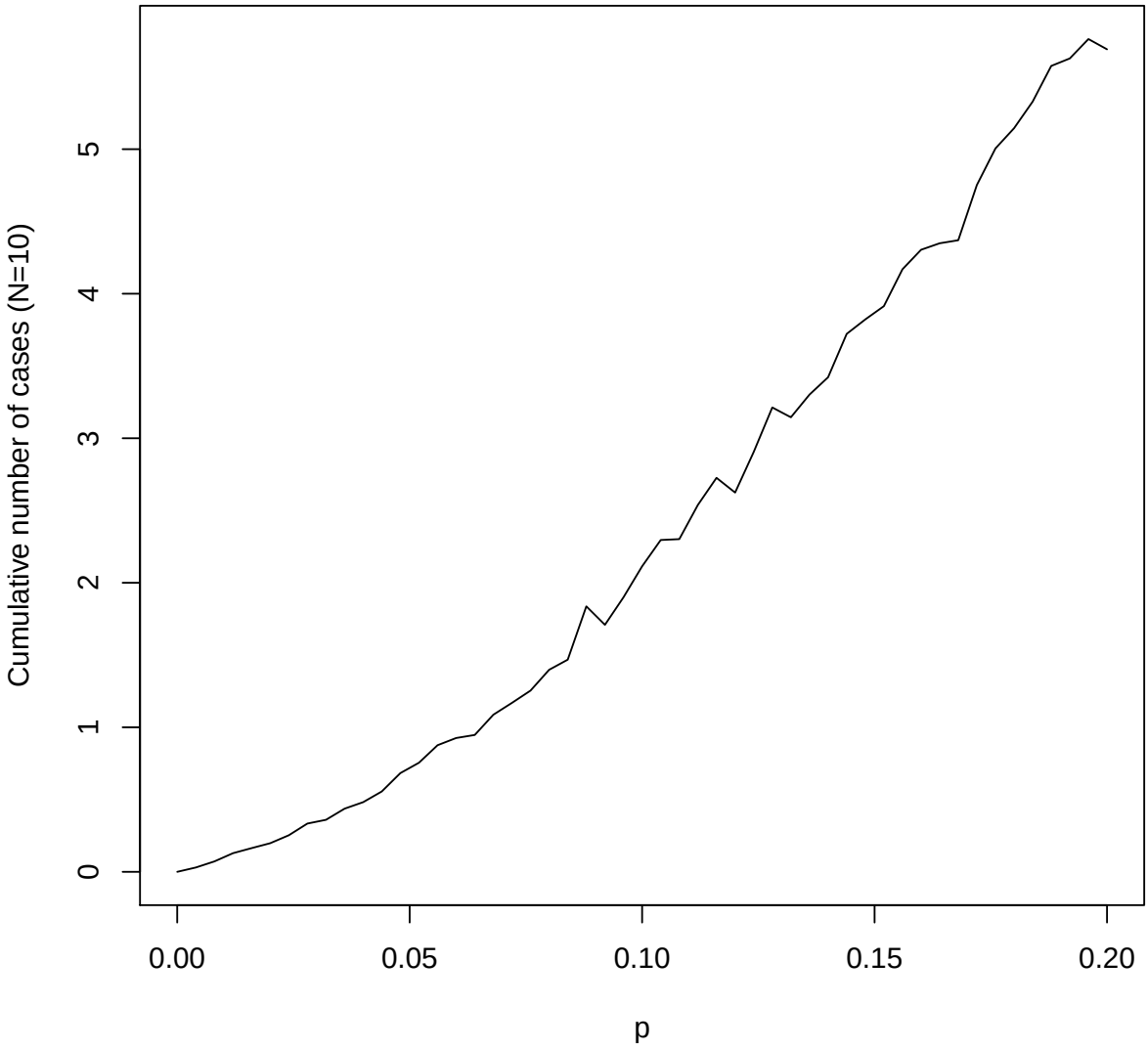
```
nseps <- 50
ps <- seq(0, 0.2, by = (0.2)/nseps)
ans <- rep(0, length(ps))
nreps <- 1000
nn <- 10
for (ii in 1:length(ps)) {
    ans[ii] <- reed.frost.average(pp = ps[ii], nn = nn, c1 = 1, t.end = 50,
        nreps = nreps, cumul.only = TRUE)
}
```

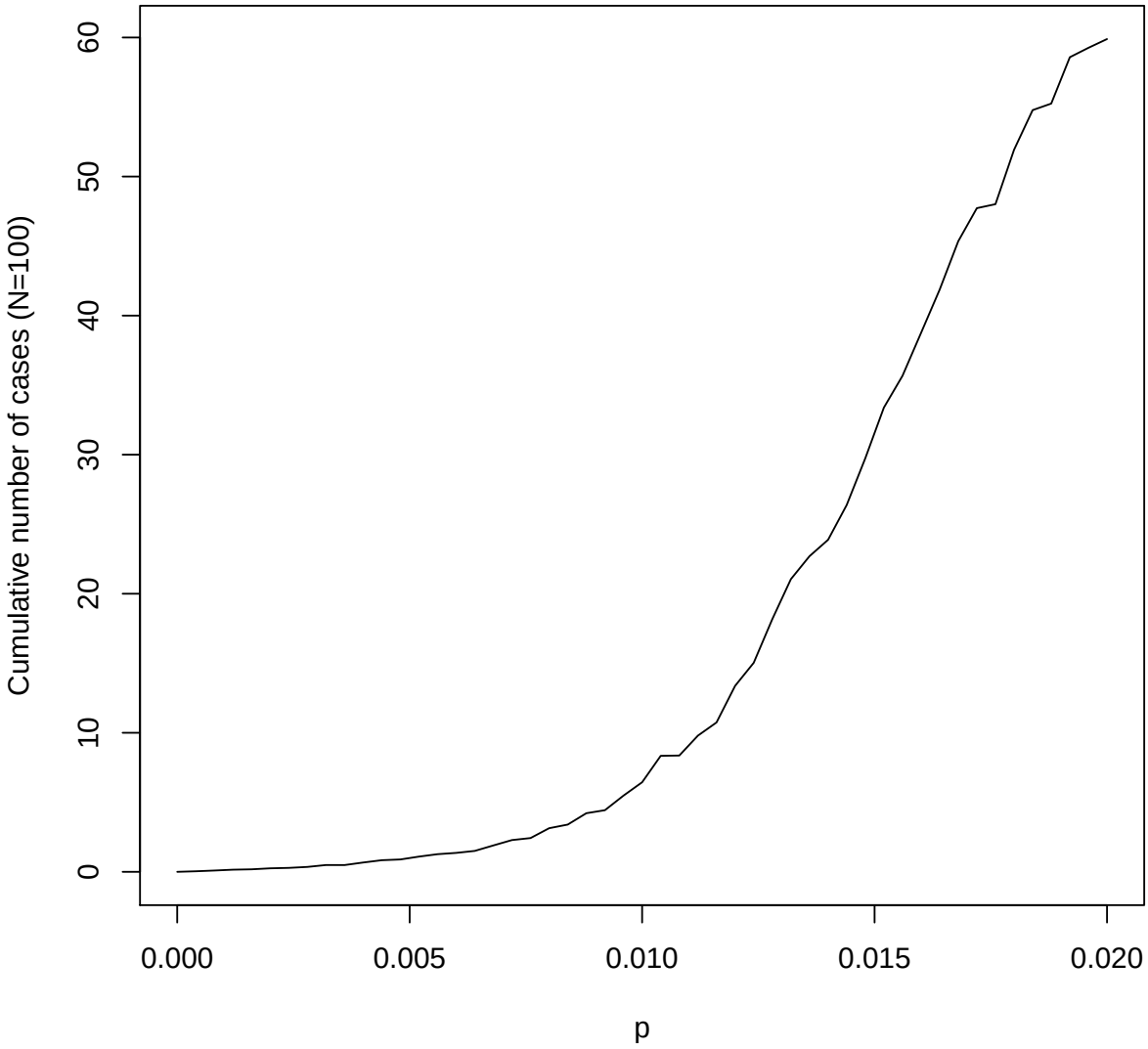
Next, we consider a population of size 100:

```
ps <- seq(0, 0.02, by = (0.02)/nseps)
ans <- rep(0, length(ps))
nn <- 100
for (ii in 1:length(ps)) {
    ans[ii] <- reed.frost.average(pp = ps[ii], nn = nn, c1 = 1, t.end = 200,
        nreps = nreps, cumul.only = TRUE)
}
```

For a population of size 1000:


Number of Cases
0
5
10
15
20
25
5
10
15
20
25
Generation


Cumulative number of cases (N=10)
0
1
2
3
4
5
0.00
0.05
0.10
0.15
0.20
p


Cumulative number of cases (N=100)
0
10
20
30
40
50
60
0.000
0.005
0.010
0.015
0.020
p

```
ps <- seq(0, 0.002, by = (0.002)/nseps)
ans <- rep(0, length(ps))
nn <- 1000
for (ii in 1:length(ps)) {
    ans[ii] <- reed.frost.average(pp = ps[ii], nn = nn, c1 = 1, t.end = 1000,
        nreps = nreps, cumul.only = TRUE)
}
```

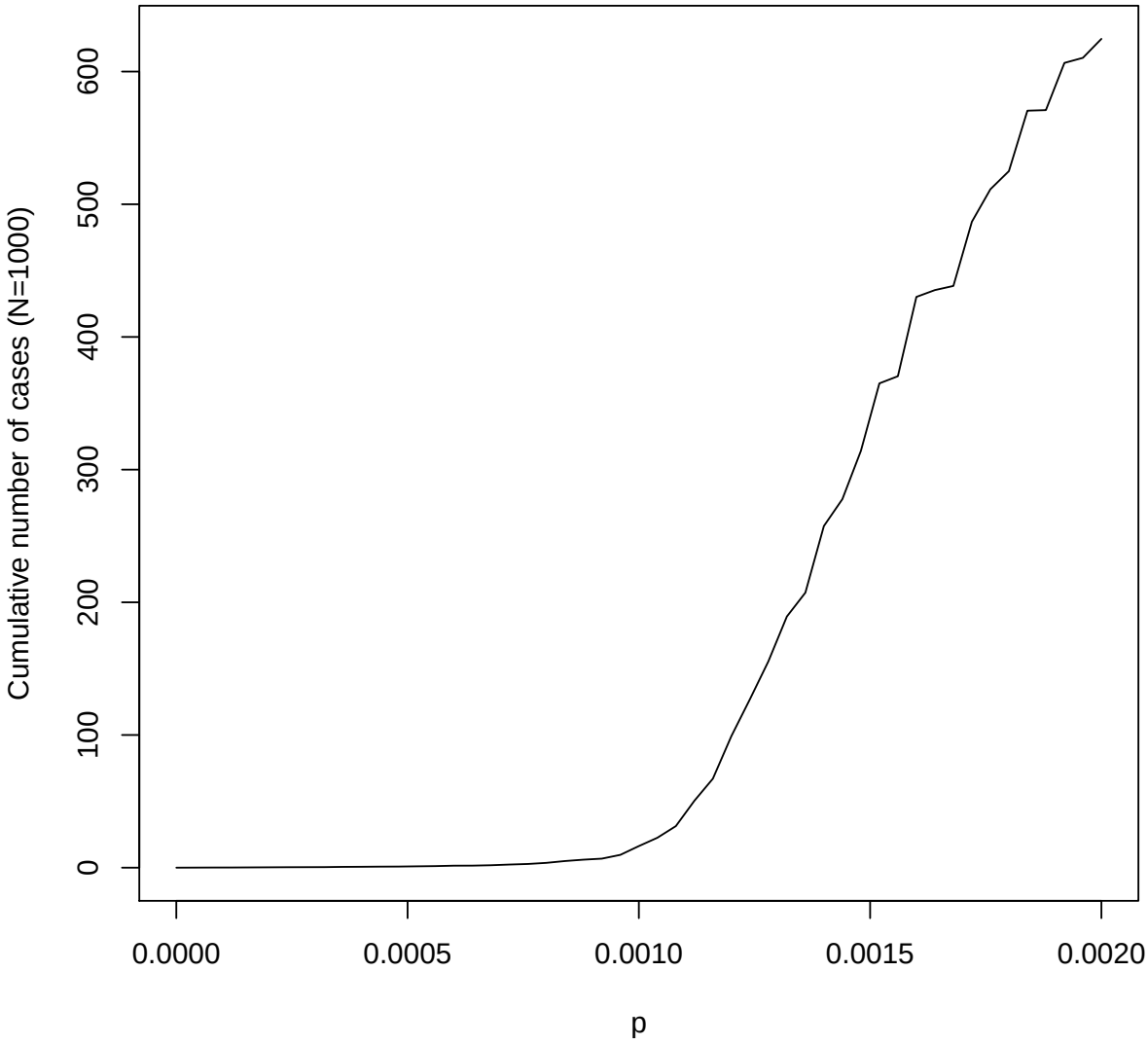
To help us understand these results, we will compute the expected number of cases that will result from a single case at the beginning of the epidemic. At the beginning of the epidemic, we have S_1 susceptibles, and one single case. The risk that each susceptible has of becoming infected is $1 - (1 - p)^1 = p$.

For a binomial distribution with N trials and p the probability of success per trial, the expected value is Np. This is what the average of a very large number of repetitions should be close to. Intuitively, imagine that you have a very large population, much larger than any possible sample. Suppose the prevalence of a risk factor is 20% in this population. If you take a sample of size 100, you expect 20 people, or 100×0.2, to have the risk factor.

For the Reed-Frost model, we expect the number of cases in the second generation to be $S_1 p$. If $S_1 p > 1$, we expect the epidemic to initially increase, and if $S_1 p < 1$, we expect the initial case to not even, on average, replace itself. In this latter circumstance, we expect a small cluster of cases, perhaps, but no large-scale epidemic.

In the examples we examined, we saw fairly small numbers of cases when we were below the critical value of p. Above this value, we began to see a substantial fraction of the population begin, on average, to become infected.

The expected number of secondary cases at the beginning of an epidemic, when everyone is susceptible, is called the **basic reproduction number** or basic reproduction ratio or basic reproductive rate, and is usually denoted R_0. For most epidemic models, we find that when the basic reproduction number is less than one, conditions do not favor epidemic spread


Cumulative number of cases (N=1000)
0
100
200
300
400
500
600
0.0000
0.0005
0.0010
0.0015
0.0020
p

when the disease is introduced, and conditions do not favor the endemic persistence of the disease.

Many authors reserve the term "basic reproduction number" to refer to a hypothetical population in which no disease control measures are present. When control measures are in place, the expected number of secondary cases an initial case can cause in a susceptible population is referred to by some other expression. Thus, if the basic reproduction number is greater than one, but the, say, realized reproduction number is less than one, the measures are sufficient to control a disease that would otherwise invade.

One way to understand the effect of a control measure is to consider a perfect vaccine administered to a large fraction of the population. Suppose that we are considering a disease for which the basic reproduction number is two. If we vaccinate, say, 80% of the population, then we have deprived the pathogen of most of its potential hosts. If we are assuming a homogeneously mixing model, then we may imagine that on average, only 20% of the contacts of the initial case are actually susceptible. The initial case may only produce 20% of the number of new cases that it would have produced without the vaccination program, or 0.4 on average. We expect the disease to not spread far in the population. Thus, it is conceivable that we could control a disease by vaccination even without complete coverage; the remaining individuals are said to be protected by *herd immunity*. However, it should be noted the crucial role of our assumption of homogeneity; we needed to conclude that if 80% of the population was vaccinated, that 80% of the contacts of a case are vaccinated. In practice, this is not often realized, and claims regarding herd immunity may need to be tempered with a careful consideration of how the vaccinated cases are distributed.

Beyond simple models

Models of realistic diseases extend the Reed-Frost model in include many features that the infection is known to have. Such extensions may include a more complex representation of the natural history. No disease really has a fixed duration of infectivity, as we assumed in the Reed-Frost model. Rather, the duration of infectivity may follow a distribution that could

be estimated, in principle, from data. Moreover, all diseases have a latent period, between the time of infection and the time of infectiousness. Infectiousness itself may vary over the course of the illness, and may preceed the appearance of specific symptoms. Infections may also differ considerably from person to person, depending on nutritional status, prior immunity, age or other factors. Diseases may be more likely to be transmitted to individuals in the same household, or to other individuals in the same risk group. For some infections, host immunity effectively prevents ever having the same disease again, but for others, such protection may not be realized. Diseases may also be transmitted by different routes, and different methods may be required to model a vector borne disease, a water borne disease, a sexually transmitted disease, or an airborne disease.

Construction of convincing models requires such considerations be examined in detail. Frequently, simplifying assumptions are made in modeling, and sometimes these assumptions serve to enhance understanding with little quantitative effect. For instance, simplifying the shape of the incubation period may have a small effect on the predicted epidemic curve. On the other hand, if a model assumes that a certain vaccine is more effective than the data indicate, or that the disease is transmissible before it can be detected through symptoms, the results may markedly change. Effective critique of a model requires understanding of both the biology and epidemiology of the pathogen, as well as the sensitivity of the mathematical conclusions to the assumptions.

Concluding remarks

Epidemic transmission models provide a valuable way to gain insights into the nature of an epidemic. Mathematical models frequently depend on data that may be difficult to collect or validate. Construction of effective models requires collaboration between medical experts and modelers; effective critique of them requires an understanding of both the biomedical assumptions as well as the mathematical details. However, models remain a valuable tool for enhancing our understanding of epidemic mechanisms, and are perhaps most valuable in examining counterfactual scenarios for disease control, where no data are yet available.

When an emerging pathogen threatens to cause an epidemic, it is unlikely that a controlled trial of different intervention strategies will be available in time.