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THE MATHEMATICAL MODELING OF EPIDEMICS

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Lecture 1: Essential epidemics.

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*Haec ratio quondam morborum et mortifer aestus
finibus in Cecropis funestos reddidit agros
vastavitque vias, exhausit civibus urbem.
nam penitus veniens Aegypti finibus ortus,
aera permensus multum camposque natantis,
incubuit tandem populo Pandionis omni.
inde catervatim morbo mortique dabantur.¹*

Lucretius

"De Rerum Natura", Liber VI, 1138-1144

Epidemics have ever been a great concern of human kind and we are still moved by the dramatic descriptions that arrive to us from the past, as in Lucretius's sixth book of "De Rerum Natura" or as in other more recent descriptions that we find in the literature. The "Black Death", the plague that spread



Figure 1: The Black Death in a picture of the 14th century

across Europe and from 1347 to 1352 and made 25 millions of victims, seems to be far from our lives, but more recent events (see Figure 2) remind us that epidemics are an actual problem for health institution that are continuously facing emerging and reemerging diseases.

¹Such a cause of plague, such a deadly influence, once in the country of Cecrops filled the field with dead and emptied the streets, draining the city of its citizens. For it arose deep within the country of Egypt, and came, traversing much sky and floating fields, and broaded at last over all the people of Pandion. Then troop by troop they were given over to disease and death.

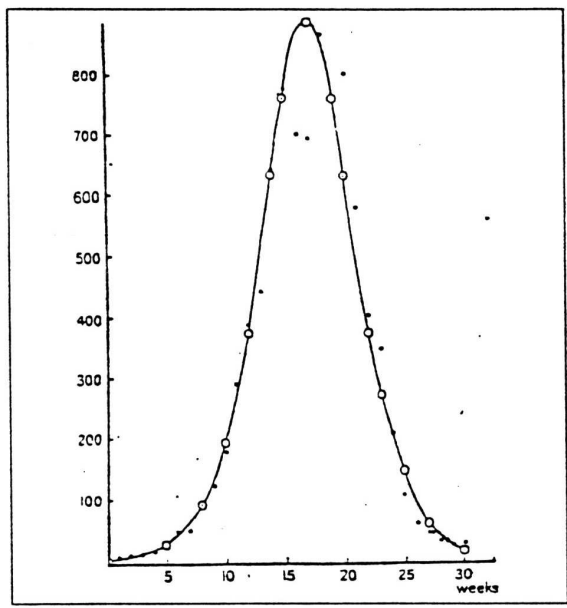


Figure 2: The plague in Bombay, 1905

The Figures 2- 5 are reports of classical data showing typical observed patterns from different occurrences. Some show a single outbreak, others show how

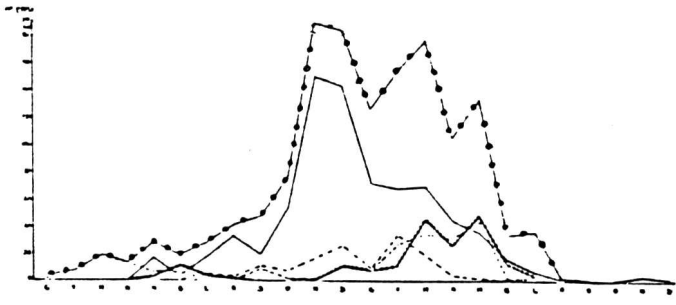


Figure 3: Measles in Trento (Italy), 1977-78

a same disease has occurred through the years. The aim of the mathematical modeling of epidemics is to identify those mechanisms that produce such patterns giving a rational description of these events and providing tools for disease control.

This first lecture is devoted to introduce the essentials of such a descriptions.

1 The basic elements for a description

Since the very early times of epidemics modeling, the basic elements for the description of infectious diseases, have been the three epidemiological classes of *susceptible*, *infectives* and *removed* individuals, respectively defined as

- those individuals who are healthy and can be infected;
- those individuals who are infected and are able to transmit the disease;
- those individuals who are immune because have been infected and now have recovered;

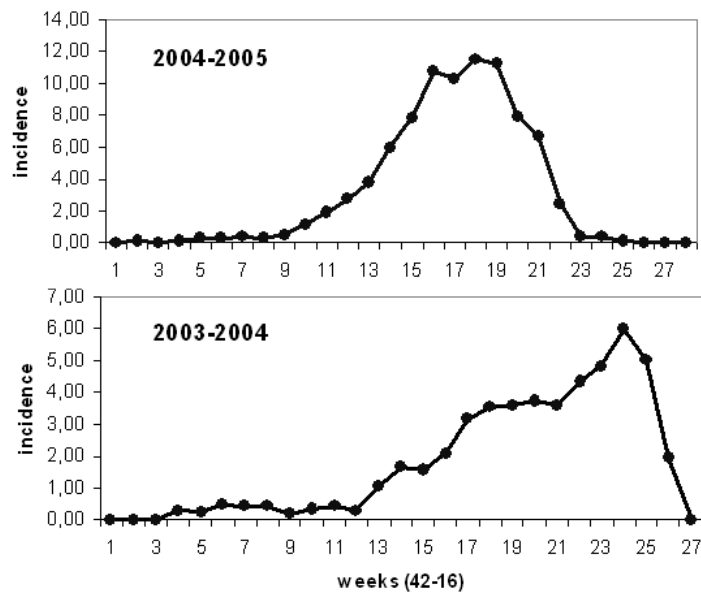


Figure 4: Influenza in Basilicata (Italy), 2003-2005

Thus the basic variables identifying the state of the population in the epidemiological perspective are

- $S(t)$ the number of susceptibles at time t ;
- $I(t)$ the number of infectives at time t ;
- $R(t)$ the number of immune at time t .

Indeed, the epidemiological classes characterizing a disease, may be more than these, but considerable insight into the phenomena can however be achieved on the basis of the above description.

After the basic state variables introduced above, further gross simplification may be introduced concerning the disease progression and effect. Namely, a basic distinction may be done between those diseases that impart lifelong immunity and those which do not. The first case leads to the so called SIR type models, the second to SIS type models. In fact, The individual path through

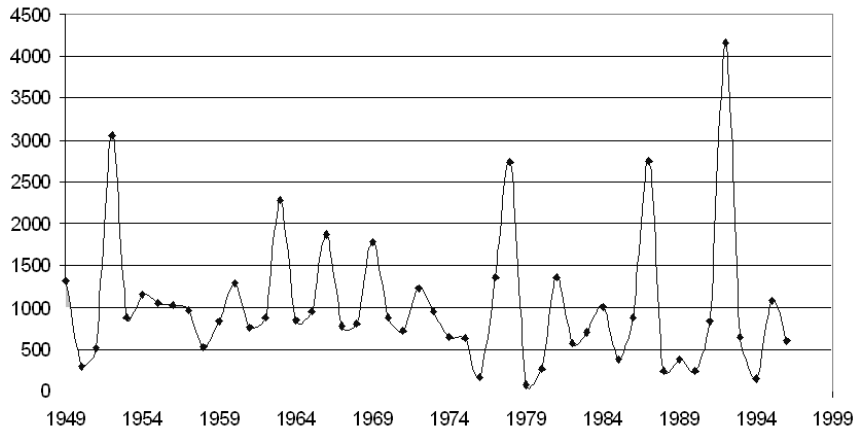


Figure 5: Measles in Trentino (Italy), 1949-1999

the epidemiological classes can be described as in Figure 6 and Figure 7 respectively. In these representations, the parameters $\lambda(t)$ and $\gamma(t)$ respectively denote the pro-capita rate at which susceptibles become infected and the rate at which infectives recover from the disease. The first parameter $\lambda(t)$, also called *force of infection*, pertains to the infection mechanism which depend on the way people mixes and contacts other people. Instead, the parameter $\gamma(t)$ is basically intrinsic to the disease and its progression within the infected individual.

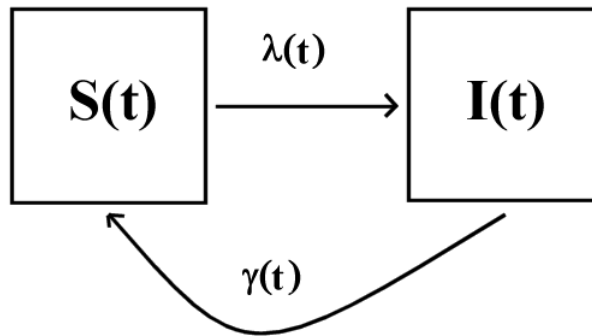


Figure 6: The S-I-S model for diseases which do not impart immunity

Both mechanisms may deserve a detailed and structured description, however the simplest constitutive assumption for the force of infection, mostly adopted in simple models, is

$$\lambda(t) = \frac{c\chi}{N(t)}I(t), \quad (1)$$

where

$$\begin{aligned}
 c &= \text{number of contacts in the time unit,} \\
 \chi &= \text{infectiveness of one contact with an infective,} \\
 N(t) &= S(t) + I(t) + R(t) = \text{total population.}
 \end{aligned}
 \tag{2}$$

Moreover, the *removal rate* $\gamma(t)$ is usually assumed to be a constant

$$\gamma(t) = \gamma = \frac{1}{\tau}
 \tag{3}$$

where τ is the average time spent as an infective, i.e. the average duration of the infection.

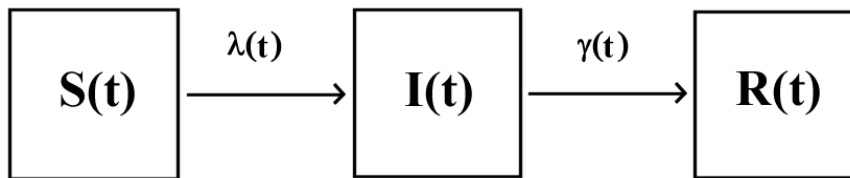


Figure 7: The S-I-R model for diseases imparting immunity

The form of $\lambda(t)$ rests upon the assumptions that the population is homogeneously mixing, that the whole population is active (instead, for some, diseases either part or all of the removed class does not participate in the mixing), that the contact rate is independent of the size of the active population and that contacts with infectives are equally infective. We note that in (1) the factor $\frac{I(t)}{N(t)}$ stands for the probability that the contacted individual is infective. Also, assumption (3) means that the progression of the disease is the same within any infective and γ measures the average fraction of recovering individuals in the time unit. With this assumption, a given group of infectives would decrease exponentially with time constant τ .

As a whole, the previous assumptions on the transmission and recovery processes resemble a sort of "mass action" mechanism and the population is considered as a "perfect" gas of particles. Nevertheless, though very simple, this setting allows to set up the basic epidemiological models. These are prototypes that shape all the effort in modeling epidemics.

2 The single epidemic outbreak

A single epidemic outbreak (as opposed to disease endemicity) occurs in a time span short enough not to have the demographic changes perturbing the dynamics of the contacts between individuals. Namely, we assume that no births and deaths occur in the population, neither for the current demographic dynamics nor for the effect of the disease that indeed would normally introduce a further cause of death.

With the gross assumptions precised above, the occurrence of a disease imparting immunity (S-I-R, see Figure 7) is described by the following system, involving the three epidemiological classes introduced above

$$\begin{cases} S'(t) = -\lambda(t)S(t) & S(0) = S_0; \\ I'(t) = \lambda(t)S(t) - \gamma I(t) & I(0) = I_0; \\ R'(t) = \gamma I(t) & R(0) = R_0. \end{cases} \quad (4)$$

where we have assumed (1)-(3) and $S_0 > 0$, $I_0 > 0$, $R_0 \geq 0$.

We soon may note that this system has a unique solution with positive components. Moreover, that adding the three equation in (4) we get

$$S'(t) + I'(t) + R'(t) = 0,$$

so that we have that the total population is constant

$$N(t) = S_0 + I_0 + R_0 = N \quad (5)$$

and is a parameter of the model, included in the force of infection (1).

A symple analysis of the asymptotic behaviour allows a detailed description of the epidemics (se also [5] and [6]). In fact, summing the first two equations in (4) we have

$$\frac{d}{dt}(S(t) + I(t)) = -\gamma I(t) < 0 \quad (6)$$

that yields

$$S(t) + I(t) \leq N$$

which implies that the solution to the system is global in time.

Moreover from the first equation we have

$$\frac{d}{dt}S(t) < 0$$

so that

$$S(t) \searrow S_\infty \text{ per } t \rightarrow \infty$$

On the other hand, (6) and (5) yield

$$\gamma \int_0^t I(s)ds = R(t) = N - S(t) - I(t) \leq N,$$

so that

$$\int_0^\infty I(s)ds < +\infty,$$

and, consequently,

$$I(t) \rightarrow N - S_\infty - \gamma \int_0^\infty I(s)ds \text{ as } t \rightarrow +\infty,$$

which implies

$$I(t) \rightarrow 0 \text{ as } t \rightarrow +\infty.$$

Thus we have that the disease goes to estinction and that the number of susceptibles reduces to S_∞ . Concerning the value of S_∞ , which is called the *size*

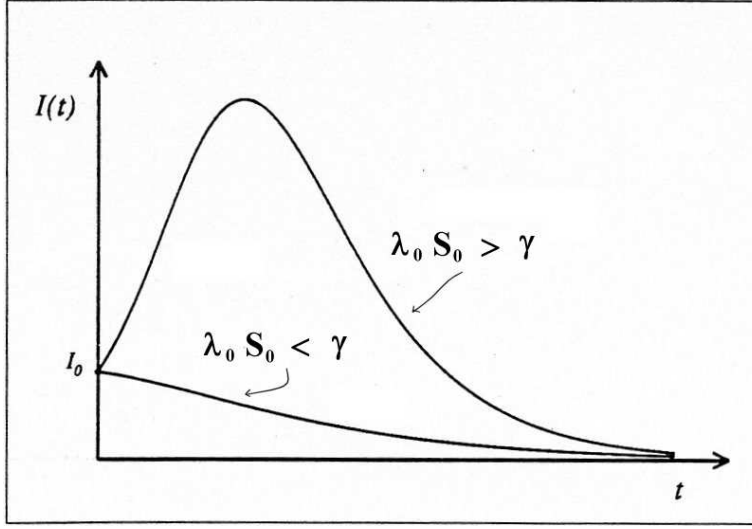


Figure 8: Solutions for problem (4) and the threshold condition for an outbreak.

of the epidemics because is a measure of its strength, from the first equation in (4) we get

$$S_\infty \geq S_0 e^{-\frac{\tau}{\gamma} N} > 0,$$

that shows how the susceptibles are not depleted at the en of the epidemic.

The way the estinction of the epidemic occurs can be seen from the second equation of (4)

$$I'(t) = [\lambda_0 S(t) - \gamma] I(t)$$

where $\lambda_0 = \frac{c\chi}{N}$. In fact we see that

$$\text{if } \lambda_0 S_0 \leq \gamma \text{ then } I'(t) < 0 \text{ for all } t > 0, \quad (7)$$

otherwise,

$$\text{if } \lambda_0 S_0 > \gamma \text{ then } I'(t) > 0 \text{ for } t < t^*, \quad (8)$$

where t^* is such that $\lambda_0 = S(t^*) = \gamma$.

The two alternatives are shown in Figure 3 where two solution corresponding to (7) and (8) are reported. Thus we have a threshold condition for a real epidemic outbreak

$$\lambda_0 S_0 > \gamma, \quad (9)$$

that can be interpreted through a significant parameter by setting

$$\mathcal{R}_0 = \frac{c\chi}{\gamma} = \text{basic reproductive number.} \quad (10)$$

This is the number of secondary cases produced, in a totally susceptible population, by a single infective individual during the time span of the infection. In fact condition (9) can be written as

$$\mathcal{R}_0 \frac{S_0}{N} > 1$$

and states that in order to have an outbreak, the number of secondary cases (in a population of N individuals and S_0 susceptibles) from a single infective must be greater than one.

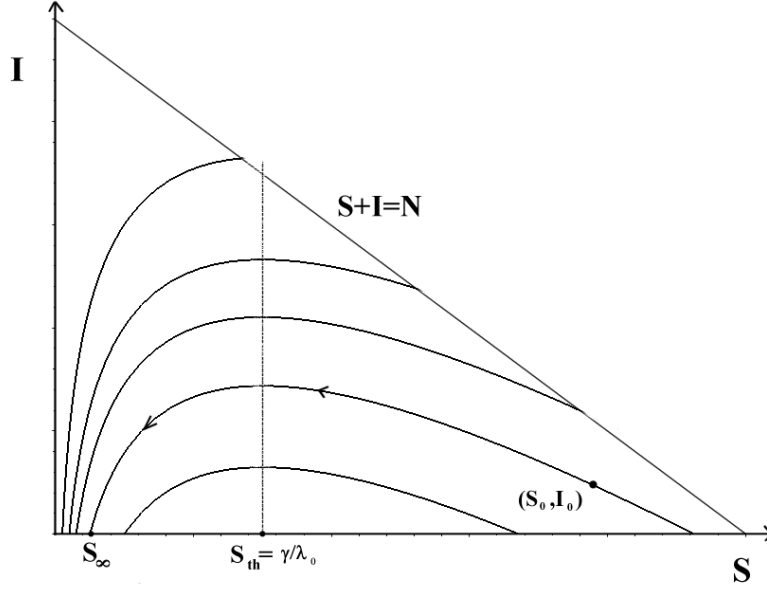


Figure 9: Phase plane for problem (4).

A phase portrait for the (S, I) trajectories of problem (4) is shown in Figure 9. Actually all trajectories are represented by the equations

$$S + I - \frac{\gamma}{\lambda_0} \ln S = const$$

for different values of the constant which depends on the initial values. From this we obtain the value of $S_\infty = \lim_{t \rightarrow \infty} S(t)$ and is implicitly given by the equation

$$S_\infty - \frac{\gamma}{\lambda_0} \ln S_\infty = S_0 + I_0 - \frac{\gamma}{\lambda_0} \ln S_0 \quad (11)$$

3 Disease endemicity

The analysis of the simple outbreak of an epidemics shows that the epidemics stops and decays due to the depletion of susceptibles below the threshold value

$$S_{th} = \frac{\gamma}{\lambda_0} = \frac{N}{\mathcal{R}_0}.$$

Thus sustained infections must occur in the presence of susceptibles replacement. Two different mechanism may lead to such replacement and consequently to *endemic states* of the disease. The first is related to non-immunizing diseases, the other to demographic input of susceptible newborns.

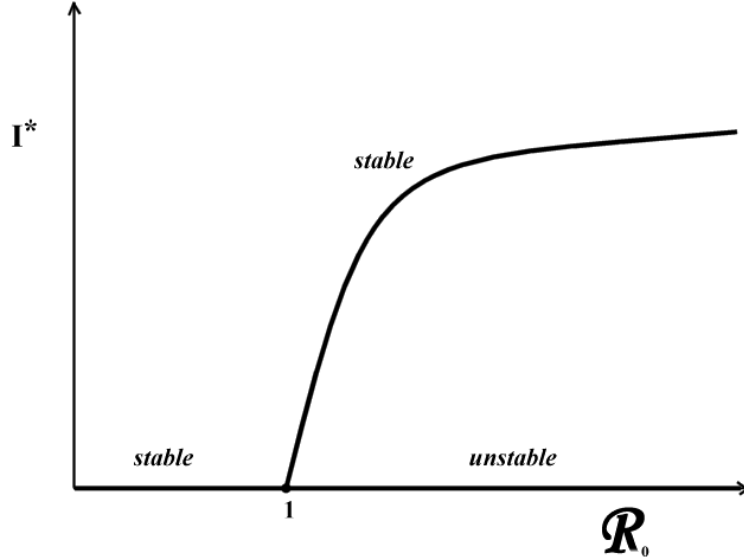


Figure 10: Bifurcation diagram for problem (12).

To examine the first we consider the S-I-S type model of Figure 6 and the relative system of equations (compare with (4))

$$\begin{cases} S'(t) = -\lambda(t)S(t) + \gamma I(t) & S(0) = S_0; \\ I'(t) = \lambda(t)S(t) - \gamma I(t) & I(0) = I_0; \end{cases} \quad (12)$$

Here the class of removed individuals is void and, since we have $S(t) + I(t) = N$, the system can be reduced to the single equation on the state variable $I(t)$

$$I'(t) = \gamma \left[\mathcal{R}_0 - 1 - \frac{\mathcal{R}_0}{N} I(t) \right] I(t),$$

that explicitly solved leads to the following dichotomy

$$\text{if } \mathcal{R}_0 \leq 1 \text{ then } I'(t) < 0 \text{ and } \lim_{t \rightarrow \infty} I(t) = 0 \quad (13)$$

$$\text{if } \mathcal{R}_0 > 1 \text{ then } \lim_{t \rightarrow \infty} I(t) = I^* = N \left(1 - \frac{1}{\mathcal{R}_0} \right). \quad (14)$$

thus we see that the basic reproduction number \mathcal{R}_0 defined in (10) acts again to determine a threshold for two alternatives. Here, extinction of the disease is opposed to the existence of a globally attractive endemic state I^* the size of which is determined by the size of \mathcal{R}_0 . This scenario is described in Figure 10 where bifurcation of steady states and exchange of stability is shown.

Concerning the effect of demographic dynamics on disease endemicity, we consider the previous S-I-R model including a simple "neutral" malthusian dynamics, i.e. we assume that births and deaths occur at the same rate so that the size of the population as a whole does not change with time. Thus, denoting

by μ both fertility and mortality we get the model

$$\begin{cases} S'(t) = \mu N - \lambda(t)S(t) - \mu S(t) & S(0) = S_0; \\ I'(t) = \lambda(t)S(t) - (\gamma + \mu)I(t) & I(0) = I_0; \\ R'(t) = \gamma I(t) - \mu R(t) & R(0) = R_0. \end{cases} \quad (15)$$

We may soon note that in this new situation the definition (10) of the basic reproduction number \mathcal{R}_0 must be changed (generalized) into the following one

$$\mathcal{R}_0 = \frac{c\chi}{\gamma + \mu}. \quad (16)$$

In fact the average duration of the disease is now depending also by the possibility of dying for natural reasons. This fact is mirrored into the conditions for endemic states to exist. Namely we see that the system above admits the steady states

$$\begin{aligned} \text{disease free equilibrium:} \quad & S^* = N, \quad I^* = 0, \quad R^* = 0 \\ \text{endemic equilibrium:} \quad & S^* = \frac{N}{\mathcal{R}_0}, \quad I^* = \frac{\mu N}{\gamma + \mu} \left(1 - \frac{1}{\mathcal{R}_0}\right), \\ & R^* = \frac{\gamma N}{\gamma + \mu} \left(1 - \frac{1}{\mathcal{R}_0}\right), \end{aligned} \quad (17)$$

and, while the disease free equilibrium (*DFE*) always exists, the endemic one stands only for $\mathcal{R}_0 > 1$ (see Figure (11)). Also stability is driven by \mathcal{R}_0 as it can

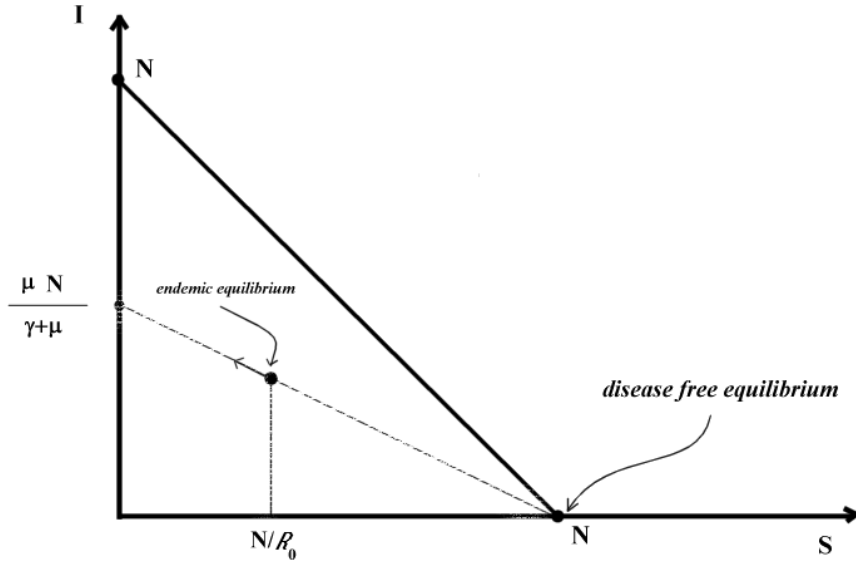


Figure 11: Steady states for problem (15).

be seen by linearization of (15) at these equilibria. In fact we have the following

Jacobian matrix for DFE .

$$J(DFE) = \begin{pmatrix} -\mu & \lambda_0 N \\ 0 & (\gamma + \mu)(\mathcal{R}_0 - 1) \end{pmatrix},$$

showing that DFE is stable for $\mathcal{R}_0 < 1$ and unstable for $\mathcal{R}_0 > 1$. For the endemic equilibrium E (existing only when $\mathcal{R}_0 > 1$) we have

$$J(E) = \begin{pmatrix} -\mu\mathcal{R}_0 & -(\gamma + \mu) \\ \mu(\mathcal{R}_0 - 1) & 0 \end{pmatrix},$$

and it is easy to see that the eigenvalues have negative real parts. In particular

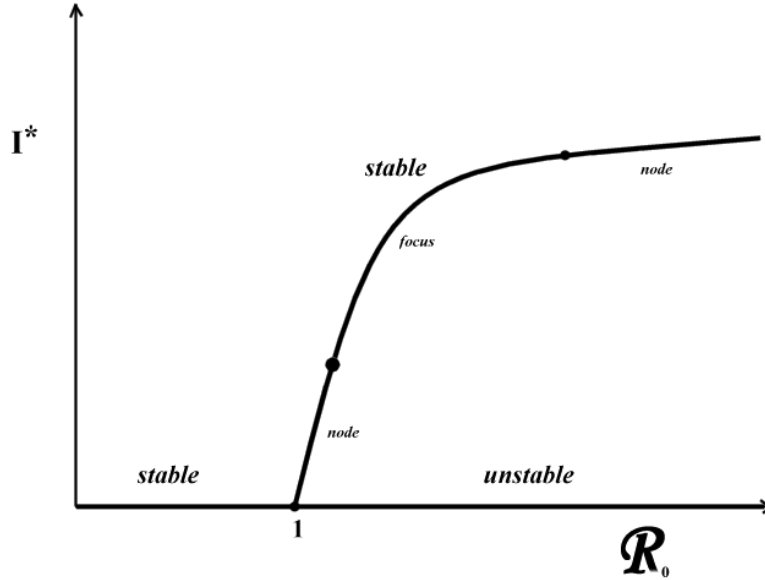


Figure 12: Bifurcation diagram for problem (15).

the endemic state E is a stable node for \mathcal{R}_0 sufficiently close to 1 or sufficiently large. For some values of the parameters a bounded interval may exist such that E is a stable focus. Actually, the condition to have oscillatory solutions is

$$\frac{\mathcal{R}_0^2}{\mathcal{R}_0 - 1} < 4 \left(\frac{\gamma + \mu}{\mu} \right)$$

and we have eigenvalues $\lambda = \alpha \pm \omega$ with

$$\alpha = -\frac{\mu\mathcal{R}_0}{2}, \quad \omega = \mu \sqrt{\frac{\mathcal{R}_0^2}{4} - \frac{\gamma + \mu}{\mu} (\mathcal{R}_0 - 1)}.$$

These also give an approximation of the time elapsed from one peak to another and the approximate damping of the solution after one oscillation

$$T = \frac{2\pi}{\omega}, \quad e^{\frac{\alpha}{\omega}}.$$

The corresponding scenario is shown in Figure 11.

A final remark concerns the global character of the previous stability results. In fact, the general theory of planar systems guarantees that previous stability properties of the steady states are actually global if we can exclude existence of periodic solutions for the system. Indeed we can show that (15) has no periodic

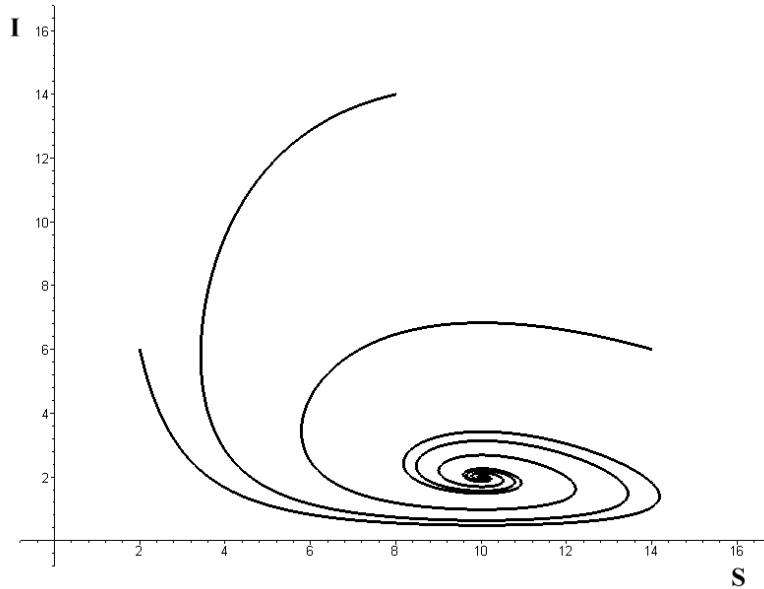


Figure 13: Sample solutions of system (15). Here $\lambda_0 = 0.1$, $\gamma = 1$, $\mu = 0.002$.

solutions via the Bendixon-Dulac principle. In fact, using

$$D(S, I) = \frac{1}{SI}$$

as an auxiliary function, we have

$$\text{Div} \left(\frac{\mu N}{SI} - \lambda_0 - \frac{\mu}{I}, \lambda_0 - \frac{\gamma + \mu}{S} \right) = -\frac{\mu N}{S^2 I} < 0,$$

thus excluding the possibility of periodic solutions in the positive orthant. Possible trajectories in the phase plane (S, I) are shown in Figure 13

4 \mathcal{R}_0 , herd immunity, vaccination

We have previously seen that in the long-term perspective, the endemicity of the disease is related to the basic reproduction number \mathcal{R}_0 . This parameter in fact can be viewed as determining the success of the disease in invading the disease free state. Indeed, if $\mathcal{R}_0 > 1$, the establishing of a disease as endemic can be produced by a single infective individual who enters into the a disease free population composed by all susceptibles. The fact that, at the end of his disease, this infective has "replaced" himself with more than one infective, produces the

epidemic outbreak driving the population to the globally attractive endemic state.

Of course, if for some reason part of the population is immune and the number of susceptibles is too low the outbreak is not going to occur. But this situation which is called *heard immunity* is not maintained in the long term perspective because the immune class tends to be empty by the continuous replacement of susceptibles by newborns.

Vaccination is the usual intervention to keep a population protected by a disease because it produces a constant number of immune people within the population, but it must be imparted at a sufficiently high rate in order to guarantee heard immunity. In this respect, the model of the previous section we may help draw some quantitative conclusion that can be used to public health institution.

Introducing vaccination into the previous model (15) amounts to a slight change. If we denote by v the rate at which susceptible people is vaccinated (and transferred into the removed class) we have

$$\begin{cases} S'(t) = \mu N - \lambda(t)S(t) - \mu S(t) - vS(t) & S(0) = S_0; \\ I'(t) = \lambda(t)S(t) - (\gamma + \mu)I(t) & I(0) = I_0; \\ R'(t) = (\gamma + v)I(t) - \mu R(t) & R(0) = R_0. \end{cases} \quad (18)$$

Then the steady states of the system become

$$\begin{aligned} \text{disease free:} \quad S^* &= \frac{\mu}{\mu + v}N, \quad I^* = 0, \quad R^* = \frac{v}{\mu + v}N \\ \text{endemic:} \quad S^* &= \frac{N}{\mathcal{R}_0}, \quad I^* = \frac{\mu N}{\gamma + \mu} \left(1 - \frac{\mu + v}{\mu \mathcal{R}_0}\right), \\ R^* &= \frac{(\gamma + v)N}{\gamma + \mu} \left(1 - \frac{\mu + v}{\mu \mathcal{R}_0}\right), \end{aligned}$$

and we see that the vaccination produces a pool of immunes in the disease free state so that the invasion condition for establishing the endemic state is

$$\frac{\mu \mathcal{R}_0}{\mu + v} > 1.$$

Consequently, to have heard immunity it should be guaranteed a vaccination rate satisfying

$$v > \mu(\mathcal{R}_0 - 1).$$

Concluding this section we must add some comments on the estimation of the significant parameters of the models discussed in this lecture. Namely we are mainly interested in estimating $\mathcal{R} - 0$ because of its central importance in the disease dynamics. In this respect, though a priori information about the disease may help to evaluate parameters like γ and χ , it is a posteriori evaluation through epidemiological data that provide estimate of \mathcal{R}_0 .

A first tool for this purpose is formula (11) that involves the number of susceptibles before and after the single outbreak. In fact, approximating $I_0 = 0$ it gives

$$\mathcal{R}_0 = \frac{\ln S_\infty - \ln S_0}{S_\infty - S_0}$$

A second possibility is to use the knowledge of susceptibles at the endemic state, in fact from (17) we get

$$\mathcal{R}_0 = \frac{N}{S^*}$$

Finally it is possible to relate \mathcal{R}_0 to the average age of attack A , i. e. the age of the individual when being infected. In fact, A equals the time spent as a susceptible before becoming an infective, and is the inverse of the force of the infection at the endemic equilibrium

$$A = \frac{1}{\mathcal{R}_0 - 1}.$$

Thus we can use the following formula to estimate \mathcal{R}_0

$$\mathcal{R}_0 = 1 + \frac{1}{\mu A}.$$

The list of references below includes some basic review articles and textbooks on epidemics, together with the celebrated paper by Kermack and McKendrick.

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