Mathematical models for infectious diseases

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Introduction

Through most of recorded history mankind has lived under the threat of infectious diseases. This includes grand pandemics like the black death in the 14th century, cholera in the 19th century and the spanish influenza of the 1920s. But there are numerous other big killers in history.

A disease can be endemic, which means that it is always present, or epidemic, which means an outbreak which fades away. Even today we experience epidemics, the influenza that strikes yearly, though with only a fraction of past time mortality.

Given the impact on society of such diseases it is important to understand their dynamics. It is not only a question about which the infectious agent is, but also a question about the dynamics of the disease spreading. Some insight into the dynamics can be obtained by utilizing mathematical models.

Bernouilli and smallpox

One of the first applications of analysis to a biological question was a question about whether to vaccinate against smallpox or not. Smallpox appeared in Europe during the 16th century and was highly contagious (comparable only to measles) and lethal.

During early 18th century a method to combat smallpox was introduced to Europe. It was called variolation, and meant that infectious material was inoculated into the skin of a susceptible person, mainly children, in order to induce a mild infection. It was not an altogether harmless process; children could die from it and it could trigger small, local, epidemics. At the time physicians argued about whether the benefits outweighed the risks.

It was in this context the mathematician Daniel Bernouilli in 1776 published a paper which adressed the following question:

Available life tables describes the mortality in the population on which it is calculated and adresses all causes of death, including small pox. How would these life tables change if one, by inoculating the whole population, eliminate all deaths in smallpox?

The life tables referred to were compiled from church records in which all deaths are reported, together with the age of the diseased. Such tables give for each age \( a \) the number of individuals \( n(a) \) that reach this age. We then have that \( n(a + 1) = r(a)n(a) \), where \( r(a) \) is the fraction that lives one further year.

Bernouilli wanted to work in continuous time (or age), so we write this as \( n(a + 1) - n(a) = -(1 - r(a))n(a) \), which we can approximate to \( n'(a) = -\mu(a)n(a) \), where \( \mu(a) = 1 - r(a) \) is the mortality rate for individuals of age \( a \). The solution to this equation is

\[
n(a) = n(0)e^{-M(a)}, \quad M(a) = \int_0^a \mu(\tau)d\tau.
\]

One such table hade been compiled by the astronomer Edward Halley (of Halley’s comet),
which was used by Bernouilli. The missing piece of information was how much longer an individual would have lived, had he not died of smallpox, and to estimate this was the purpose of Bernouilli’s paper.

So Bernouilli writes \( n(a) = s(a) + t(a) \), where \( s(a) \) is the number that has survived age \( a \) and survived smallpox, whereas \( t(a) \) is the number that at age \( a \) still not have had smallpox, and therefore are still susceptible to the disease. Let \( \mu(a) \) denote the rate of death from other causes than smallpox. The assumptions Bernouilli made are now summarized in the following two equations.

\[
\begin{align*}
    t'(a) &= -(\lambda(a) + \mu(a))t(a), \\
    n'(a) &= -p(a)\lambda(a)t(a) - \mu(a)n(a).
\end{align*}
\]

Here \( \lambda(a) \) is the rate at which susceptibles get infected with smallpox, and \( p(a) \) is the fraction of people with smallpox that die of it. Note that \( t(0) = n(0) \).

What Bernouilli wants is to find an expression for \( n(0)e^{-M(a)} \) in numbers that can be measured. This is the function that would give the life table in the absence of smallpox. The first equation is simple to solve:

\[
t(a) = n(0)e^{-\Lambda(a)-M(a)}, \quad \Lambda(a) = \int_0^a \lambda(\tau) d\tau.
\]

Inserting this into the second equation we get

\[
n'(a) + \mu(a)n(a) = -p(a)\lambda(a)n(0)e^{-M(a)}e^{-\Lambda(a)}.
\]

Multiplication with the integrating factor \( e^{M(a)} \) leads to

\[
e^{M(a)}n(a) - n(0) = -n(0) \int_0^a p(\tau)\lambda(\tau)e^{-\Lambda(\tau)} d\tau.
\]

To be able to proceed Bernouilli assumes that \( p(a) = p \) is age independent, so we can write

\[
e^{M(a)}n(a) - n(0) = n(0)p(e^{-\Lambda(a)} - 1)
\]

(since \( \Lambda(0) = 0 \)), i.e.

\[
n(0)e^{-M(a)} = \frac{n(a)}{(1 - p) + pe^{-\Lambda(a)}}.
\]

Now we have a useful expression, but we know neither \( p \) nor \( \Lambda(a) \). Bernouilli assumes that also \( \lambda(a) = \lambda \) is independent of \( a \) and claims that at least approximately

\[
p = \lambda = 1/8.
\]

From this, and Halley’s life table, Bernouilli can estimate what a life table would look like if smallpox could be eliminated as a cause of death. He illustrated that by adding a column in Halley’s table, but we show the result graphically below.
From this Bernouilli computed that the median lifespan would increase from approximately 26.5 years to almost 30 year, had smallpox been eliminated. He also corrected for the mortality due to the inoculation process, which he claimed reduced the median with only one and a half month.

To what extent this analysis had an impact on the debate is unclear, and became essentially irrelevant a few years later when Edward Jenner discovered that one could replace the risky variolation process with a safe vaccination.

**To model the spread of a contagious disease**

We will now consider how we can model the dynamics of a disease like smallpox. We assume we have a disease which only transfer between humans in a population of fixed size. We also assume that when you get the disease you either die or become immune so that you cannot have the disease twice during the time period of interest.

We make a compartment model in which we divide the population into three groups: at time $t$ we have

- $S(t)$ which is the number of susceptible individuals,
- $I(t)$ which is the number of infected individuals, spreading the disease. The key is spreading the disease, so for some diseases you enter this compartment when you are still in the incubation period with no symptoms and for other diseases you might be sick but not infectious, in which case you are not in this class.
- $R(t)$ which is the number of individuals removed, i.e. those who have had the disease and are now either immune or dead.

Graphically we can display this as

$$S(t) \rightarrow I(t) \rightarrow R(t)$$
where we assume that \( S(t) + I(t) + R(t) = N \) = the size of the population. Note that if we know \( S(t) \), \( I(t) \) we also know \( R(t) \), but \( R(t) \) is important since it usually is what can be estimated from data.

Consider a small time interval of length \( h \). Let \( S_0 = S(t) \) and \( S_1 = S(t+h) \) and similarly for \( I(t) \). Let \( p \) be the probability that a given susceptible gets infected by a given infective during the time period \([t, t+h]\). We assume that the population mixes well, so that a given susceptible is infected by at least one of the \( I_0 \) infected individuals is \((1−p)\). With \( a = −\ln(1−p) \) this means that

\[
S_1 = (1−p)S_0 = e^{-aI_0}S_0.
\]

For the \( I_0 \) individuals we assume that a fraction \( b \) of these, \( 0 < b < 1 \), remains infected at time \( t+h \), so that

\[
I_1 = bI_0 + (1−e^{-aI_0})S_0.
\]

We want to change this model to a model in continuous time, by letting \( h \to 0 \). Both \( a \) and \( b \) depends on \( h \), with \( a(0) = 0, b(0) = 1 \). We therefore get

\[
\begin{align*}
S(t+h) - S(t) &= (e^{-aI(t)} - 1)S(t), \\
I(t+h) - I(t) &= (b(h - 1)I(t) + (1-e^{-aI(t)})S(t).
\end{align*}
\]

With \( K = a'(0) \) and \( \mu = b'(0) \), passing to the limit gives us the two differential equations

\[
\begin{align*}
S'(t) &= -KS(t)S(t) \\
I'(t) &= KI(t)S(t) - \mu I(t)
\end{align*}
\]

Here both \( K \) and \( \mu \) are positive constants. \( K \) is the probability rate with which a contact results in a new infective, whereas we can interpret \( 1/\mu \) to be the average time an infected individual is spreading the disease. In addition to these two equations we have that

\[
R'(t) = -I'(t) - S'(t) = \mu I(t) \quad \Rightarrow \quad R(t) = \mu \int_0^t I(s)ds.
\]

From the equations for \( S, I \) we can draw some important conclusions:

a) \( S(t) \) is a strictly decreasing function. Since

\[
I'(t) = K(S(t) - \rho)I(t), \quad \rho = \mu/K,
\]

we see that if \( S(t) < \rho \) when \( t = 0 \) it holds for all \( t \), and then \( I'(t) < 0 \) for all \( t \). The number \( \rho^{-1} = K\mu \) measures the number of infective contacts an infective individual manages during his sickness, and is called the contact number for the disease.

b) If \( S(0) > \rho \) we have that \( I(t) \) increases until \( S(t) = \rho \) and decreases thereafter. It means that we get an outbreak of the disease, but as soon as the number of susceptibles reaches the critical number \( \rho \) the number of infectives start to decrease.
c) If we consider $I$ a function of $S$ we have that

$$I'(S) = \frac{I'(t)}{S'(t)} = -1 + \frac{\rho}{S}.$$ 

This can be integrated to

$$I(S) - I(S_0) = -(S - S_0) + \rho \ln \frac{S}{S_0},$$

where $S_0$ is arbitrary. We see that $I(S) \to -\infty$ when $S \to 0^+$, which means that there is a $S_\infty > 0$ such that $I(S_\infty) = 0$. This in turn means that the outbreak ends before everyone has been infected – some always escape the disease. This is illustrated in the graph below, where numbers are normalized by $N$.

![Graph showing the relationship between infected and susceptible individuals with different values of $\rho$.](image)

d) Equation (1) means that $I(t) + S(t) - \rho \ln S(t)$ is time independent, so

$$I(t) + S(t) - \rho \ln S(t) = N - \ln S(0).$$

Thus $S_\infty$ is given by the equation

$$S_\infty - \rho \ln S_\infty = N - \rho \ln S(0).$$

From this we can estimate $\rho$ if we know how many individuals there were before the epidemic and how many were susceptible after it died out (normally we can take $S(0) = N$ here.)

In general we cannot measure $I(t)$ during an outbreak; only those that seek medical help or die can be identified. From health authority records we have at best only estimates of $R(t)$, for which we have that

$$R'(t) = \mu I(t) = -\mu \frac{S'(t)}{KS(t)} = -\rho \frac{S'(t)}{S(t)}.$$ 

We see that $S(t) = S(0)e^{-R(t)/\rho}$, so

$$R'(t) = \mu(N - R(t) - S(0)e^{-R(t)/\rho}).$$
If the epidemic is small (relatively speaking) we can approximate the exponential with its Maclaurin series of order 2, which gives us an equation which can be solved.

The model discussed here was published in 1927 by Kermack and McKendrick, and they applied it to data from a plague epidemic in Bombay 1905–6. The graph on the right is their data; the curve is their estimate of $R'(t)$.

The plague is a disease that has been important during history. As far as we know the first outbreak in Europe was the black death in the middle of the 14th century when it may have killed about 1/3 of its population. But it continued to be smaller epidemics over the coming centuries up to the 19th century.

**Remark** An alternative derivation of the equations is to start by defining the Markov process

$$
(\begin{array}{c}
(I, S) \\
(I, S)
\end{array}) \rightarrow (\begin{array}{c}
(I + 1, S - 1) \\
(I - 1, S)
\end{array})
$$

**Transition**

$$
KS^\frac{S}{N} = NK\frac{S}{N} I
$$

**Intensity**

$$
\mu I = N\mu\frac{I}{N}
$$

In summary, the transition $(S, I) \rightarrow (S + \theta_1, I + \theta_2)$ occurs with intensity $f((S, I), \theta)$, where

$$
f(x, (1, -1)) = Kx_1x_2, \quad f(x, (-1, 0)) = \mu x_1, \quad f(x, \theta) = 0 \text{ others.}
$$

Comparing with the discussion in an earlier chapter we have the mean intensities

$$
F(x) = (1, -1)f(x, (1, -1)) + (-1, 0)f(x, (-1, 0)) = (Kx_1x_2 - \mu x_1, -Kx_1x_2,
$$

which leads to the system

$$
\begin{cases}
x'_1(t) = Kx_1(t)x_2(t) - \mu x_2(t) \\
x'_2(t) = -Kx_1(t)x_2(t).
\end{cases}
$$

**The plague epidemic in Eyam**

After the black death there were smaller plague epidemics all the way up to the 19th century. One such outbreak struck the small village Eyam in the 1660th. It came from the more well-known Great Plague in London 1665-66 which killed approximately 1 in 6 of its inhabitants. A taylor in Eyam received some cloths from London 1665 which contained some plague bearing rat fleas. The first victim was buried in September the same year.
During the following 9 months another 76 villagers died, without the epidemic really getting up to speed. During the winter months some 6–7 deaths occurred each month. But when summer came the epidemic geared up. The table below shows the number of deaths each month during the following five months 1666:

<table>
<thead>
<tr>
<th>Month</th>
<th>June</th>
<th>July</th>
<th>August</th>
<th>September</th>
<th>October</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>19</td>
<td>56</td>
<td>77</td>
<td>24</td>
<td>14</td>
</tr>
</tbody>
</table>

On June 1 the village had \( N = 273 \) inhabitants.

The graph above shows a cumulative version of these data together with a model fit. For the model we have used only the first three points to estimate the parameters using a nonlinear least squares estimation procedure. The estimates obtained were

\[
K = \frac{4.4226}{273} \quad \text{och} \quad \mu = 2.416.
\]

We can interpret \( 30/\mu \approx 12 \) as the number of days a person is spreading the disease. These data says that

\[
\rho = \frac{2.416}{4.4226} \times 273 = 0.546N
\]

(which means there should be an outbreak, since \( S(0) \approx N > \rho \)). To prevent the outbreak we need to diminish \( K \), which means that people need to stay at home as much as possible. The number of individuals \( S_\infty \) that are estimated to survive the epidemic are given by the non-trivial solution to the equation

\[
S_\infty - \rho \ln S_\infty = 273 - \rho \ln 273,
\]

which is \( S_\infty = 71 \). Based on the first three months of data, this is the number of villages that we expect should survive the outbreak, and is somewhat similar to the observed number 83. The disagreement could indicate that the epidemic is still not over. In fact, it came back after the winter months.

If we assume that we actually had 83 survivors, we can estimate \( \rho \) from

\[
83 - \rho \ln 83 = 273 - \rho \ln 273 \quad \Leftrightarrow \quad \rho = 0.586 \, N,
\]

which is close to the observation we have.
How can we prevent an epidemic?

The condition for an outbreak is $S(0) > \rho$, so we can either increase $\rho$ or decrease $S(0)$. But $\rho = \mu/K$, so we can increase it by increasing $\mu$, i.e. decrease the time infectives spread the disease, och by decreasing $K$, which means imposing restrictions on how much infectives may be allowed outdoors. The first option is sometimes possible by giving antibiotics, the second option is a political decision about curfews and closing public places.

But antibiotics do not work on virus diseases like smallpox. For such diseases there is often an alternative: decrease $S(0)$ by vaccination. Introduce the number

$$R_0 = \frac{S(0)}{\rho} = \frac{KS(0)}{\mu},$$

which is called the basic reproduction rate for the infection and gives the number of individuals a given infective will infect in a completely susceptible population. What we have seen is that if every infective infects more than one susceptible, i.e. $R_0 > 1$, we have an outbreak.

In order to decide what part of a population we need to vaccinate we need an estimate of $R_0$. An estimate mentioned for smallpox is 5. If we vaccinate the proportion $p$ of the susceptible population, we get the new basic reproduction rate

$$\tilde{R}_0 = (1 - p)R_0$$

and to get that below one we need to have

$$p > 1 - \frac{1}{R_0}.$$

For smallpox that means we need to vaccinate 80% of the population in order to eliminate the disease.

Based on this a large eradication programme was started by WHO in 1967 in order to eliminate smallpox, and in October 1979 the world was declared free of smallpox (outside laboratories). One reason this was successfull is that smallpox has no animal reservoir.

Can we eradict other so-called child diseases? The table to the right provides approximative data for some of them

<table>
<thead>
<tr>
<th>disease</th>
<th>$R_0$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>polio</td>
<td>5</td>
<td>0.80</td>
</tr>
<tr>
<td>rubella</td>
<td>7</td>
<td>0.86</td>
</tr>
<tr>
<td>varicella</td>
<td>11</td>
<td>0.91</td>
</tr>
<tr>
<td>mumps</td>
<td>12</td>
<td>0.92</td>
</tr>
<tr>
<td>measles</td>
<td>16</td>
<td>0.94</td>
</tr>
</tbody>
</table>

We see that polio ha approximately the same $R_0$ as smallpox, so WHO started a big eradiction program in 1988, which has reduced the presence of this disease considerably. Today it is endemic in only four countries: Afganistan, India, Nigeria and Pakistan.

Modifying the SIR model

The dynamics of all infectious diseases do not fit into the simple SIR model discussed so far. On one hand we have not considered incubation times and some diseases do not
give long-term immunity (but survival). Common colds belong to the latter group, and
what we call the “winter vomiting disease” seems to provide more or less none immunity.
Another assumption is that the population is constant all the time (including deaths from
the disease in the count); no individual immigrate and no one runs away from the disease.
But there are many opportunities to build on the model and account for various other
things of interest.

**Example 1** The opposite of a disease with a 100% mortality is one that gives no
immunity and no deaths, so infectives become susceptibles as soon as they have
stopped spreading the disease. In such a case $I(t) + S(t) = N$ so we have only one
equation, e.g.,

$$I(t) = KI(t)(N - I(t)) - \mu I(t).$$

In this case we have that $I(t) \to \frac{KN}{K + \mu}$ when $t \to \infty$, which means that the disease is
endemic.

**Example 2** A model that extends the SIR model which includes a transient immunity
may look like

$$\begin{cases}
S'(t) &= rR(t) - KI(t)S(t) \\
I'(t) &= KI(t)S(t) - \mu I(t) \\
R'(t) &= \mu I(t) - rR(t)
\end{cases}$$

In order to analyse it, we first nondimensionalize:

a) Divide all group numbers by $N$ so that e.g. $S(t)$ measures the fraction of the
population that is susceptible,

b) Introduce $\tau = KNt$ as new time, except that we continue denoting it $t$,

c) Introduce the constants

$$\rho = \frac{\mu}{KN}, \quad \kappa = \frac{r}{KN}.$$  

Then we get the following system of differential equations:

$$\begin{cases}
S'(t) &= \kappa R(t) - I(t)S(t) \\
I'(t) &= I(t)S(t) - \rho I(t) \\
R'(t) &= \rho I(t) - \kappa R(t)
\end{cases}$$

Since $S(t) + I(t) + R(t) = 1$ this can be reduced to a system involving only $S$ and $I$:

$$\begin{cases}
S'(t) &= \kappa(1 - I(t) - S(t)) - I(t)S(t) \\
I'(t) &= I(t)S(t) - \rho I(t)
\end{cases}$$

As before we need to have $\rho < S(0) < 1$ for an outbreak.
Equilibria (in \((S, I)\)) are given by the equations
\[\kappa(1 - I - S) - IS = 0, \quad IS - \rho I = 0,\]
which gives us either the trivial solution \((1, 0)\) plus a solution \((\rho, I^*)\), where
\[I^* = \frac{\kappa(1 - \rho)}{\kappa + \rho} .\]
Again we see that we need to have \(\rho < 1\).

Next we want to investigate the stability of these, and for this we compute the system derivative:
\[
\begin{pmatrix}
-\kappa - I & -\kappa - S \\
I & S - \rho
\end{pmatrix} .
\]
In \((1, 0)\) this is
\[
\begin{pmatrix}
-\kappa & -\kappa - 1 \\
0 & 1 - \rho
\end{pmatrix} ,
\]
which has eigenvalues are \(-\kappa\) and \(1 - \rho\). If \(\rho > 1\) this is a stable equilibrium, but it is a saddle when \(\rho < 1\). In the point \((\rho, I^*)\) we have
\[
\begin{pmatrix}
-\kappa - I^* & -\kappa - \rho \\
I^* & 0
\end{pmatrix} .
\]
Its trace is equal to \(-\kappa + I^* = -\kappa \frac{\kappa + 1}{\kappa + \rho} < 0\), whereas the determinant is
\[I^*(\kappa + \rho) = \kappa(1 - \rho) > 0 .\]
It means that this equilibrium is stable when it exists. When \(\kappa\) is small it is approached in an oscillatory way, as exemplified in the graph below.

Conclusion: under these assumptions we see that a disease will not necessarily be epidemic (and if it is it will have multiple outbreaks that decrease with time) but it will become endemic.
A simple model for malaria

Many tropical diseases can not be accurately modeled by the models above, because the life cycle of the pathogen is much more complicated. As an example of this we will discuss a simple model for malaria.

Malaria is a serious and often lethal disease caused by what is called a plasmodium. The disease is endemic in most of the tropical and subtropical regions of the world. It is not spread from person to person. Instead it requires both humans (and other warm-blooded animals) and the mosquito *Anopheles* which transfer it to humans so that the plasmodium can complete its life cycle.

The life cycle of the plasmodium is illustrated in the figure to the right (from Wikipedia), which in a very short version is as follows.

![Life Cycle of the Malaria Parasite](image)

Infection in a human starts when a female mosquito (the males only eat plant juices) sucks blood, and at the same time infects the plasmodium, which is in the so-called sporozite stage. These sporozites are transported by the blood until they reach the liver, where they mature and, after an incubation time of a few days, divide and become so-called merozoites, which returns to the blood.

In the blood the merozoites are transformed into trofozites, which penetrates the red blood cells, where they grow (eating hemoglobin – recall the discussion on sickle cell anemia) and divide until they burst out of the host cell in order to invade other red blood cells.

Some of the merozoites develop a sexual stage, gametocytes, which are the ones that infect mosquitos. This occurs when a human is biten by a mosquito and in relation to this the female gametocyte is fertilized and develops into an ovocyte in the intestines of the mosquito. Here the sporozites are developed after about 10 days and moves to the salivary glands of the mosquito, mature and wait to be injected into a new human.
Our aim is to pick the most important aspects of this complicated life cycle with the purpose of developing a simple model for dynamics of the disease. We consider two populations:

a) \( N(t) \) is the number of humans that are infected with malaria,

b) \( M(t) \) is the number of female mosquitos that carry the sporozoite. In what follows mosquito means female mosquito.

The total number of humans is \( N \) and the total number of mosquitos is \( M \), both of which are considered constant. It is also convenient to introduce \( m = M/N \), which is the number of mosquitos per human.

Increase in \( N \) occurs with a rate that depends on the number of mosquitos sticks per person per time unit, \( am \), where \( a \) is the number of mosquitoes sticks and individual gets from a given mosquito per time unit. If we multiply this with the fraction of infected mosquitos and the fraction of non-infected humans and the probability \( b \) that a non-infected individual who receives a stick by an infected mosquito becomes infected, we see that new infective humans appear with a rate of

\[
ab \frac{M}{N} y(t)(1 - x(t))
\]

where

a) \( x(t) = N(t)/N \) is the proportion humans with malaria

b) \( y(t) = M(t)/M \) is the proportion malaria carrying (female) mosquitos.

The mosquito population becomes infected at a rate that is proportional to the number of sticks per mosquito per time unit, times the probability that a mosquito that stick does not already carry malaria, times the probability that the individual that is stuck is already having malaria. In other words

\[
a(1 - y)x.
\]

If we to this add the fact that the mosquito has limited life span and that the disease duration in humans also is limited in time, we get the following two differential equations

\[
\begin{align*}
x'(t) &= \theta y(t)(1 - x(t)) - rx(t), \\
y'(t) &= ax(t)(1 - y(t)) - \mu y(t),
\end{align*}
\]

where \( \theta = abm \). Here \( 1/r \) is the average sickness period for a human and \( 1/\mu \) the mosquitos average life span.

The equilibria are the points \((x, y)\) that satisfies

\[
\begin{align*}
\theta y(1 - x) - rx &= 0 \quad \iff \quad y = \frac{rx}{\theta(1 - x)} \\
ax(1 - y) - \mu y &= 0 \quad \iff \quad y = \frac{ax}{ax + \mu}
\end{align*}
\]

The first of these curves has the slope \( r/\theta \) when \( x = 0 \), increases monotonously and approaches infinity when \( x \to 1 \). The second equation has slope \( a/\mu \) when \( x = 0 \), increases monotonously and approaches 1 as \( x \to \infty \). This gives us two cases:
a) If \( r/\theta > a/\mu \) the curves will not intersect, which means the only equilibrium is the origin.

b) If \( r/\theta < a/\mu \) there is one further intersection between the two curves, which defines a second equilibrium.

We see that the quotient

\[
R = \frac{a\theta}{r\mu} = \frac{ma^2b}{\mu r}
\]

is of fundamental importance. The graph below illustrates the two cases.

When \( R < 1 \) we see that malaria will be eradicated. When \( R > 1 \) we can write the second equilibria as

\[
x = \frac{R - 1}{R + \kappa}, \quad y = \frac{R - 1}{R} \frac{\kappa}{1 + \kappa}, \quad \text{där} \quad \kappa = \frac{a}{\mu}
\]

and in order to investigate its stability we compute the (general) system derivative

\[
A = \begin{pmatrix}
-\theta y - r & \theta(1 - x) \\
\theta(1 - y) & -ax - \mu
\end{pmatrix}
\]

For it we have \( \text{Tr} A = \theta y + r + ax + \mu < 0 \), and \( \det A = (\theta y + r)(ax + \mu) - a\theta(1 - x)(1 - y) \).

a) In \( (0, 0) \) we have that \( \det A = r\mu - a\theta = r\mu(1 - R) \), which is positive if and only if \( R < 1 \). So the origin is a stable knot if \( R < 1 \) but a saddle point if \( R > 1 \).

b) In the other equilibrium we have \( \det A = r(a + \mu)x/(1 - x) > 0 \), so it is always stable.

From this we can have some good guesses on what we need to do to eliminate Malaria, but we leave that discussion to the reader.