INSA INSTITUT NATIONAL DES SCIENCES APPLIQUÉES LYON

Biomathematics 1

Introduction of epidemiological models

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Micro- vs macro-parasitic diseases

Infectious diseases can be classified in two categories:

1. Those due to virus or bacteria → the **micro-parasitic diseases** (*e.g.*, measles, flu, gastroenteritis)
2. Those due to worms (that will be mainly found in developing countries) → the **macro-parasitic diseases** (*e.g.*, filariasis, nematode worms within organisms)

In addition to the size of the infectious agent, micro-parasites reproduce within the host and are transmitted directly from one host to another.
Macro-parasites have much more complex life cycles, with secondary hosts or transport hosts.

Micro-parasitic diseases

In this course, we will deal with **micro-parasitic diseases** and the associated mathematical models which come under the **dynamic systems theory** as introduced in lectures.

The basic mathematical techniques you will need are available from the following web site (menu "COURS", then "Théorie des systèmes dynamiques"): `http://bmm.univ-lyon1.fr/`

We will come back to these techniques while relying on numerical simulations, which you will perform under the  software.

Modelling micro-parasitic diseases

It may be tempting to model the population dynamics of both hosts and infectious agents, however:

- It is almost impossible to measure or estimate the population size of infectious agents;
- The distribution of infectious agents within hosts is not homogeneous;
- Infectious agents do not circulate freely in the environment;
- The encounter between hosts and infectious agents is not random.

In addition, we must to take into account that micro-parasitic epidemics spread through close contacts between susceptible (healthy) and infected hosts.

Compartment modelling (SIR)

All micro-parasitic disease models are **compartmental models**, based on different classes of hosts, relative to their state of health :

- Healthy hosts (or **Susceptible**) who may contract the disease through contact with...
- **Infective** hosts (or contagious or infecting) who will transmit the disease;
- **Removed, Recovered or Immune** hosts who can no longer contract the disease through contact, because they have become immune, have been placed in isolation, or have died.

Compartment modelling (SIR)

In these compartment models, variables of interest are therefore the numbers of individuals in each class at time t:

- Variable $S(t)$, for susceptible hosts;
- Variable $I(t)$, for infective hosts;
- Variable $R(t)$, for recovered hosts.

Note that if the disease under interest confers a *temporary immunity*, individuals in class R may return to the class S.

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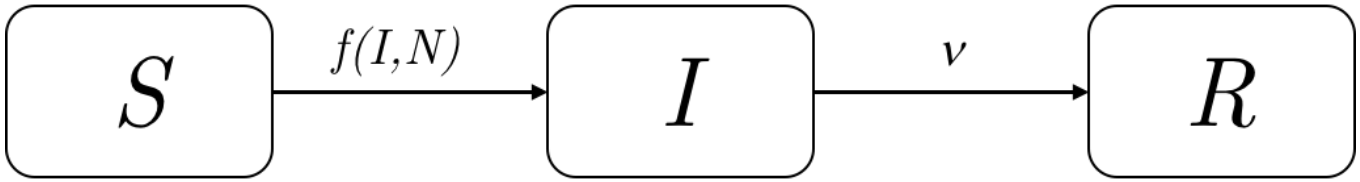
Basic hypotheses

In SIR type models, the following assumptions are always made:

- The transmission is **horizontal**, *i.e.*, only by contacts;
- The epidemic cycle is short, allowing births, deaths, immigration and emigration, as well as any other event that may alter the dynamics of the host population, to be neglected;
- The total population size remains **constant** and equal to $N = S(t) + I(t) + R(t)$.

Other hypotheses may be added depending on the complexity of the disease under consideration.

Schematic diagram



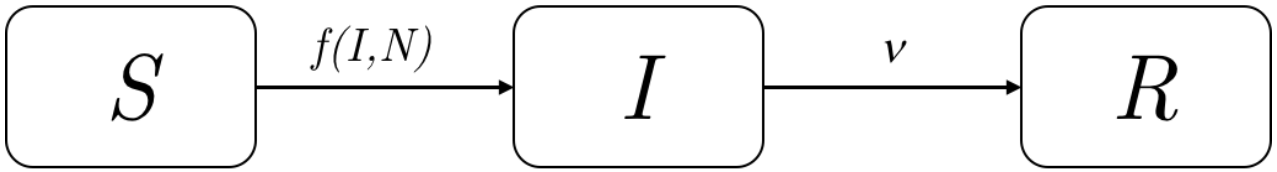
- Function $f(I,N)$ represents the **force of infection**, in $[t]^{-1}$; In general, $f(0,N)=0$ and $f(I,N)$ increases with I while decreasing with N;
- Parameter ν is the **recovery rate**, in $[t]^{-1}$. (that is the immunity acquisition rate or the immunization rate);
- All individuals are **identical** within a class (there is no inter-individual or intra-class variability).

Expression of the force of infection

The **incidence** is defined as the number of cases of a disease occurring in a population during a given time interval.
The **disease transmission rate** is usually denoted via parameter β. (infection rate or contagion rate).

- If the incidence follows a mass action law, the transmission is **density-dependent** and in general we write $f(I,N) = \beta I$.
  → Airborne diseases: a doubling of the infected population can lead to a doubling of the transmission rate (*e.g.*, flu)
- Otherwise, transmission is **frequency-dependent** and in general we write $f(I,N) = \beta I/N$
  → Sexually transmitted diseases: transmission is dependent on the average frequency of sexual contacts per individual, $\forall$ number of healthy individuals (*e.g.*, AIDS)

Equations of model *SIR*



$$\begin{cases} \frac{dS(t)}{dt} = & -f(I(t),N) \times S(t) \\ \frac{dI(t)}{dt} = & f(I(t),N) \times S(t) & -\nu I(t) \\ \frac{dR(t)}{dt} = & \nu I(t) \end{cases}$$

It is easy to check that the total population size does not change over time:

$$\frac{dS(t)}{dt} + \frac{dI(t)}{dt} + \frac{dR(t)}{dt} = 0 \Leftrightarrow S(t) + I(t) + R(t) = N$$

Plan détaillé

The model of Kermack & McKendrick (1927)

In 1927, Kermack & McKendrick proposed the very first SIR model with an infection strength **dependent on density**:

$$\begin{cases} \frac{dS(t)}{dt} = & -\beta \times I(t) \times S(t) \\ \frac{dI(t)}{dt} = & \beta \times I(t) \times S(t) & -\nu I(t) \\ \frac{dR(t)}{dt} = & & \nu I(t) \end{cases}$$

Plague epidemic in Bombay (India, 1906)

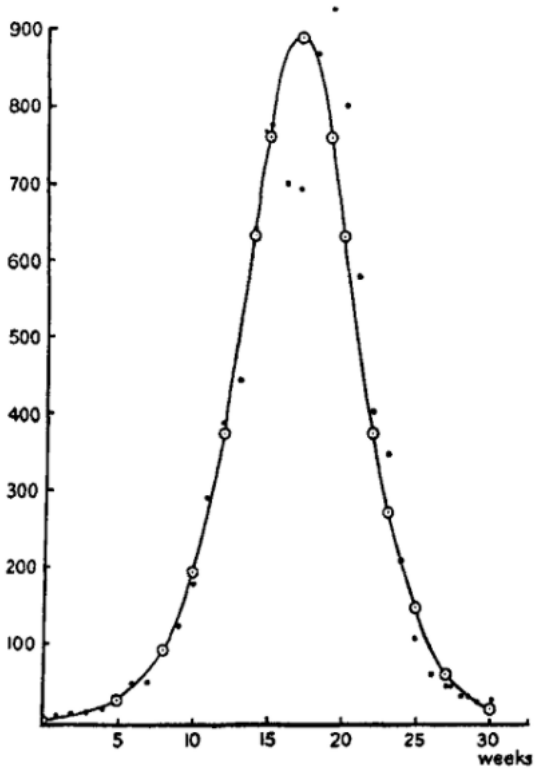


Figure: From Kermack & McKendrick (1927).

Number of deaths per week as a function of the weather during a plague epidemic in Bombay (India) between 17/12/1905 and 21/07/1906.

The outcome being fatal in 80 to 90% of the cases, we can consider that this graph approximately representsthe quantity

$$\frac{dR(t)}{dt}$$

Flu epidemic (England, 1978)

BRITISH MEDICAL JOURNAL 4 MARCH 1978

EPIDEMIOLOGY

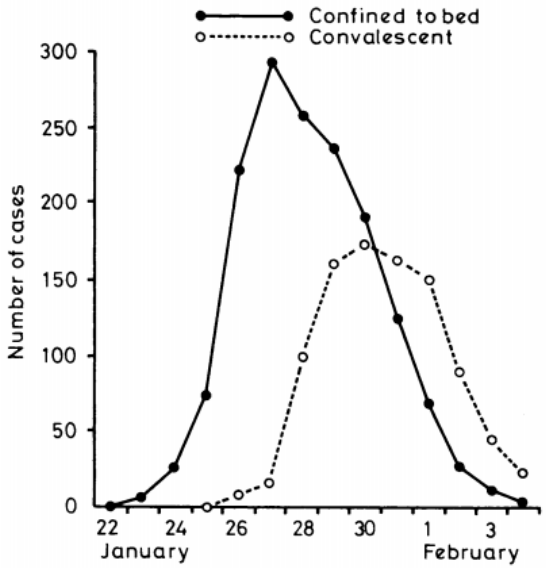
Influenza in a boarding school

The following notes are compiled by the Communicable Disease Surveillance Centre (Public Health Laboratory Service) and the Communicable Diseases (Scotland) Unit from reports submitted by microbiological laboratories, community physicians, and environmental health officers.

During January an epidemic of influenza occurred in a boarding school in the north of England. A total of 763 boys between the ages of 10 and 18 were at risk, all except 30 being full boarders; the staff were from the surrounding villages. There were 113 boys between the ages of 10 and 13 in the junior house, while the rest were divided into 10 houses of about 60 boys each.

The Easter term began on 10 January, with boys returning from all over Britain and some from Europe and the Far East. One boy from Hong Kong had a transient febrile illness from 15 to 18 January. On Sunday 22 January three boys were in the college infirmary. The graph shows the daily total number confined to bed or convalescent during the epidemic: 512 boys (67%) spent between three and seven days away from class, and 83% of the boys in the junior house were affected. Of about 130 adults who had some contact with the boys, only one, a house matron, developed similar symptoms.

Most of the boys who became ill first complained of feeling very tired, with headache as



signs had temperatures of 105°-106°F (40°-41°C). Many had mild reddening of the anterior pillars of the fauces, but the throat never looked as inflamed as symptoms suggested. In only five boys were there abnormal signs on chest examination. Symptoms subsided quickly once the boys were confined to bed. They were allowed up 36 hours after their temperatures had returned to normal and back to classes two to four days later, depending on the severity of the attack. The average time off sick was five to six days.

sounds in his right lung. He was given ampicillin and by next morning his temperature was 99°F (37°C) and his chest clear. Five days later he went home to convalesce. Four boys developed wheezy bronchitis. Two received ampicillin and two tetracycline. All recovered quickly and were back at work in seven to eight days. Four boys with otitis media, with bulging red ear drums, responded to ampicillin within 48 hours and none had any aural discharge. One boy had sinusitis, which again responded to ampicillin. He was in bed for seven days and off work for ten days. In all, only 10 of the 512 boys who became ill received antibiotics.

Throat swabs were taken from eight boys, and influenza A viruses similar to A/USSR/90/77 (H1N1) were isolated from six. The spread of this virus through the school was much more rapid than in the outbreaks due to influenza B in November 1954 and to influenza A (Asian flu) H2N2 in October 1957. These two epidemics reached their peak in two weeks and lasted four weeks. This year's epidemic reached a peak in seven days and was over in 13 days. Influenza vaccine (Fluvirin) had been given to 630 boys in October 1977—as had been the practice for some years. The incidence of influenza among the boys had been low except in those years in which a definite antigenic shift occurred. The fact that this is the first major outbreak of influenza at the school since the Asian flu suggests that in-

Flu epidemic (England, 1978)

The previous paper is extracted from the *British Medical Journal* which reports a case of **flu epidemic** in an English boarding school for boys in 1978.

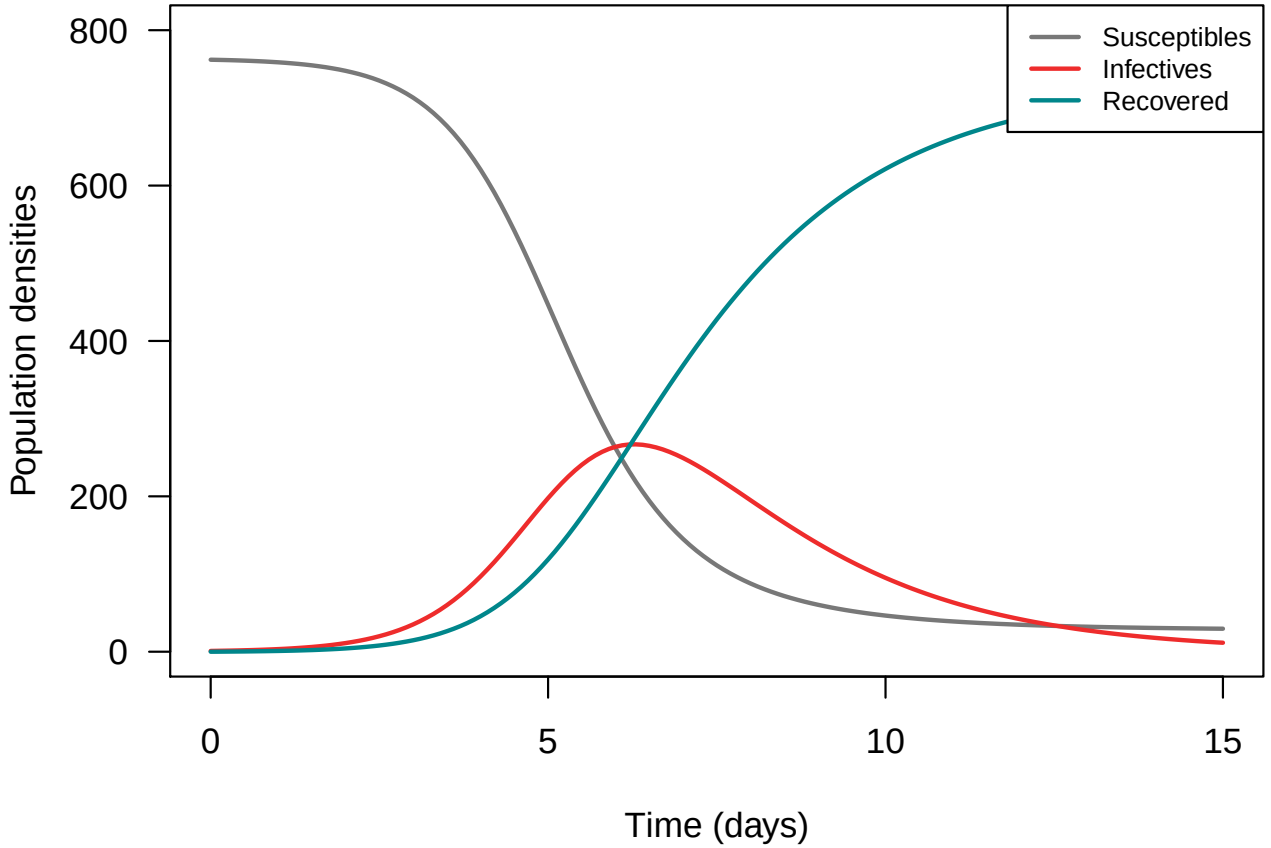
This flu have started with only one infected boy in a total population of 763 individuals.

The epidemic lasted 15 days.

The data provided concern only the number of individuals bedridden each day, which can be assimilated to the number of infected individuals (variable $I(t)$).

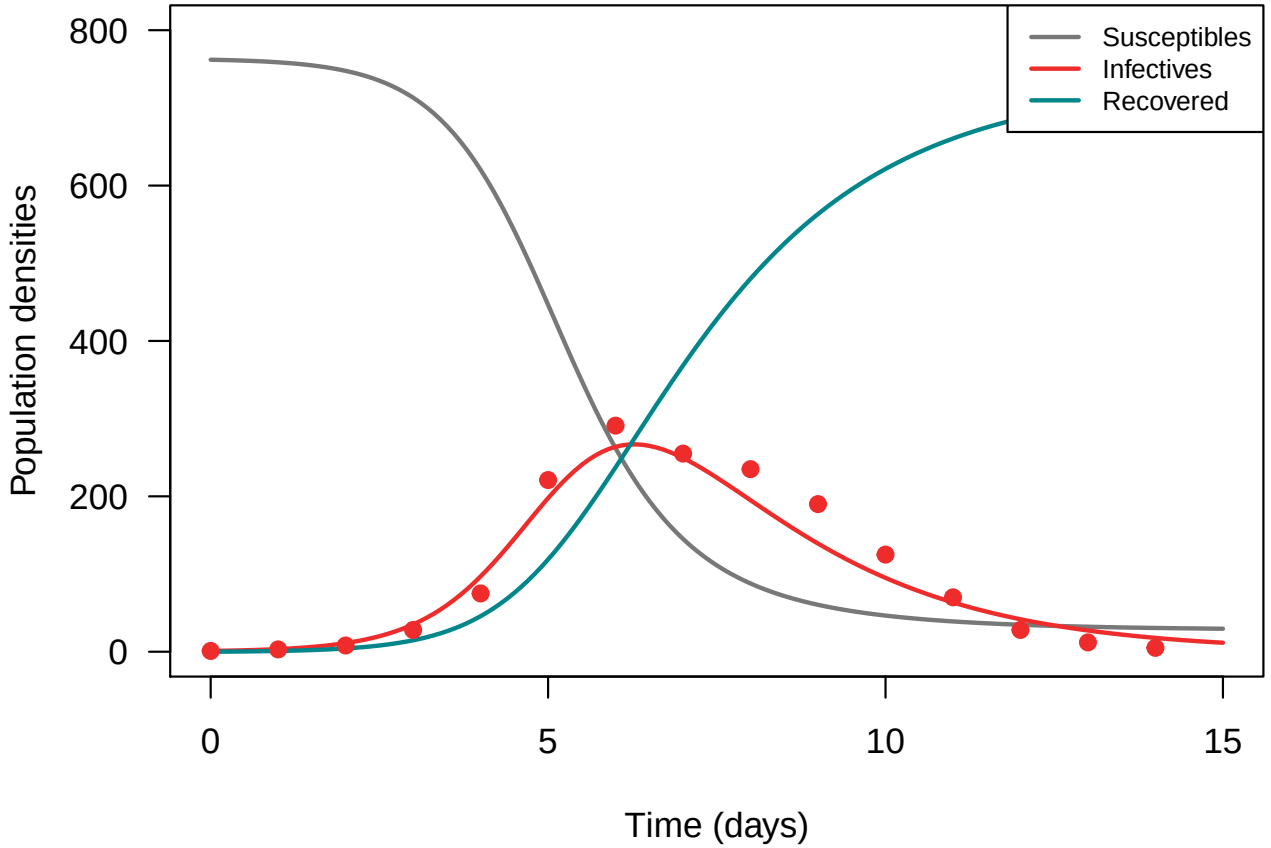
Simulation of Kermack & McKendrick model

Parameter values: $\beta = 0.00225\ t^{-1}$ and $\nu = 0.5\ t^{-1}$.
Initial condition: (762,1,0).



Adequacy to epidemiological data

Parameter values: $\beta = 0.00225\ t^{-1}$ and $\nu = 0.5\ t^{-1}$.
Initial condition: (762,1,0).



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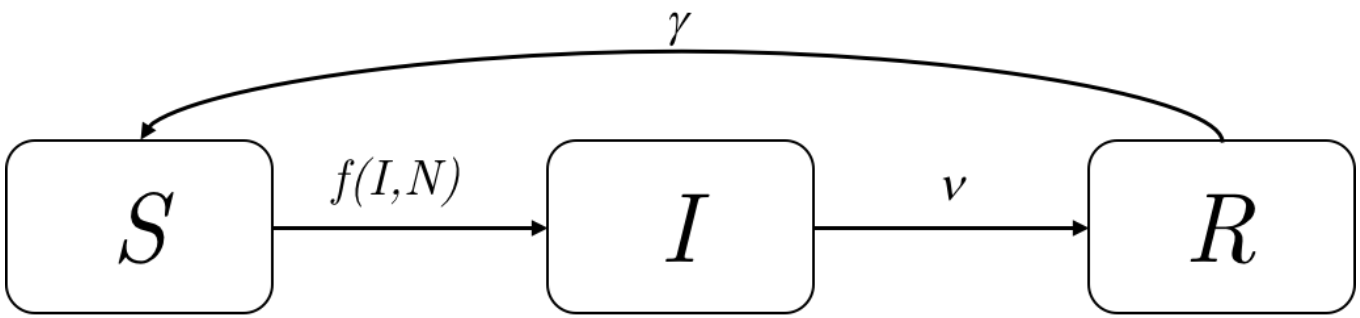
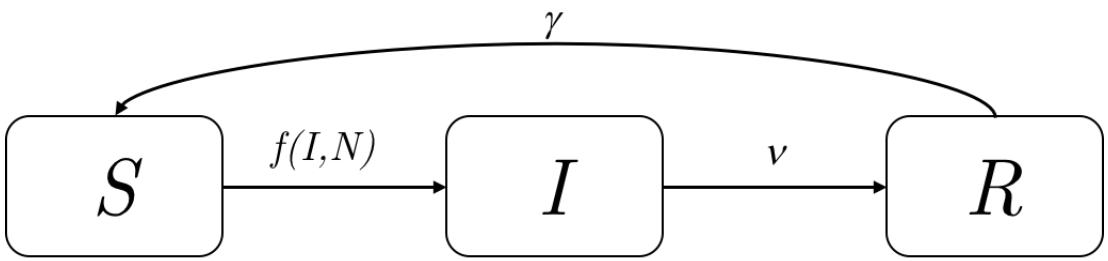
Generalisation of model SIR

The SIR model can be generalised by considering that immunity is lost after a while and that recovered individuals become susceptible again.
If we assume that this process is proportional to $R(t)$, with γ being the rate of proportionality (in $[t]^{-1}$), then:



Equations of model $SIRS$



$$\begin{cases} \frac{dS(t)}{dt} = & -f(I(t),N) \times S(t) & +\gamma R(t) \\ \frac{dI(t)}{dt} = & f(I(t),N) \times S(t) & -\nu I(t) \\ \frac{dR(t)}{dt} = & \nu I(t) & -\gamma R(t) \end{cases}$$

$\gamma = 0$ brings us back to model SIR.

Equations of the density-dependent $SIRS$ model

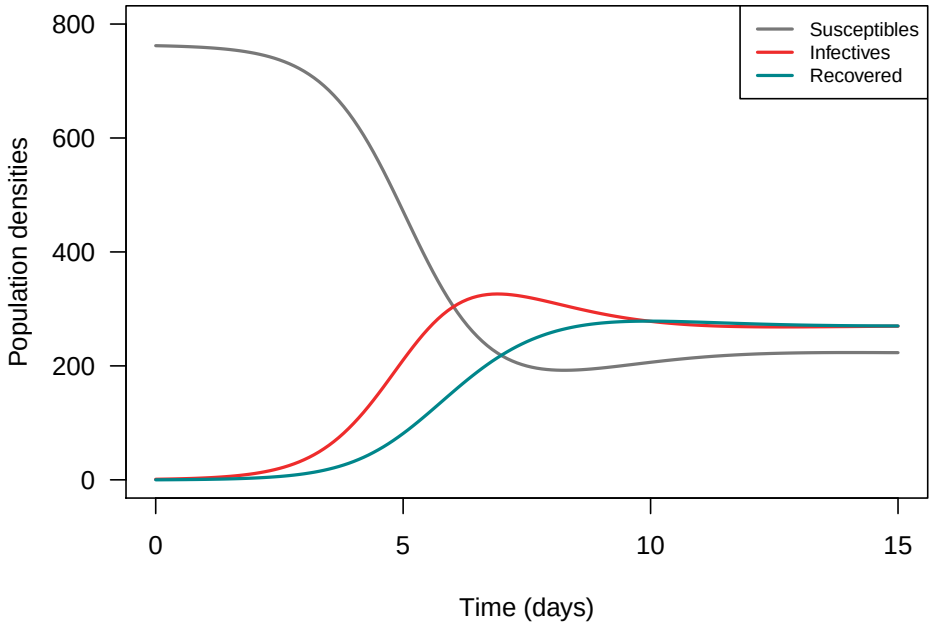
With a density-dependent infection force the following system is obtained:

$$\begin{cases} \frac{dS(t)}{dt} = -\beta I(t) S(t) + \gamma R(t) \\ \frac{dI(t)}{dt} = \beta I(t) S(t) - \nu I(t) \\ \frac{dR(t)}{dt} = \nu I(t) - \gamma R(t) \end{cases}$$

Let's look at the simulations under the same conditions as for the SIR model but adding parameter γ.

Simulation of model $SIRS$

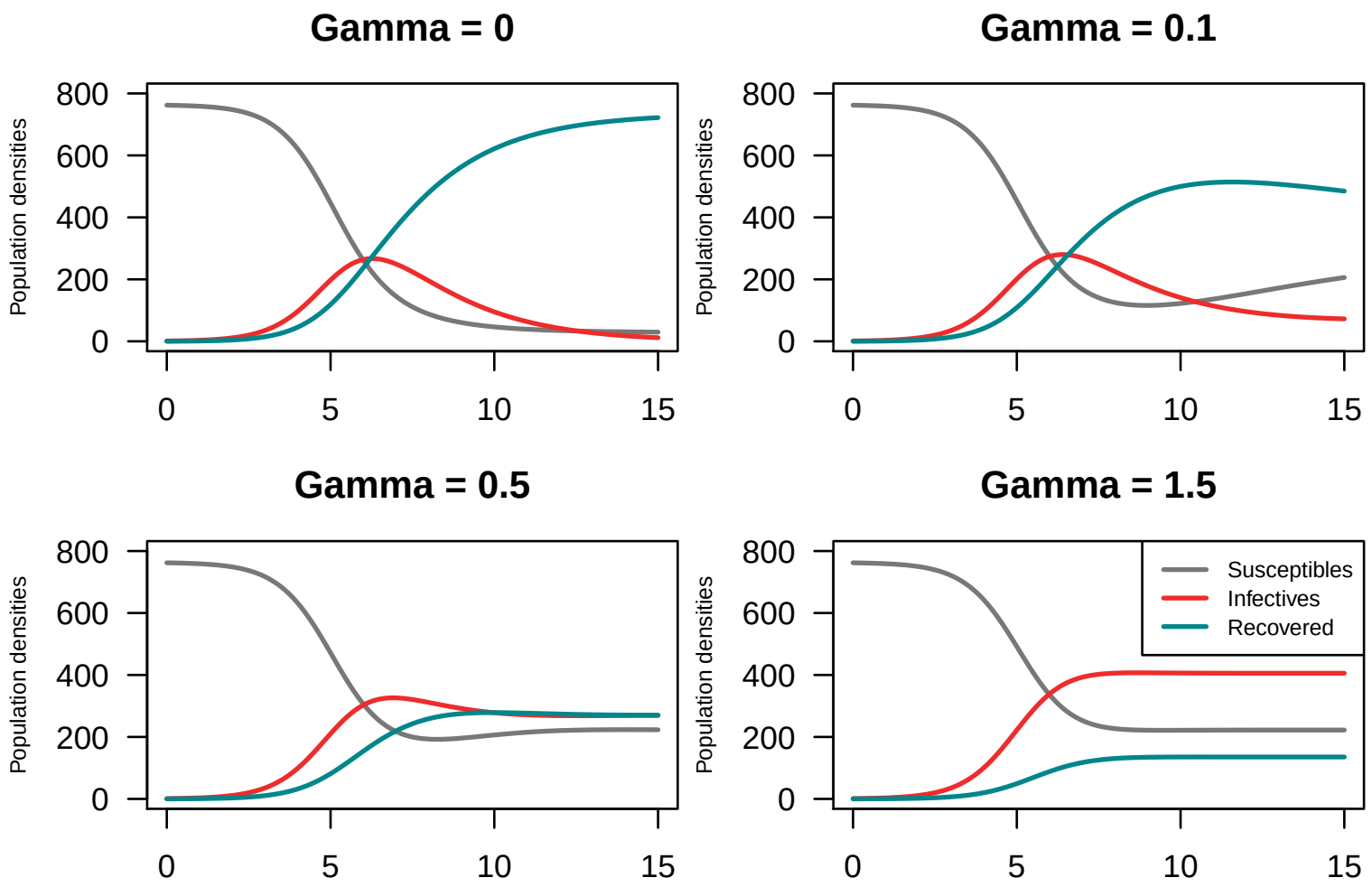
Parameter values: $\beta = 0.00225\ t^{-1}$, $\nu = 0.5\ t^{-1}$ and $\gamma = 0.5\ t^{-1}$.
Initial condition: (762,1,0).



→ With a SIR model, after a while, there are only resistant individuals left. With a $SIRS$ model and the addition of parameter γ, the three classes are able to co-exist.

Effect of parameter γ values

$\gamma = 0$: model SIR.



Equilibrium points of model $SIRS$

As in Kermack & McKendrick model, here again $S(t)+I(t)+R(t)=$ constant.

We can look for equilibrium points of model $SIRS$, *i.e.*, the constant solutions that verify:

$$\left\{\begin{array}{l}\frac{dS(t)}{dt}=0\\ \frac{dI(t)}{dt}=0\\ \frac{dR(t)}{dt}=0\end{array}\right. \Leftrightarrow \left\{\begin{array}{l}-\beta S^* I^* + \gamma R^* = 0\\ \beta S^* I^* - \nu I^* = 0\\ \nu I^* - \gamma R^* = 0\end{array}\right.$$

By using $N = S^* + I^* + R^*$, we get two equilibrium points:

$$S_1^* = N \quad I_1^* = 0 \quad R_1^* = 0$$

$$S_2^* = \frac{\nu}{\beta} \quad I_2^* = \gamma\frac{N-S_2^*}{\nu+\gamma} \quad R_2^* = \frac{\nu I_2^*}{\gamma} \quad \text{Endemic equilibrium}$$

Equilibrium points interpretation

In the 3D space (S, I, R) :

- Equilibrium point $(N, 0, 0)$: all individuals in the population are healthy, the disease has been eradicated;

- Equilibrium point (S_2^*, I_2^*, R_2^*): the three classes of individuals co-exist, given that S_2^*, I_2^* and R_2^* are > 0, which implies $S_2^* < N \Leftrightarrow \frac{\nu}{\beta} < N$.
  Indeed, $I_2^* = \gamma \frac{N - S_2^*}{\nu + \gamma}$ so that $I_2^* > 0$ if $S_2^* = \frac{\nu}{\beta} < N$

→ The population must be large enough for the disease to become endemic.

Interpretation of ratio $\frac{\nu}{\beta}$

- Since ν is the recovery rate from class I (in $[t]^{-1}$ unit), the average period of infectivity (or contagion) is $1/\nu$ (unit $[t]$).
- The β/ν ratio is the fraction of the population that is in contact with infected individuals during the period of contagion.
- The quantity $R_0 = N\frac{\beta}{\nu}$ is called the **intrinsic reproduction rate of the disease** or the basic reproduction rate (May, 1983).

$\rightarrow$ R_0 represents the number of secondary infections generated by the introduction of a single infected individual into a population of healthy individuals.

$$\frac{\nu}{\beta} < N \Leftrightarrow R_0 > 1$$

Qualitative analysis of model $SIRS$

Since the total population is constant, we can eliminate one of the three variables and write the model in dimension 2:

$$S(t) + I(t) + R(t) = N \Leftrightarrow R(t) = N - S(t) - I(t)$$

Then the system becomes:

$$\begin{cases} \frac{dS(t)}{dt} = -\beta I(t) S(t) + \gamma (N - S(t) - I(t)) \\ \\ \frac{dI(t)}{dt} = \beta I(t) S(t) - \nu I(t) \end{cases}$$

We will now try to plot the trajectories, *i.e.*, the $(S(t), I(t))$ curves, based on the properties of the system. We can choose the default phase plane (S, I).

Phase plane drawing

Phase plane drawing

Parameterisation for simulations

In what follows, we keep the same parameter values as before:

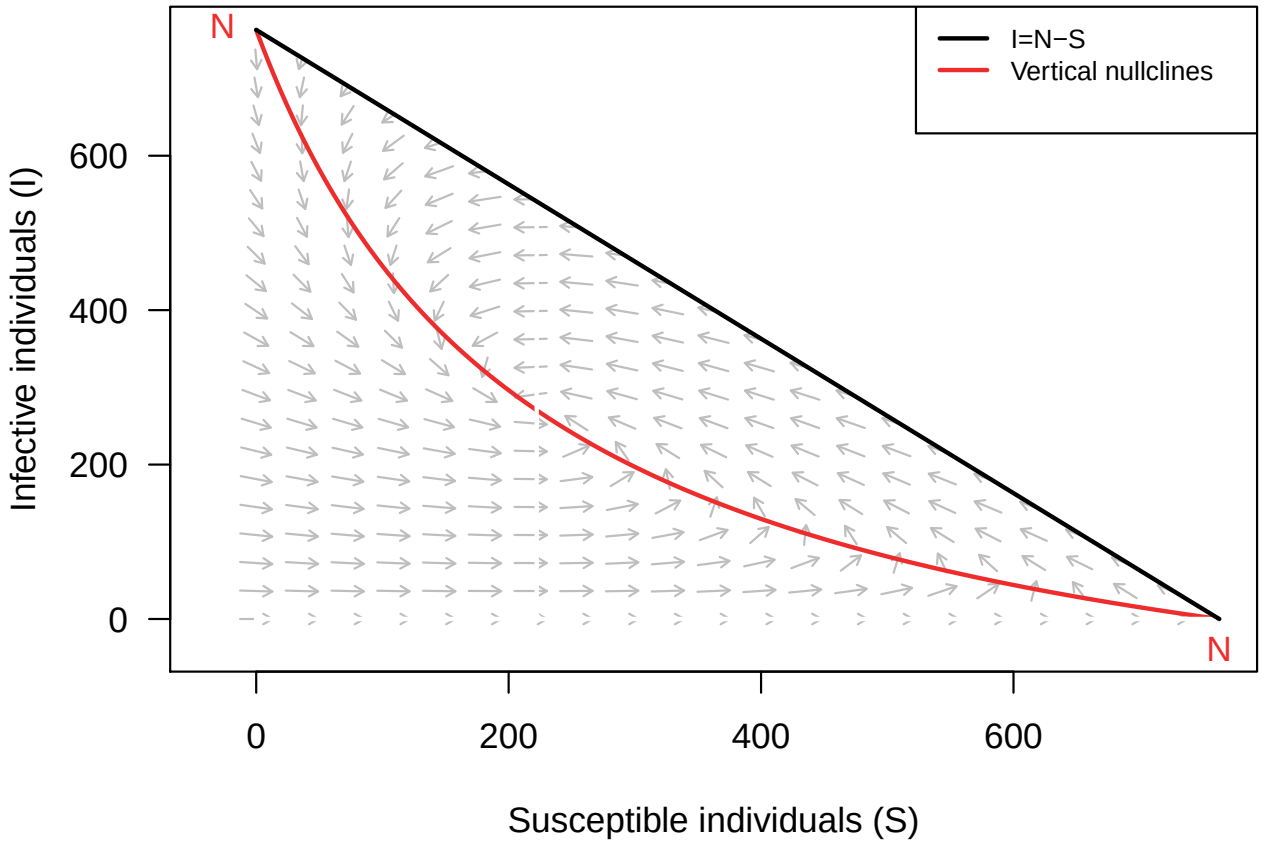
- $\beta = 0.00225\ t^{-1}$
- $\nu = 0.5\ t^{-1}$
- $\gamma = 0.5\ t^{-1}$
- $N = 763$, the total population size

Phase plane drawing: $R_0 > 1 \Leftrightarrow \frac{\nu}{\beta} < N$

Vertical nullclines

$\frac{dS}{dt} = 0 \Leftrightarrow \beta SI = \gamma(N - S - I) \Leftrightarrow I = \frac{\gamma(N-S)}{\beta S + \gamma}$

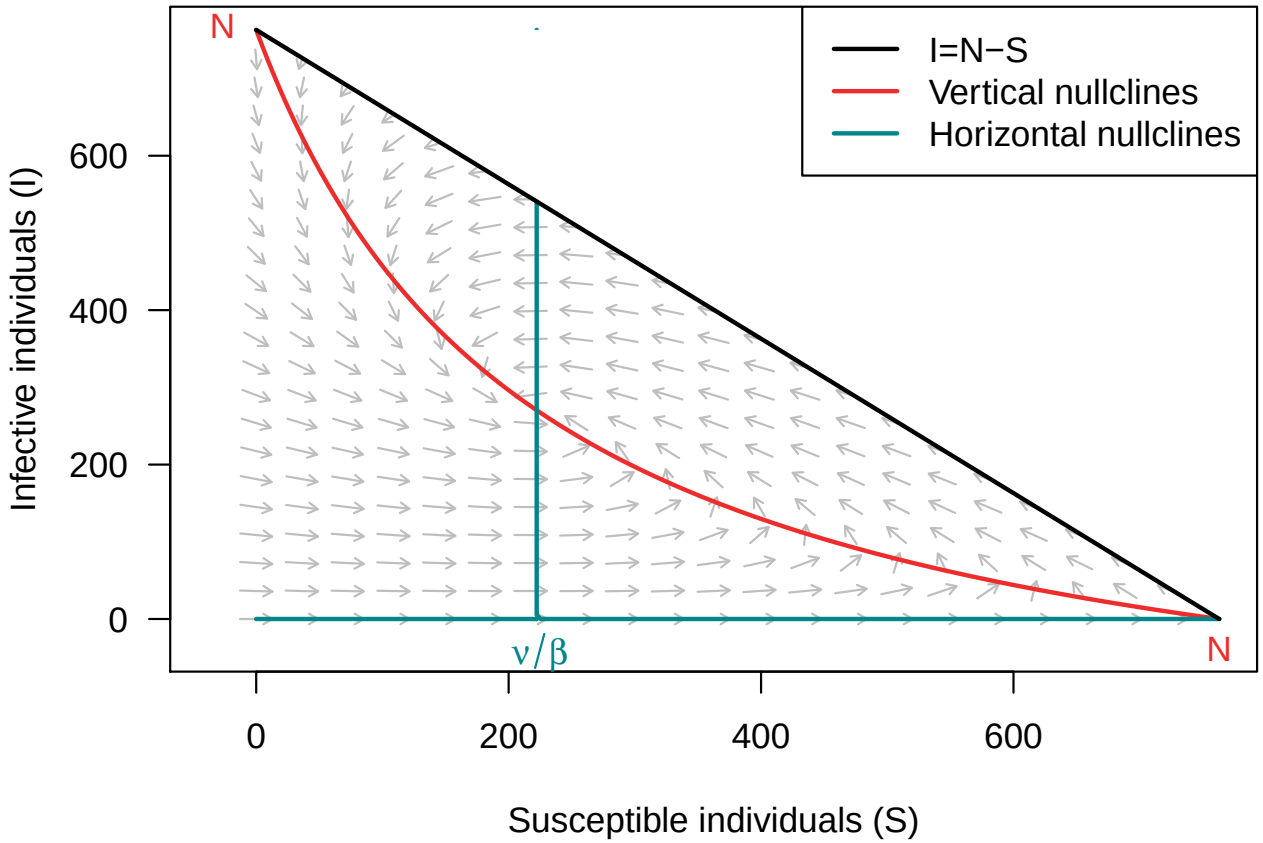
It is a decreasing curve going through $(0, N)$ and $(N, 0)$.



Phase plane drawing: $R_0 > 1 \Leftrightarrow \frac{\nu}{\beta} < N$

Horizontal nullclines

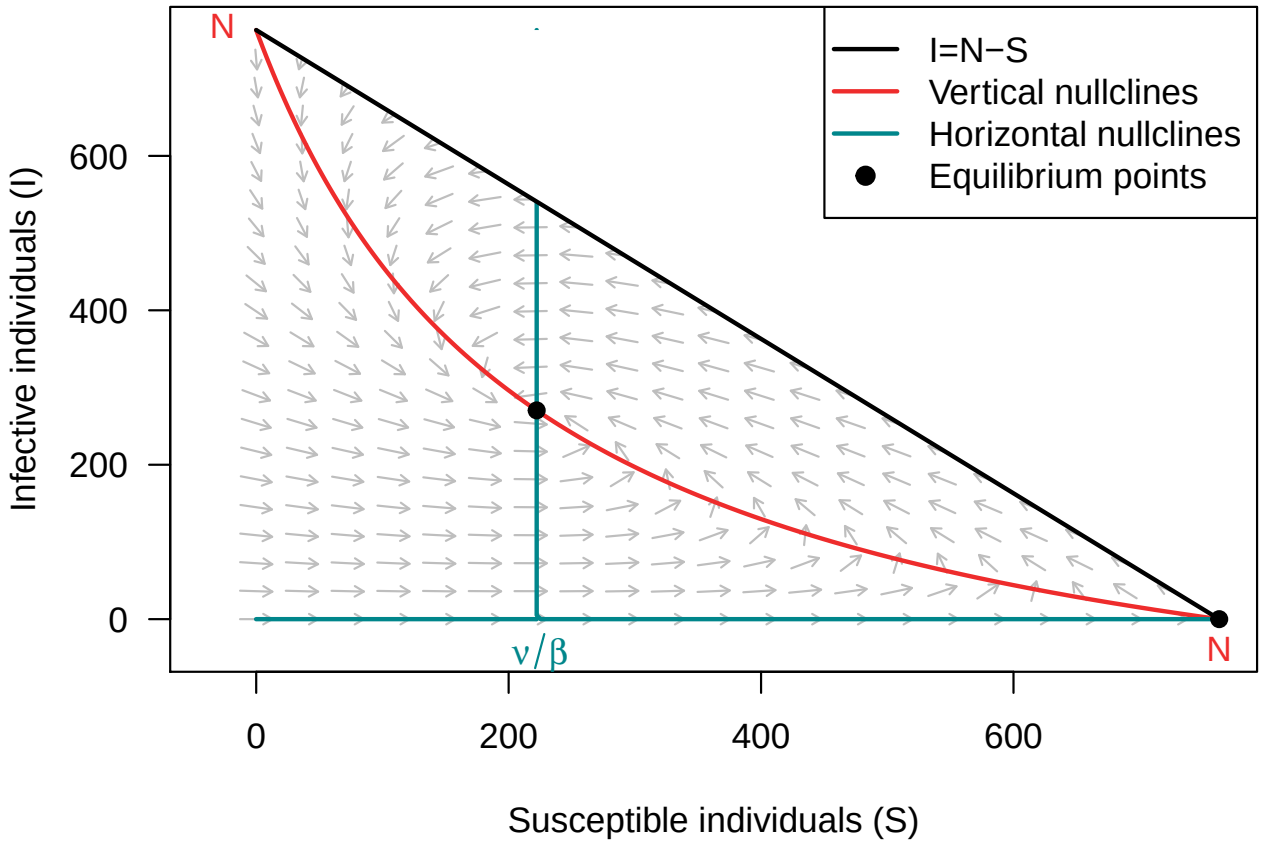
$\frac{dI}{dt} = 0 \Leftrightarrow \beta SI - \nu I = 0 \Leftrightarrow I = 0$ or $S = \nu/\beta$. These equations correspond to horizontal and vertical lines, respectively.



Phase plane drawing: $R_0 > 1 \Leftrightarrow \frac{\nu}{\beta} < N$

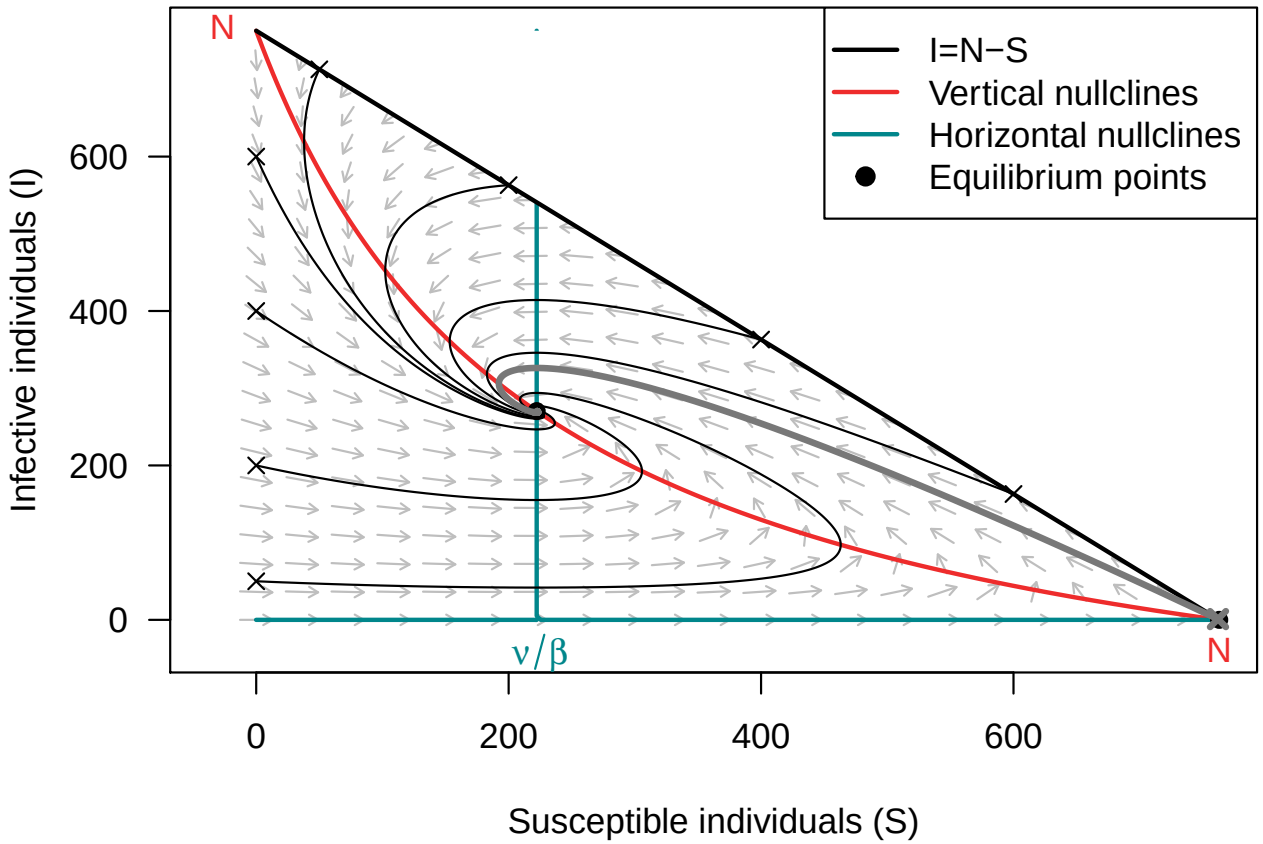
Equilibrium points

Given their definition, equilibrium points are at the intersection of the vertical and horizontal nullclines.



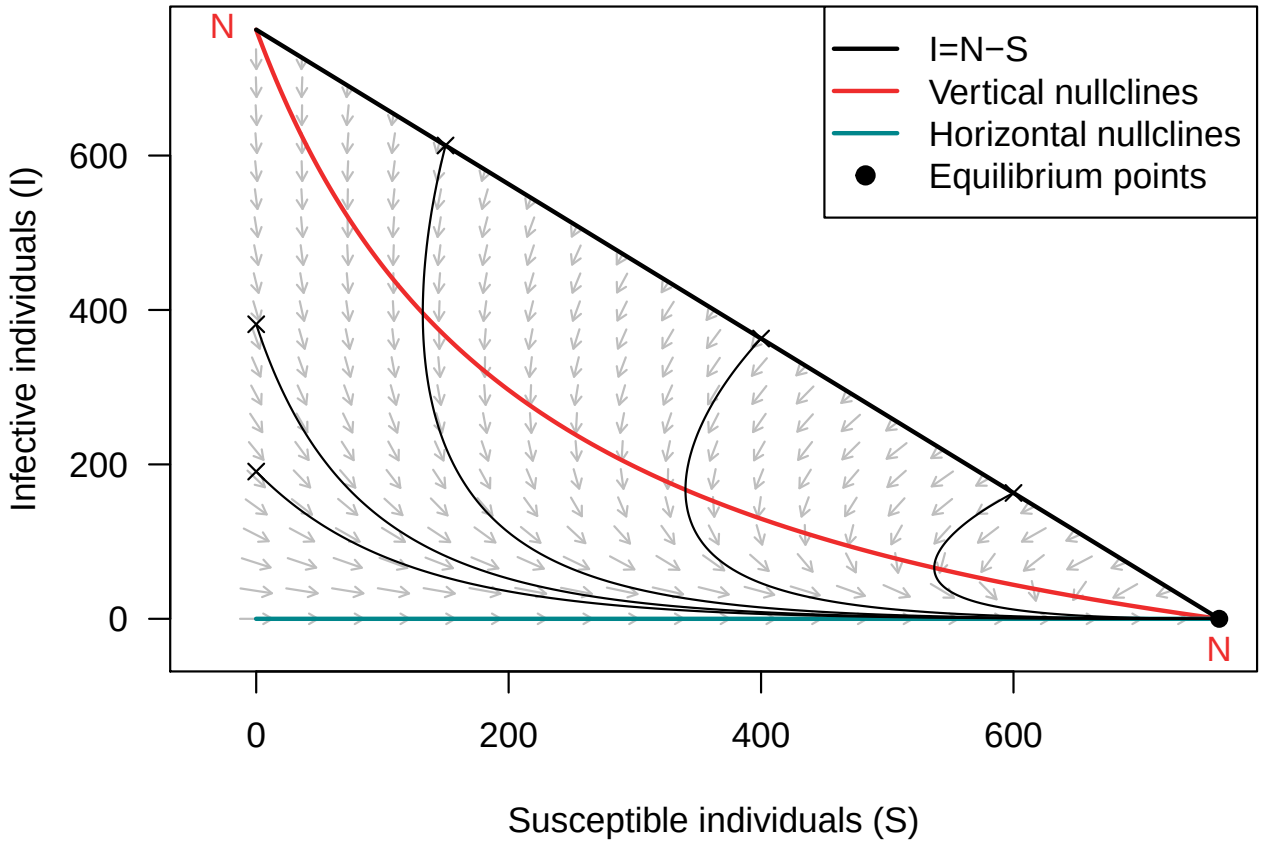
Phase plane drawing: $R_0 > 1 \Leftrightarrow \frac{\nu}{\beta} < N$

Trajectories



$\forall$ the initial condition, the dynamics of the system converge towards the endemic equilibrium point: the epidemic maintains.

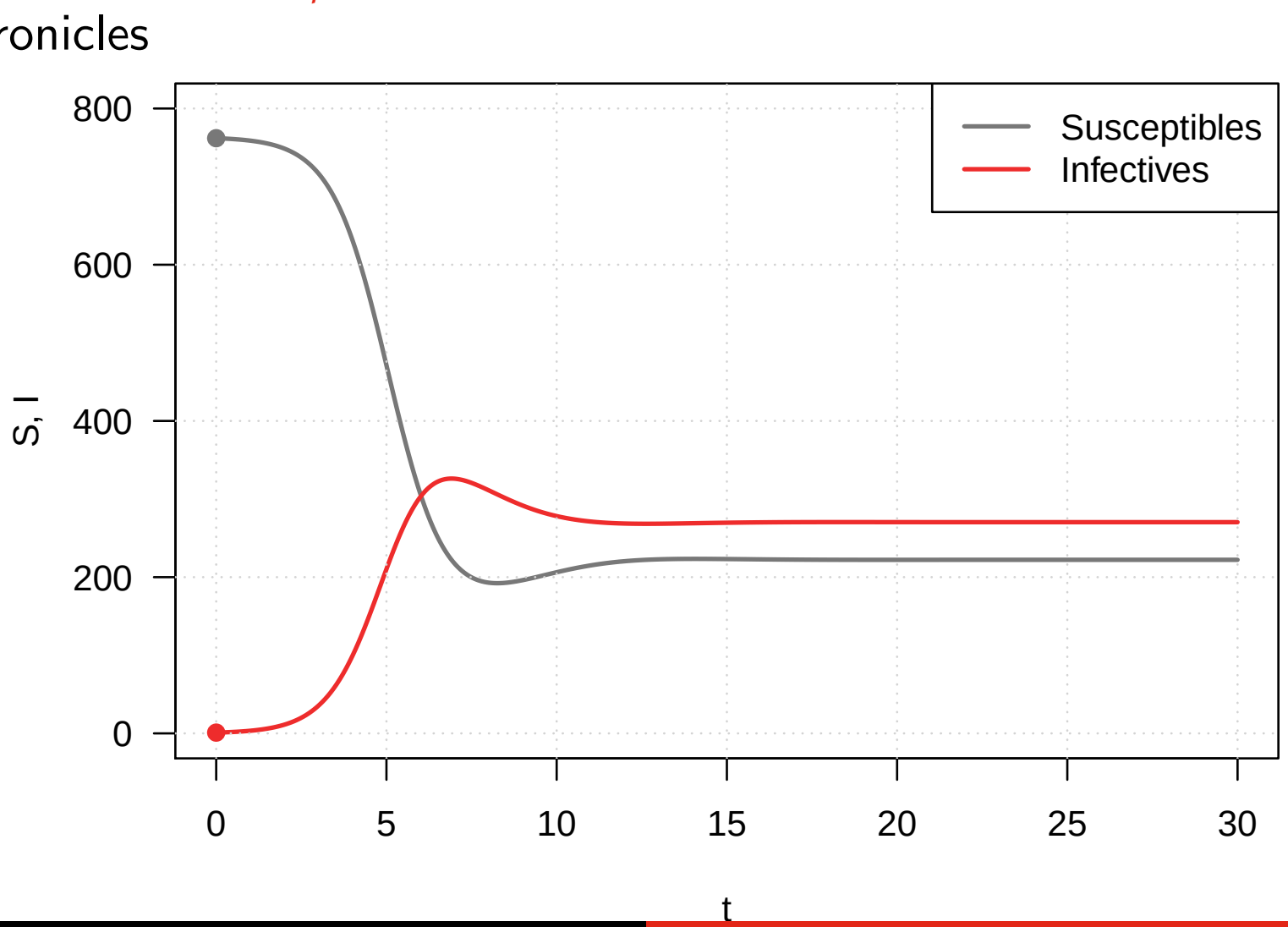
Phase plane drawing: $R_0 < 1 \Leftrightarrow \frac{\nu}{\beta} > N$



$\forall$ the initial condition, the dynamics of the system converge towards the equilibrium point $(N,0)$: the disease is eradicated.

What can be said about the dynamics time course?

Chronicles when $R_0 > 1 \Leftrightarrow \frac{\nu}{\beta} < N$



What can be said about the dynamics time course?

Chronicles when $R_0 < 1 \Leftrightarrow \frac{\nu}{\beta} > N$