Introduction to infectious disease modelling

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1. Introduction

Overview of the course

Day 1

- Introduction to infectious disease modelling

Day 2

- PRACTICAL – Deterministic models in R
- Introduction to stochastic models

Day 3

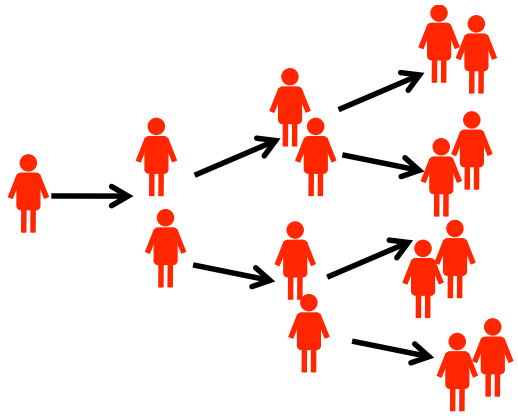
- Applications of modelling
- PRACTICAL – stochastic models in R

Day 4

- Model fitting and inference (+ PRACTICAL)

The reproduction number R

The number of secondary cases an infectious person generates.



What does this depend on?

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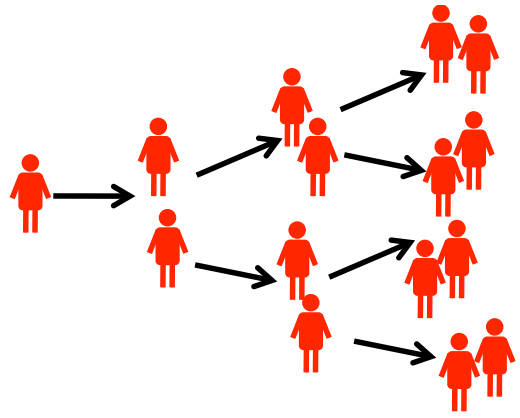

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2. The probability of transmission given contact, p
3. The duration of infectiousness, D
4. The proportion of contacts that are susceptible, s

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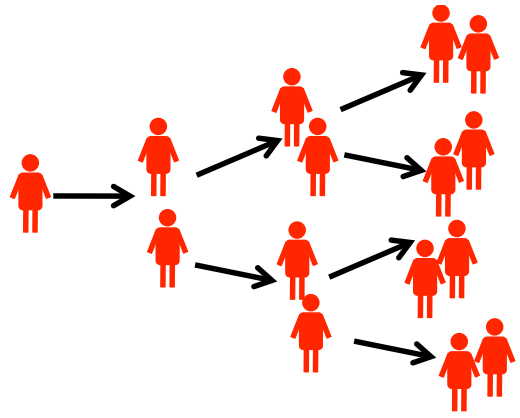

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3. The duration of infectiousness, D
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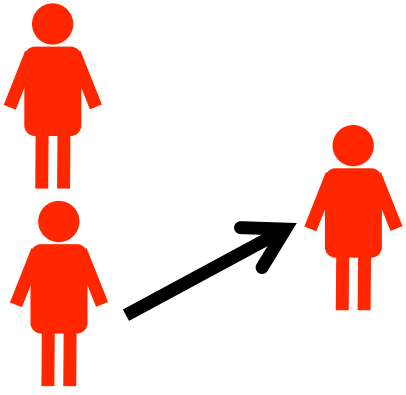
A simple model would suggest: $R = c \times p \times D \times s$

The basic reproduction number R_0

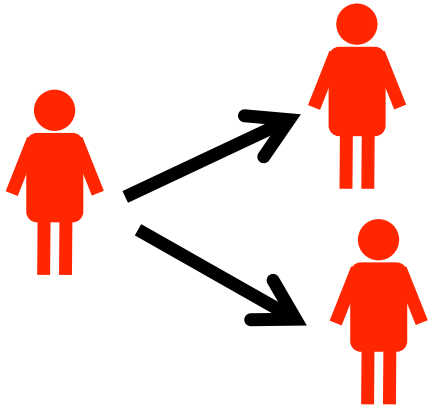
The average number of secondary infectious cases resulting from the introduction of a single infectious case into a totally susceptible population

$$R_0 < 1$$



Number of cases decreases

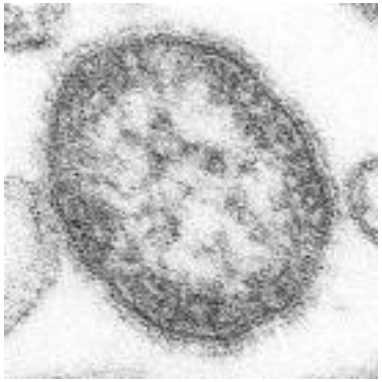
$$R_0 > 1$$



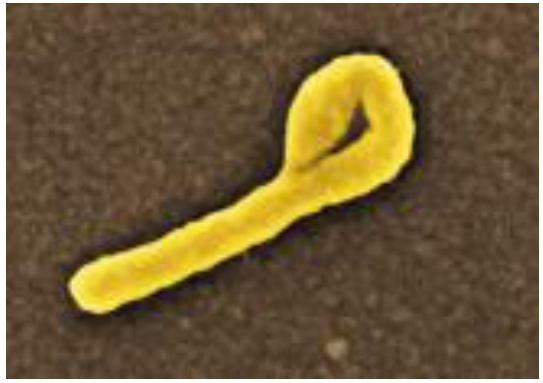
Number of cases increases

R_0 of infectious diseases

Can you arrange these diseases according to their value of R_0?

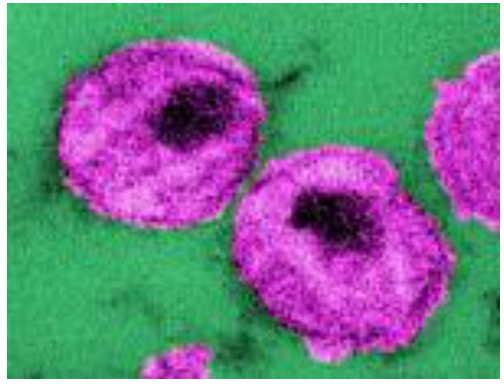


Measles



Ebola

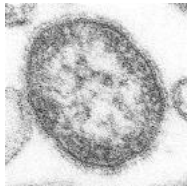
Malaria



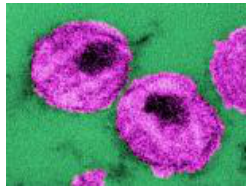
HIV

Empirical values of R_0

Malaria
R_0 10-100



Measles
R_0 5-18



HIV
R_0 2-12

Ebola
R_0 1.5-2.5


DEATHS
8
1
FLU-1
SMALLPOX-3
POLIO-
4/6

More empirical values of R_0

Infection	Geographical location	Time period	R_0
Measles	Cirencester, England	1947–50	13–14
	England and Wales	1950–68	16–18
	Kansas, USA	1918–21	5–6
	Ontario, Canada	1912–13	11–12
	Willesden, England	1912–13	11–12
	Ghana	1960–8	14–15
	Eastern Nigeria	1960–8	16–17
Pertussis	England and Wales	1944–78	16–18
	Maryland, USA	1943	16–17
	Ontario, Canada	1912–13	10–11
Chicken pox	Maryland, USA	1913–17	7–8
	New Jersey, USA	1912–21	7–8
	Baltimore, USA	1943	10–11
	England and Wales	1944–68	10–12
Diphtheria	New York, USA	1918–19	4–5
	Maryland, USA	1908–17	4–5
Scarlet fever	Maryland, USA	1908–17	7–8
	New York, USA	1918–19	5–6
	Pennsylvania, USA	1910–16	6–7
Mumps	Baltimore, USA	1943	7–8
	England and Wales	1960–80	11–14
	Netherlands	1970–80	11–14
Rubella	England and Wales	1960–70	6–7
	West Germany	1970–7	6–7
	Czechoslovakia	1970–7	8–9
	Poland	1970–7	11–12
	Gambia	1976	15–16
Poliomyelitis	USA	1955	5–6
	Netherlands	1960	6–7
Human Immunodeficiency Virus (Type I)	England and Wales (male homosexuals)	1981–5	2–5
	Nairobi, Kenya (female prostitutes)	1981–5	11–12
	Kampala, Uganda (heterosexuals)	1985–7	10–11

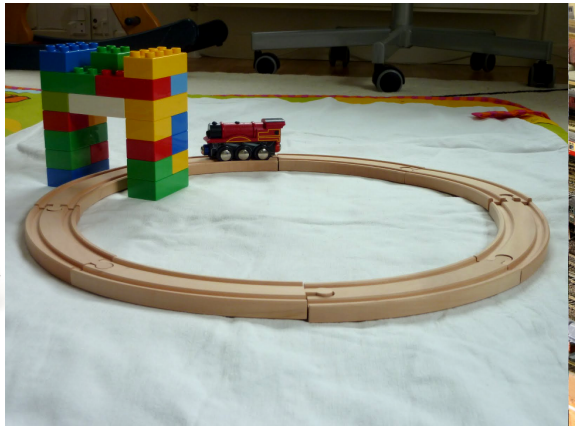
Different R_0 values for a given diseases

R_0 for a disease can have different values depending on factors such as:

- Population density and contact patterns
- Host factors (e.g., immunity)
- Seasonality
- Control measures

2. Mathematical models

What is a (mathematical) model?



A simplified description, especially a mathematical one, of a system or process, to assist calculations and predictions

Oxford English Dictionary

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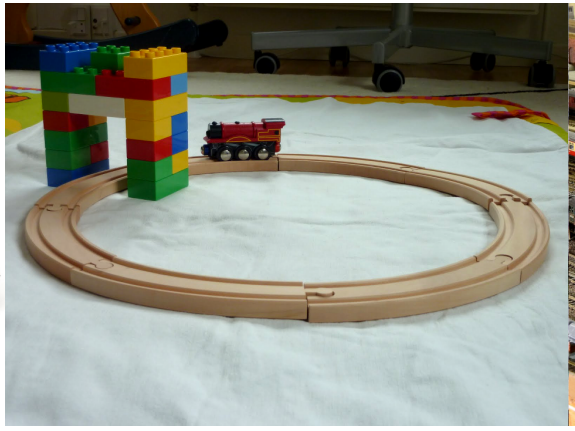

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Infectious disease model

- a set of equations describing transmission in a population
- an attempt to capture key processes, ignoring unnecessary detail

Why model?

1. understand transmission dynamics
    - Examples:
        - who are the risk groups?
        - where are the hotspots?
        - what is the impact of asymptomatic infection?
    - highlight gaps in knowledge, data needs, etc
2. assess control strategies
    - Examples
        - limited vaccine supply, how should it be distributed?
        - travel restrictions, etc.
        - school closures?
3. predict future course
    - Examples
        - how many cases do we expect next week?
        - are we approaching the peak of an outbreak?
        - what is the impact of a changing climate?

Purpose of mathematical models

All models are wrong but some are useful

George P. Box

3. Compartmental models

Compartmental models

- Divide a population of N people into compartments, depending on infection status

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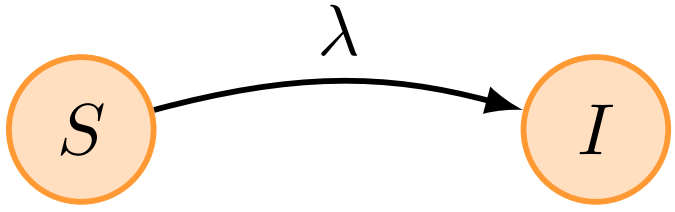
A simple compartmental model



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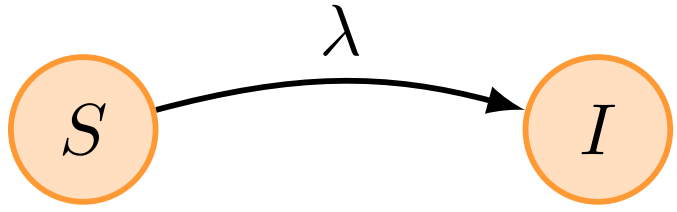

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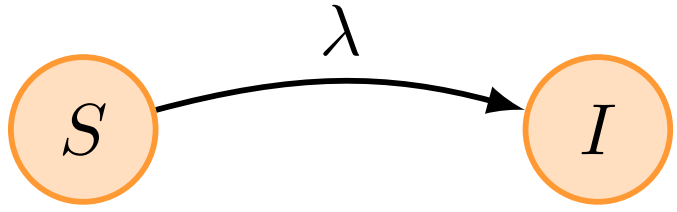

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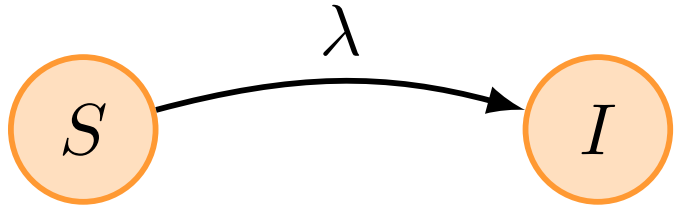

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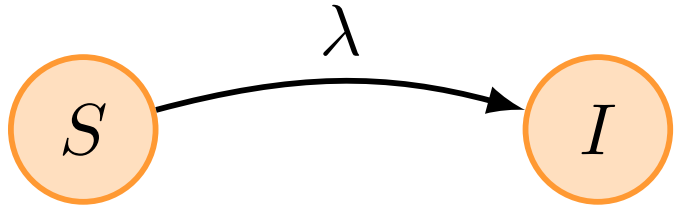

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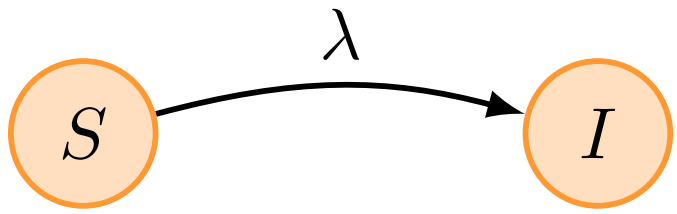
- I: Number of infectious
- S and I are the compartments. They are state variables, i.e. they change over time.
- $N = S + I$ is the population size. N is a parameter, i.e. it does not change.

The force of infection in the SI model



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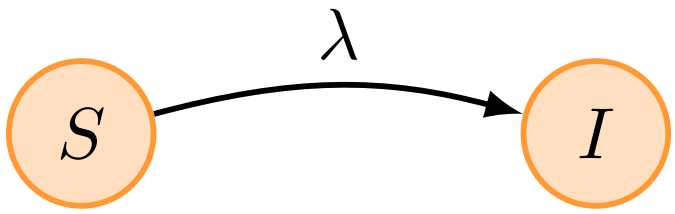

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- It is the probability that a susceptible person gets infected per unit time (i.e., per day, week, month year, …)
- What is this probability?

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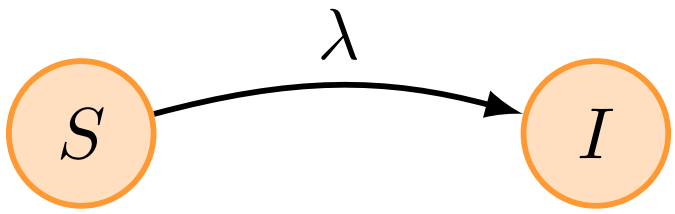

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(Probability that contact is infectious) I/N

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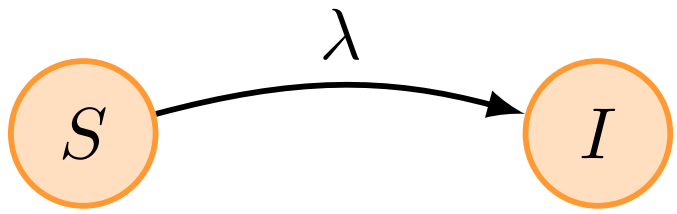

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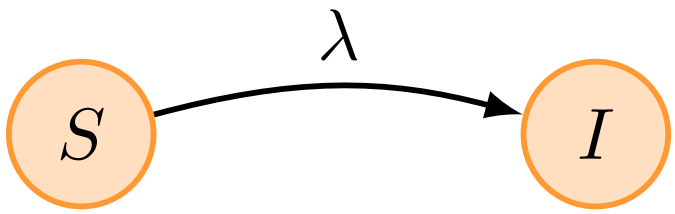
- We often write $\beta = c \times p$, so that $\lambda = \beta I/N$
- β is called the infection rate, a parameter

The principle of mass action



$$\lambda = \beta \frac{I}{N}$$

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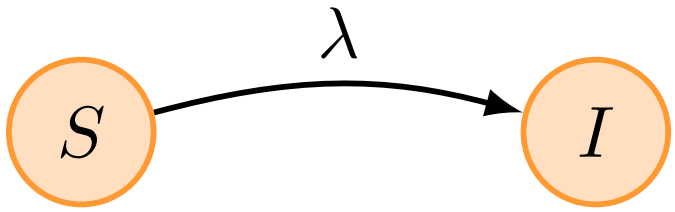

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- This implies that every person in the population has the same probability of getting in infectious contact with everyone else.

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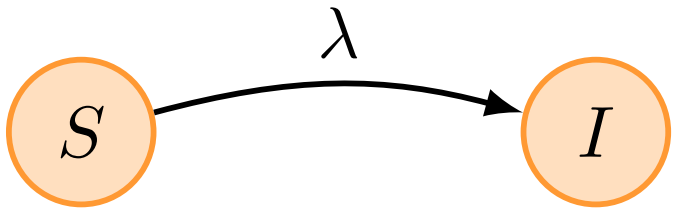

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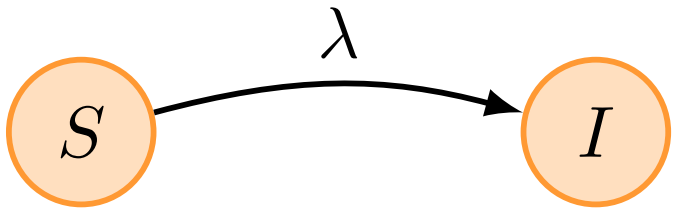

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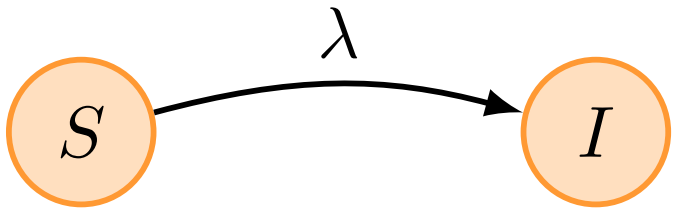
- Is this realistic?

The principle of mass action



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    - No – think influenza, HIV, Ebola, …

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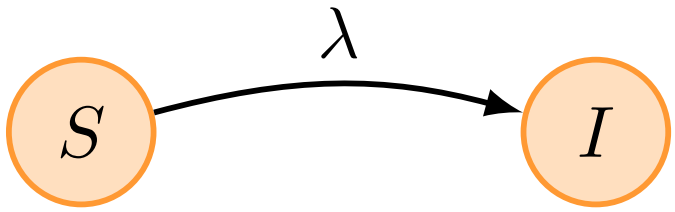

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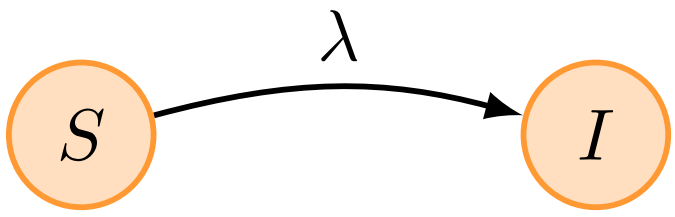
  - But: sometimes it is a good model

Writing the SI model as differential equations



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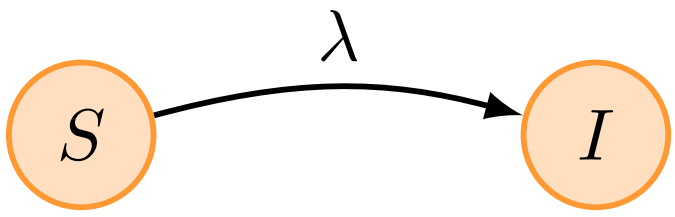

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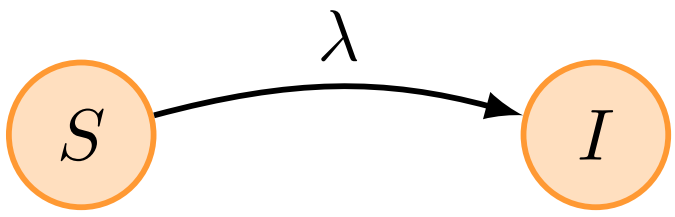

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- How does the number of people susceptible and infectious change over time?

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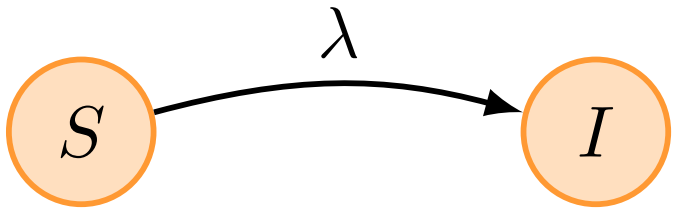

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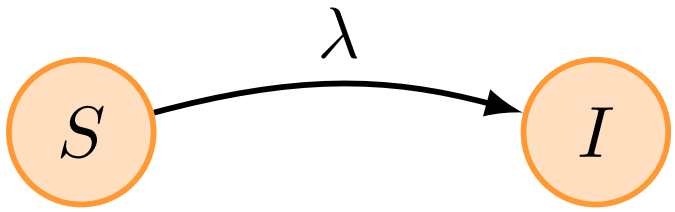

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$$dI/dt = +\lambda S$$

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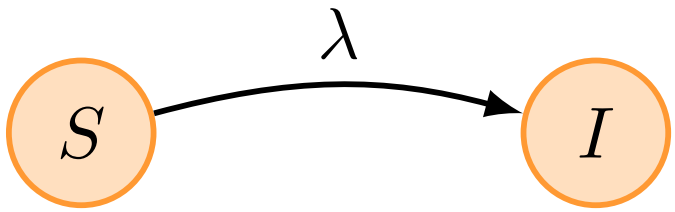

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- How does the number of people susceptible and infectious change over time?

If we replace λ as above:

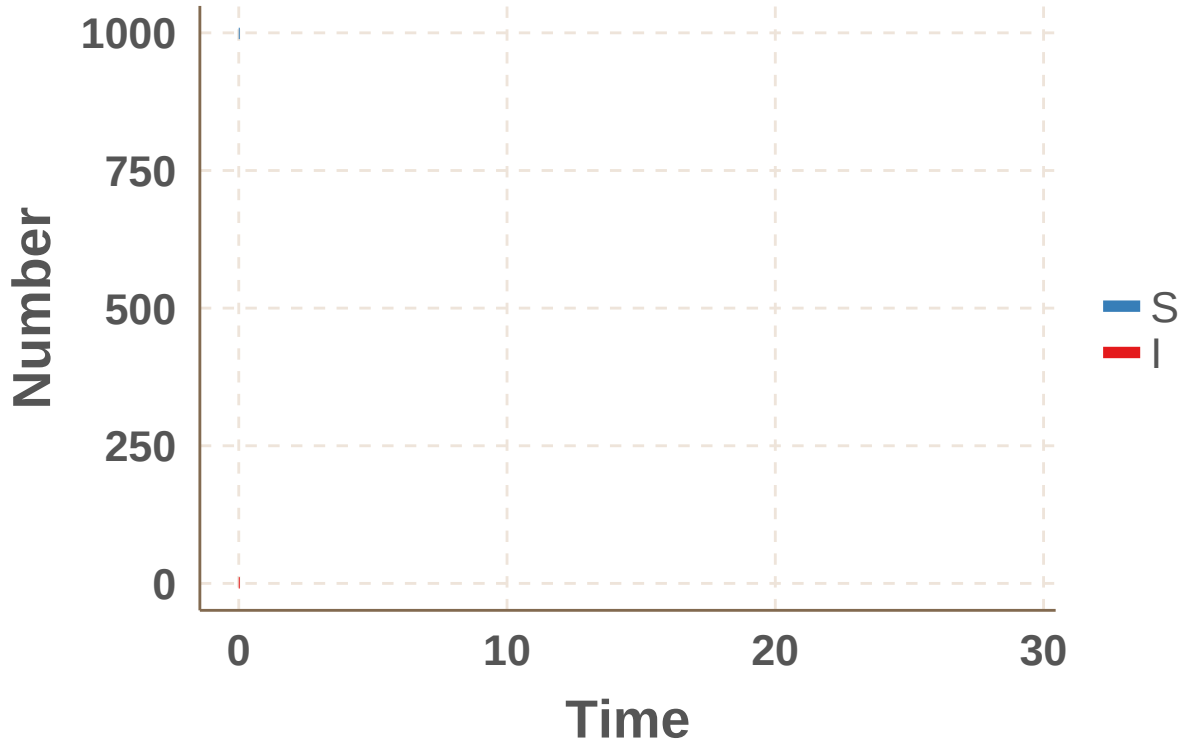
$$dS/dt = -\beta \frac{I}{N} S$$

$$dI/dt = +\beta \frac{I}{N} S$$

Simulating the SI model using differential equations

$$dS/dt = -\beta \frac{I}{N} S$$

$$dI/dt = +\beta \frac{I}{N} S$$



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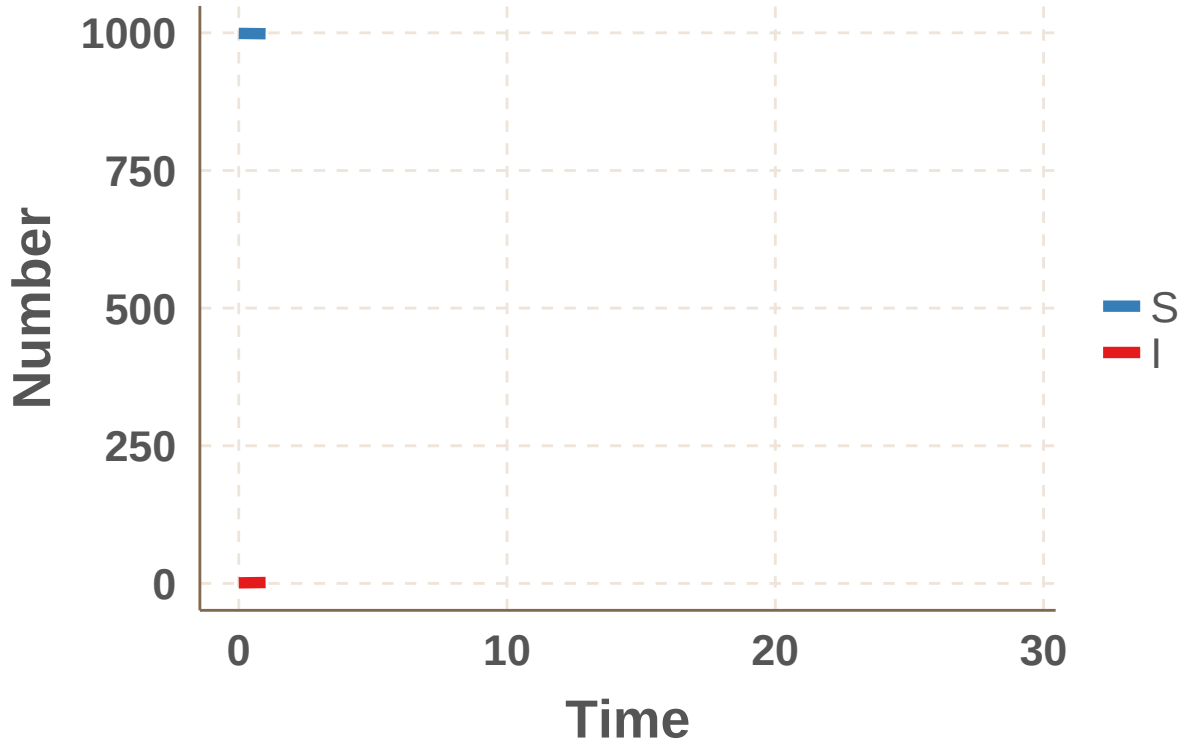

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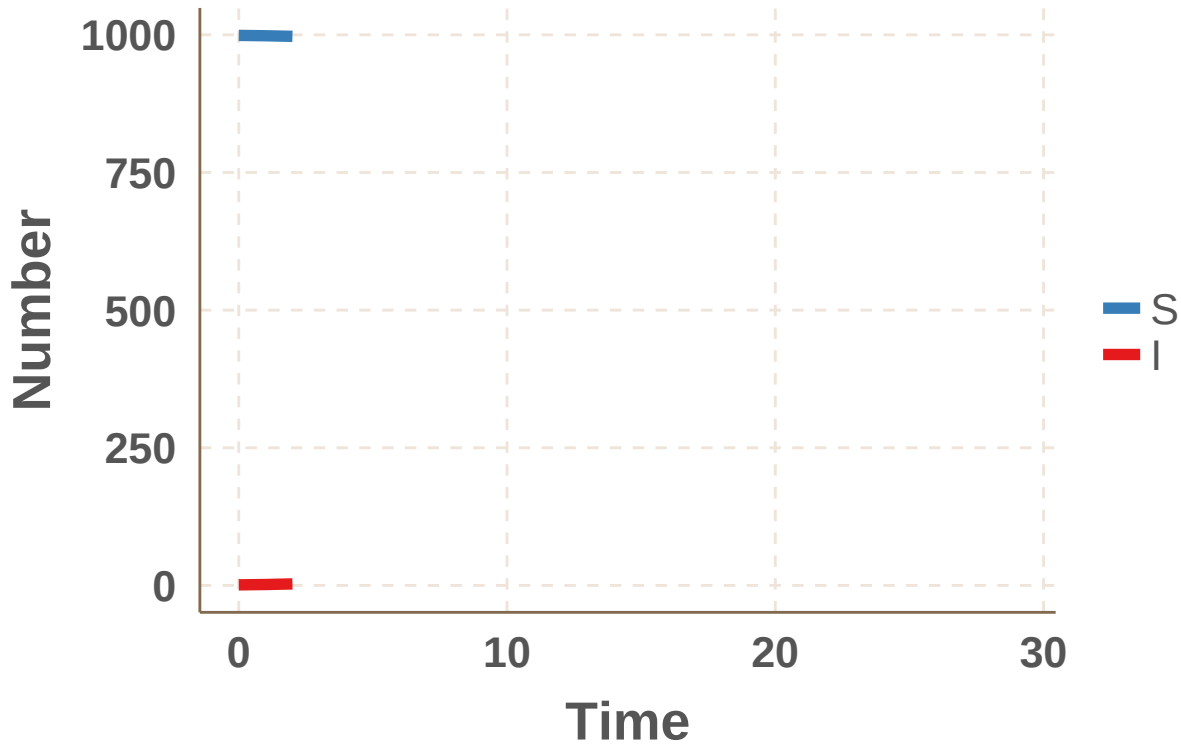

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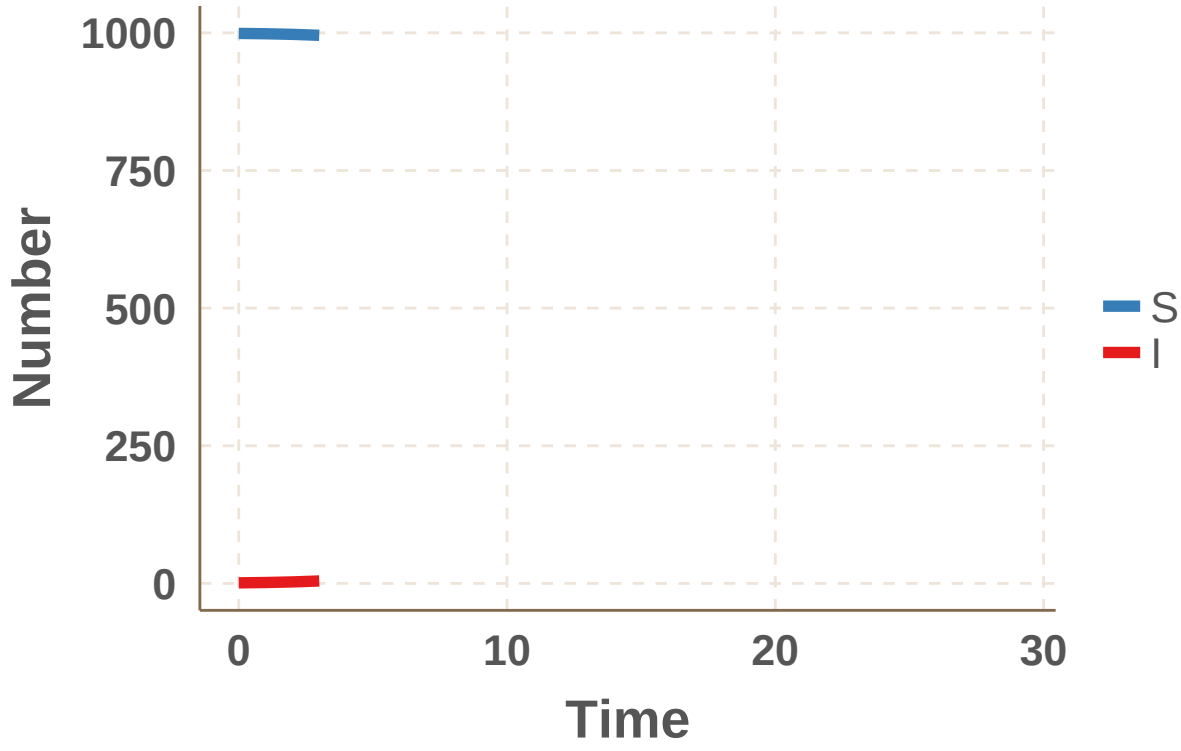

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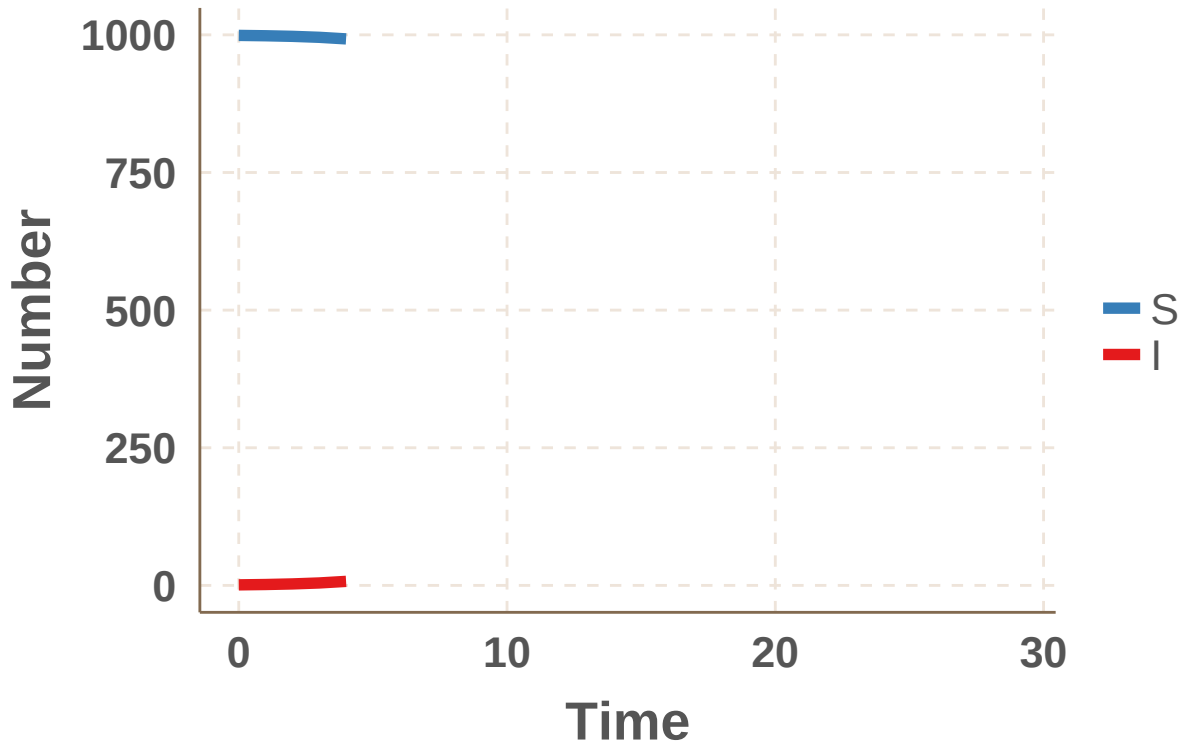

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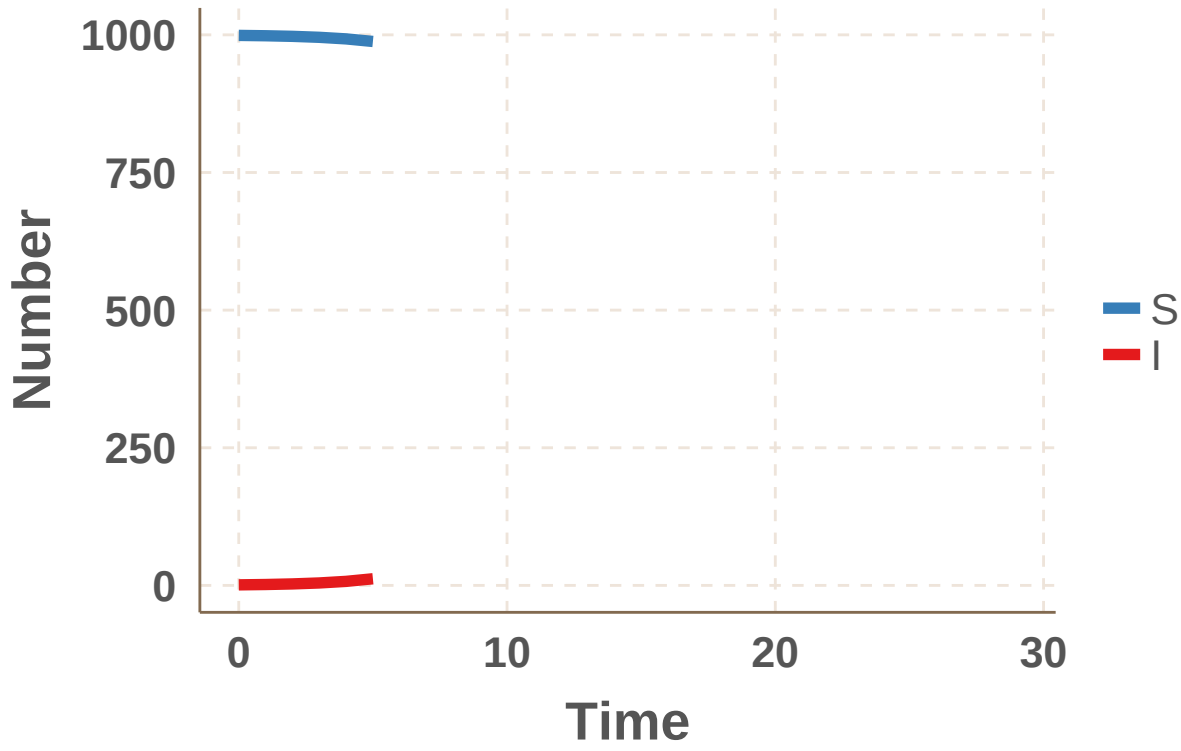

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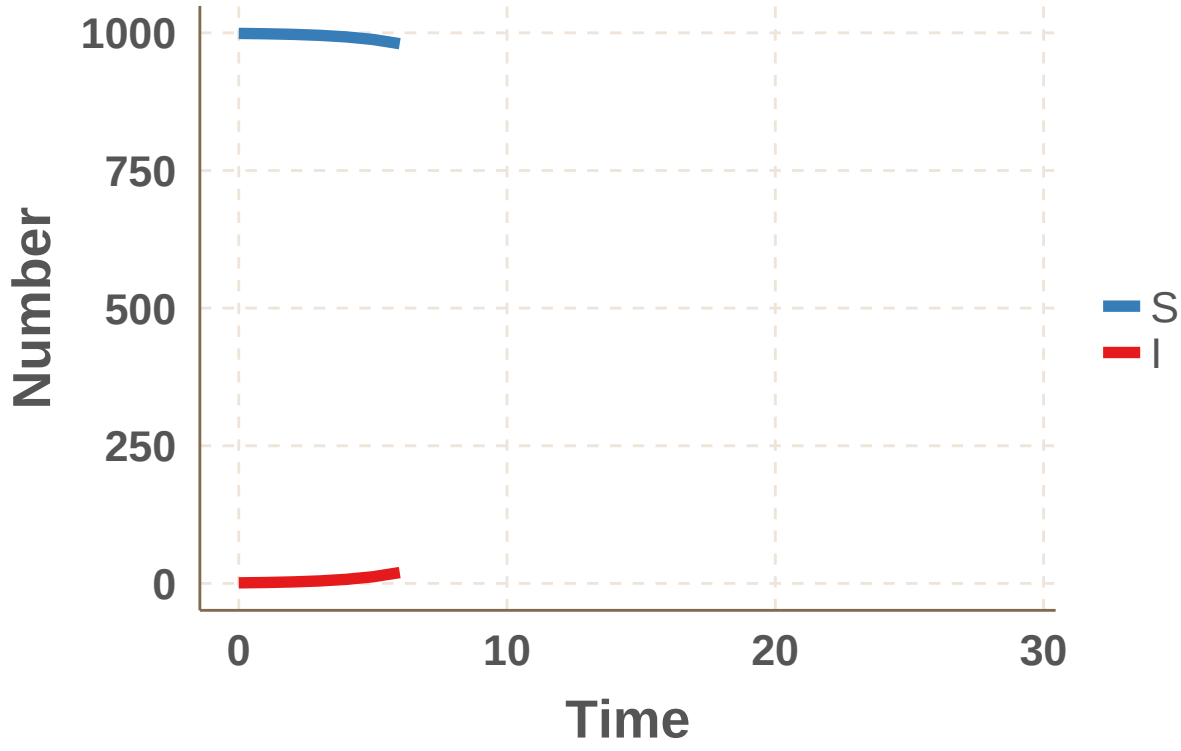

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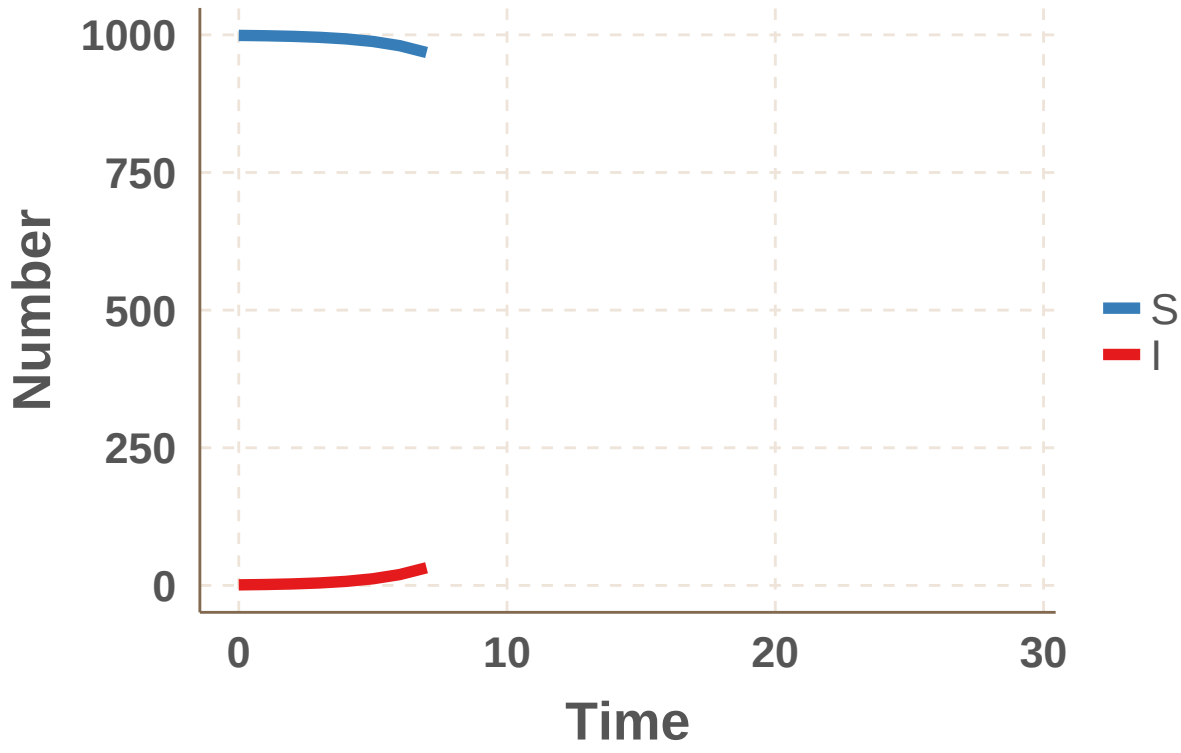

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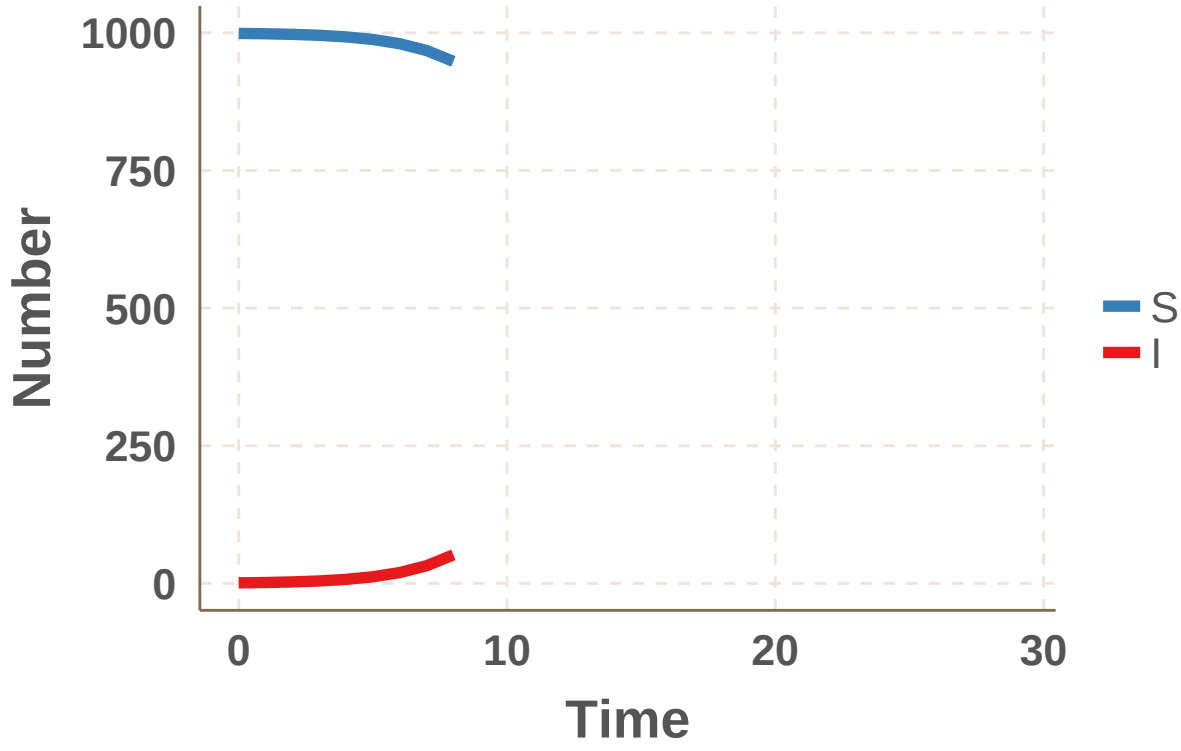

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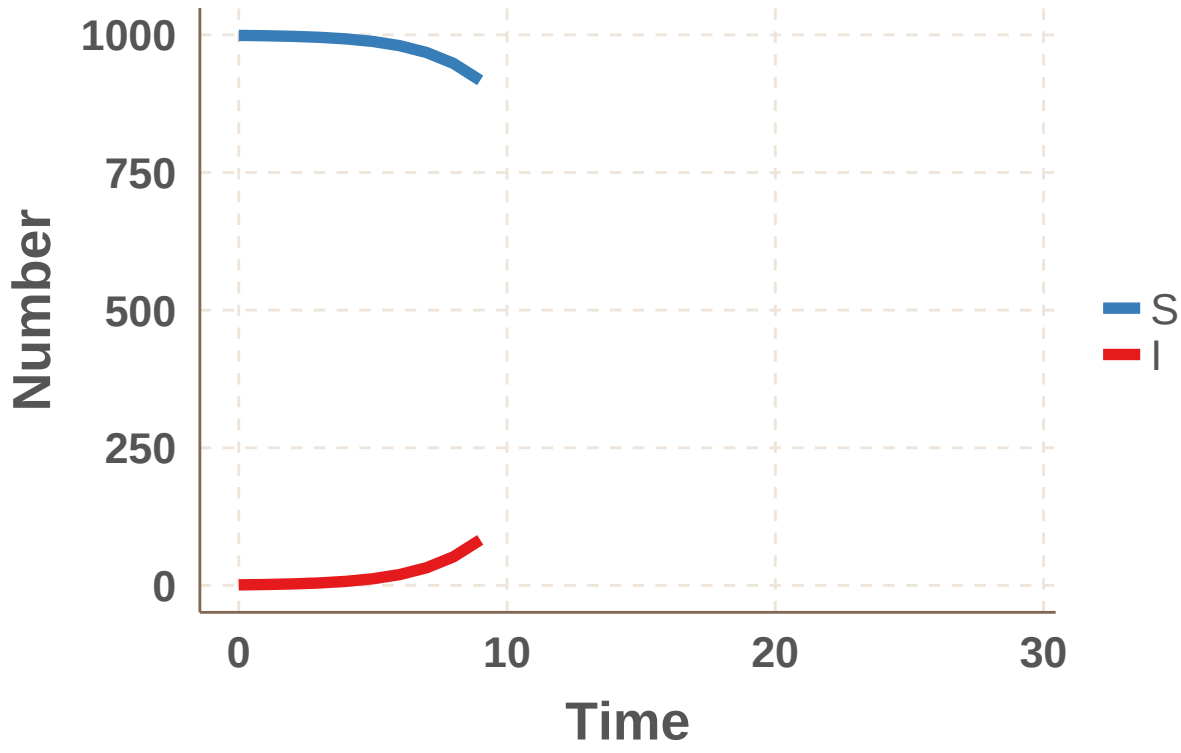

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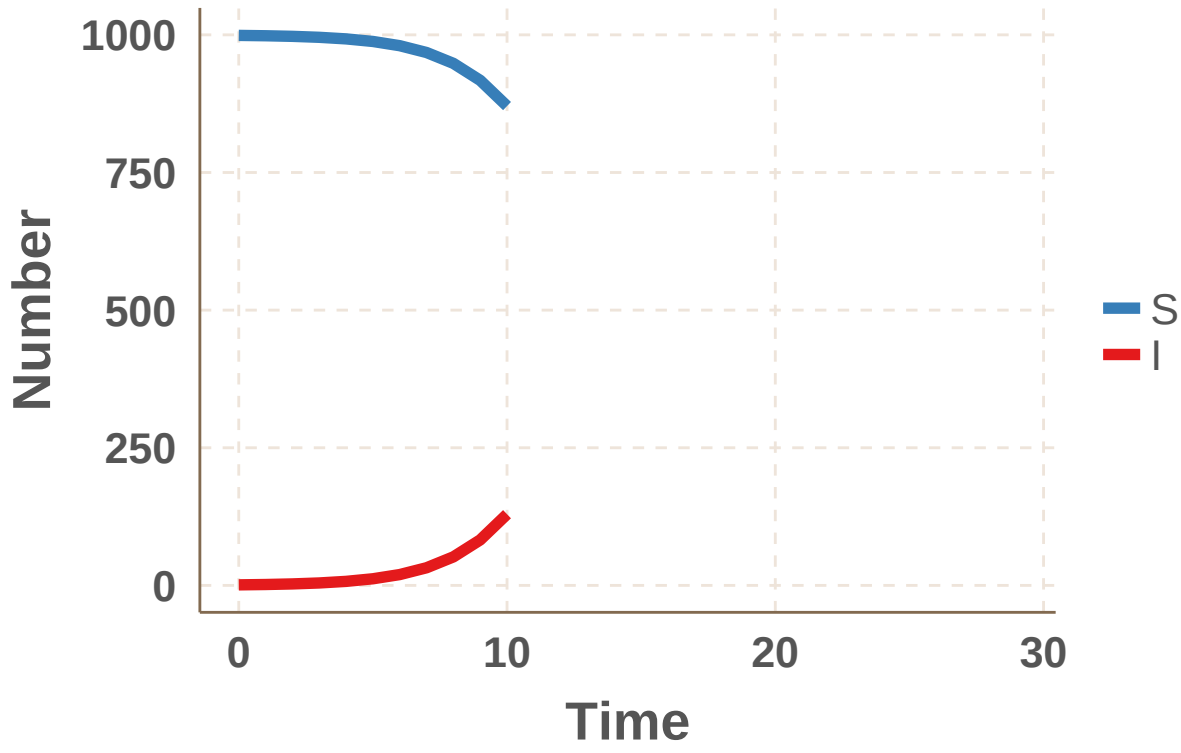

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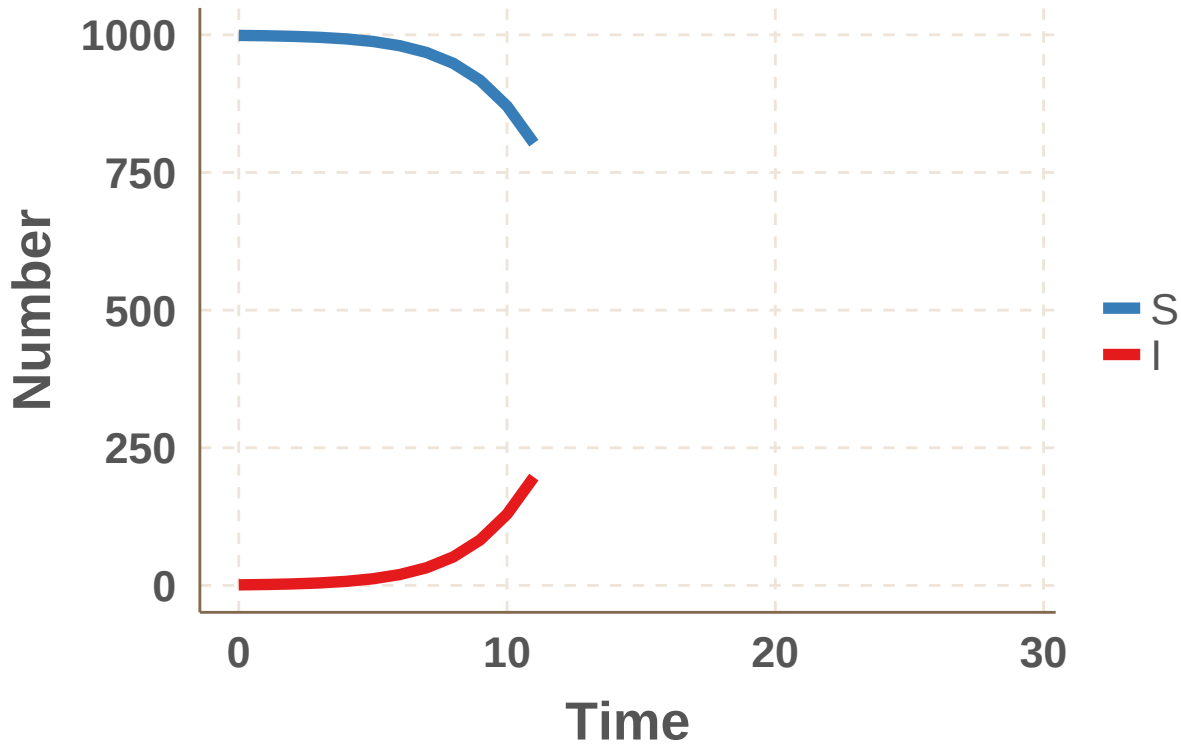

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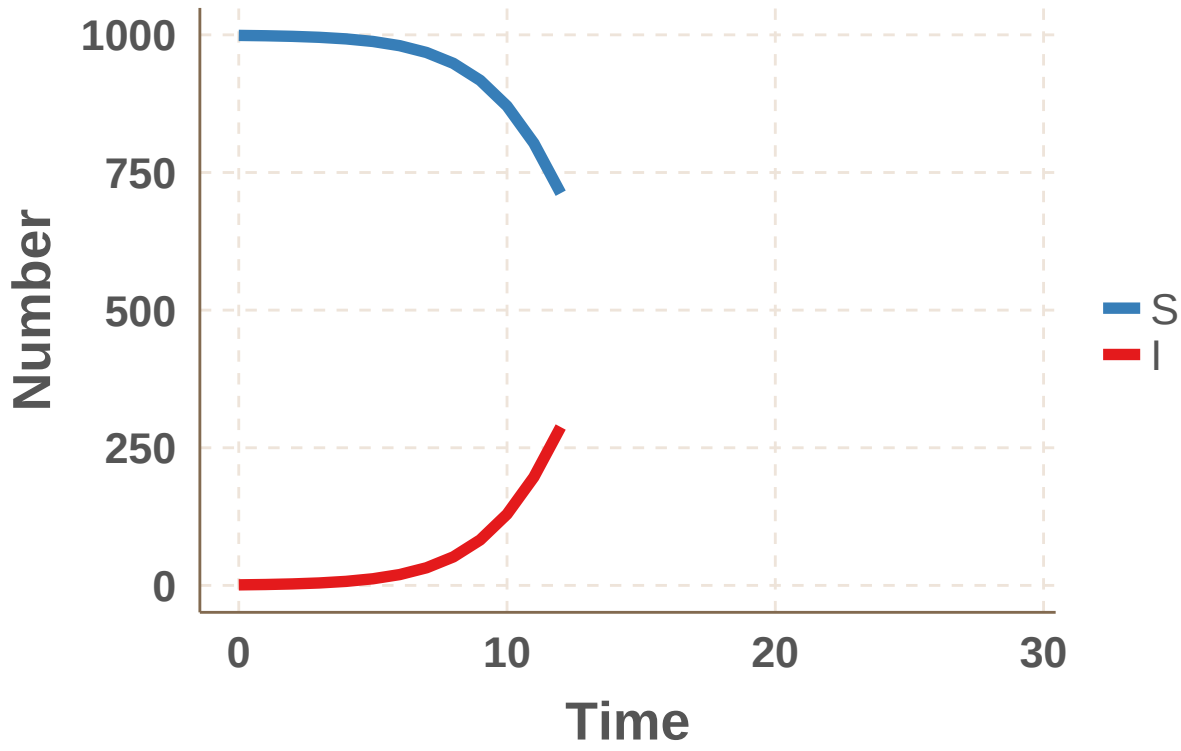

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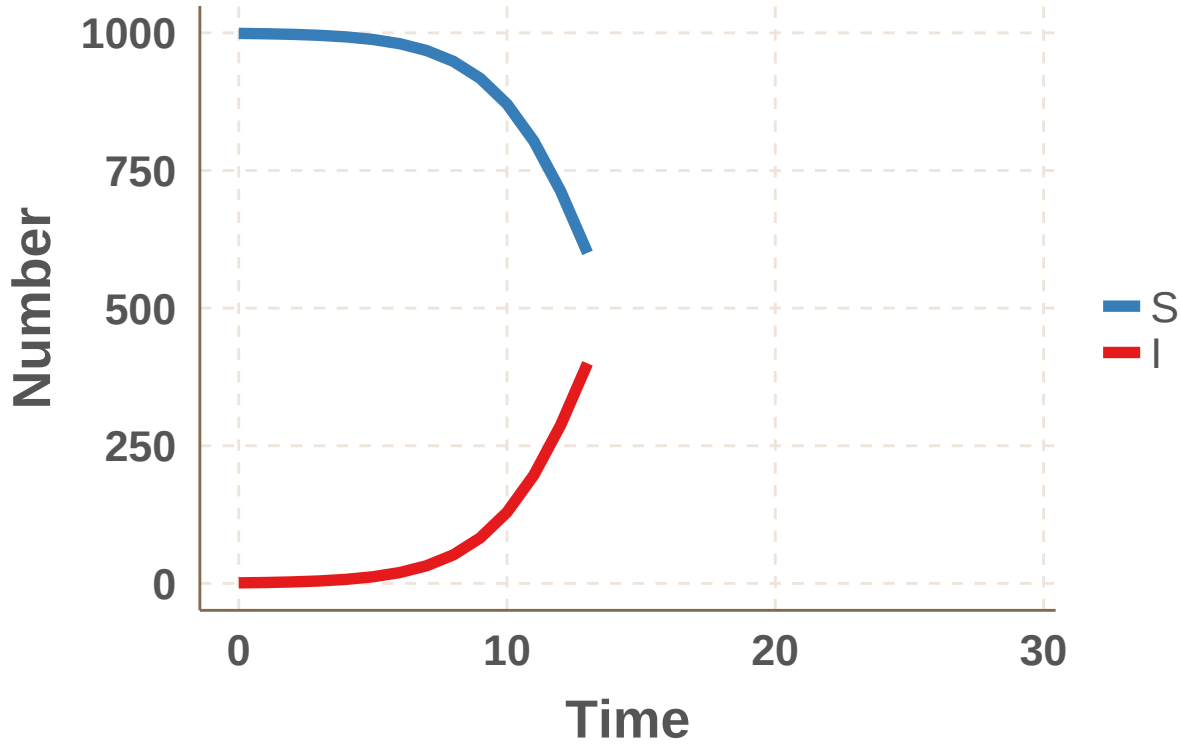

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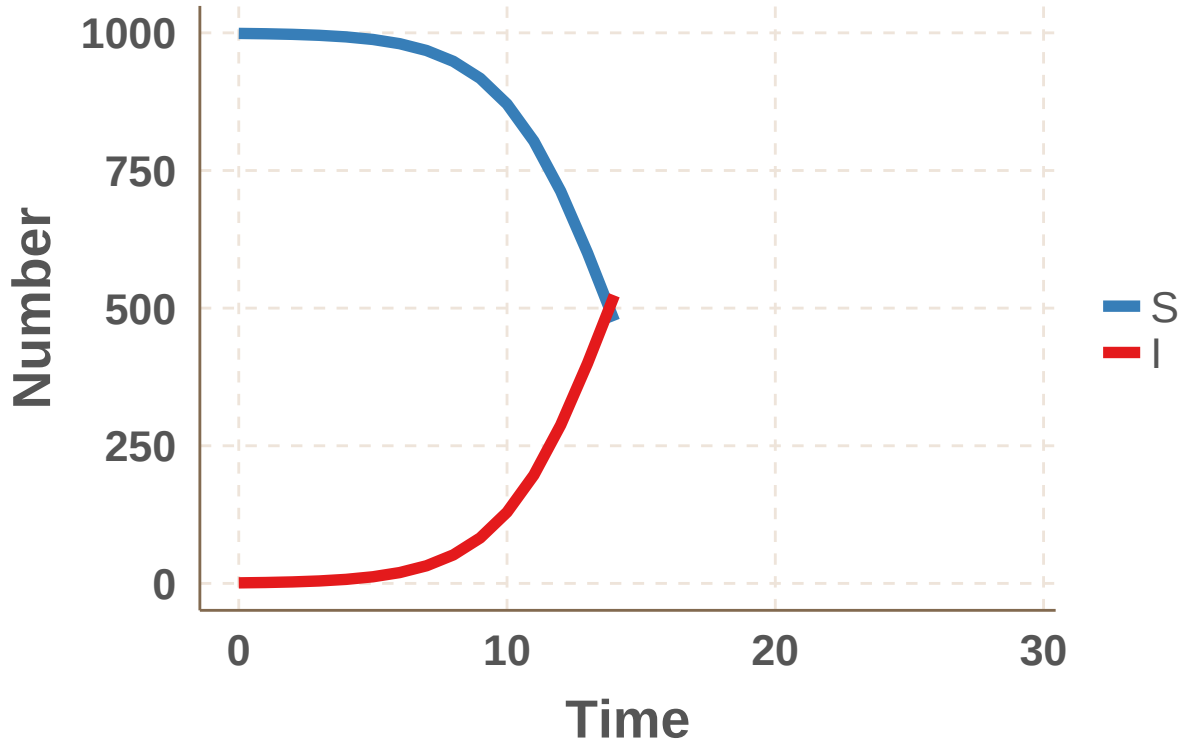

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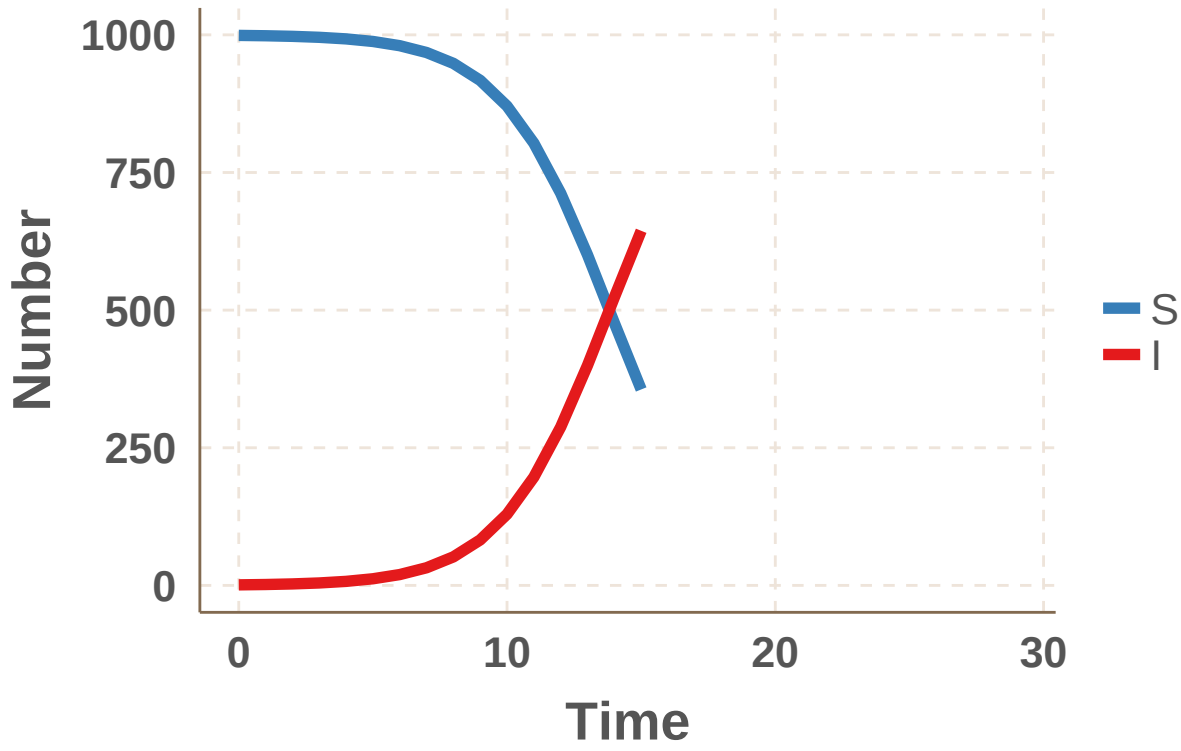

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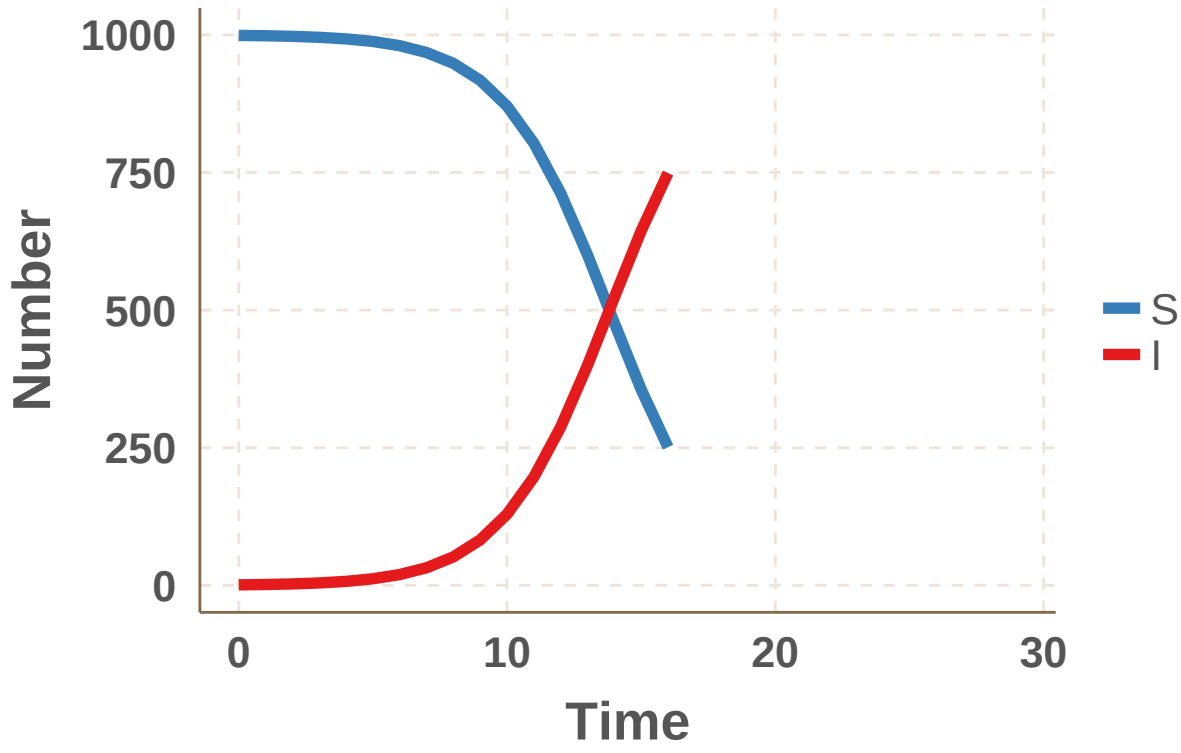

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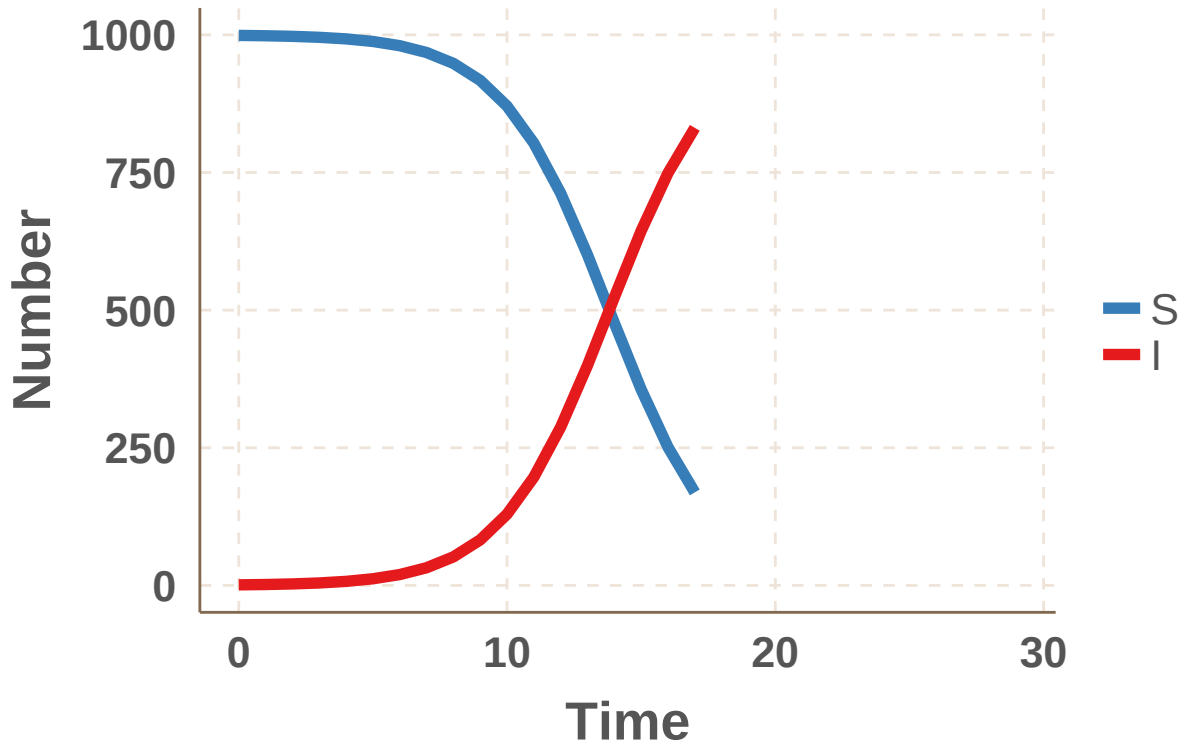

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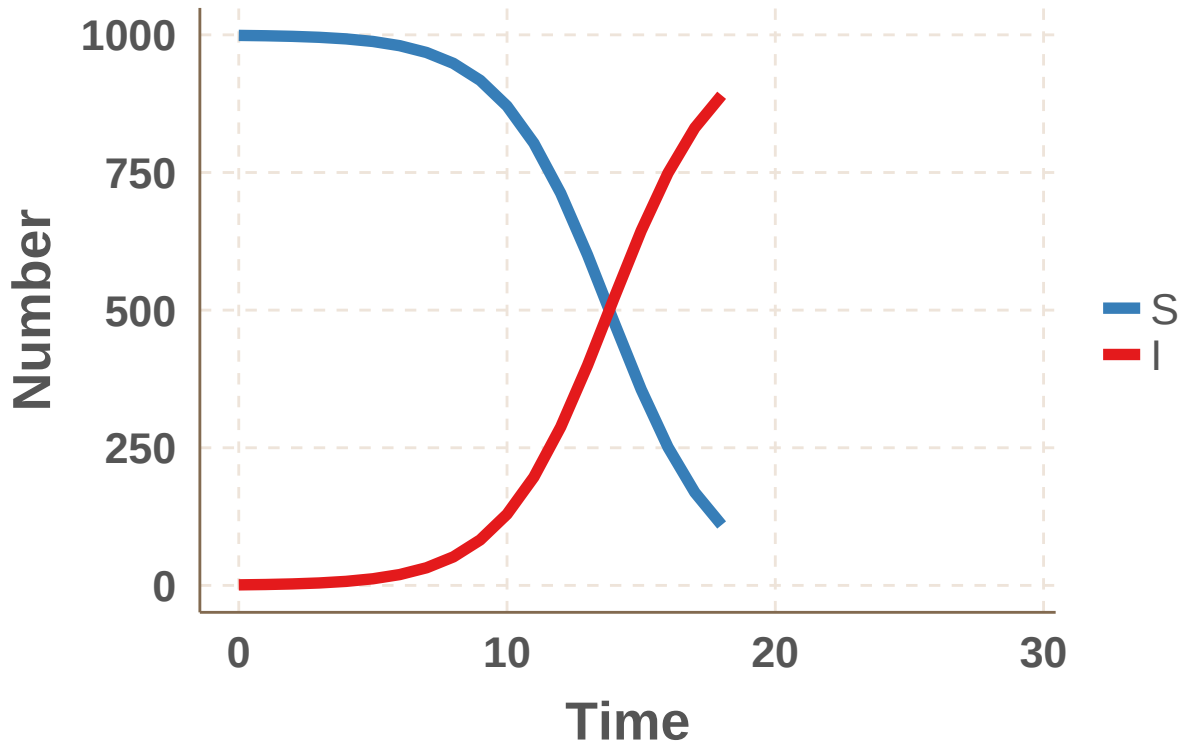

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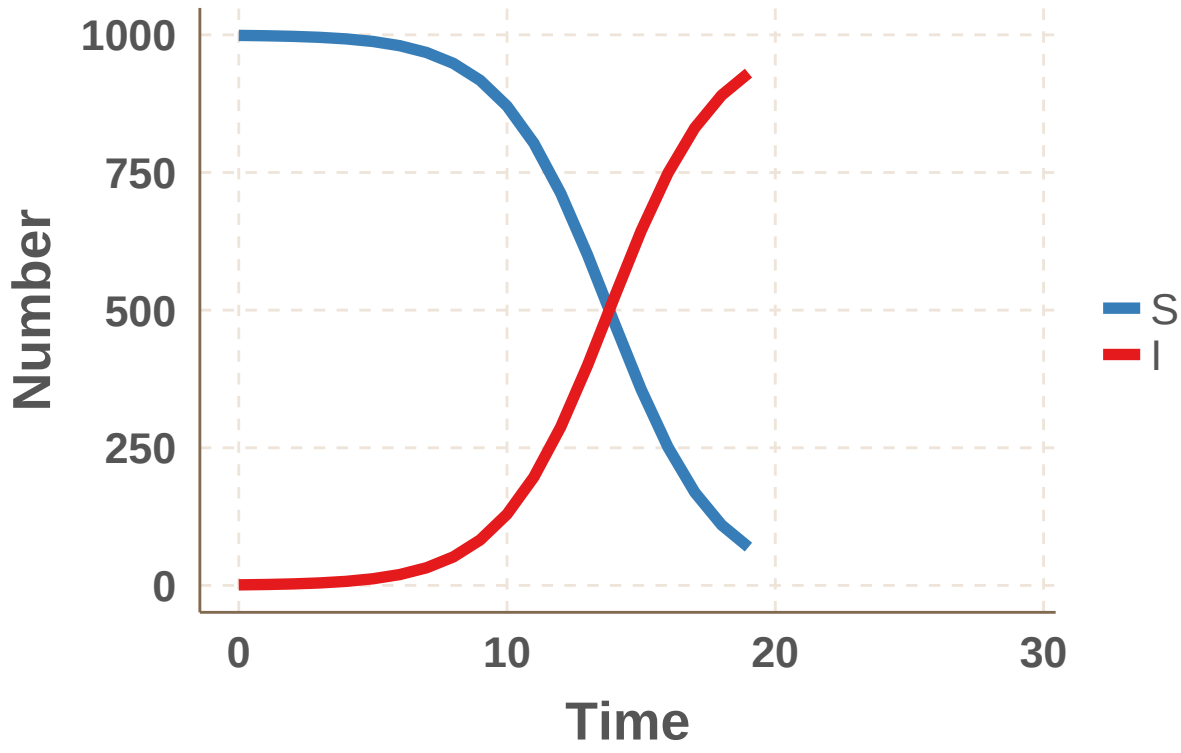

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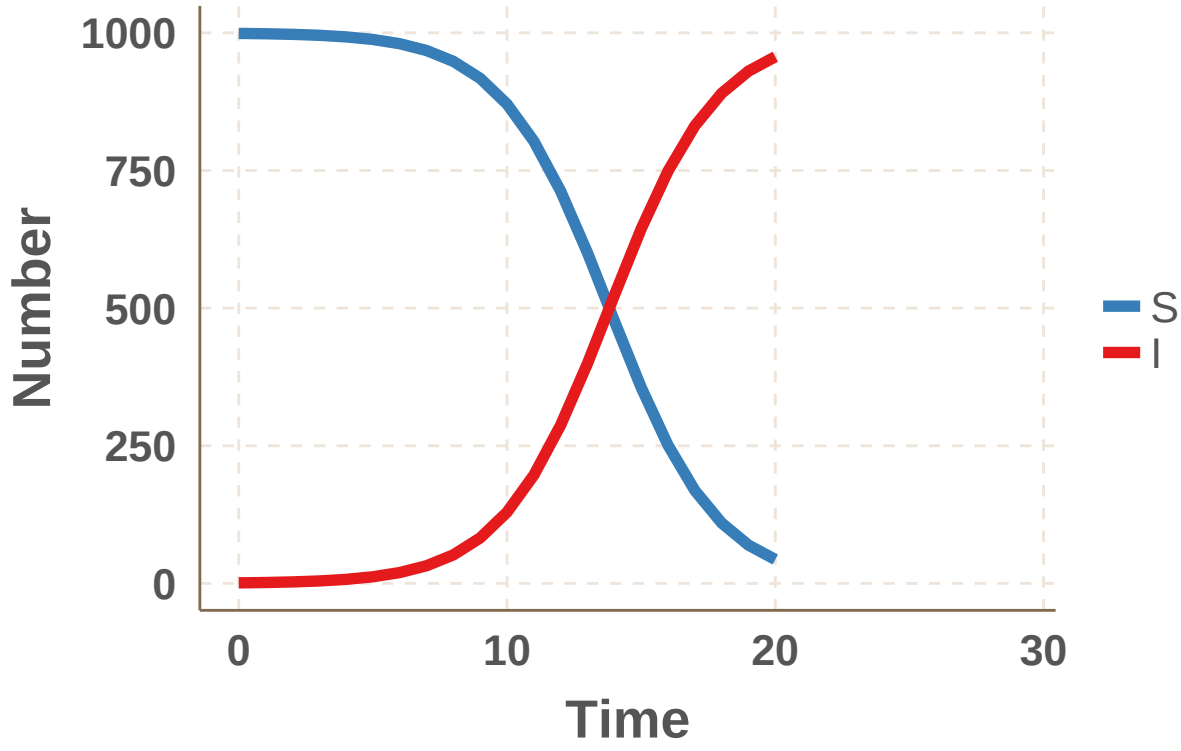

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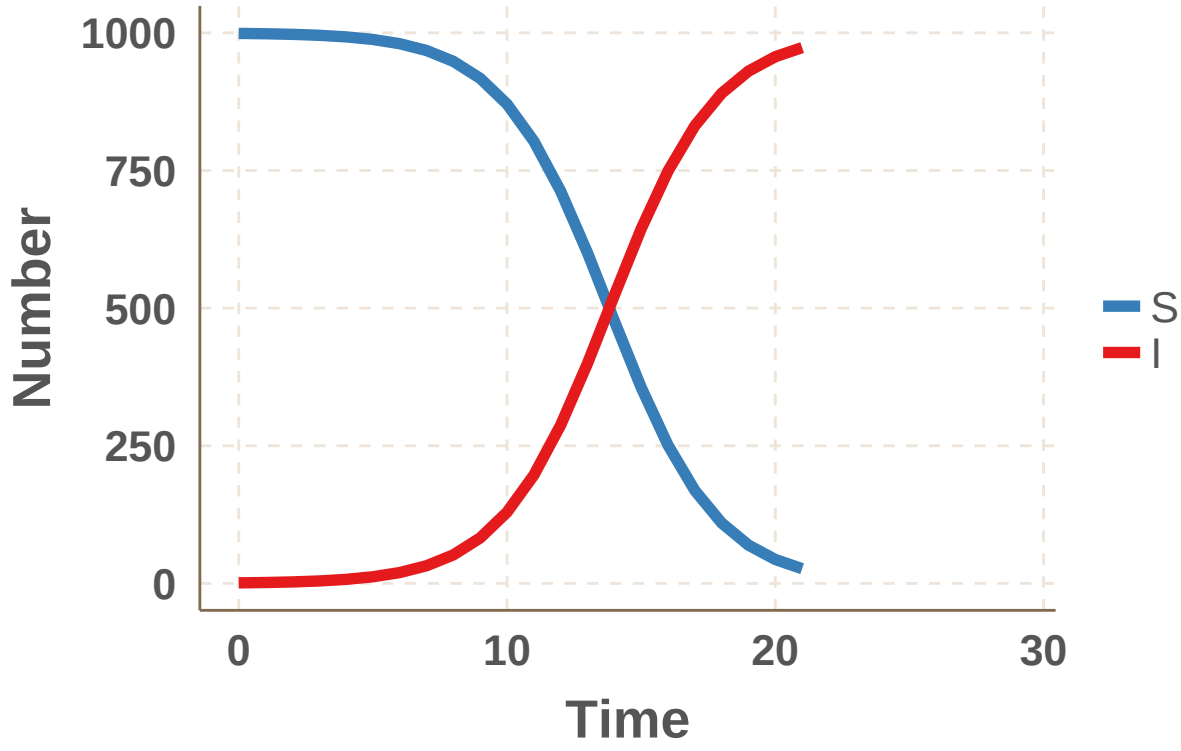

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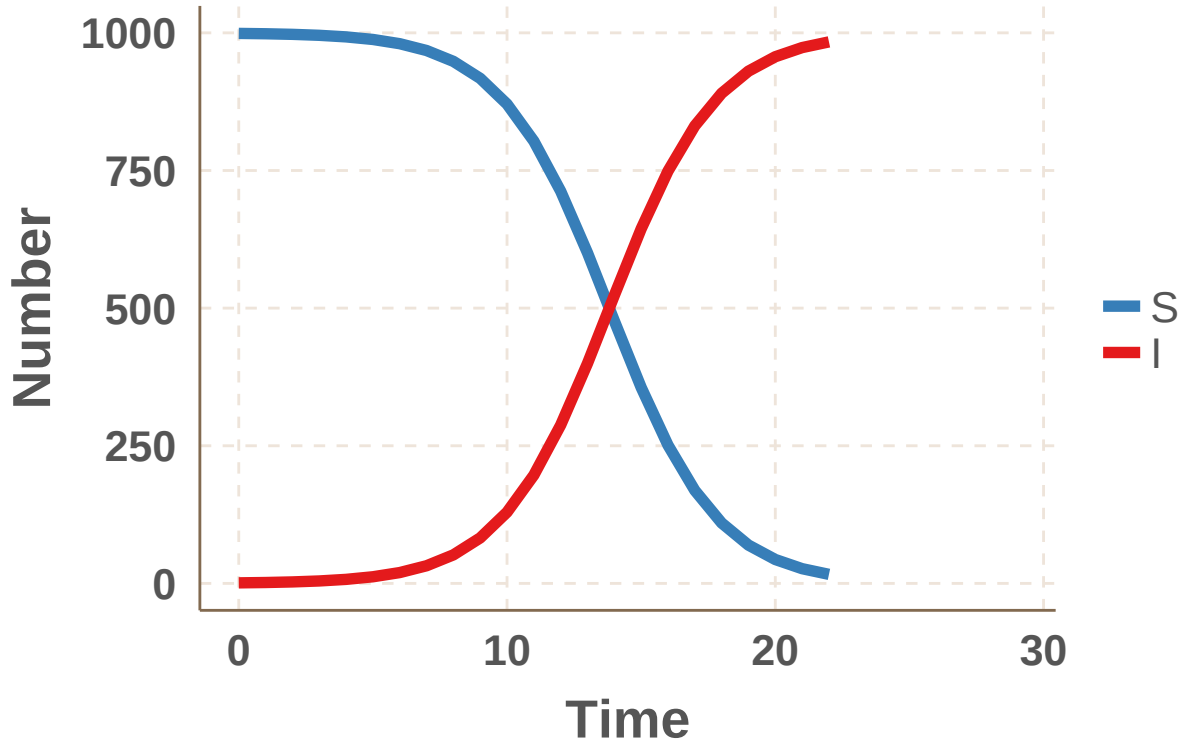

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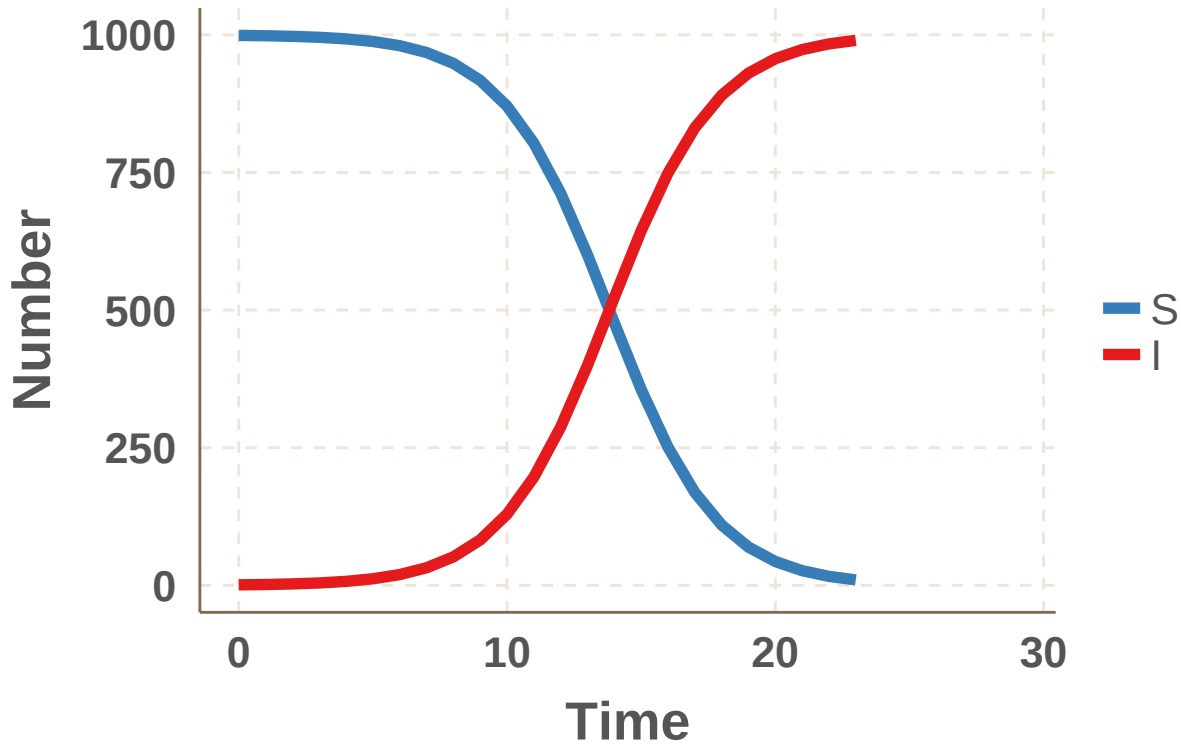

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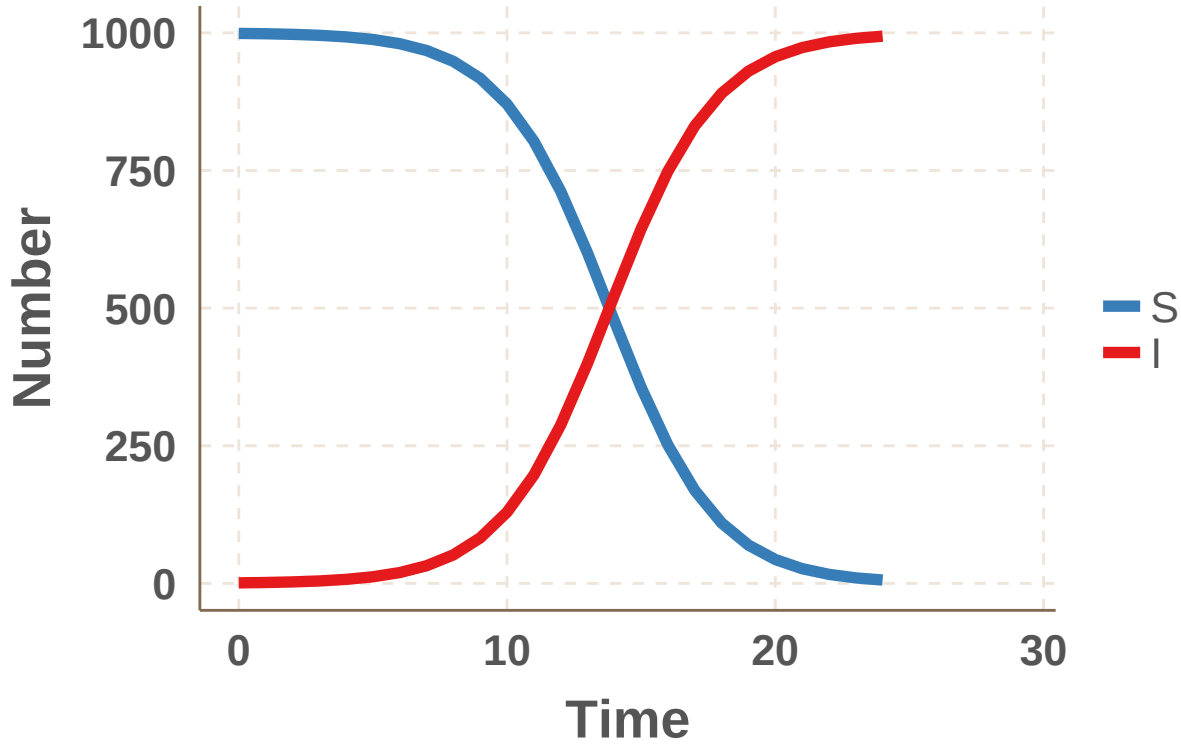

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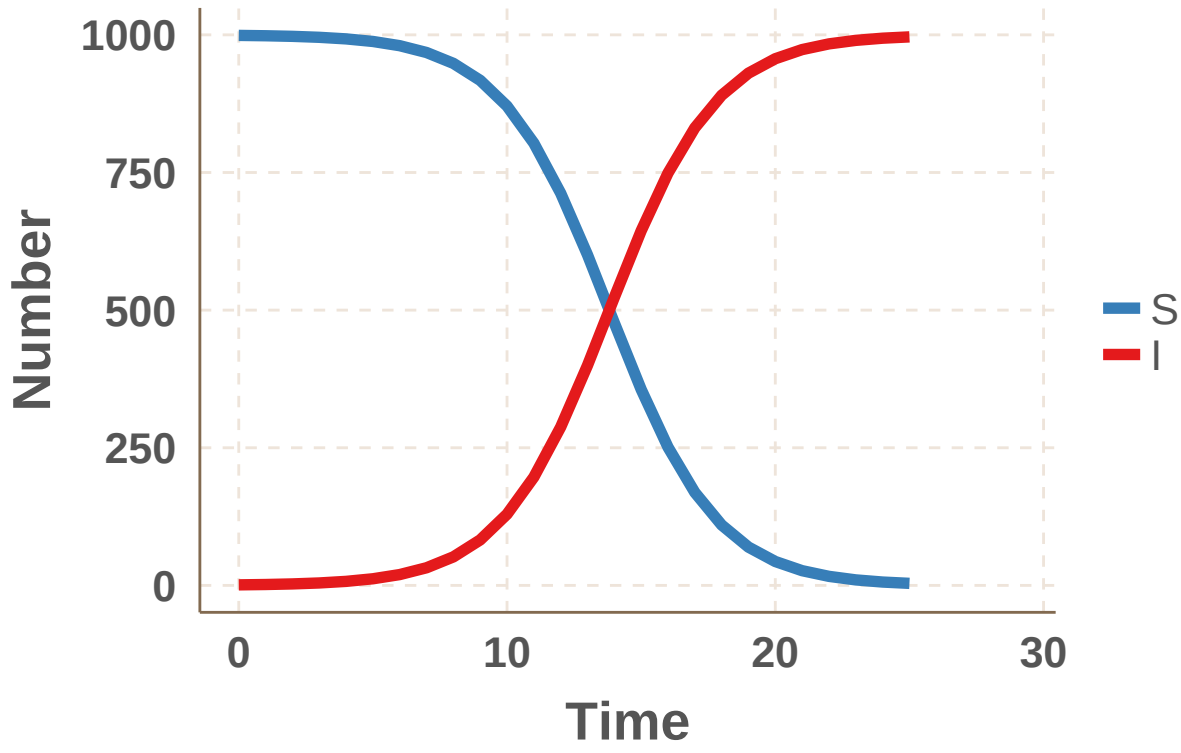

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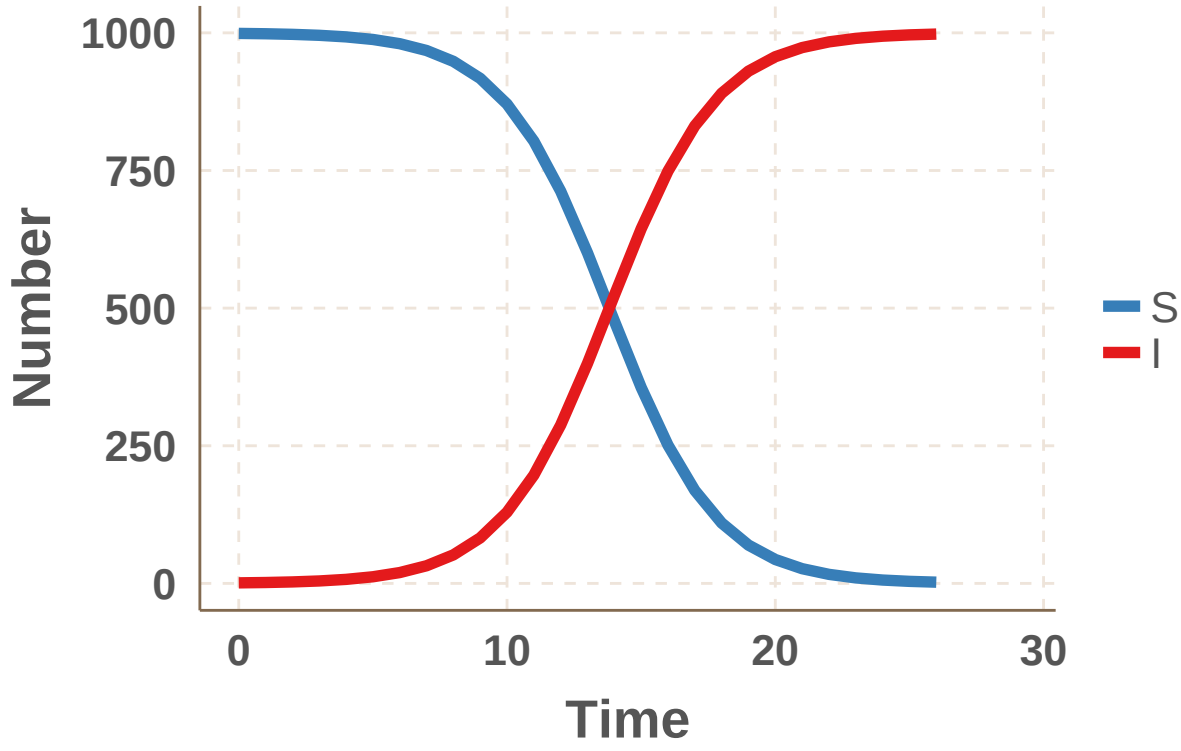

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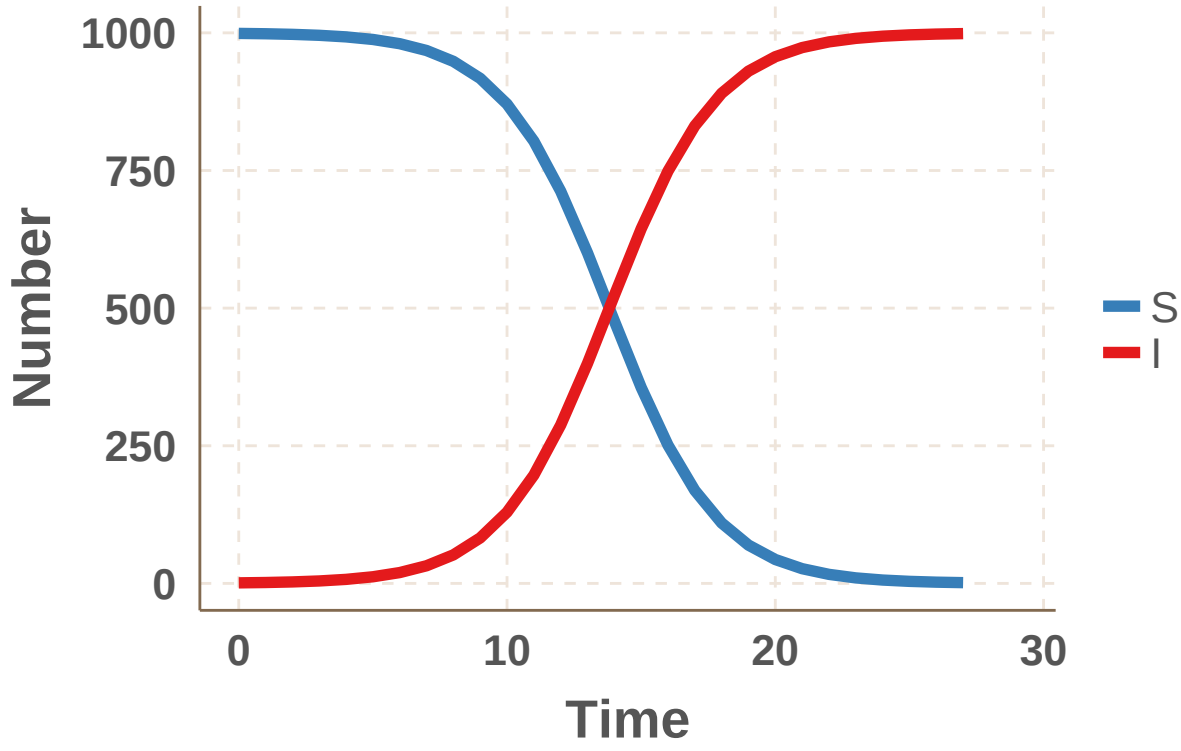

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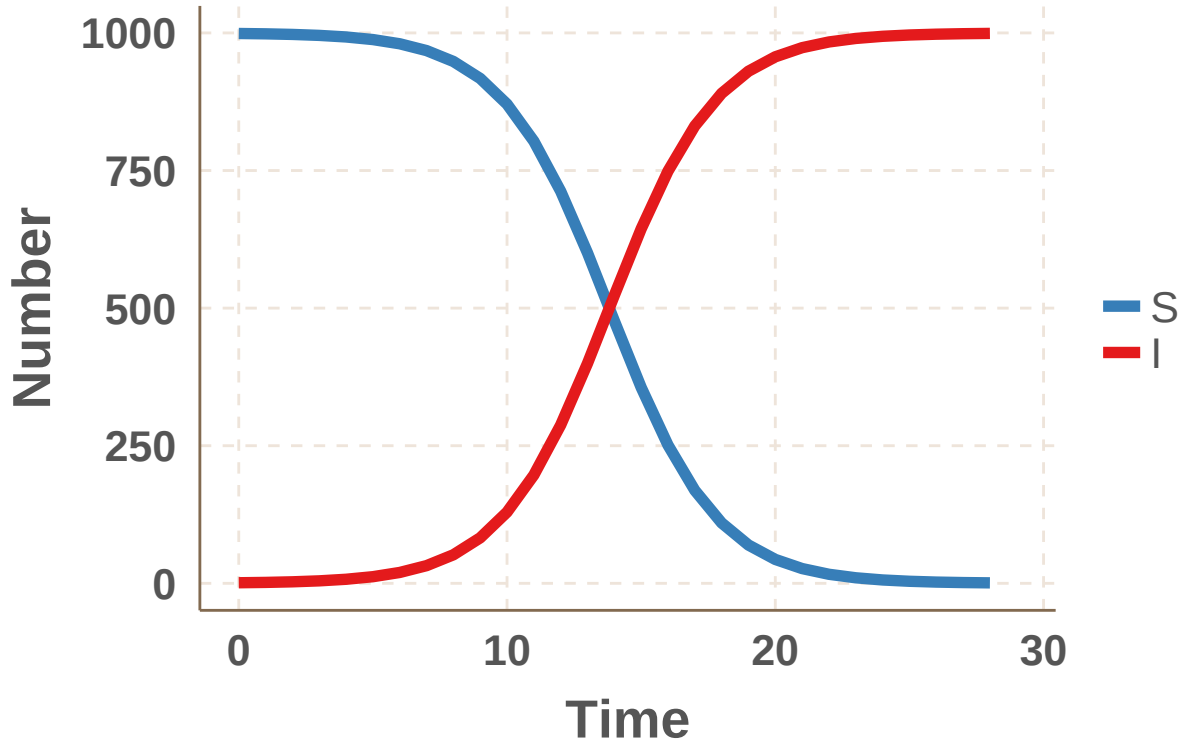

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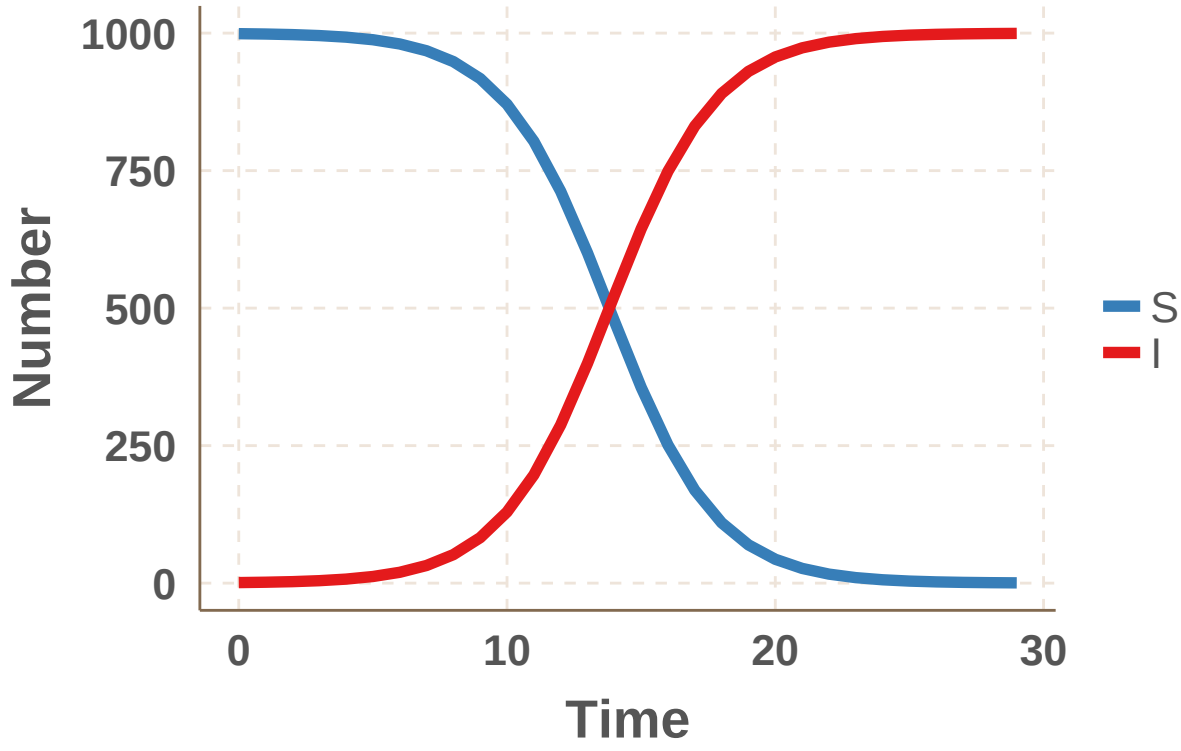

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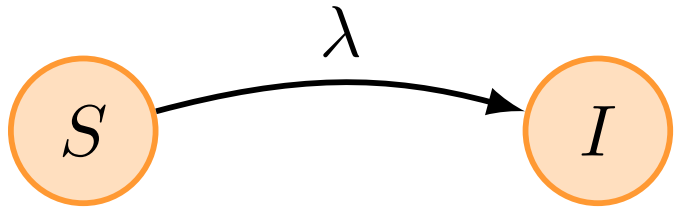

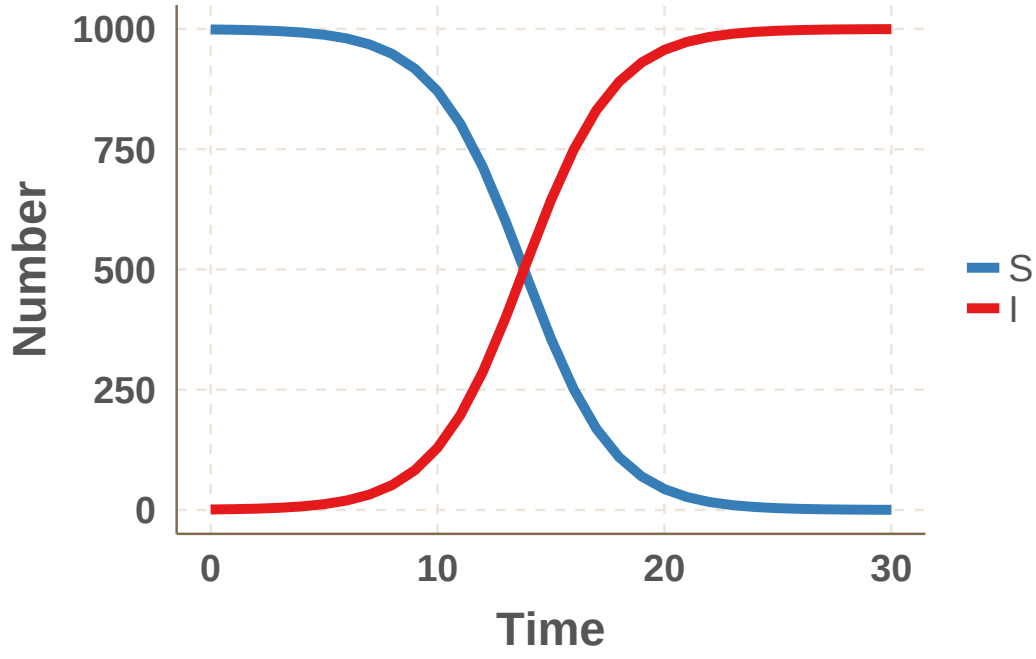

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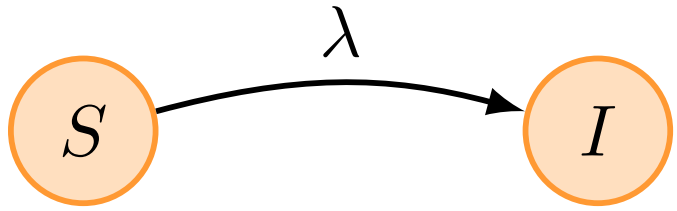

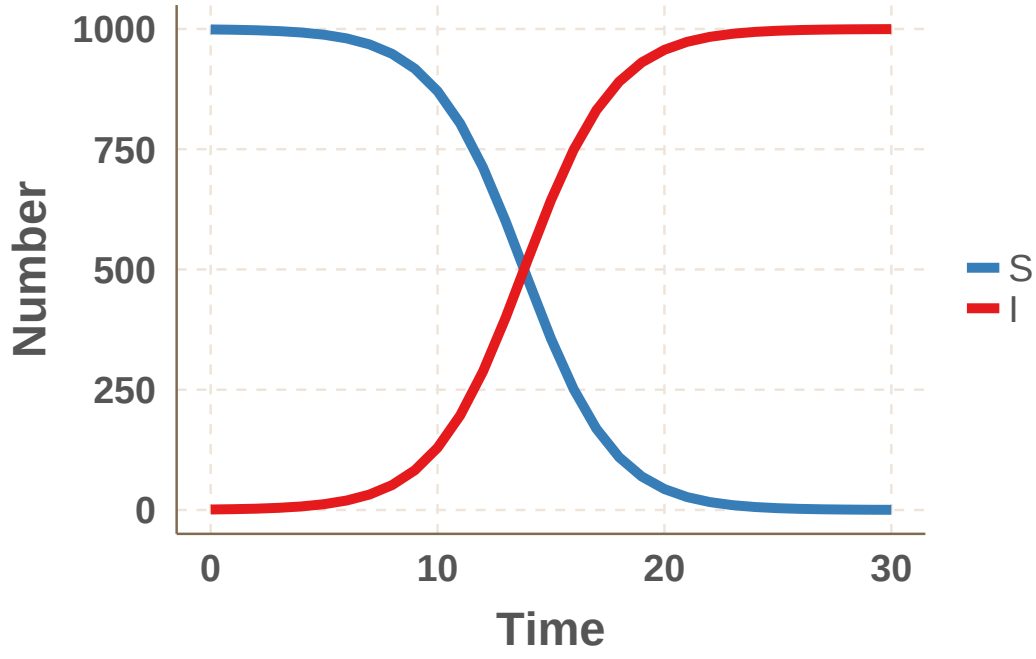

- Everyone in the population eventually gets infected

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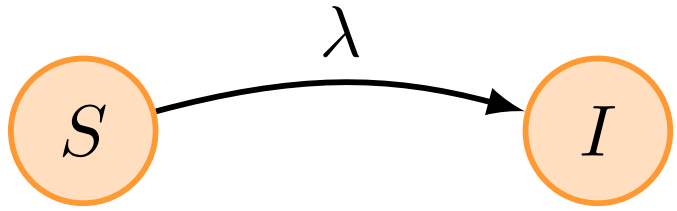

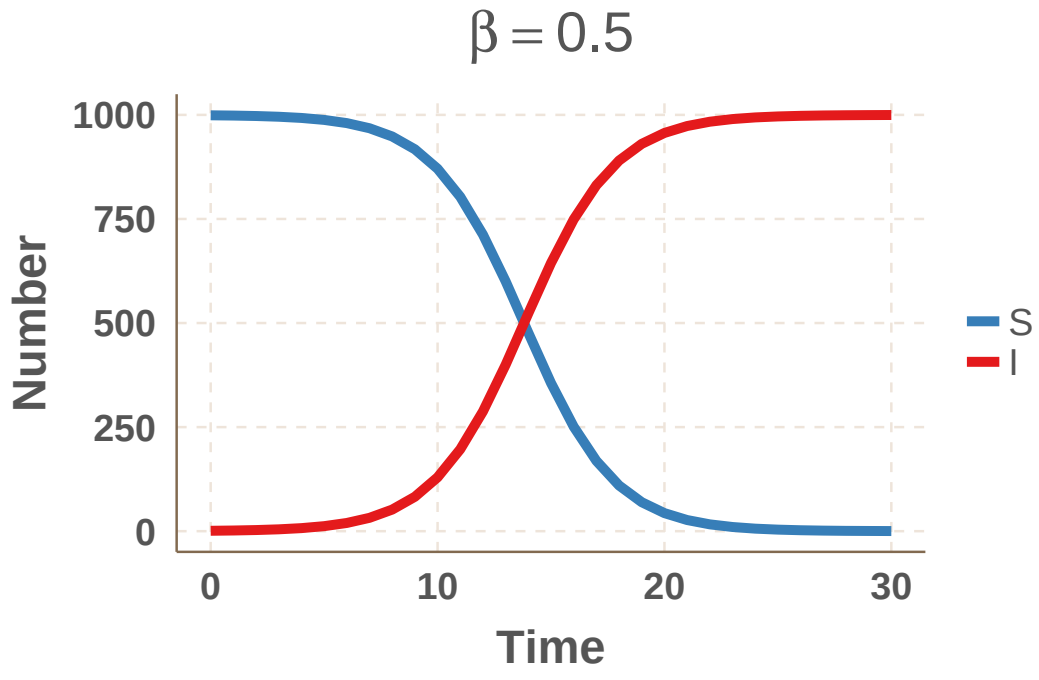

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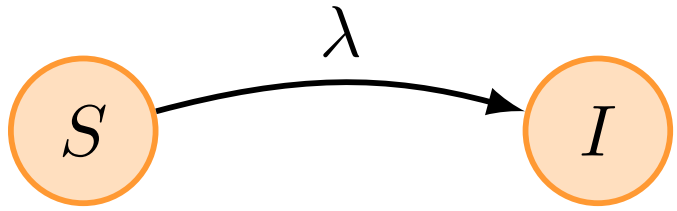

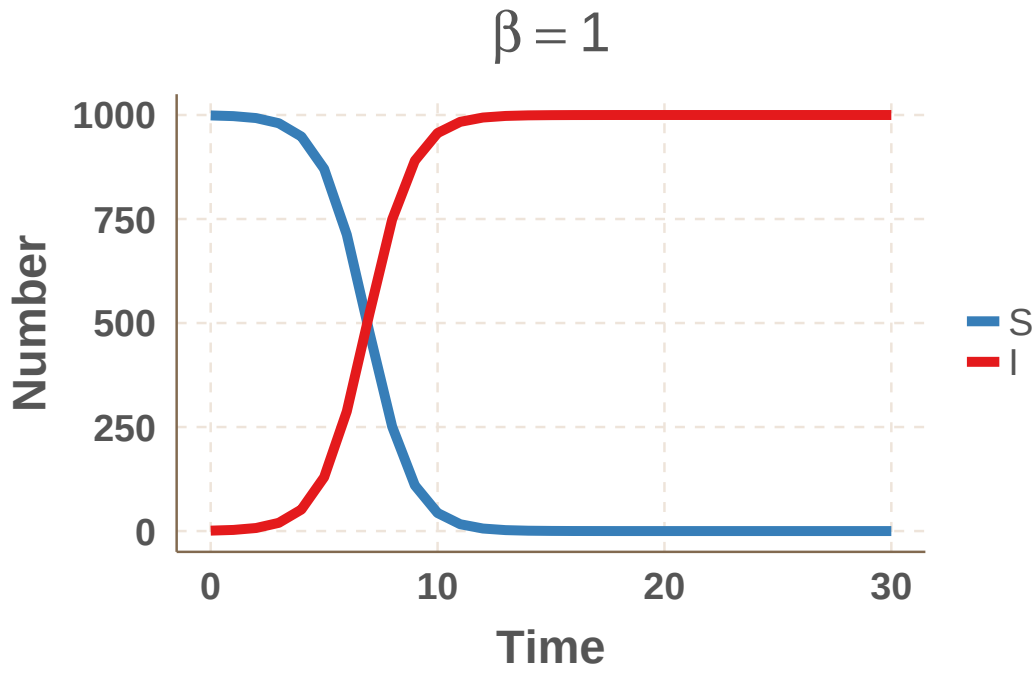

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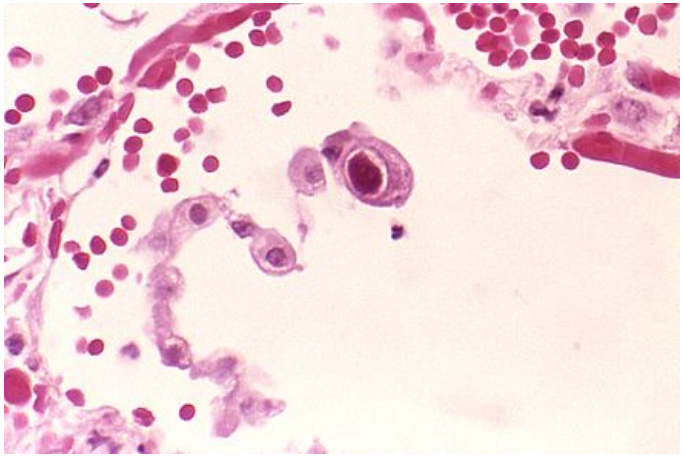

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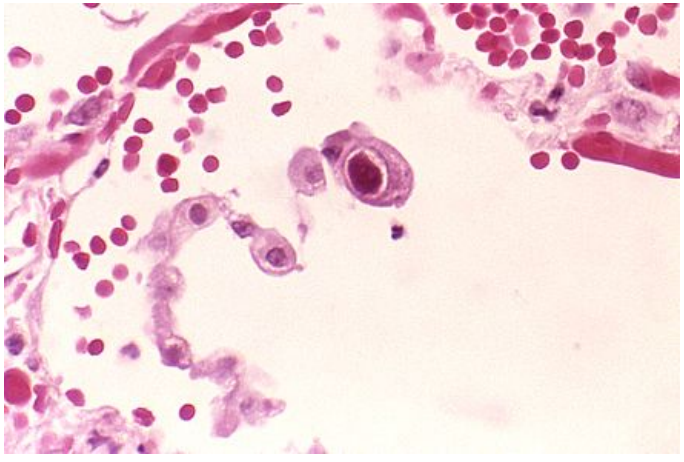

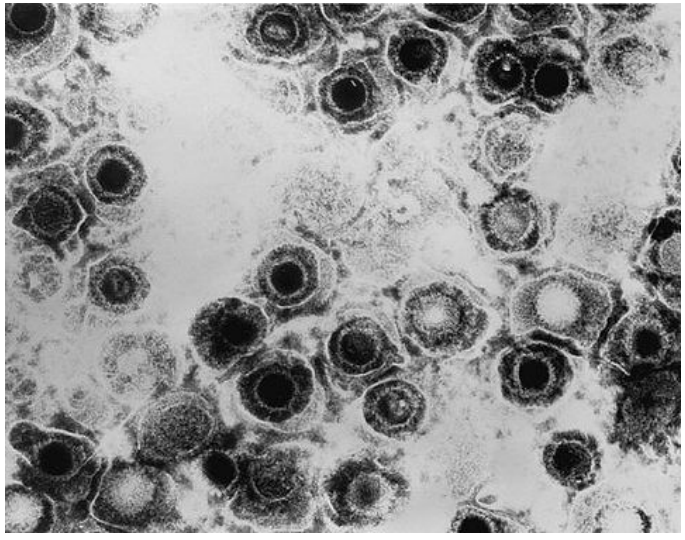

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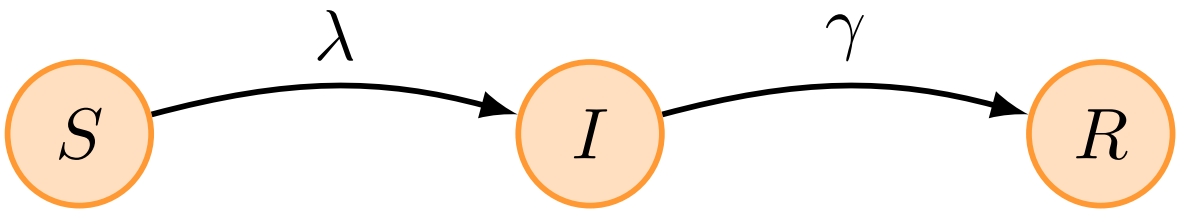
- This is not the case for most infections (e.g., influenza, measles, etc.)
- Recovery from infection usually implies (some) immunity

The SIR model



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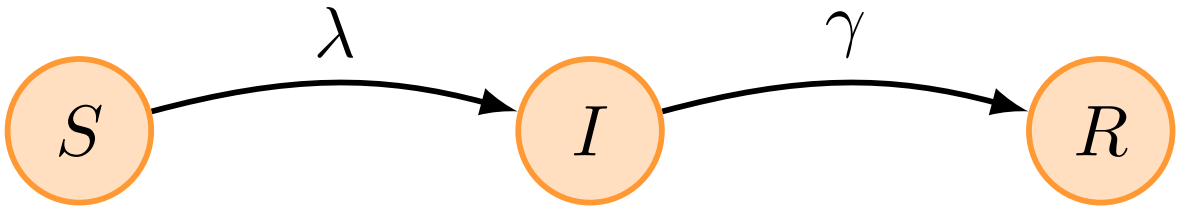
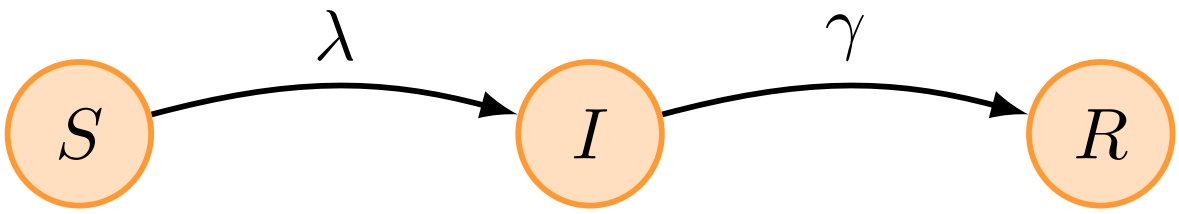


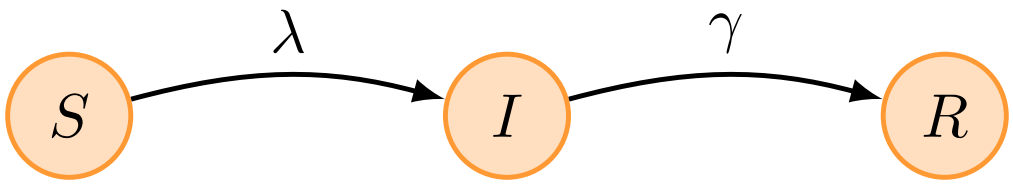
- R: Number of recovered (immune) people

The SIR model



- R: Number of recovered (immune) people
- γ: recovery rate, or the probability of recovery per day (or per week, or per year). This is the inverse of the duration of infection D: $\gamma = 1/D$

Writing the SIR model as differential equations



$$\lambda = \beta \frac{I}{N}$$

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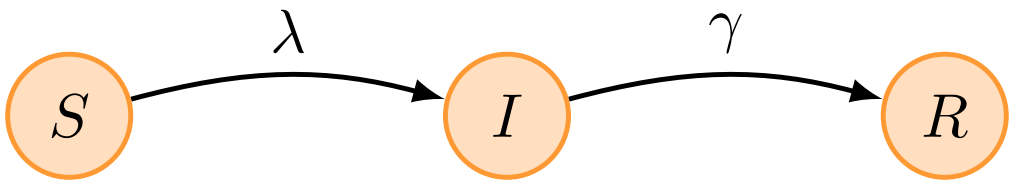

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- S: Number of people susceptible

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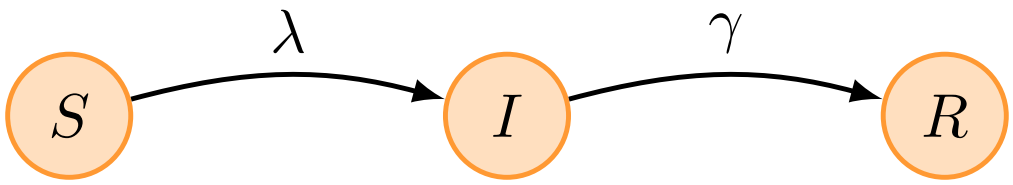

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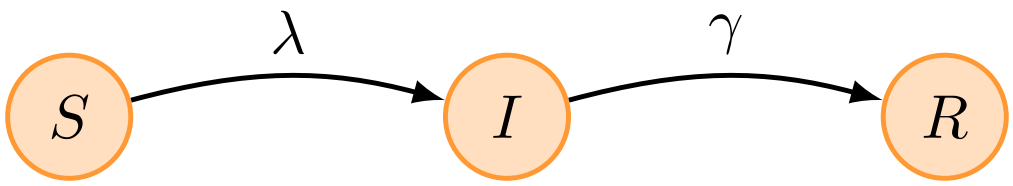

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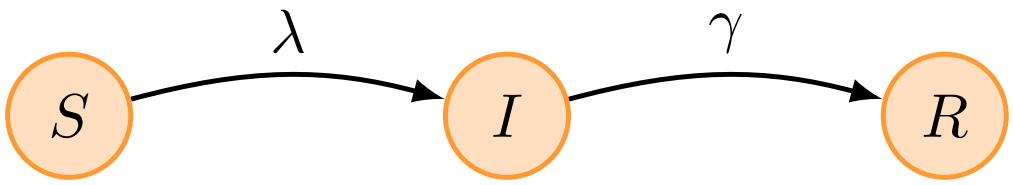

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- How does the number of people susceptible, infectious and recovered change over time?

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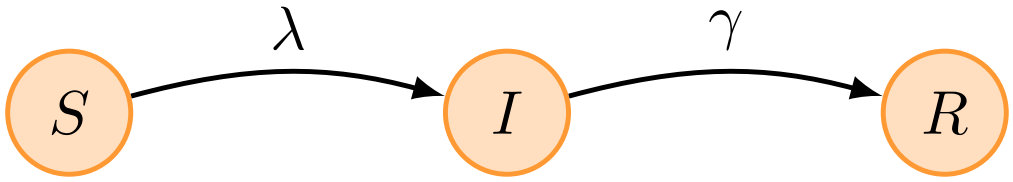

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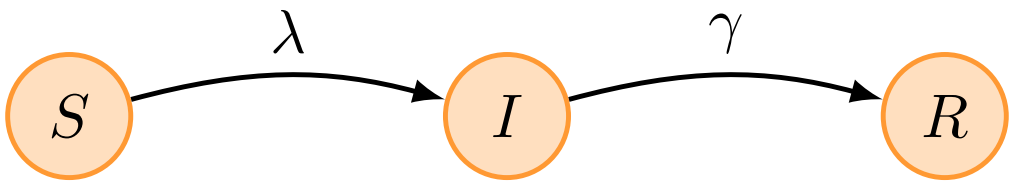

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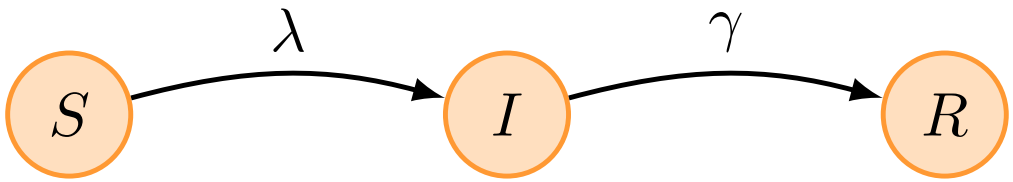

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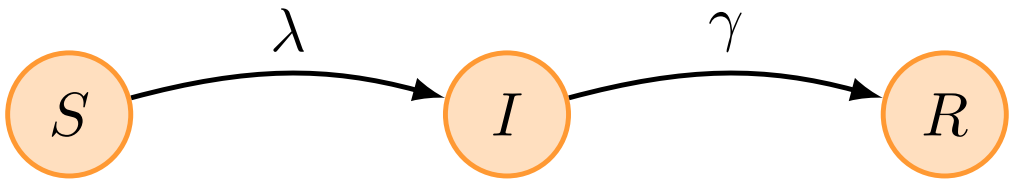

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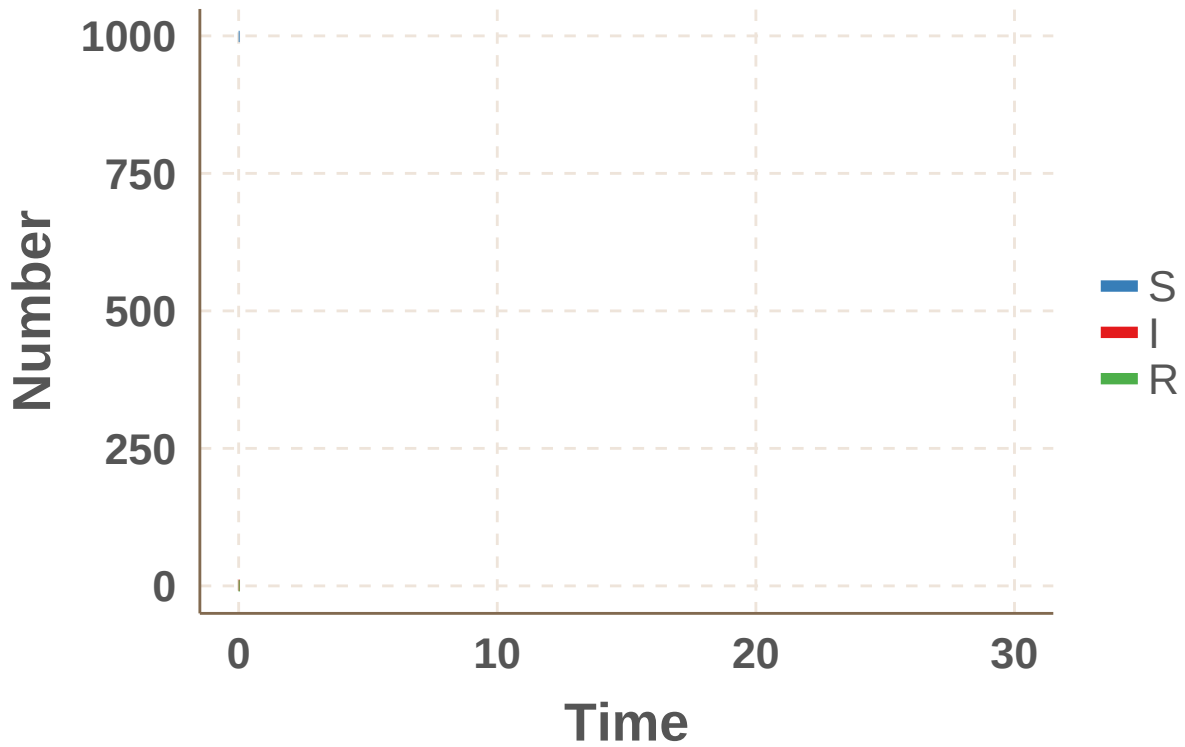

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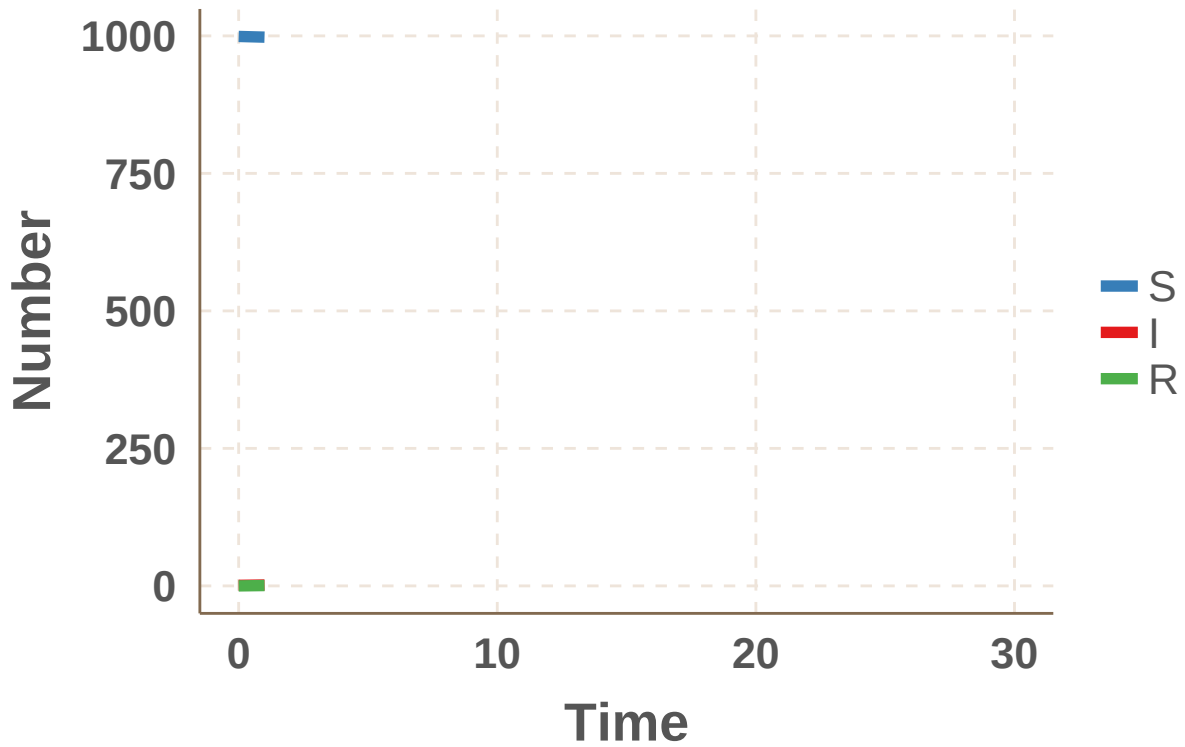

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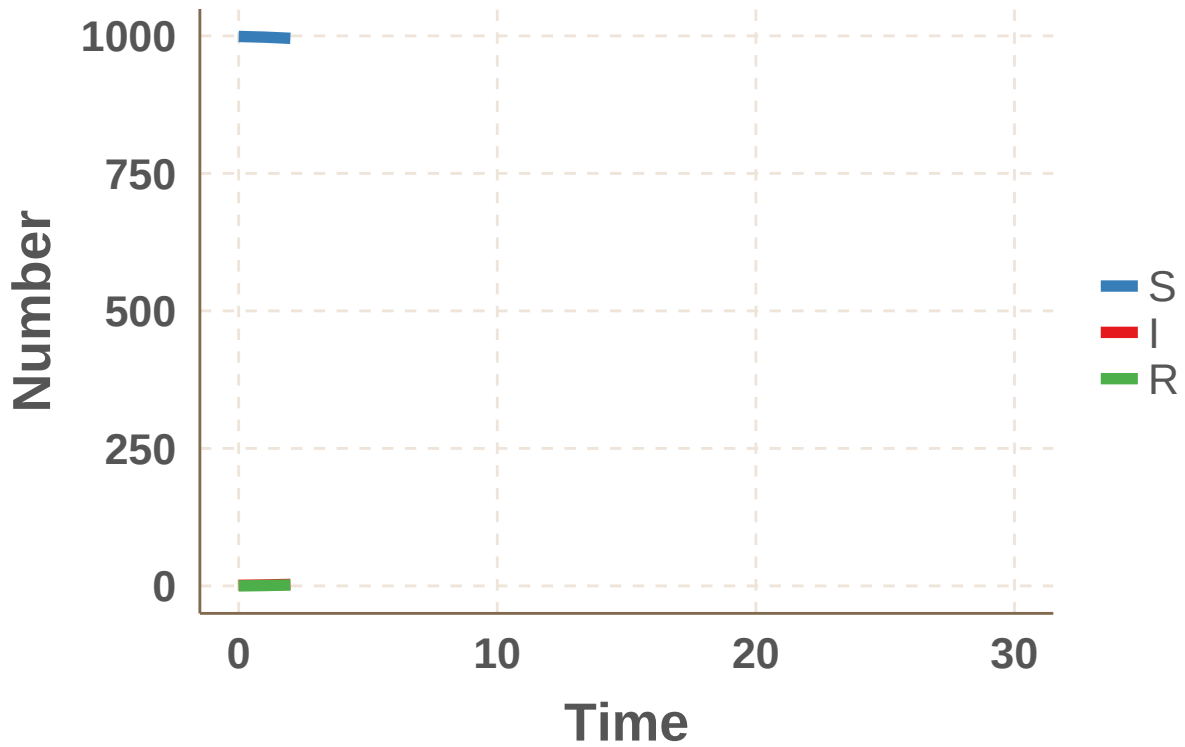

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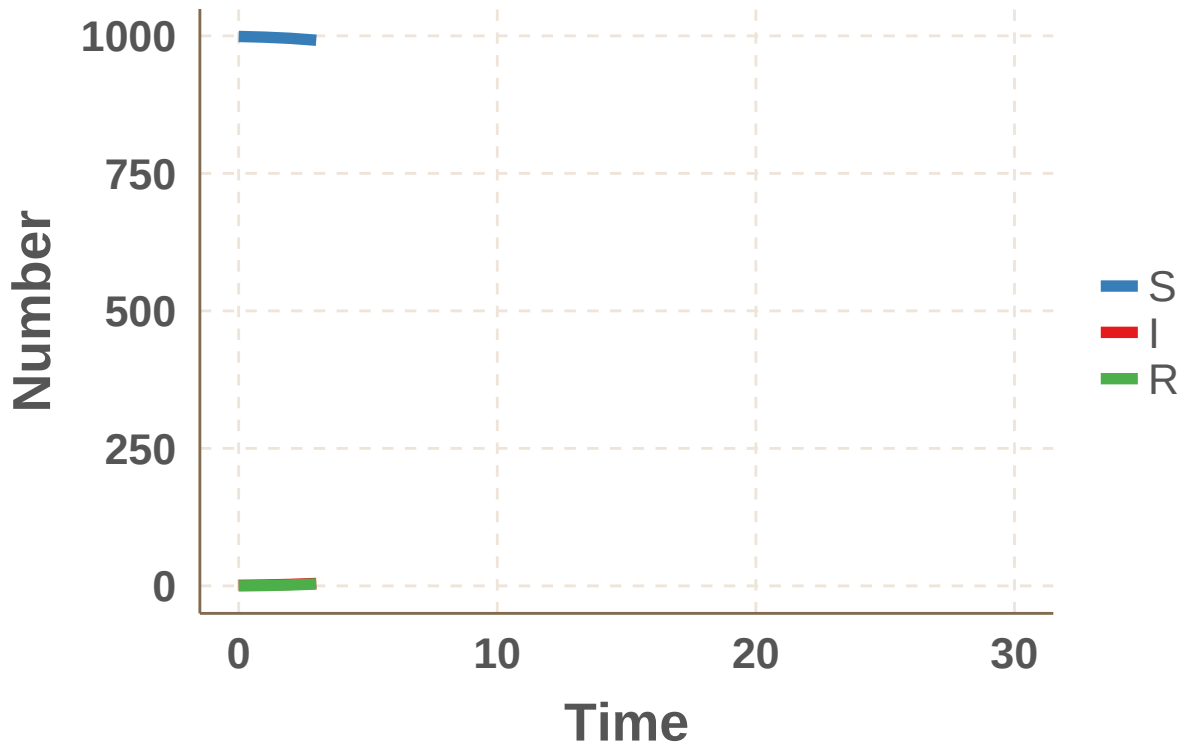

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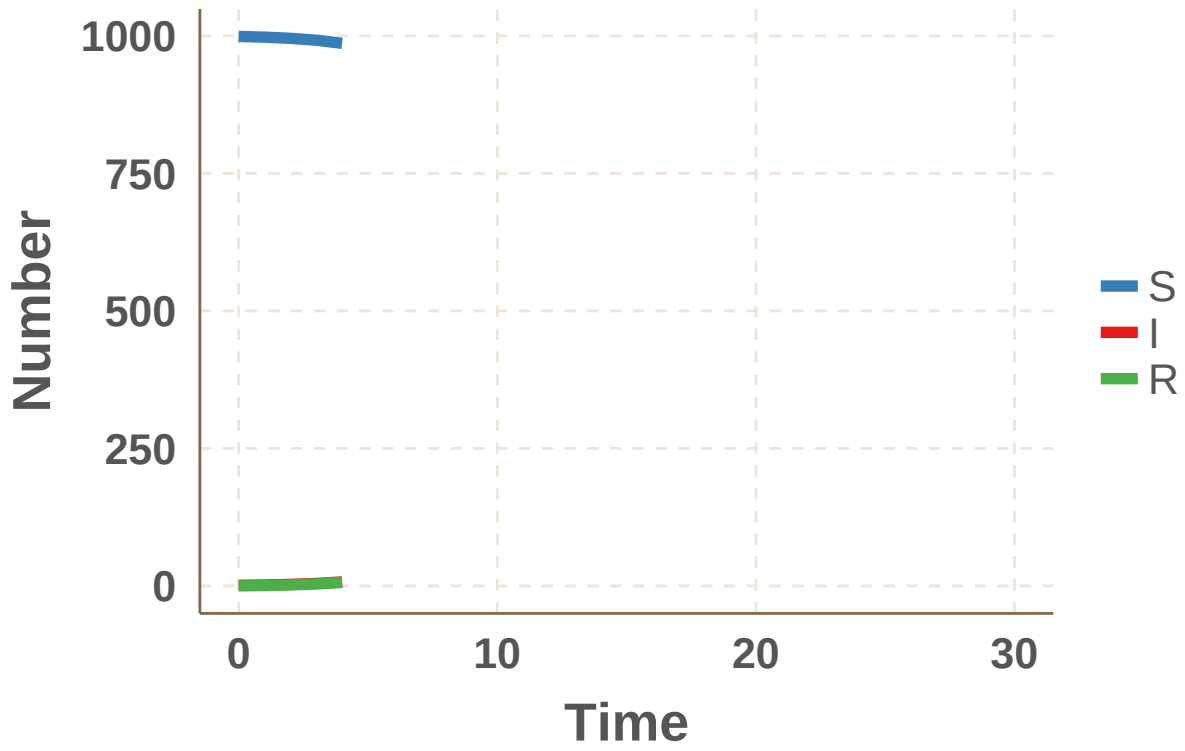

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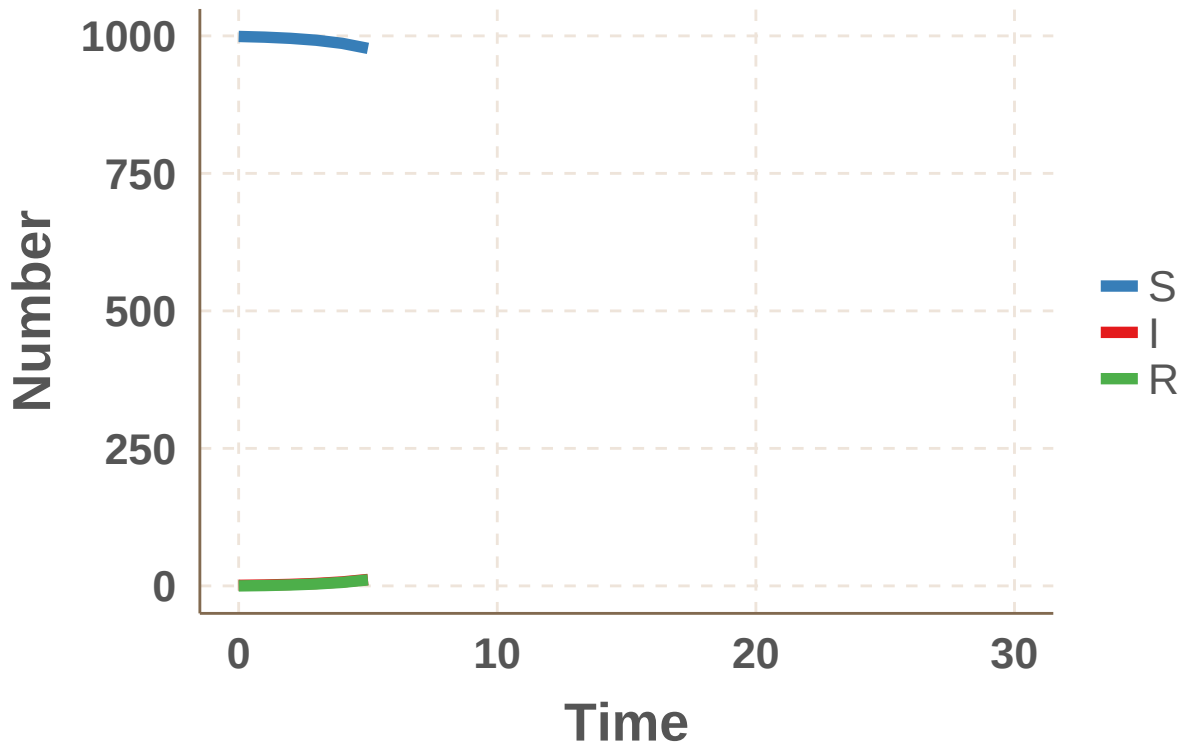

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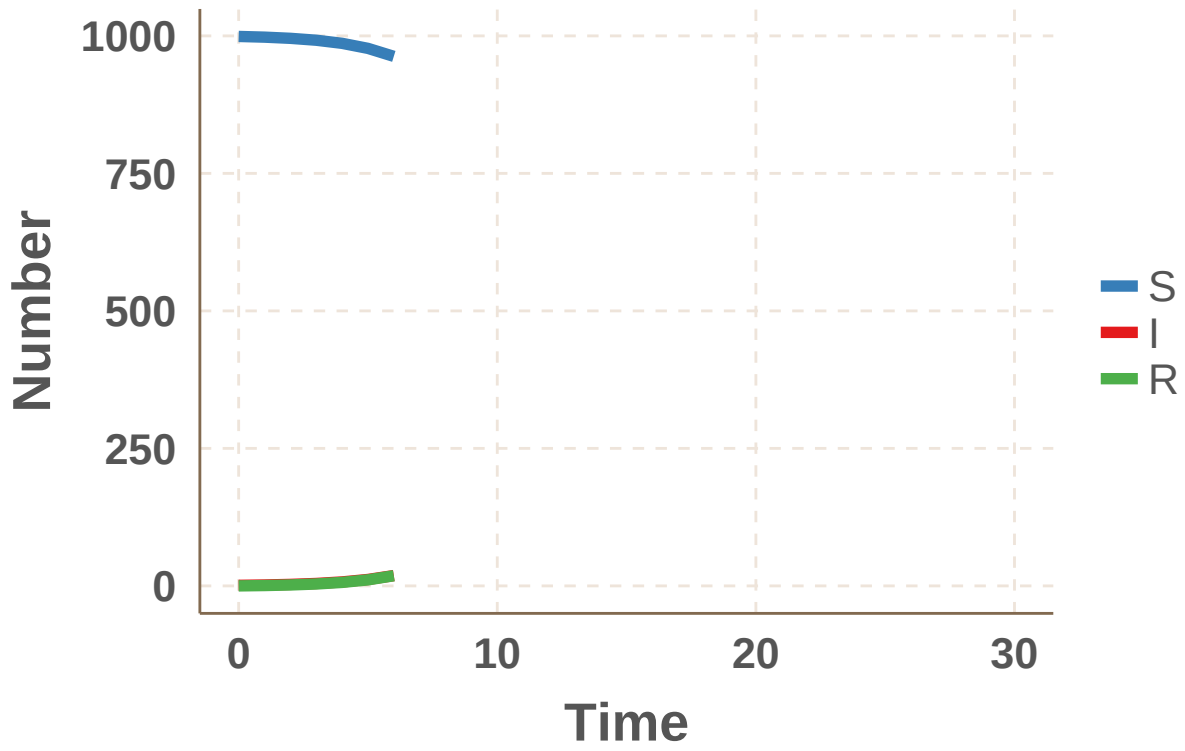

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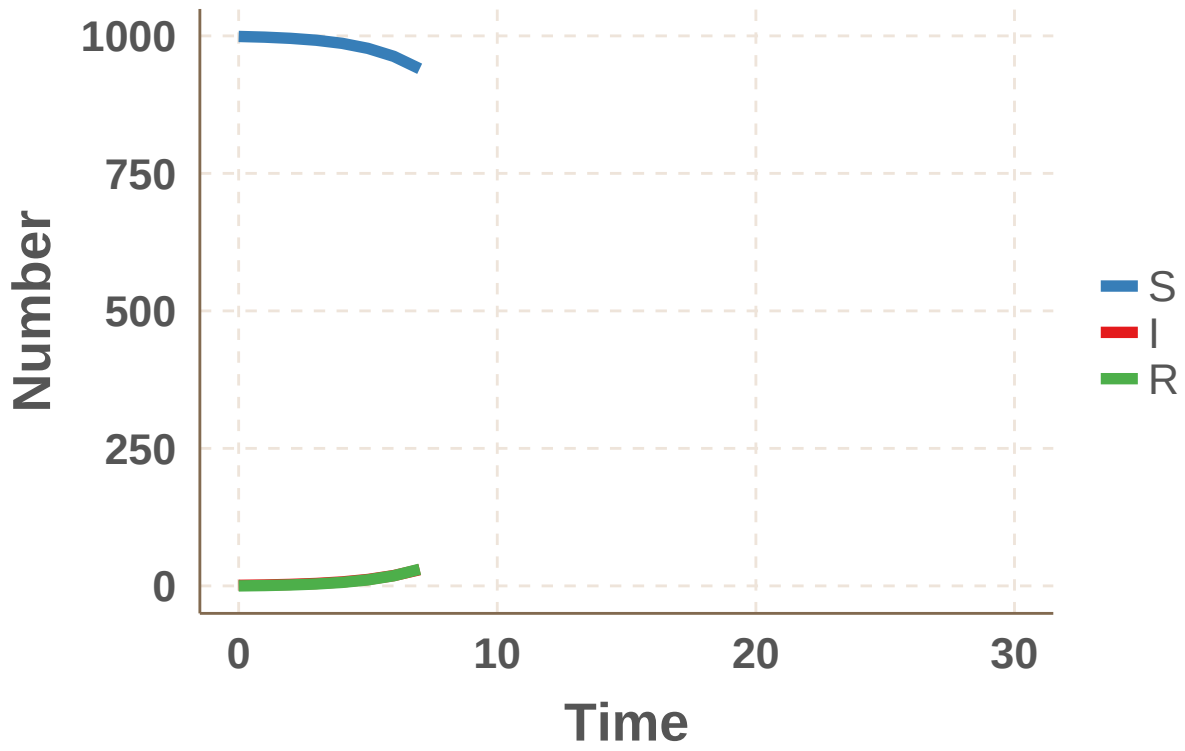

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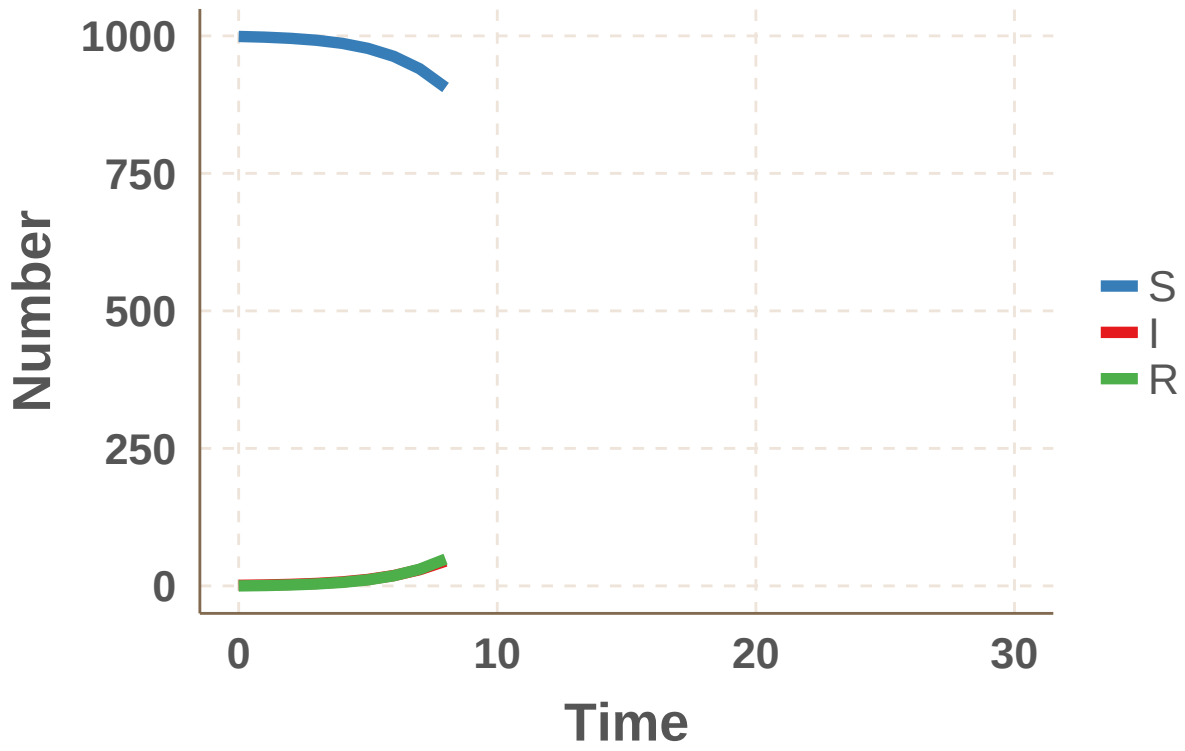

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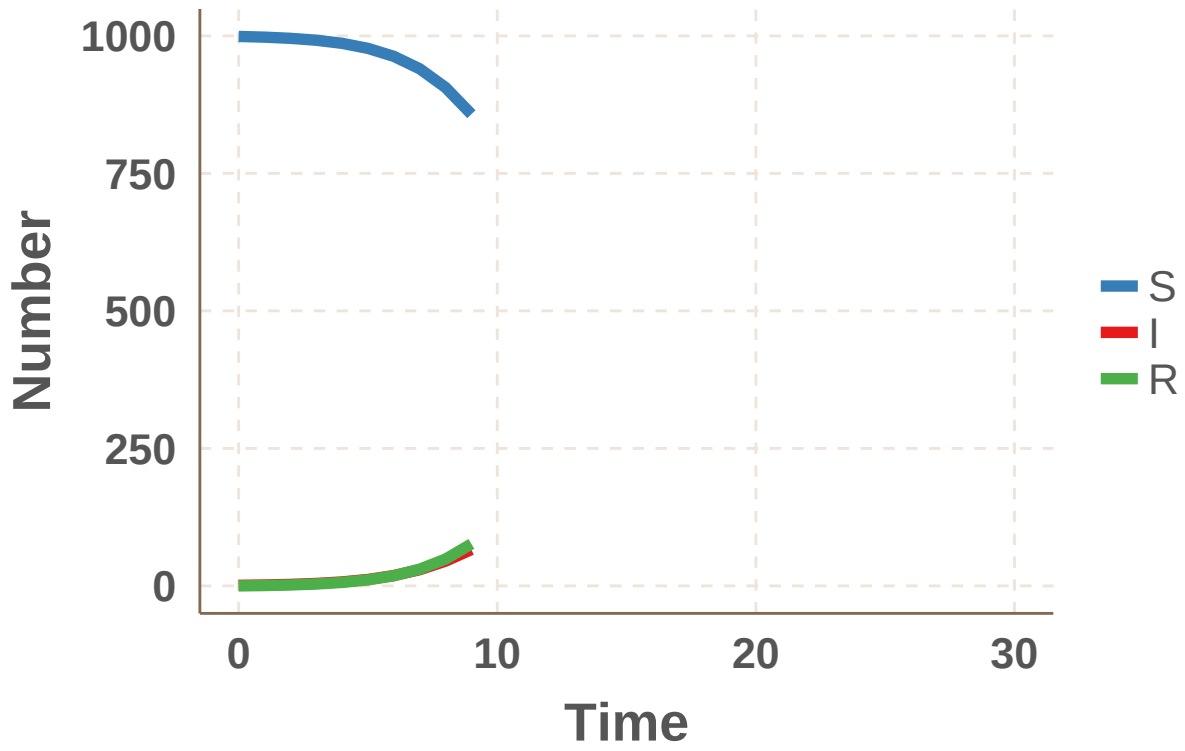

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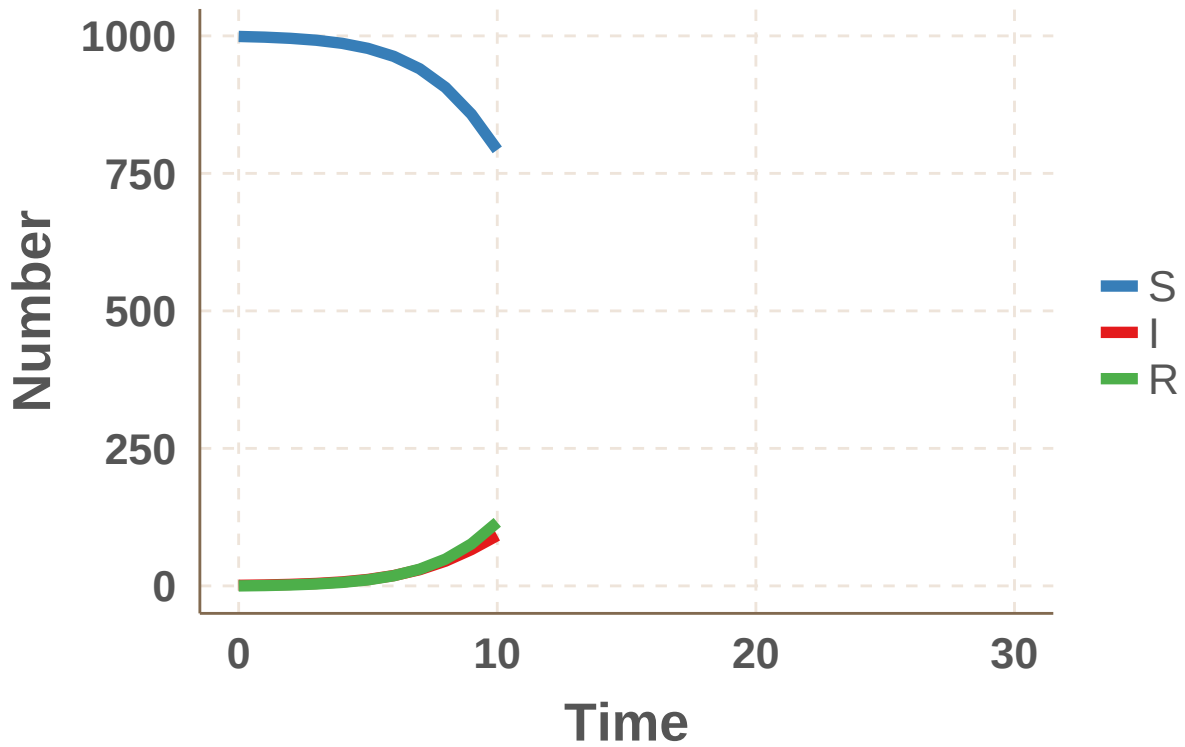

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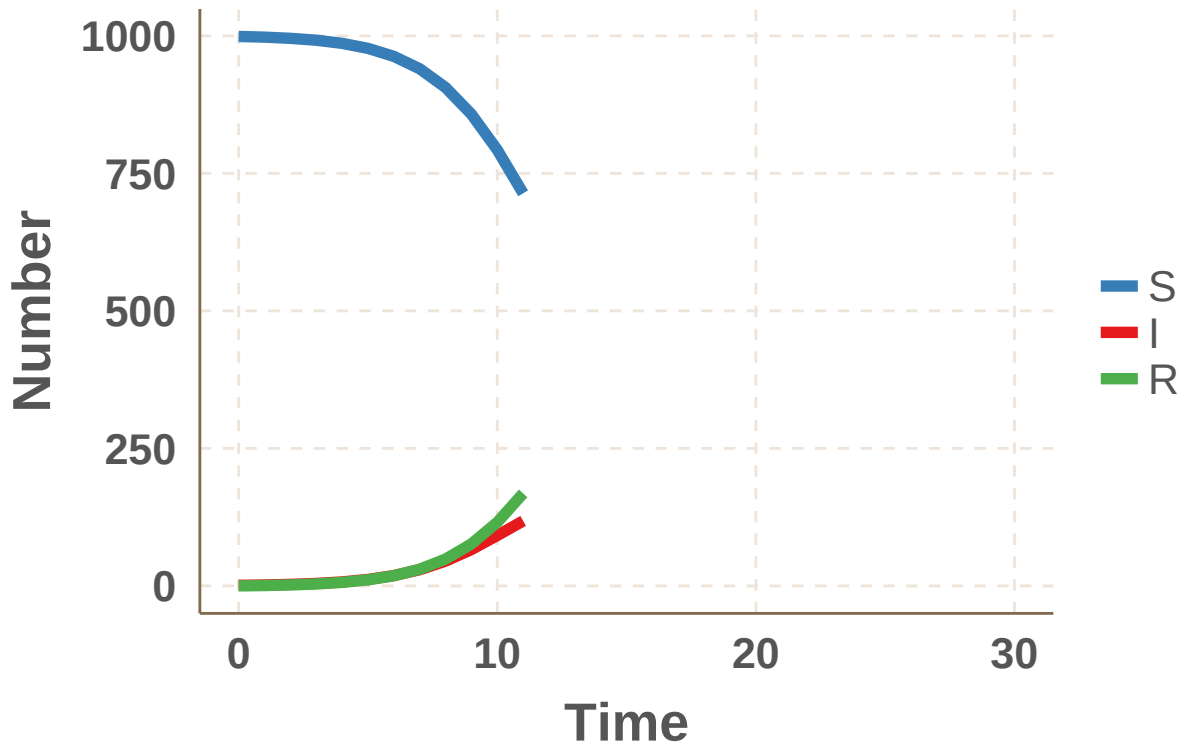

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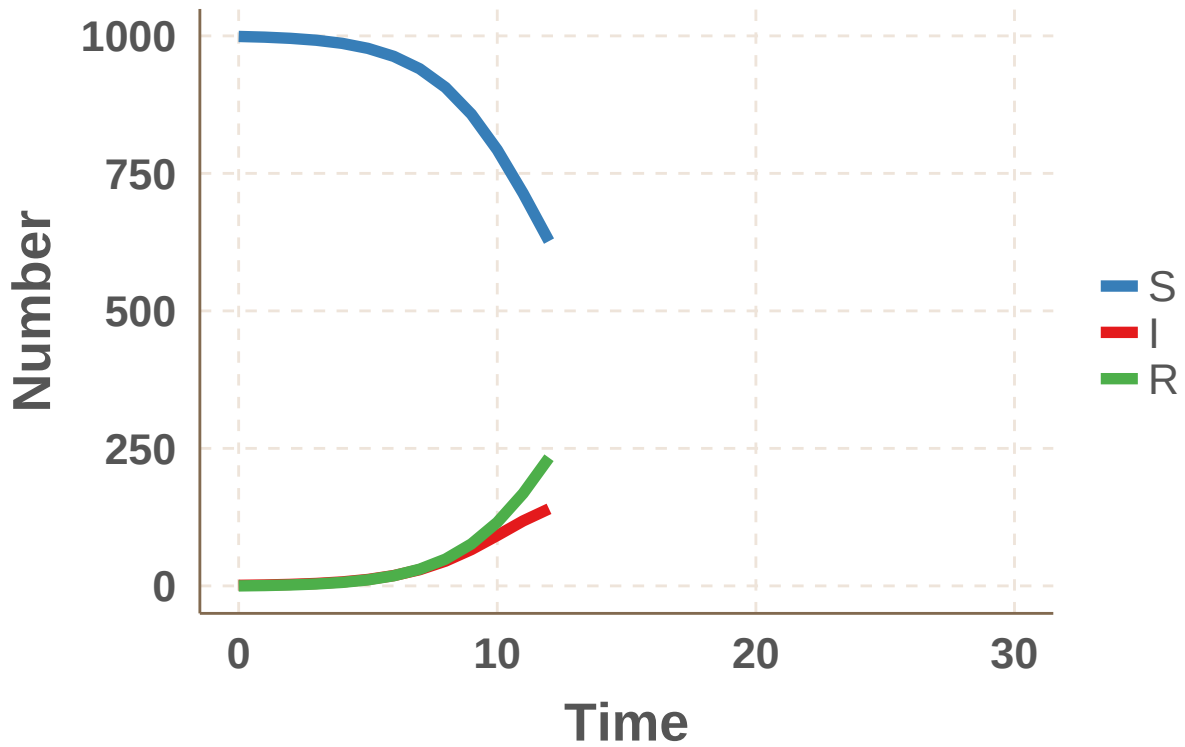

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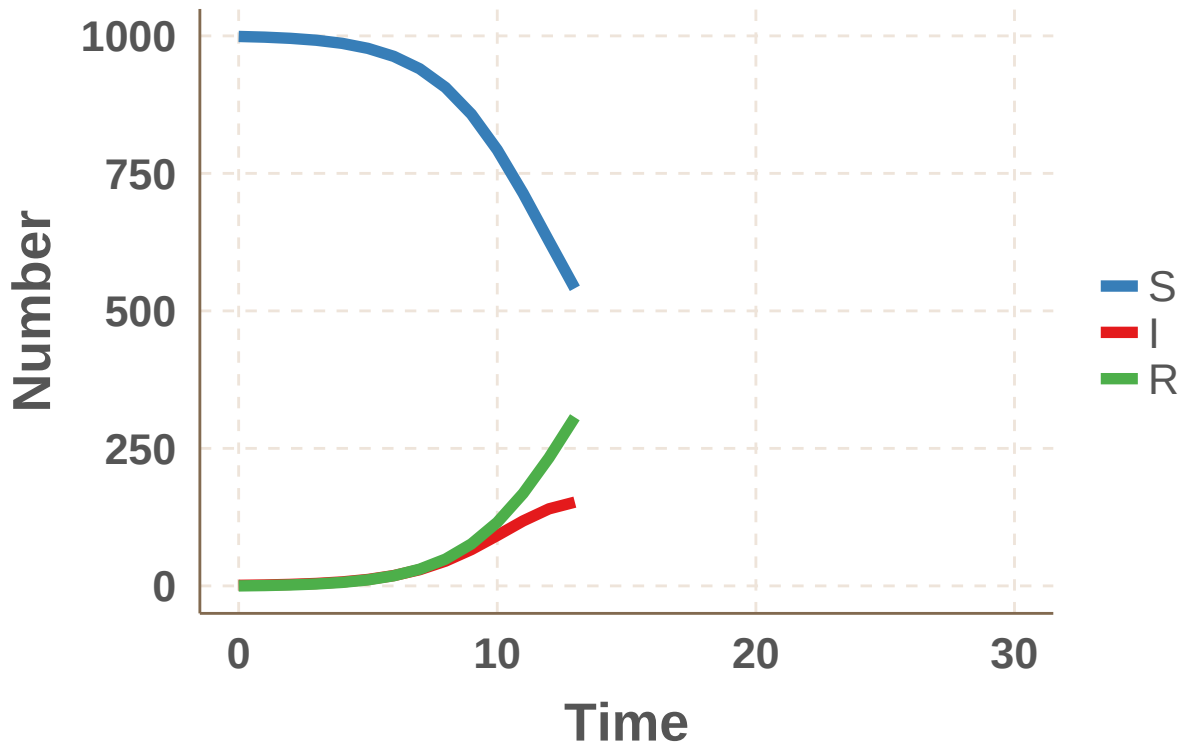

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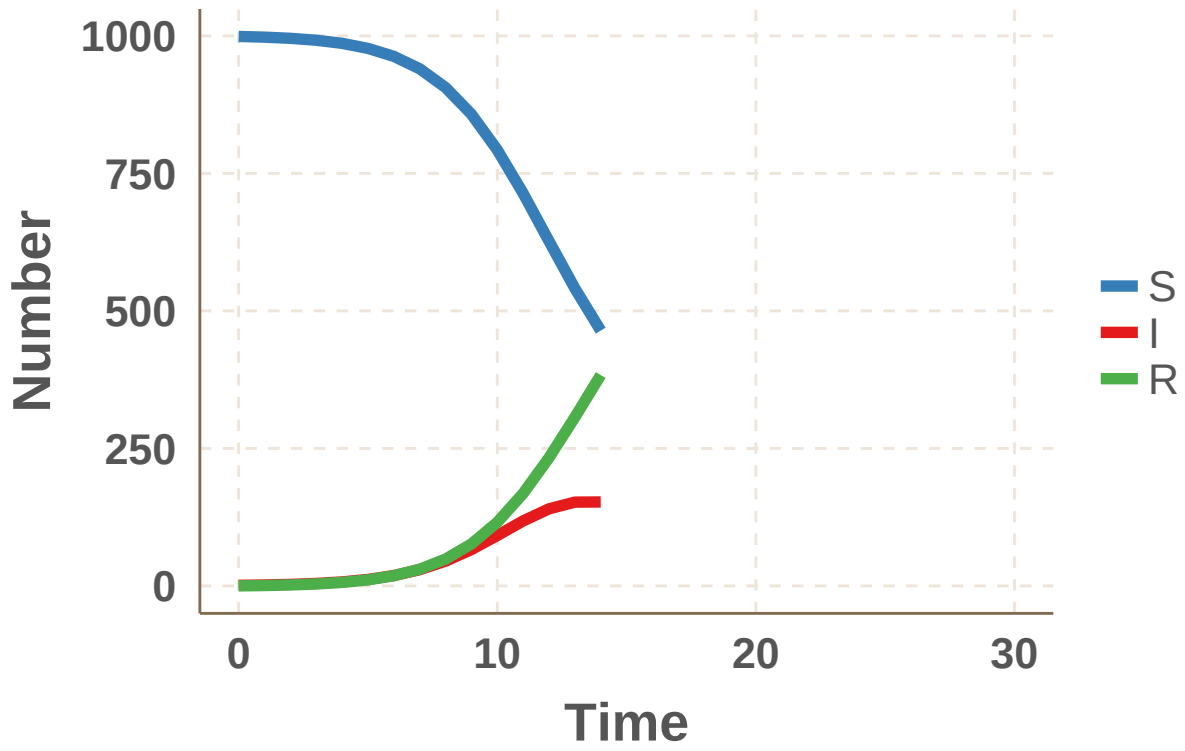

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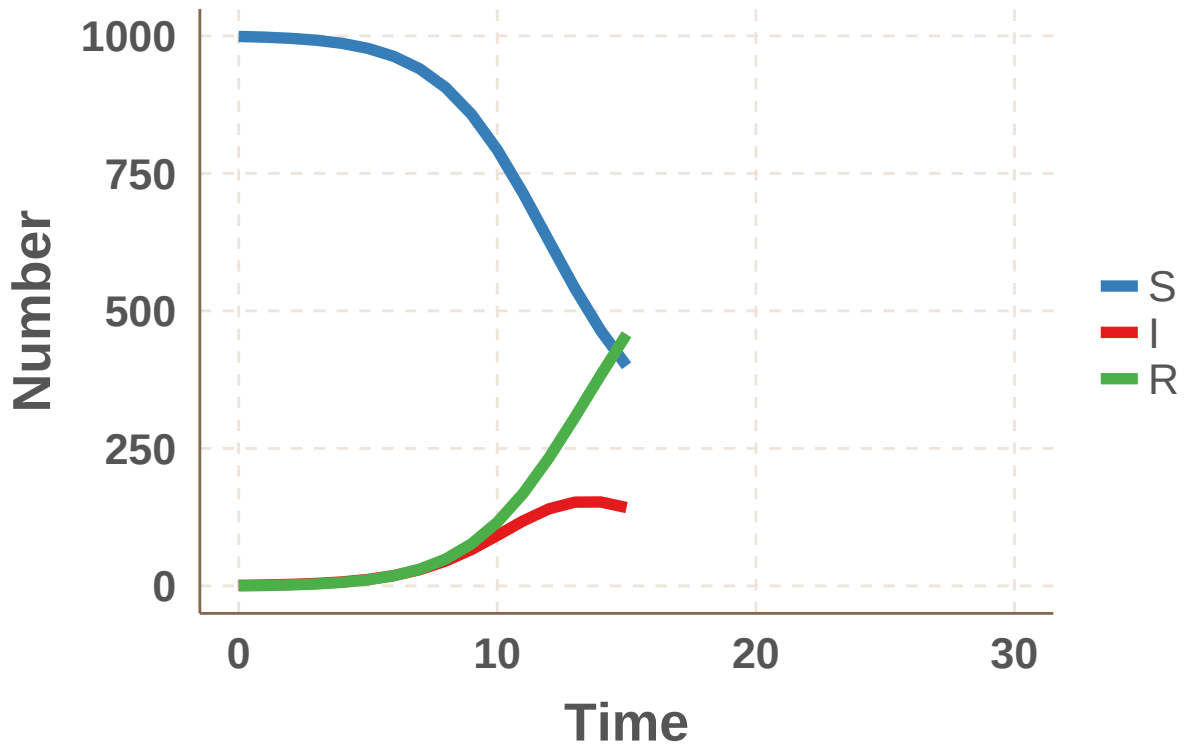

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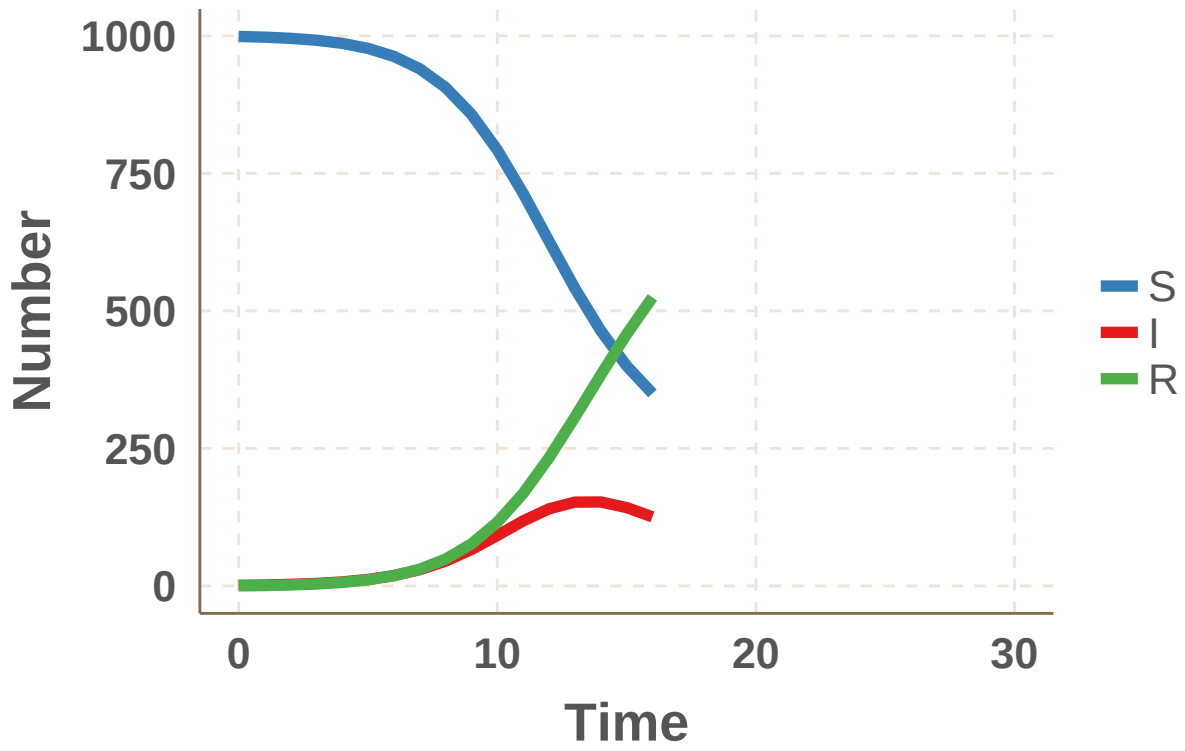

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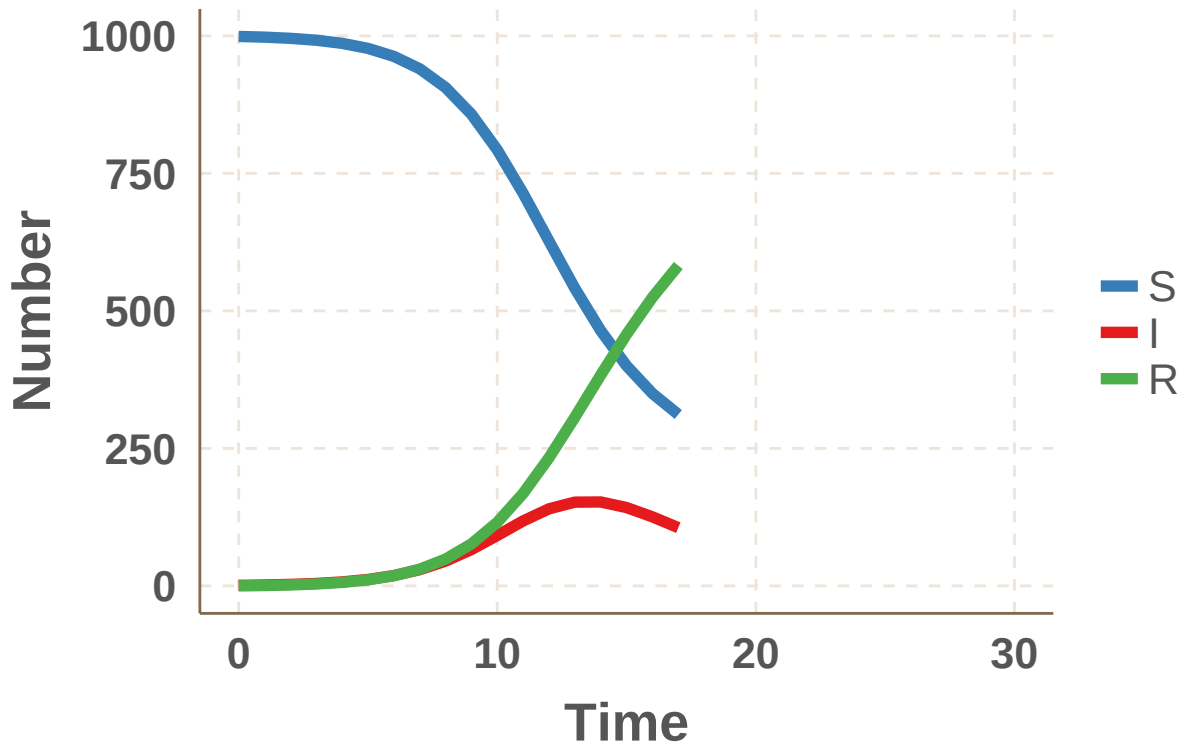

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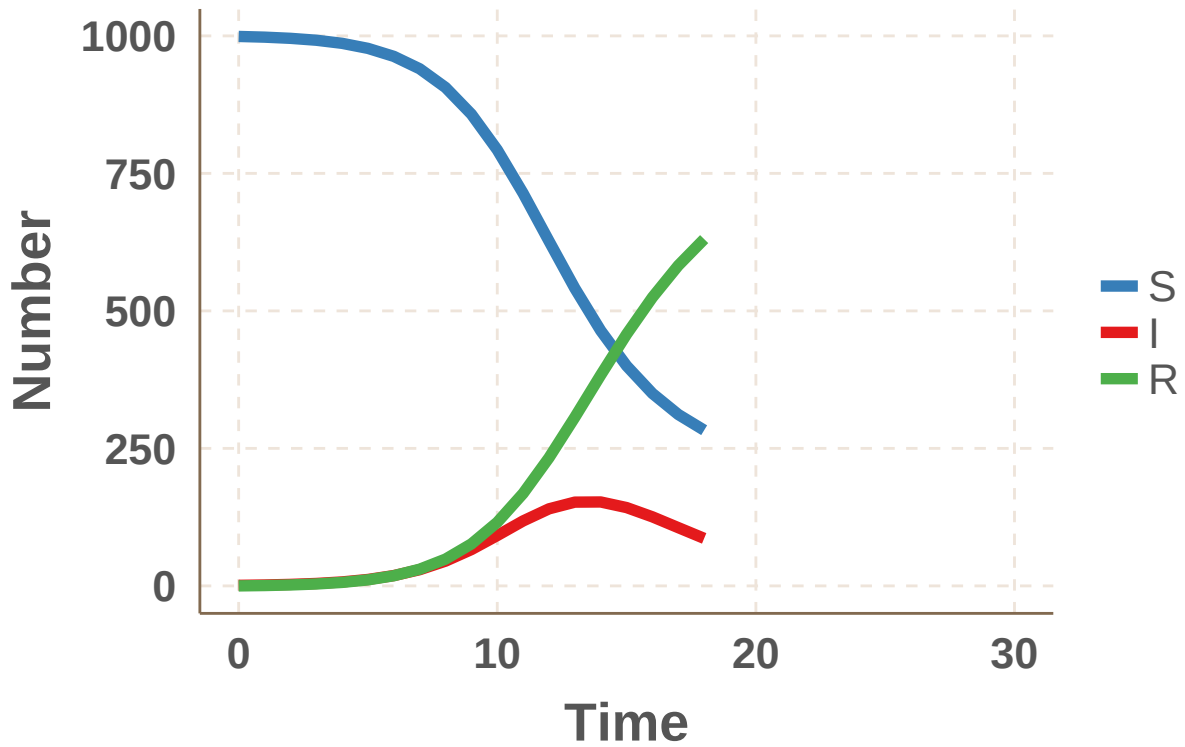

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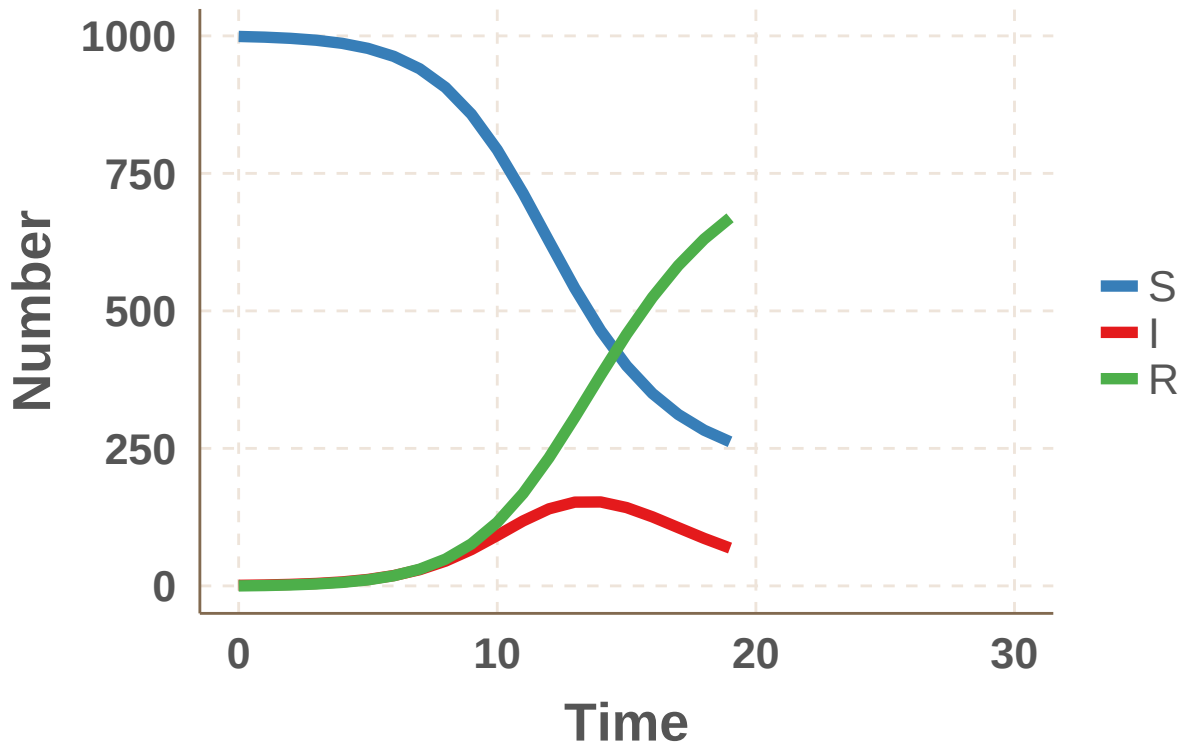

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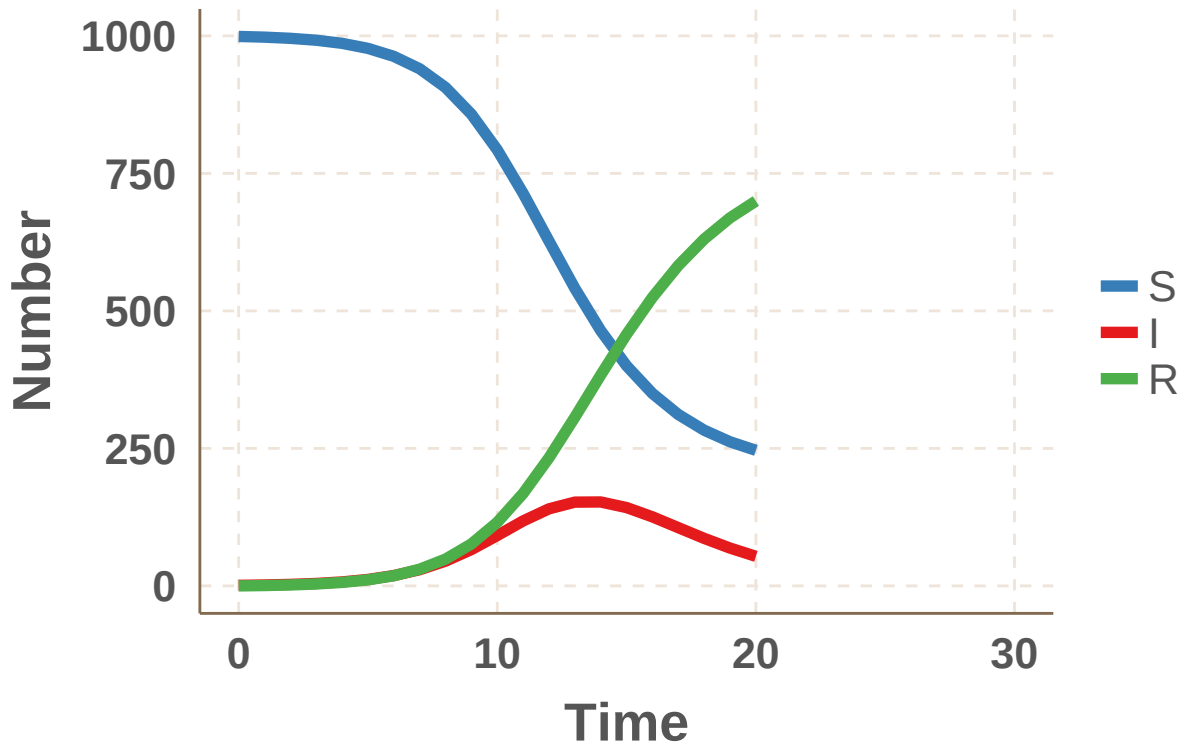

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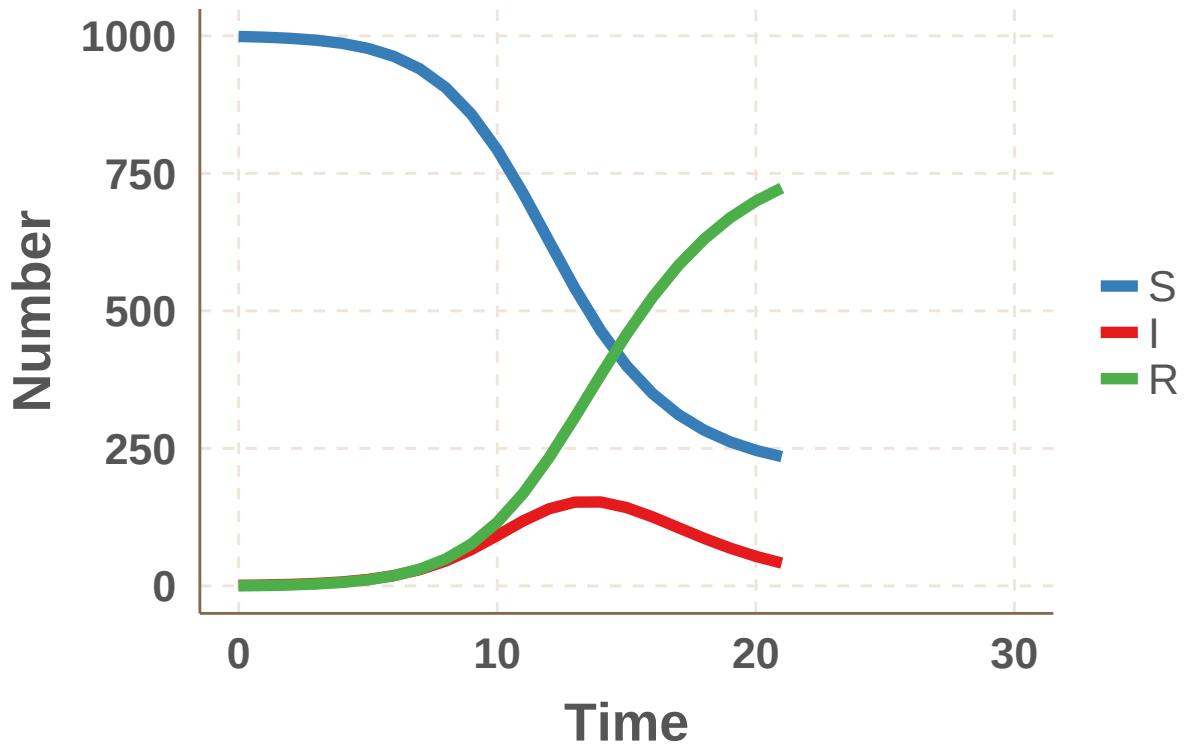

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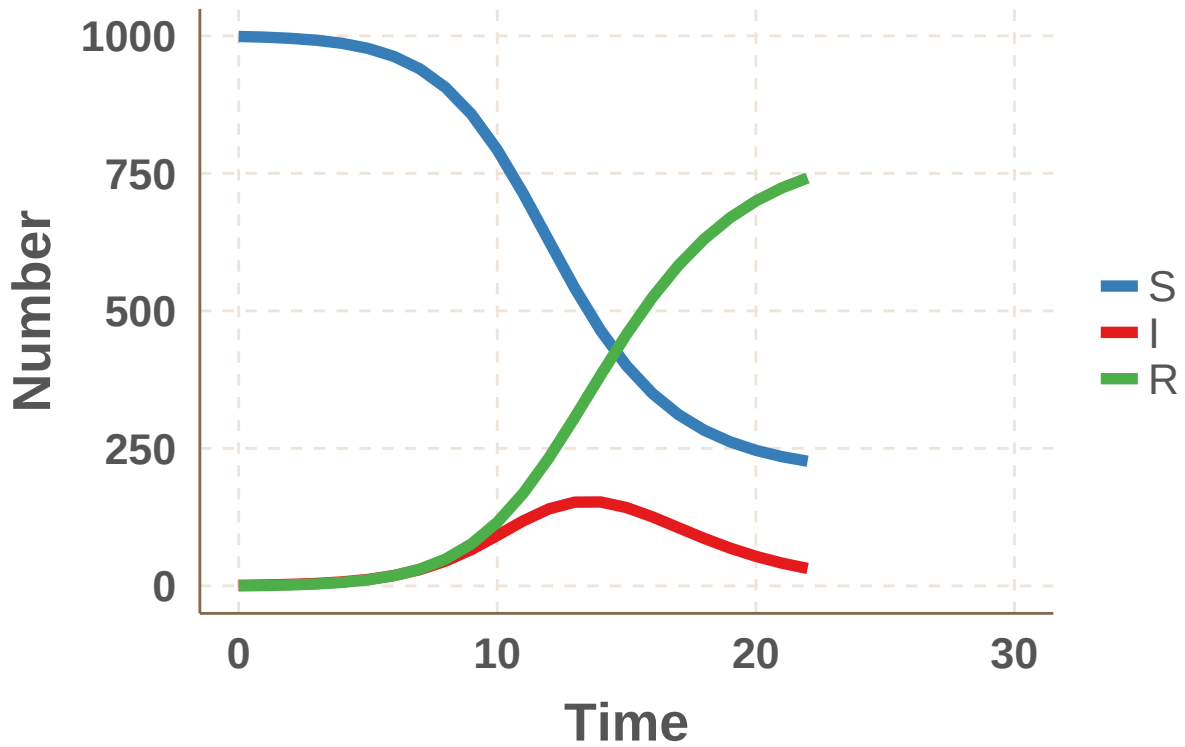

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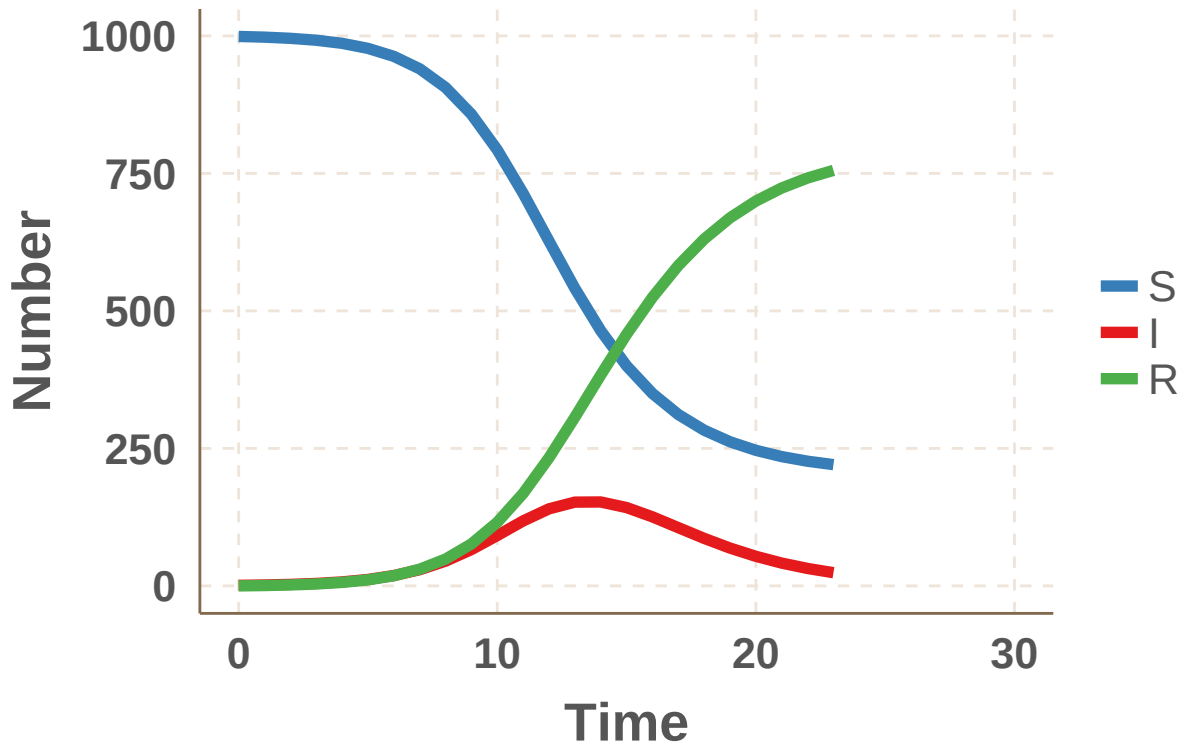

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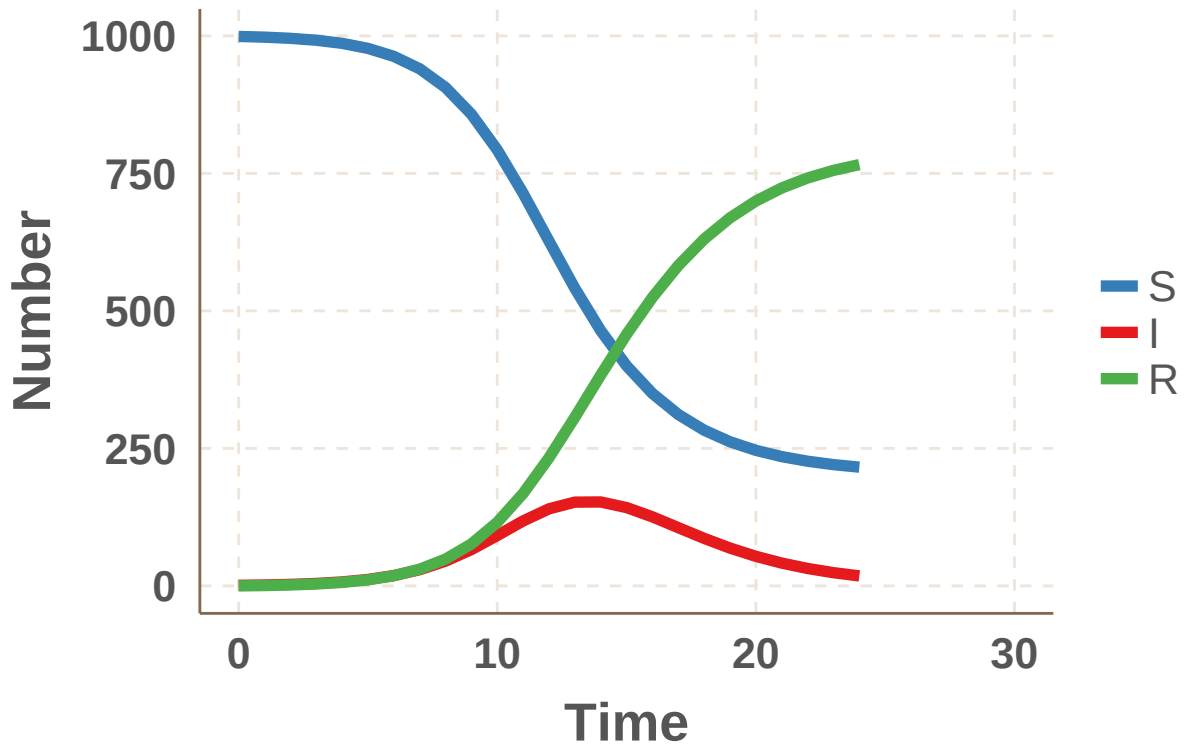

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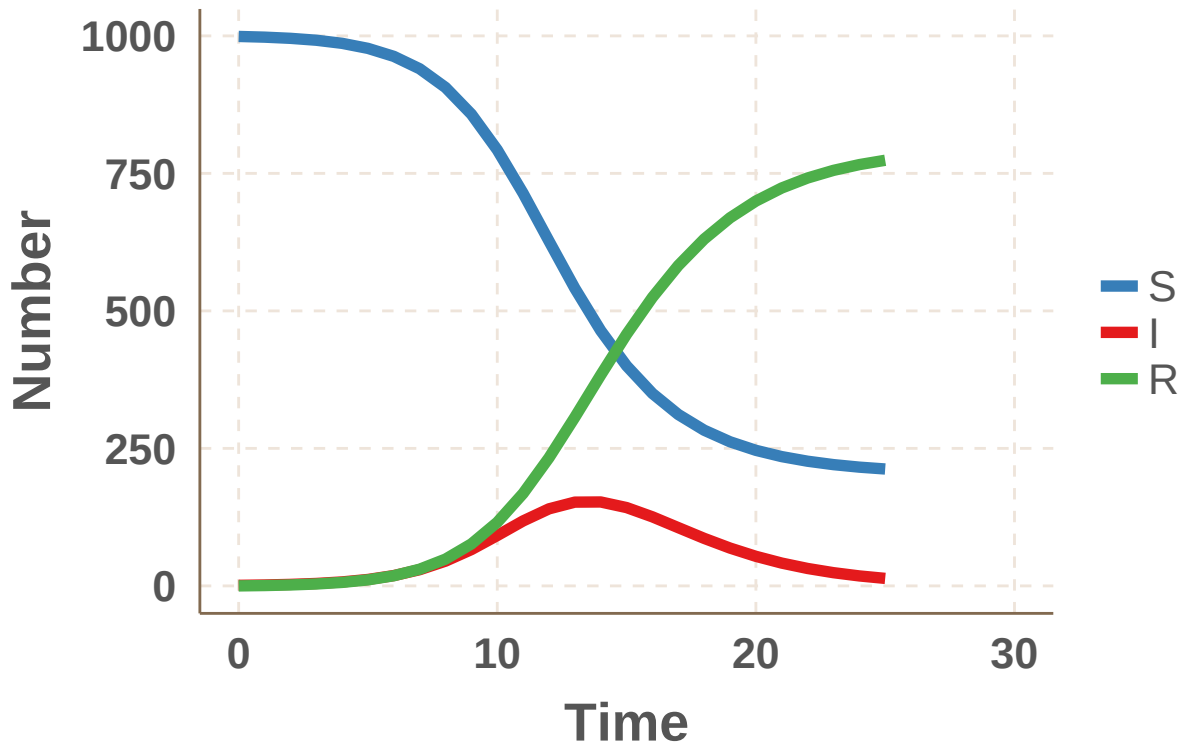

Simulating the SIR model using differential equations

$$dS/dt = -\beta \frac{I}{N} S$$

$$dI/dt = +\beta \frac{I}{N} S - \gamma I$$

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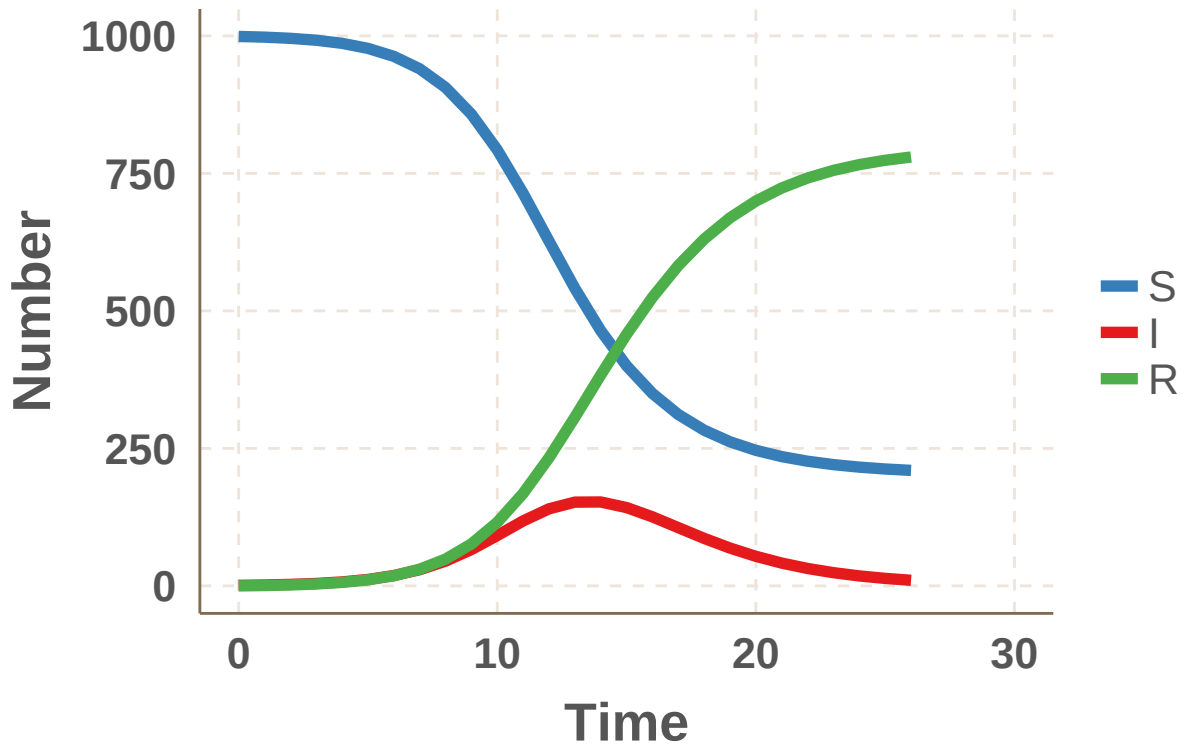

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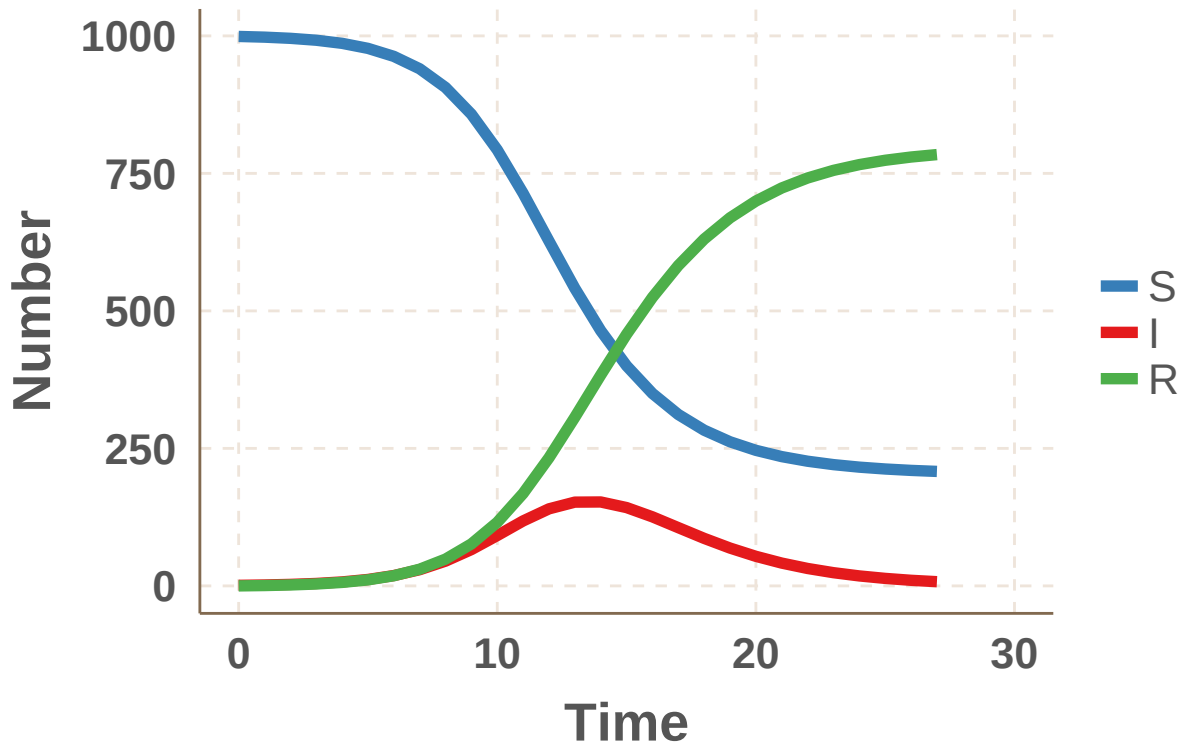

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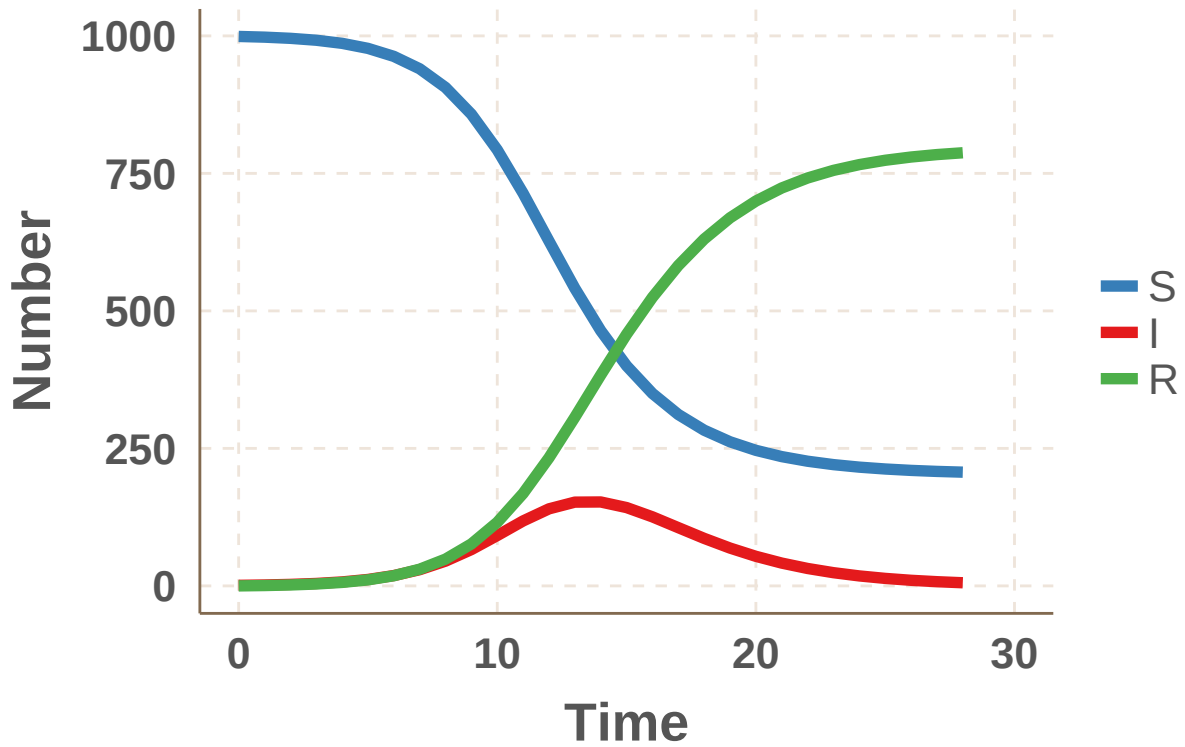

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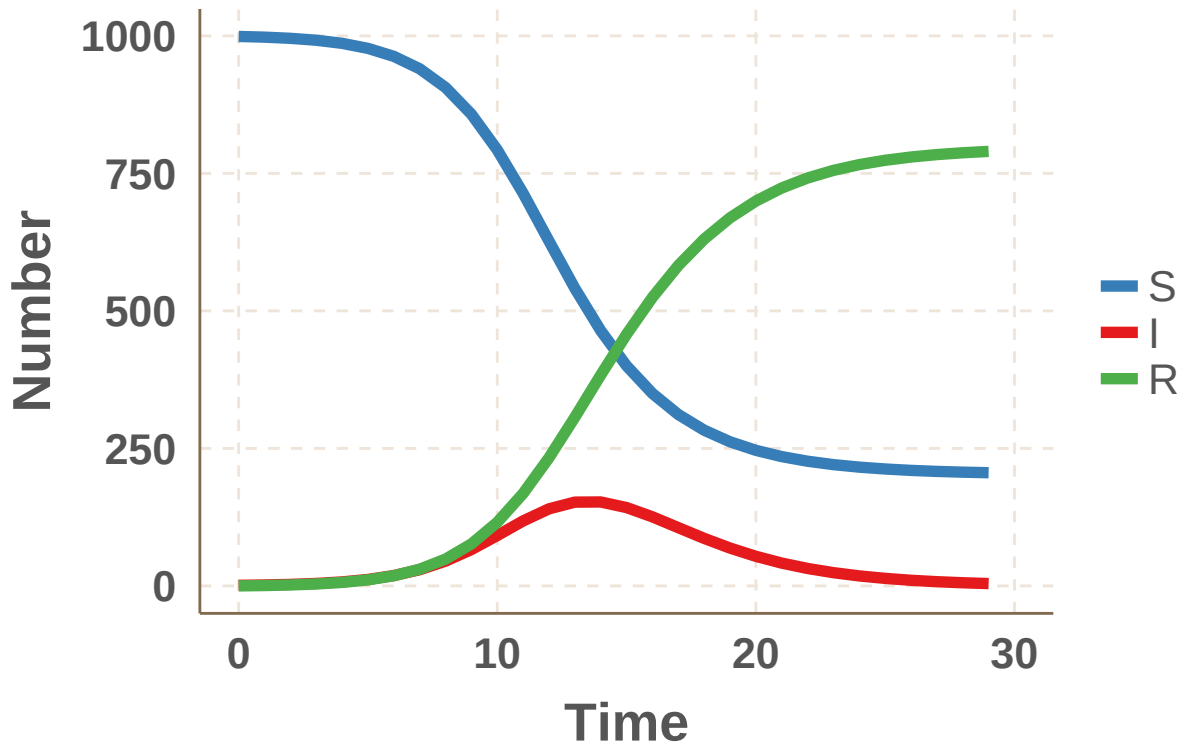
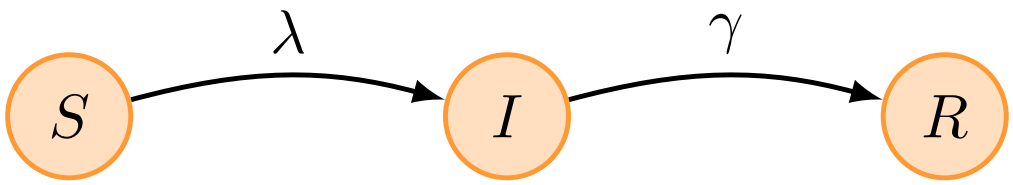


Properties of the SIR model



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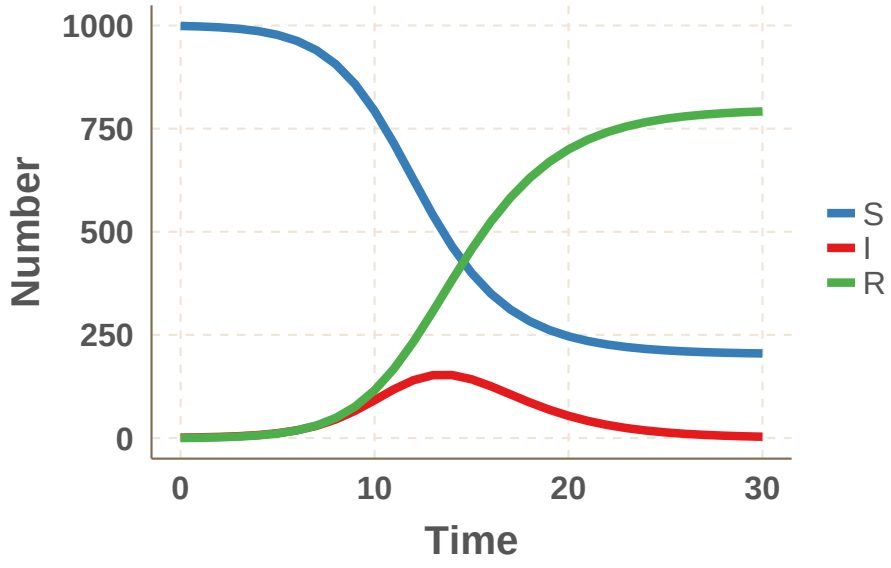

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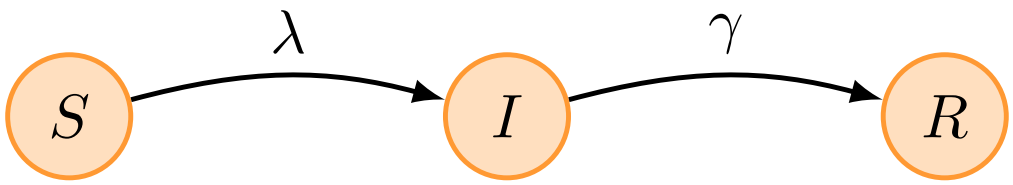

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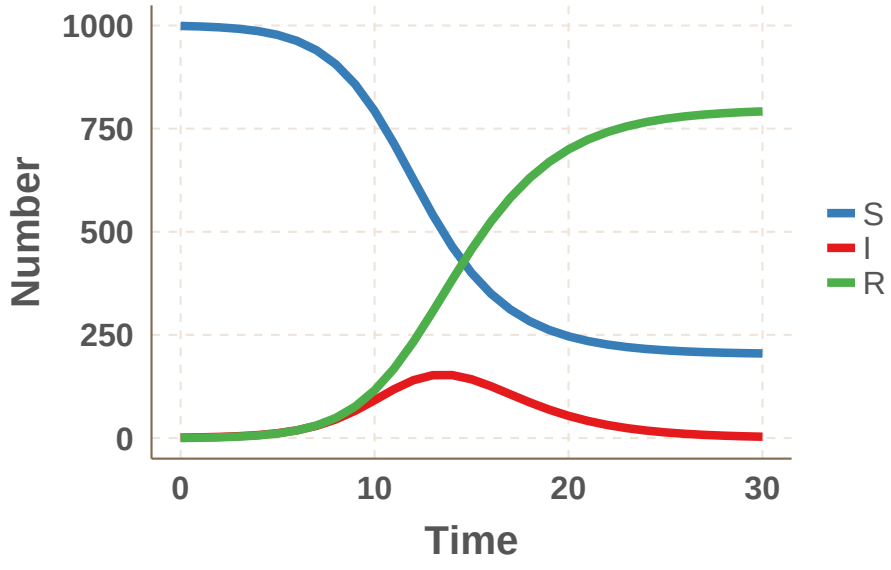
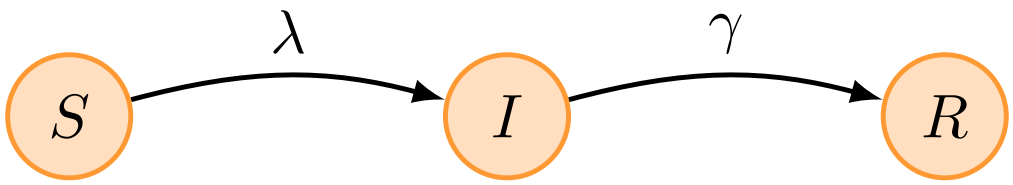


- Not everyone in the population eventually gets infected.

Properties of the SIR model



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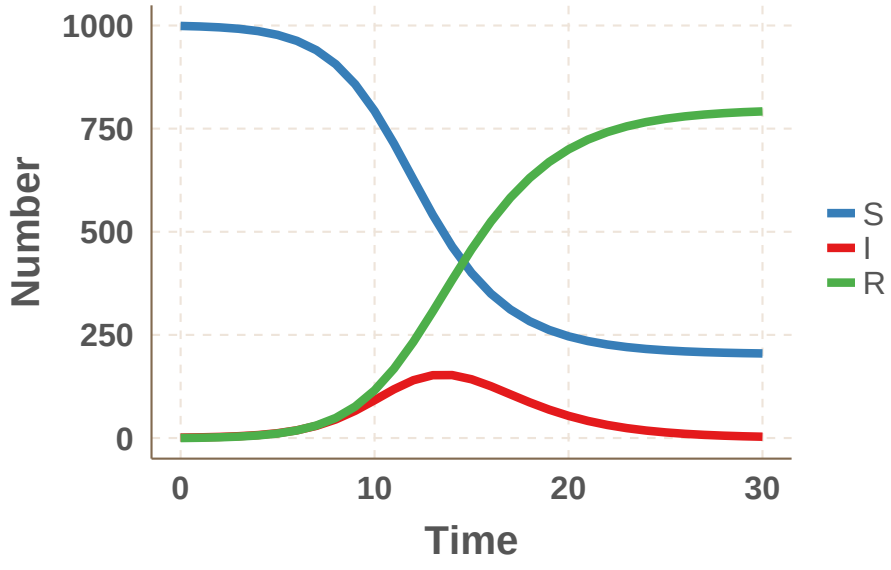

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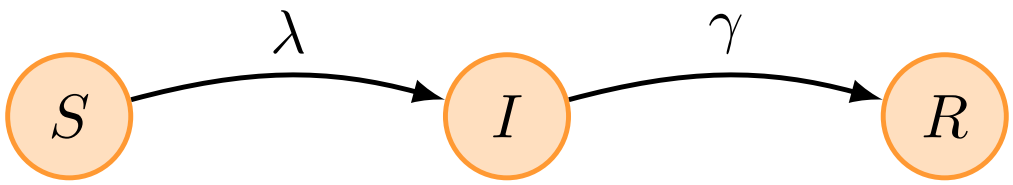

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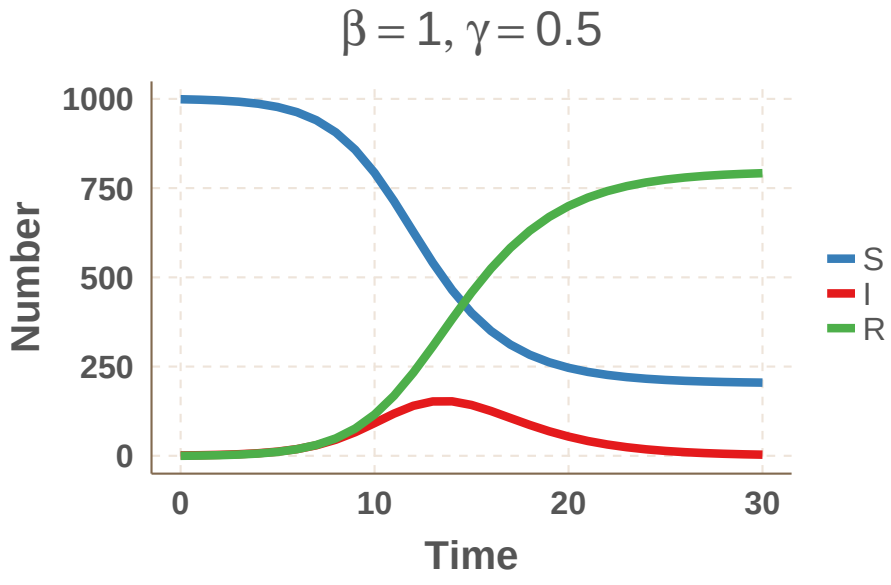

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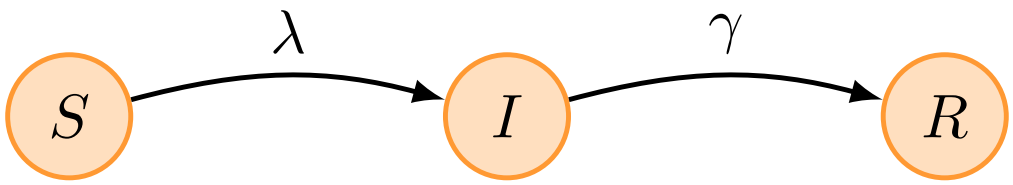

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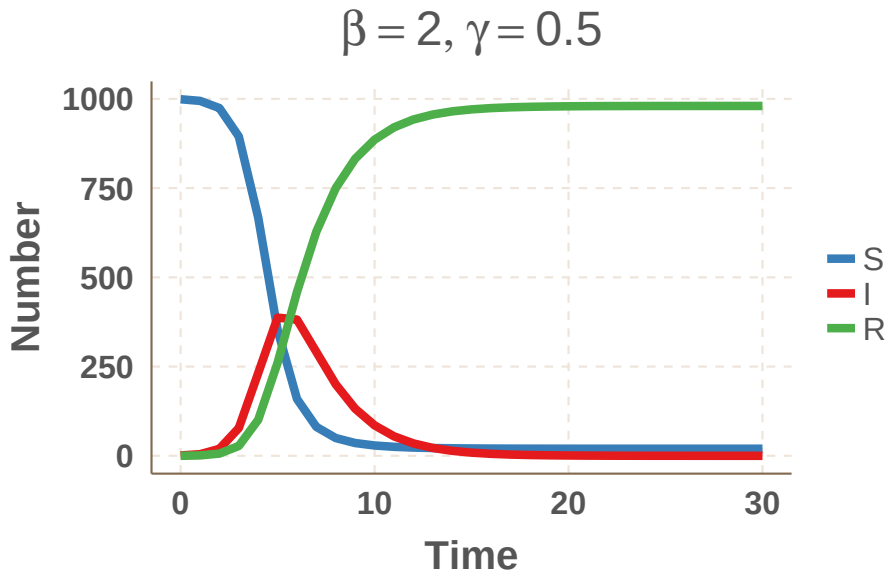

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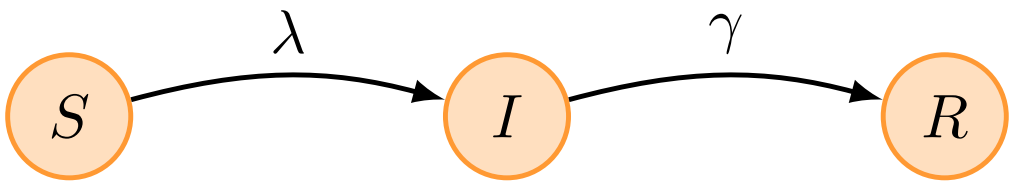

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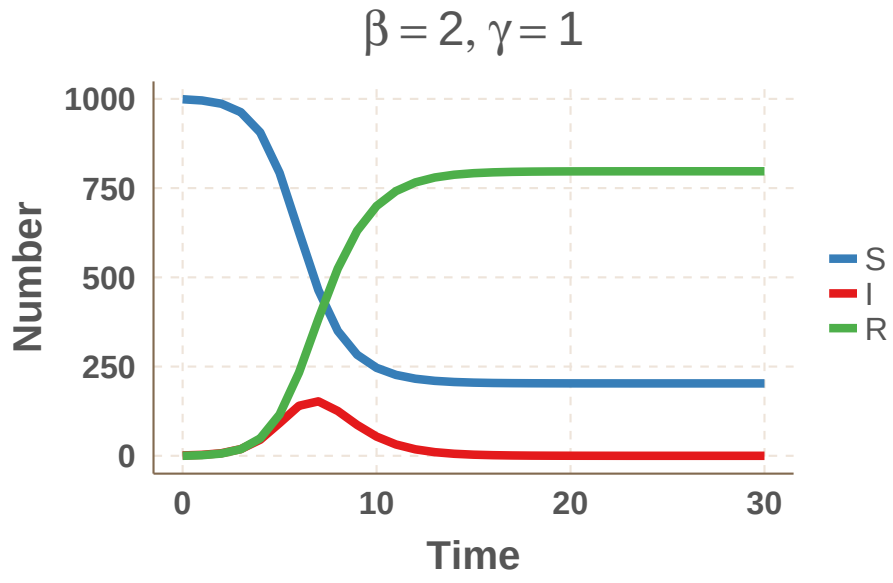
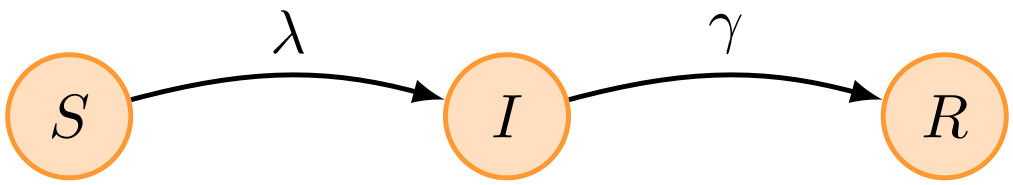


- Not everyone in the population eventually gets infected.
- The time and height of the peak, and the total number of people infectious depends on β and γ

Properties of the SIR model



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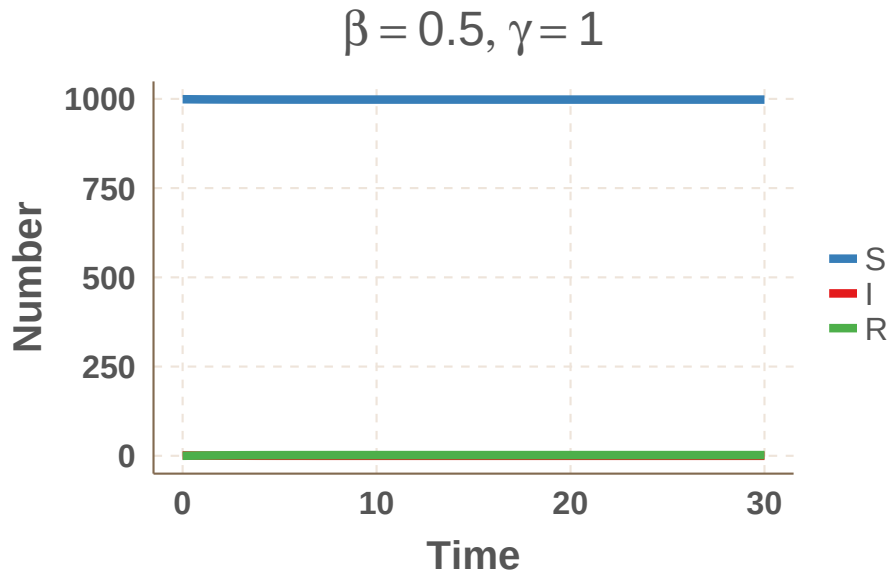
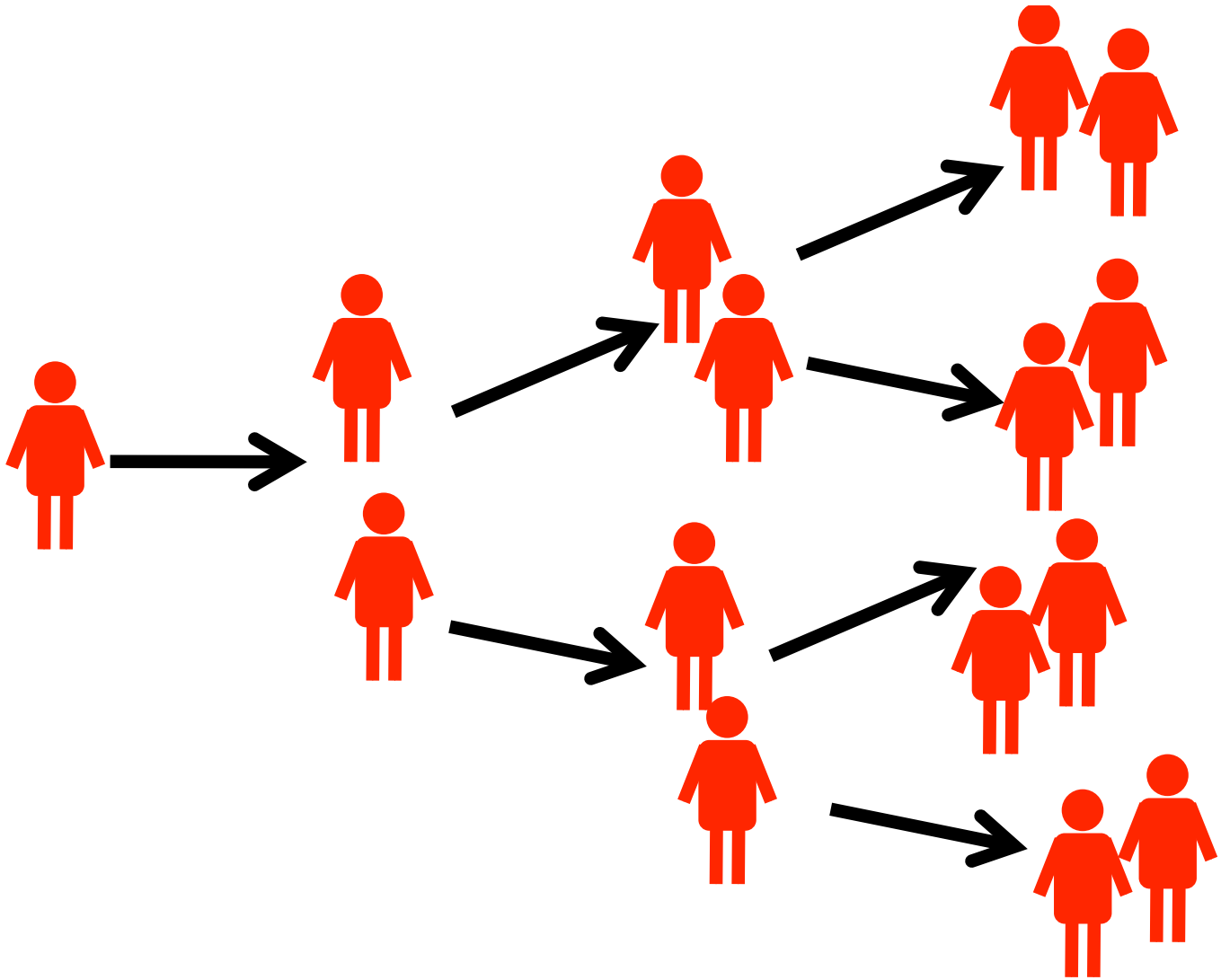


- Not everyone in the population eventually gets infected.
- The time and height of the peak, and the total number of people infectious depends on β and γ
- Sometimes almost nobody gets infected

4. The basic and net reproduction numbers

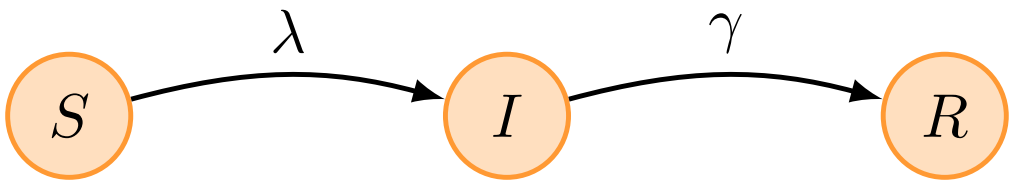
Definition

The average number of secondary infectious cases resulting from the introduction of a single infectious case into a totally susceptible population



The basic reproduction number in the SIR model

The average number of secondary infectious cases resulting from the introduction of a single infectious case into a totally susceptible population



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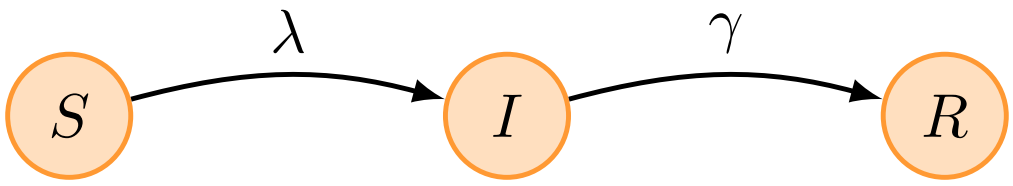
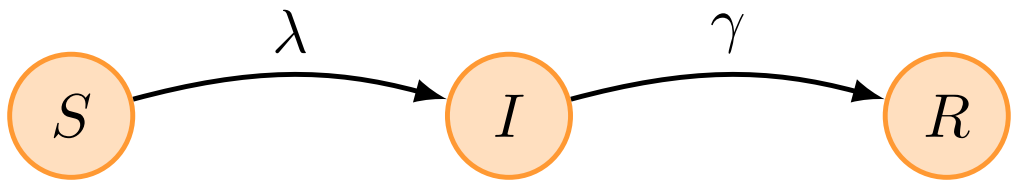


$$\lambda = \beta \frac{I}{N}$$

- single infectious case: $I = 1$

The basic reproduction number in the SIR model

The average number of secondary infectious cases resulting from the introduction of a single infectious case into a totally susceptible population



$$\lambda = \beta \frac{I}{N}$$

- single infectious case: $I = 1$
- totally susceptible population: $S = N$

The basic reproduction number in the SIR model

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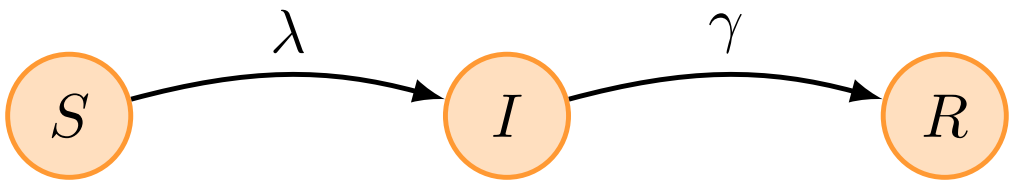
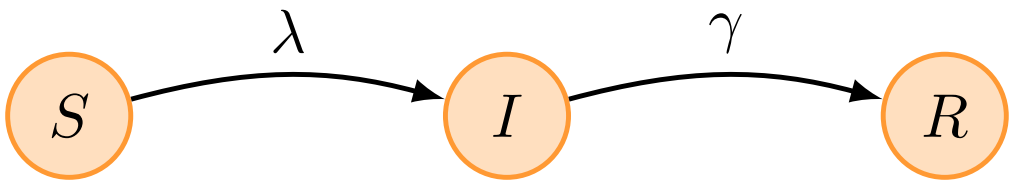


$$\lambda = \beta \frac{I}{N}$$

- single infectious case: $I = 1$
- totally susceptible population: $S = N$
- force of infection from a single infectious case: $\lambda = \beta \frac{I}{N} = \beta \frac{1}{N}$

The basic reproduction number in the SIR model

The average number of secondary infectious cases resulting from the introduction of a single infectious case into a totally susceptible population



$$\lambda = \beta \frac{I}{N}$$

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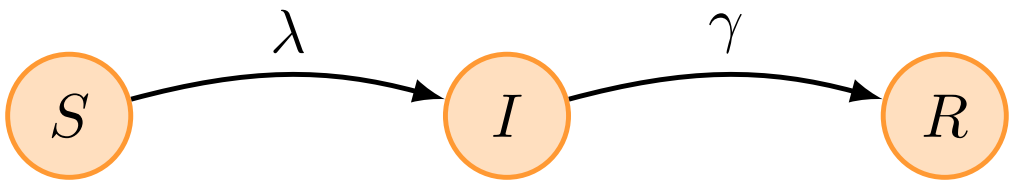
- force of infection from a single infectious case: $\lambda = \beta \frac{I}{N} = \beta \frac{1}{N}$
- number of secondary infectious cases per time: $\lambda S = \beta \frac{1}{N} N = \beta$

The basic reproduction number in the SIR model

The average number of secondary infectious cases resulting from the introduction of a single infectious case into a totally susceptible population



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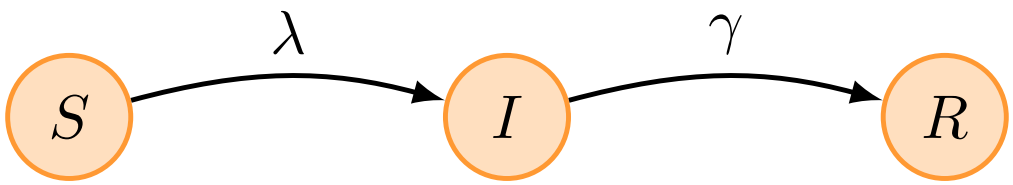

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- single infectious case: $I = 1$
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- number of secondary infectious cases per time: $\lambda S = \beta \frac{1}{N} N = \beta$
- total number of secondary infectious cases:

$$R_0 = \beta D = \frac{\beta}{\gamma}$$

Properties of R_0 in the SIR model

How does the number of infected change?

$$dI/dt = \beta \frac{I}{N} S - \gamma I$$

Properties of R_0 in the SIR model

How does the number of infected change?

$$dI/dt = \beta \frac{I}{N} S - \gamma I$$

If we start with a single infectious person ($I = 1, S \approx N$), then we have

$$dI/dt = \beta - \gamma = \frac{1}{\gamma}(R_0 - 1)$$

Properties of R_0 in the SIR model

How does the number of infected change?

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The number of infectious will

- increase if $R_0 > 1$
- decrease if $R_0 < 1$

The value of R_0 reveals if a newly introduced disease will spread or die out.

R_0 and outbreaks

$$R_0 = \beta D = \frac{\beta}{\gamma}$$

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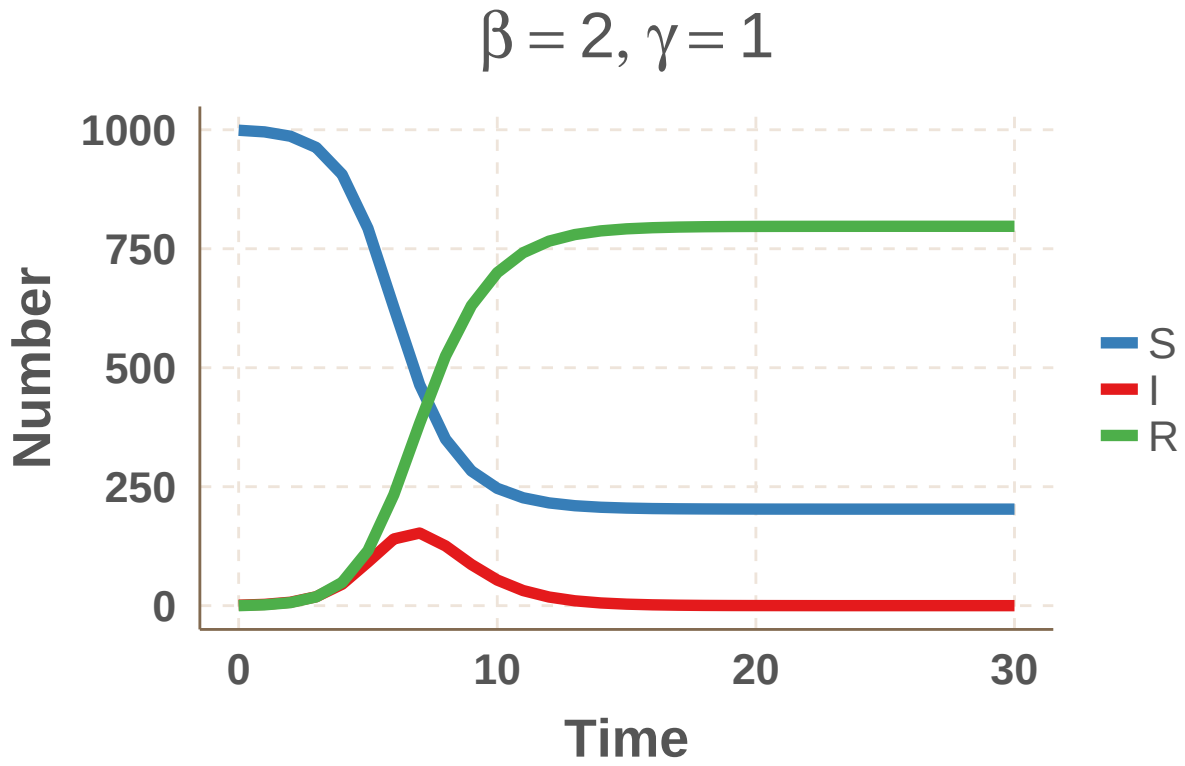

$R_0 = 2$

R_0 and outbreaks

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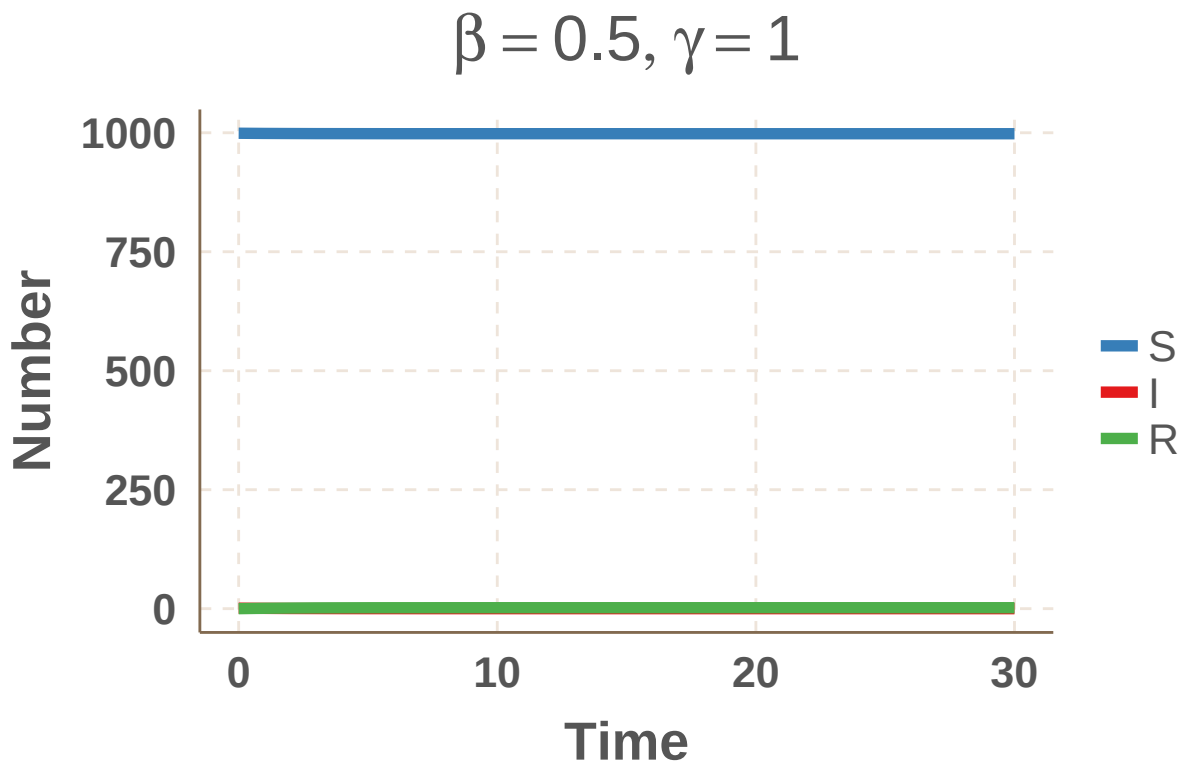
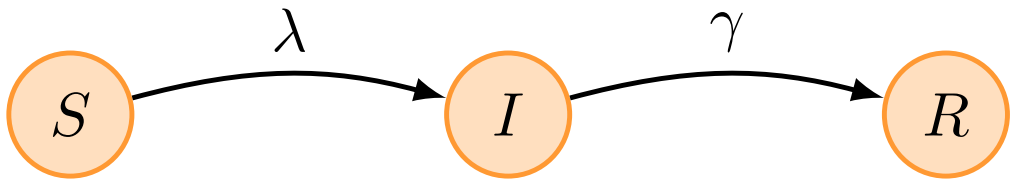


$R_0 = 0.5$

The net reproduction number

The average number of secondary infectious cases resulting from each infectious case in a given population.



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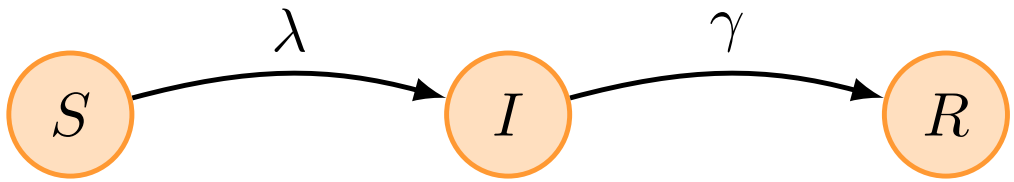

- force of infection from each infectious case: $\lambda = \beta \frac{I}{N}$

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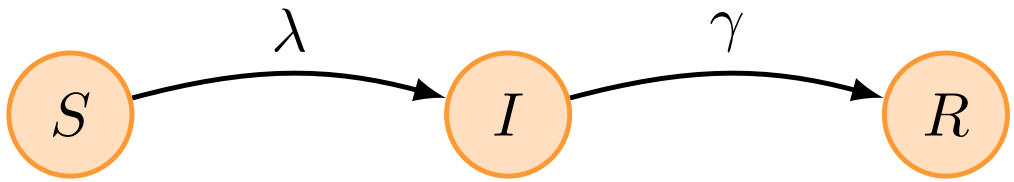

- force of infection from each infectious case: $\lambda = \beta \frac{I}{N}$
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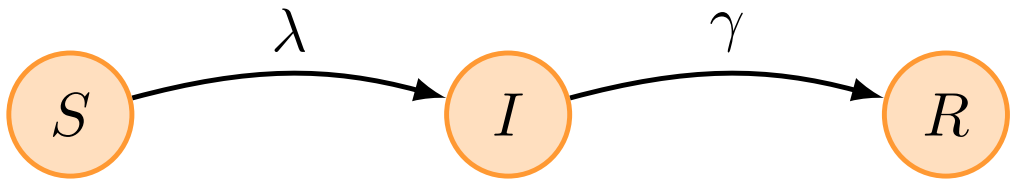

- force of infection from each infectious case: $\lambda = \beta \frac{I}{N}$
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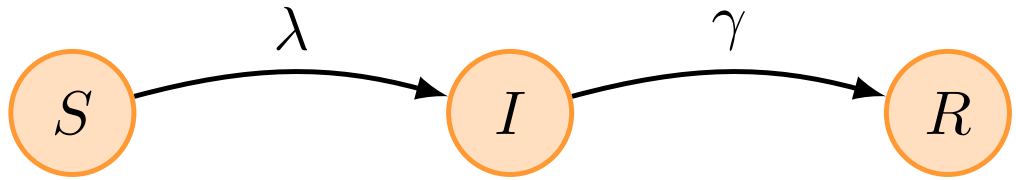

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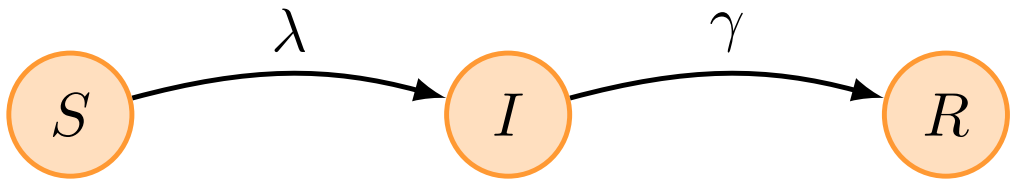
- total number of secondary infectious cases: $\lambda S D = \frac{\beta}{\gamma} \frac{I}{N} S$
- average number of secondary infectious cases: $\frac{\lambda S D}{I}$

$$R_n = \frac{\beta}{\gamma} \frac{S}{N} = R_0 \frac{S}{N}$$

The net reproduction number

The average number of secondary infectious cases resulting from each infectious case in a given population.



- force of infection from each infectious case: $\lambda = \beta \frac{I}{N}$
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- average number of secondary infectious cases: $\frac{\lambda S D}{I}$

$$R_n = \frac{\beta}{\gamma} \frac{S}{N} = R_0 \frac{S}{N}$$

The net reproduction number is the basic reproduction number multiplied with the proportion of the population that is currently susceptible.

Properties of R_n in the SIR model

$$R_n = \frac{\beta}{\gamma}\frac{S}{N}$$

How does the number of infectious change over time?

$$dI/dt = \beta \frac{I}{N} S - \gamma I$$

We can rewrite this as

$$dI/dt = I\gamma(R_n - 1)$$

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The value of R_n determines if, at any time, a disease will increase or decrease.

R_n and outbreaks

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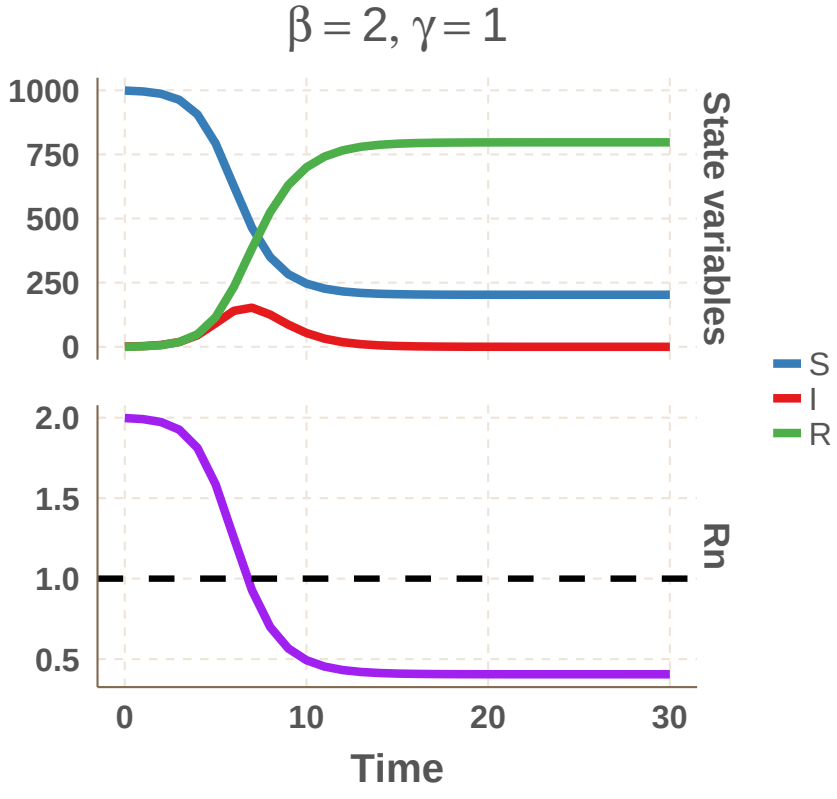

$R_0 = 2$

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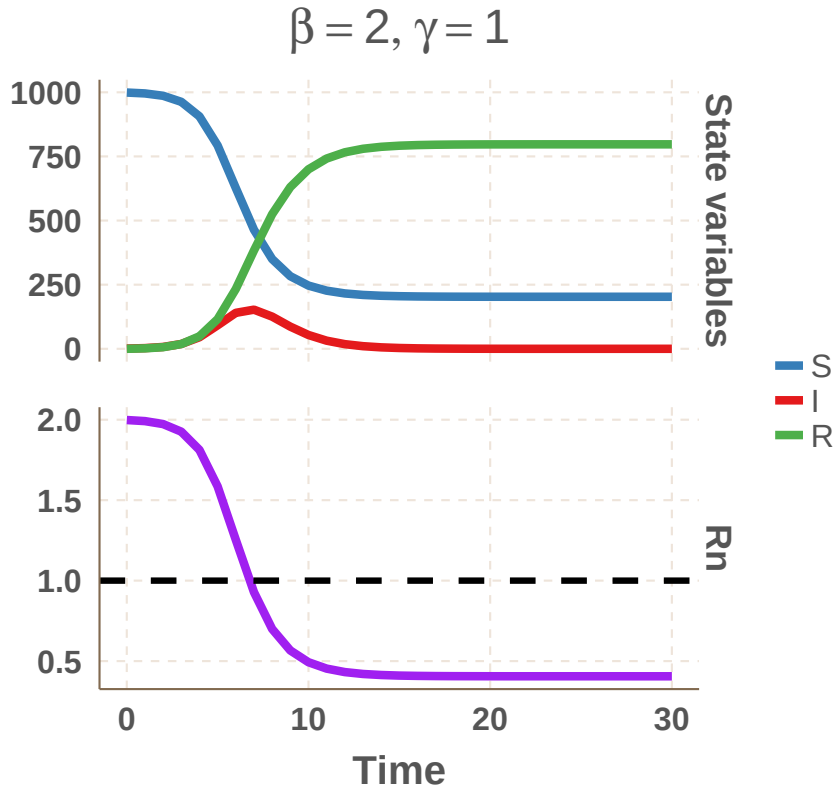

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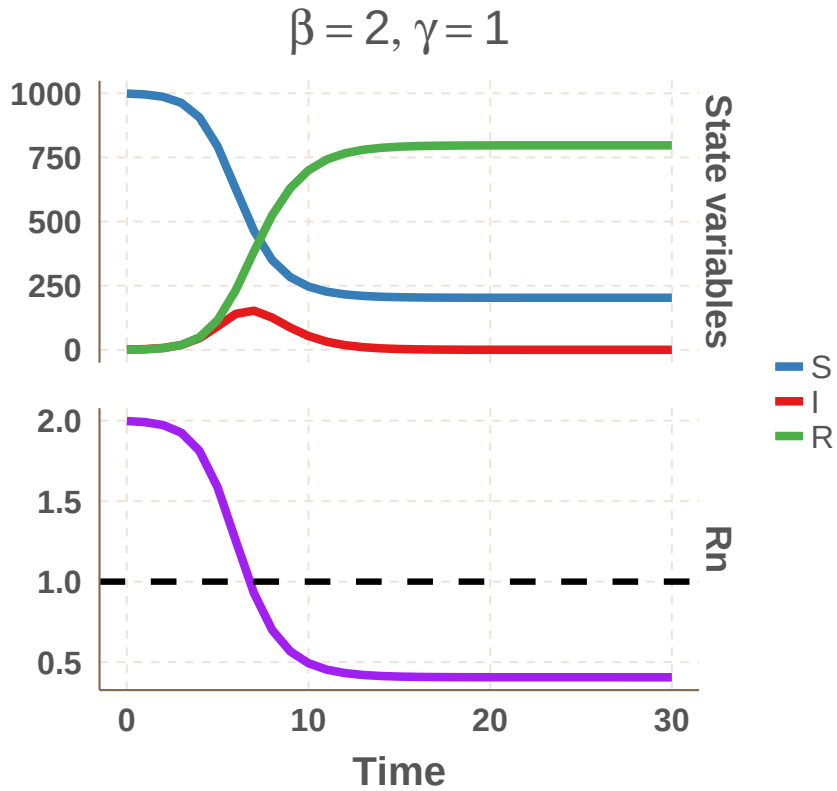

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- Important: You do not have to vaccinate everyone (herd immunity)

Examples: The herd immunity threshold

Infectious disease	Herd immunity threshold (%)
Malaria	99
Measles	90-95
Whooping cough	90-95
Chickenpox	85-90
Mumps	85-90
Rubella	82-87
Polio	82-87
Diphtheria	82-87
Smallpox	70-80
Influenza	40-60

Applications of the SIR model

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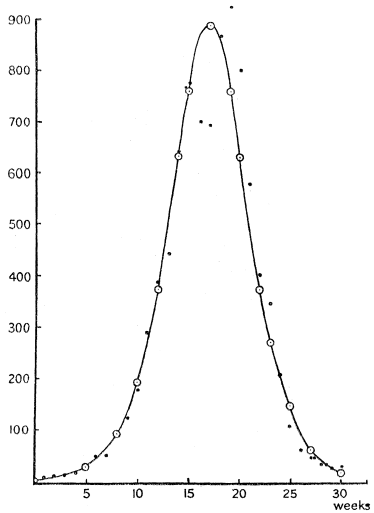

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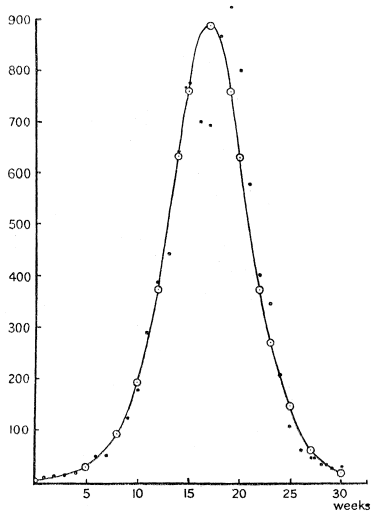

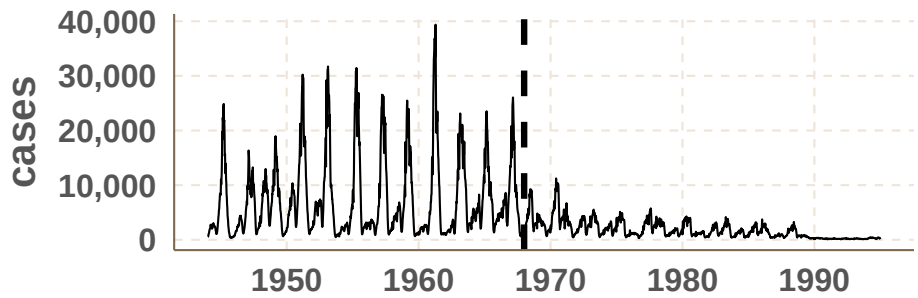

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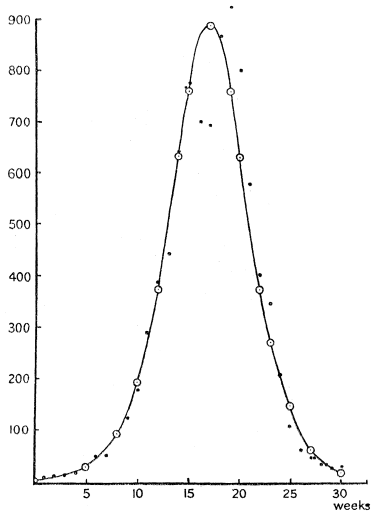

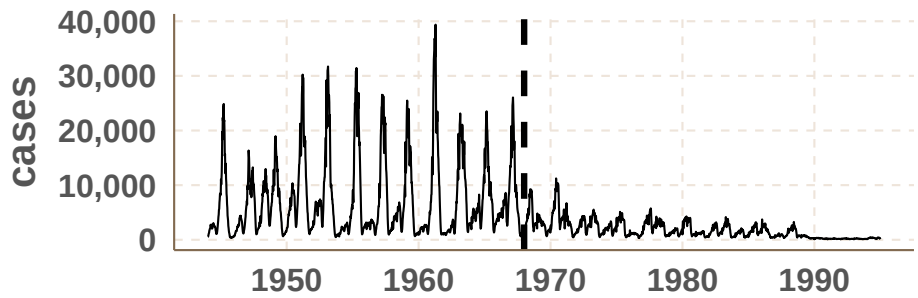

5. Modelling endemic diseases

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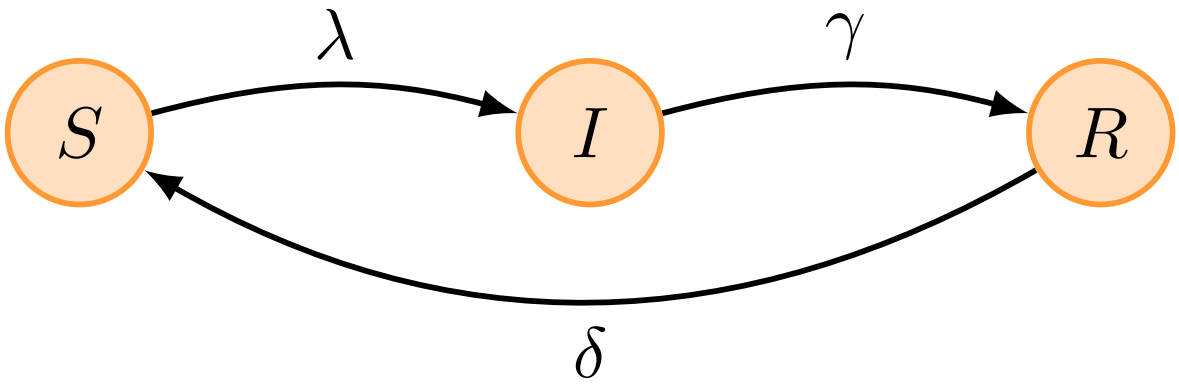

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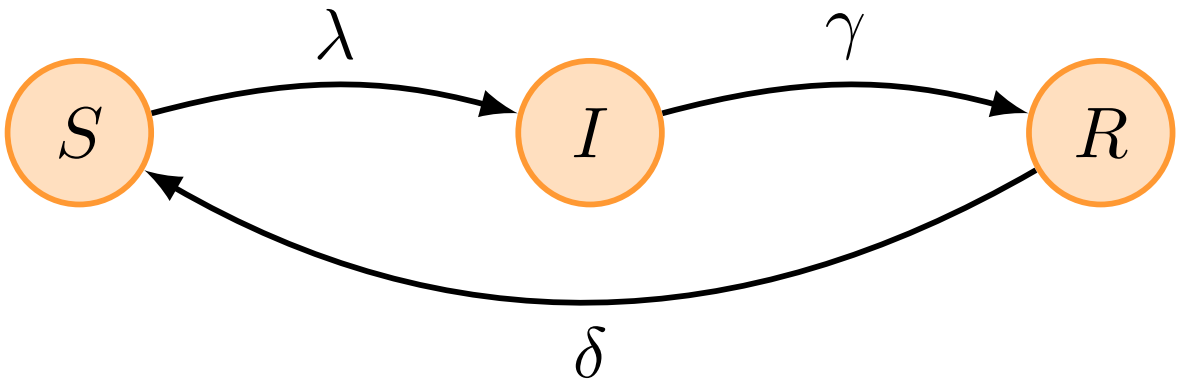

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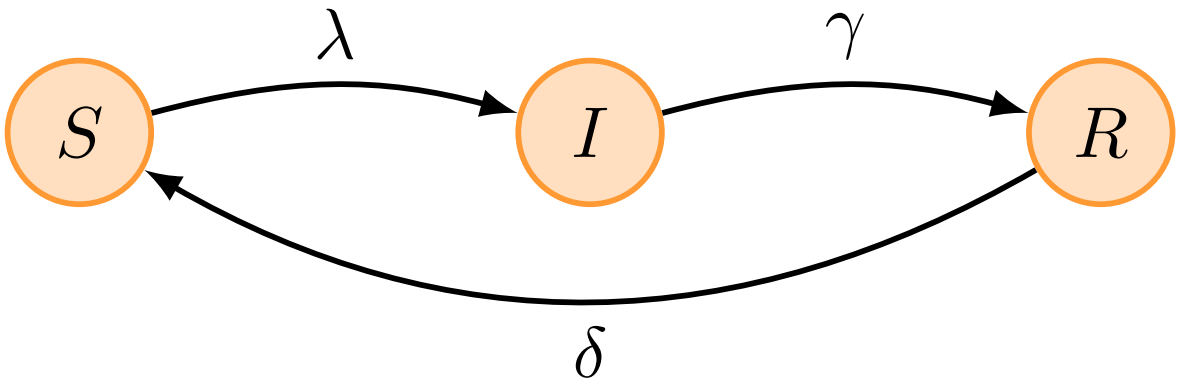

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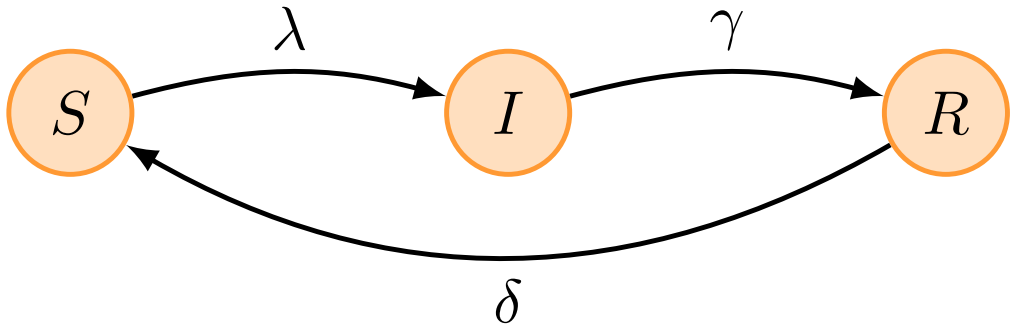

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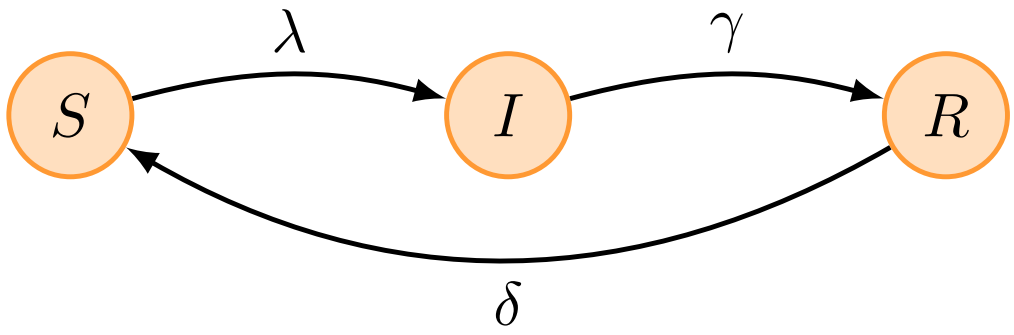

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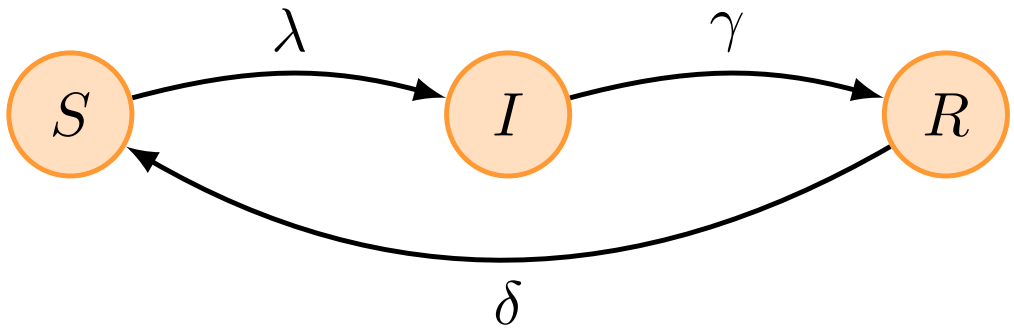

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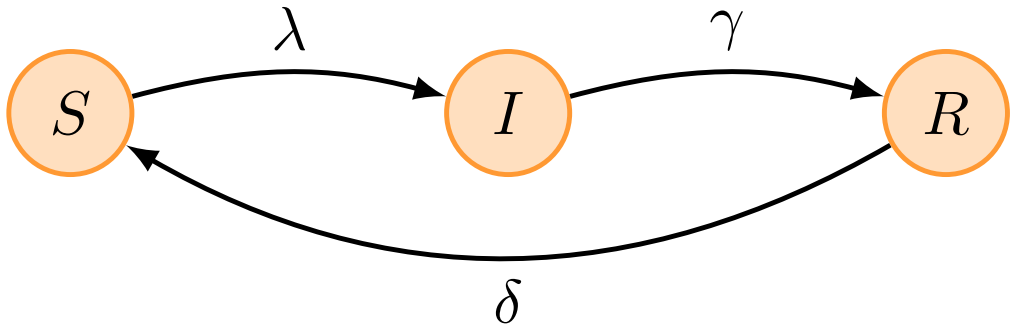

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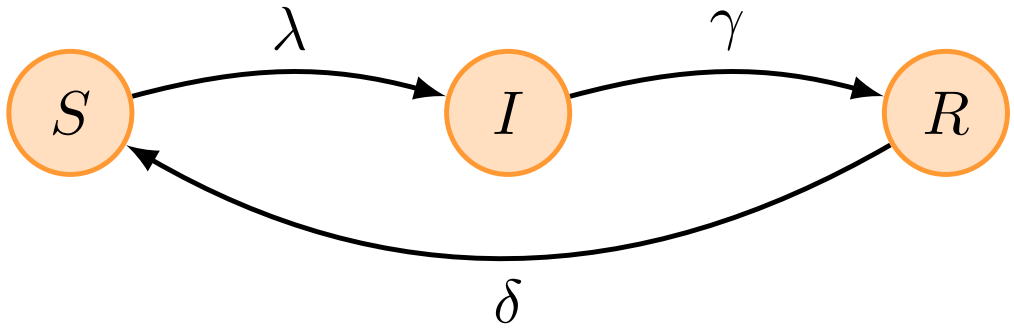

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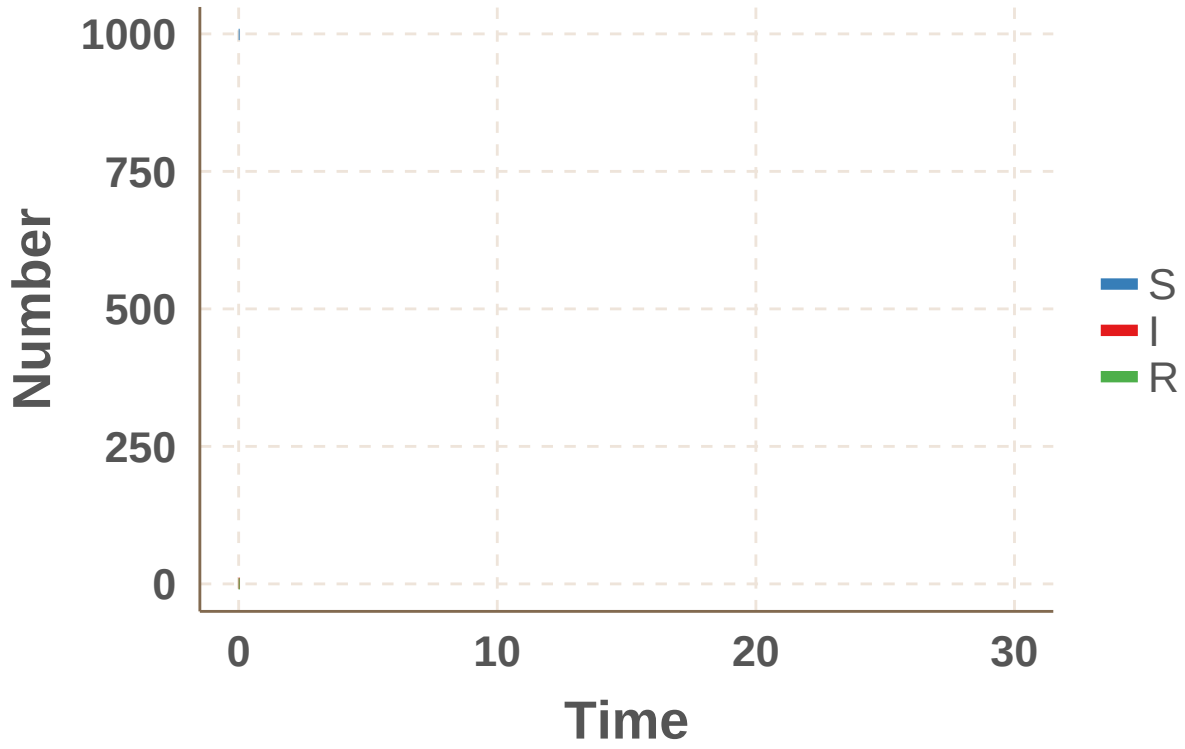

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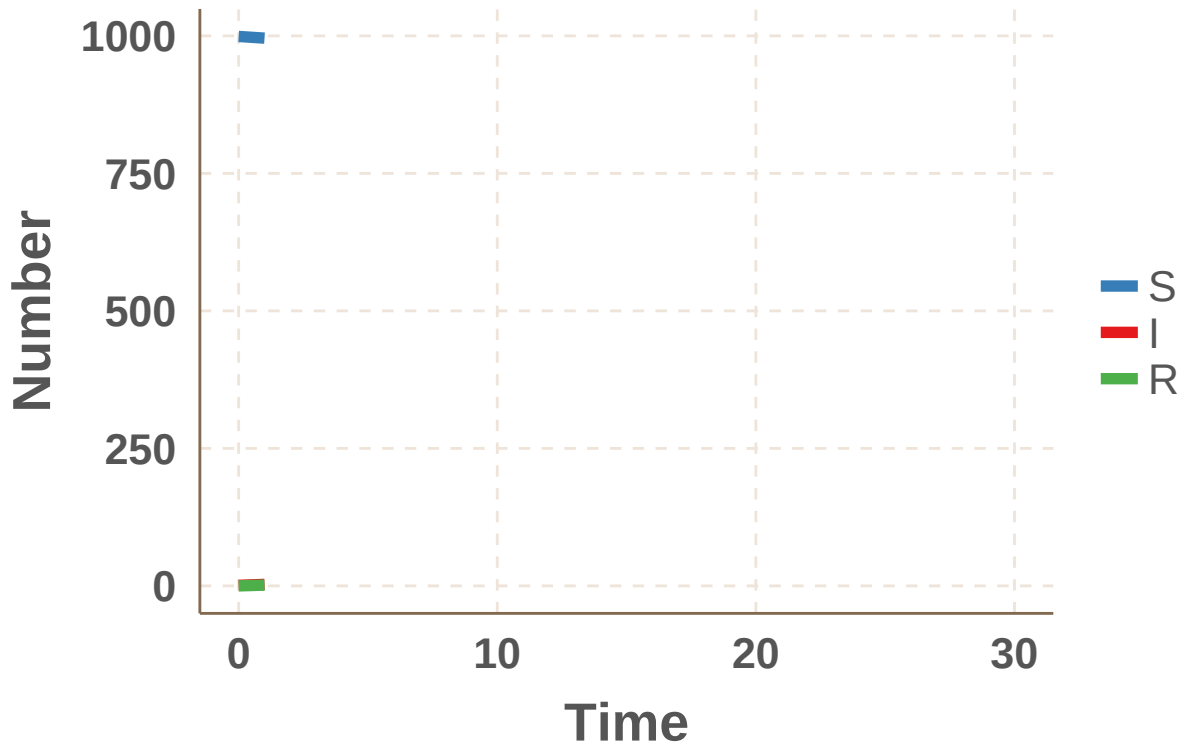

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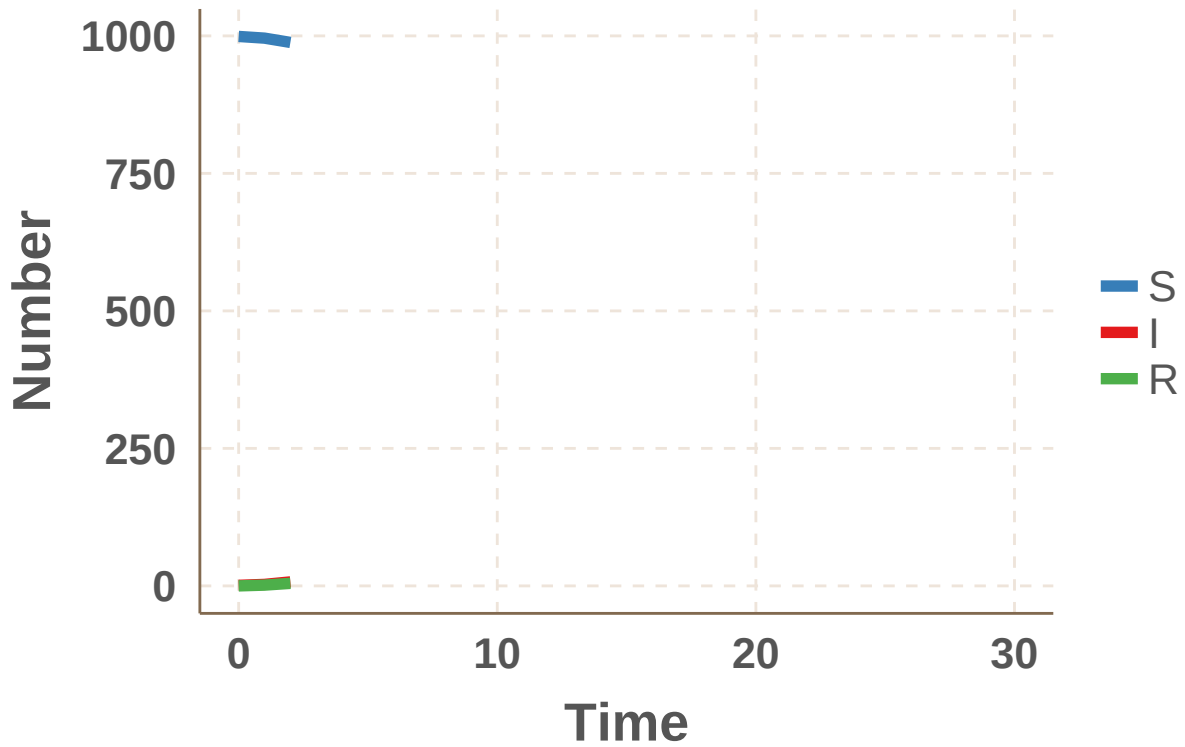

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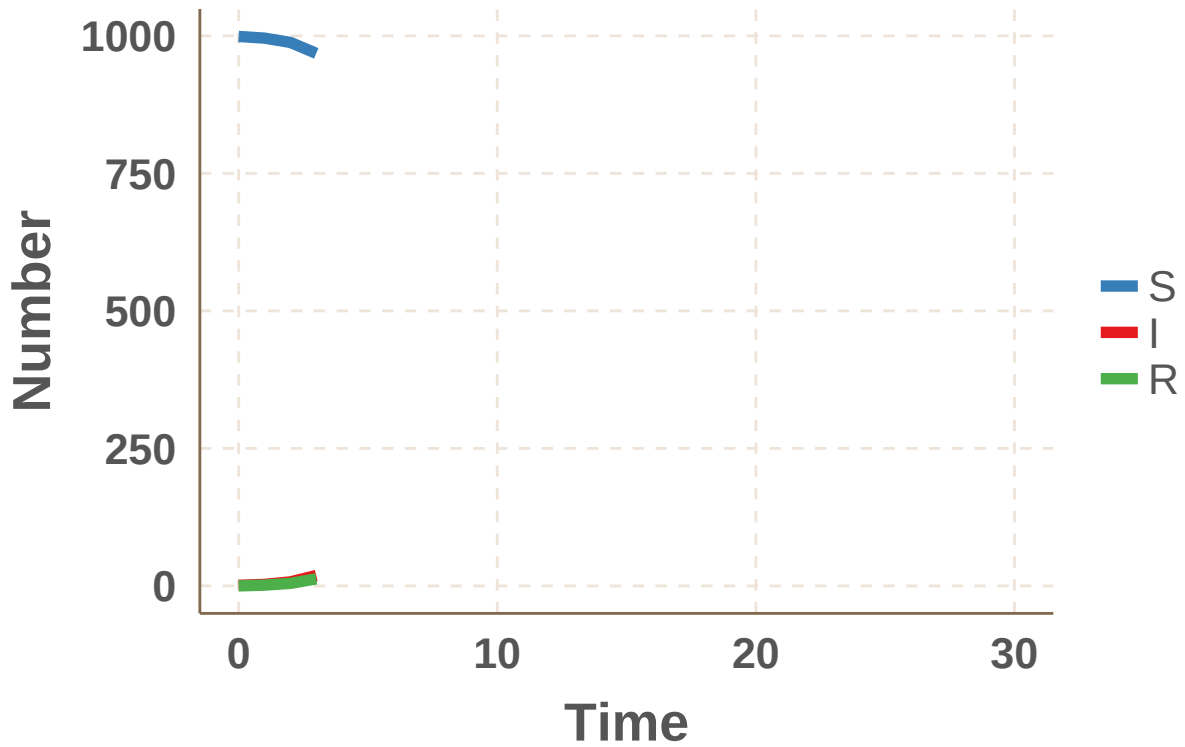

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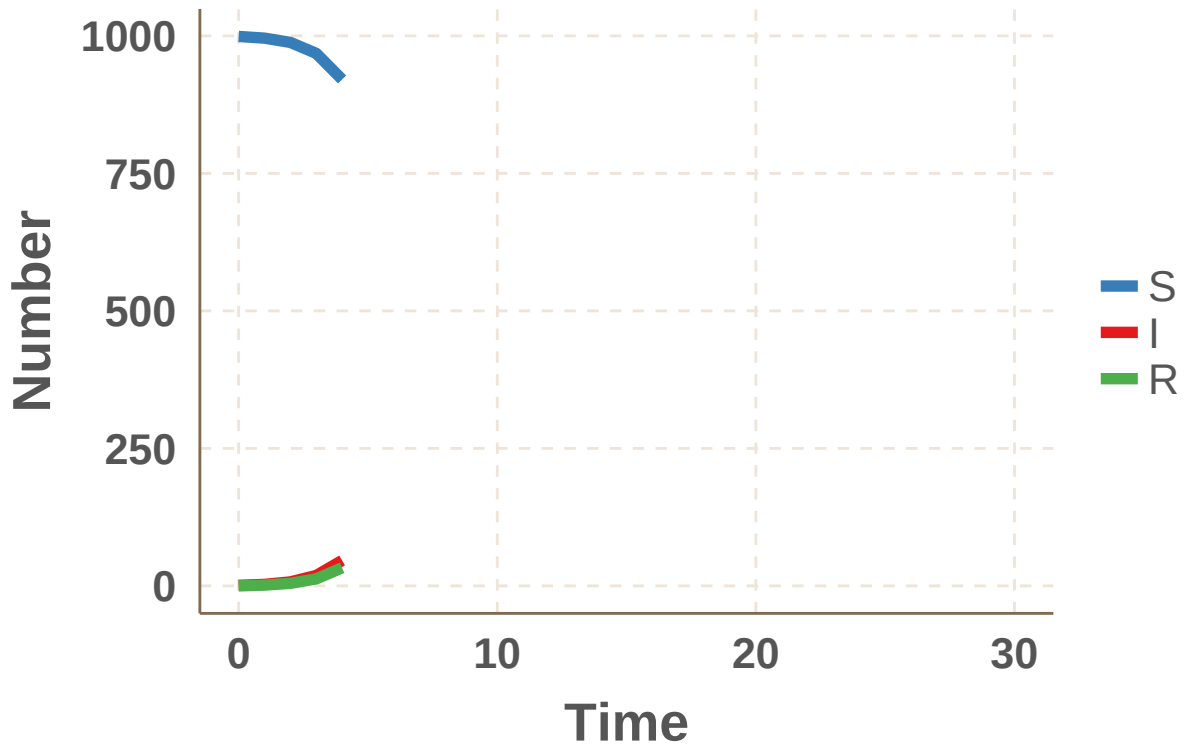

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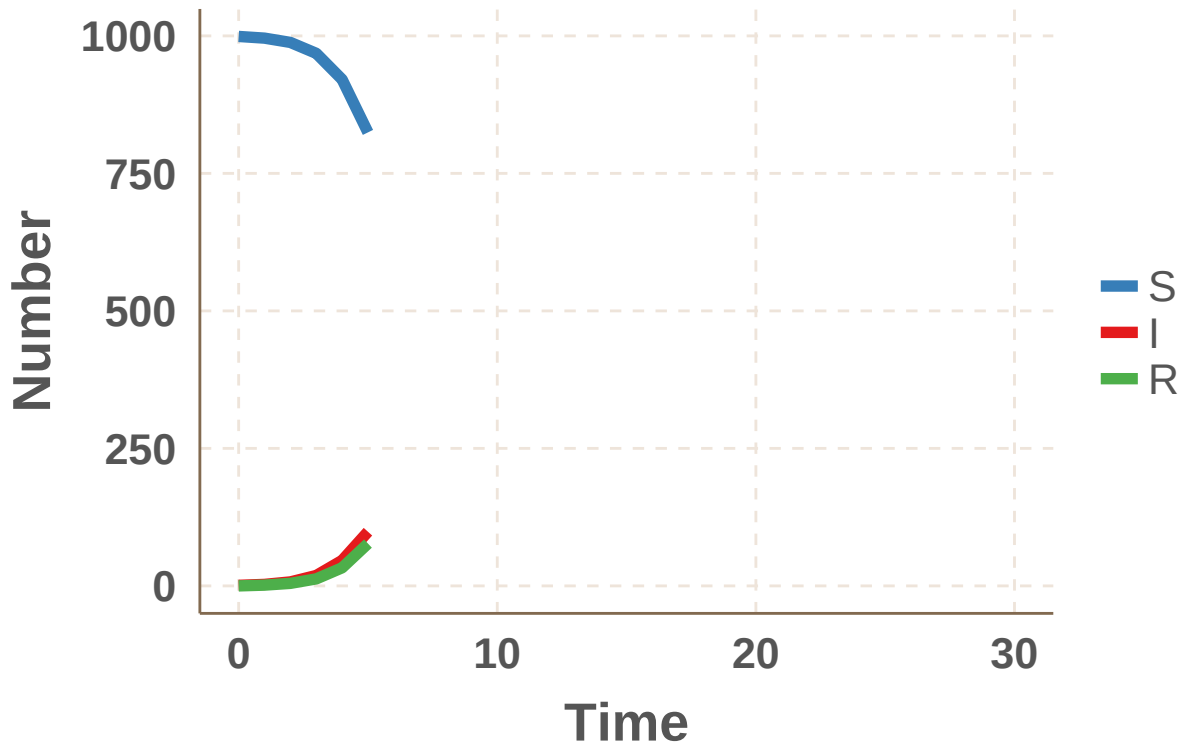

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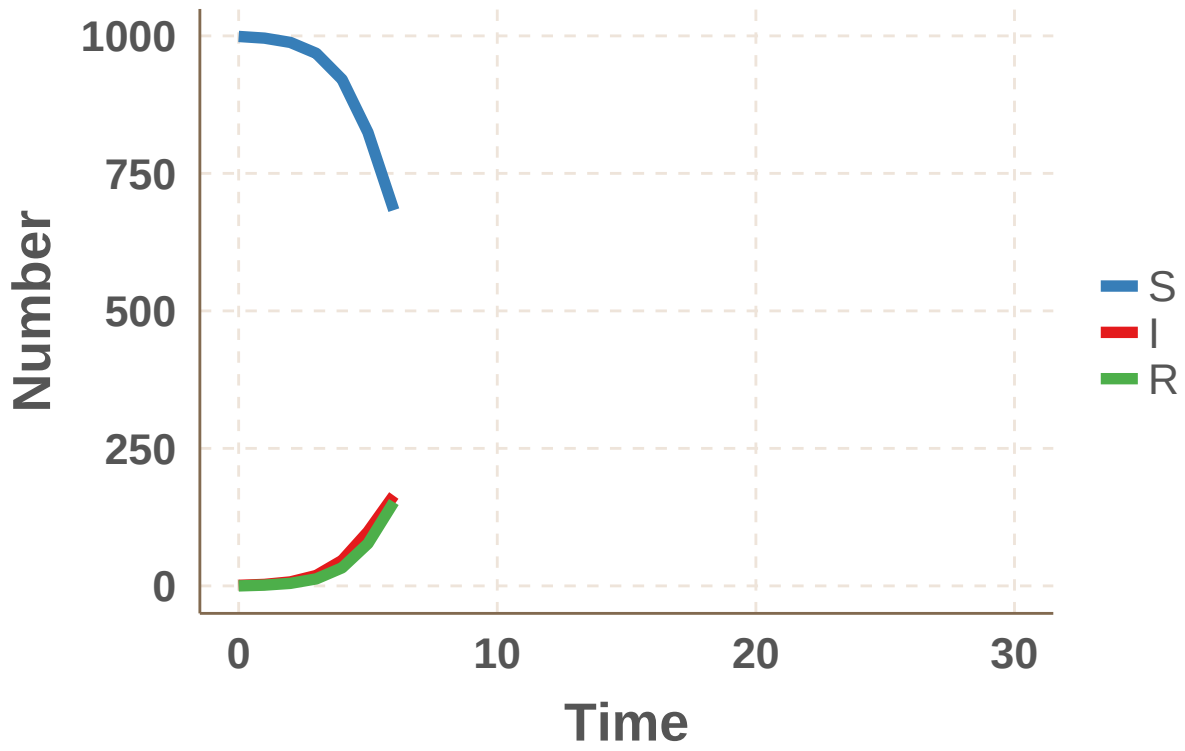

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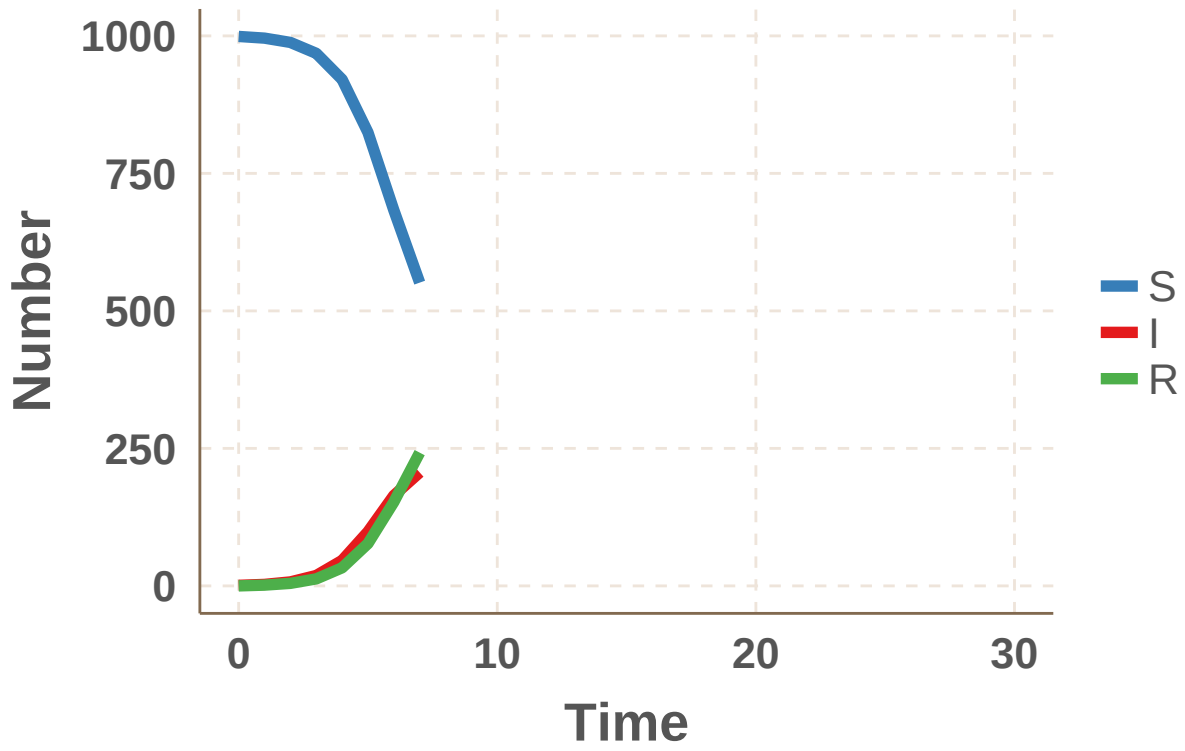

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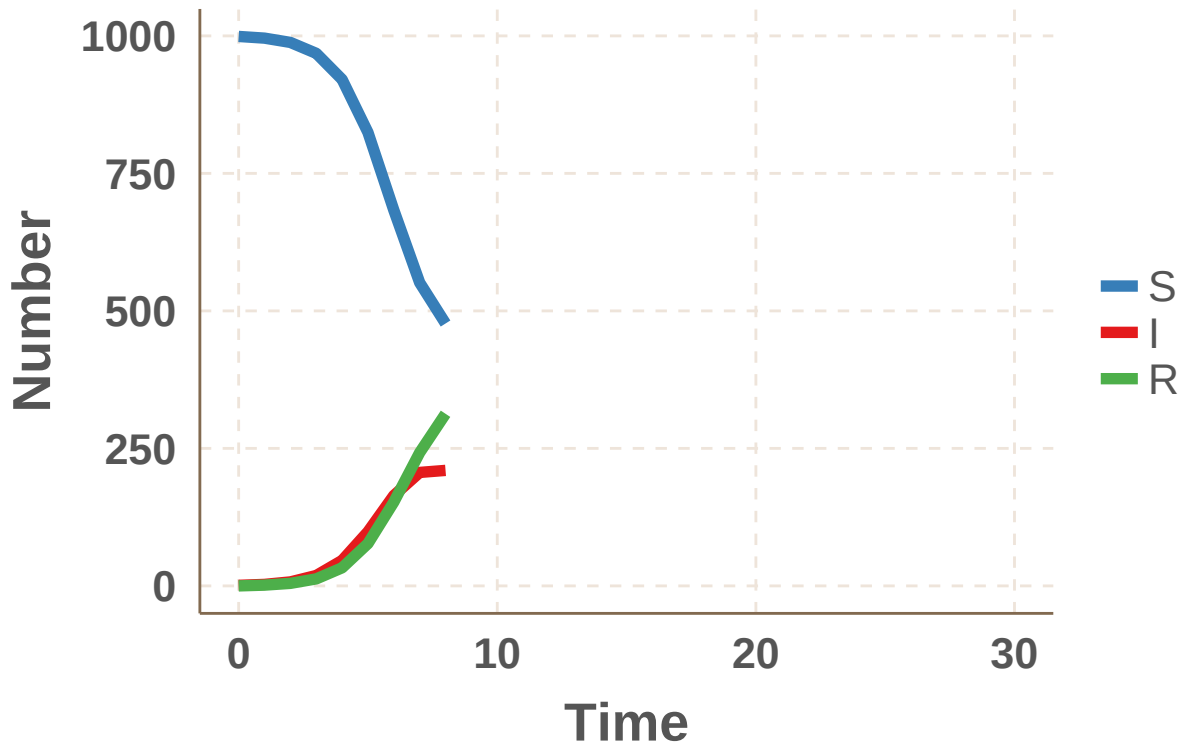

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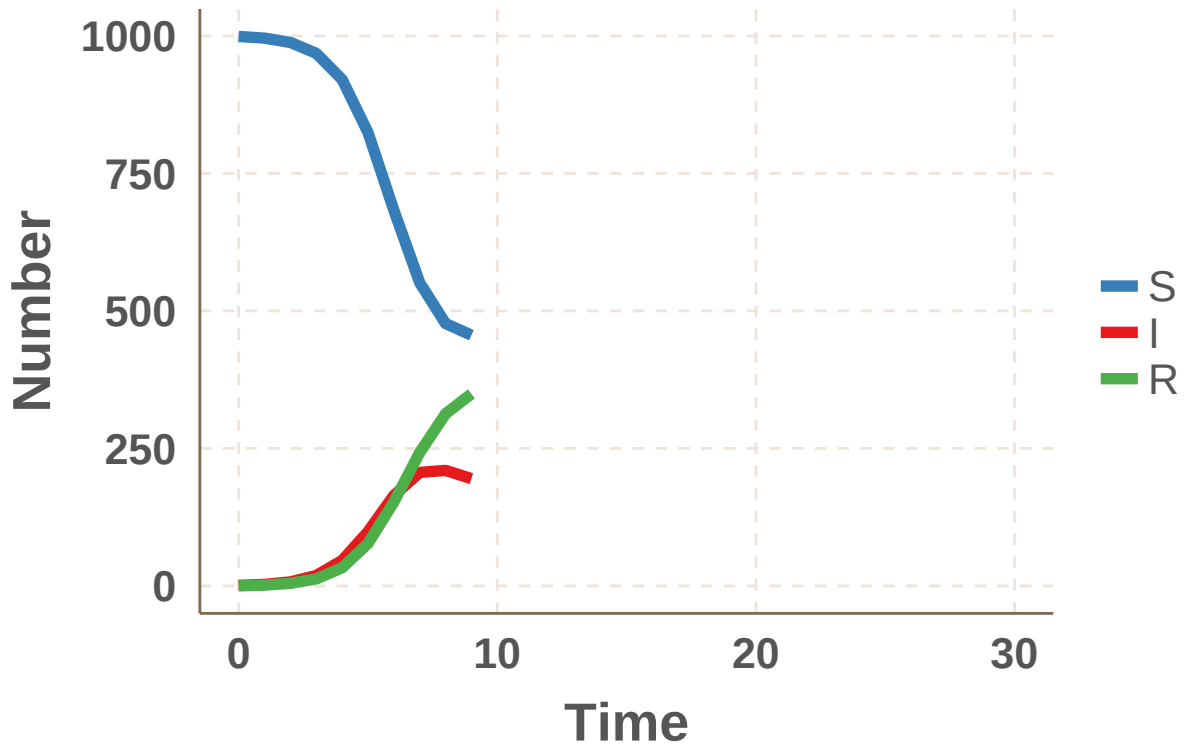

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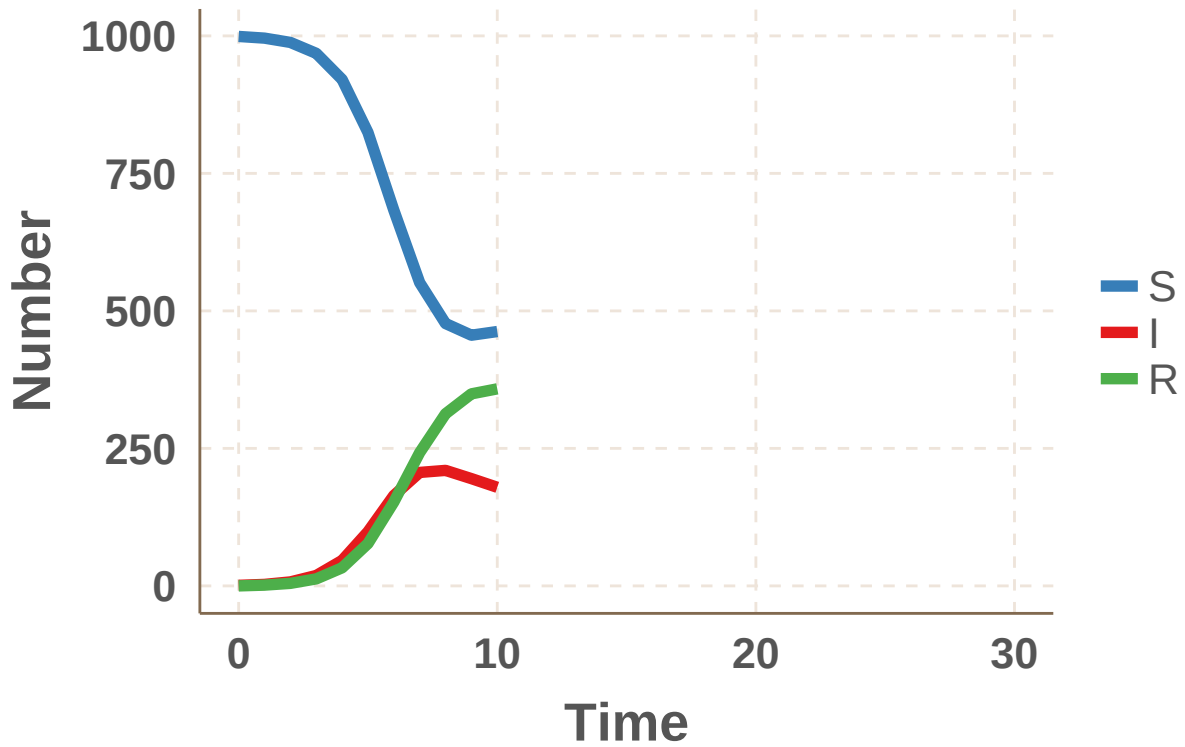

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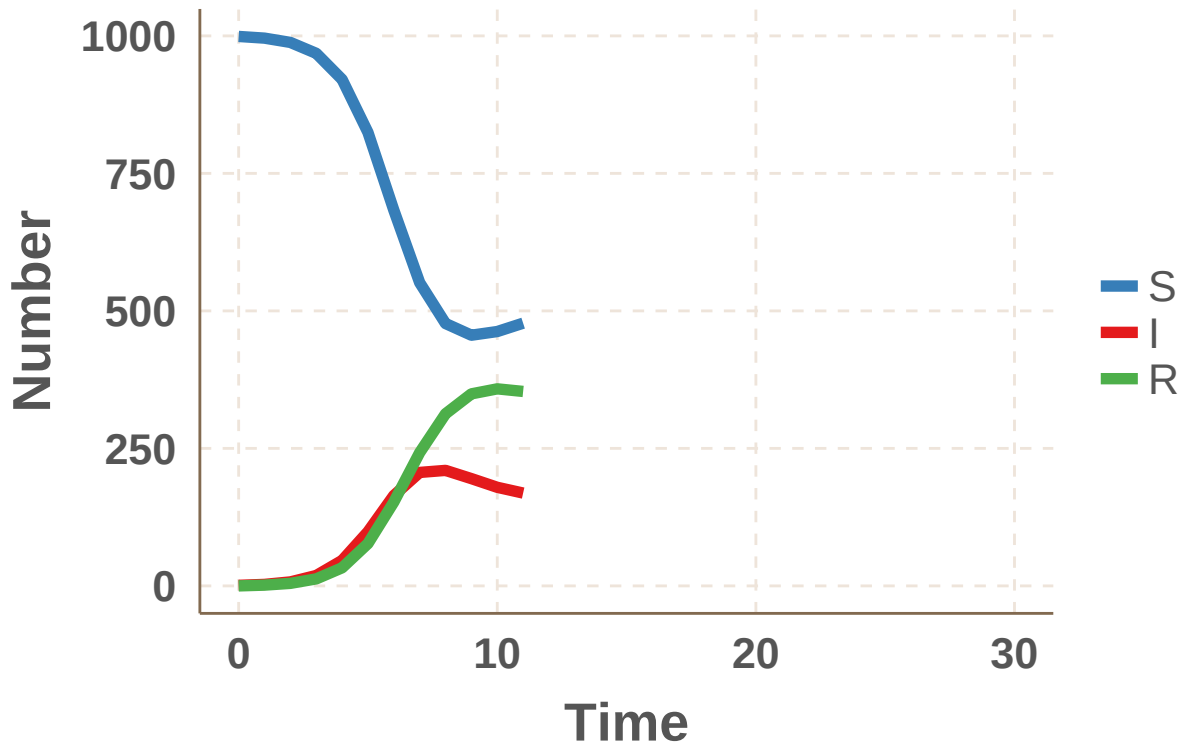

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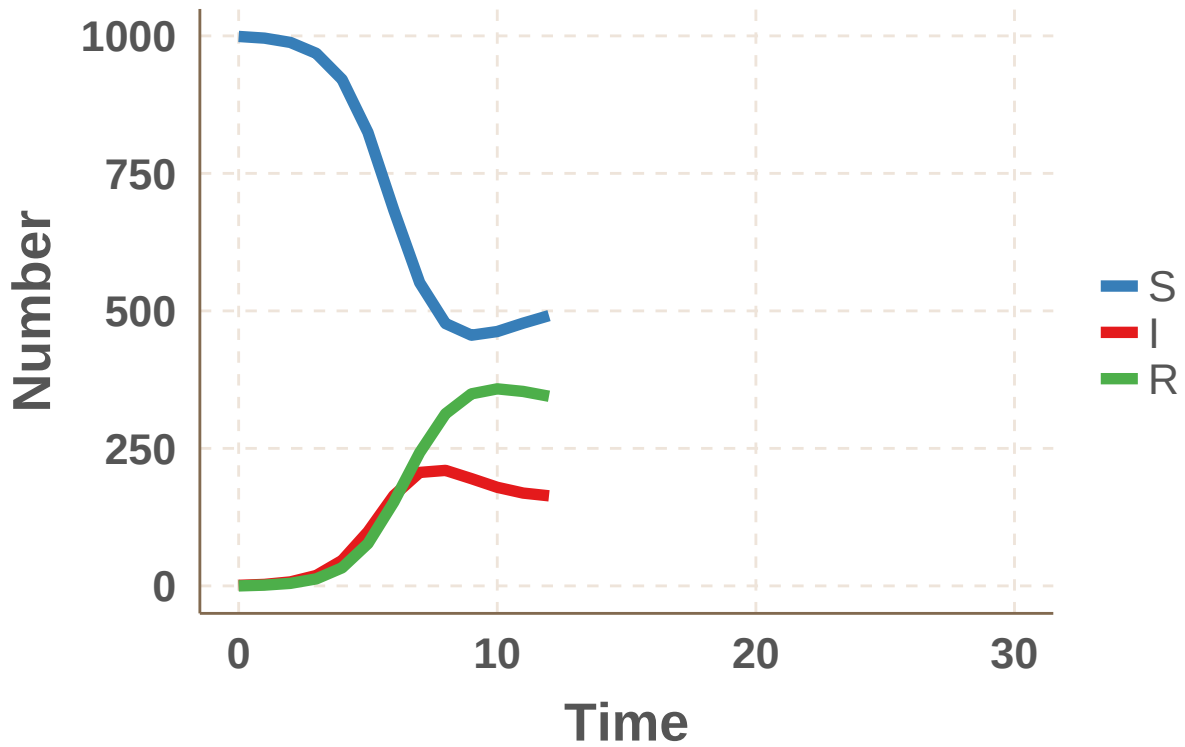

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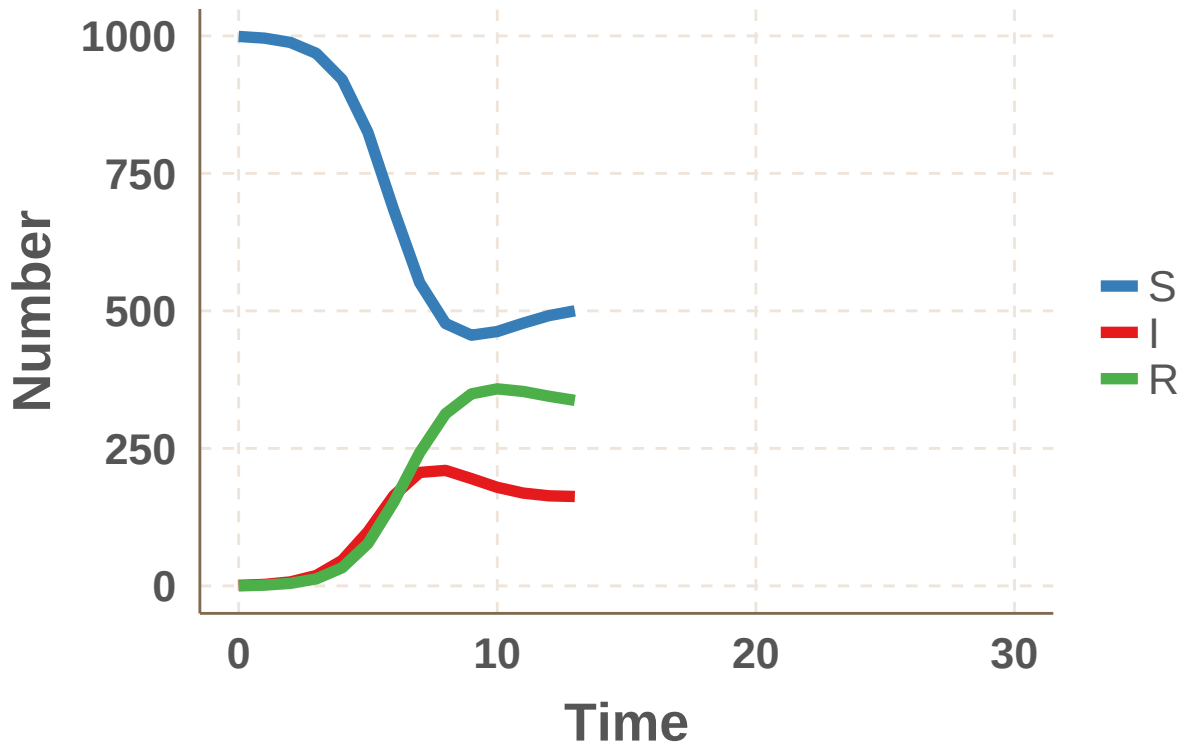

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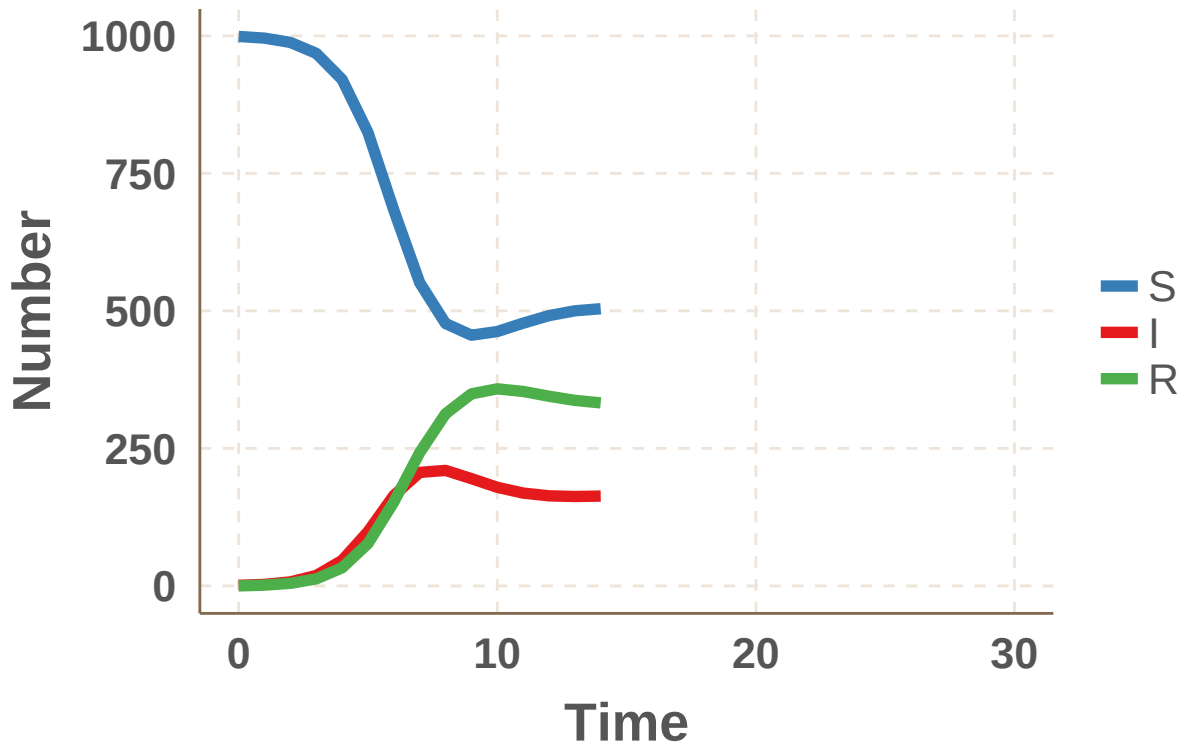

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$$dS/dt = -\beta \frac{I}{N} S + \delta R$$

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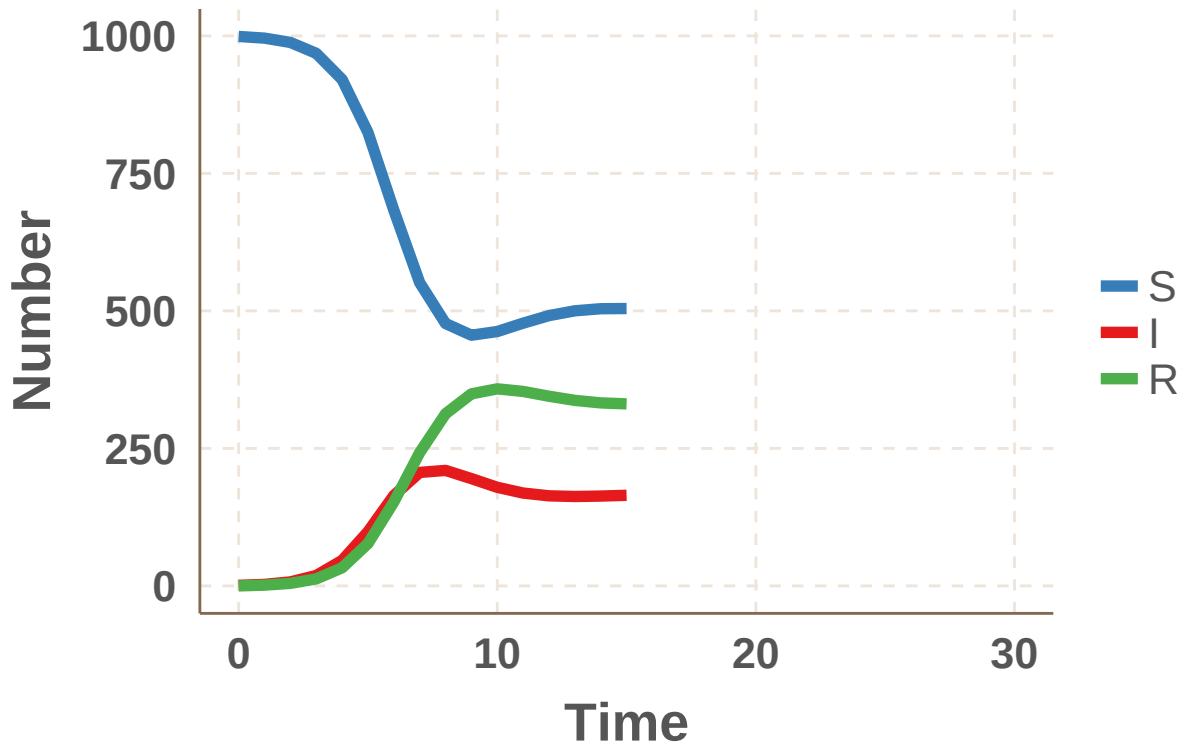
$$dR/dt = +\gamma I - \delta R$$



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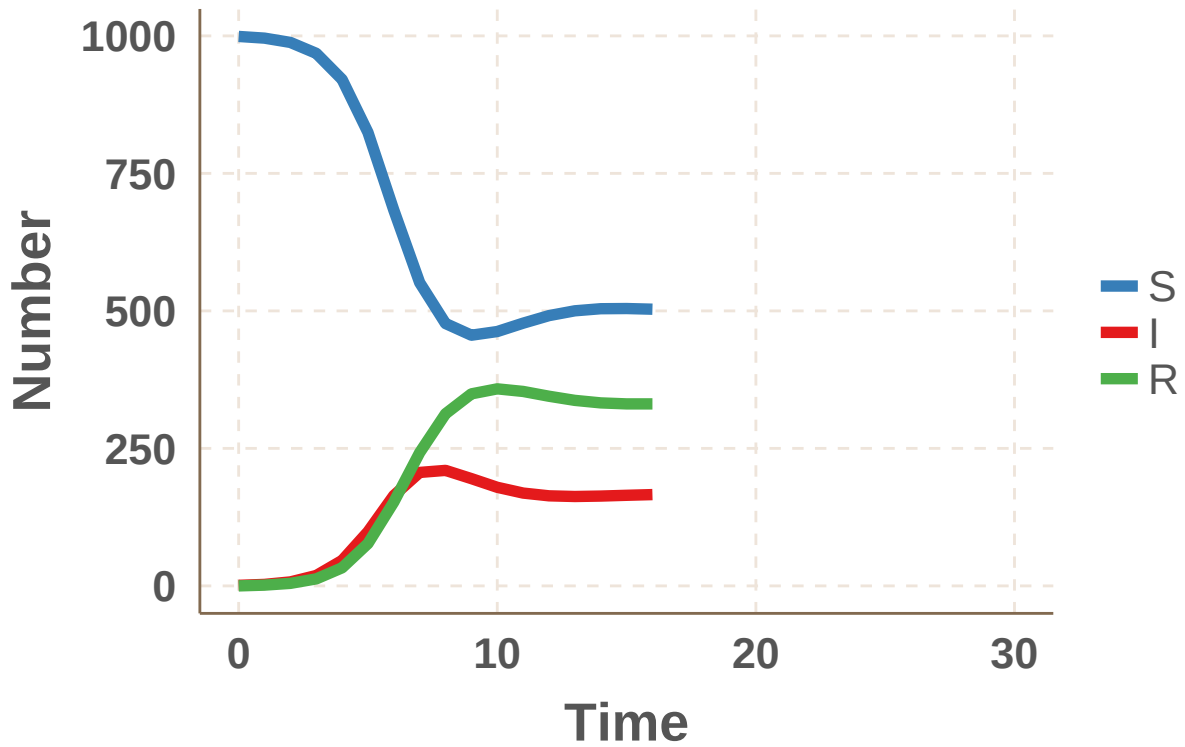

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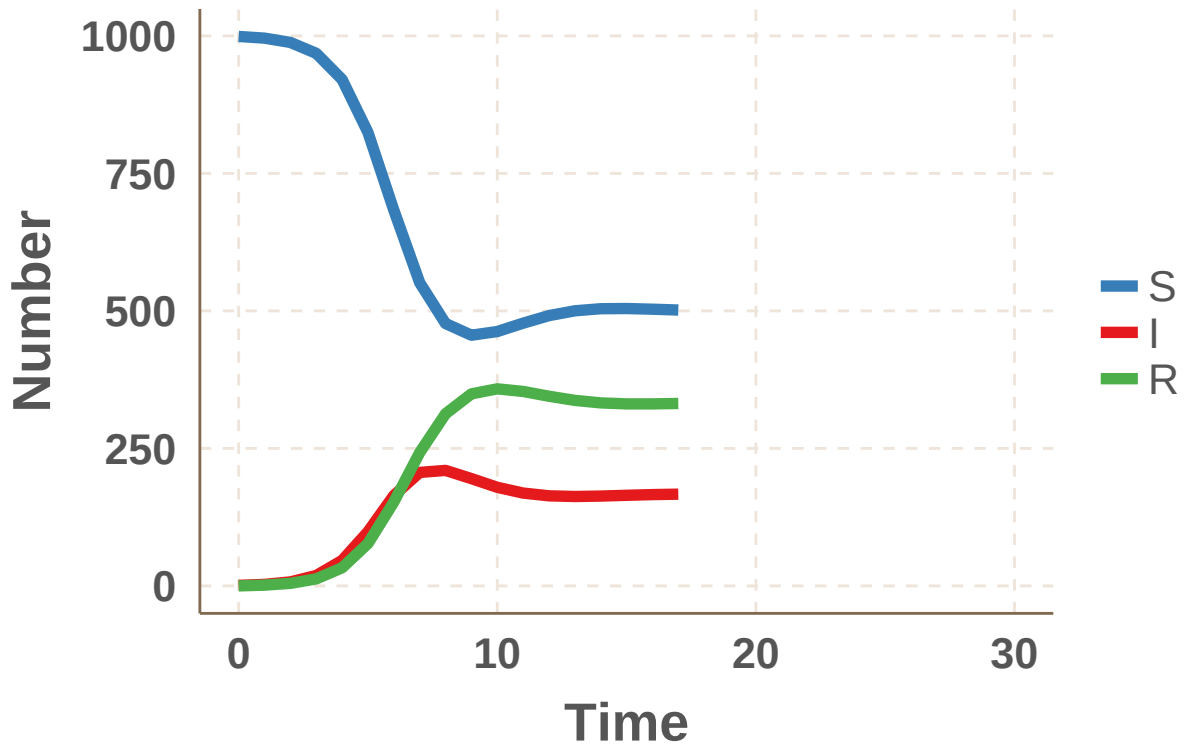

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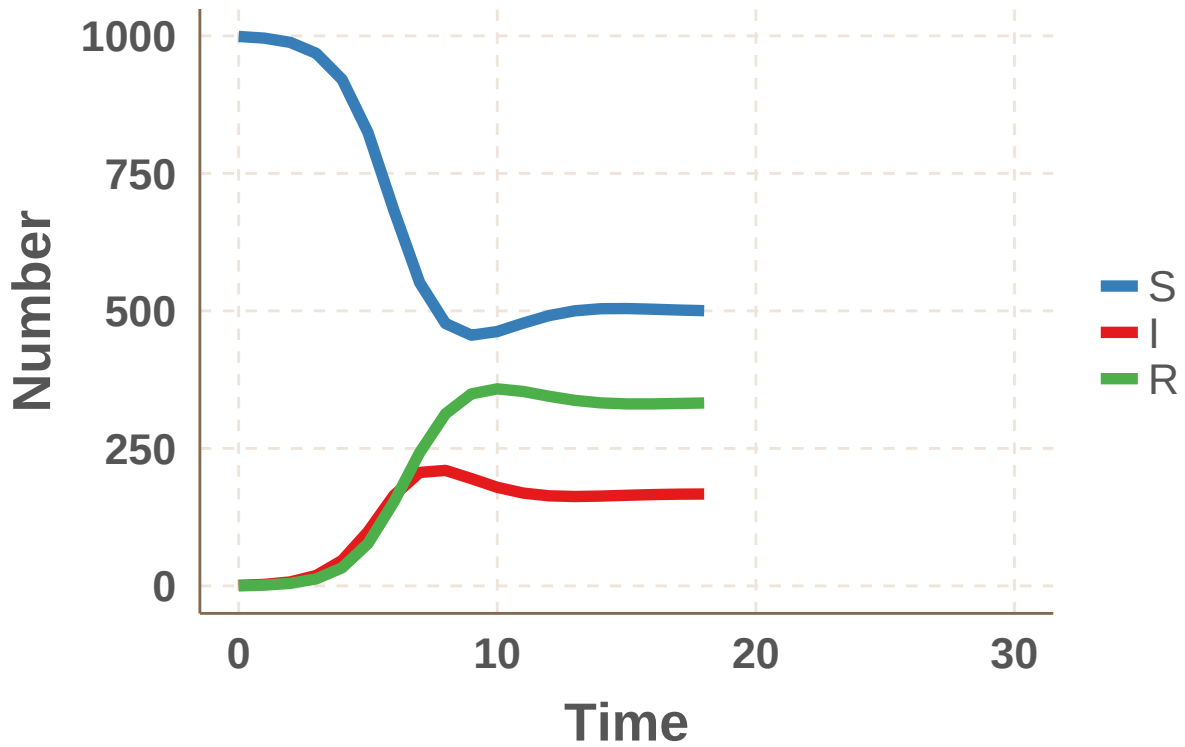

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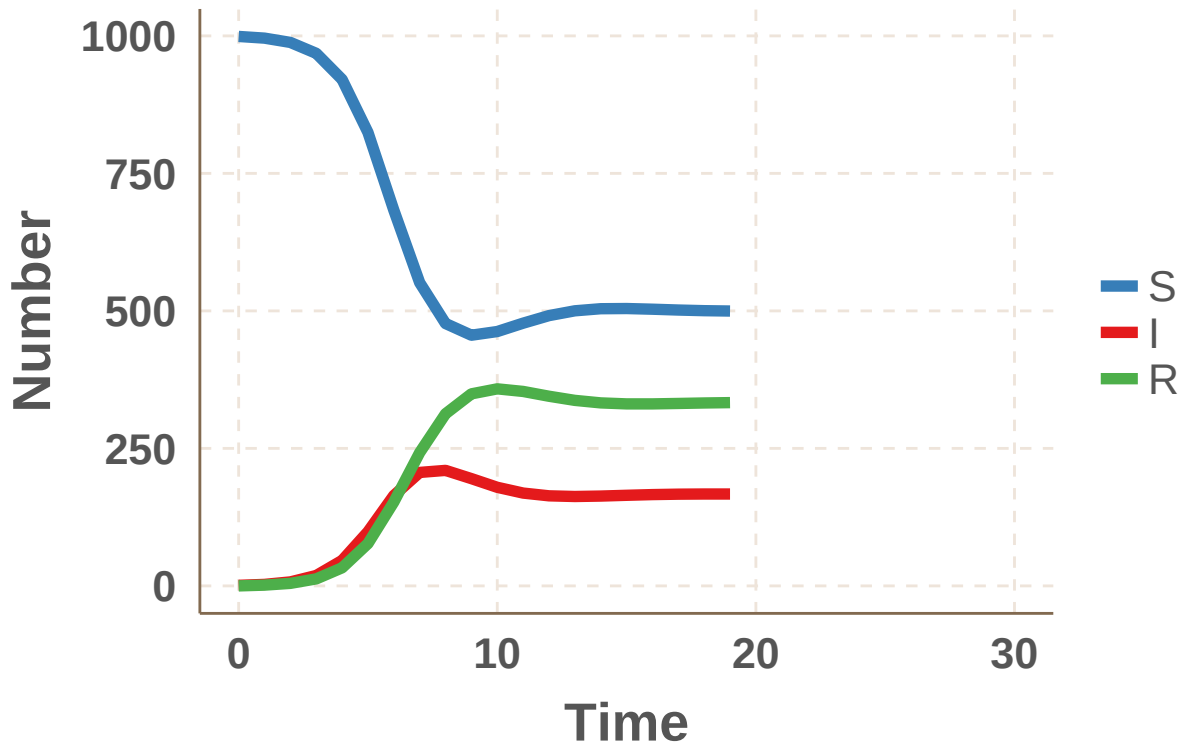

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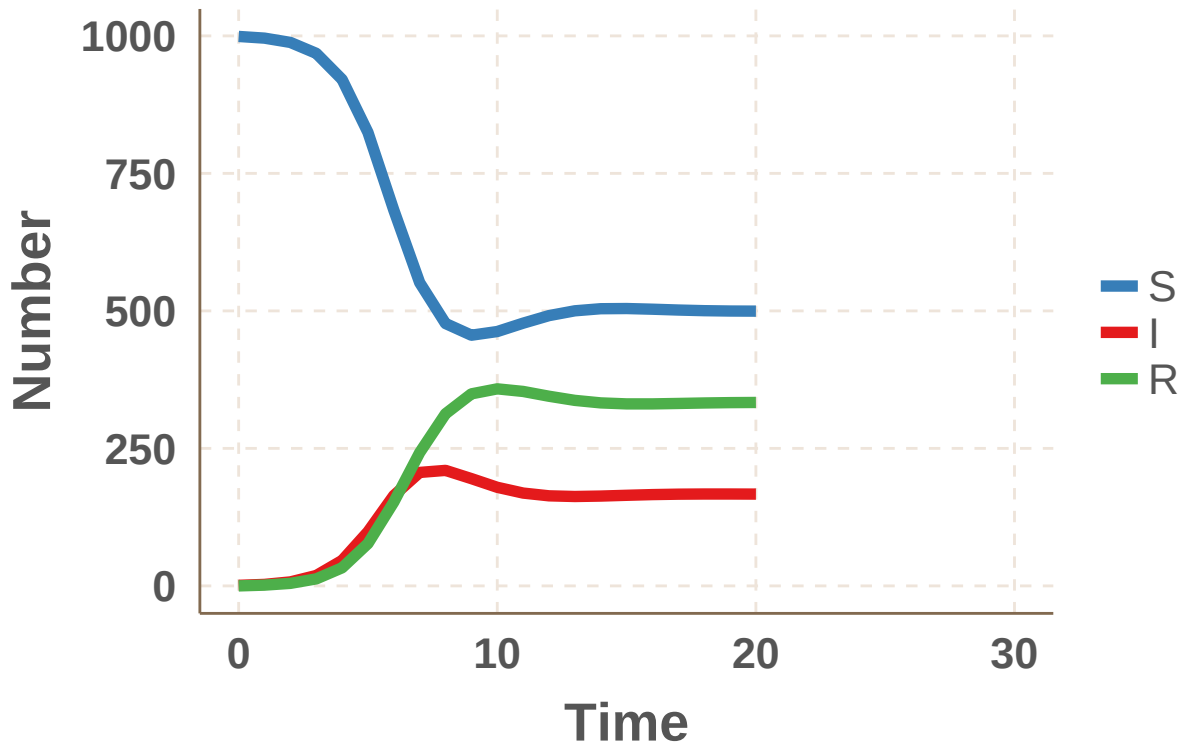

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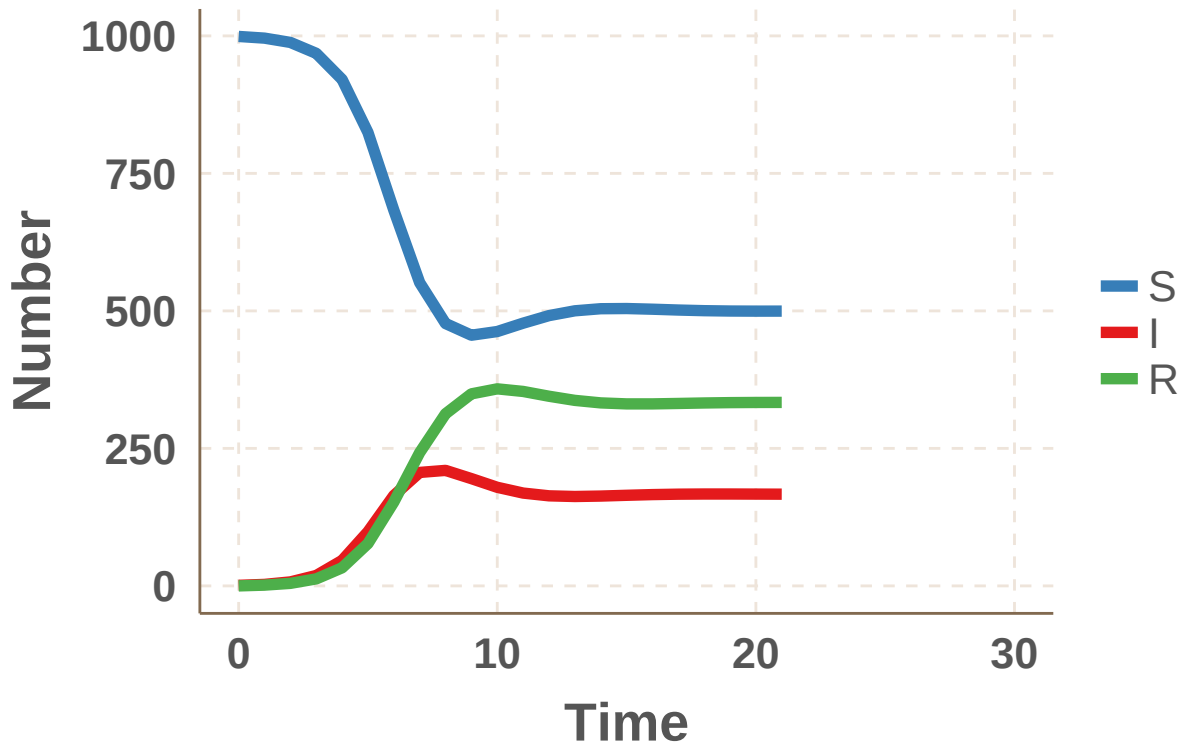

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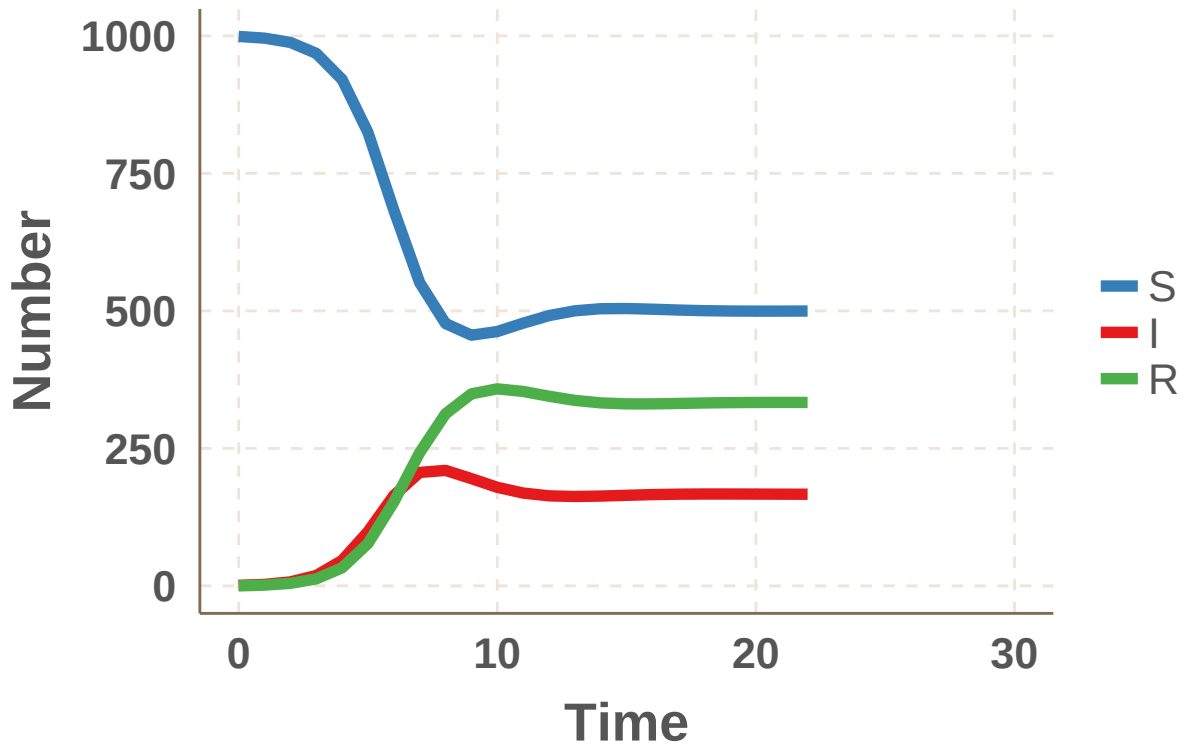

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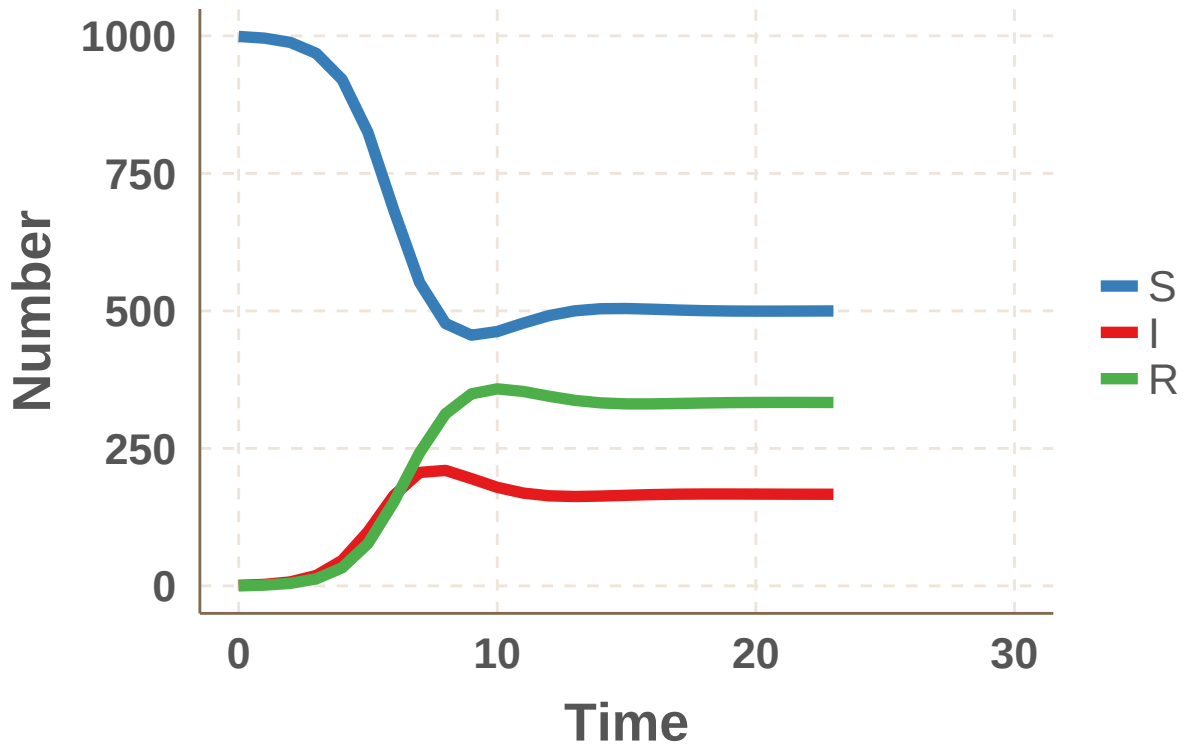

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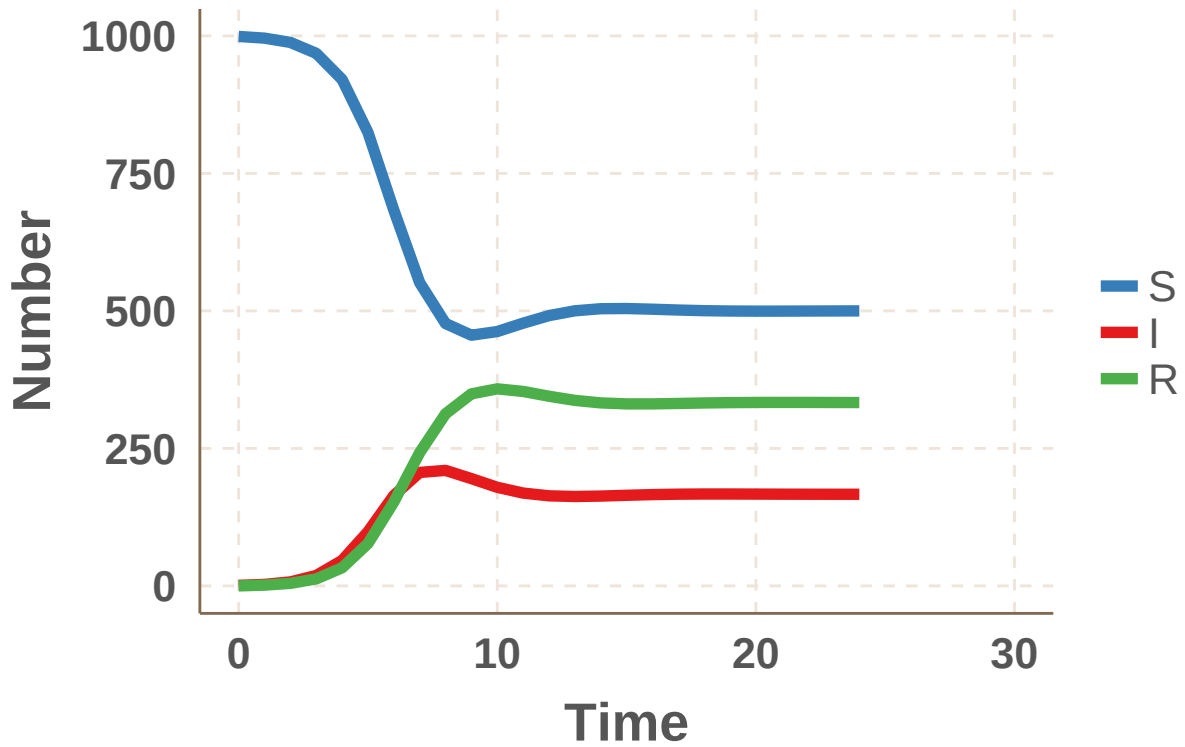

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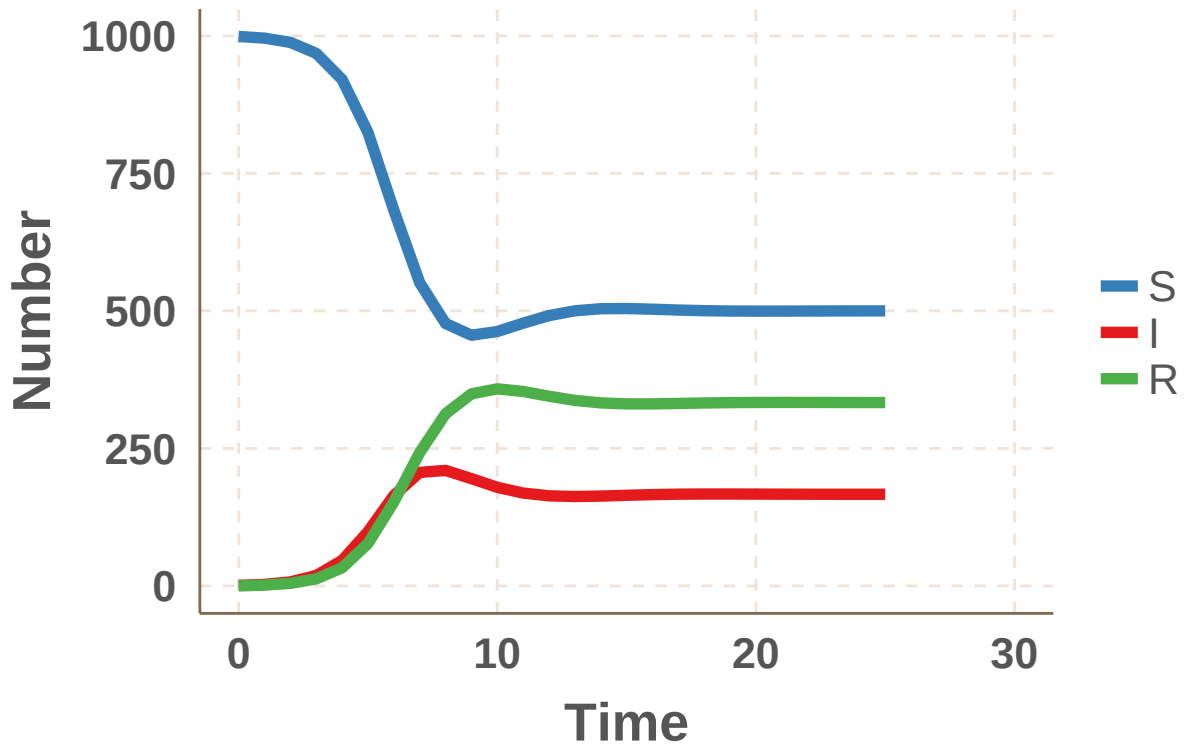

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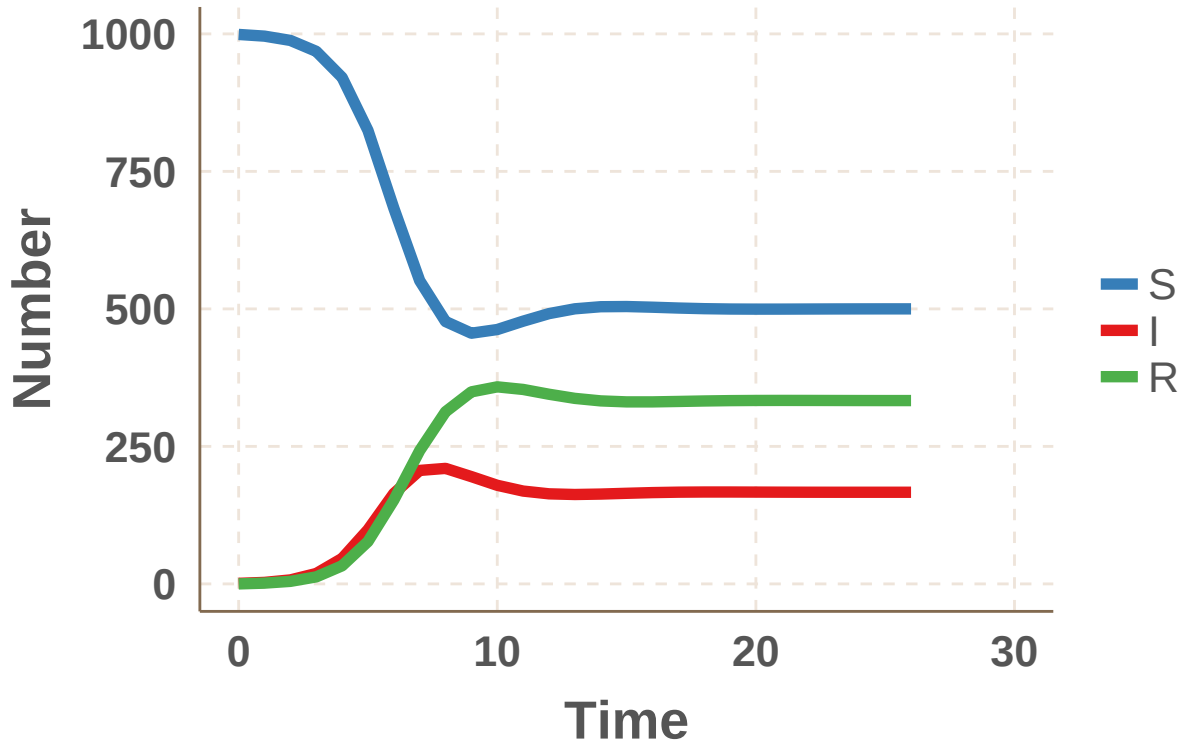

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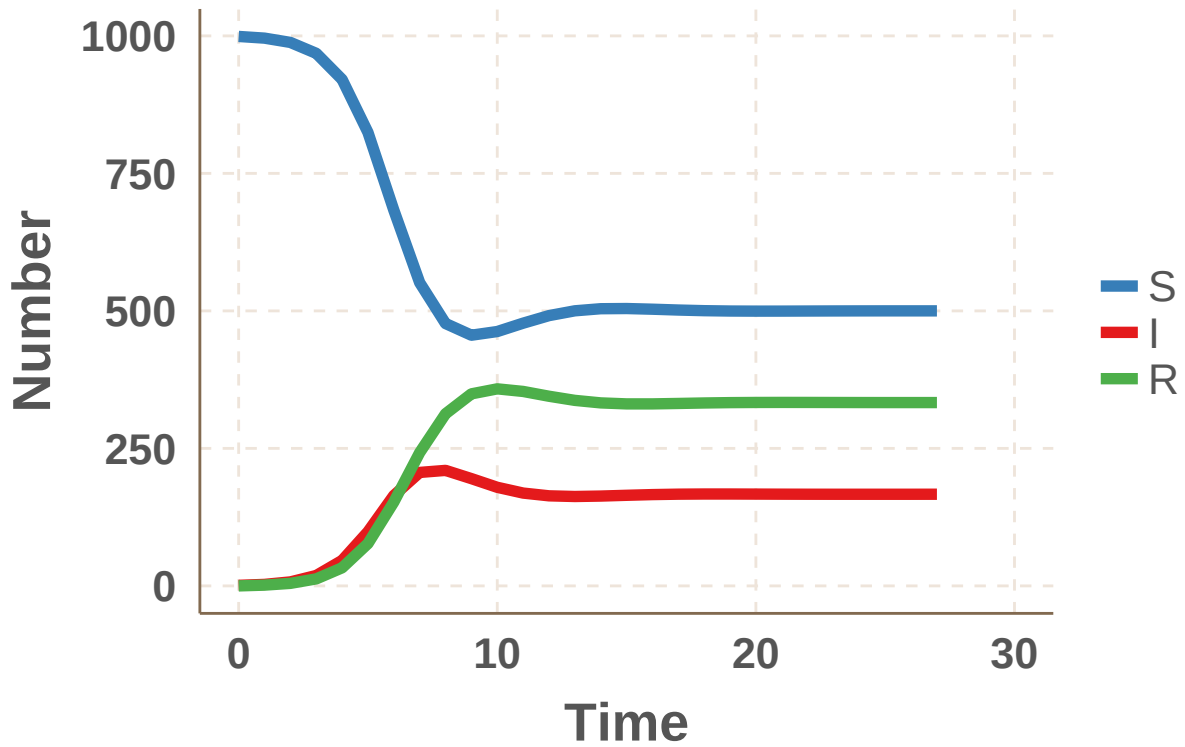

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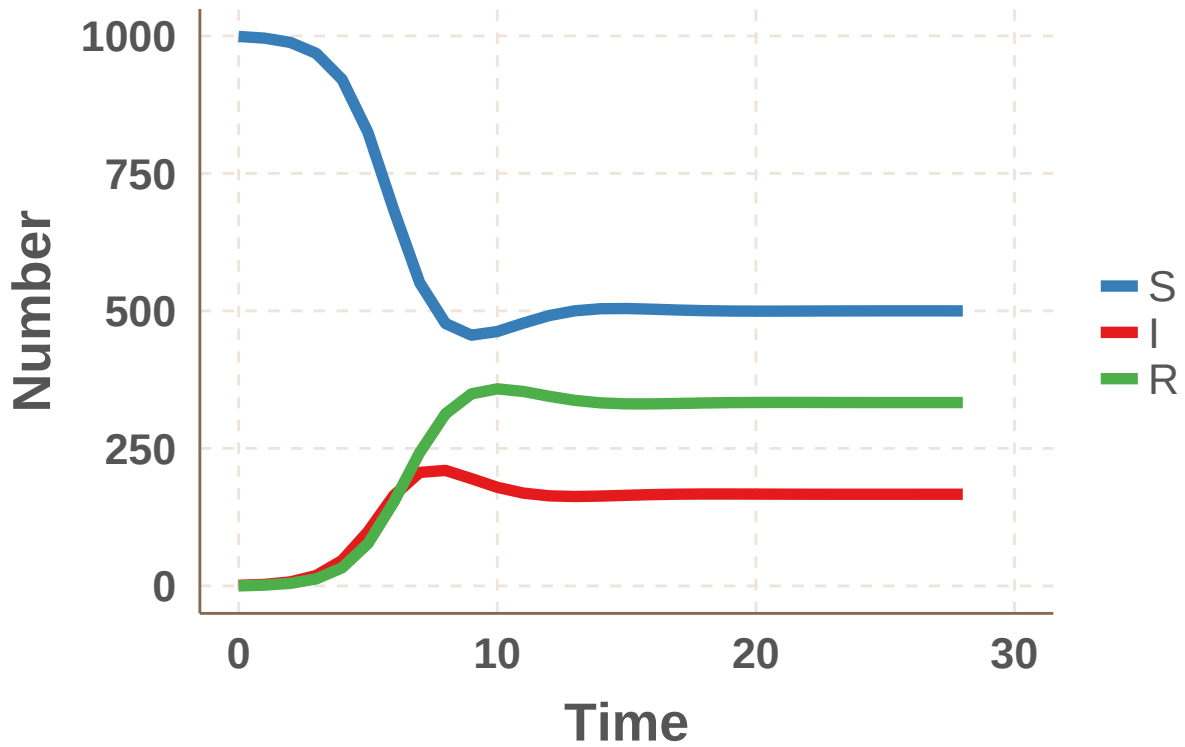

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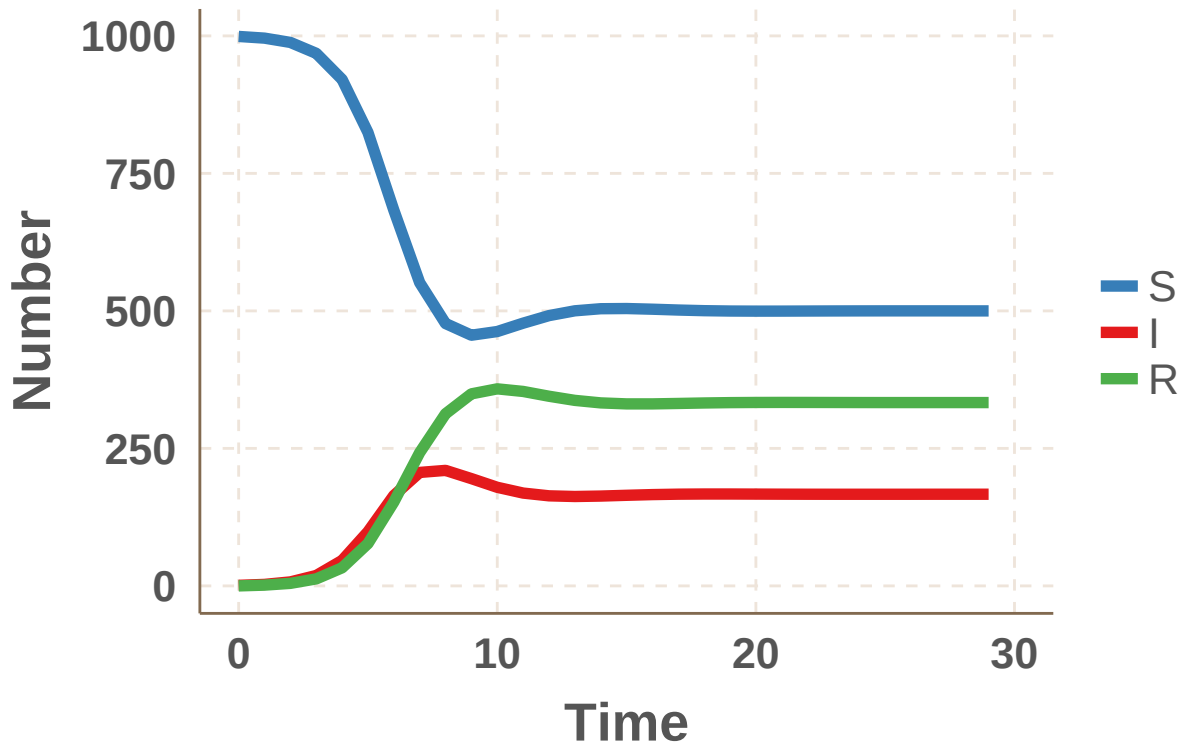
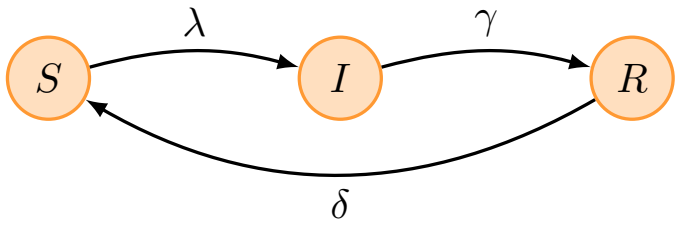
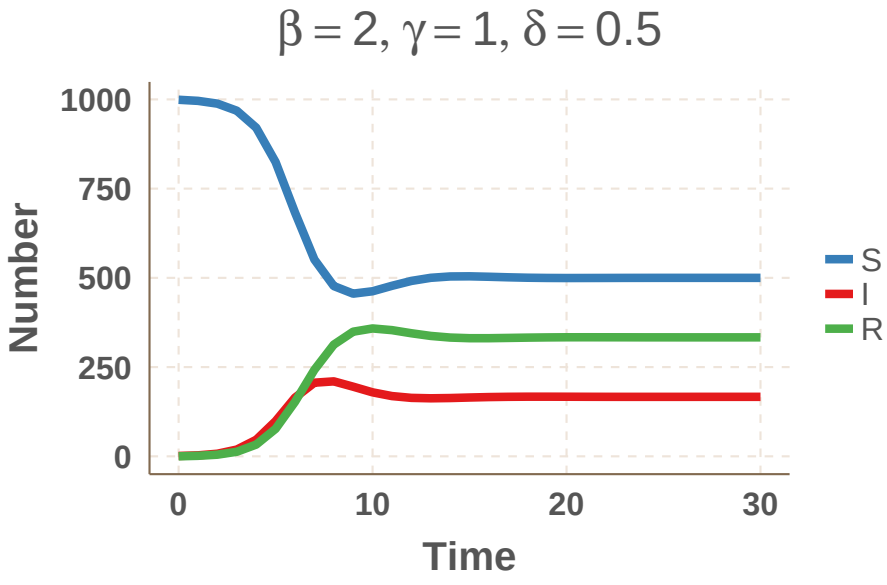


Properties of the SIRS model





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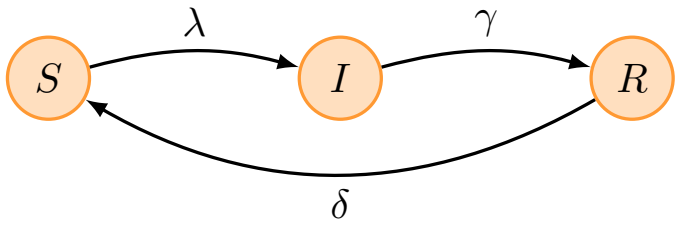

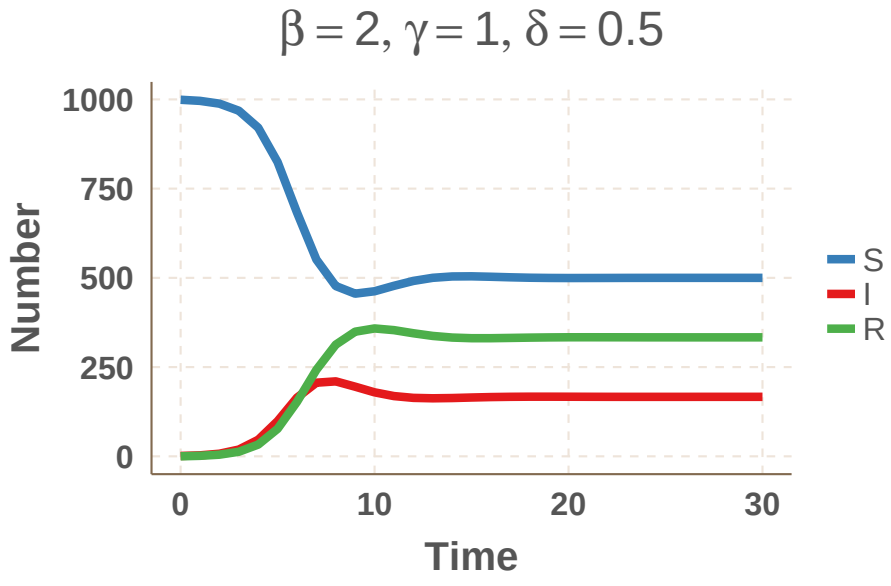

- The infection becomes endemic (does not die out)

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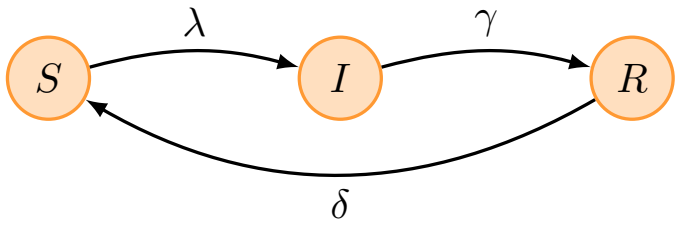

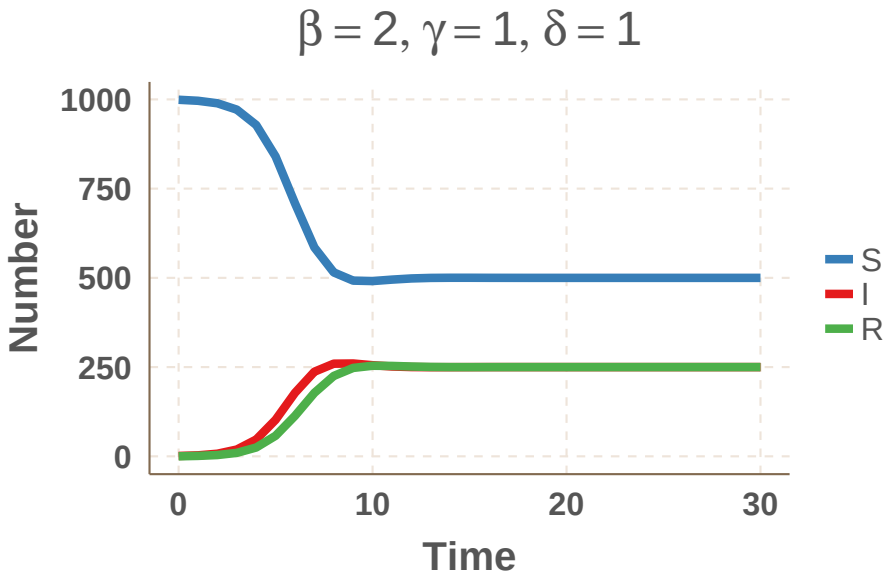

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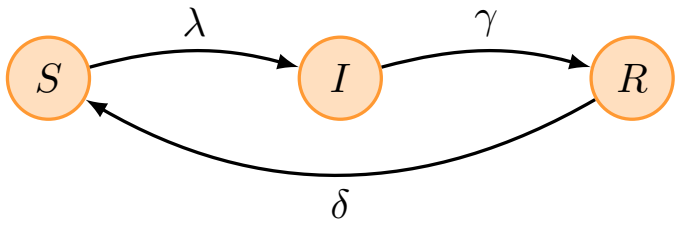

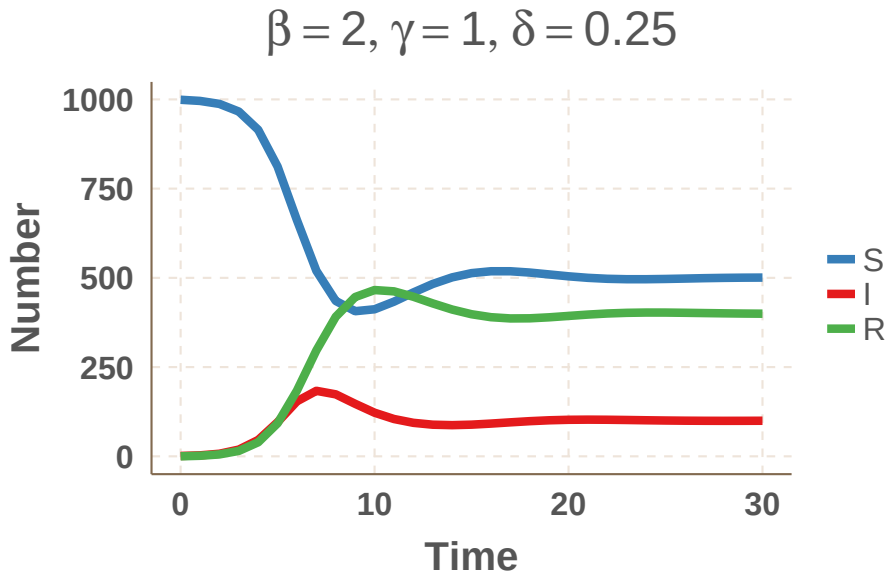

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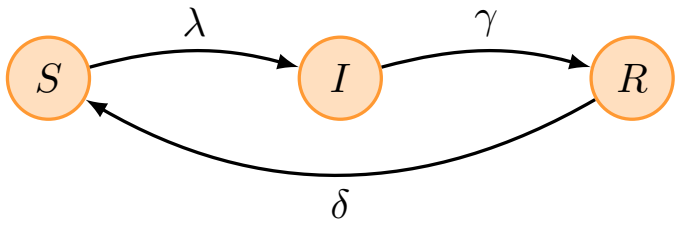
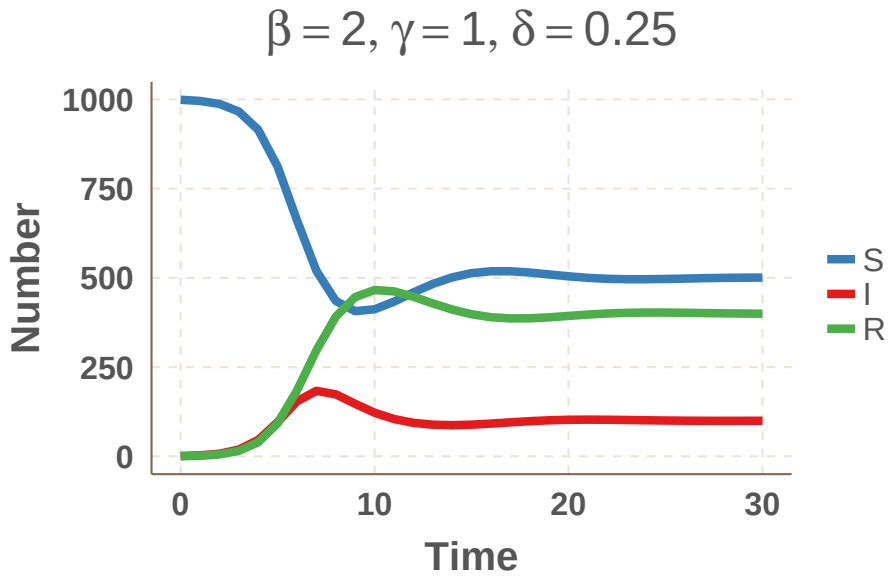
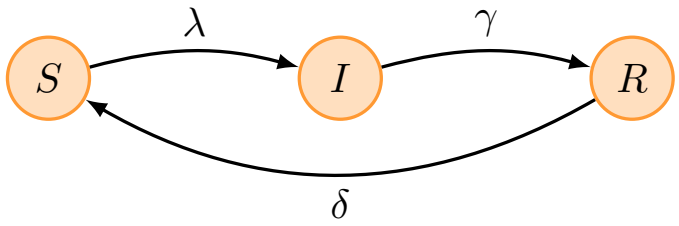
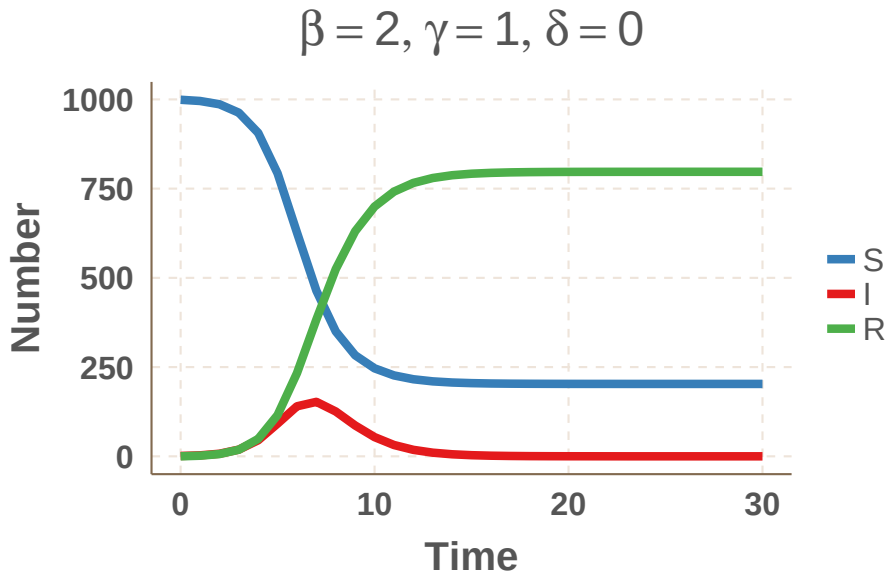




- The infection becomes endemic (does not die out)
- The number of people infectious at any time depends on β, γ and δ

Properties of the SIRS model

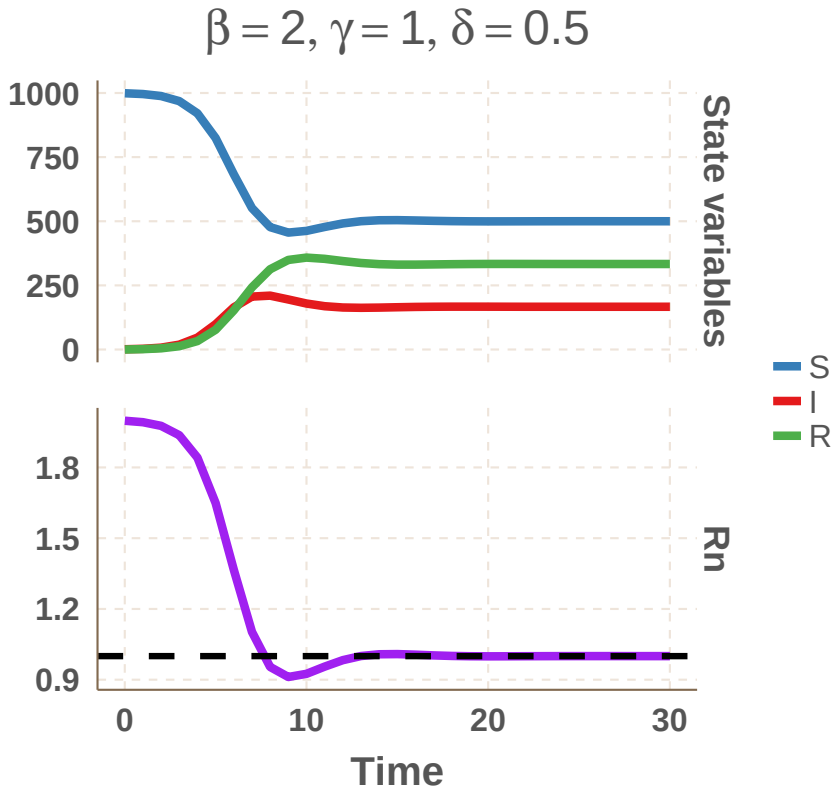




- The infection becomes endemic (does not die out)
- The number of people infectious at any time depends on β, γ and δ
- If $\delta = 0$, this is the SIR model, and the disease dies out

R_n and endemic diseases

The value of R_n determines if, at any time, a disease will increase or decrease.



$R_0 = 2$

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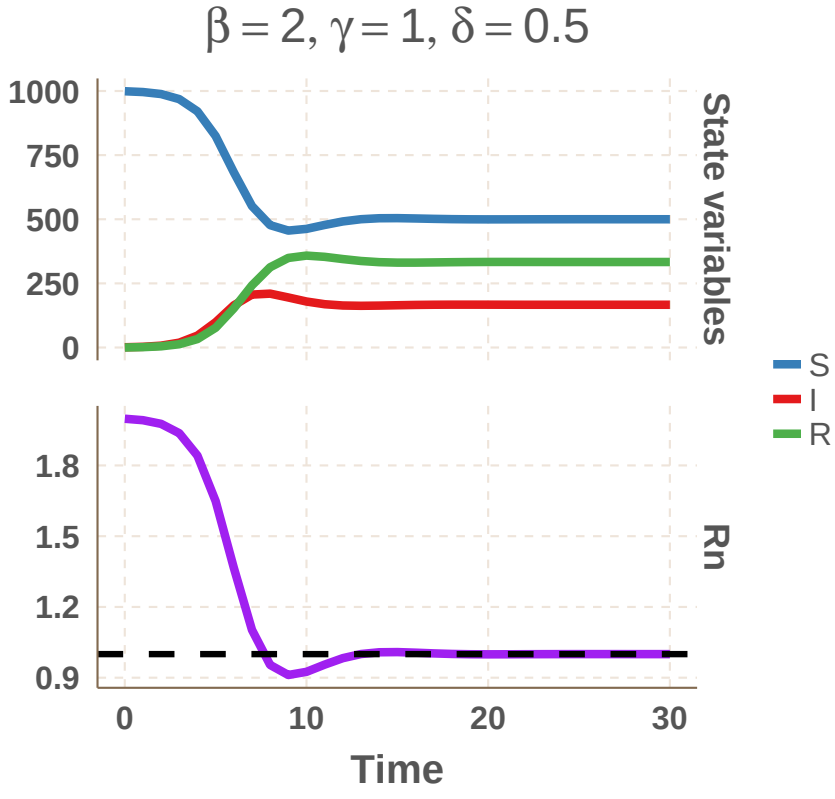

$R_0 = 2$

- At the beginning, $R_n = R_0$

R_n and endemic diseases

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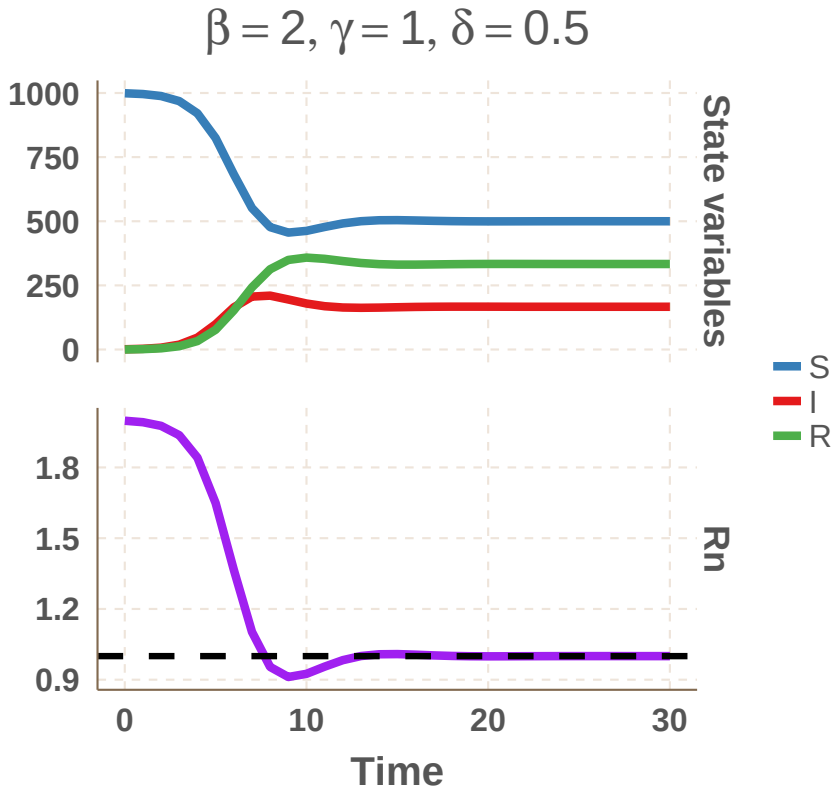

$R_0 = 2$

- At the beginning, $R_n = R_0$
- At endemic level, $R_n = 1$

Applications of the SIRS model

- Immunity is lost (after a while)
- The infection reaches an endemic level

For which infection is this a good model?

Applications of the SIRS model

- Immunity is lost (after a while)
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For which infection is this a good model?

- Cholera?

Applications of the SIRS model

- Immunity is lost (after a while)
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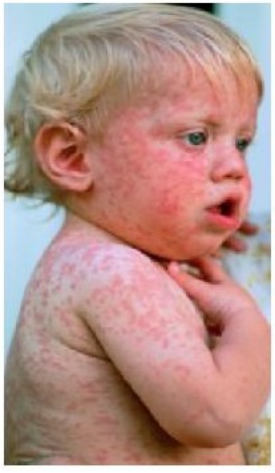
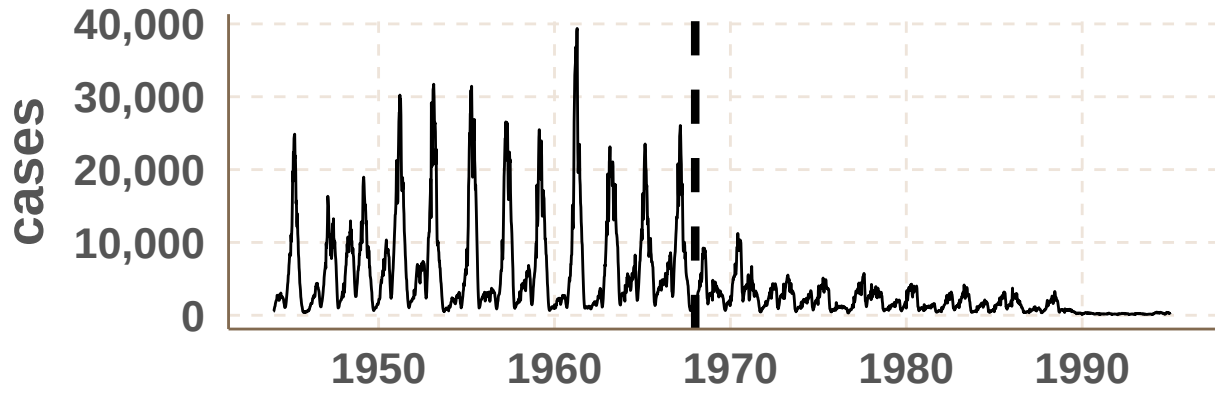
For which infection is this a good model?

- Cholera?
- Measles?

What about measles?

What about measles?





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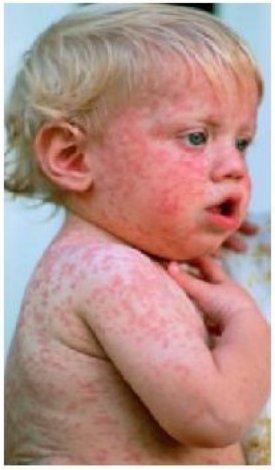
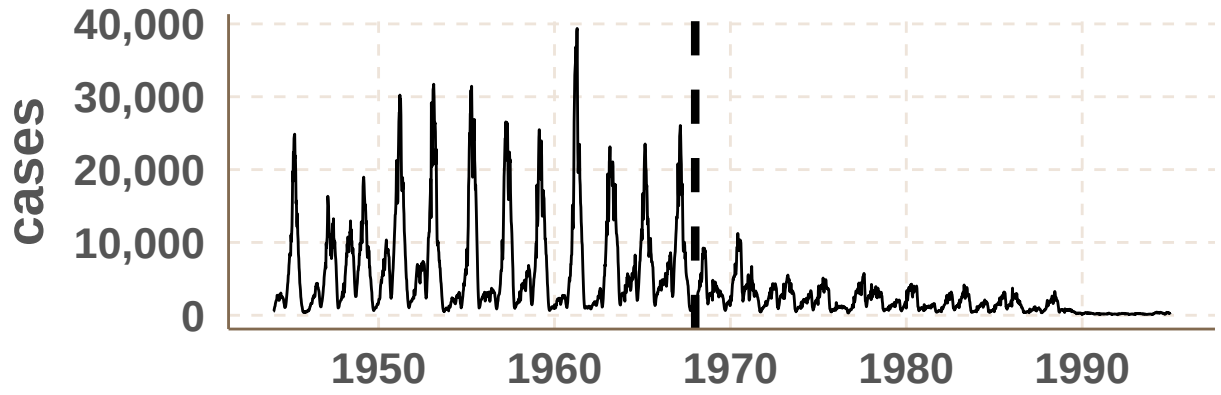
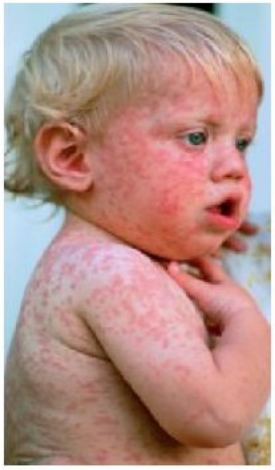
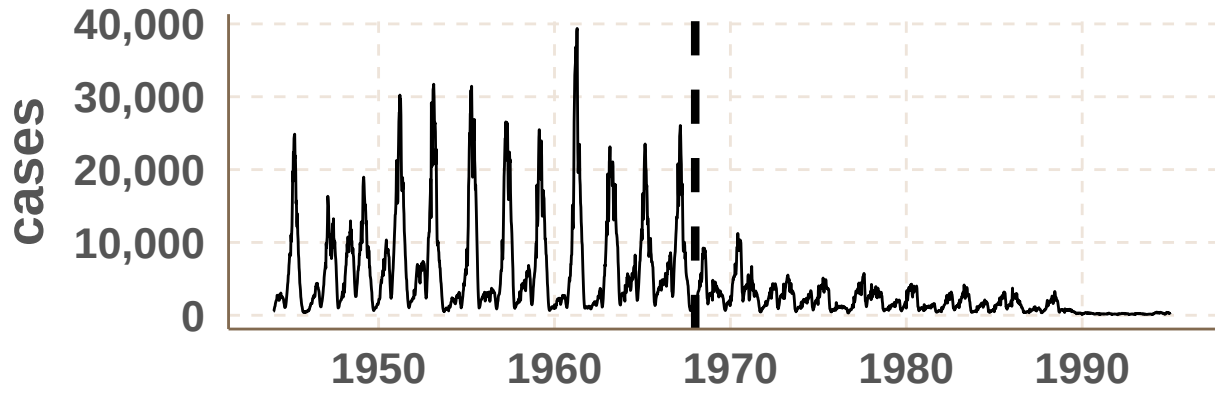




- Measles infection confers lifelong immunity (SIR model?)

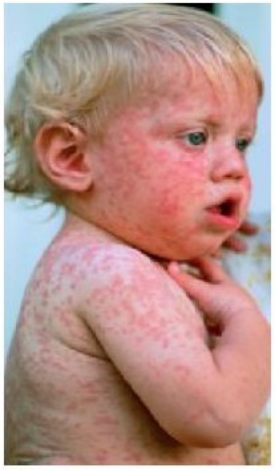
What about measles?

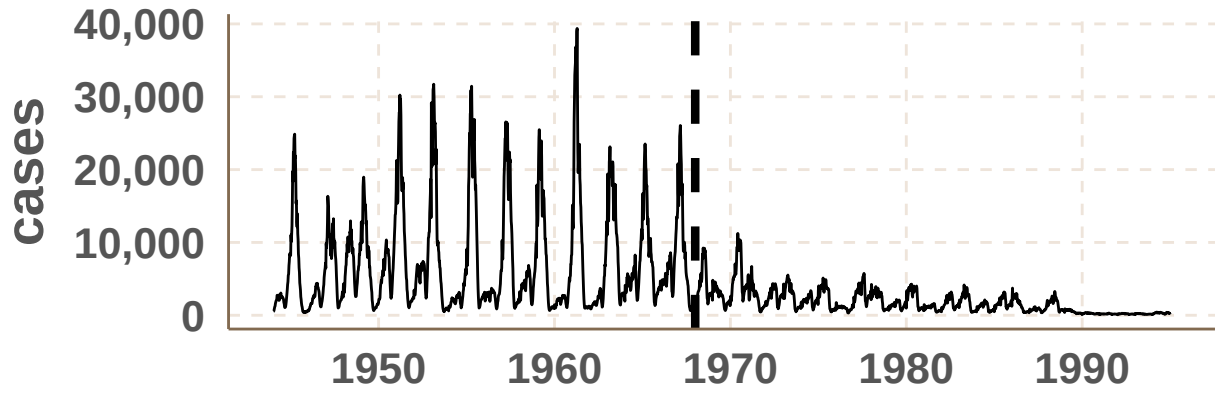




- Measles infection confers lifelong immunity (SIR model?)
- Occurred in 2-year cycles

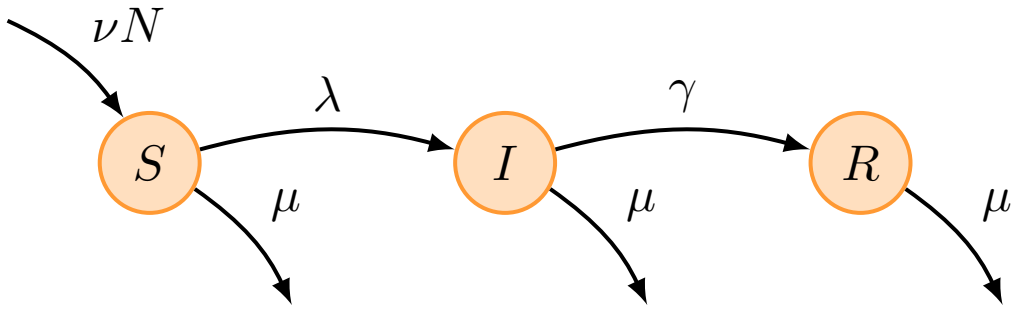
What about measles?





- Measles infection confers lifelong immunity (SIR model?)
- Occurred in 2-year cycles
- New susceptibles through births ("childhood" disease)

The SIR model with births (and deaths)



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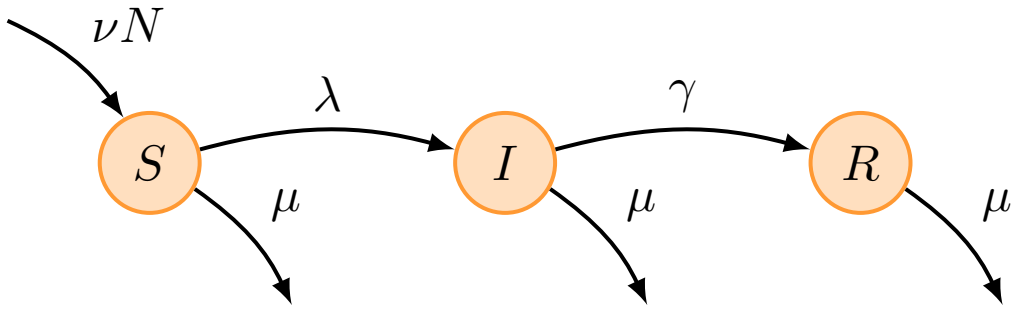
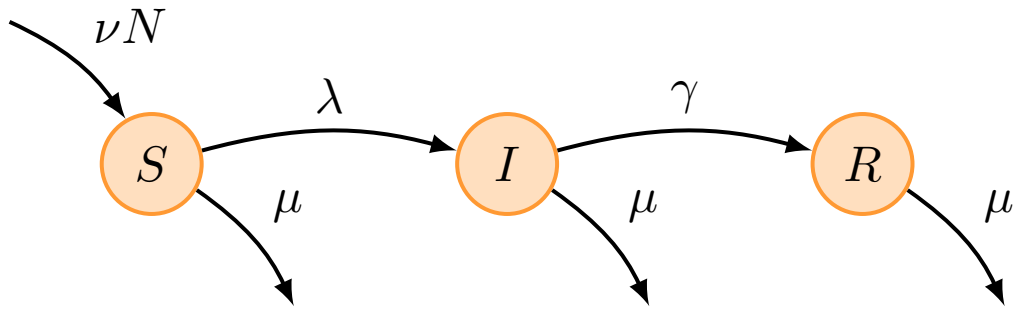


- ν is the per-capita birth rate

The SIR model with births (and deaths)



- ν is the per-capita birth rate
- μ is the per-capita death rate. It is the inverse of the life expectancy L

$$\mu = \frac{1}{L}$$

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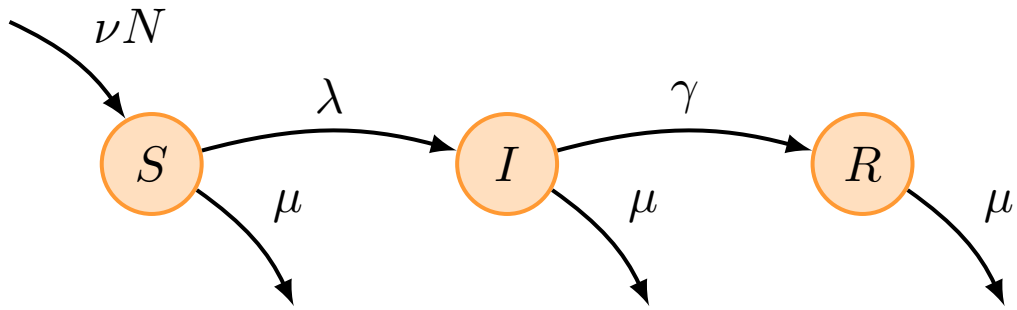

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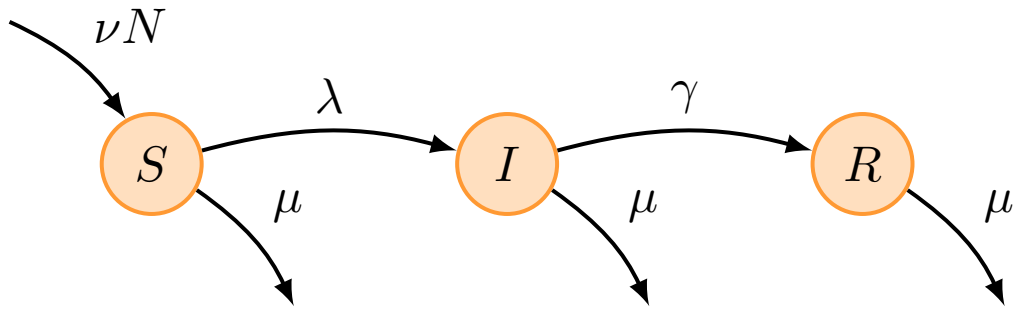

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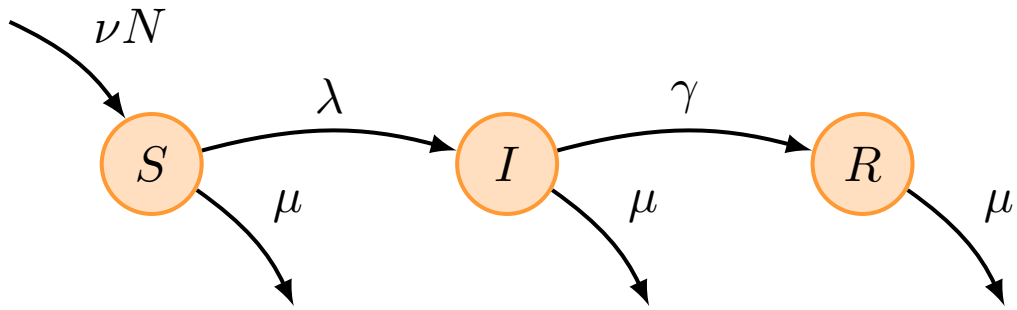

- ν is the per-capita birth rate
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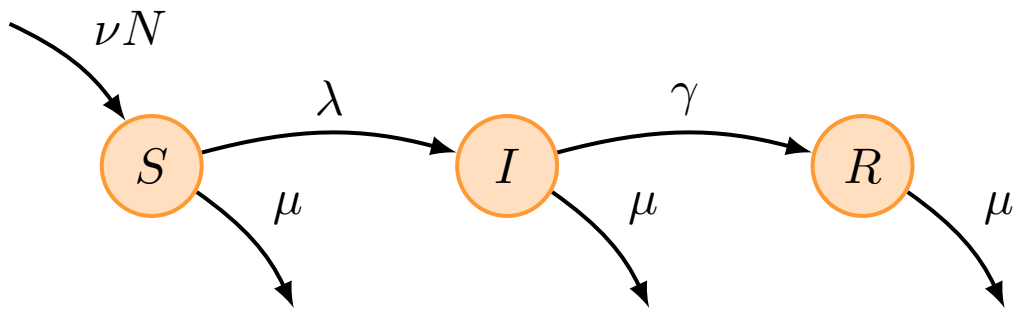
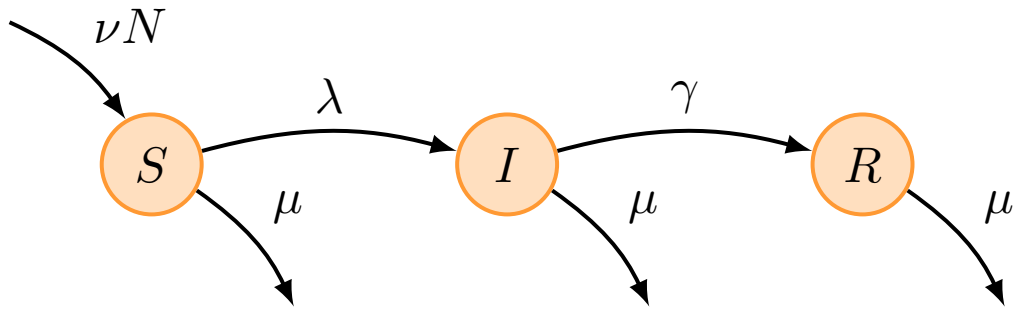
- If $\mu = \nu$: population size N stays constant
- If $\nu > \mu$: population grows
- If $\mu < \nu$: population shrinks

The SIR model with births/deaths as differential equations



- S: Number of people susceptible
- I: Number of people infectious
- R: Number of people recovered
- How does the number of people susceptible, infectious and recovered change over time?

The SIR model with births/deaths as differential equations



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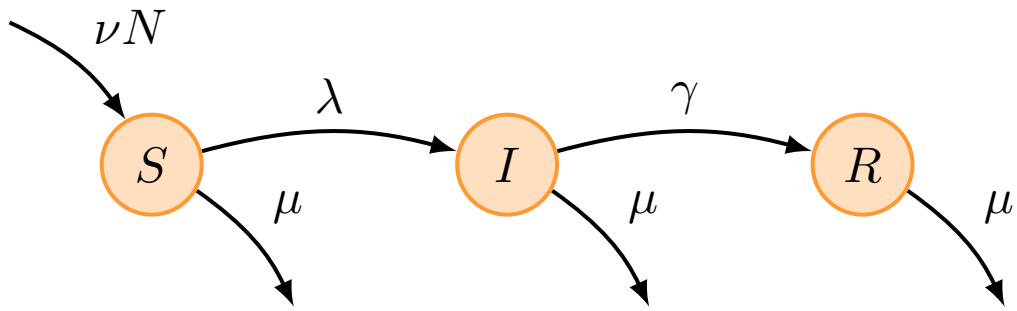

- S: Number of people susceptible
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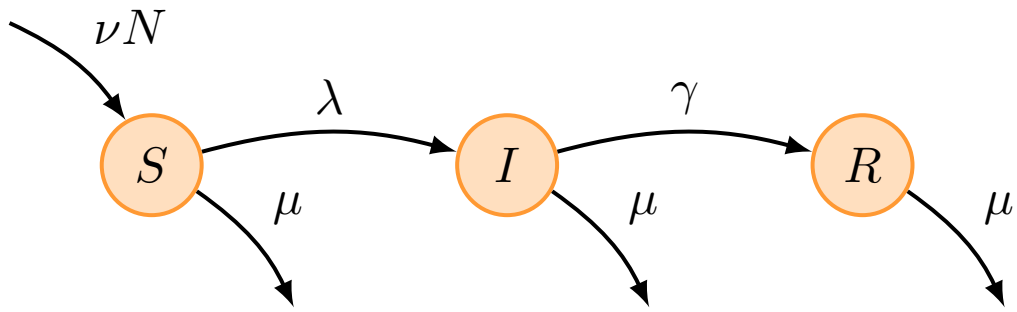

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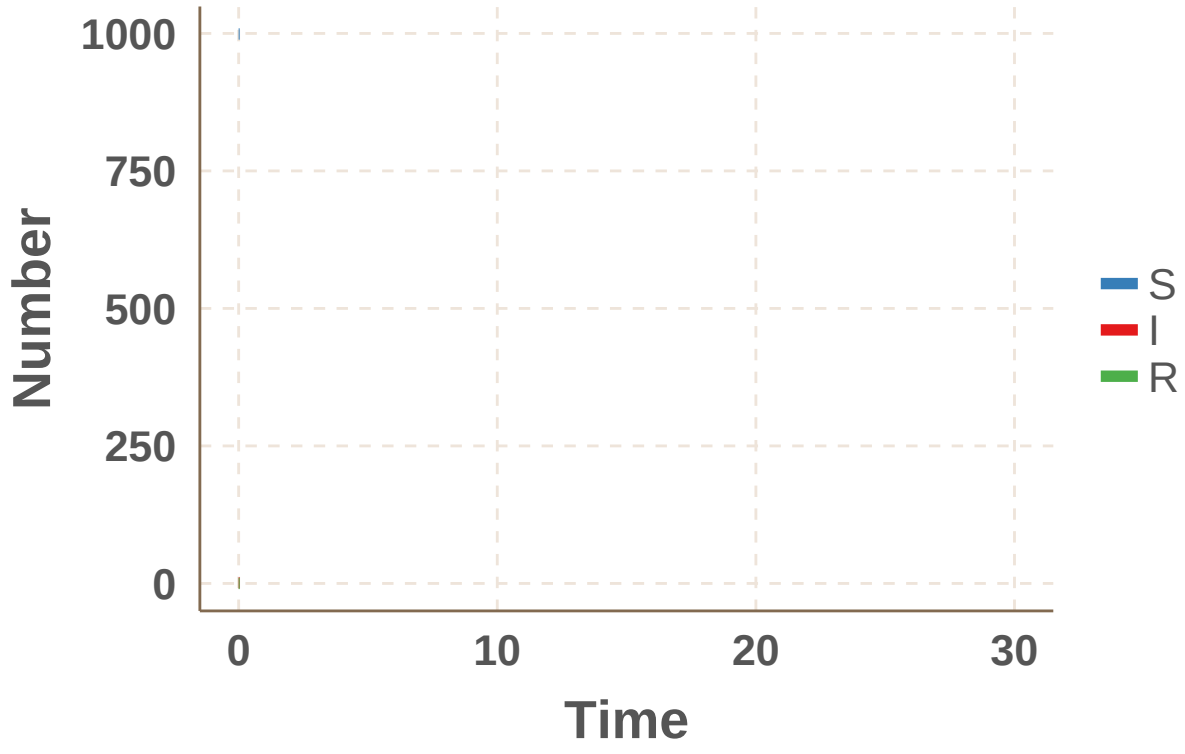

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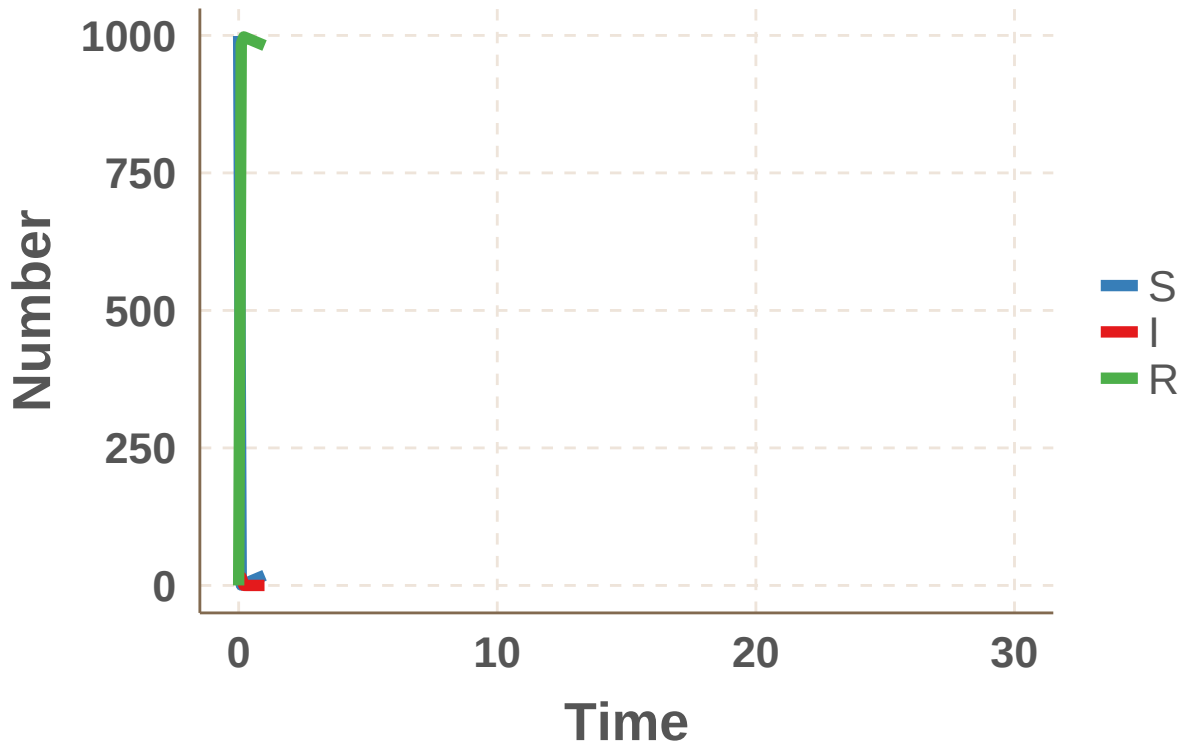

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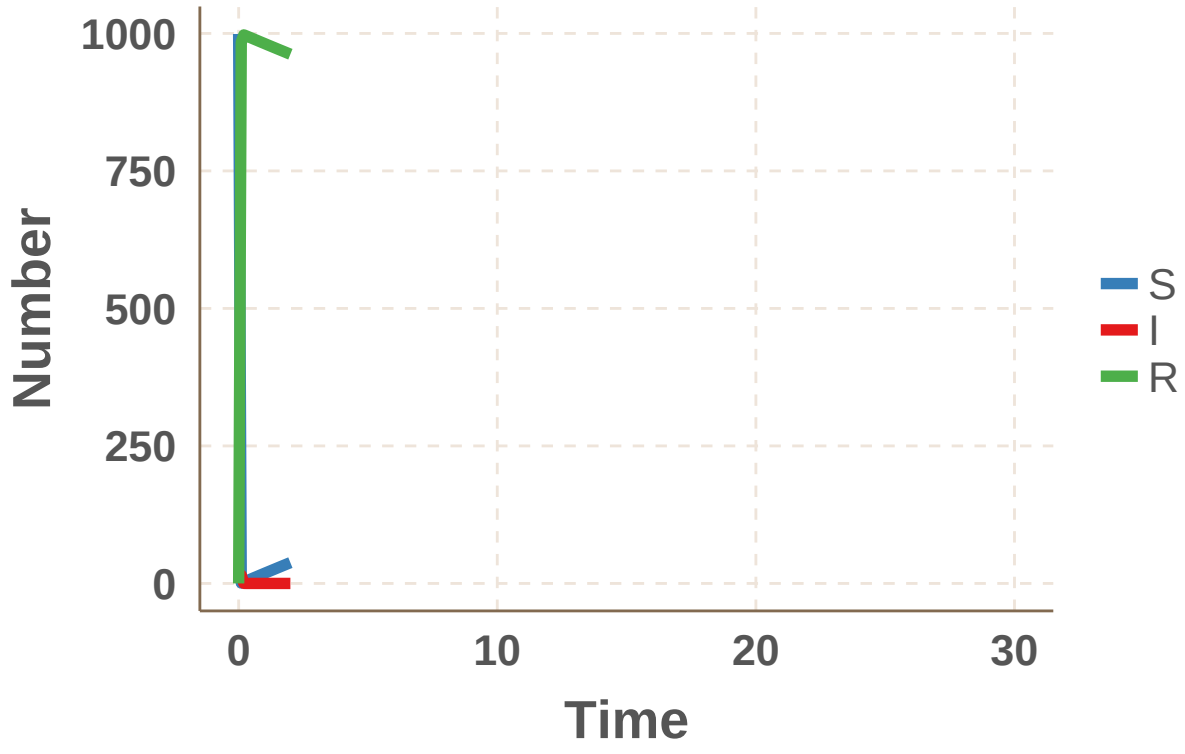

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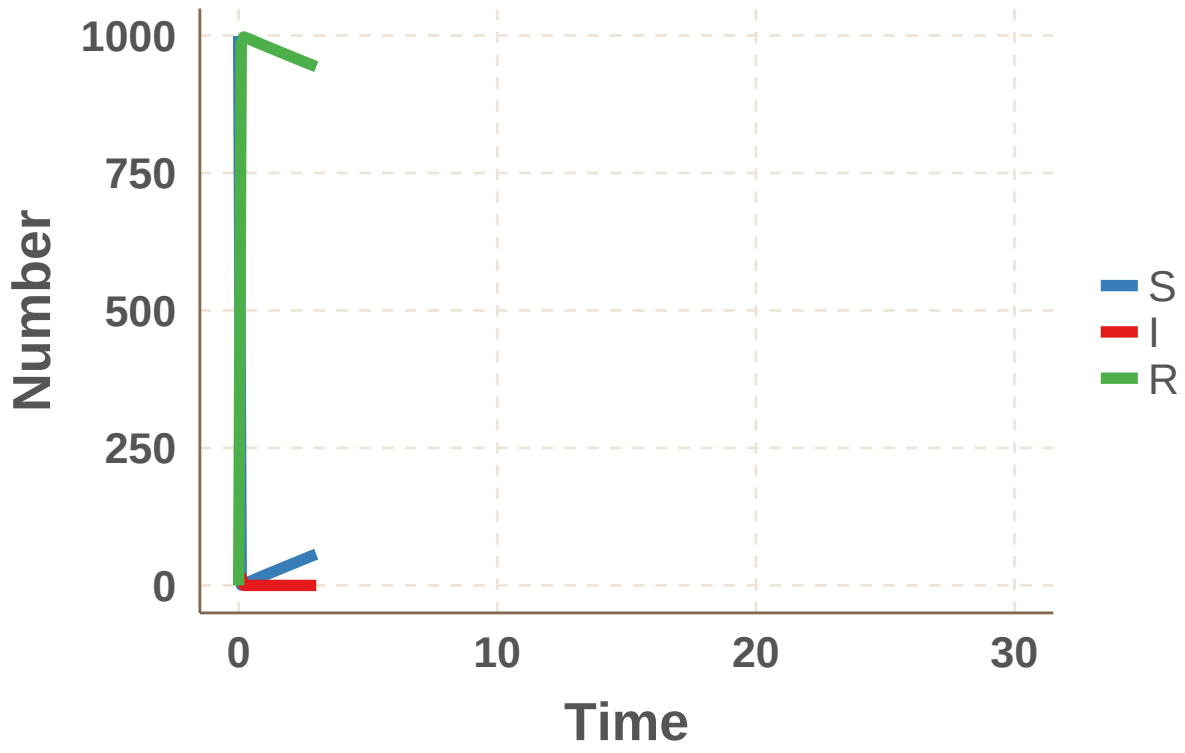

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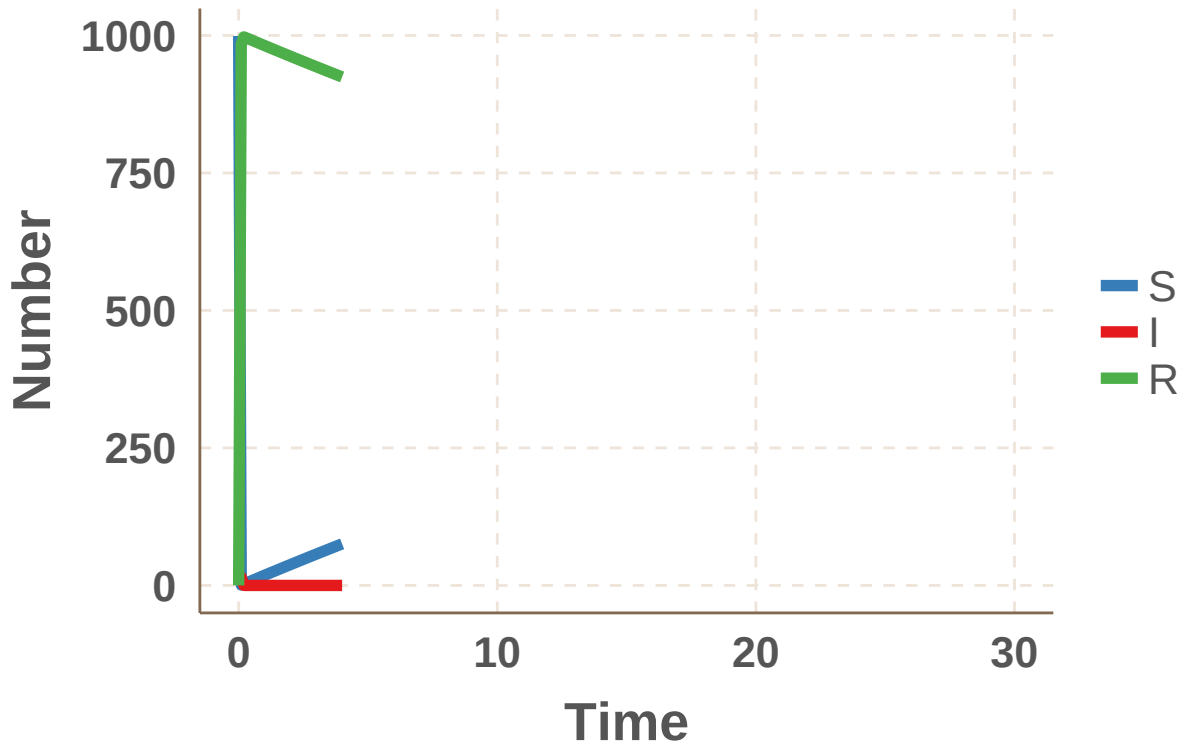

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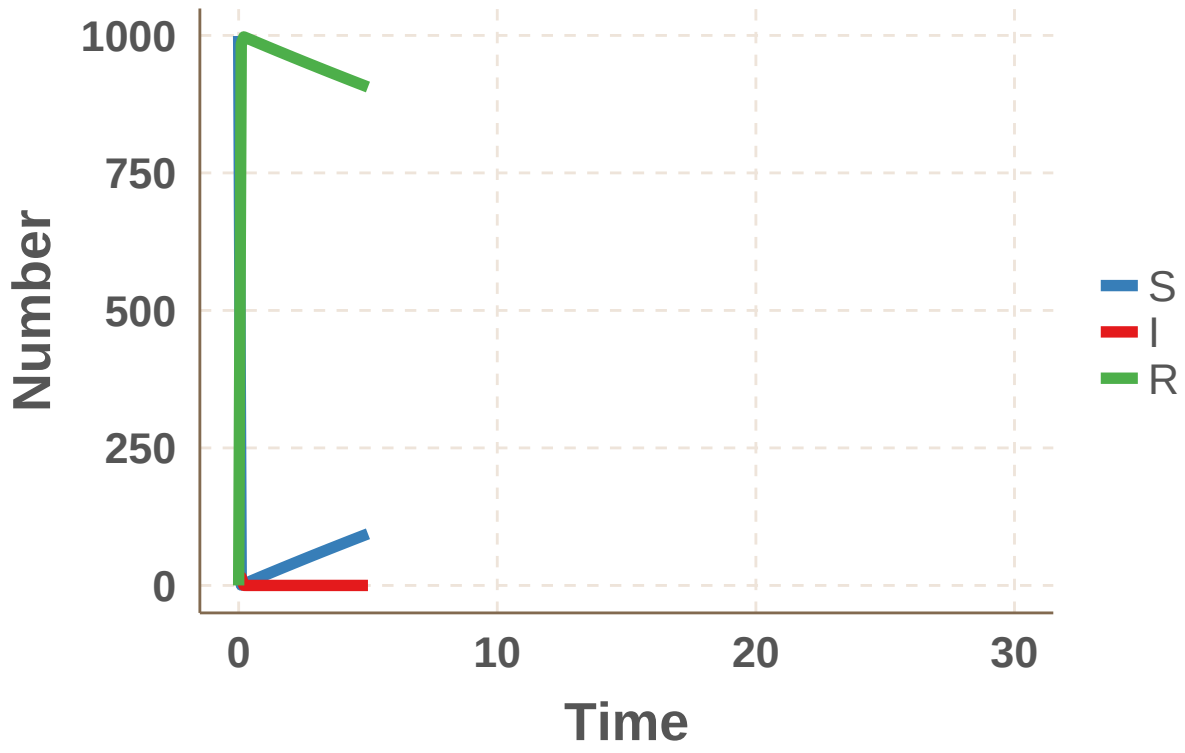

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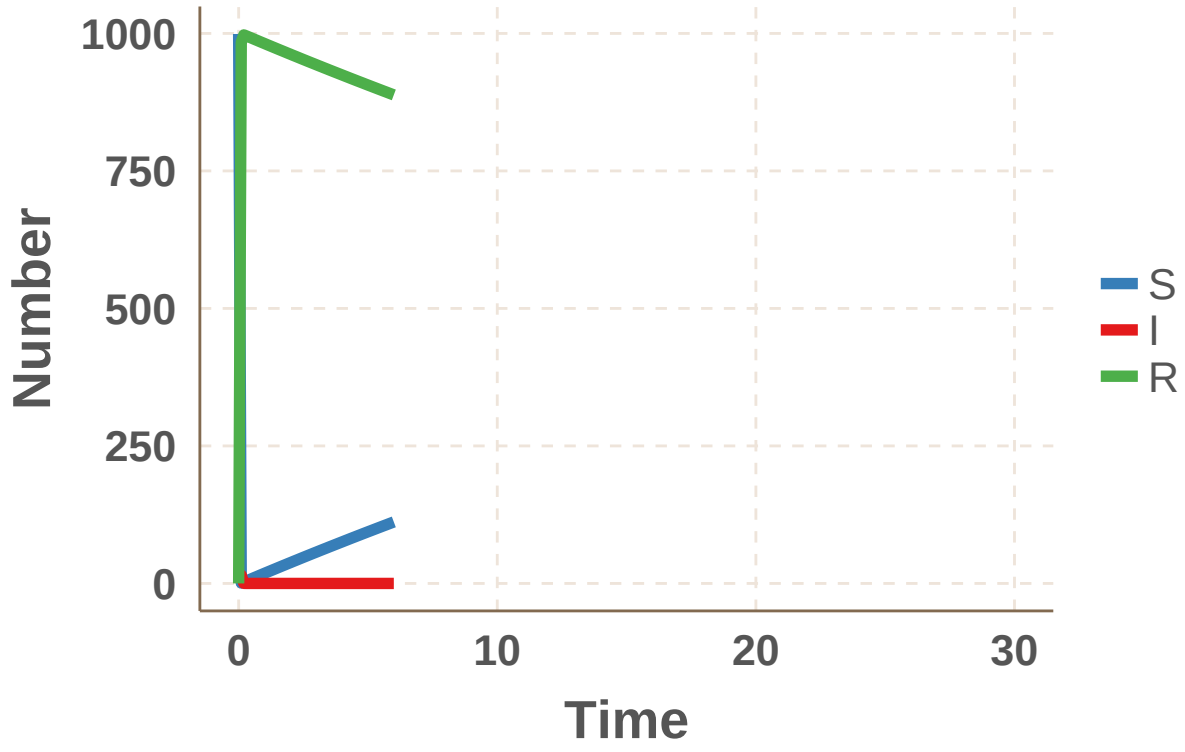

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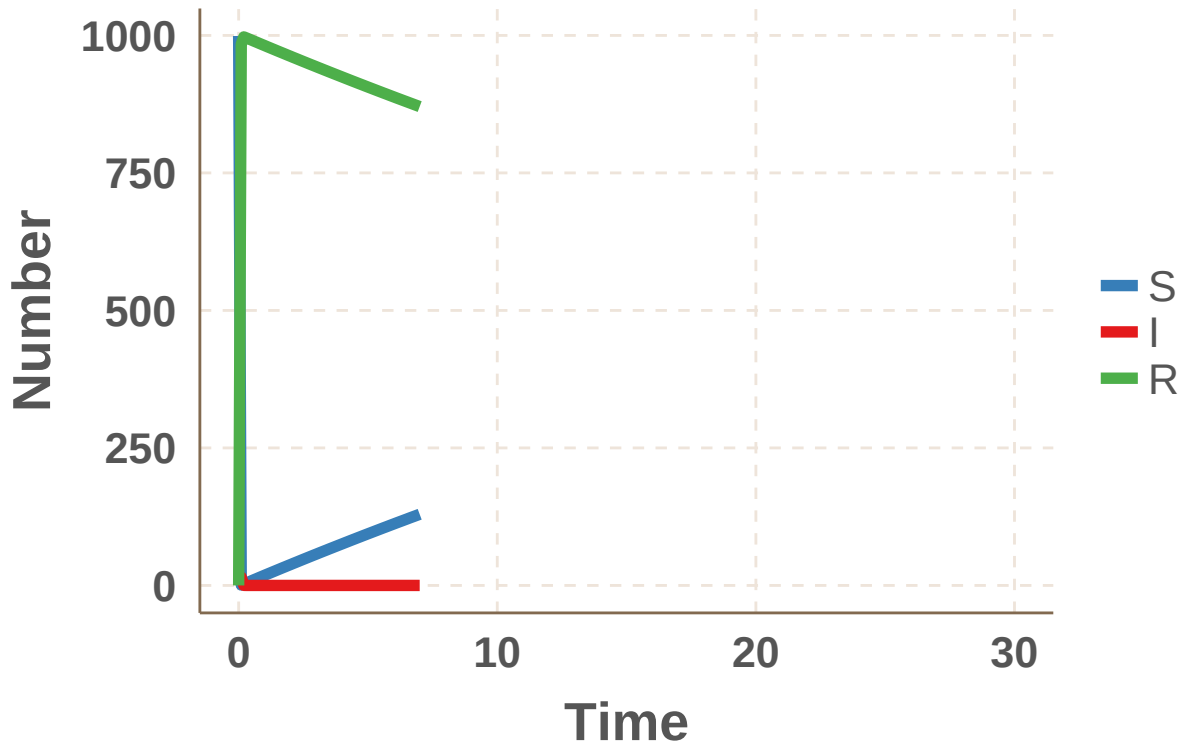

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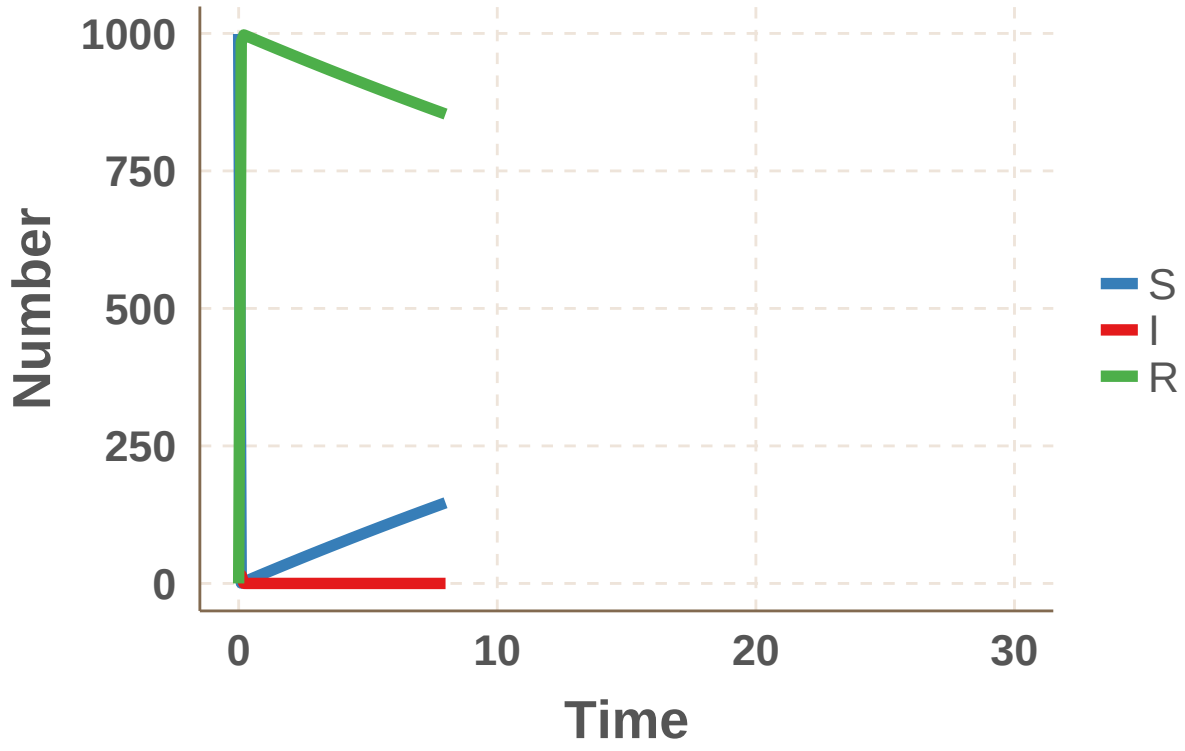

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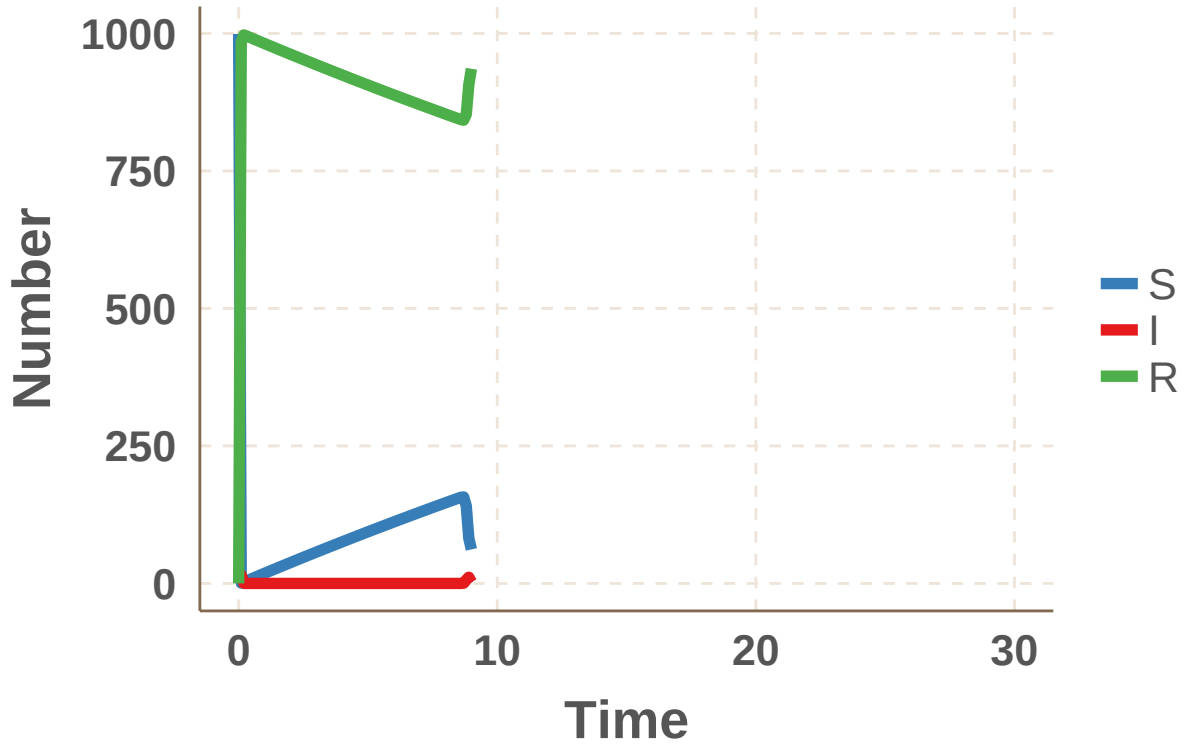

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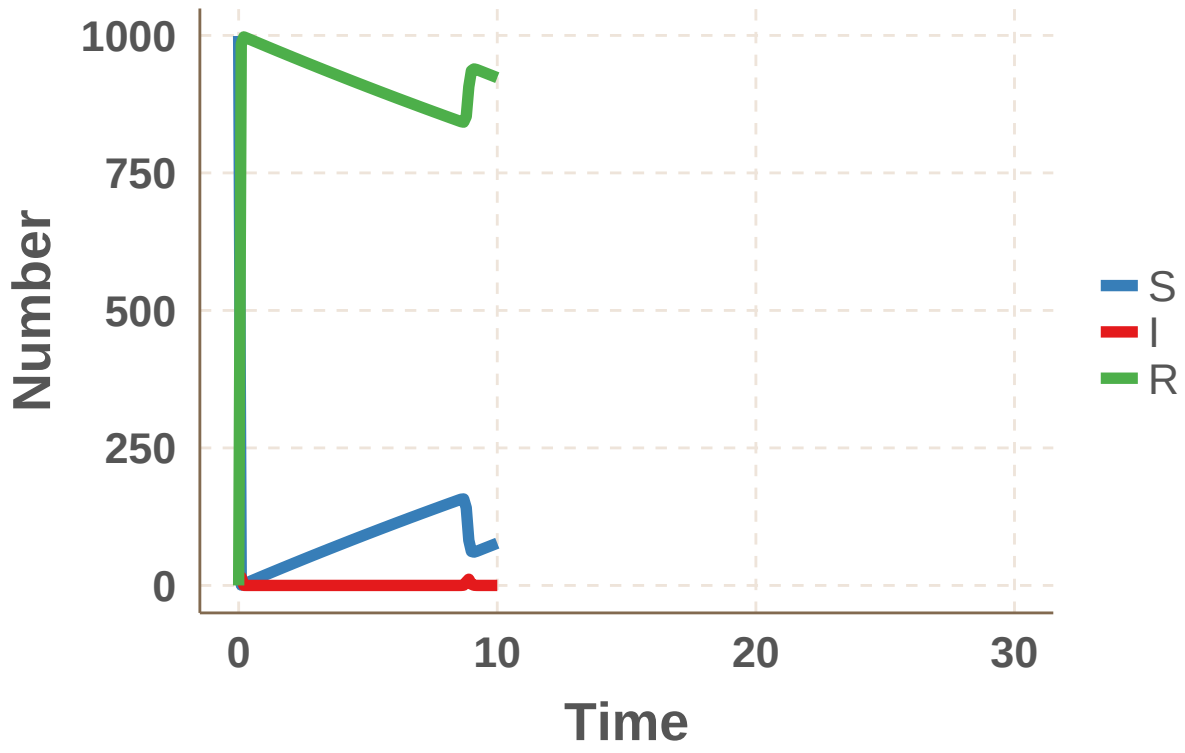

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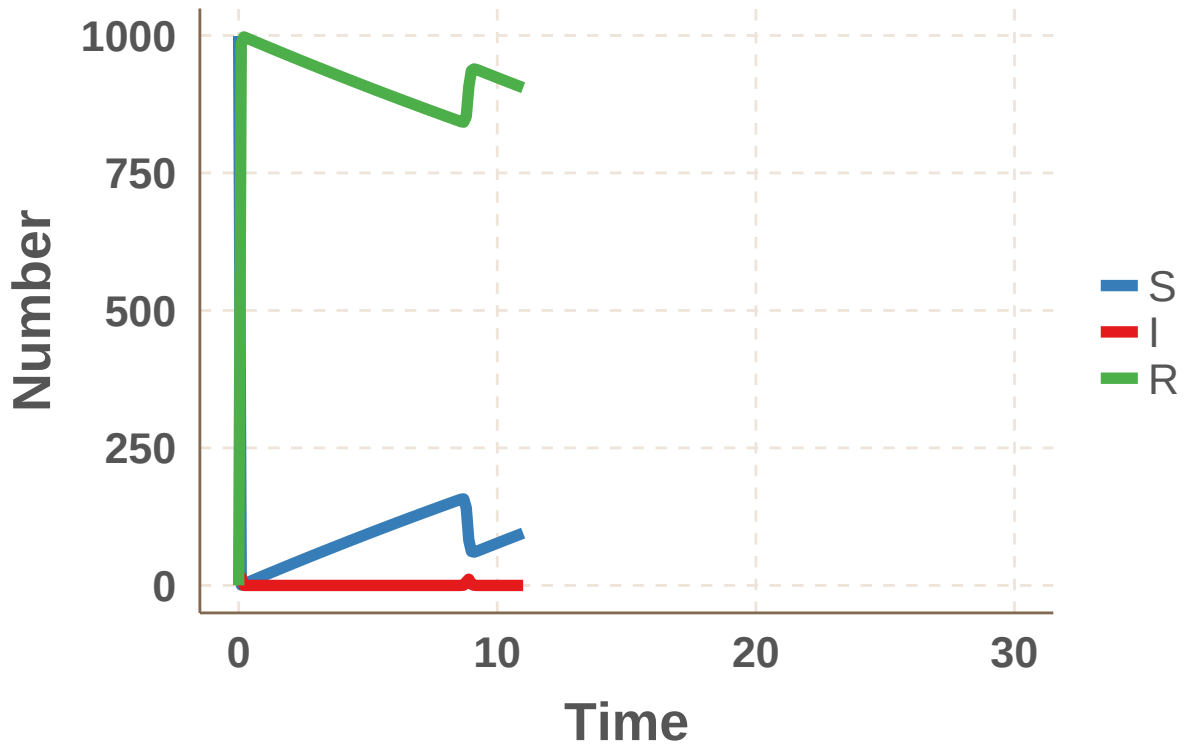

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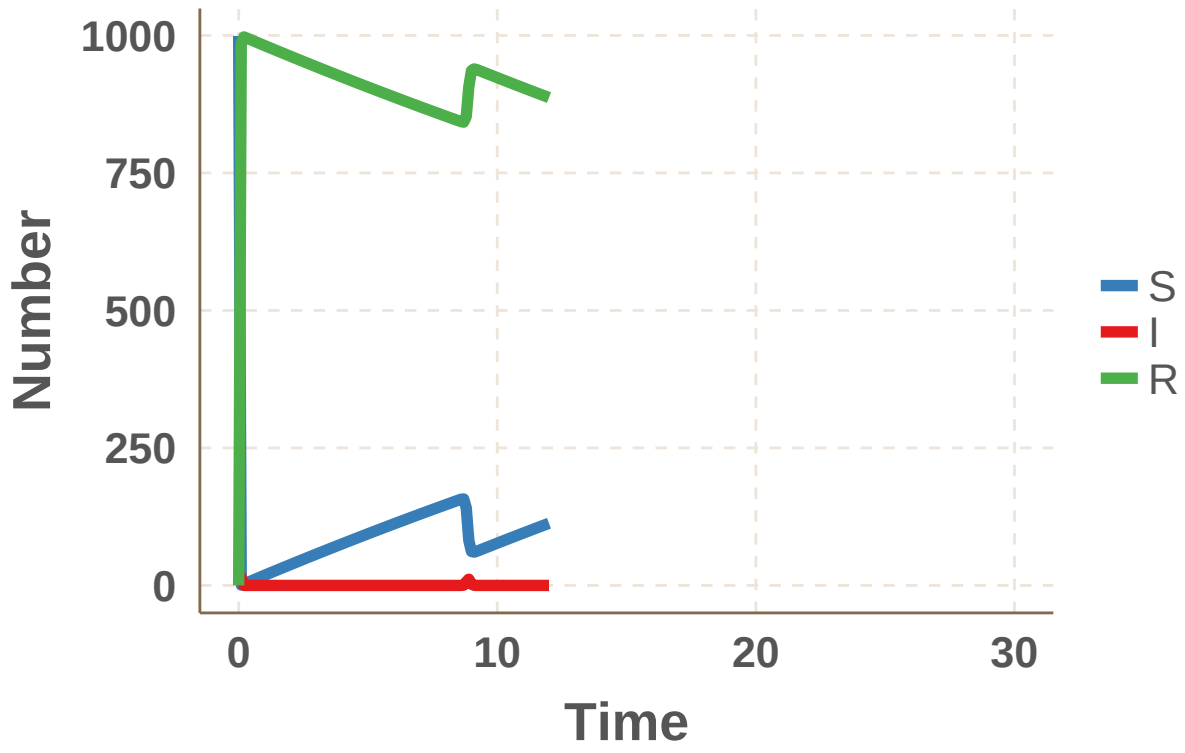

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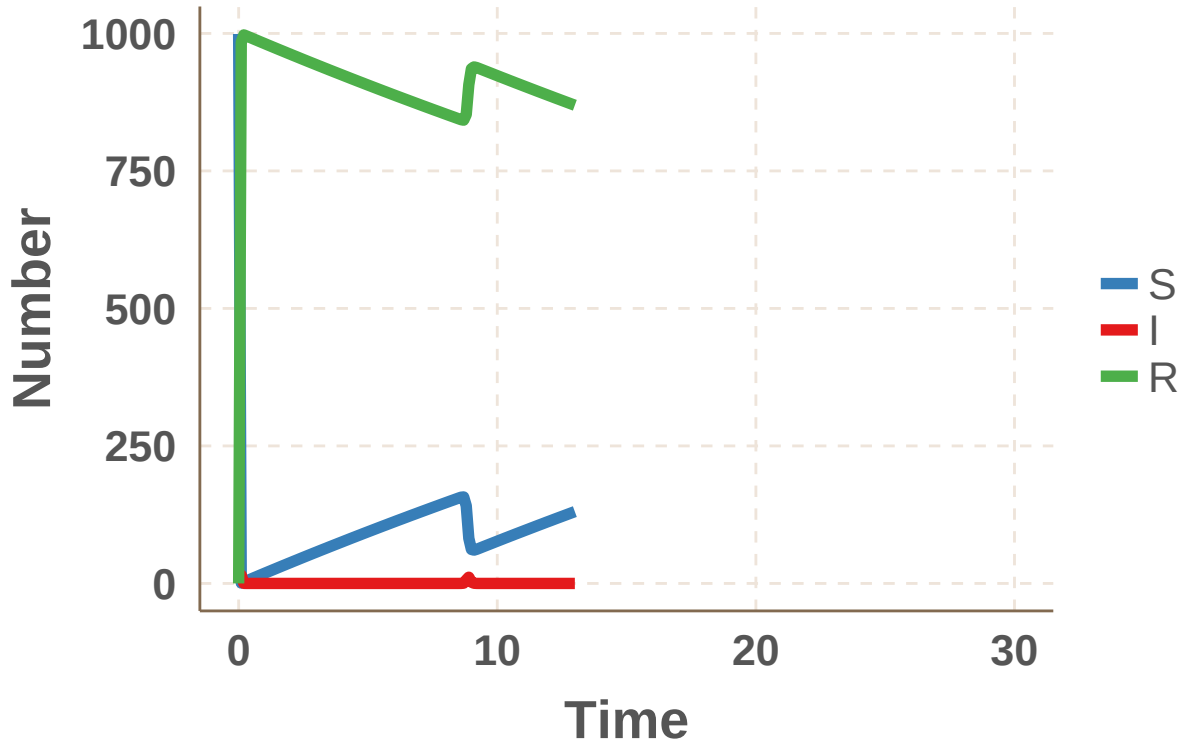

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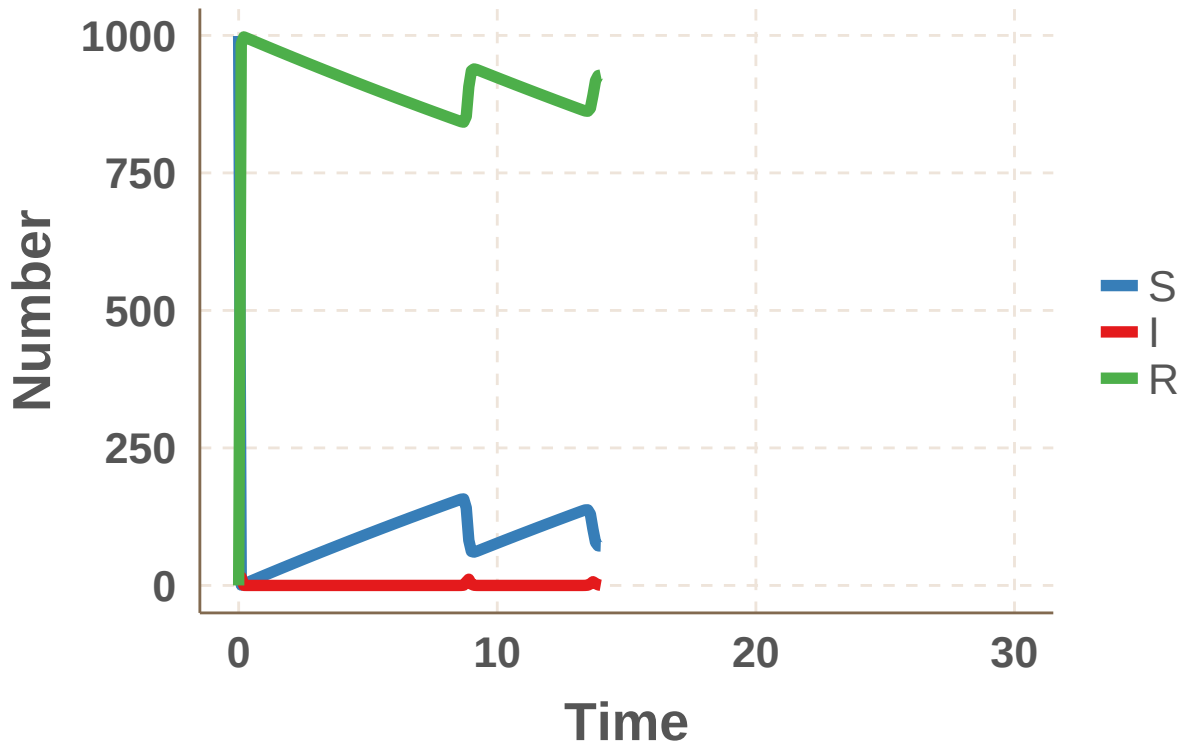

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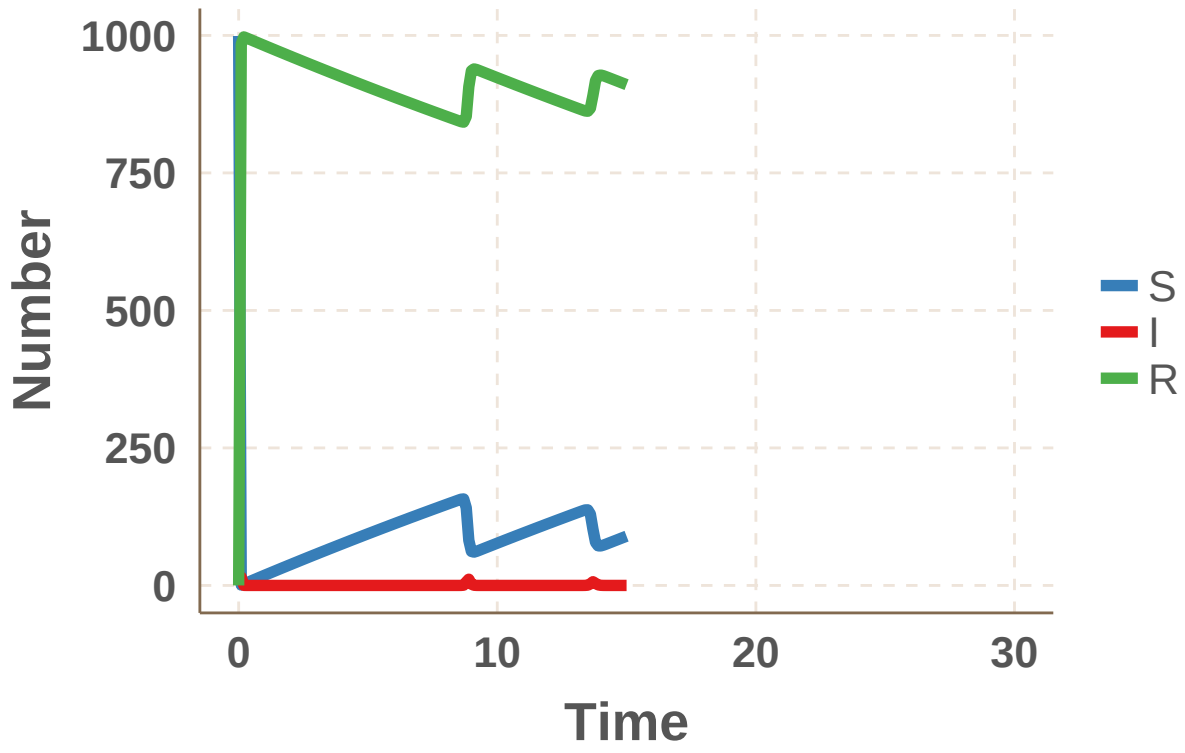

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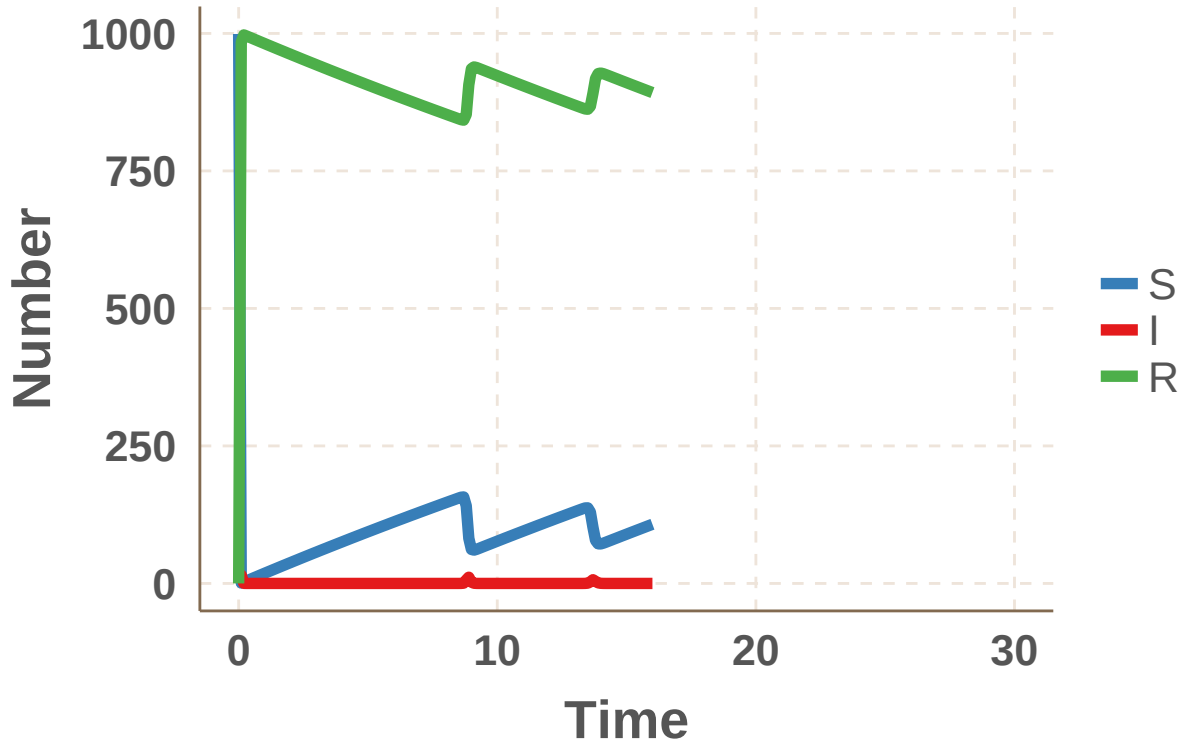

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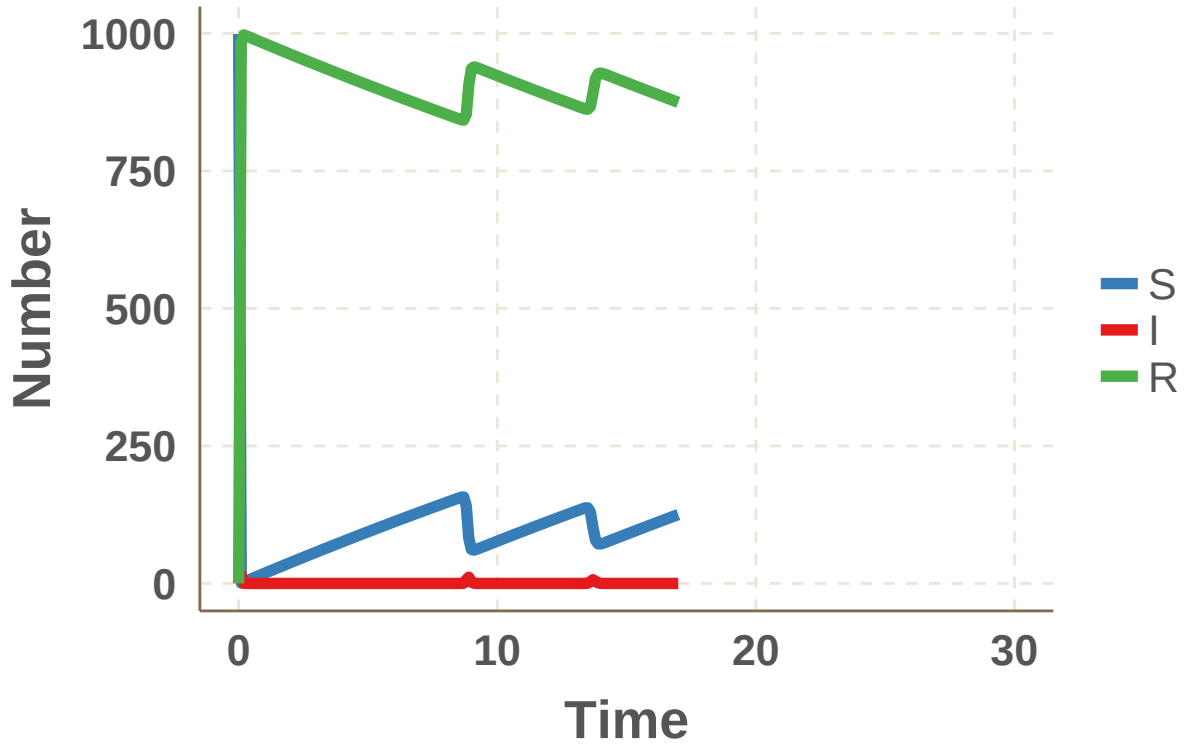

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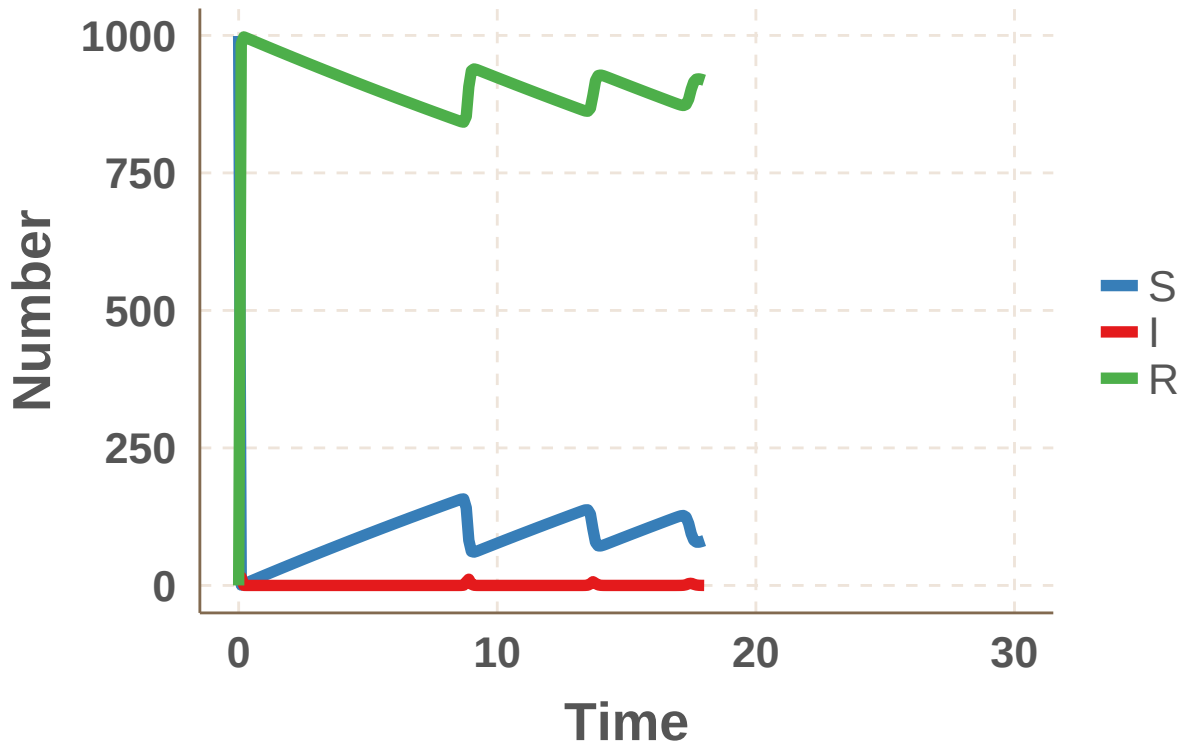

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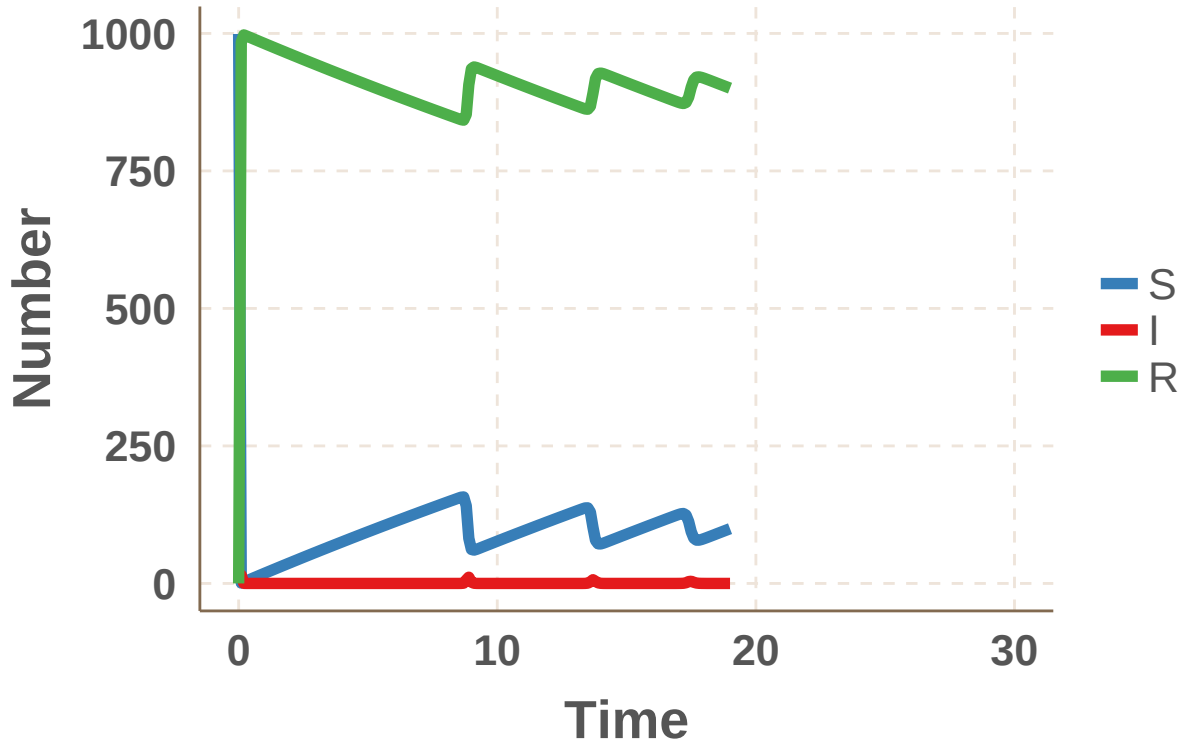

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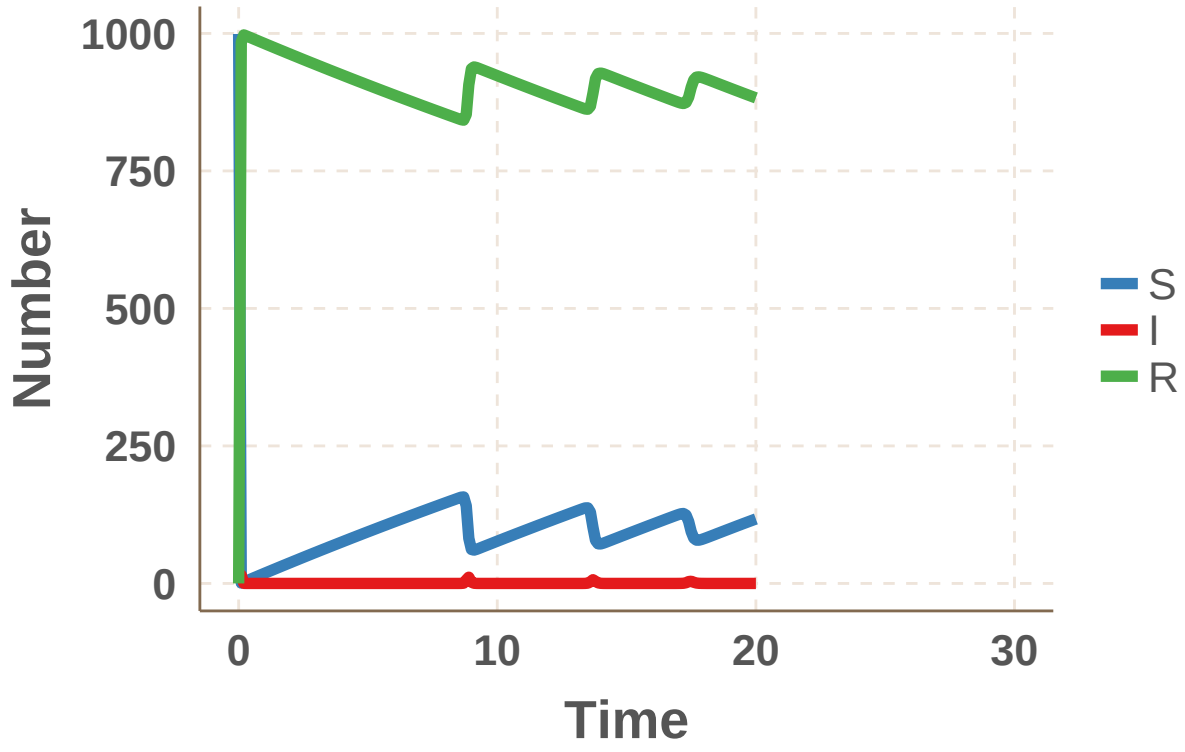

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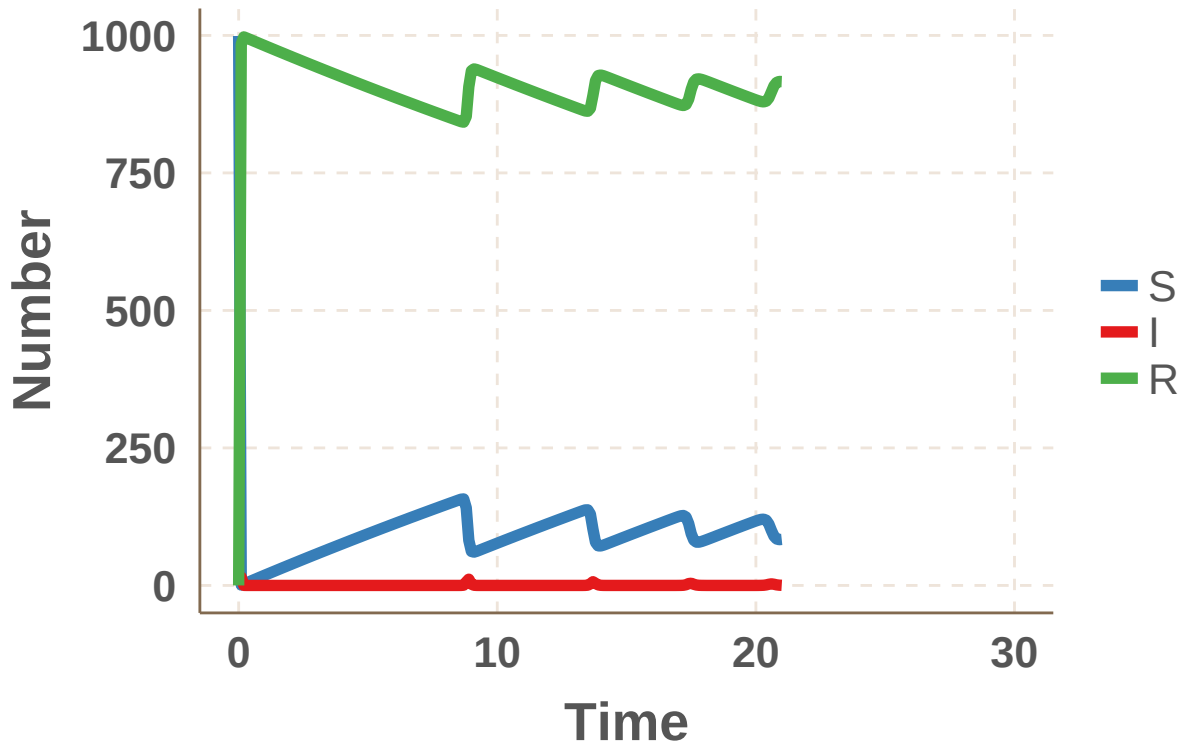

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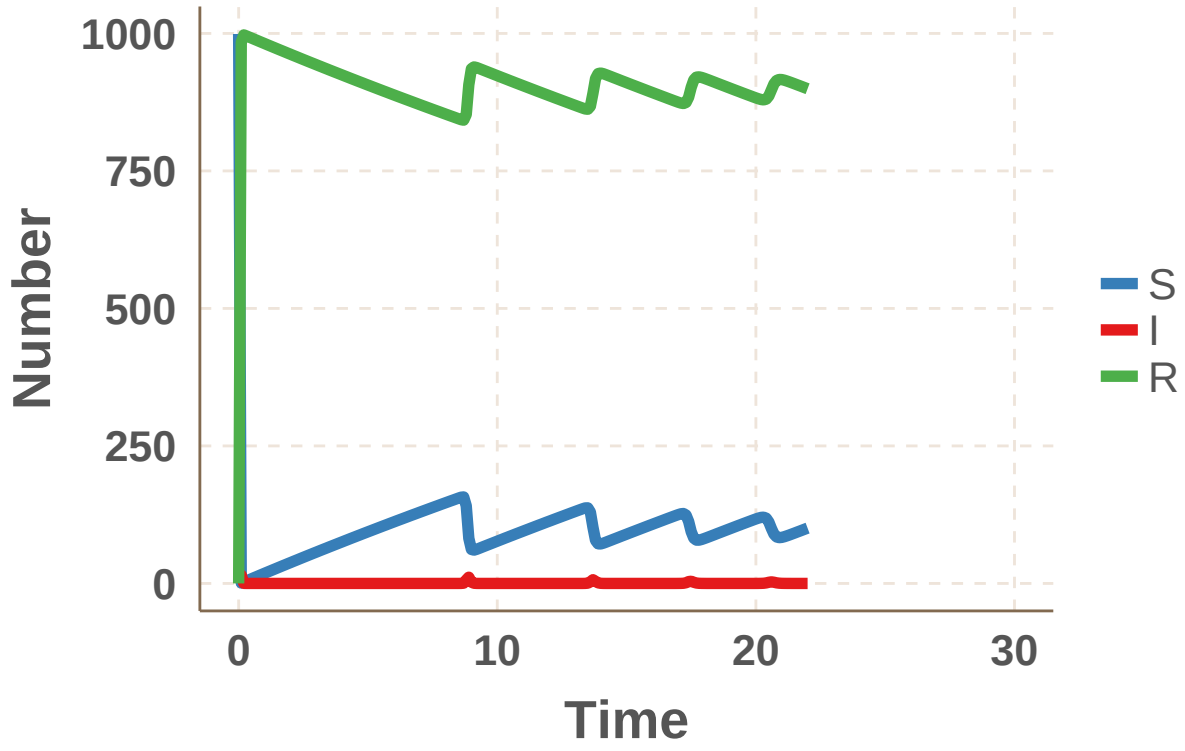

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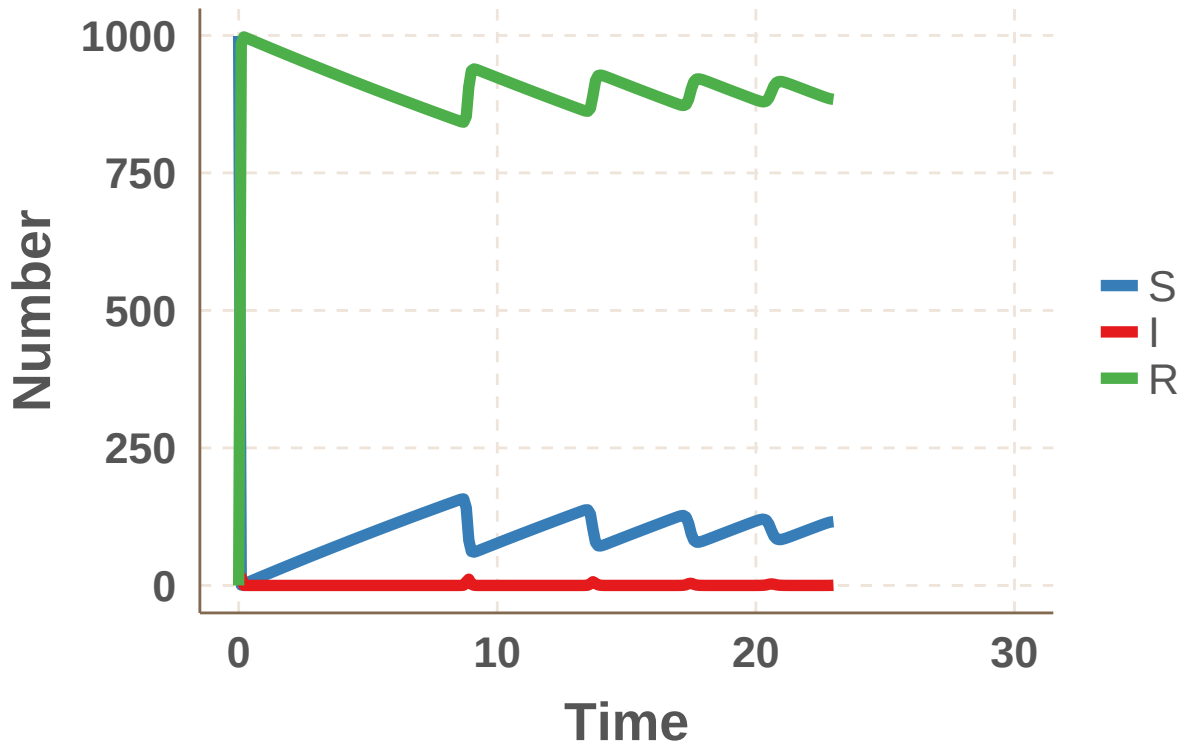

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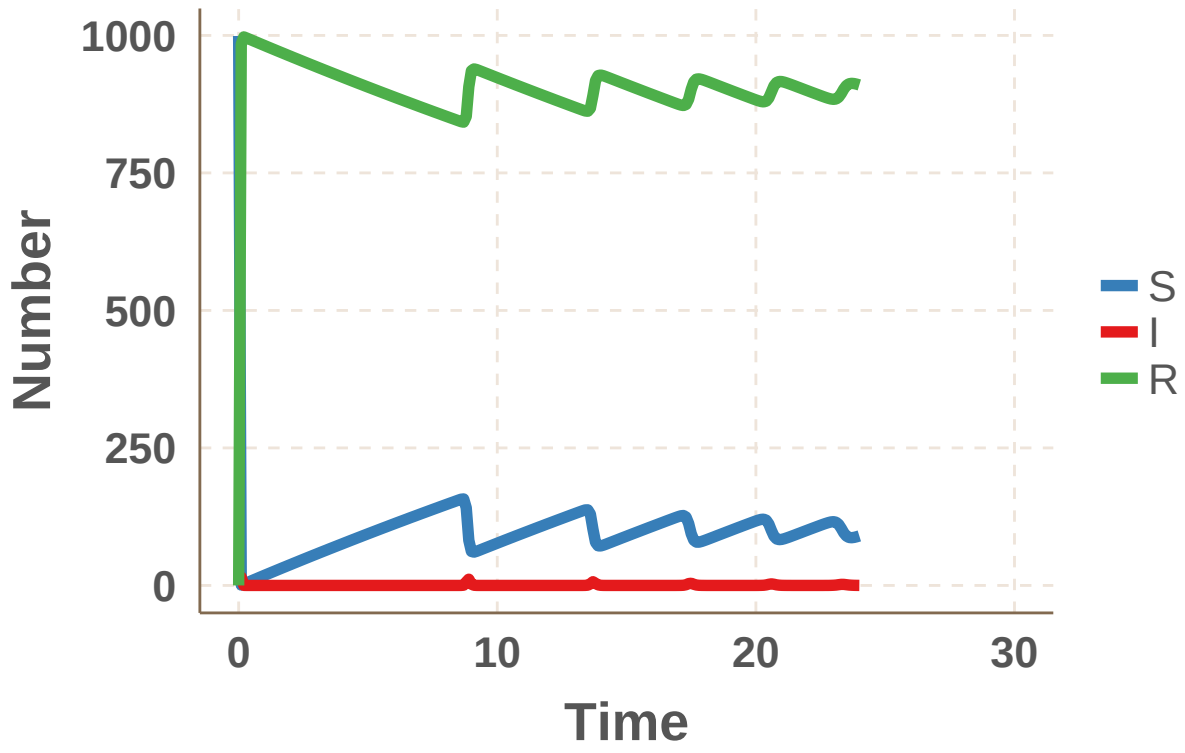

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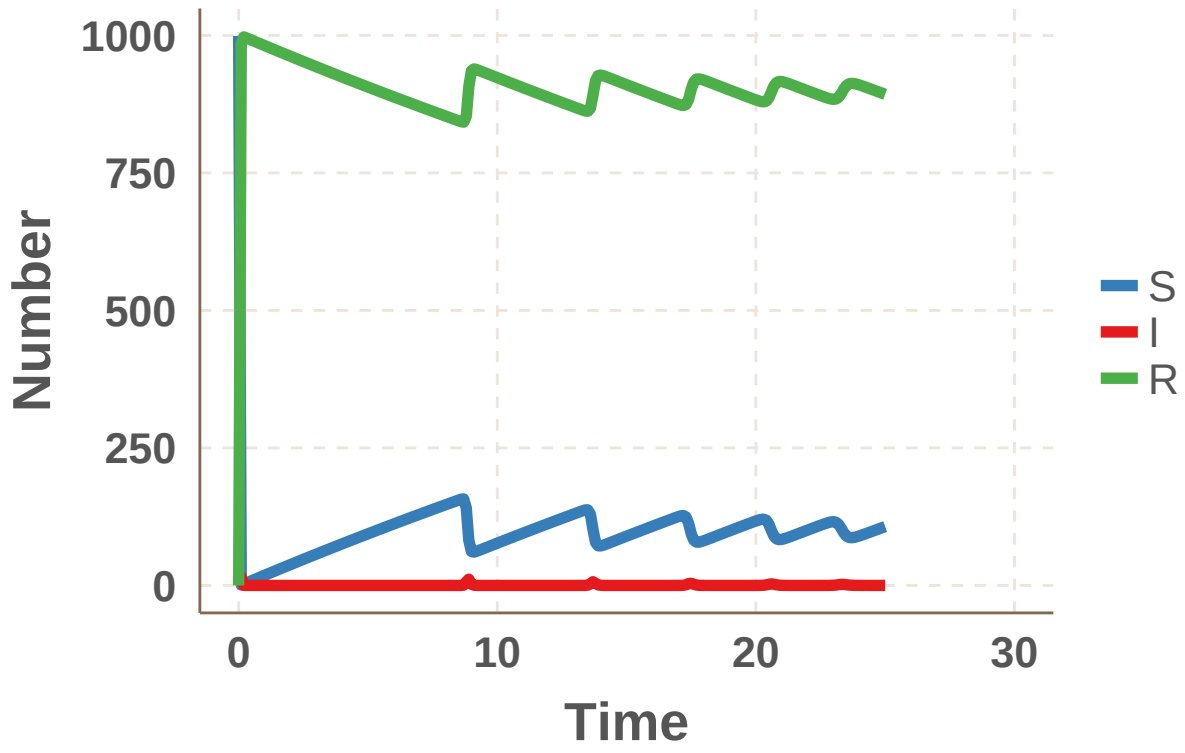

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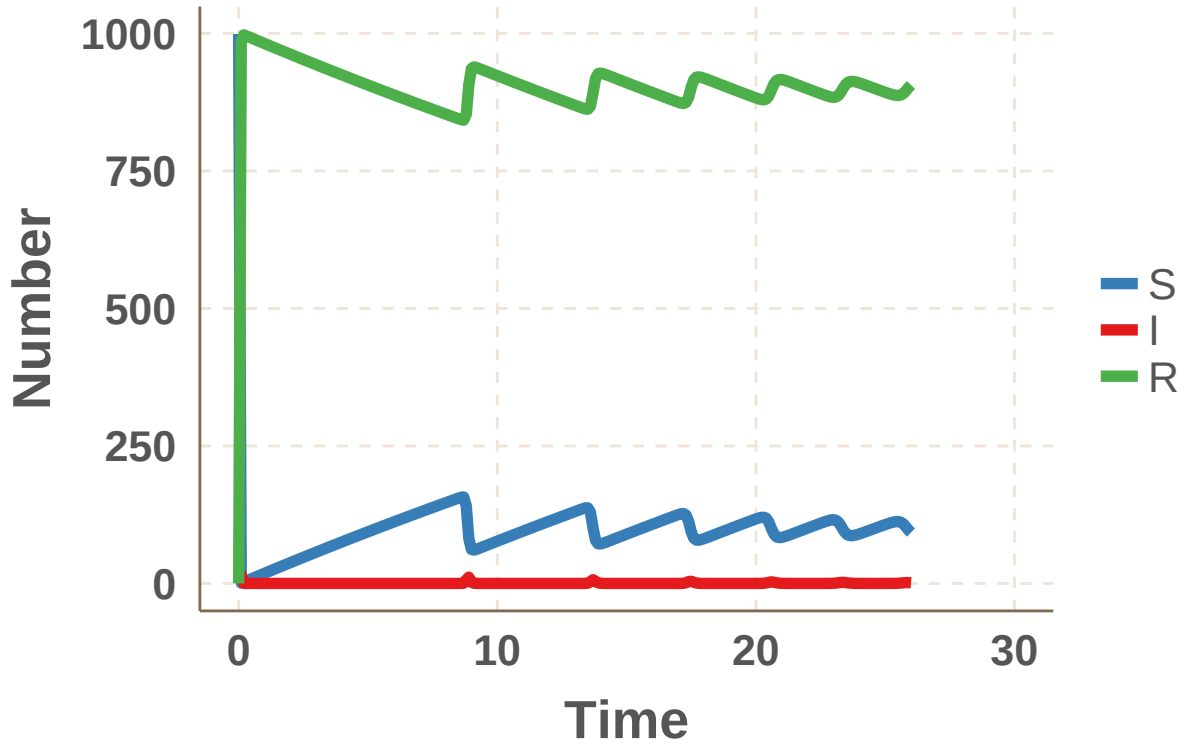

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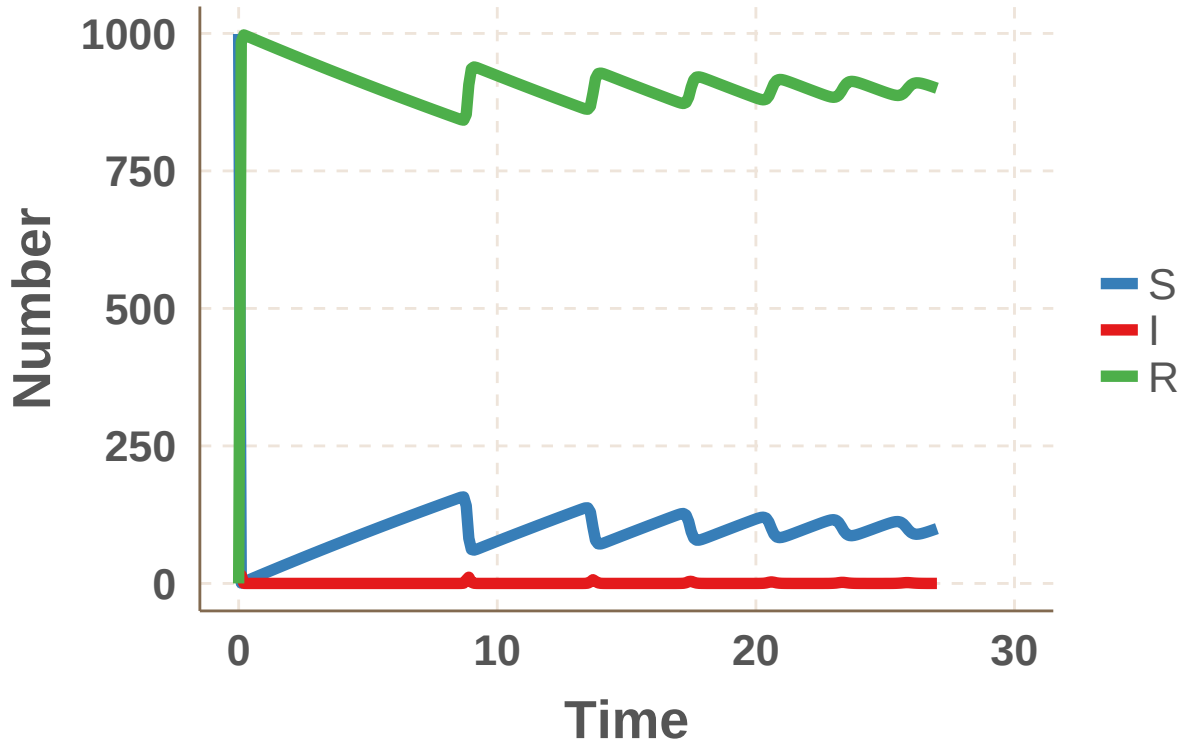

Simulating the SIR model with births/deaths using differential equations

$$dS/dt = -\lambda S + \nu N - \mu S$$

$$dI/dt = +\lambda S - \gamma I - \mu I$$

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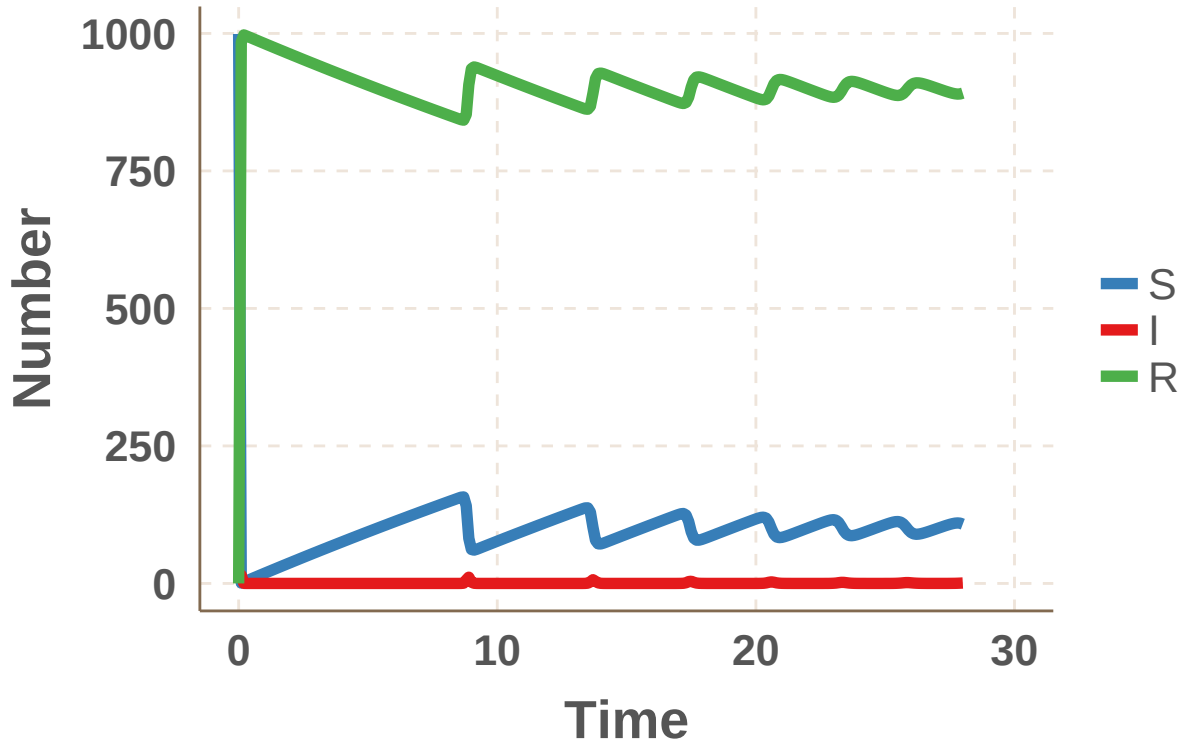

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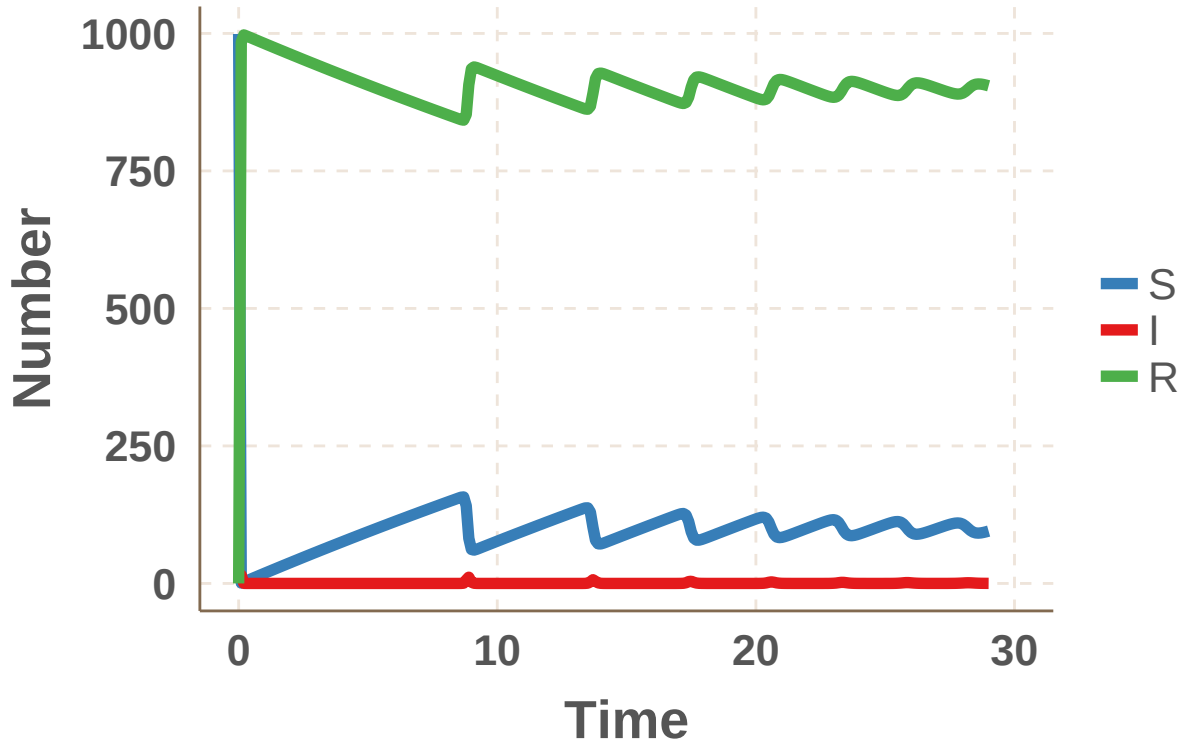
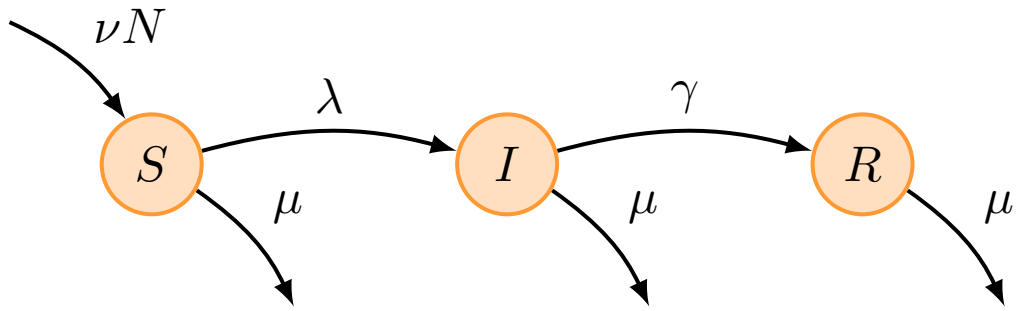
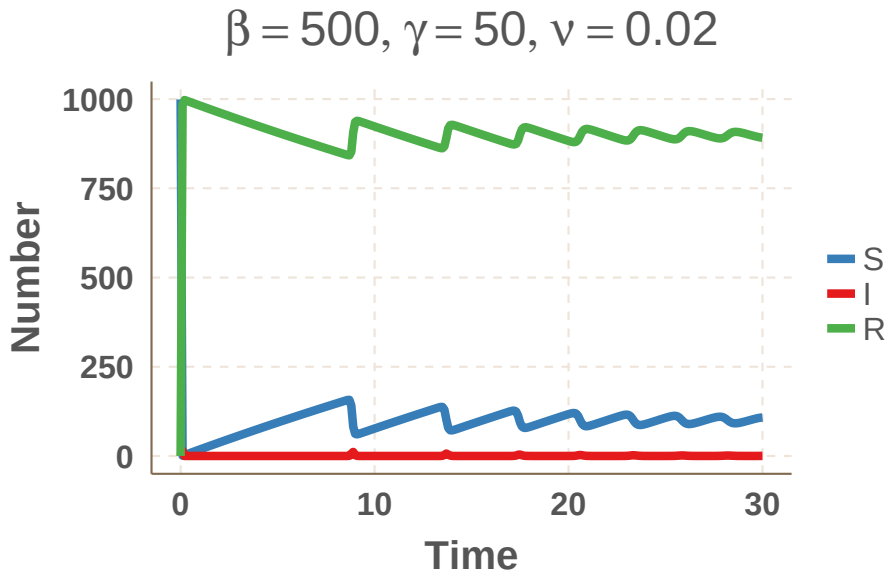


Properties of the SIR model with births/deaths





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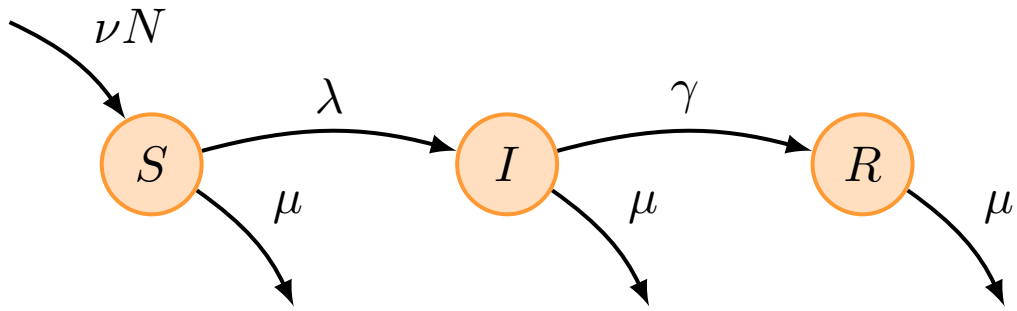

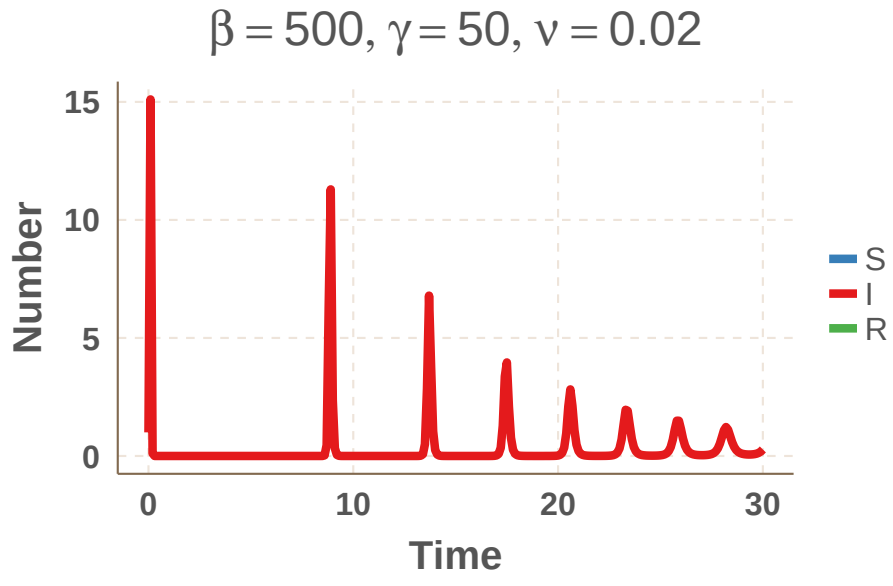

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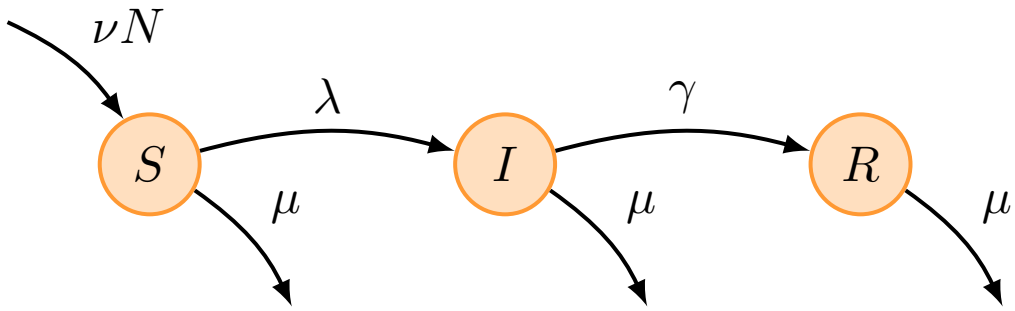
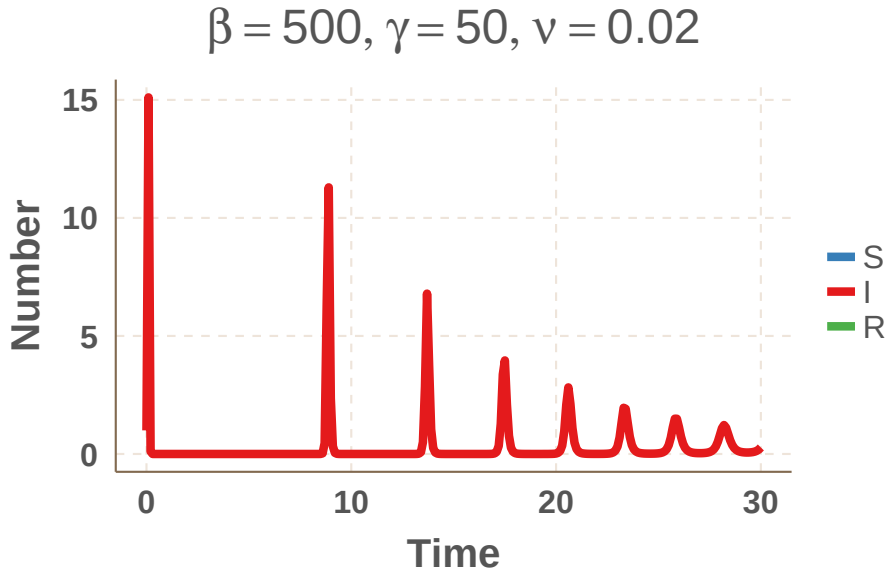
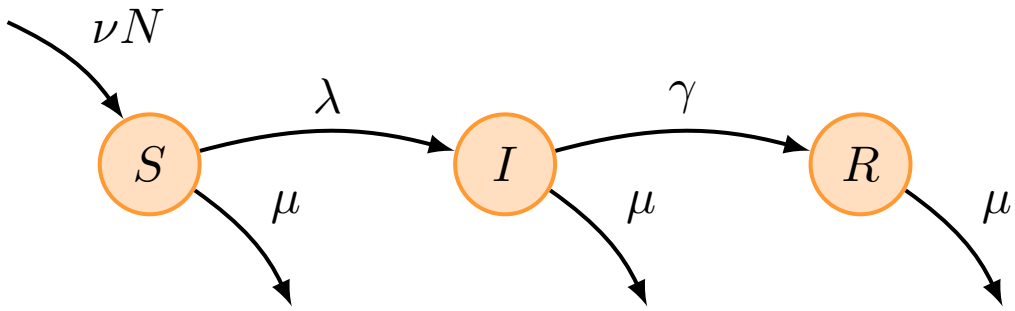
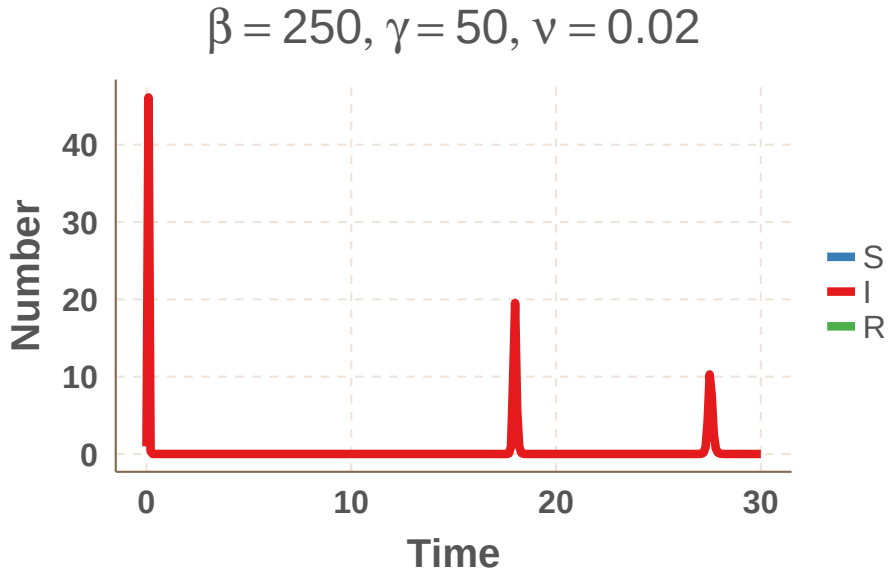




- The infection appears in cycles

Properties of the SIR model with births/deaths





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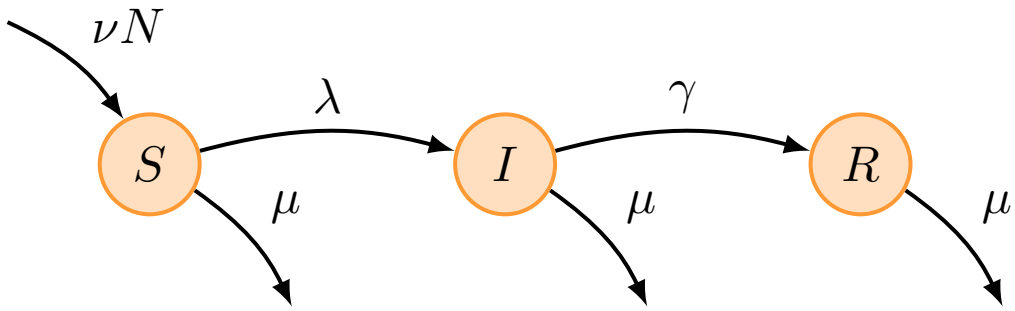

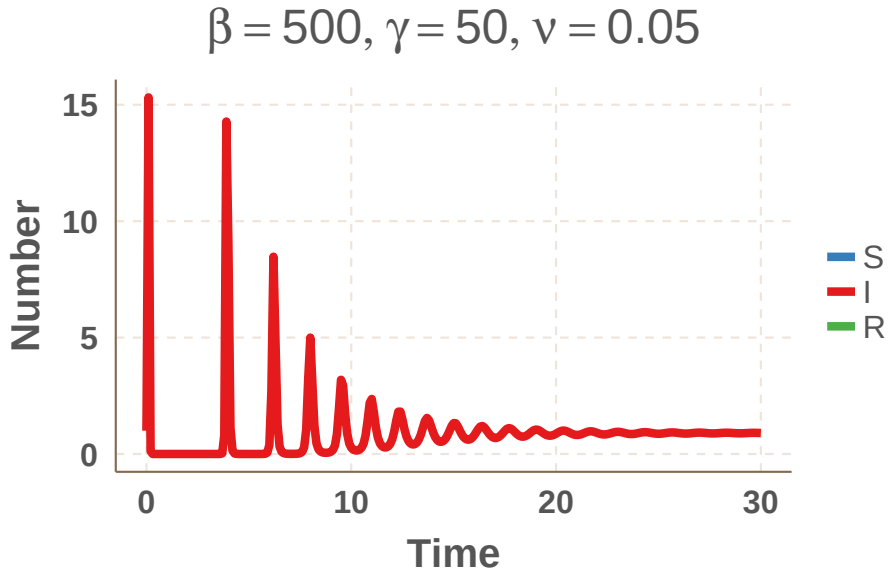

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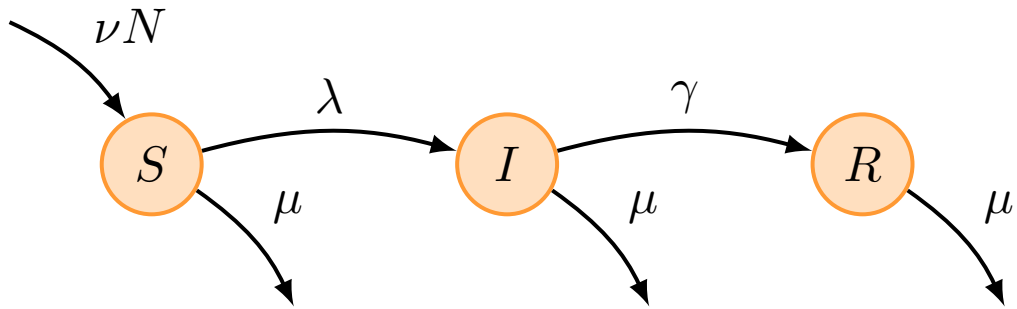
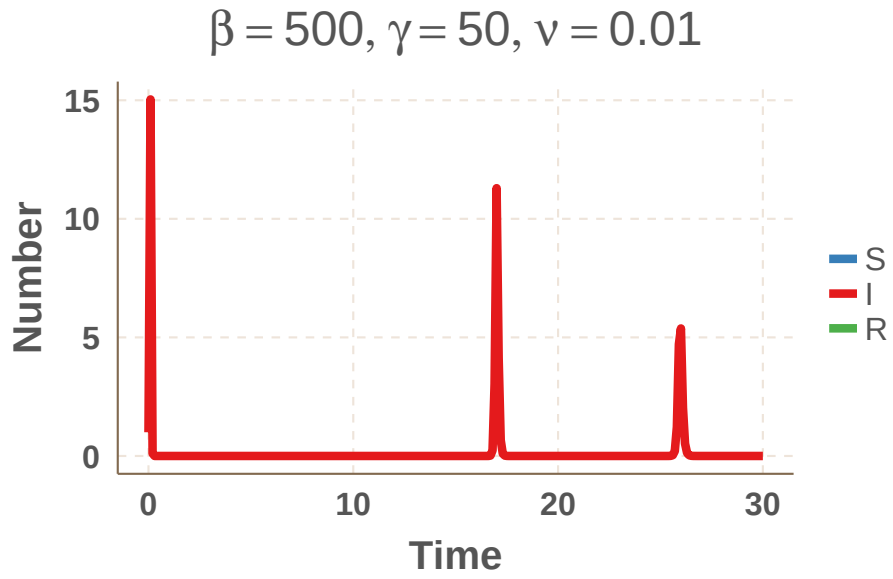
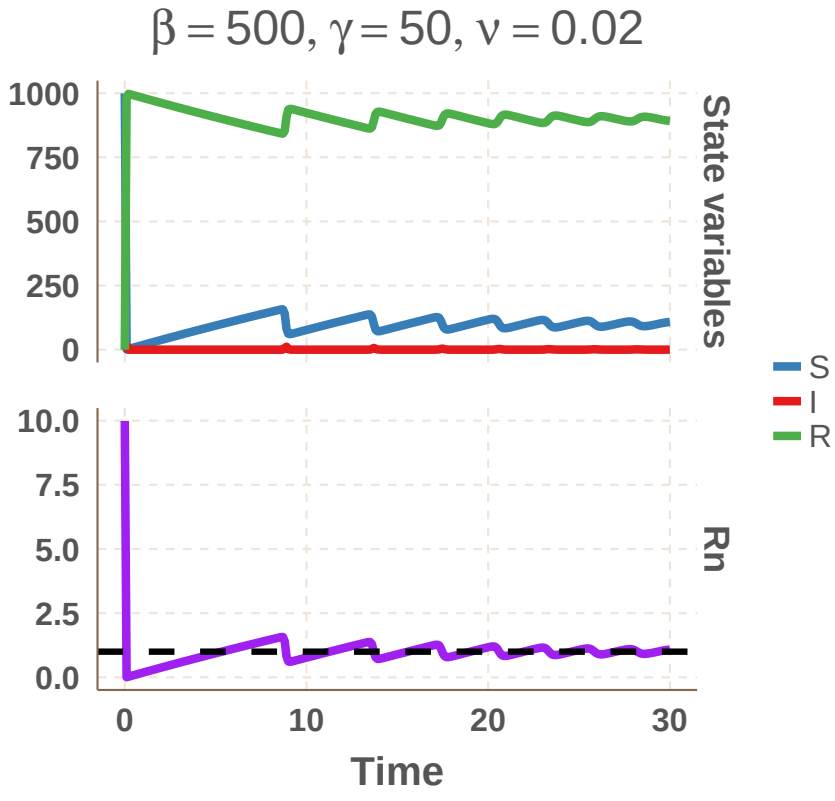




- The infection appears in cycles
- The height and frequency of cycles depends on β, γ and ν

R_n and cycles

The value of R_n determines if, at any time, a disease will increase or decrease.



$R_0 = 10$

R_n and cycles

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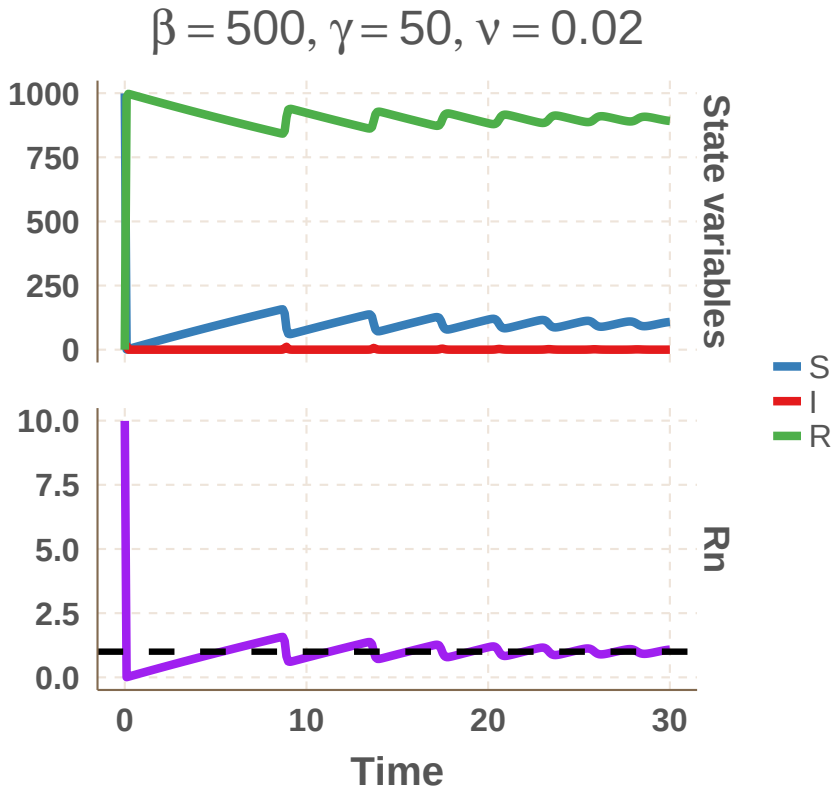

$R_0 = 10$

- At the beginning, $R_n = R_0$

R_n and cycles

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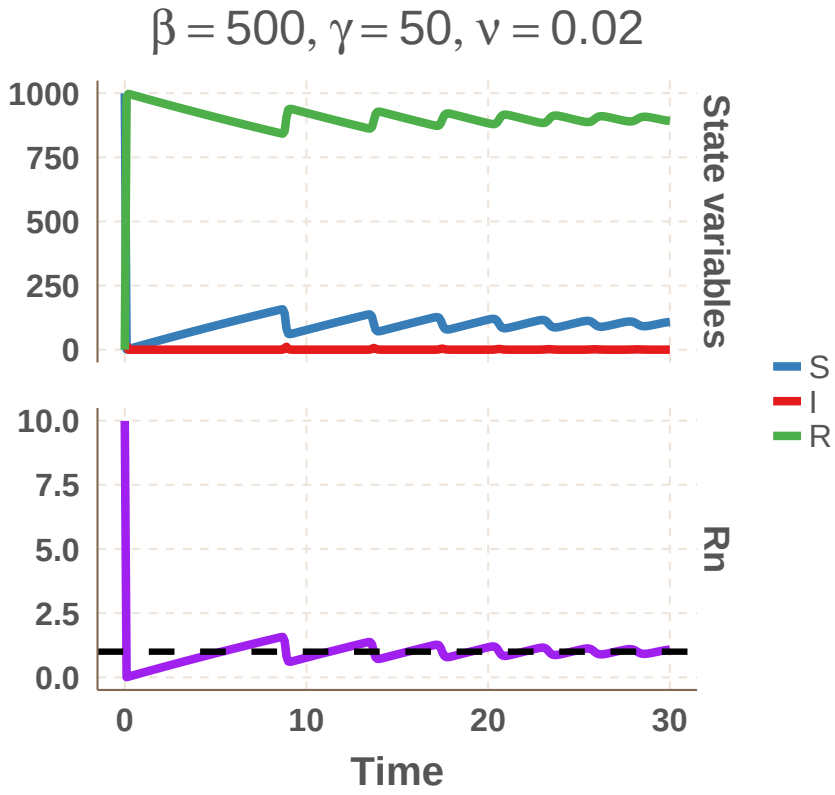
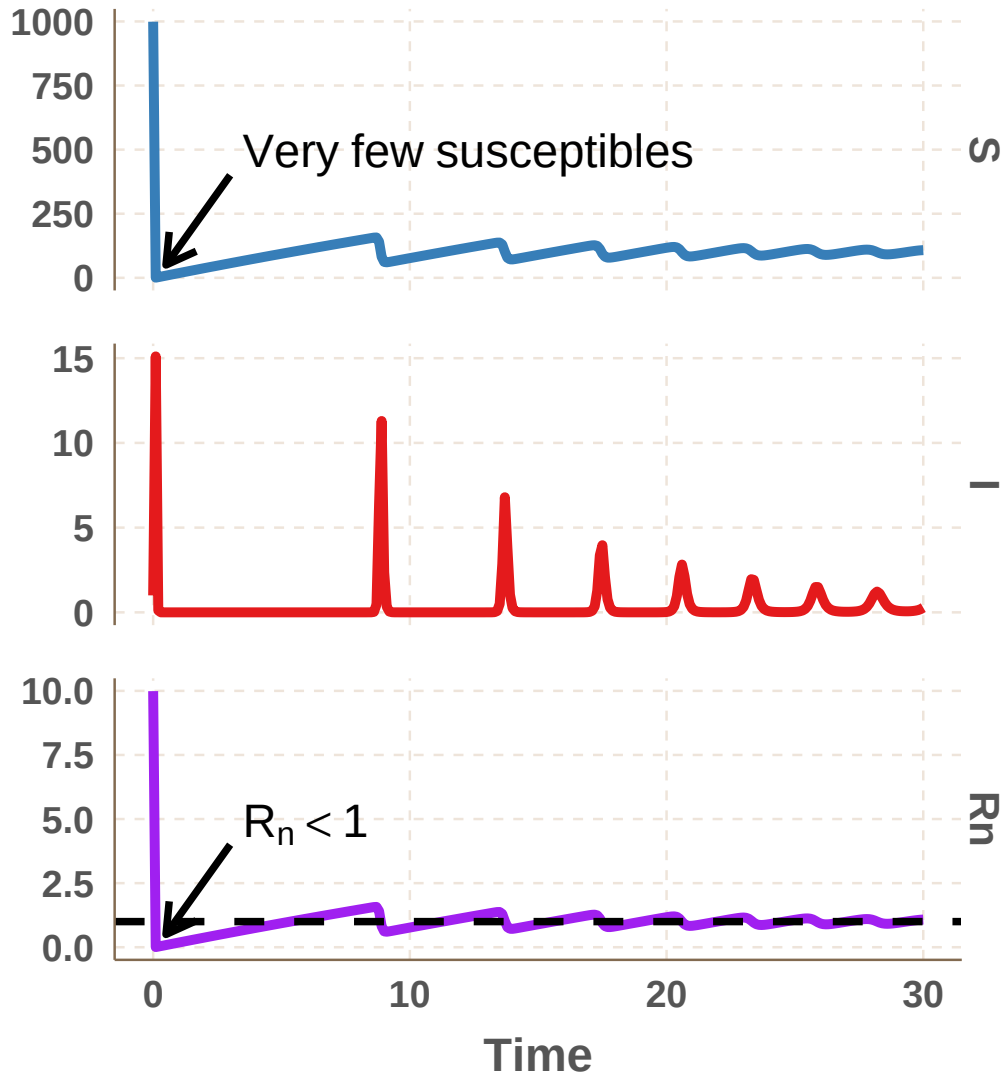


$R_0 = 10$

- At the beginning, $R_n = R_0$
- At endemic level, R_n oscillates around 1

A closer look at cycles

A closer look at cycles



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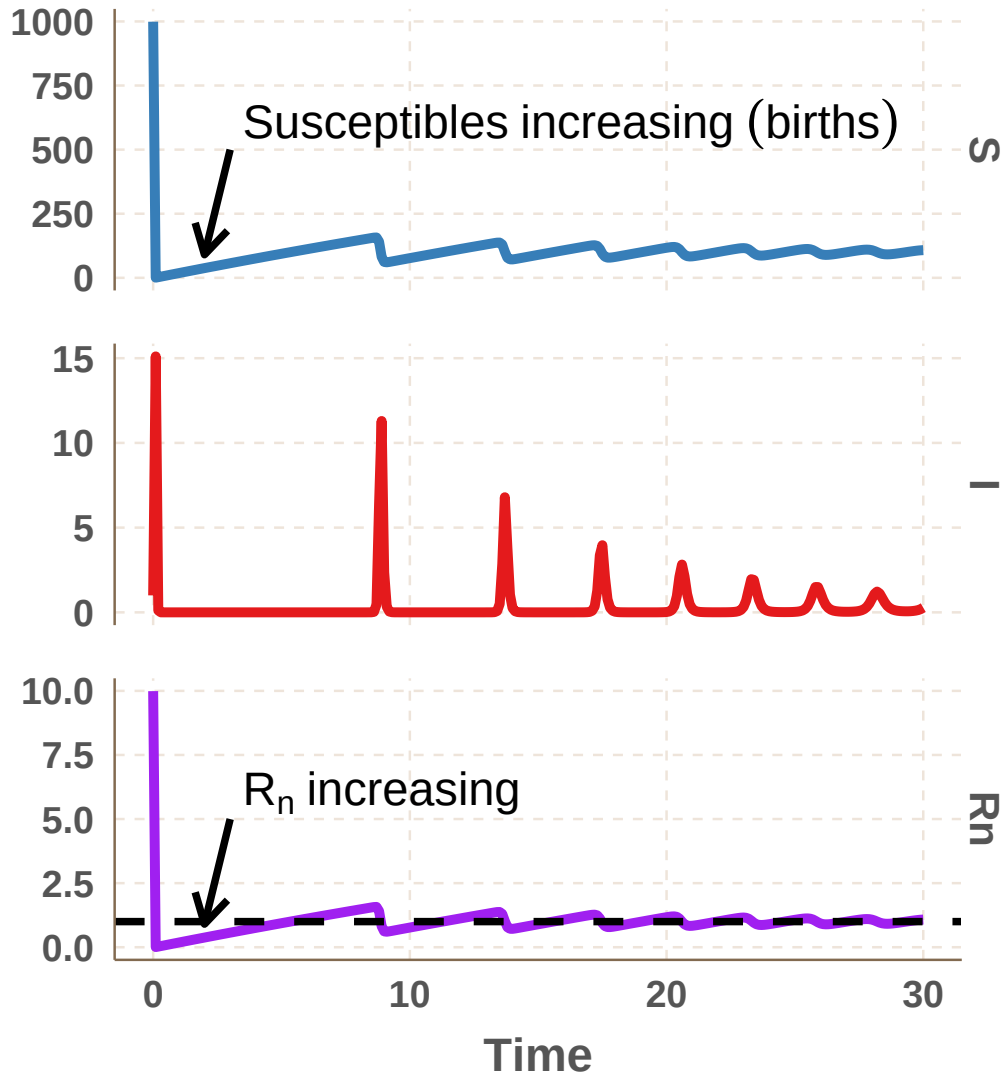

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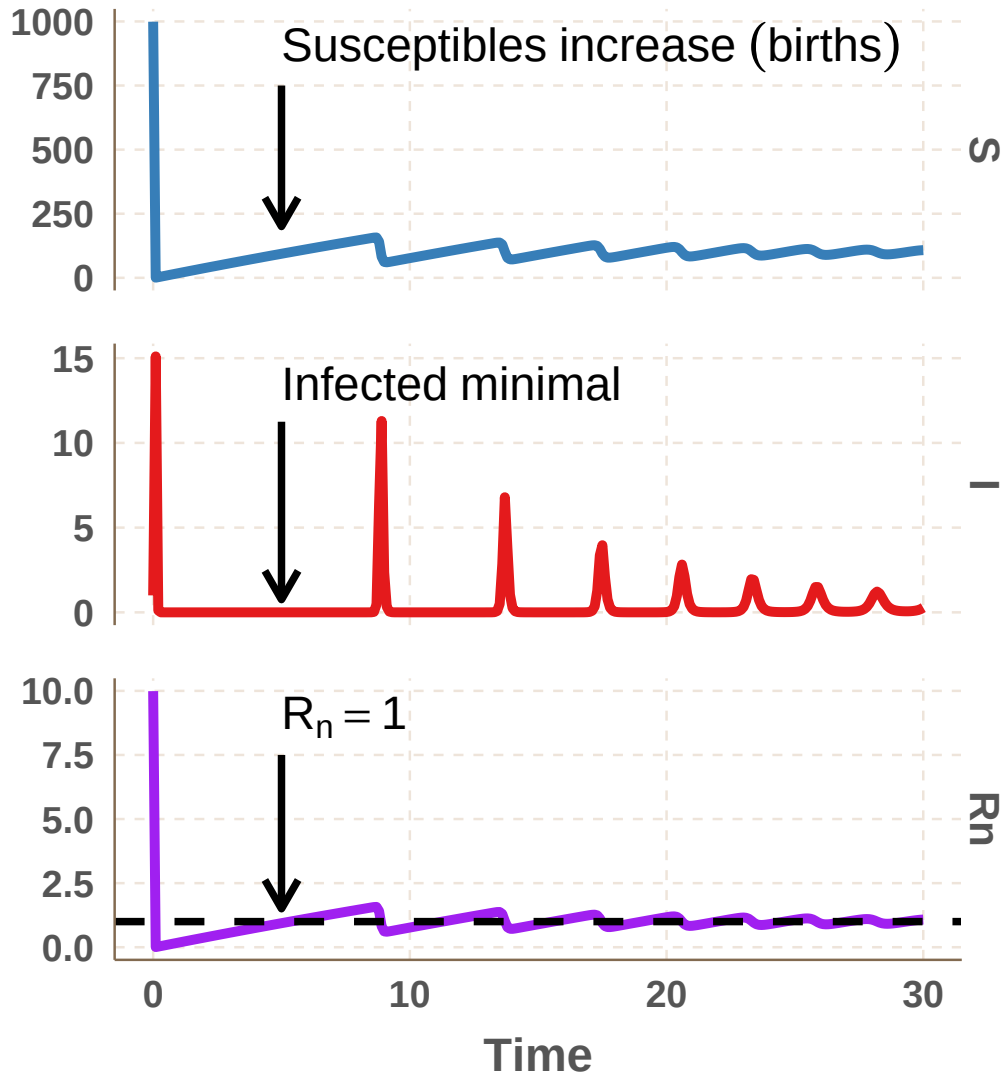

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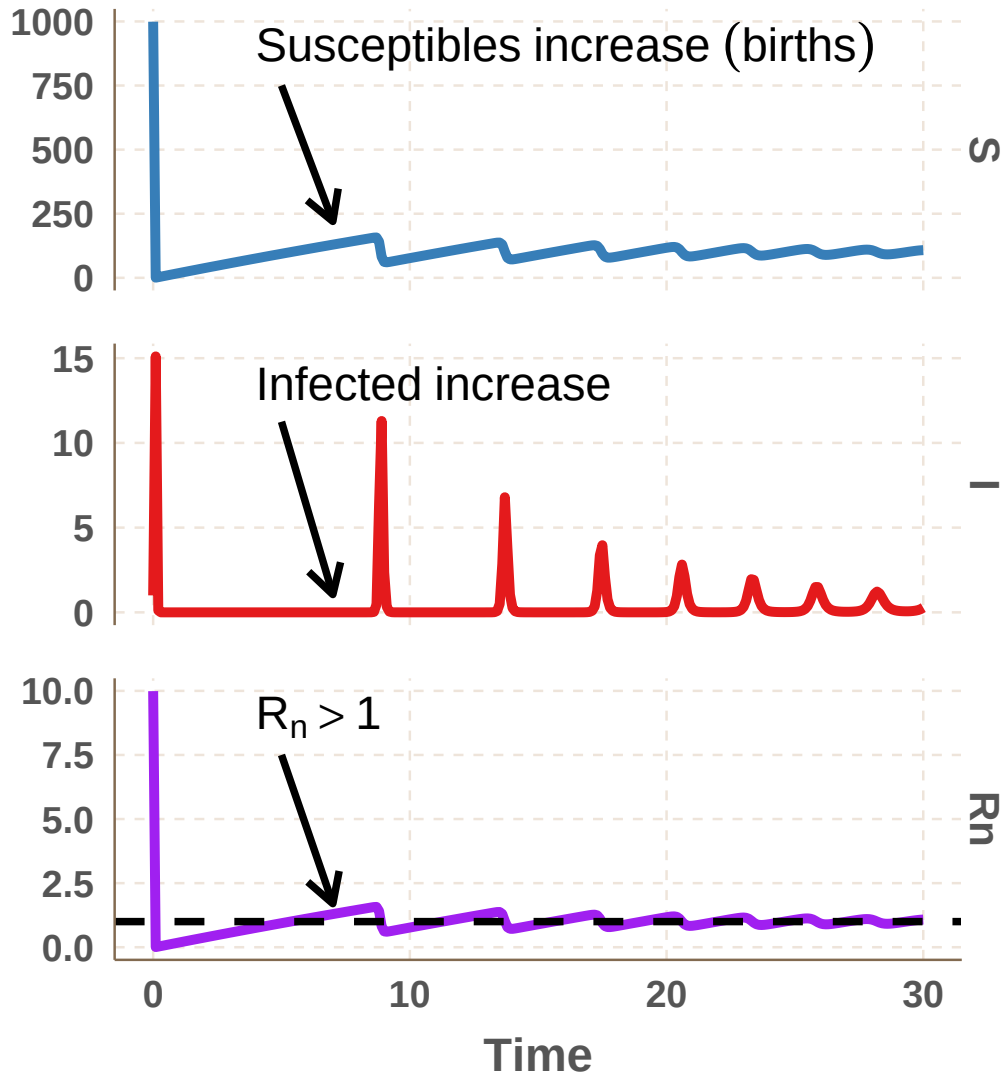

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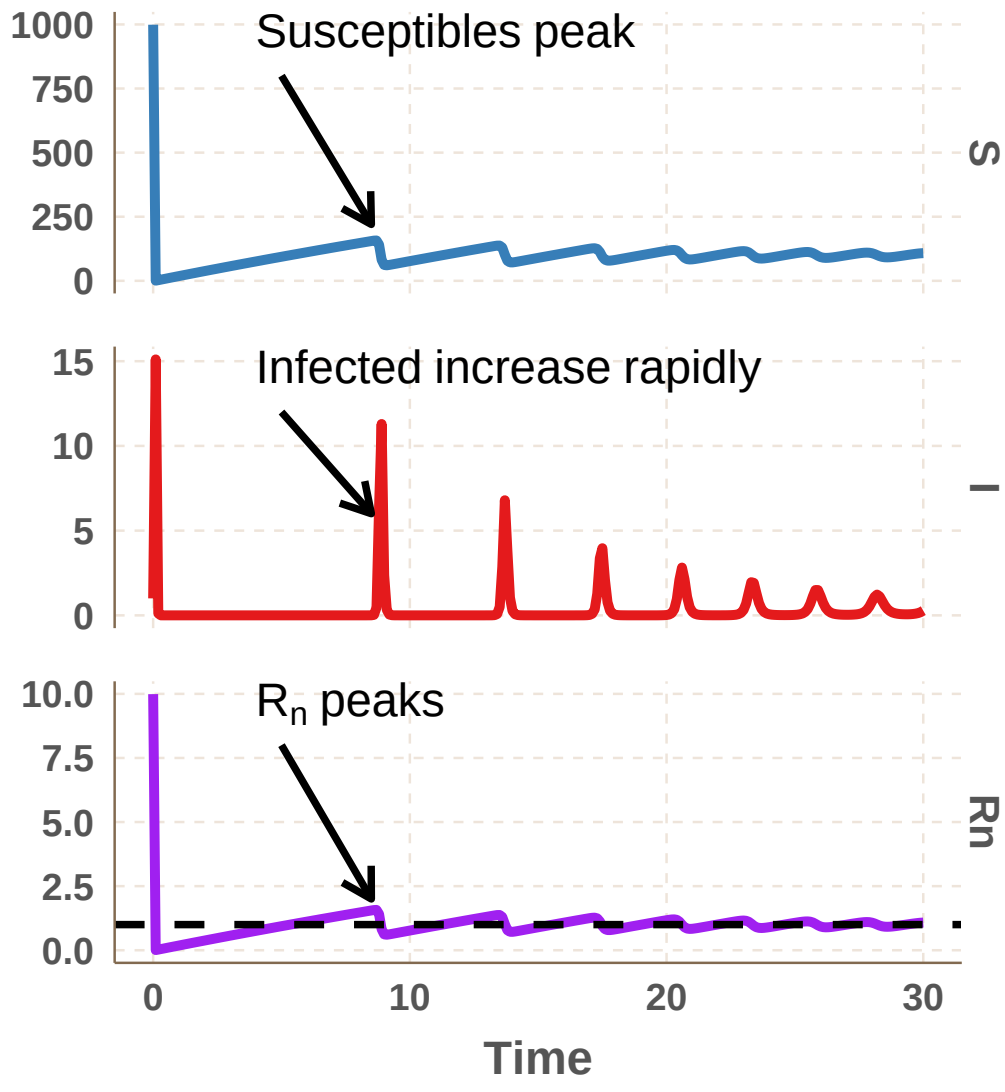

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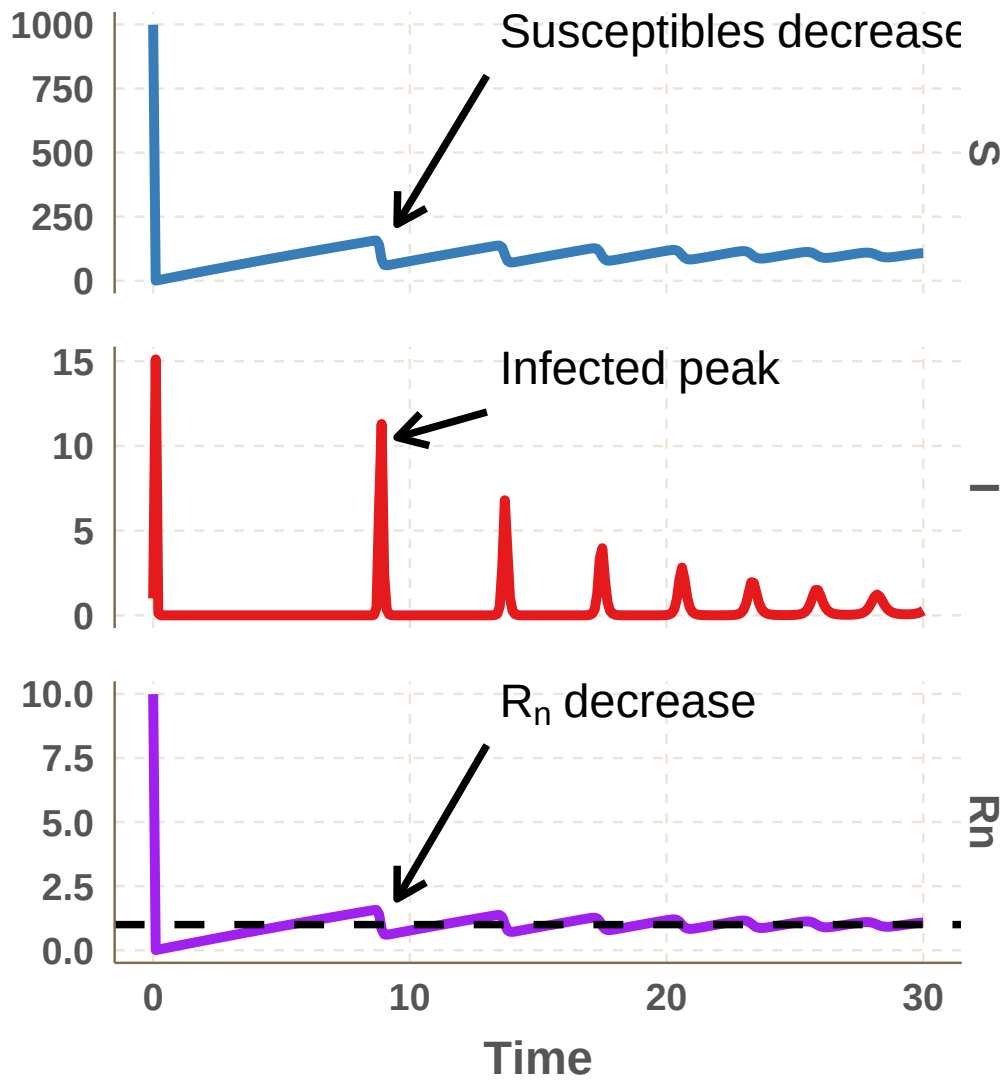

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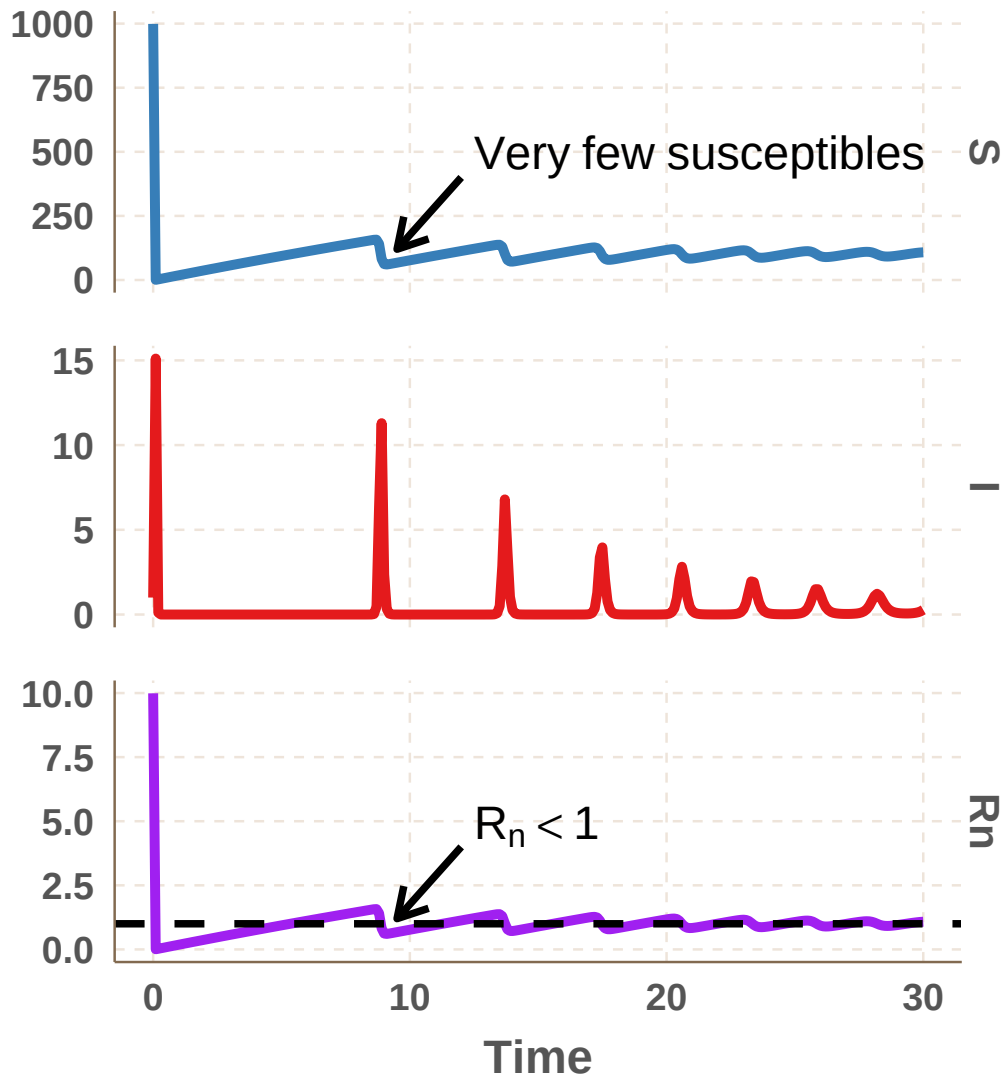
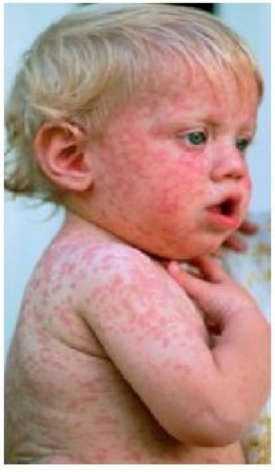
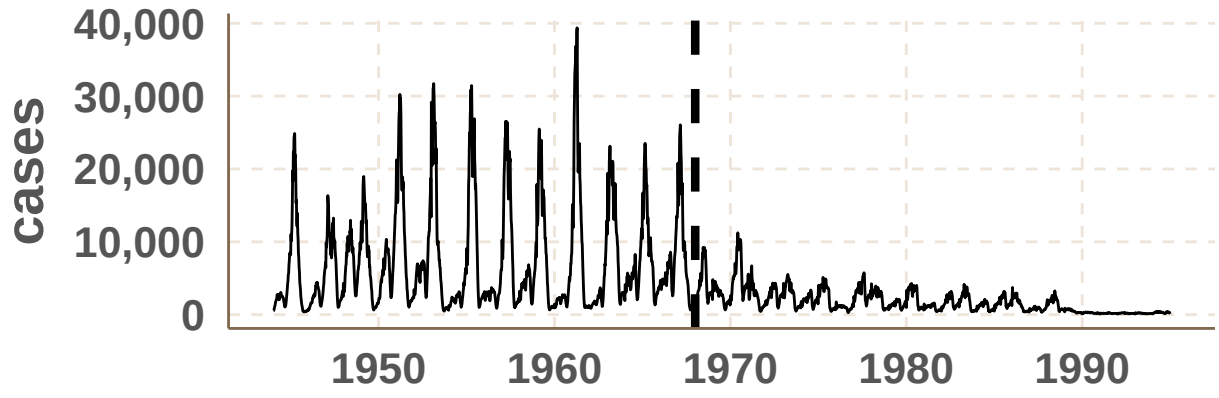


The cycle begins again

What about measles?





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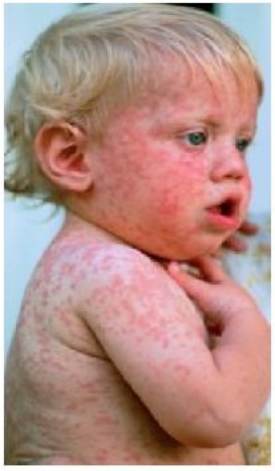
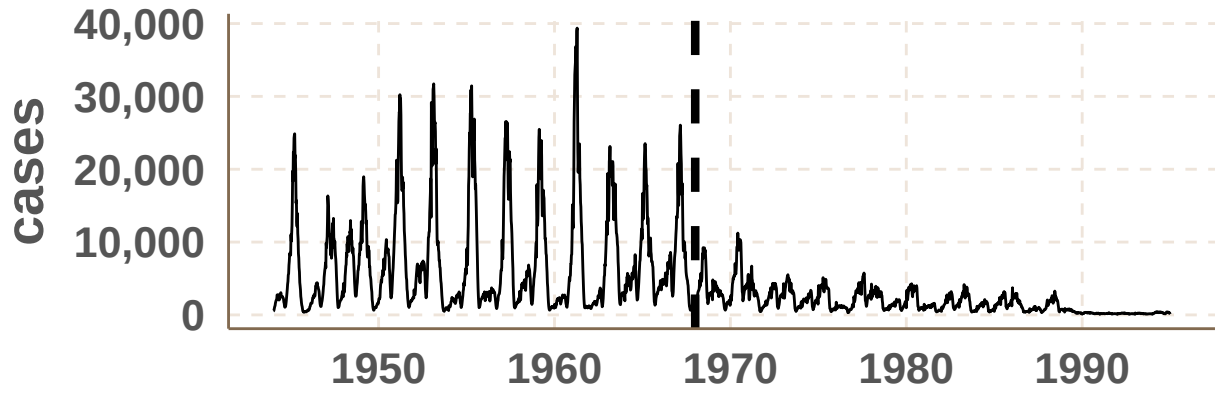
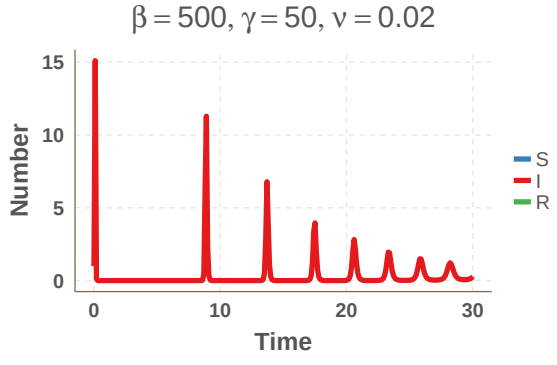
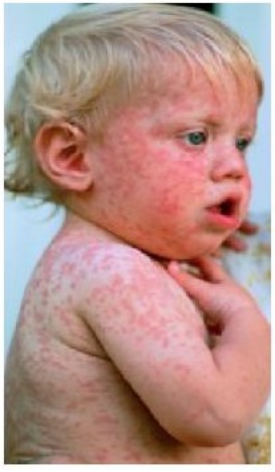


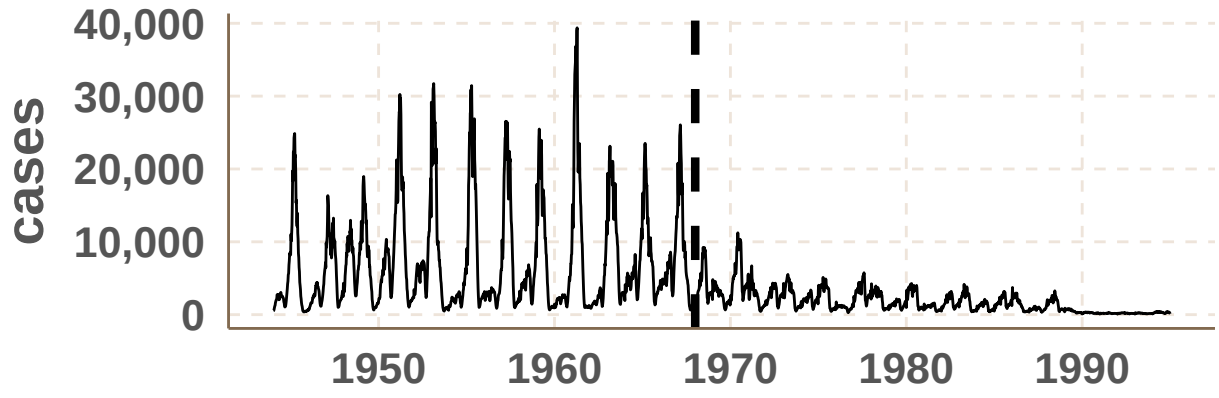




- In the SIR model with births/deaths, the endemic cycles decline over time

What about measles?





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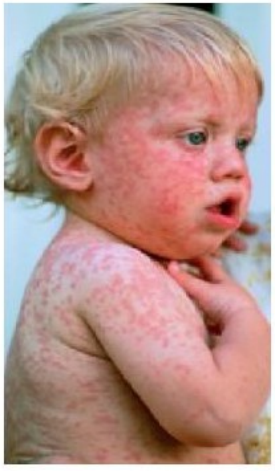

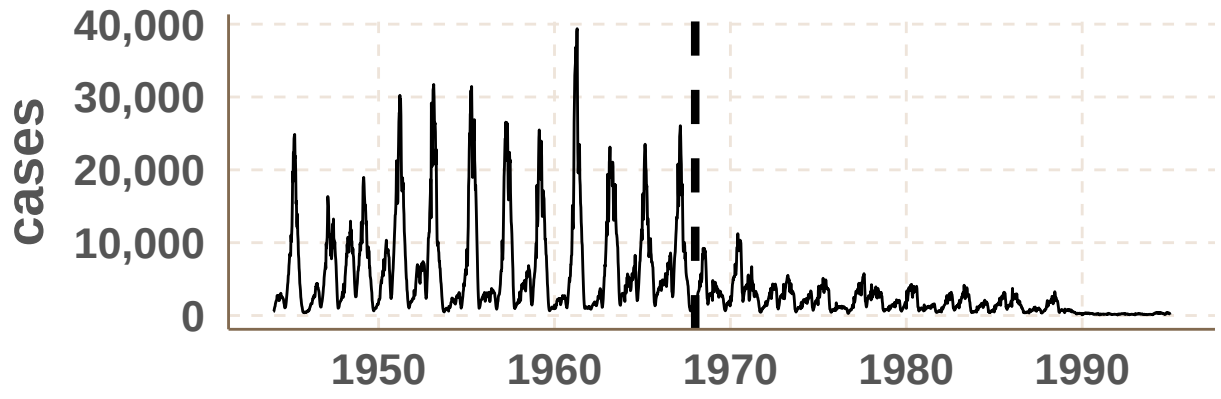

- stable cycles occur if contact rate β changes periodically
- so-called seasonal forcing by the school year (transmission is low in the summer vacation)

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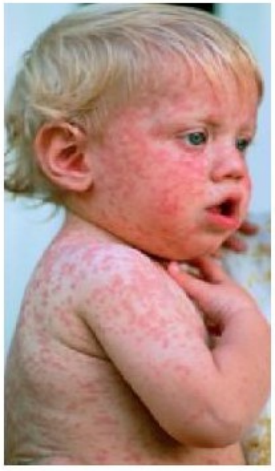

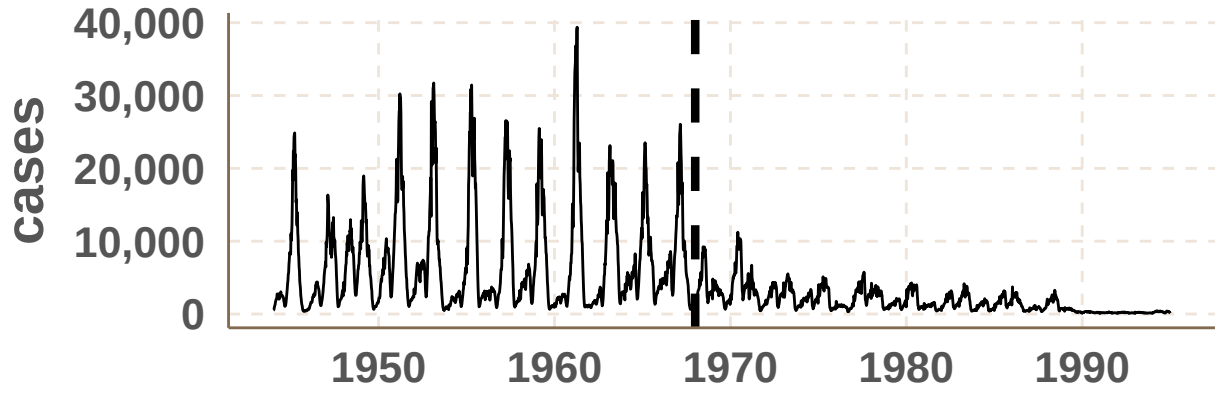

- stable cycles occur if contact rate β changes periodically
- so-called seasonal forcing by the school year (transmission is low in the summer vacation)
- it can be shown that the interepidemic period T (the time between peaks of infection) is given by

$$T \approx 2\pi\sqrt{\frac{D}{b(R_0-1)}}$$

Interepidemic periods – theory vs data

Infection	Location	Inter-epidemic period Calculated	Observed
Measles	England and Wales 1948-68	2	2
	Aberdeen, Scotland 1883-1902	2	2
	Baltimore, USA 1900-27	2	2
	Paris, France 1880-1910	2	2
	Yaounde Cameroon, 1968-75	1-2	1
	Ilesha, Nigeria, 1958-61	1-2	1
Rubella	Manchester, UK 1916-83	4-5	3.5
	Glasgow, Scotland, 1929-64	4-5	3.5
Mumps	England and Wales 1948-82	3	3
	Baltimore, USA 1928-73	3-4	2-4
Polio	England and Wales, 1948-65	4-5	3-5
Smallpox	India, 1868-1948	4-5	5
Chickenpox	New York City, USA, 1928-72	3-4	2-4
	Glasgow, Scotland, 1929-64	3-4	2-4
Scarlet fever	England and Wales, 1897-1978	4-5	3-6
Diphtheria	England and Wales, 1897-1979	4-5	4-6
Pertussis	England and Wales, 1970-82	3-4	3-4

6. Extending simple models

Extending simple models

Compartmental models can be easily extended

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- Maternal immunity

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Simple vs. complex models

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- Maternal immunity
- Carrier states (asymptomatic infection)
- Disease-related mortality
- Heterogeneity (age, risk, space, social context, etc…)

Simple vs. complex models

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Simple vs. complex models

- More complex models need more (good) data

Extending simple models

Compartmental models can be easily extended

- Maternal immunity
- Carrier states (asymptomatic infection)
- Disease-related mortality
- Heterogeneity (age, risk, space, social context, etc…)

Simple vs. complex models

- More complex models need more (good) data
- Without good data, simple models are recommended

Why model?

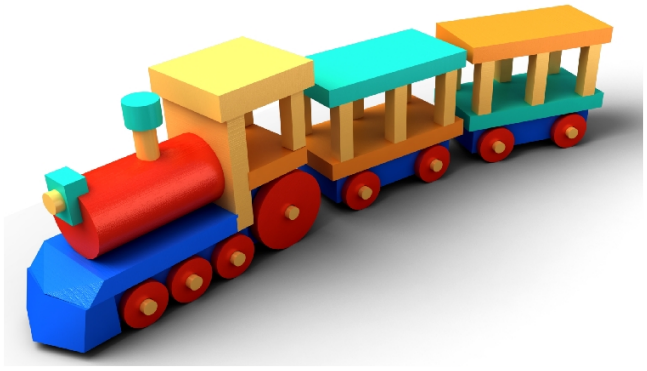
1. understand transmission dynamics
2. assess control strategies
3. predict future course

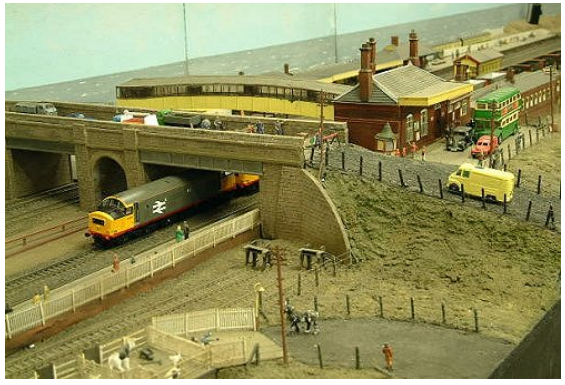
Why model?

1. understand transmission dynamics
2. assess control strategies
3. predict future course

- Modelling can be used to make powerful predictions, many of which have been confirmed by field data
- We have seen how to build simple models to describe the spread of an infection in a population
- Models are frequently used to investigate the impact of interventions such as vaccination.

Models must be challenged

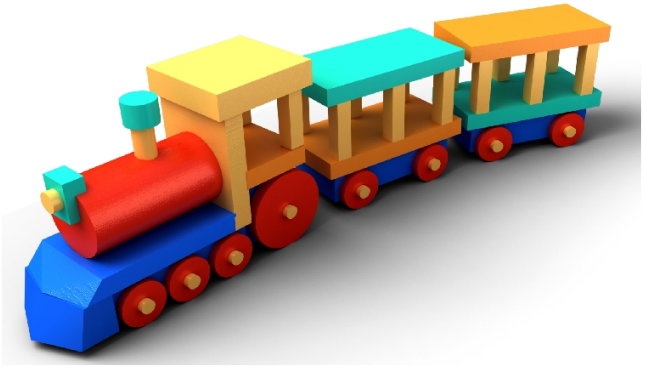


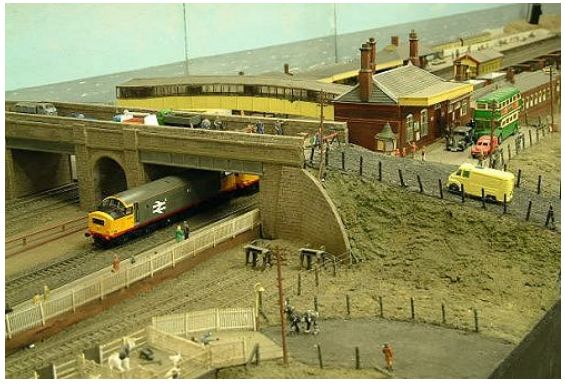


Simple

Complicated

Models must be challenged





Simple

Complicated

- What is wrong with the model?
- What are the assumptions; are they reasonable?
- How would you improve the model?
- Are the right data available?

7. Summary

Summary I

- A mathematical model of an infectious disease is a mathematical description (through rules and equations) of the dynamical process of infectious disease transmission in a population.
- Compartmental models divide the population into compartments. They describe the model with state variables and parameters
- Two basic compartmental models are the SI model and the SIR model
- We can simulate these models using differential equations
- The value of R_0 reveals if a newly introduced disease will spread or die out.
- The value of R_n determines if, at any time, a disease will increase or decrease.
- The proportion of the population one needs to vaccinate to prevent outbreaks is $1 - \frac{1}{R_0}$ (herd immunity threshold)

Summary II

- Endemic diseases are ones that are established in a population, and do not die out
- The simple SI or SIR models do not describe endemic diseases, because there is no source of new susceptibles
- The SIRS model describes diseases that can be endemic through *loss of immunity“ (e.g., influenza)
- The SIR model can describe endemic diseases if we include births
- The SIR model with births produces cycles
- Sustained cycles only occur when there is seasonal forcing (e.g., school year)