Continuous modelling by ODEs

Biological moduli as ODEs: systems of equations

Computational Biology

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Last lecture: scalar problems

Initial value problem: find $x(t)$ such that

$$\begin{cases} \dfrac{dx}{dt} = f(x(t)), \\ x(0) = x_0. \end{cases} \qquad (\text{I})$$

> ### Picard-Lindelöf theorem $(*)$
>
> Let $f : D \subset \mathbb{R} \to \mathbb{R}$ a Lipchitz continuous function[1], i.e., there exists a positive constant L such that $|f(x) - f(y)| \leqslant L|x - y|$, for all $x, y \in D$. If the initial condition of (I) lies in D ($x_0 \in D$), there exists $T > 0$ such that (I) has a unique solution $x(t)$ for $t \in [0, T]$.

Note: Solutions to different initial conditions never intersect. Why?

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[1]A continuously differentiable function is always Lipschitz continuous (on a bounded domain $D \subset \mathbb{R}$)

Today: systems of equations

System of differential equations: find $x(t) = (x_1(t), \ldots, x_n(t))$
such that
$$\frac{d}{dt} \begin{pmatrix} x_1(t) \\ \vdots \\ x_n(t) \end{pmatrix} = \begin{pmatrix} f_1(x_1, \ldots, x_n) \\ \vdots \\ f_n(x_1, \ldots, x_n) \end{pmatrix}$$
with appropriate initial conditions.

Note: The Picard-Lindelöf theorem holds true for systems of
differential equations; in this case, the functions $f_1, \ldots, f_n$ must be
Lipchitz continuous in all its arguments. The same result also
holds, with small changes, for non autonomous equations.

We will consider three cases:

1. reaction kinetics;

2. interacting populations;

3. spread of an infection disease.

Case 1: Reaction kinetics

▸ Consider x the concentration of a substrate X (e.g. mRNA,
protein, small molecule, metabolite, any reagent).

▸ The decay $dx/dt = kx$, $k < 0$ can be seen as a kinetic
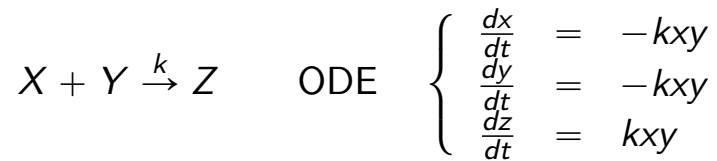reaction (in which we are not interested in the product of the
degradation):
$$X \xrightarrow{k}$$

▸ Law of Mass Action: when 2 or more reactants are involved in
a reaction step, the reaction rates are proportional to the
product of their concentrations.

▸ Justification: macroscopic version of collision theory.

▸ Validity: constant temperature; medium must be well-mixed;
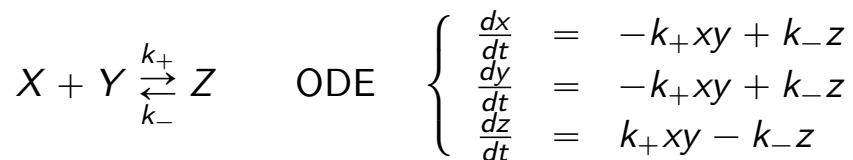# of molecules must be high.

Elementary reaction kinetics

▸ **Bimolecular reaction**

$$X + Y \xrightarrow{k} Z \qquad \text{ODE} \quad \begin{cases} \frac{dx}{dt} &= -kxy \\ \frac{dy}{dt} &= -kxy \\ \frac{dz}{dt} &= kxy \end{cases}$$

▸ **Dissociation**

$$Z \xrightarrow{k} X + Y \qquad \text{ODE} \quad \begin{cases} \frac{dx}{dt} &= kz \\ \frac{dy}{dt} &= kz \\ \frac{dz}{dt} &= -kz \end{cases}$$

▸ **Reversible dissociation**

$$X + Y \underset{k_-}{\overset{k_+}{\rightleftarrows}} Z \qquad \text{ODE} \quad \begin{cases} \frac{dx}{dt} &= -k_+xy + k_-z \\ \frac{dy}{dt} &= -k_+xy + k_-z \\ \frac{dz}{dt} &= k_+xy - k_-z \end{cases}$$

Elementary reaction kinetics

Conservation laws (e.g. mass conservation) can be used to reduce the number of equations involved.

Example: for
$$\begin{cases} \frac{dx}{dt} &= -k_+xy + k_-z \\ \frac{dy}{dt} &= -k_+xy + k_-z \\ \frac{dz}{dt} &= k_+xy - k_-z \end{cases}$$
mass conservation implies
$$\begin{cases} \frac{d(x+z)}{dt} &= 0 \\ \frac{d(y+z)}{dt} &= 0 \end{cases} \Rightarrow \begin{cases} x(t) + z(t) &= x_0 + z_0 = a_0 \\ y(t) + z(t) &= y_0 + z_0 = b_0 \end{cases}$$
and hence the system of 3 ODEs reduces to the scalar ODE
$$\frac{dz}{dt} = k_+(a_0 - z)(b_0 - z) - k_-z.$$
Once we solve this ODE for $z(t)$ we can recover
$$x(t) = a_0 - z(t) \quad \text{and} \quad y(t) = b_0 - z(t).$$

Matlab code

Exercise 2.10: Use the Matlab function ode45 to solve the initial value problem (IVP)

$$\begin{cases} \frac{dz}{dt} = k_+(a_0 - z)(b_0 - z) - k_- z, & t \in (0,3], \\ z(0) = 0. \end{cases}$$

with $k_+ = 1$, $k_- = 1$ and $x_0 = 1$, $y_0 = 2$.

```
% Matlab code to solve Exercise 1
x0 = 1; y0 = 2; z0 = 0;    % initial conditions
a0 = x0 + z0; b0 = y0 + z0;        % constants
kp = 1; km = 1;                    % rates
f = @(t,z) kp*(a0-z).*(b0-z)-km*z; % ODE function
[t, z] = ode45(f, [0 3], z0);      % solve ODE
x = a0 - z; y = b0 -z;
plot(t, x, t, y, t, z)     % plot the solutions
xlabel('time'), ylabel('concentrations')
legend('x','y','z')
set(gca,'FontName','Helvetica','FontSize',20)
```
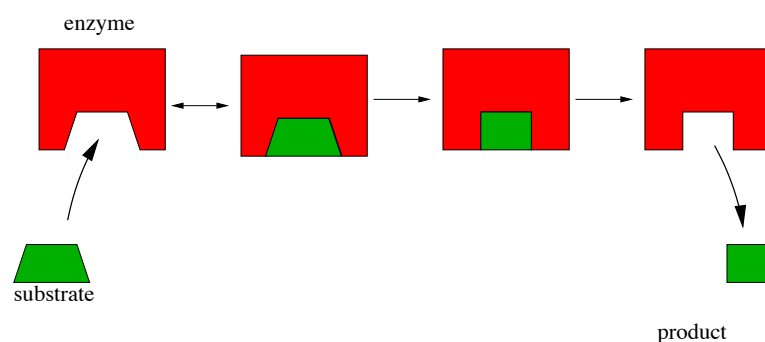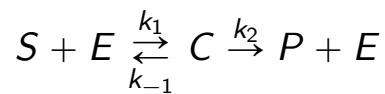
Enzyme catalyzed reactions

Most reactions need to be catalyzed to take place at interesting rates.

enzymes = proteins that convert specific reactants (called substrates) into products while remaining basically unchanged.

Enzyme catalyzed reactions

Rate of production depends nonlinearly on the concentration of the substrate

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \overset{k_2}{\rightarrow} P + E$$

- S = substrate
- E = enzyme
- C = complex ("$= [ES]$")
- P = product

Exercise 2.11: Obtain the system of ODEs

$$\begin{cases} \frac{ds}{dt} &=& -k_1 se + k_{-1} c \\ \frac{de}{dt} &=& -k_1 se + (k_{-1} + k_2)c \\ \frac{dc}{dt} &=& k_1 se - (k_{-1} + k_2)c \\ \frac{dp}{dt} &=& k_2 c \end{cases}$$

that is complemented with the initial conditions

$$s(0) = s_0, \quad e(0) = e_0 \ll s0 \quad c(0) = 0 \quad p(0) = 0.$$

Enzyme catalyzed reactions

Simplifications:

- last equation does not feedback $\Rightarrow$ We can ignore it and get $p(t)$ by integration once we have $c(t)$;
- conservation of mass for the enzyme:

$$\frac{de}{dt} + \frac{dc}{dt} = 0 \Rightarrow e(t) + c(t) = \text{ const } = e_0.$$

Then another equation can be eliminated

$$\begin{cases} \frac{ds}{dt} &=& -k_1 s(e_0 - c) + k_{-1} c \\ \frac{dc}{dt} &=& k_1 s(e_0 - c) - (k_{-1} + k_2)c \end{cases}$$

Exercise 2.12: Solve the previous system of differential equations for $t \in [0, 25]$, considering the parameter

$$k_1 = 1 \quad k_{-1} = 0.15, \quad k_2 = 0.4$$

and the initial conditions

$$s_0 = 1, \quad e_0 = 0.5, \quad c_0 = 0.$$

Matlab code

```matlab
% Matlab code to solve Exercise 3
tint = [0, 25];                     % time interval
s0 = 1; c0 = 0; x0 = [s0, c0];  % initial conditions
[t,x] = ode45(@fmm2, tint, x0); % solve ODE
plot(t,x,'LineWidth',3) ; legend ('substrate', 'complex')
set(gca,'FontName','Helvetica','FontSize',20)

function dxdt = fmm2(t,x)
% System of 2 ODEs for enzyme reaction
% with Michaelis-Menten kinetics
k1 = 1; k1m = 0.15; k2 = 0.4; e0 = 0.5; % parameters
s = x(1); c = x(2); % extract the states from the vector z
% ODEs
dsdt = - k1*s*(e0 - c) + k1m*c;
dcdt = k1*s*(e0 - c) - (k1m + k2)*c;
% output vector
dxdt = [dsdt; dcdt];
end
```

Michaelis-Menten kinetics: hyperbolic responses

The following system of equations can be further simplified

$$\begin{cases} \frac{ds}{dt} &= -k_1 s(e_0 - c) + k_{-1}c \\ \frac{dc}{dt} &= k_1 s(e_0 - c) - (k_{-1} + k_2)c \end{cases}$$

Quasi steady state approximation: after a transient period on which the enzyme fills up, the amount of complex C stays (almost) the same:

$$\frac{dc}{dt} = 0 \Rightarrow c = \frac{e_0 s}{K_m + s} \quad \text{where } K_m = \underbrace{\frac{k_{-1} + k_2}{k_1}}_{\text{Michaelis const.}}$$
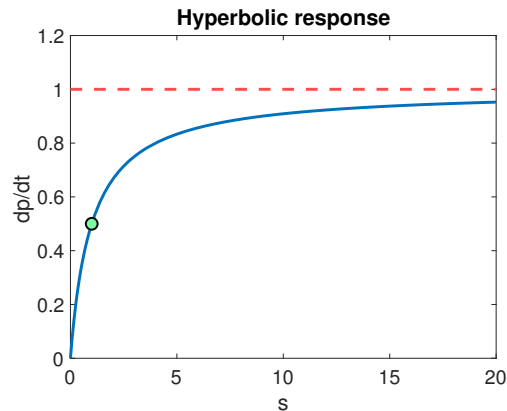
then reduces to a scalar ODE

$$\frac{ds}{dt} = -\frac{V_m s}{K_m + s} \quad \text{where } V_m = k_2 e_0. \quad \left(\frac{dp}{dt} = k_2 c = \frac{V_m s}{K_m + s} \right)$$

Michaelis-Menten kinetics: hyperbolic responses

Exercise 2.13: Plot the the production rate of the reaction product
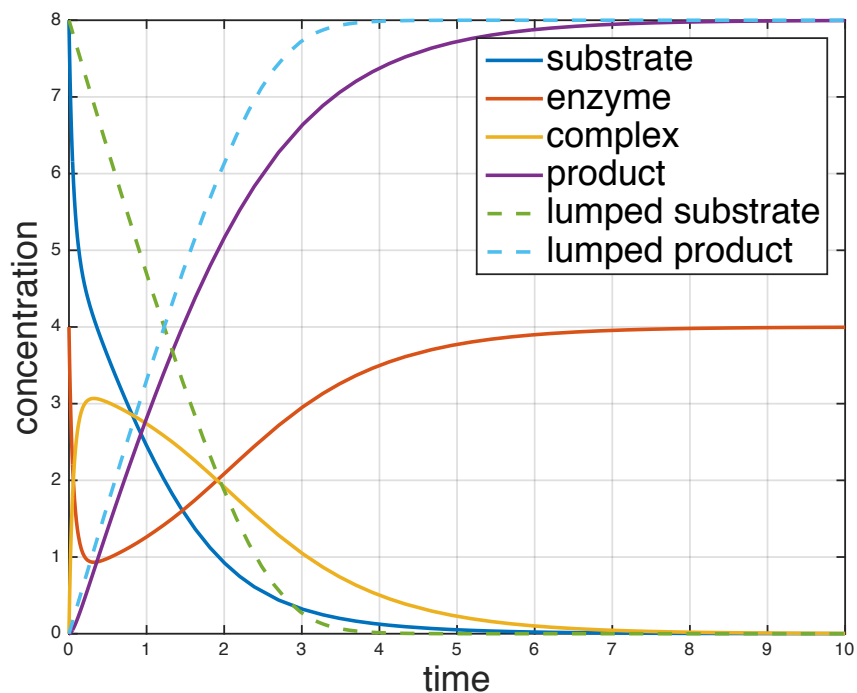
$$\frac{dp}{dt} = \frac{V_m s}{K_m + s}$$

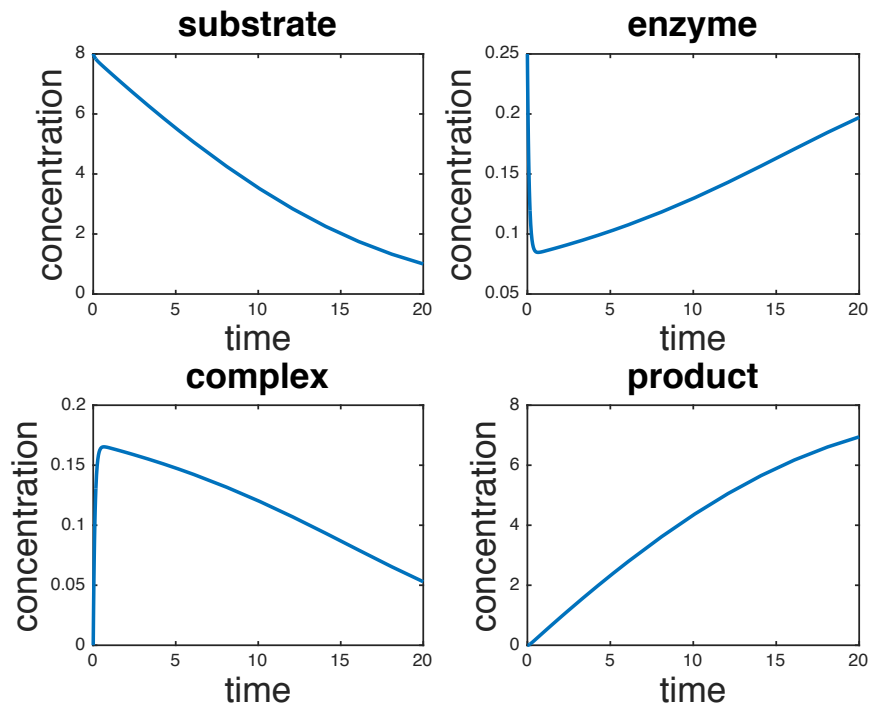as a function of s, considering $V_m = 1$, $Km = 1$ and $s \in [0, 20]$.

Note: 1. $V_m =$ upper bound for dp/dt; 2. $K_m =$ value of s such that $dp/dt = 1/2 V_m$; 3. $V_m/K_m =$ initial slope of dp/dt.

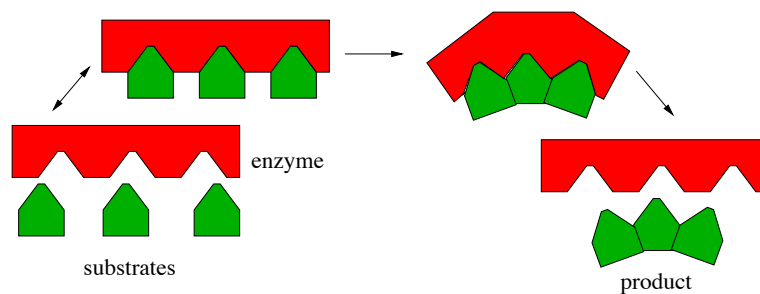
Michaelis-Menten kinetics: time-scales

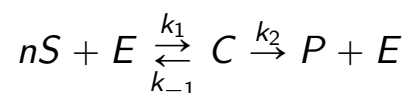# Michaelis-Menten kinetics: time-scales

Cooperativity

When n molecules of substrate must fit together with the enzyme in order for the reaction to take place.

Examples: ligand binding to cell surface receptors; binding of transcriptor factors to DNA to control gene expression.

Kinetics

$$nS + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \overset{k_2}{\rightarrow} P + E$$

Cooperativity

Exercise 2.14: Obtain the system of ODEs

$$\begin{cases} \frac{ds}{dt} &= -k_1 s^n e + n k_{-1} c \\ \frac{de}{dt} &= -k_1 s^n e + (k_{-1} + k_2) c \\ \frac{dc}{dt} &= k_1 s^n e - (k_{-1} + k_2) c \\ \frac{dp}{dt} &= k_2 c \end{cases}$$

After the quasi steady state approximation, we may prove

$$\frac{dp}{dt} = V_m \frac{s^n}{K_m + s^n}.$$

Modifying $K_m := K_m^n$ and considering the (positive feedback) Hill function

$$h^+(s, K_m, n) = \frac{s^n}{K_m^n + s^n}$$
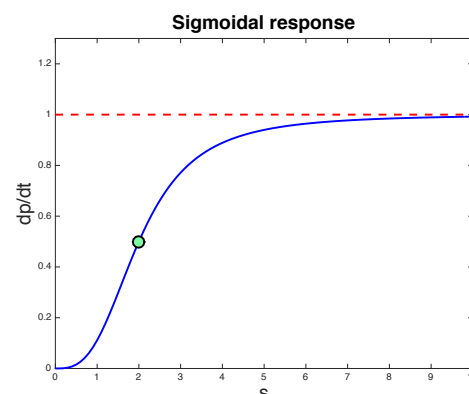
we have

$$\frac{dp}{dt} = V_m h^+(s, K_m, n).$$

Hill kinetics: sigmoidal responses

Common modules for saturated growth rate:

$$h^+(s, K_m, n) = \frac{s^n}{K_m^n + s^n}.$$

Note:

1. K_m = value of s at which h^+ reaches $1/2$ of the saturation value;

2. n = Hill parameter.

Sigmoidal response

Exercise 2.15: Plot the (negative feedback) Hill function for negative growth :

$$h^-(s, K_m, n) = 1 - \frac{s^n}{K_m^n + s^n} = \frac{K_m^n}{K_m^n + s^n}.$$
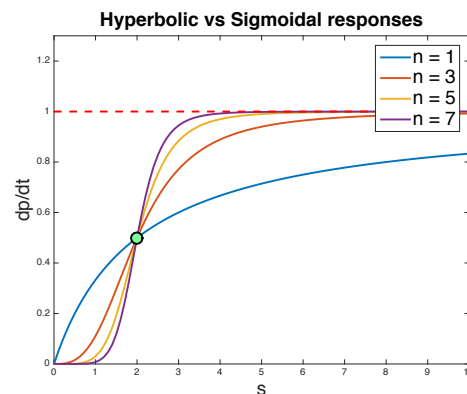
Hyperbolic vs Sigmoidal responses

Consider

$$\frac{dp}{dt} = V_m \frac{s^n}{K_m^n + s^n}.$$

- ▸ For $n = 1$ the graph of the formation rate is hyperbolic.
- ▸ For $n > 1$ it is sigmoidal.

Differences:

- ▸ $n = 1$ graph is concave;
- ▸ $n > 1$ the graph changes the concavity (different stability properties).

When n grows the sharpness of the transition increases; tends to a boolean switch (ultrasensitive response; "all or nothing" behaviour)

Case 2: General population interaction model

Consider the general two-species interaction model

$$\begin{cases} \frac{dx_1}{dt} &= \alpha x_1 + \beta x_1 x_2 \\ \frac{dx_2}{dt} &= \gamma x_2 + \delta x_1 x_2 \end{cases}$$

α	β	γ	δ	
+	+	+	−	Predator (x_1) - prey (x_2) model
+	+	−	−	
−	+	+	−	
−	+	−	−	
+	+	+	+	Mutualism or symbiosis model
+	+	−	+	
−	+	−	+	
+	−	+	−	Competition model
+	−	−	−	
−	−	−	−	

Predator/Prey or Lotka-Volterra model

Consider the dynamics of a closed ecological system, in which two species interact: predator (variable x_1) and prey (variable x_2). The behaviour of the population can be described by

$$\begin{cases} \frac{dx_1}{dt} & = & -\alpha x_1 + \beta x_1 x_2 \\ \frac{dx_2}{dt} & = & \gamma x_2 - \delta x_1 x_2 \end{cases}$$

where

- $\alpha > 0$ is the mortality rate of predators in absence of prey;
- $\beta > 0$ the reproduction rate of predators per unit prey;
- $\gamma > 0$ is the prey reproduction rate and
- $\delta > 0$ the rate at which prey is eaten by predators (per unit prey), which is equivalent to mortality rate of pray per unit of predator.
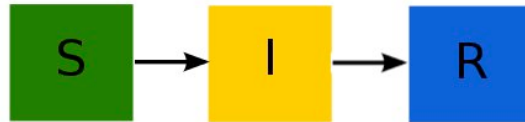

Predator/Prey or Lotka-Volterra model

Exercise 2.16: Obtain the following plot.
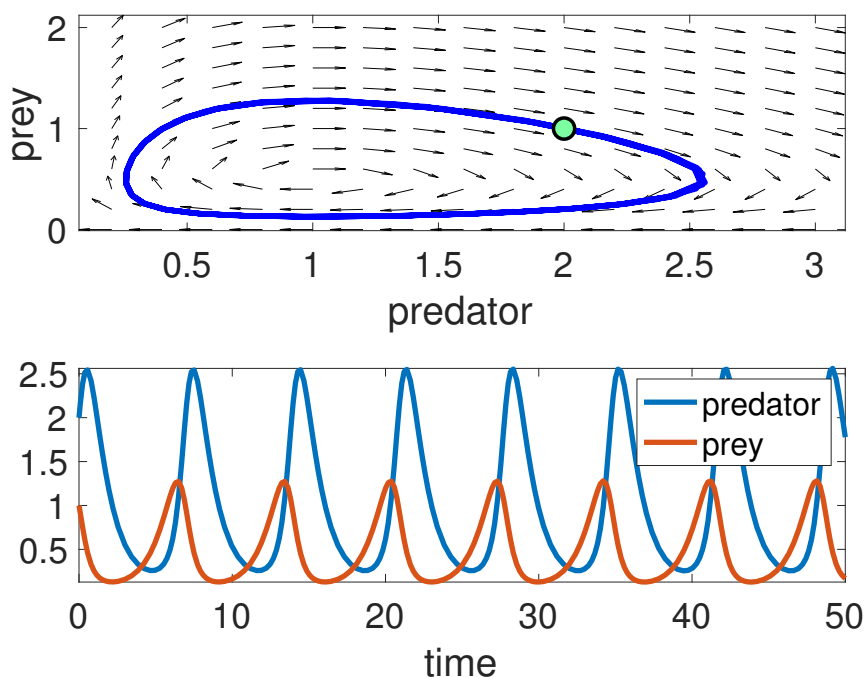
Case 3: Epidemic model SIR

Epidemic model for the spread of an infectious disease (e.g *influenza* or covid19)

1. The dependent variables are: S = susceptible; I = infected; R = recovered;
2. The independent variable is: t = time
3. Assume that the rate of infection is proportional to the number of contacts between susceptible and infected individuals.

Epidemic model SIR

Let:

▸ $\beta > 0$ be the infection rate

β is the average number of contacts per person per time, multiplied by the probability of disease transmission in a contact between a susceptible and an infectious person.

▸ $\gamma > 0$ be the recovery rate

If an individual is infectious for an average time period D, then $\gamma = 1/D$.

Epidemic model SIR

The rate at which a susceptible individual becomes infected is given by

$$\beta(I/N)$$
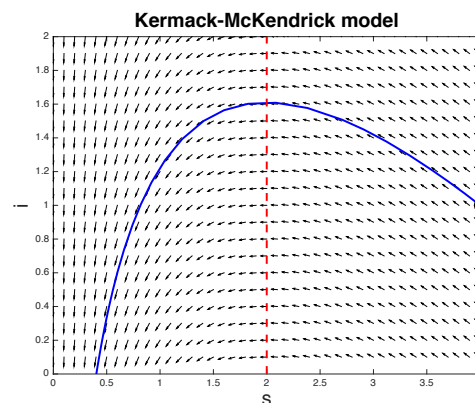
where N is the total number of people in the population.

Classical SIR model:

$$
\begin{cases}
\dfrac{dS}{dt} &= -\beta SI/N \\[2ex]
\dfrac{dI}{dt} &= \beta SI/N - \gamma I \\[2ex]
\dfrac{dR}{dt} &= \gamma I
\end{cases}
$$

Kermack-McKendrick model

$$
\begin{cases}
\dfrac{dS}{dt} &= -\beta SI/N \\[2ex]
\dfrac{dI}{dt} &= \beta SI/N - \gamma I
\end{cases}
$$

Exercise 8: Prove that, if

$$R_0 \frac{S}{N} < 1, \quad \text{with} \quad R_0 = \frac{\beta}{\gamma},$$

the infection deceases.

The value $S = N/R_0$ is the critical population size to sustain an epidemic.

Matlab code: Kermack-McKendrick mode

```matlab
% Kermack-McKendrick model (N = 1)
tint  = [0 6];                         % time interval
S0 = .9; I0 = .1; x0 = [S0 I0];  % initial conditions
[t, x] = ode45(@KM, tint, x0);   % solve ODE
plot(t, x,'LineWidth',3)         % plots

function dxdt = KM(t, x)
% Kermack-McKendrick system of ODEs
%   dS/dt = -beta SI
%   dI/dt = beta SI - gama I
beta = 3; gama = 1;
S = x(1); I = x(2);  % extract the values from x
% ODEs
dSdt = -beta*S*I;
dIdt = beta*S*I - gama*I;
% output vector
dxdt = [dSdt; dIdt];
end
```

Basic/effective reproduction number

We proved that, if $R_0 \frac{S}{N} < 1$, with $R_0 = \frac{\beta}{\gamma}$, the infection deceases.

Basic reproduction number: The value

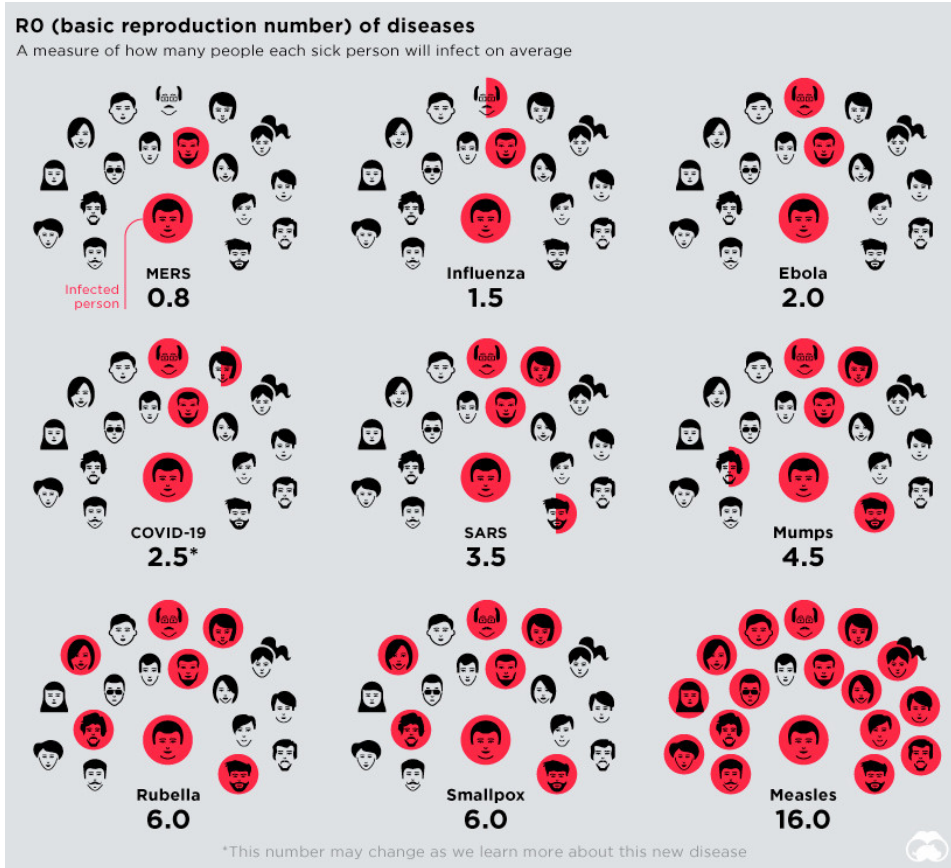$$R_0 = \frac{\beta}{\gamma}$$

indicates how contagious the disease is. Expresses the average number of people who will contract the disease from one infected person.

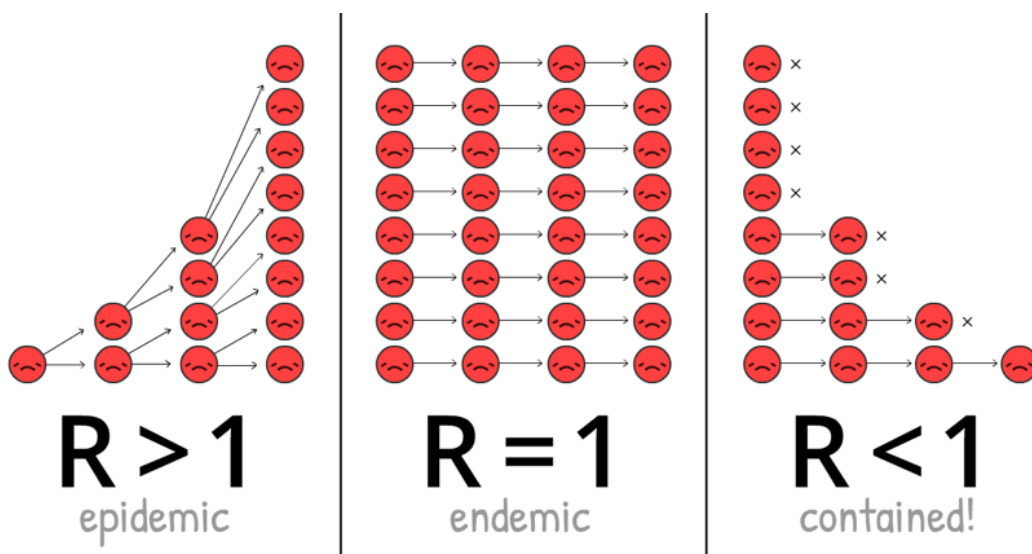Effective reproduction number: The main goal is to keep

$$R_t = R_0 \frac{S}{N} < 1.$$

Different values of R_0

RO (basic reproduction number) of diseases
A measure of how many people each sick person will infect on average

Infected person | MERS 0.8

Influenza 1.5

Ebola 2.0

COVID-19 2.5*

SARS 3.5

Mumps 4.5

Rubella 6.0

Smallpox 6.0

Measles 16.0

*This number may change as we learn more about this new disease

Keep $R_t < 1$

R > 1
epidemic

R = 1
endemic

R < 1
contained!

Herd immunity

The main goal is to keep

$$R_t = R_0 \frac{S}{N} < 1.$$

Then

$$R_0 \frac{S}{N} < 1 \iff \frac{S}{N} < \frac{1}{R_0} \iff -\frac{S}{N} > -\frac{1}{R_0} \iff \underbrace{1 - \frac{S}{N}}_{p} > 1 - \frac{1}{R_0}.$$

Herd immunity: The percentage $p = 1 - S/N$ of population immune to the disease must be greater than $1 - 1/R_0$.

For COVID-19 (delta variant): $R_0 = 5.08$ and so

$$p > 1 - 1/5.08 \approx 0.8,$$

i.e., 80% of the total population should be immune to the disease.

Homework #6: Brusselator (Ilya Prigogine)

Exercise 2.17: The Brusselator is a theoretical model for a type of autocatalytic reaction. Is characterised by the reactions

| molecular reaction	rate coefficient	rate of reaction
$A \longrightarrow X$	k_1	$r_1 = k_1 a$
$B + X \longrightarrow Y + D$	k_2	$r_2 = k_2 b x$
$2X + Y \longrightarrow 3X$	k_3	$r_3 = k_3 x^2 y$
$X \longrightarrow E$	k_4	$r_4 = k_4 x$

1. Considering all the rate coefficients equal to 1 and $da/dt = db/dt = 0$, prove that the system for the products $u(t) = x(t)$, $v(t) = y(t)$ is

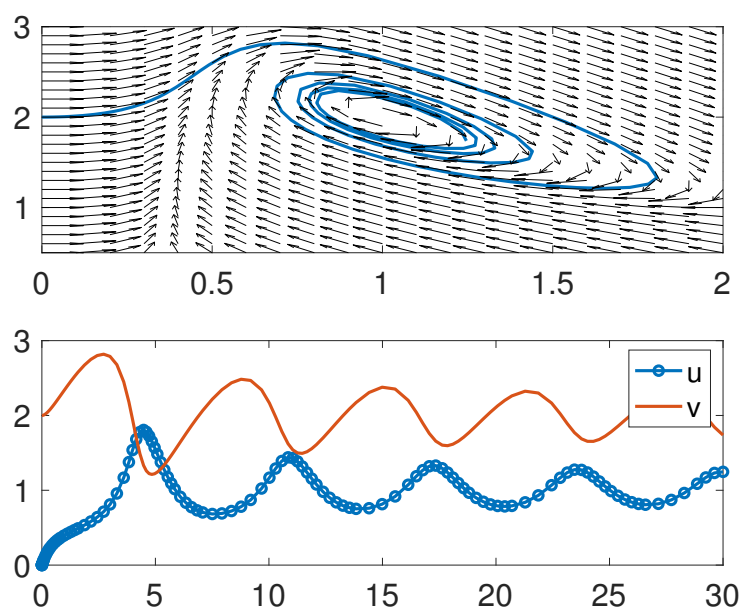$$\begin{cases} \frac{du}{dt} = a + u^2 v - (b+1)u \\ \frac{dv}{dt} = bu - u^2 v. \end{cases}$$

2. Prove that point $P = \left(a, \frac{b}{a}\right)$ is the unique equilibria of the system (by linearization, we may conclude that it is unstable if and only if $b > a^2 + 1$).

3. Obtain the plots in the next pages, where $u(0) = 0$, $v(0) = 1$ and $t \in [0, 30]$.

Homework #6: Stable case: $a = 1$ and $b = 1$
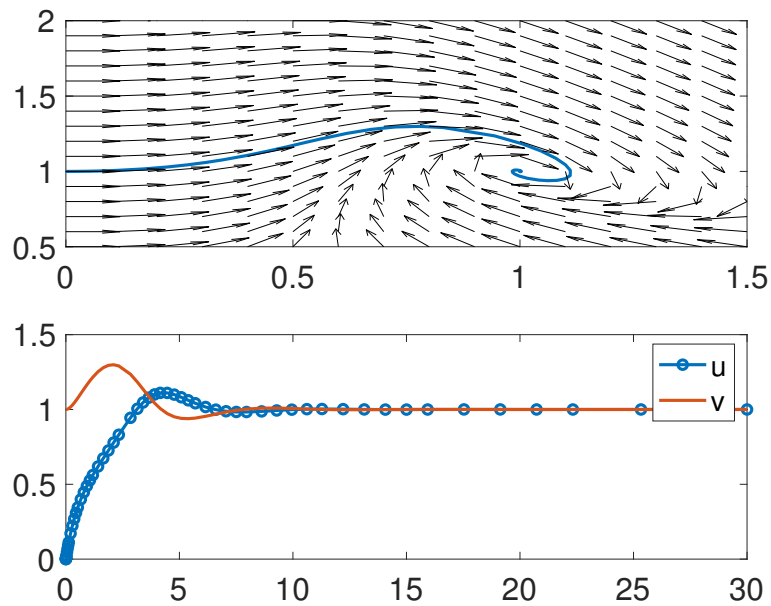
Homework #6: Quasi-unstable case: $a = 1$ and $b = 2$

Homework #6: Unstable case: $a = 1$ and $b = 3$