



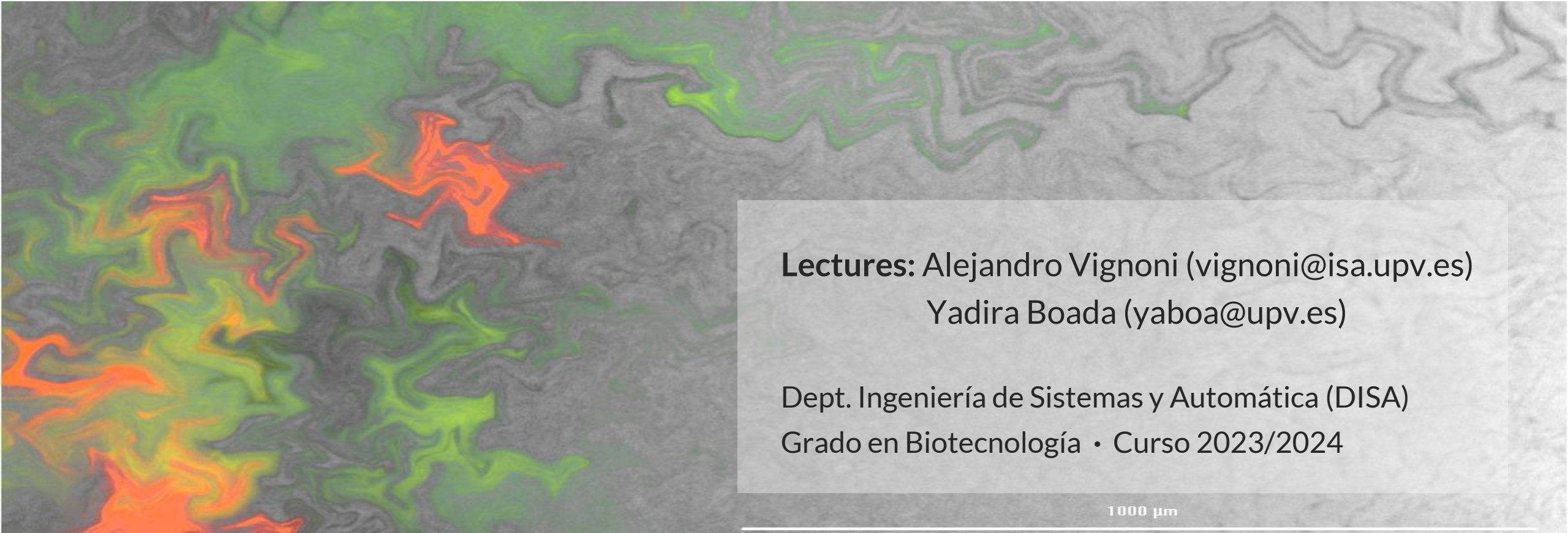
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Synthetic Biology and
Biosystems Control Lab

Synthetic Biology

Introduction to mathematical modelling applied to biology



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Dept. Ingeniería de Sistemas y Automática (DISA)
Grado en Biotecnología • Curso 2023/2024

1000 μm

Summary

1. What is a dynamic model?
2. Finding a solution
3. Examples of dynamic models in biology

1. What's a dynamic model?

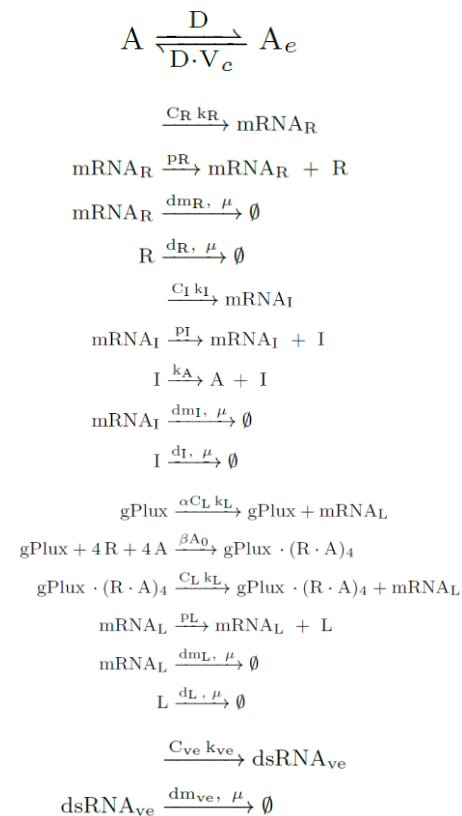
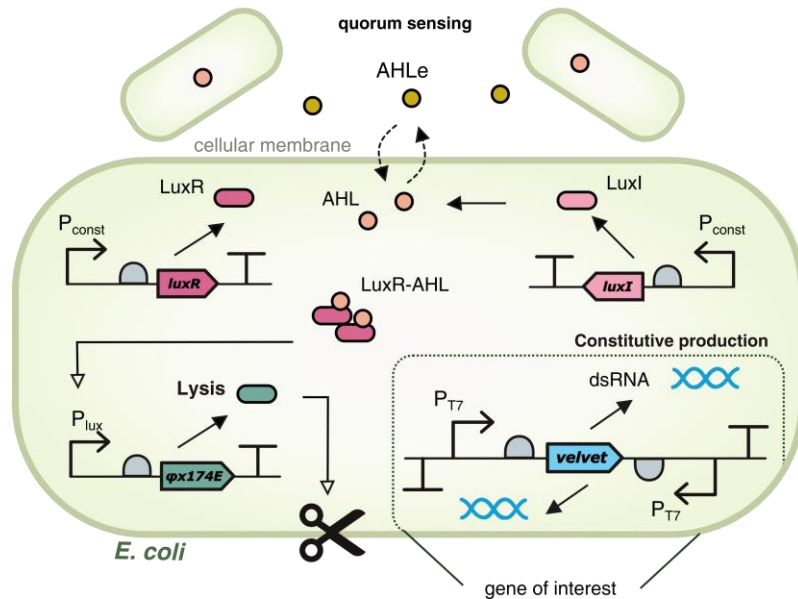
Schematic model



Biochemical
Reaction
Model



Mathematical Model (ODEs)



$$\begin{aligned}
 \frac{d[N]}{dt} &= \mu N(N_0 - N) - \frac{kL^n}{L_0^n + L^n} N && \text{cells death} \\
 \frac{d[A_e]}{dt} &= D(-NV_c[A_e] + N[A]) + \frac{kL^n}{L_0^n + L^n} N - d_{Ae}[A_e] \\
 \frac{d[A]}{dt} &= D(V_c[A_e] - [A]) + k_A[I] - d_A[A] - \mu[A] \\
 \frac{d[R]}{dt} &= \frac{C_R k_R P_R}{d_{mR} + \mu} - d_R[R] - \mu[R] \\
 \frac{d[I]}{dt} &= \frac{C_I k_I P_I}{d_{mI} + \mu} - d_I[I] - \mu[I] \\
 \frac{d[L]}{dt} &= \frac{C_L k_L P_L}{d_{mL} + \mu} \left(\alpha + \frac{\beta \left(\frac{[R][A]}{A_0} \right)^4}{1 + \left(\frac{[R][A]}{A_0} \right)^4} \right) - d_L[L] - \mu[L] \\
 \frac{d[Ve]}{dt} &= C_{ve} k_{ve} - d_{m_{ve}}[Ve] - \mu[Ve] && \text{dsRNA of target gene}
 \end{aligned}$$

But what is an Ordinary Differential Equation (ODE)?

These are equations with **variables** and their **derivatives**

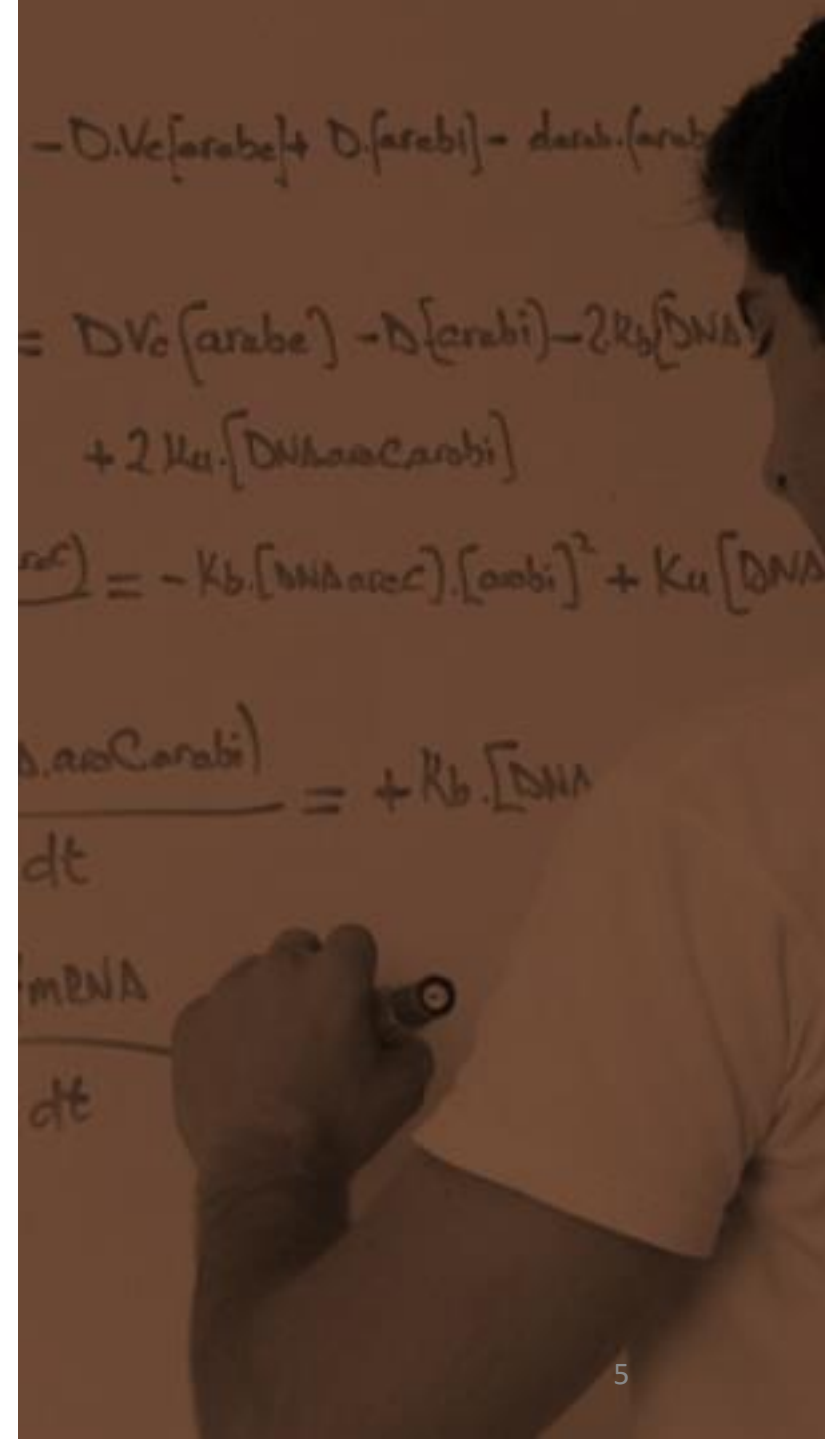
If we have any function (the typical one):

$$y = f(t) \quad (y \text{ only depends on the variable } t, \text{ but we could have } y = f(t, x_1, x_2, \dots, x_n))$$

Do you remember the definition of the derivative of a function?

$$\dot{y} = \frac{df(t)}{dt} = \lim_{h \rightarrow 0} \frac{f(t+h) - f(t)}{h} \quad (\text{we can have higher order derivatives } y'', y''', y^{(n)})$$

But they can be very
challenging and difficult!!



2. Finding a solution...

⚠ **Analytically:** solving for the unknown...



⚠ **Numerically:** in an approximate way.

$$\dot{y} \simeq \frac{f(h+h) - f(x)}{h}$$

(with an h very small)



Why do we use ODEs?

Differential equations describe biological behaviour, physical laws, human activities, and much more....



$$\left(-\frac{\partial V}{\partial t} - \frac{1}{2}\sigma^2 S^2 \frac{\partial^2 V}{\partial S^2}\right) \Delta t = r \left(-V + S \frac{\partial V}{\partial S}\right) \Delta t$$

$$rV = \frac{\partial V}{\partial t} + \frac{1}{2}\sigma^2 S^2 \frac{\partial^2 V}{\partial S^2} + rS \frac{\partial V}{\partial S}$$

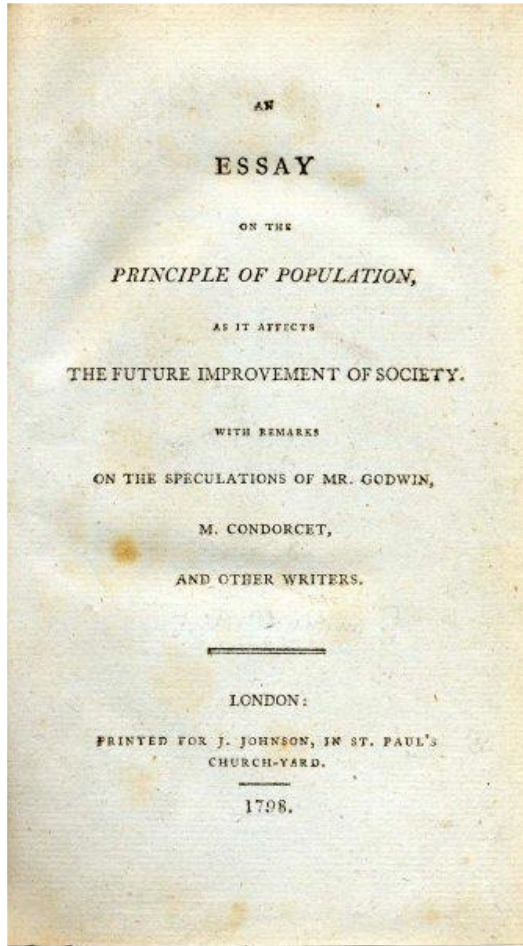
And the set of equations that describe a system or a phenomenon...
is known as ODE model

Software for analyzing and simulating ODEs



- [MATLAB](#), a technical computing application (MATrix LABoratory) FREE LICENSE WITH iGEM
- [Maxima](#), an open-source [computer algebra system](#).
- [COPASI](#), a free software package for the integration and analysis of ODEs.
- [GNU Octave](#), a high-level language, primarily intended for numerical computations.
- [Scilab](#), an open source application for numerical computation.
- [Maple](#), a proprietary application for symbolic calculations.
- [Mathematica](#), a proprietary application primarily intended for symbolic calculations.
- [Julia \(programming language\)](#), a high-level language primarily intended for numerical computations.
- [SageMath](#), an open-source application that uses a Python-like syntax with a wide range of capabilities spanning several branches of mathematics.
- [SciPy](#), a Python package that includes an ODE integration module.
- [GNU R](#), an open source computational environment primarily intended for statistics, which includes packages for ODE solving.

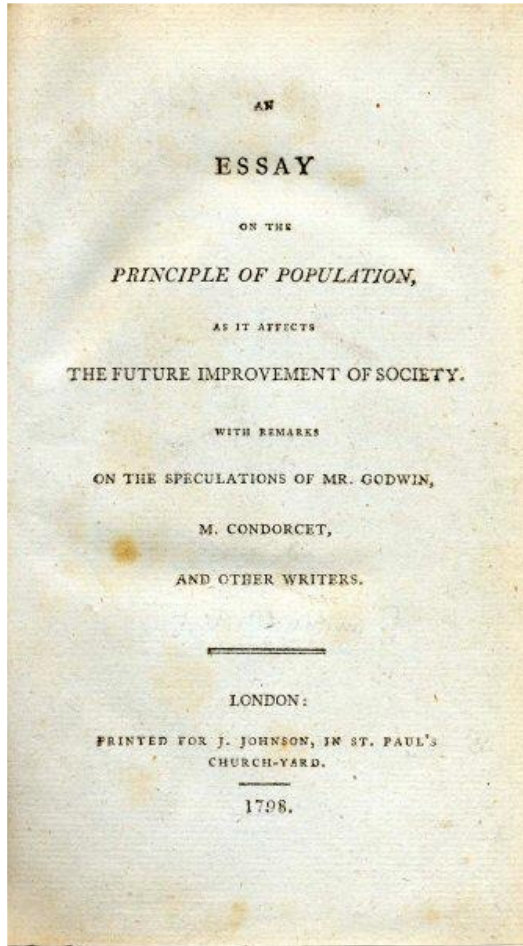
3. Example of ODE Model: Malthus growth



- According to Malthus (1789) a population $P(t)$ at instant t , grows proportional to $P(t)$:

$$\frac{dP(t)}{dt} = kP(t)$$

Example of ODE Model: Malthus growth



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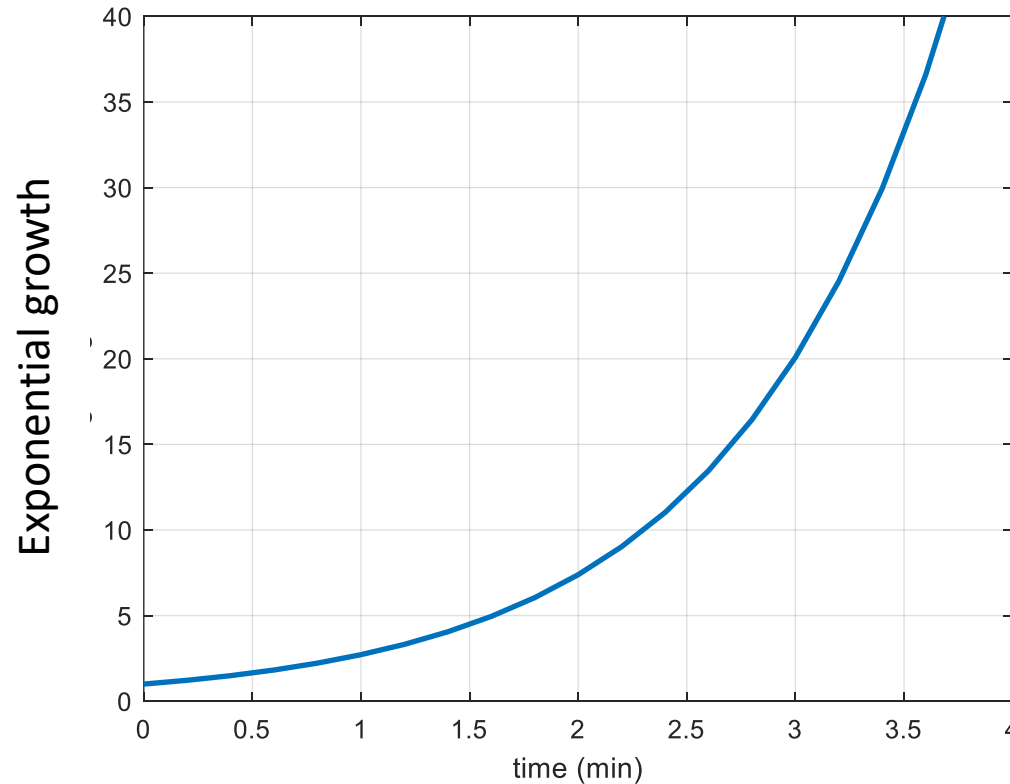
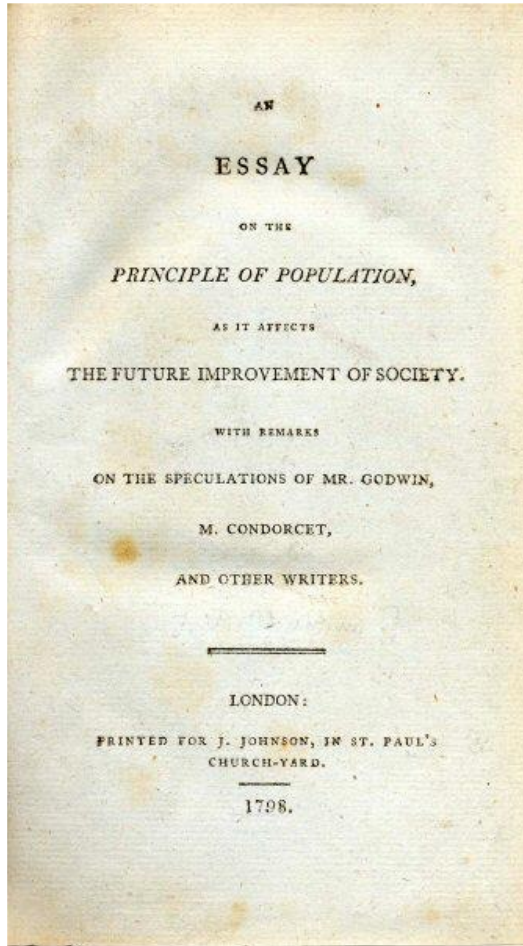
$$\frac{dP(t)}{dt} = kP(t)$$

- This equation can be variable-separated (P and t) to obtain an analytical solution by integration:

$$P(t) = P(0)e^{kt}$$

$\forall t \geq 0, P(0)$ initial population

Example of ODE Model: Malthus growth



ulation $P(t)$ at
t):

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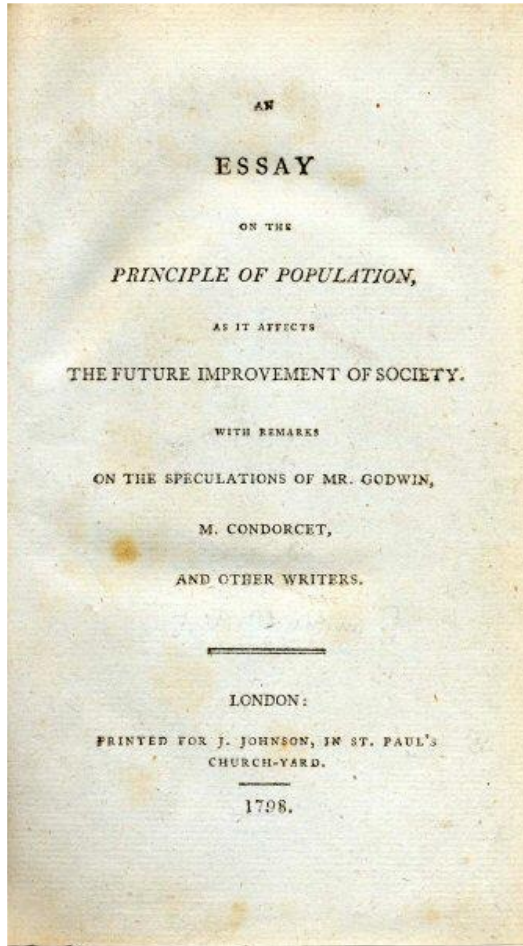
ion



Exponential_growth.mlx

ODEs_Exp_Growth_pyLab.ipynb

Example of ODE Model: Malthus growth



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- However, in reality **populations do not grow unbounded**, but they have a limit -> Logistic Equation

Logistic equation for Growth

Difference equation: the state is characterized by previous states.

$$x_{n+1} = F(x_n)$$

When $F(x_n)$ is non-linear (mathematically) or depends on the density (biologically)

review article

Simple mathematical models with very complicated dynamics

Robert M. May*

First-order difference equations arise in many contexts in the biological, economic and social sciences. Such equations, even though simple and deterministic, can exhibit a surprising array of dynamical behaviour, from stable points, to a bifurcating hierarchy of stable cycles, to apparently random fluctuations. There are consequently many fascinating problems, some concerned with delicate mathematical aspects of the fine structure of the trajectories, and some concerned with the practical implications and applications. This is an interpretive review of them.

Logistic equation for Growth

Difference equation: the state is characterized by previous states.

$$x_{n+1} = F(x_n)$$

When $F(x_n)$ is non-linear (mathematically) or depends on the density (biologically)

Logistic equation: $F(x_n) = \mu \cdot x_n(1 - x_n)$

Normalized to [0,1]: $P_{n+1} = \mu \cdot P_n(1 - P_n)$

The above modeling can represent the growth of a population (P) from time n to n+1, which is proportional to the number of individuals and decreases as it approaches the maximum.

review article

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Logistic equation for Growth

Biological Populations with Nonoverlapping Generations: Stable Points, Stable Cycles, and Chaos

Abstract. Some of the simplest nonlinear difference equations describing the growth of biological populations with nonoverlapping generations can exhibit a remarkable spectrum of dynamical behavior, from stable equilibrium points, to stable cyclic oscillations between 2 population points, to stable cycles with 4, 8, 16, . . . points, through to a chaotic regime in which (depending on the initial population value) cycles of any period, or even totally aperiodic but bounded population fluctuations, can occur. This rich dynamical structure is overlooked in conventional linearized analyses; its existence in such fully deterministic nonlinear difference equations is a fact of considerable mathematical and ecological interest.

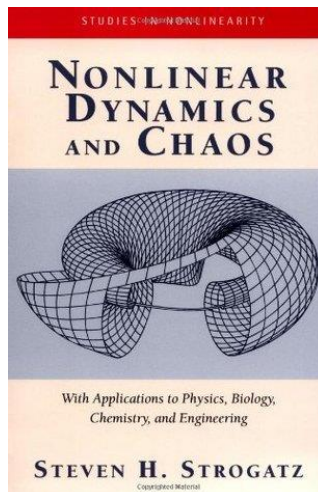
ROBERT M. MAY

Biology Department, Princeton

University, Princeton, New Jersey 08540



https://en.wikipedia.org/wiki/Periodical_cicadas



Populations of individuals generally overlap, but in some cases, such as the cicadas, the population regenerates every 13 to 17 years!

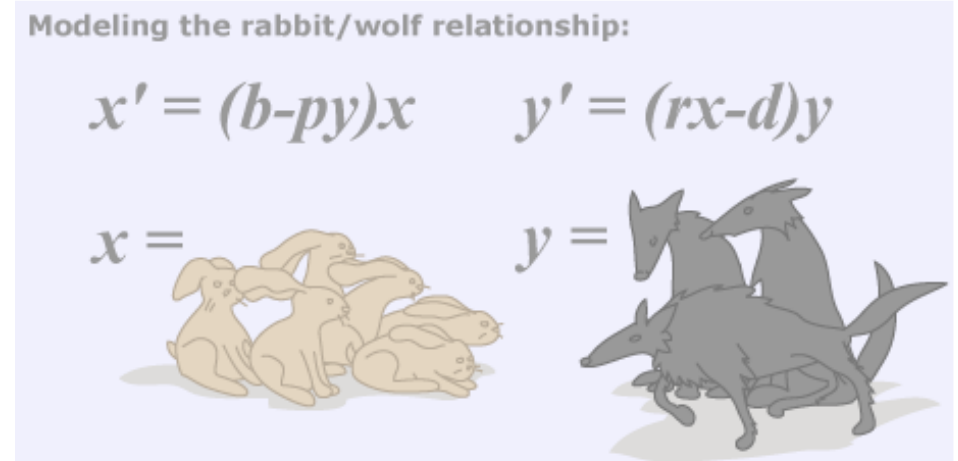
Edward Lorenz: Chaos Theory

Example of ODE Model: Volterra-Lotka

Consider, in isolation, two populations that interact with each other, one being prey and the other predator.

Let us denote by $x(t)$ the **prey** population and by $y(t)$ the predator population.

$$\left\{ \begin{array}{l} \text{Predator: } \frac{dy(t)}{dt} = \delta x(t)y(t) - \gamma y(t) \\ \text{Prey: } \frac{dx(t)}{dt} = \alpha x(t) - \beta x(t)y(t) \end{array} \right.$$



These equations cannot be solved independently
depending on the initial populations of each species and parameter values, different behaviours may occur.

Example of ODE Model: Volterra-Lotka

$$\left\{ \begin{array}{l} \text{Predator: } \frac{dy(t)}{dt} = \delta x(t)y(t) - \gamma y(t) \\ \text{Prey: } \frac{dx(t)}{dt} = \alpha x(t) - \beta x(t)y(t) \end{array} \right.$$

The population of preys:

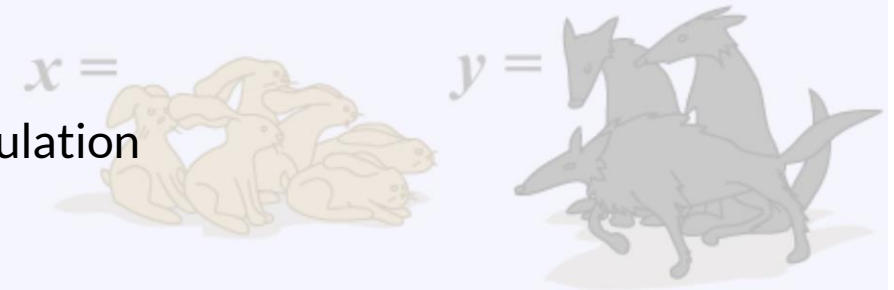
- grows proportionally to their size,
- decreases proportionally to its size and to the size of the predators population.

The population of predators:

- grows proportionally to their size and to the size of the preys population
- decreases proportionally to its size.

Modeling the rabbit/wolf relationship:

$$x' = (b - py)x \quad y' = (rx - d)y$$



This model can be further refined by including modifications to the terms according to different considerations, but its dynamics is interesting itself. *Let's see it!*

Example of ODE Model: Volterra-Lotka

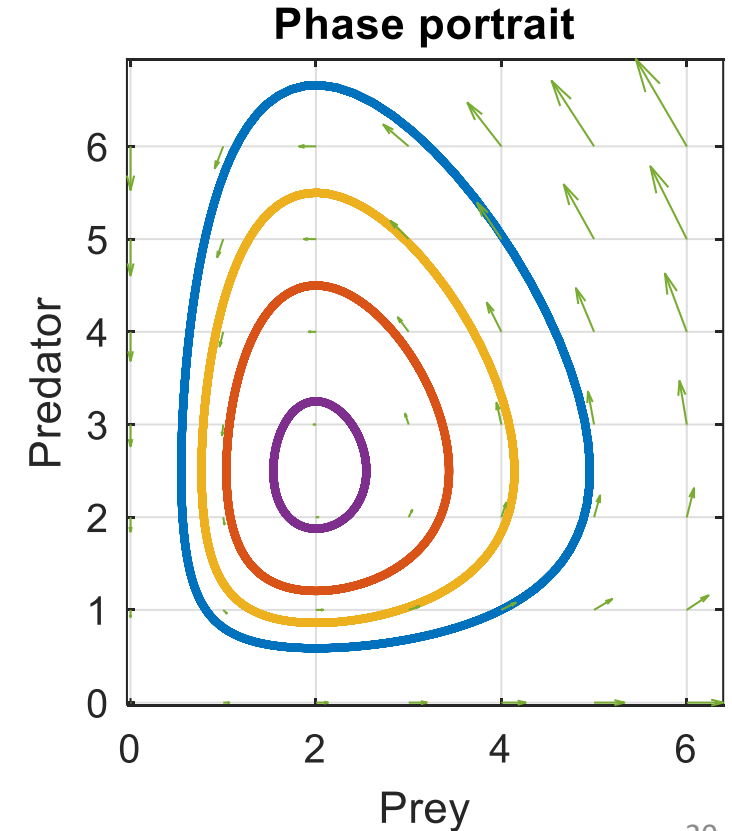
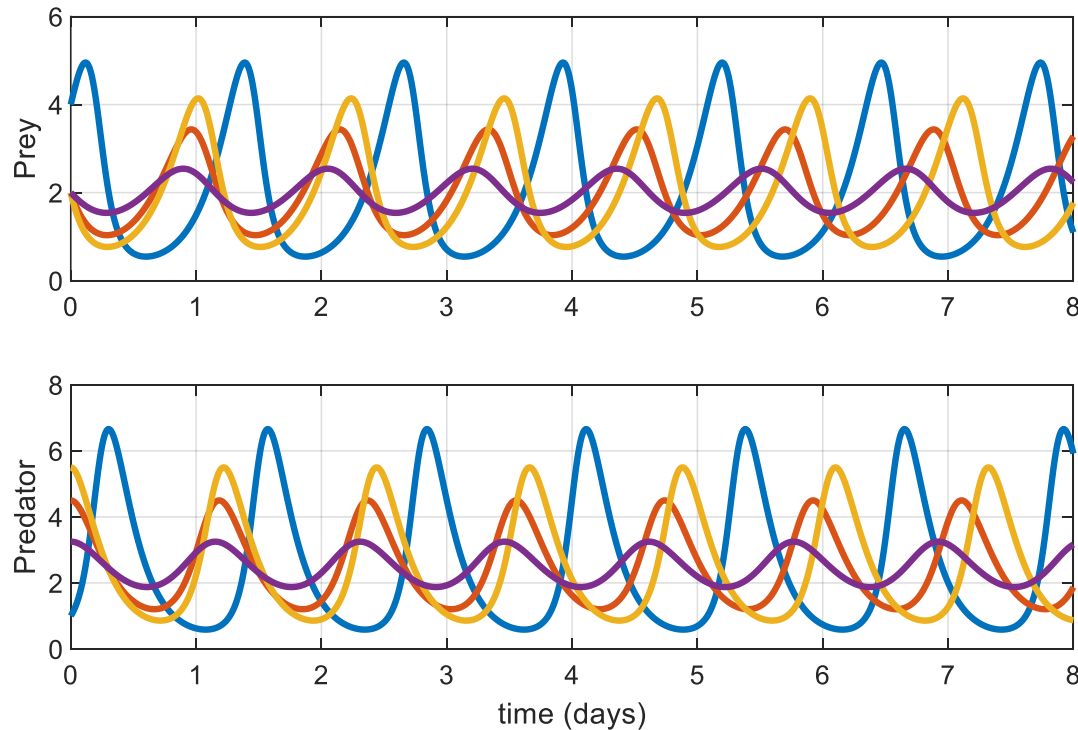
$$\left\{ \begin{array}{l} \text{Predator: } \frac{dy(t)}{dt} = \delta x(t)y(t) - \gamma y(t) \\ \text{Prey: } \frac{dx(t)}{dt} = \alpha x(t) - \beta x(t)y(t) \end{array} \right.$$

Example of ODE Model: Volterra-Lotka

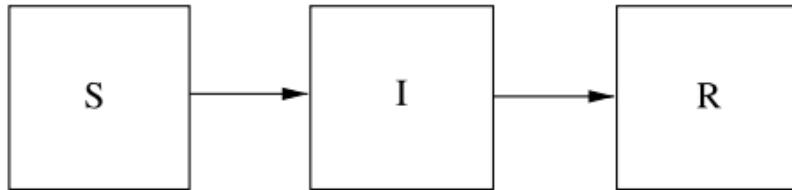


Volterra_Lotka_Phase_Port_Example.mlx

$$\left\{ \begin{array}{l} \text{Predator: } \frac{dy(t)}{dt} = \delta x(t)y(t) - \gamma y(t) \\ \text{Prey: } \frac{dx(t)}{dt} = \alpha x(t) - \beta x(t)y(t) \end{array} \right.$$



Example of ODE Model: SIR models



Possible states: susceptible (S), infected (I), recovered (R).

WHEN ZOMBIES ATTACK!: MATHEMATICAL MODELLING OF AN OUTBREAK OF ZOMBIE INFECTION

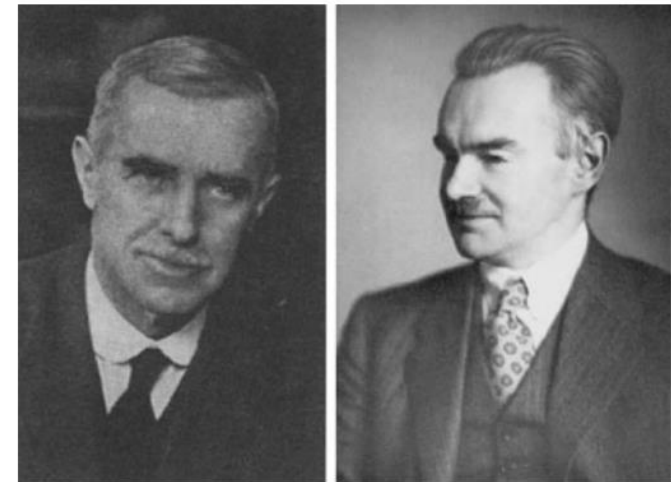
Philip Munz^{1*}, Ioan Hudea^{1†}, Joe Imad^{2‡}, Robert J. Smith^{2§}

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[Kermack–McKendrick theory](#)



In: Infectious Disease Modelling Research Progress

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Modelling in Symbolic

Example of ODE Model: SIR models (zombie version SZR)

Variables: Susceptible (S)
Zombie (Z)
Removed (R)

$$\left\{ \begin{array}{l} S' = \Pi - \beta SZ - \delta S \\ Z' = \beta SZ + \zeta R - \alpha SZ \\ R' = \delta S + \alpha SZ - \zeta R. \end{array} \right.$$

Parameters:

Π : Human birth rate (constant)

β : Rate of humans infected by Zombies (converted)

δ : Death rate of humans (not related to zombie attack)

ζ : Cadaver to zombie conversión rate

α : Rate of Zombies murdered by Humans

Law of mass action: $\beta SZ = (\beta N) \left(\frac{S}{N}\right) Z$,

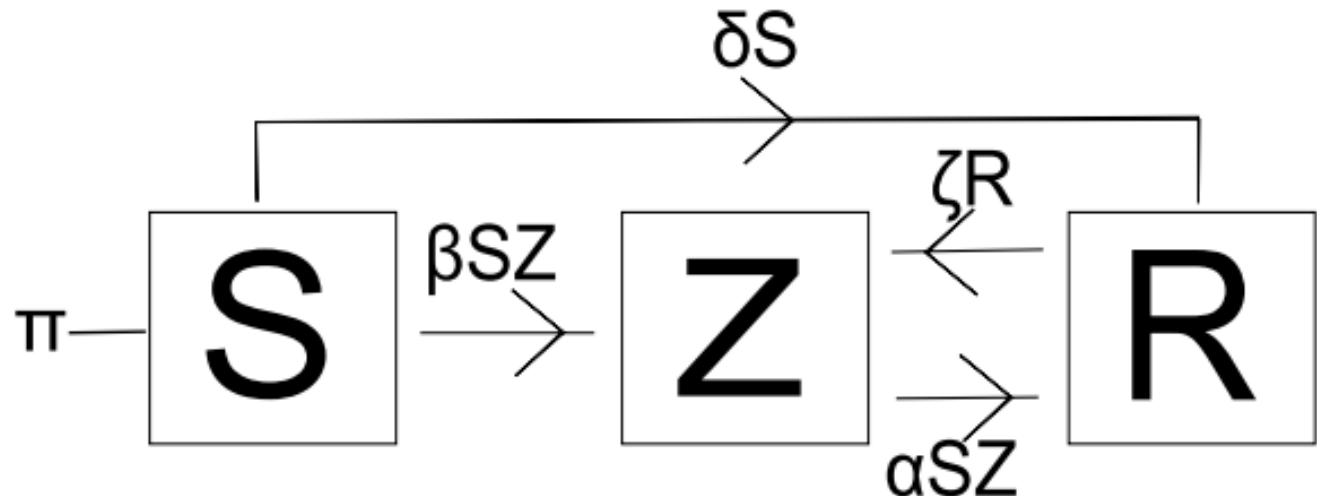
Z Zombies meet βN humans from which $\frac{S}{N}$ are susceptible of being infected.

Example of ODE Model: SIR models (zombie version SZR)

Variables: Susceptible (S)
Zombie (Z)
Removed (R)

$$\begin{cases} S' &= \Pi - \beta SZ - \delta S \\ Z' &= \beta SZ + \zeta R - \alpha SZ \\ R' &= \delta S + \alpha SZ - \zeta R. \end{cases}$$

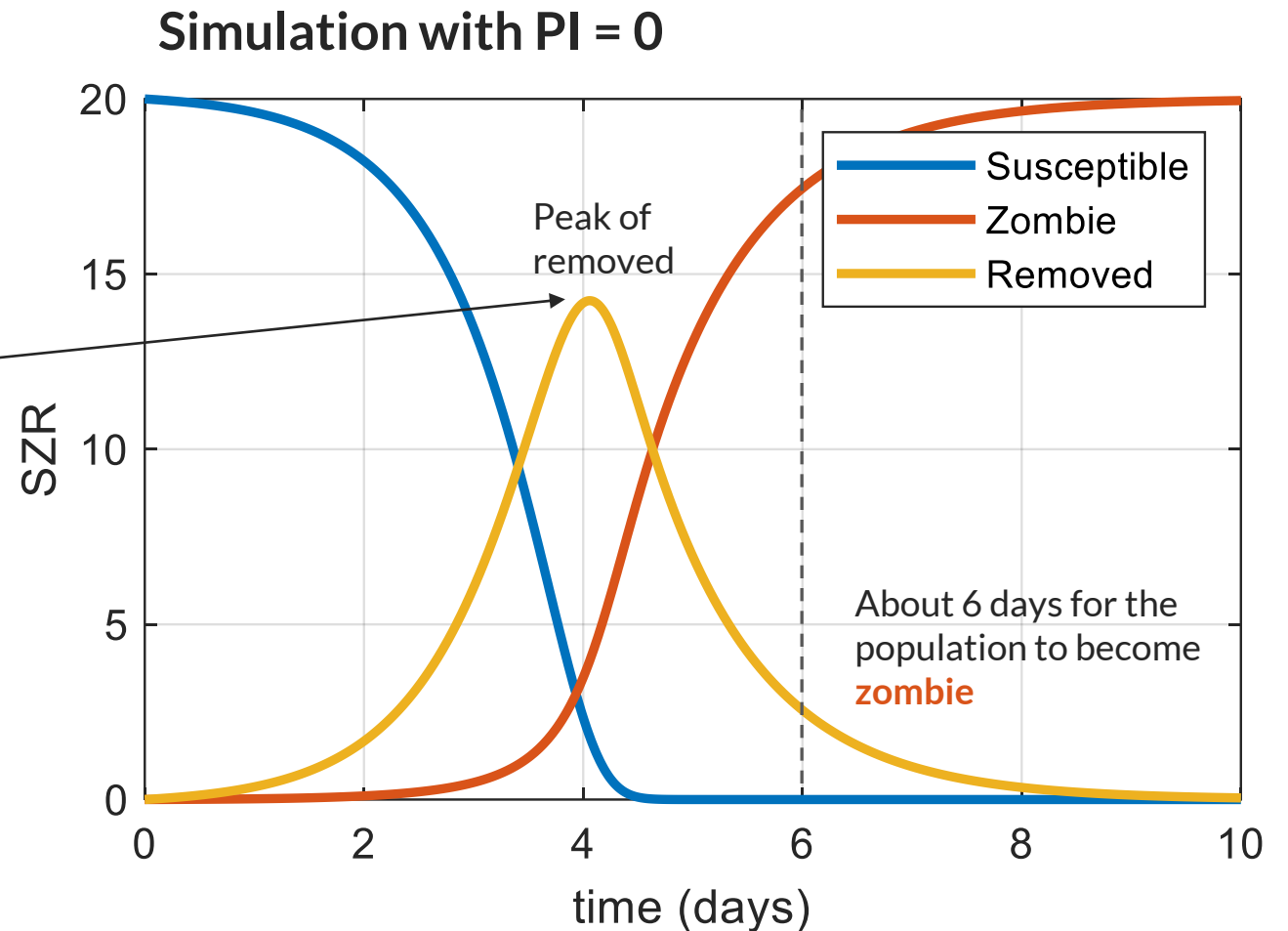
Compartmental models



Example of ODE Model: SIR models (zombie version SZR)

$$\begin{cases} S' &= \Pi - \beta SZ - \delta S \\ Z' &= \beta SZ + \zeta R - \alpha SZ \\ R' &= \delta S + \alpha SZ - \zeta R. \end{cases}$$

We can remove 14 zombies for 4 days only, before an imminent zombie attack!



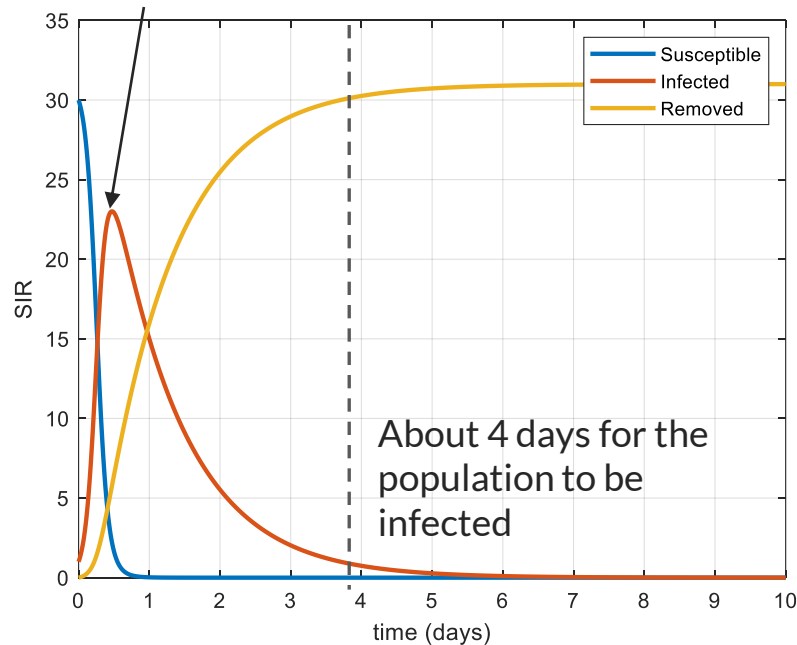
SIR_model_SZR.mlx.mlx

SIR models: Modeling a Pandemic

Variables: Susceptible (S)
Infected (I)
Removed (R)

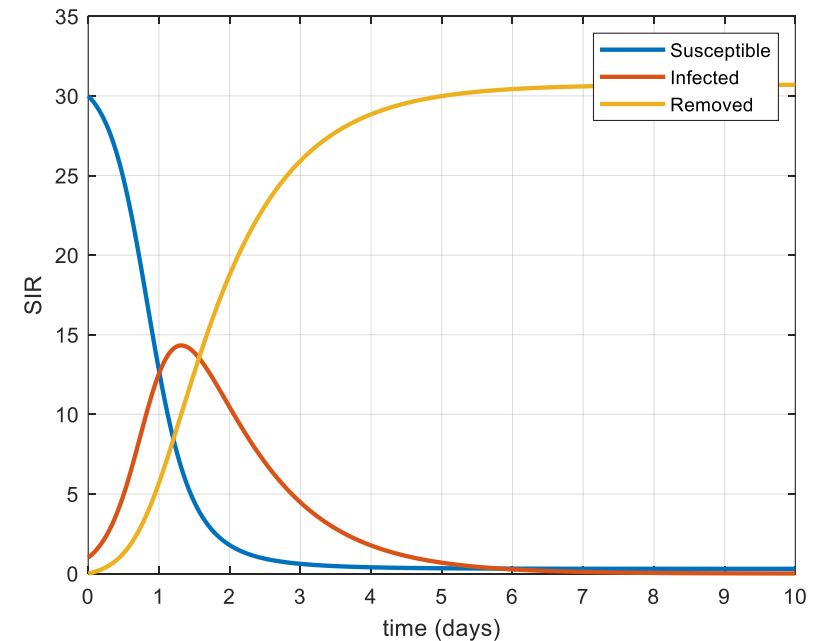
$$\begin{cases} \dot{S} = -\beta I \frac{S}{N} \\ \dot{I} = \beta I \frac{S}{N} - \gamma I \end{cases}$$

Peak (23 infected out of 30)
in less than 1 day



Modelling in SynBio

Flattening the curve! (less infected)



Extended SIR models: Modeling a Pandemic

A mathematical model for the spatiotemporal epidemic spreading of COVID19

Alex Arenas,^{1,*} Wesley Cota,^{2,3,4} Jesús Gómez-Gardeñes,^{2,4,†} Sergio Gómez,¹
Clara Granell,^{2,4} Joan T. Matamalas,⁵ David Soriano,^{2,4} and Benjamin Steinegger¹

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²*Department of Condensed Matter Physics, University of Zaragoza, E-50009 Zaragoza, Spain*

³*Departamento de Física, Universidade Federal de Viçosa, 36570-900 Viçosa, Minas Gerais, Brazil*

⁴*GOTHAM Lab – BIFI, University of Zaragoza, E-50018 Zaragoza, Spain*

⁵*Harvard Medical School & Brigham and Women's Hospital, Boston MA 02115, USA*

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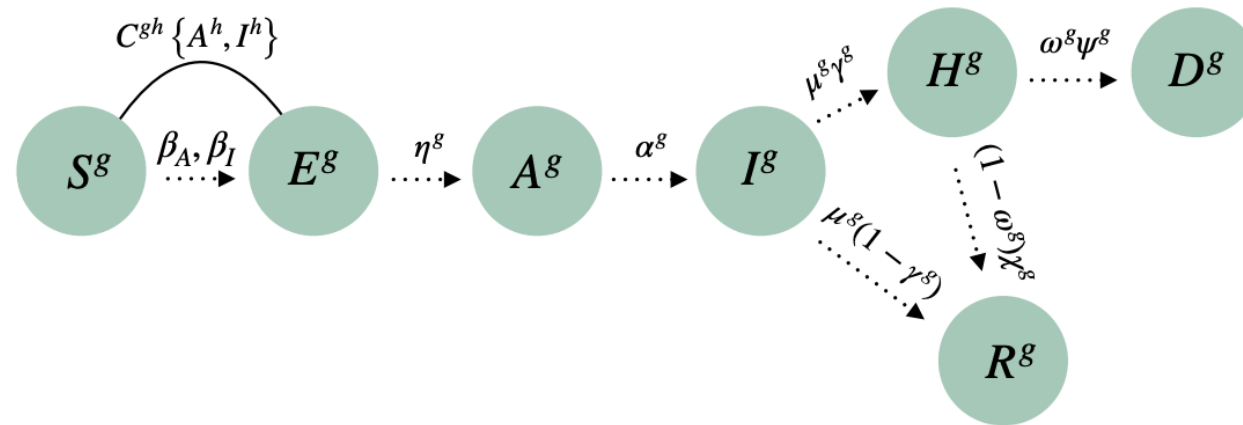


FIG. 1. Compartmental epidemic model proposed in this study. The acronyms are susceptible (S^g), exposed (E^g), asymptomatic infectious (A^g), infected (I^g), hospitalized to ICU (H^g), dead (D^g), and recovered (R^g), where g denotes for all cases the age stratum.

How to model a Pandemic?

<https://www.investigacionyciencia.es/revistas/investigacion-y-ciencia/una-crisis-csmica-798/cmo-modelizar-una-pandemia-18561>

Example of good data (visualization and care)

<https://elpais.com/sociedad/2021-03-15/el-coronavirus-en-espana-dia-a-dia-asi-evolucionan-casos-ingresos-y-muertos.html>