MATHEMATICAL AND COMPUTER MODELLING OF NONLINEAR BIOSYSTEMS I

Ph. D. Programme 2013/2014

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PhD STUDIES
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UNIA EUROPEJSKA EUROPEJSKI FUNDUSZ SPOŁECZNY
Project co-financed by European Union within the framework of European Social Fund

LECTURE I: Logistic equation in ODE version: the simplest way of nonlinear description of saturated growth of a population. Analysis of a single ODE.

The aim of the first and also next two lectures is to describe the changes in a single population size under some assumptions on the population growth.

We start from the simple linear description of the growth.

The idea of this simple description is very old and comes from XIX century.

In 1798 English demographer Thomas Malthus published his famous essay:

An Essay on the Principle of Population

in which he claimed that the number of humans in the world increased according to the geometrical progress, while the food resources increased as arithmetic one.

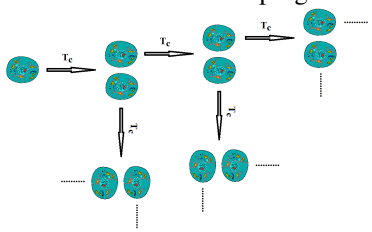
Let us recall that a sequence $(x_n)_{n\in\mathbb{N}}$ is called the **geometric progression** if

$$\frac{x_{n+1}}{x_n} = q = \text{const}, \quad \text{for any } n \in \mathbb{N},$$

where q is called the **quotient** of that progression, while it is called the **arithmetic progression** if

$$x_{n+1} - x_n = d = \text{const}, \quad \text{for any } n \in \mathbb{N},$$

where d is called the **difference** of the arithmetic progression.



Synchronous division of cells: example of the process leading to the geometric progression $x_n = 2^n$.

For both sequences we can easily calculate the general term. Clearly,

- for the geometric progression: if x_0 is the first term, then $x_1 = qx_0$, next $x_2 = qx_1 = q^2x_0$ and so on. Therefore, $x_n = q^n x_0$ and this statement can be proved using mathematical induction.

- for the arithmetic progression: if x_0 is the first term, then $x_1 = x_0 + d$, $x_2 = x_1 + d = x_0 + 2d$ and so on, yielding $x_n = x_0 + nd$.

As for both sequences we want to reflect the growth process, we need to assume $q > 1$ and $d > 0$. Otherwise the sequences are not increasing.

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It is obvious that in such a case the rate of growth of the arithmetic progression is much smaller than for the geometric one, such that

$$\lim_{n\to\infty} \frac{x_0 q^n}{x_0 + nd} = \infty \quad \text{for} \quad q > 1,\ d > 0.$$

This obviously implies that there must be a catastrophe when the number of people exceeds the food resources, and this was the main idea of Malthus who noticed that people should stop to reproduce so fast.

Now, we try to propose a continuous version of Malthus model as a basis for further modelling.

We want to describe the change of the **number of individuals** of some species $\mathcal{P}$ in any arbitrary time interval $[t, t + \Delta t]$.

Let $N(t)$ be the number of individuals at time t. Assume that the **growth rate** r, defined as a number of offspring (or daughters in other words) per one mother (or parent) in one time unit, is constant.

Moreover, assume that the only process we observe is reproduction.

Then

$$N(t + \Delta t) - N(t) = rN(t)\Delta t.$$

Dividing both sides by Δt we obtain the **difference quotient** for $N(t)$. Hence,

$$\lim_{\Delta t\to 0} \frac{N(t + \Delta t) - N(t)}{\Delta t} = \frac{dN(t)}{dt} = rN(t).$$

In the following we will use the notation

$$\frac{dN}{dt} = \dot{N},$$

and with this notation the Malthus model reads

$$\dot{N} = rN, \tag{1}$$

where we omit the variable t, as the right-hand side of Eq. (1) does not depend on t explicitly.

In general, if we consider an equation for which the right-hand side does not depend on t explicitly, then we call such equation **autonomous**.

For any autonomous equation an initial condition can be describe as a pair $(0, N_0)$, where $t_0 = 0$ is the initial time-point and $N_0 = N(0)$ is the initial value for the variable N.

Moreover, if (t_0, x_0) is any initial condition, then the solution for this condition with $t_0 \neq 0$ is just a shift of the solution for $t_0 = 0$.

It is easy to see that the solution of the initial problem for Eq. (1) with $N(0) = N_0$ is

$$N(t) = N_0 \exp(rt),$$

while for $N(t_0) = N_0$,

$$N(t) = N_0 \exp\left(r(t - t_0)\right).$$

In the case we describe there is $r > 0$, as it reflects the number of offspring. Hence, $N(t) \to \infty$ exponentially as $t \to \infty$ for any $N_0 > 0$.

Notice, that $N(t)$ is described as a continuous function starting from N_0 at $t = 0$ and increasing to ∞. This means that $N(t)$ takes values from $\mathbb{R}$, not only natural.

Hence, we need to redefine the variable $N(t)$ — in fact, it reflects not the number of individuals, but the **density** of the population, that is the number of individuals per the unit of area (or volume, depending on the species).

Now, we want to think about the assumptions we need to pose to obtain the Malthus model.

I As the growth rate r is constant, this means that it is the same independently of the number of individuals, and therefore the process of reproduction has no limits even if the number of individuals is arbitrarily large.
Hence, the environment in which the species $\mathcal{P}$ lives is **unbounded**, meaning that for any individual there is enough food, place and other resources necessary for living.

II The population is **homogenous**, that is all individuals are identical. A new born individual is mature (can have offspring) from the very beginning.

III Individuals are **uniformly distributed** in the space.

Assumption III is necessary for the proper definite of the variable $N(t)$.

Moreover, the description in the language of **Ordinary Differential Equations (ODEs)** needs this assumption and needs also the assumption that $N(t)$ is sufficiently large.

Clearly, we should remember that having only very few individuals we should not describe the population using ODEs.

On the other hand, Assumptions I and II oversimplify reality, so we need to think of at least some changes in the model.

However, we should notice that such type of assumptions (especially I) can be satisfied for laboratory breeding yeasts even for long time.

Notice that we do not assume any death process in the original Malthus model, but we can easily include this process in the same way as growth, that is if $s > 0$ is the death rate, then instead of Eq. (1) we obtain

$$\dot{N} = rN - sN = \tilde{r}N.$$

From this birth/death model we obtain:

- either the same dynamics as before, $N(t) \to \infty$ as $t \to \infty$, when $\tilde{r} > 0$,
- or the population is stationary, $N(t) \equiv N_0$, when $\tilde{r} = 0$,

- or the population becomes extinct, $N(t) \to 0$ as $t \to \infty$, when $\tilde{r} < 0$.

The coefficient $\tilde{r}$ is called **net growth rate** or the growth **per capita**.

Negative net growth rate means that the number of deaths is larger than the number of births.

However, we typically assume that $\tilde{r} > 0$ and omit 'tilde', for simplicity.

Now, we assume that the environment is bounded, and this leads to **competition** between individuals.

Therefore, instead of Eq. (1) we consider

$$\dot{N} = rN - f(N). \tag{2}$$

The function $f(N)$ in Eq. (2) reflects competition which appears when there is too many individuals comparing to the environmental resources.

The model of the form (2) was proposed after a long discussion on the Malthus model in the mid-XIX century by Belgian mathematician, Pierre Francois Verhulst.

What form of the function f can be proposed?

We should remember that the only filed of applications of mathematics known in Verhulst time was physics.

Hence, Verhulst adapted the idea of collisions between particles in ideal gas to the competition between individuals.

Clearly, if N is the number of particles, then the number of collisions is proportional to N^2, yielding $f(N) \sim N$.

Eventually, the **logistic** (or Verhulst, sometimes Pearl-Verhulst) equation reads

$$\dot{N} = rN - bN^2 \qquad \text{or} \qquad \dot{N} = rN\left(1 - \frac{N}{K}\right), \tag{3}$$

where:

- $r > 0$ is the net growth rate of the population (reflecting the maximal *per capita* growth rate for small population size);
- $b > 0$ is the competition coefficient;
- $K = \frac{r}{b} > 0$ is so-called carrying capacity for the environment, reflecting optimal population size (that is how many individuals can live in this environment without problems).

To explain the role of K we need to study the solution dynamics.

In the case of Eq. (3) the solutions can be calculated, as it is an equation with separated variables.

Before we calculate the solution, we can notice, that changing the dependent variable

$$x(t) = \frac{N(t)}{K}$$

we obtain the equation with only one parameter r.

Clearly,

$$\dot{x} = \frac{\dot{N}}{K} = r\frac{N}{K}\left(1 - \frac{N}{K}\right) = rx(1-x).$$

This means that from the mathematical point of view the logistic equation is one-parameter equation.

Notice, that new variable $x(t)$ is undimensional, as both $N(t)$ and K are calculated in [number of individuals/area].

The undimensionalization procedure is common in complex models. It allows to reduce the number of parameters and makes the model analysis easier.

We should also notice that it is possible to change time such that there is no parameters in the logistic model.

More precisely, introducing $s = rt$ and $y(s) = x(t)$ we obtain

$$\frac{dy}{ds} = \frac{dx(t(s))}{ds} = \frac{dx}{dt}\frac{dt}{ds} = \frac{1}{r}rx(1-x) = y(1-y).$$

In the new variables both dependent and independent variables are undimensional.

Let us consider the undimensional equation

$$\dot{y} = y(1-y). \tag{4}$$

Calculating the solution for initial data $y(0) = y_0 = x_0 = \frac{N_0}{K}$ we obtain

$$\int_{y_0}^{y(t)} \frac{dy}{y(1-y)} = \int_0^t d\eta.$$

To solve this equation we need to rewrite the left-hand side in the form of simple quotients. We have:

$$\frac{1}{y(1-y)} = \frac{1}{y} + \frac{1}{1-y} = \frac{1}{y-1} - \frac{1}{y}.$$

$$\int_{y_0}^{y(s)} \frac{dy}{y(1-y)} = \int_{y_0}^{y(s)} \frac{1}{y-1}dy - \int_{y_0}^{y(s)} \frac{1}{y}dy,$$

and knowing that

$$\int \frac{dy}{y} = \ln|y| + C, \quad \int \frac{dy}{y-1} = \ln|y-1| + C$$

we obtain

$$\int_{y_0}^{y(s)} \frac{dy}{y(1-y)} = \ln\left|\frac{y(s)-1}{y_0-1}\right| - \ln\left|\frac{y(s)}{y_0}\right| = \ln\left|\frac{(y(s)-1)y_0}{y(s)(y_0-1)}\right|.$$

Hence,

$$\ln\left|\frac{(y(s)-1)y_0}{y(s)(y_0-1)}\right| = s \quad \Longrightarrow \quad \left|\frac{(y(s)-1)y_0}{y(s)(y_0-1)}\right| = \mathrm{e}^s.$$

In the following we shall notice that:

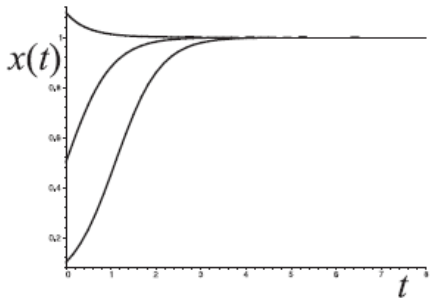
- if $y_0 > 0$, then $y(s) > 0$;
- if $y_0 > 1$, then $y(s) > 1$;
- if $y_0 < 1$, then $y(s) < 1$.

Hence,

$$y(s) = \frac{y_0}{y_0 - (y_0-1)\,\mathrm{e}^{-s}} \quad \Longrightarrow \quad x(t) = \frac{x_0}{x_0 - (x_0-1)\,\mathrm{e}^{-rt}}.$$

Analysing the graph of $x(s)$ we find that

- $x = 1$ ($N = k$) is a steady state of the logistic equation;
- if $x_0 > 1$, then $x(t)$ is decreasing;
- if $x_0 \in (0, 1)$, then $x(t)$ is increasing.



From the analysis above we see that the positive steady state $N = K$ of the logistic equation Eq. (3) is globally stable in $\mathbb{R}^+$.

In general, analysing the dynamics of single autonomous ODE of the form

$$\dot{x} = F(x), \quad F : \mathbb{R} \to \mathbb{R}, \tag{5}$$

we need to consider several problems.

Studying solutions of Eq. (5) we should analyse the following problems:

I existence and uniqueness of solutions;

II non-negativity of solutions;

III prolongation of solutions for all $t > 0$;

IV steady states (stationary solutions, equilibrium states) with their local and, possibly, global stability.

Regarding I:

- Continuity of F guarantees existence of solutions, but is not sufficient for uniqueness.

  Example:

  $$\dot{x} = \sqrt{x}, \quad x(0) = 0. \tag{6}$$

  It is obvious, that $\bar{x} = 0$ is the steady state for Eq. (6).

  On the other hand, we can use the method of variable's separation to solve Eq. (6):

  $$\int \frac{dx}{\sqrt{x}} = \int dt \quad \Longrightarrow \quad 2\sqrt{x} = t + C \quad \Longrightarrow \quad x(t) = \left(\frac{t+C}{2}\right)^2, \; C = \text{const.}$$

  For $x(0) = 0$ we obtain $x(t) = \frac{t^2}{4}$ which is another solution of Eq. (6).

  In fact, for any $a > 0$ taking

  $$x(t) = \begin{cases} 0 & \text{for} \quad x < a \\ \frac{(t-a)^2}{4} & \text{for} \quad x > a \end{cases}$$

  we obtain infinitely many solutions of Eq. (6).

- From the theory of ODEs we know that for F being locally Lipschitz, that is for any compact set $\mathcal{S} \in \mathbb{R}$ there exists $L > 0$ such that

  $$|F(x) - F(y)| <= L\,|x - y|\,, \quad \text{for any} \quad x, y \in \mathcal{S},$$

  the solution for any initial data $(0, x_0)$ exists and is unique.

- If F is of class $\mathbf{C}^1$ (that is has continuous derivative), then it is locally Lipschitz (with Lipschitz constant calculated as $\max\{F'(x)\}$ which is achieved on every compact set whenever F' is continuous), which guarantees that solutions are unique.

Notice, that in one dimensional case uniqueness means that solutions do not cross each other, yielding monotonicity (**permanent oscillations** are not possible in a single DDE).

Regarding II:

- If the equation we study is of the form

  $$\dot{x} = xg(t, x), \tag{7}$$

then all solutions are positive, as

$$x(t) = x_0 \exp\left(\int_{t_0}^{t} g(s, x(s))ds \right) > 0 \quad \text{if} \quad x_0 > 0.$$

Similarly, in n-dimensional case, for any equation of the system that can be written in the form

$$\dot{x}_i = x_i g(t, x), \quad x = (x_1, \ldots, x_n), \quad i \in \{1, \ldots, n\},$$

we get the non-negativity result.

- In general, the method of proving non-negativity is the contradiction method – we assume that the solution can become negative and show that it is impossible.

  We will discuss this method for specific examples in the future.

Regarding III:

- For linear equations we know that solutions exists for all $t \in \mathbb{R}$.

  However, we should remember that there are equations for which solutions does not exists for all $t \in \mathbb{R}$.

  Example:

$$\dot{x} = x^2, \quad x(0) = x_0 > 0. \tag{8}$$

  Solving Eq. (8) we obtain

$$\int_{x_0}^{x(t)} \frac{dx}{x^2} = \int_0^t dt \quad \Longrightarrow \quad -\frac{1}{x}\Big|_{x_0}^{x(t)} = t \quad \Longrightarrow \quad x(t) = \frac{1}{\frac{1}{x_0} - t},$$

  yielding

$$\lim_{t \to \frac{1}{x_0}^-} x(t) = \infty.$$

  Therefore, the solution of Eq. (8) exists only for $t < \frac{1}{x_0}$.

- On the other hand, knowing that the solution is positive, to get global existence of solutions we need to control their growth. Therefore, if the growth does not exceed linear one, then solutions exist for all $t > 0$.

Regarding IV:
Let x^* denote the steady state for Eq. (5), that is $F(x^*) = x^*$.

- Local stability can be analysed using linearization method under the assumption that x^* is hyperbolic.

  In any case we study the linear system:

$$\dot{y} = F'(x^*)y, \tag{9}$$

where $y = x - x^*$ is the difference between x and the steady state x^*.

This linear system has $y = 0$ as the unique steady state and this state is stable for $F'(x^*) < 0$, while $F'(x^*) > 0$ implies instability, because near 0 the non-linear part does not influence the dynamics much.

Notice, that if $F'(x^*) = 0$, then we are able to get completely different dynamics of the non-linear model comparing to the linear one.

Example:

Let us again consider

$$\dot{x} = x^2,$$

for which the linear part is 0.

Therefore, after linearization we have $\dot{y} = 0$ yielding $y(t) = y_0$, while x is increasing and $x(t) \to +\infty$ as $t \to \frac{1}{x(0)}$.

This shows that linearization cannot be used in such a case.

In n-dimensional case the situation can be much more complex: any linear system is described by the Jacobi matrix $dF(x^*)$ of the system, and the linearization method can be used under the assumption that $dF(x^*)$ has no eigenvalues on the imaginary axis.

More precisely, we look for zeros of the polynomial:

$$W(\lambda) = \det\left(dF(x^*) - \lambda\mathbb{I}\right),$$

where $\mathbb{I}$ is the identity matrix in $\mathbb{R}^n$.

W is called the characteristic polynomial for Eq. (5), while its zeros are eigenvalues.

- Global stability is much more complex problem.

  For $n = 1$ it can be studied using the phase portrait method.

  Sometimes this method gives results also for $n = 2$.

  In general, for $n \in \mathbb{N}$, the common method of studying global stability is to propose Lyapunov functional.

  A function $L : \mathbb{R}^n \to \mathbb{R}$ is the Lyapunov functional for Eq. (5) if:

  – L is positive definite ($L(x)$ is non-negative and $L(x) = 0$ only for $x = 0$),

  – the derivative along solutions of Eq. (5) ($\dot{L} = \frac{dL}{dt} = \mathrm{grad}L \cdot F$) is negative definite.

  There are several various versions of the Lyapunov or LaSalle – Lyapunov stability/instability theorem.

  We will discuss it studying specific problems.

Now, we come back to the logistic equation, Eq. (3).

We discuss problems I – IV for Eq. (3) in details.

Regarding I:

$F(x) = rx\left(1 - \frac{x}{K}\right)$ is a polynomial of second degree, and therefore is of class $\mathbf{C}^1$, guaranteeing existence and uniqueness of solutions for any initial data $N_0 > 0$.

Regarding II:

It is obvious that Eq. (3) is of the form (7) with $g(t, x) = r\left(1 - \frac{x}{K}\right)$.

Hence, $N_0 > 0 \Longrightarrow N(t) > 0$ for all t for which the solution exists.

Regarding III:

Positivity of solutions implies:

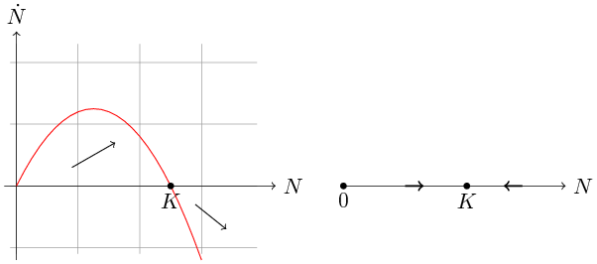
$$\dot{N} < rN,$$

and this means that the growth is at most linear and solutions exists for all $t > 0$.

Regarding IV:

Now, we explain the method of **phase portrait** on the example of the logistic equation.

For the logistic equation the right-hand side is described by the function $F(N) = rN\left(1 - \frac{N}{K}\right)$.



F is a parabola. It has two zeros: $N^0 = 0$ and $N^* = K > 0$. Looking at the graph of F it is easy to see that the solution is increasing for $N \in (0, K)$ and decreasing for $N > K$.

There are two **steady states** (that is solutions do not changing in time)

- $N^0 = 0$,
- $N^* = K$.

We can study stability of these solutions easily. Stability (in the sense of Lyapunov) means that the solution with initial data near the steady state remains in the neighbourhood of it.

However, for single ODE it is the same as asymptotic stability, which means that the solution starting near the steady state tends to it for $t \to +\infty$.

Moreover, we can have global stability, if all solutions tend to the unique steady state in the specific region $\mathbb{R}^+$ in our case.

- $N^0 = 0$ is unstable, because any solution $N(t)$ starting with $N_0 > 0$ is increasing; therefore it does not remain in the neighbourhood of 0, which is the necessary condition for stability (in the sense of Lyapunov);
- for $N^* = K$, and we easily see that $F(N) > 0$ for $N \in (0, K)$, and $F(N) < 0$ for $N > K$, meaning stability of N^*.

Moreover, we have

- if $N_0 > K$, then $N(t) > K$ for any $t \quad 0$ (and for the inverse inequality it is the same);
- in both intervals $(0, K)$ and (K, ∞) the solution is monotonic;
- this means that the solution has a limit.

Notice, that in any case we have bounded and monotonic solution and therefore, it has a finite limit as $t \to \infty$.

If the solution has a limit, then it tend to a steady state of the system (as the derivative also has a limit).

Therefore $N(t) \to K$ as $t \to \infty$.

It remains to check convexity/concavity of the solution.

Let us calculate the second derivative:

$$\frac{d^2N}{dt^2} = \frac{d}{dt}\left(\dot{N}\right) = \frac{d}{dN}F(N)\frac{dN}{dt} = r\left(1 - \frac{2N}{K}\right)\dot{N}.$$

Hence, the solution has an inflection point when there exists $\bar{t}$ such that $N(\bar{t}) = 0$.

Moreover, the curve $N(t)$ is convex for $N \in (0, K/2)$ and $N > K$, while it is concave for $N \in (K/2, K)$.

Similar analysis can be made for any single ODE assuming uniqueness of solutions.

Moreover, we can propose the following Lyapunov functional:

$$L(N) = N - K - K \ln \frac{N}{K}, \quad N > 0.$$

Clearly,

$L(K) = 0$ and $L'(N) = 1 - \frac{K}{N}$, so L is increasing for $N > K$, decreasing for $L \in (0, K)$ and L has a minimum at K. Therefore, L is positive definite.

The derivative of L along the solution of Eq. (3) reads

$$\dot{L} = \frac{N - K}{N} rN\left(1 - \frac{N}{K}\right) = -r\frac{(N - K)^2}{K},$$

and therefore this derivative is negative definite.

We also have $L(N) \to \infty$ as $t \to \infty$.

Moreover, all solutions are bounded, because if $N_0 \in (0, K)$, then $N(t) \in (0, K)$, while if $N_0 > K$, then $N(t)$ is decreasing, meaning that

$$N(t) < \quad = \max\{N_0, K\}.$$

This implies that the positive steady state K is globally stable in $\mathbb{R}^+$.

How to find Lyapunov functional for Eq. (3)?

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We start from the change of variables $y = N - K$, such that $y = 0$ is the steady state in the variable y.

$$\dot{y} = r(y + K)\left(1 - \frac{y + K}{K}\right) = -ry\frac{y + K}{K}.$$

As we want to have $\dot{L}$ negative definite, we assume that $\dot{L}(y) = -ay^2$, $a > 0$.

Hence,

$$L'(y) \cdot \left(-ry\frac{y + K}{K}\right) = -ay^2 \quad \Longrightarrow \quad L'(y) = \frac{aK}{r}\frac{y}{y + K},$$

yielding

$$L(y) = \frac{aK}{r}\int\left(1 - \frac{K}{y + K}\right)dy \quad \Longrightarrow \quad L(y) = y - K\ln(y + K) + C,$$

for $a = \frac{r}{K}$ and C such that $L(0) = 0$.

We obtain $C = K \ln K$, implying $L(y) = y - K \ln \frac{y+K}{K}$.

Lecture II: Various processes associated with the dynamics of a single population described in the framework of ODE

Now, we come back to modelling problems and give another interpretation for Eq. (3).

Ecologists think that the simple change of the population size $\dot{N}(t)$ is not the best way of the description of the population dynamics.

They propose to use the per capita growth rate:

$$\frac{\dot{N}}{N}$$

as a description of the population dynamics.

Coming back to the Malthus model we have this per capita growth rate constant:

$$\frac{\dot{N}}{N} = r.$$

However, it is obvious that in bounded environment it should depend on the population size. Therefore,

$$\frac{\dot{N}}{N} = f(N).$$

Moreover, f should be a decreasing function of the population size that starts from r for $N = 0$, and then r is the maximal growth rate of the population.

From mathematical point of view the simplest form of such function reads

$$f(N) = r - bN,$$

that is f is linear decreasing.

From biological point of view it is not easy to get the logistic equation as a mathematical description for some heuristic model.

However, we have shown (Bodnar, Foryś, 2007) that this equation can be obtained as an approximation of the solution of the reaction-consumption model reflecting the growth of radially symmetric cellular colony growing in a Petri dish.

This equation has the same qualitative dynamics as the Greenspan model obtained for the growth of radially symmetric tumour in $\mathbb{R}^3$, that is:

$$\dot{V} = rV\left(1 - \left(\frac{V}{K}\right)^{2/3}\right),$$

where:

- V reflects the tumour volume at time t;

- r is the maximal growth rate;
- K is the maximal tumour size that can be achieved under the diffusion process, without external supply of nutrients (oxygen and glucose).

On the other hand, the most commonly used tumour growth model is the Gompertz equation. This equation was proposed by Benjamin Gompertz.

Benjamin Gompertz was a British self-educated mathematician and actuary, who became a Fellow of the Royal Society. Gompertz is now best known for his Gompertz law of mortality, a demographic model published in 1825.

He proposed a double exponential curve for the description of human population dynamics.

Many years later Anna Laird rediscovered the Gompertz cure and used it to model the growth of tumour, fitting the cure to experimental data.

This curve occurred to be a solution to some differential equation which is called the Gompertz model now.

It reads

$$\dot{V} = -rV \ln \frac{V}{K}. \tag{10}$$

Notice, that the right-hand side of Eq. (10) is not defined for $V = 0$.

From the biological point of view the state $V = 0$ should be available as a steady state of Eq. (10), as it reflects the absence of tumour, that is a healthy organism.

However, we know that the limit

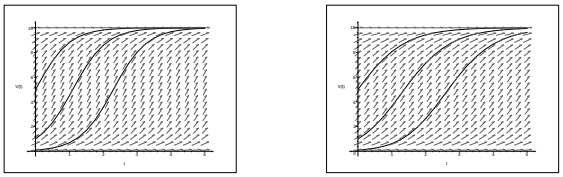
$$\lim_{x \to 0} x \ln x = 0,$$

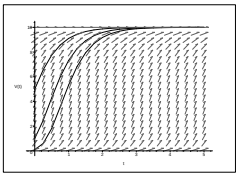
and therefore we can extend the right-hand side of Eq. (10) to $V = 0$.

As we have mentioned before, these three equations have the same qualitative dynamics. Clearly,

- for $V \in (0, K)$ the solution increases to K;
- for $V > K$ the solution decreases to K;
- there exists an inflection point $\tilde{V} \in (0, K)$, but the magnitude of $\tilde{V}$ depends on the model.

logistic Greenspan





Gompertz

Now, we come back to the logistic equation Eq. (3) to discuss the process of migrations.

Commonly, there are two distinct forms of migration:

- migration constant in time,
- migration proportional to the population size.

The first type of migrations is typical for example for fishery or hunting. Fishing on a see we assume some constant yield per some time (a year, typically).

However, we can also imagine the second type of fishing, where we just catch fishes every day (month, year) not assuming any bounds for the yield. Having the same fishing intensity we obtain the yield proportional to the population size.

In the first case the model with migration has the following form:

$$\dot{N} = rN\left(1 - \frac{N}{K}\right) + m, \tag{11}$$

where m is the migration coefficient, $m > 0$ for immigration, while $m < 0$ for emigration.

The right-hand side of Eq. (11) reads $F_1(N) = rN\left(1 - \frac{N}{K}\right) + m$.

- Assume $m < 0$.

  The graph of F_1 is moved down comparing to the graph of $F(N) = rN\left(1 - \frac{N}{K}\right)$.

  We have three different dynamics, depending on the magnitude of $|m|$:

  (1) If $rK/4 > |m|$, then the original steady states 0 and K change to $N_1^1 = \frac{rK - \sqrt{r^2K^2 - 4r|m|K}}{2r} > 0$ and $N_1^2 = \frac{rK + \sqrt{r^2K^2 - 4r|m|K}}{2r} < K$.
  Looking at the graph of F_1 we see that

  – for $N_0 < N_1^1$ the solution decreases, and moreover the population become extinct in finite time (all individual emigrate in some time $\tilde{t} < \infty$);

  – for $N_0 \in (N_1^1, N_1^2)$ the solution increases, and therefore tends to N_1^2;

  – for $N_0 > N_1^2$ the solution decreases, and therefore tends to N_1^2.

  (2) If $rK/4 = |m|$, then the original steady states 0 and K stick to one steady state $N_1 = \frac{K}{2}$.

  Looking at the graph of F_1 we see that

  – for $N_0 < N_1$ the solution decreases, and moreover the population become extinct in finite time (all individual emigrate in some time $\tilde{t} < \infty$);

– for $N_0 > N_1$ the solution decreases as well, but now tends to N_1.

At $m_{cr} = -rK/4$ we observe a bifurcation.

Any qualitative change of the model dynamics with the changes of some *bifurcation parameter* is called a bifurcation.

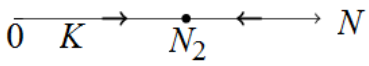
We see that for $m > m_{cr}$ steady states of the model disappears.

(3) If $rK/4 < |m|$, then there is no steady state and all solutions decreases, yielding the population extinction (again in finite time).

- Assume $m > 0$.

  The graph of F_1 is moved up comparing to the graph of $F(N)$.

  Therefore, the original steady state 0 disappears, while the positive steady state K increases to $N_2 = \frac{rK+\sqrt{r^2K^2+4rmK}}{2r} > K$.



  It is easy to see that all solutions tend to N_2.

Considering migrations proportional to the population size, we obtain the following equation:

$$\dot{N} = rN\left(1 - \frac{N}{K}\right) + mN, \tag{12}$$

where $|m|$ is the intensity of migration.

We again can get different dynamics depending on the magnitude of $m \in \mathbb{R}$.

- If $m > -r$, that is $m + r > 0$, then Eq. (12) has always the same form as Eq. (3), there is only quantitative difference, as the net growth rate and carrying capacity change.

  Clearly, we can rewrite Eq. (12) as

$$\dot{N} = (r+m)N\left(1 - \frac{rN}{(r+m)K}\right) = \tilde{r}N\left(1 - \frac{N}{\tilde{K}}\right), \tag{13}$$

  where $\tilde{r} = r + m$ and $\tilde{K} = \frac{(r+m)K}{r}$.

  It is obvious that in the case of immigration $\tilde{r} > 0$ and $\tilde{K} > K$, while for emigration we have inverse inequalities.

  We see that the main difference between constant and proportional to the population size migration is that in the second case 0 remains the steady state.

- If $m = -r$, then $\tilde{r} = 0$ in Eq. (13), so only quadratic term appears on the right-hand side of this equation.

  It is obvious that $\dot{N} < 0$ for all $t > 0$, and as 0 is the unique steady state, the solution decreases to it. Moreover, the population extinction cannot occur in the finite time, as for constant migration.

- If $m < -r$, then $\tilde{r} < 0$ in Eq. (13), and we easily see that the model dynamics is qualitatively the same as for $m = -r$.

  At $m_{cr} = -r$ we observe a bifurcation.

Notice, that from both models of migrations we can get the same corollary:

> Fishing should not be too intensive,
> if we want to keep the population alive.
> Caching too many individuals comparing to the popula-
> tion growth rate always leads to the population extinction.

Now, we can think about slightly different interpretation of Eq. (12).

Imagine, that there is another population of predators present in the environment.

Assuming that the number of predators is constant, and simplifying the process of hunting to random movement of the predator which catches preys with some intensity m we obtain

$$\dot{N} = rN\left(1 - \frac{N}{K}\right) - mVN,$$

where $V = \text{const}$ is the number of predators.

However, we can be slightly critical to this equation, as the predation term (called also predator functional response) $\Phi_1(N) = mVN$ means, that the predator can eat arbitrary many preys, which is not true in reality.

Trying to make the functional response more realistic, we should propose a function which is bounded, like

$$\Phi_2(N) = m\frac{N}{1 + nN},$$

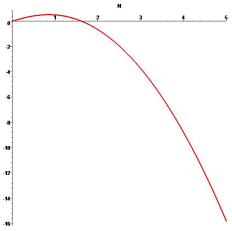
and we see that $\Phi_2 \approx \Phi_1$ for N small.

The function Φ_2 is called Holling disc equation or, in terms of functional response, type II functional response.

Therefore, with this type II functional response we obtain the model

$$\dot{N} = rN\left(1 - \frac{N}{K}\right) - m\frac{N}{1 + nN} = N\left(r - r\frac{N}{K} - \frac{m}{1 + nN}\right), \tag{14}$$

and looking at the right-hand side of Eq. (14) we see that if $m < r$, there are two steady states 0 and positive $\bar{N} < K$.



As the right-hand side of Eq. (14) looks like parabola, we conclude that the steady state $\bar{N}$ is globally stable in $\mathbb{R}^+$.

The type II functional response can be derived using the following line of reasoning.

We assume that the number of preys caught by a predator is proportional to the prey density and to the time spent in actual search.

The time spent searching is less than total amount of time allocated to food-gathering activities by the time needed to handle individual prey items.

Hence, if M is the number of preys caught during the food-gathering period, T is the duration of that period, N is the prey density, s is the effective searching rate and h is the handling time, then

$$M = sN(T - hM),$$

giving

$$\Phi(N) = \frac{M}{T} = \frac{sN}{1 + shN}.$$

Another type of predator influence is observed in the model with so-called Allee effect.

Populations in which we observe this effect, decreases their size, if it falls below a certain threshold.

Typically, we think about the Allee effect in the context of predation, as the dynamics of the prey population is affected by it

In this effect we assume that there are always a lot of predators. Therefore, if the prey population is small, the predators eat the available individuals and population of preys become extinct.

The simplest form of the model reflecting the Allee effect reads

$$\dot{N} = rN\,(N - N_{\mathrm{cr}})\left(1 - \frac{N}{K}\right), \quad N_{\mathrm{cr}} \in (0, K), \tag{15}$$

where N_{cr} is called predation trap.

It is easy to check that:

- there are three steady states $N_1 = 0$, $N_2 = N_{\mathrm{cr}}$, $N_3 = K$;
- if $N_0 \in (0, N_{\mathrm{cr}})$, then $\dot{N} < 0$, so the solution decreases to 0;
- if $N_0 \in (N_{\mathrm{cr}}, K)$, then $\dot{N} > 0$, so the solution increases to K;
- if $N_0 \in (K, \infty)$, then $\dot{N} < 0$, so the solution decreases to K.

In this model we observe bistability, which means that there are two stable steady states, N_1 and N_3, and to which of the states the solution tends is dependent on N_0.

Lecture III: Discrete logistic equation: the simplest way to chaotic behaviour

Now, we make a discretization of the logistic equation approximating

$$\frac{dN}{dt} \approx \frac{N(t+\Delta t) - N(t)}{\Delta t}.$$

Hence,

$$\frac{N(t+\Delta t) - N(t)}{\Delta t} = rN(t)\left(1 - \frac{N(t)}{K}\right).$$

Assume that $\Delta t = 1$ and denote $N(t) = N_t$.

We obtain

$$N_{t+1} = N_t + rN_t\left(1 - \frac{N_t}{K}\right) = (1+r)N_t\left(1 - \frac{N_t}{K_1}\right), \quad \text{where} \quad K_1 = \frac{K(1+r)}{r}.$$

Let us introduce new variable $x_t = \frac{N_t}{K_1}$ and denote $a = 1 + r$, then

$$x_{t+1} = ax_t(1 - x_t), \quad t \in \mathbb{N} \tag{16}$$

which is known as the discrete logistic equation.

Notice, that due to the biological interpretation $a > 1$ and $x_t \in [0, 1]$.

The terms of the sequence x_t are obtained as iterations of the function

$$F(x) = ax(1 - x).$$

To preserve non-negativity of all terms in the sequence (x_t) we should assume that a does not exceed 4, as if $a > 4$, then $\max\{F(x) : \ x \in [0, 1]\} = \frac{a}{4} > 1$.

On the other hand, assuming that the net growth rate $r < 0$ in the continuous case, we can also consider $a < 1$.

Eventually, we study Eq. (16) in $[0, 1]$ for $a \in (0, 4]$.

It should be noticed that for $a = 4$ the dynamics of Eq. (16) is equivalent to the dynamics of the system generated by "tent" function:

$$T(x) = 2x \quad \text{for} \quad x \in \left[0, \frac{1}{2}\right], \quad T(x) = 2 - 2x \quad \text{for} \quad x \in \left[\frac{1}{2}, 1\right].$$

The function T is know as "chaos generating". Moreover, all functions from the interval $[0, 1]$ onto this interval having its graph similar to the graph of T (and F as well) have the same property.

We will not define the notion of chaos precisely – there is now common accepted definition of chaos. We will only mark important properties of chaotic behaviour later.

Let us come back to Eq. (16). We start the analysis for looking for steady states.

Notice, that $\bar{x}$ is a steady state of Eq. (16) if it is a constant point of F, that is

$$\bar{x} = F(\bar{x}) \quad \Longrightarrow \quad \bar{x}_0 = 0, \;\; \bar{x}_1 = \frac{a-1}{a}.$$

We see that the positive steady state $\bar{x}_1$ exists for $a > 1$. Moreover, for any $a > 1$ there is $\bar{x}_1 \in (0, 1)$.

Studying local stability of steady states we use the method of linearization, as for continuous model. Notice, that the corresponding linear model is just the geometric progress:

$$y_t = F'(\bar{x})y_t, \quad y_t = x_t - \bar{x},$$

and therefore

- stability is for $|F'(\bar{x})| < 1$,
- instability for $|F'(\bar{x})| > 1$,
- $|F'(\bar{x})| = 1$ is the critical case and the method of linearization cannot be applied.

Moreover, if $F'(\bar{x})$ is positive, then (y_t) is monotonic, while if $F'(\bar{x})$ is negative, then (y_t) oscillates.

It should be noticed that in general case, when we study n-dimensional discrete model, the condition guaranteeing stability is that all eigenvalues of the Jacobi matrix $dF(\bar{x})$ lie inside unit circle.

Let us calculate:

$$F'(x) = a(1-2x) \quad \Longrightarrow F'(0) = a, \quad F'\left(\frac{a-1}{a}\right) = a\left(1 - 2\frac{a-1}{a}\right) = 2 - a.$$

We look for $a > 1$ such that $|2 - a| < 1$.

We easily see that:

- if $a \in (0, 1)$, then the only steady state $\bar{x}_0 = 0$ is locally stable;
- if $a > 1$, then $\bar{x}_0$ loses stability and the positive steady state $\bar{x}_1$ appears;
- if $a \in (1, 2)$, then $F'(\bar{x}_1) \in (0, 1)$ and $\bar{x}_1$ is locally stable and (x_t) is monotonic for x_0 near $\bar{x}_1$;
- if $a \in (2, 3)$, then $F'(\bar{x}_1) \in (-1, 0)$, $\bar{x}_1$ is locally stable and (x_t) oscillates around $\bar{x}_1$ for x_0 near $\bar{x}_1$;
- if $a > 3$, then both $\bar{x}_0$ and $\bar{x}_1$ are unstable.

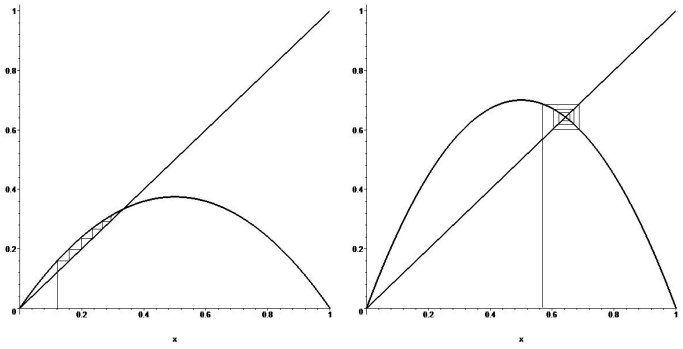
Moreover, we are able to show global stability of $\bar{x}_0$ for $a < 1$ and for $a = 1$ as well, and global stability of $\bar{x}_1$ for $a \in (1, 3]$.

This can be done either using standard methods for studying sequences (either (x_t) is monotonic, or it has two monotonic sub-sequences (x_{2t}) and (x_{2t+1}) and as any bounded and monotonic sequence has a limit, we obtain:

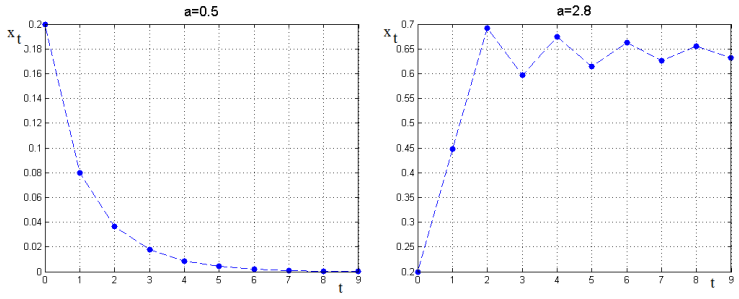
$$x_t \to g \;\text{ and }\; x_{t+1} \to g \quad \Longrightarrow \quad g = F(g),$$

that is g is a steady state) or using the graphical method called cob-webbing.

In this cob-webbing method we draw the graph of $F(x)$ and the straight line $y = x$ and trace the sequence (x_t): from x_0 we go to the first term $x_1 = F(x_0)$ on the graph of F, then we go to the straight line $y = x$ still having x_1, then we go to the graph of F obtaining $x_2 = F(x_1)$, etc.



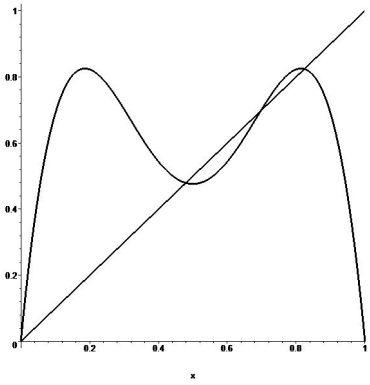
Examples of cob-webbing for $a = 1.5$ (left) and $a = 2.8$ (right). In both figures $x_t \to \bar{x}_1$, but one sequence is monotonic, and the other is oscillating.



Two examples of solutions of Eq. (16) – monotonic sequence that tends to $\bar{x}_0$ (left) and oscillating sequence tending to $\bar{x}_1$ (right).

What is the dynamics of Eq. (16) for larger values of a?

We can calculate that for $a > 3$ there exists a non-trivial periodic solution of period 2.



Clearly, such periodic orbit is formed from steady states of the second iteration

$$F^2(x) = F(F(x)) = a^2x(1-x)\big(1-ax(1-x)\big).$$

We look for steady states of F^2 different from $\bar{x}_0$ and $\bar{x}_2$.

We obtain:

$$x^1 = \frac{1+a+\sqrt{-3-2a+a^2}}{2a}, \quad x^2 = \frac{1+a-\sqrt{-3-2a+a^2}}{2a},$$

where $F(x^1) = x^2$ and $F(x^2) = x^1$, $F^2(x^i) = x^i$, $i = 1, 2$.

We can check stability of the periodic orbit (x^1, x^2) analyzing stability of x^i as steady states of F^2.

Calculating the derivative of F^2 we obtain:

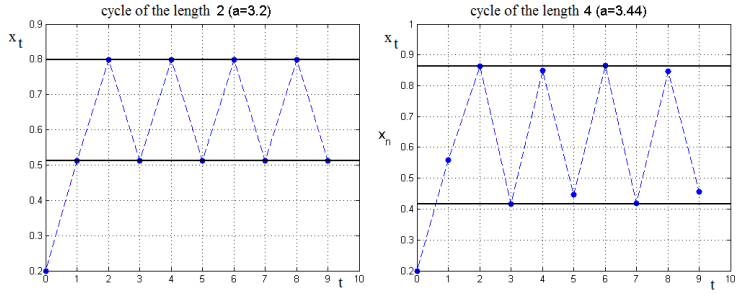
$$\left(F^2\right)'(x) = -4a^3x^3 + 6a^3x^2 - (2a^3 + 2a^2)x + a^2 \;\rightarrow\; \left(F^2\right)'(x^1) = \left(F^2\right)'(x^2) = 4 + 2a - a^2,$$

and we see that $\left|\left(F^2\right)'(x^1)\right| < 1$ for $a \in (3, 1+\sqrt{6})$.

We say that at $a = 3$ there is a period-doubling bifurcation.

It occurs that for $a = 1 + \sqrt{6}$ the next period-doubling bifurcation appears.

There is periodic orbit of period 4, which is stable on some interval, and so on.



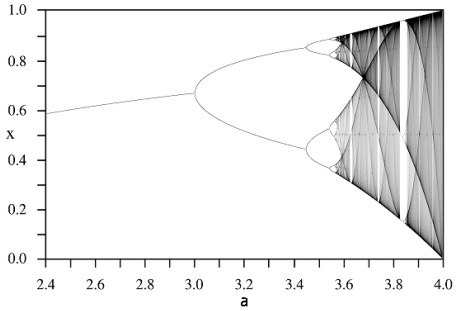
In fact we run down all orbits of period 2^n, $n \in \mathbb{N}$.

Next, orbits of period $p \cdot 2^n$ appear, running down all even periods, and eventually, orbits of odd periods occur, ending with period 3, for $a < a^* \approx 3.569...$

Between $a = a^*$ and $a = 4$ non-periodic solutions are observed as well.

For $a = 4$ we are able to prove that chaotic dynamics is observed.

Bifurcation diagram is called the Feigenbaum tree, while a^* is the Feigenbaum number.



What are the properties of chaos?

As we see, there are many periodic orbits – to be more precise, chaotic dynamics requires density of periodic orbits. This means that in a neighbourhood of any orbit there exist some periodic orbits.

Another property is sensitivity to initial data. This means that even if the first terms of two sequences generated by the iterations of F are very close, the terms of these sequences can be far.

We have also some kind of "inverse" property – sets that are initially far become close after some iterations.

The most popular and best known is the sensitivity to initial data.

There is a famous story that flying butterfly can be the reason of tsunami in completely different place.

However, we should notice that this property is in fact not necessary in the definition of chaos, it is just a consequence of other more important properties.

At the end of this topic we make a remark on the Sharkovsky order and its connection with the discrete logistic equation dynamics.

In 1964 Ukrainian mathematician Oleksandr Sharkovsky proposed a specific order in $\mathbb{N}$:

$$\begin{array}{ccccccccccc}
3 & > & 5 & > & 7 & > & 9 & > & \dots & (2n+1)2^0 & \dots \\
3\cdot 2 & > & 5\cdot 2 & > & 7\cdot 2 & > & 9\cdot 2 & > & \dots & (2n+1)2^1 & \dots \\
3\cdot 2^2 & > & 5\cdot 2^2 & > & 7\cdot 2^2 & > & 9\cdot 2^2 & > & \dots & (2n+1)2^2 & \dots \\
 & & \vdots & & & & & & & & \\
\dots & & 2^n & > & \dots & > & 2^2 & > & 2 & > & 1
\end{array}$$

Sharkovsky proved that if $F : [0,1] \to [0,1]$ (or $F : \mathbb{R} \to \mathbb{R}$) is continuous and F has a periodic point of period m (period means least period here, that is $F^m(x) = x$ for all $x \in [0,1]$ and $F^k(x) \neq x$ for $k < m$), then it also has orbits of all orbits $n < m$ according to the Sharkovsky order.

The best known corollary from the Sharkovsky theorem is that period 3 implies all other periods.

This property was rediscovered by T.Y. Li and J.A. York in 1975 in their article "Period three implies chaos" (American Mathematical Monthly, 82: 985).

Notice, that the assumption on continuity is important for this result, as $f(x) = \frac{1}{1-x}$ has all points of period 3. Clearly,

$$f^2(x) = \frac{1}{1-\frac{1}{1-x}} = \frac{x-1}{x} \text{ and } f^3(x) = \frac{1}{1-\frac{x-1}{x}} = x.$$

Lecture IV:
Classic Lotka-Volterra model describing prey-predator interactions.
****
The method of phase portraits for two ODEs

In this lecture we turn to the next topic – interactions between individuals of two species. Modelling such situation we will use our knowledge from the first part of the course.

We start from the oldest and probably the best know model called predator-prey model or Lotka-Volterra model. This model was proposed parallel by

- Lotka as a description of hypothetical biochemical oscillator,
- Voletrra as a description of two interacting populations description.

It also has been published independently by Lotka in 1925 and Volterra in 1926.

Proposing this model Volterra tried to explain some kind of paradox (as it was thought about that time) regarding the population of predator fishes in Adriatic after the First World War.

Fishermen noticed that their yield (meaning number of caught fishes) increased after the war. It seemed strange not only for them but also for ecologists who interested in this topic. They expected that the size of any population should decrease during the war.

Volterra proposed very simple model of predator-prey interactions that was able to explain this seeming paradox.

Now, we will introduce the model proposed by Volterra and study its properties.

We start from the heuristic model that describes basic ideas of predator-prey interactions.

Let $\mathcal{E}_1$ denotes the prey population, while $\mathcal{E}_2$ denotes predators.

Let us consider the inner dynamics of $\mathcal{E}_1$ (that is the dynamics in the absence of predators). We assume that this dynamics is governed by Malthusian law. meaning that the growth of preys is unbounded in the absence of predators.

The inner dynamics of $\mathcal{E}_2$ is also of that type, but the death process is described in this cease. Clearly, in the absence of preys, predators have no food, and therefore they are not able to reproduce, which leads to the population extinction.

Hence, separating $\mathcal{E}_1$ and $\mathcal{E}_2$, we obtain the system of equations

$$\begin{aligned} \dot{V} &= rV, \\ \dot{P} &= -sP, \end{aligned} \tag{17}$$

describing time-dependent dynamics of $V(t)$ and $P(t)$ that reflect the size of prey and predator populations, respectively. Parameters $r, s > 0$ describe the growth rate of preys and the death rate of predators.

On the other hand, if both species are present in the environment, we observe hunting of predators on preys. Assuming that meeting between individuals of both species are

random, then the number of preys that can be caught by one predator is proportional to the size of preys population, and vice versa, the number of predator that can hunt on one prey is proportional to the size of predator population.

Therefore, the hunting term is proportional to $V(t)P(t)$.

It is obvious that not every hunting ends with the success of predator. It depends on the speed on both prey and predator, the smartness of them and so on.

If the predator bagged a prey, then some part of biomass of bagged preys is used up by predators for reproduction. Finally, we obtain the following system

$$\begin{aligned} \dot{V} &= rV - aVP, \\ \dot{P} &= -sP + abVP, \end{aligned} \tag{18}$$

where r, s as before while a measures effectiveness of hunting and b is the biomass conversion rate (meaning conversion of biomass into offspring).

Now, we turn to the model analysis, following the steps listed previously.

I. Existence and uniqueness of solutions.

It is easy to see that the right-hand side of Eq. (18) is polynomial, hence is of class $\mathbf{C}^1$ and this guarantees existence and uniqueness of solutions.

II. Non-negativity of solutions.

Due to the form of the right-hand side we can rewrite both equations of Eq. (18) in the exponential form

$$V(t) = V_0 \exp\left(rt - a\int_0^t P(s)ds\right), \quad P(t) = P_0 \exp\left(-st + ab\int_0^t V(s)ds\right),$$

where (V_0, P_0) is the initial data.

It is obvious that:

- if $V_0 = 0$, then $V(t) \equiv 0$;
- if $V_0 > 0$, then $V(t) > 0$ for all $t > 0$;
- if $P_0 = 0$, then $P(t) \equiv 0$;
- if $P_0 > 0$, then $P(t) > 0$ for all $t > 0$.

III. Prolongation of solutions for all $t > 0$.

We know that for any (V_0, P_0) there exists $\bar{t} > 0$ such that the solution of Eq. (18) exists for $t \in [0, \bar{t})$.

Knowing that the solution is non-negative for non-negative initial data we can estimate

$$\dot{V} <= rV \quad \Longrightarrow \quad V(t) <= V_0\, e^{rt} < V_0\, e^{r\bar{t}} := V_{\max}, \text{ for } t < \bar{t}.$$

This means that V is non-negative and exponentially bounded, meaning that the derivative of V is bounded as well, yielding that blow-up of the solution is impossible.

Therefore, $V(t)$ can be prolonged for all $t > 0$.

Similar arguments give

$$\dot{P} <= (abV_{\max} - s)\,P \quad \Longrightarrow \quad P(t) <= P_0\,\mathrm{e}^{(abV_{\max}-s)t} < P_0\,\mathrm{e}^{(abV_{\max}-s)\bar{t}},\ \text{for } t < \bar{t},$$

yielding the existence of solutions of Eq. (18) for all $t > 0$.

IV. Steady states analysis.

Looking for steady states one needs to solve the system of equation that reads

$$\begin{aligned} 0 &= V(r - aP), \\ 0 &= P(abV - s). \end{aligned} \tag{19}$$

From Eq. (19) we easily see that

- if $V = 0$, then $P = 0$, and therefore $(0, 0)$ is the steady state of Eq. (18);
- if $r - aP = 0$, then $P = \frac{r}{a}$, and therefore $V = \frac{s}{ab}$, which gives the positive steady state $(\bar{V}, \bar{P}) = \left(\frac{s}{ab}, \frac{r}{a}\right)$.

Studying local stability we calculate the Jacobi matrix $J = dF(\bar{x})$, where $F(x)$ is the right-hand side of Eq. (18), $x = (V, P)$, while $dF(\bar{x})$ is the derivative of F evaluated at the steady state $\bar{x}$, where $\bar{x} = (0, 0)$ or $\bar{x} = (\bar{V}, \bar{P})$.

Then the system linearized around $\bar{x}$ reads:

$$\dot{x} = \bar{x} + J(\bar{x})(x - \bar{x}).$$

We have

$$J(V, P) = \begin{pmatrix} r - aP & -aV \\ abP & abV - s \end{pmatrix},$$

This matrix reads

- $$J(0, 0) = \begin{pmatrix} r & 0 \\ 0 & -s \end{pmatrix},$$

  for the trivial steady state $(0, 0)$, and therefore the eigenvalues are $\lambda_1 = r$ and $\lambda_2 = -s$, yielding this state is a saddle;

- $$J(\bar{V}, \bar{P}) = \begin{pmatrix} 0 & -a\bar{V} \\ ab\bar{P} & 0 \end{pmatrix},$$

  for the positive steady state, and therefore $\lambda_{1,2} = \pm i\sqrt{a^2 b\bar{V}\bar{P}} = \pm i\sqrt{rs}$, yielding this state is a centre for the linearized system, and therefore the linearization theorem cannot be applied and we need to look for another tools to analyse this state.

In general, we use the method of phase portrait to look at the two-dimensional system dynamics.

The phase space is $\mathbb{R}^2$ from mathematical point of view.

However, for biological point of view we are interested in non-negative values of V and P, and therefore we restrict our analysis to $\mathcal{P} = (\mathbb{R}^+)^2$.

In $\mathcal{P}$ we analyse orbits of Eq. (18) as either functions $P = P(V)$ or $V = V(P)$.

For this curves we have

$$\frac{dP}{dV} = \frac{dP}{dt} \cdot \frac{1}{\frac{dV}{dt}}, \quad \frac{dV}{dP} = \frac{dV}{dt} \cdot \frac{1}{\frac{dP}{dt}},$$

and we see that

- $\frac{dP}{dV} > 0$ for $\frac{dP}{dt} > 0$ and $\frac{dV}{dt} > 0$ or $\frac{dP}{dt} < 0$ and $\frac{dV}{dt} < 0$;
- $\frac{dP}{dV} < 0$ for $\frac{dP}{dt} > 0$ and $\frac{dV}{dt} < 0$ or $\frac{dP}{dt} < 0$ and $\frac{dV}{dt} > 0$;
- $\frac{dP}{dV} = 0$ for $\frac{dP}{dt} = 0$ and the curve $P(V)$ has possible extrema for such points;
- $\frac{dV}{dP} > 0$ for $\frac{dV}{dt} > 0$ and $\frac{dP}{dt} > 0$ or $\frac{dV}{dt} < 0$ and $\frac{dP}{dt} < 0$;
- $\frac{dV}{dP} < 0$ for $\frac{dV}{dt} > 0$ and $\frac{dP}{dt} < 0$ or $\frac{dV}{dt} < 0$ and $\frac{dP}{dt} > 0$;
- $\frac{dV}{dP} = 0$ for $\frac{dV}{dt} = 0$ and the curve $V(P)$ has possible extrema for such points.

This shows that the phase space $\mathcal{P}$ is divided by null-clines, that is the curves defined as $\dot{V} = 0$ or $\dot{P} = 0$, into the regions in which

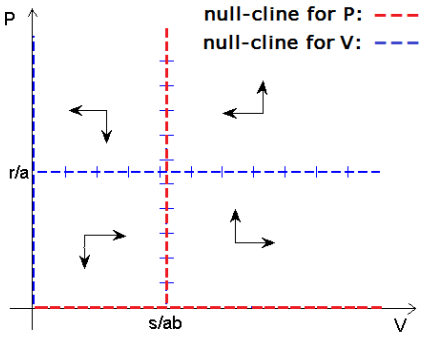
- $\dot{P} > 0$ and $\dot{V} > 0$,
- $\dot{P} > 0$ and $\dot{V} < 0$,
- $\dot{P} < 0$ and $\dot{V} > 0$,
- $\dot{P} < 0$ and $\dot{V} < 0$,

while on the null-clines orbits have possible maxima and minima.

In the case of Eq. (18) null-clines are described as

- $V = 0$ or $P = \frac{r}{a}$ for the variable V;
- $P = 0$ or $V = \frac{s}{ab}$ for the variable P.

Therefore, we have four regions in $\mathcal{P}$:



Looking at the sketch of phase portrait we see that any solution with positive initial data encircles the positive steady state.

However, we are not able to guess the exact shape of orbits:

- they can look like in the linear case (closed orbits),
- can be spirals going into the steady state,
- can be spirals going outside the steady state,
- can be some closed orbits around the steady state and orbits can be attracted or repelled by such orbits.

In the following we prove that the dynamics of Eq. (18) is like in the linear model, that is $(\bar{V}, \bar{P})$ is a centre and all solutions with positive initial data are closed orbits.

In addition, we should check the dynamics for $V = 0$ or $P = 0$.

Clearly, if $V = 0$, then $V \equiv 0$ due to the uniqueness of solutions. Then $\dot{P} = -sP$, so P decreases to 0 exponentially as $t \to +\infty$.

If $P = 0$, then $P \equiv 0$ yielding $V = rV$, and therefore $V \to \infty$ exponentially.

Notice, that the dynamics for $V = 0$ or $P = 0$ is just a consequence of the inner dynamics of the species.

Now, we focus on the global dynamics of Eq. (18) for positive initial data.

We can use either the method of first integral or Lyapunov functionals.

Calculating the first integral we notice that on orbits of Eq. (18) we have

$$\frac{dP}{dV} = \frac{P(abV - s)}{V(r - aP)} \quad \text{for} \quad V \neq \frac{s}{ab}.$$

We obtain equation with separated variables, and integrating it we get

$$\frac{\exp(abV + aP)}{V^s P^r} = C.$$

We are able to show that this yield closed orbits of Eq. (18).

On the other hand, we can use the method of the variables separation to calculate Lyapunov functional.

To do it let us change variables such that $(\bar{V}, \bar{P})$ is moved to $(0, 0)$, that is

$$x = V - \bar{V}, \quad y - P - \bar{P}.$$

In new variables we have

$$\begin{array}{rclcl} \dot{x} & = & (x + \bar{V})(r - a(y + \bar{P})) & = & -ay(x + \bar{V}), \\ \dot{y} & = & (y + \bar{P})(-s + ab(x + \bar{V})) & = & abx(y + \bar{V}). \end{array}$$

We are looking for Lyapunov functional in the form of separated variables, that is

$$L(x, y) = L_1(x) + L_2(y).$$

Calculating the derivative of L along the solution we obtain

$$\frac{dL}{dt} = L_1'(x)\dot{x} + L_2'(y)\dot{y} = -ay(x+\bar{V})L_1'(x) + abx(y+\bar{P})L_2'(y).$$

The method requires the derivative along solutions is also of the same form, that is

$$\frac{dL}{dt} = \hat{L}_1(x) + \hat{L}_2(y).$$

Recall that we want to have $\frac{dL}{dt} <= 0$ and $\frac{dL}{dt} = 0$ for $x = y = 0$.

This yields

$$\frac{(x+\bar{V})L_1'(x)}{x} = b\frac{(y+\bar{P})L_2'(y)}{y} = C.$$

Therefore,

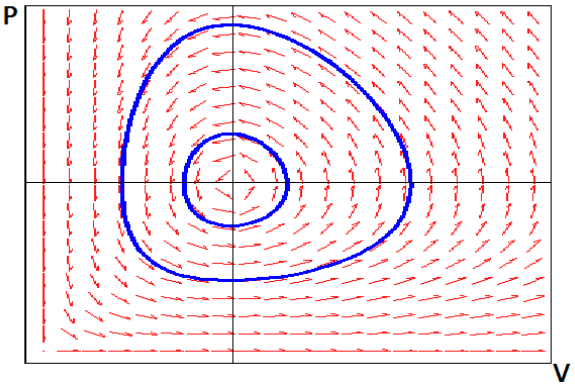
$$L_1(x) = C\Big(x - \bar{V}\ln(x+\bar{V}) + A_1\Big), \quad L_2(x) = \frac{C}{b}\Big(y - \bar{P}\ln(y+\bar{P}) + A_2\Big),$$

where A_i, $i = 1, 2$, should be chosen such that $L_1(0) = L_2(0) = 0$.

Eventually,

$$L(x,y) = b\left(x - \bar{V}\ln\frac{x+\bar{V}}{\bar{V}}\right) + \left(y - \bar{P}\ln\frac{y+\bar{P}}{\bar{P}}\right).$$

One can easily check that $L(x,y) > 0$ for $(x,y) \neq (0,0)$ and $\frac{dL}{dt} = 0$ on the orbits of the system. This means that solutions are periodic.



The next property of Eq. (18) we are able to prove is preservation of mean value.

Let (V_m, P_m) be a mean value on some trajectory of Eq. (18). As it is periodic, there is some $T > 0$ being its period. Then

$$V_m = \frac{1}{T}\int_0^T V(t)dt, \quad P_m = \frac{1}{T}\int_0^T P(t)dt$$

Let us rewrite Eq. (18) in the form

$$\begin{aligned} \frac{\dot{V}}{V} &= r - aP, \\ \frac{\dot{P}}{P} &= -s + abV, \end{aligned}$$

and integrate it from 0 to T:

$$\begin{aligned} 0 &= \int_0^T \frac{\dot{V}}{V} = rT - a\int_0^T P(t)dt, \\ 0 &= \int_0^T \frac{\dot{P}}{P} = -sT + ab\int_0^T V(t)dt, \end{aligned}$$

Hence,

$$P_m = \frac{r}{a} = \bar{P}, \quad V_m = \frac{s}{ab} = \bar{V}.$$

This means that the mean value on every trajectory is the same and equal to the positive steady state.

This agrees with the well-know ecological rule of mean values preservation.

We see that the proposed model reflects two basic ecological properties of predator-prey dynamics, that is oscillatory behaviour and mean preservation.

Now, let us consider the problem of fishermen studied by Volterra. Assume that they caught both species (prey and predators) with the same intensity c and the yield is proportional to the population size.

Then Eq. (18) coverts to the system with fishing

$$\begin{aligned} \dot{V} &= rV - aVP - cV, \\ \dot{P} &= -sP + abVP - cP. \end{aligned} \tag{20}$$

As in the case of logistic equation we need to assume $r > c$, otherwise the prey population becomes extinct, yielding extinction of predators.

If $r > c$, then we have the same predator-prey system but with different coefficients $\tilde{r} = r - c$, $\tilde{s} = s + c$.

Let us now analyse the influence of fishing on the mean of solutions.

If $(\tilde{V}_m, \tilde{P}_m)$ denotes the mean value of solution for Eq. 20, then

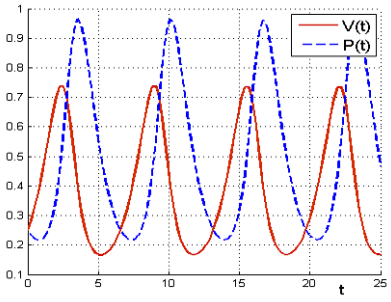
$$\tilde{V}_m = \frac{\tilde{s}}{ab} > V_m, \quad \tilde{P}_m = \frac{\tilde{r}}{a} < P_m.$$

This shows that the mean value of predator is smaller in the case of fishing, while the mean value of preys is larger.

We have got an explanation of the seeming paradox observed by fishermen after the First World War.

During the war the ecosystem tried to come back to its natural (without fishing) means. This led to increase of the predator population size.

This simple model reflects the ecological rule that fishing or hunting is always favourable for preys and unfavourable for predators. This rule is well know nowadays but was not so obvious at the beginning of XX century.



On the other hand, the model has also bad properties, both from biological and mathematical point of view.

Main criticism considers the order of oscillations of preys and predators.

Looking at the graphs of solutions we see that picks for P follow picks for V, while in nature the inverse order is typically observed.

From the mathematical point of view the bad property is structural instability. What does it mean?

The system of equations is structurally stable if the small change of the right-hand side (in the space of functions) does not influence qualitative system dynamics.

In the case of Eq. (18) even very small change of the right-hand side can lead to the change of the model dynamics, as the structure of centre is very sensitive to changes.

However, this type of structurally unstable models is not common. Typically, we will study the models which are structurally stable.

In the general case we will use two very useful theorems allowing to study global dynamics of systems in $\mathbb{R}^2$.

Poincaré - Bendixson Theorem Given a differentiable real dynamical system defined on an open subset of the plane, then every non-empty compact ω-limit set of an orbit, which contains only finitely many fixed points, is either: – a fixed point,

– a periodic orbit, or

– a connected set composed of a finite number of fixed points together with homoclinic and heteroclinic orbits connecting these.

Moreover, there is at most one orbit connecting different fixed points in the same direction. However, there could be countably many homoclinic orbits connecting one fixed point.

A homoclinic orbit is a trajectory of a flow of a dynamical system which joins a saddle equilibrium point to itself. More precisely, a homoclinic orbit lies in the intersection of the stable manifold and the unstable manifold of an equilibrium.

A heteroclinic orbit (sometimes called a heteroclinic connection) is a path in phase space which joins two different equilibrium points.

Dulac - Bendixson Criterion Given a differentiable real dynamical system, let $\mathcal{D} \subset \mathbb{R}^2$ be a simple connected region and assume that there exist a function $B : \mathbb{R}^2 \to \mathbb{R}$

continuously differentiable in $\mathcal{D}$ which does not change its sign and

$$\frac{\partial(BF_1)}{\partial x_1} + \frac{\partial(BF_2)}{\partial x_2} \not\equiv 0,$$

where $F = (F_1, F_2)$ denotes the right-hand side of the system, then there is no closed orbit in $\mathcal{D}$.

Typically, for bi-linear systems defined in $(\mathbb{R}^+)^2$ the function $B(x_1, x_2) = \frac{1}{x_1 x_2}$ can be used.

Lecture V:
Prey-predator model with carrying capacity for preys. Competition and mutualism.

Now, we describe some change in classic Lotka-Volterra model which leads to the model being structurally stable.

Recall that in the classic model the underlying dynamics for prey species is Malthusian.

As it was discussed for single population dynamics models, there are natural bounds on the growth of the species in real environments.

Therefore, it seems to be more reasonable to assume the logistic growth for preys.

This yields the following system of equations

$$\begin{aligned} \dot{V} &= rV\left(1-\tfrac{V}{K}\right) - aVP, \\ \dot{P} &= -sP + abVP, \end{aligned} \tag{21}$$

where $V(t)$ and $P(t)$ reflect the size of prey and predator populations, respectively, $r > 0$ and $s > 0$ describe the growth rate of preys and the death rate of predators, K is the prey carrying capacity, a measures effectiveness of hunting and b is the biomass conversion rate.

Eq. (21) is known as predator-prey model with carrying capacity for preys. Notice, that if K is large, then the right-hand side of Eq. (21) differs little from the right-hand side of the classic Lotka-Volterra model. Moreover, when $K \to \infty$, we obtain this classic model in the limit, as V is bounded (we will show it below).

Turning to the model analysis, we will not do it so precisely as before.

Clearly, existence, uniqueness, non-negativity and prolongation for all $t > 0$ can be shown exactly as before, for the classic model.

Notice, that for $P = 0$ we have the logistic equation for preys, meaning that in the horizontal axis in the phase plane $(\mathbb{R}^+)^2$ there is a steady state, namely $(K, 0)$, and this state attracts solutions with initial data $(V_0, 0)$, $V_0 > 0$.

In the vertical axis the behaviour of solutions is the same as for the classic model, that is for the initial data $(0, P_0)$ the solution $(0, P(t)) \to (0, 0)$.

Moreover, the dynamics in both axes shows that $(0, 0)$ is a saddle.

As solutions are positive for positive initial data, we have

$$\dot{V} < rV\left(1-\frac{V}{K}\right) \quad \Longrightarrow \quad V(t) <= V_M := \max\{V_0, K\}.$$

Therefore, we can restrict our analysis for $V <= K$ as if $V > K$, then V decreases.

We easily see that the null-cline for P is defined as for the classic model:

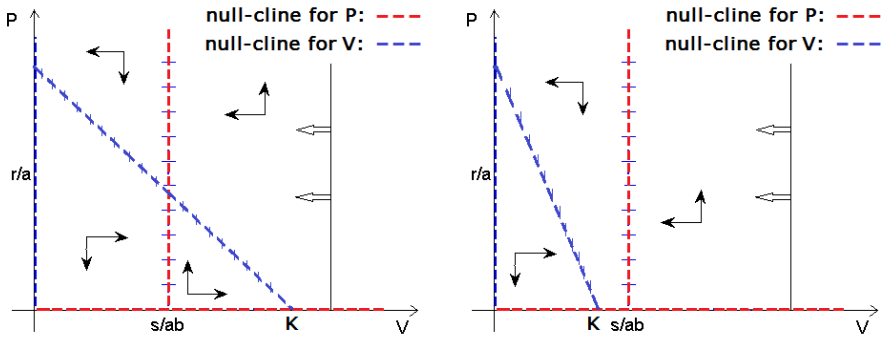
$$\dot{P} = 0 \quad \Longleftrightarrow \quad P = 0 \text{ or } V = \frac{s}{ab},$$

while for V we have

$$\dot{V} = 0 \quad \Longleftrightarrow \quad V = 0 \text{ or } P = \frac{r}{a}\left(1-\frac{V}{K}\right).$$

The dynamics inside $(\mathbb{R}^+)^2$ depends on the magnitude of K.

- If $K > \frac{s}{ab}$, then there exists a positive steady state.
- If $K <= \frac{s}{ab}$, then there are only steady states lying on the axis.



Notice, that any orbit is bounded. Clearly, V is bounded. If P is unbounded, then it must remain in the region $V > \frac{s}{ab}$. However, both variables are monotonic in this region, and therefore $V \to g >= \frac{s}{ab}$ and $P \to \infty$.

This implies that for any $L > 0$ there exists $\bar{t} > 0$ such that for $t > \bar{t}$ we have

$$\dot{V} < V(r - aP) < -LV \quad \Longrightarrow \quad V(t) <= V(\bar{t})\,\mathrm{e}^{-Lt} \quad \Longrightarrow \quad V(t) \to 0,$$

which contradicts the assumption on g.

As solutions are bounded, Poincaré-Bendixson Theorem yields the specific form of them.

- There is no homoclinic orbit, as the axes are the stable and unstable manifold for $(0, 0)$.
- There is one heteroclinic orbit in the horizontal axis, which joins $(0, 0)$ and $(K, 0)$.
- If there is no positive steady state, then every solution with positive initial data tends to $(K, 0)$.
- If there exists the positive steady state $(\bar{V}, \bar{P})$ with $\bar{V} = \frac{s}{ab}$, then all solutions with positive initial data encircle this positive steady state.

If the positive steady state exists, we can use either the Lyapunov function proposed for the classic model or Dulac-Bendixson Criterion to show global stability of $(\bar{V}, \bar{P})$.

Let us use $B(V, P) = \frac{1}{VP}$ in DB Criterion.

$$\frac{\partial BF_1}{\partial V} + \frac{\partial BF_2}{\partial P} = \frac{\partial}{\partial V}\left(\frac{r}{P}\left(1 - \frac{V}{K} - a\right)\right) + \frac{\partial}{\partial P}\left(-\frac{s}{V} + ab\right) = -\frac{r}{KP} < 0,$$

and therefore there is no closed orbit inside the phase space $(\mathbb{R}^+)^2$.

Corollary 1. *All solutions of Eq.* (21) *with positive initial data tend either to* $(K, 0)$ *or to* $(\bar{V}, \bar{P})$*, depending on the magnitude of* K*.*

Calculating eigenvalues we can also check that $(\bar{V}, \bar{P})$ is either a focus or a node.

Jacobi matrix for Eq. (21) reads:

$$JF(V,P) = \begin{pmatrix} -r\frac{\bar{V}}{K} & -a\bar{V} \\ ab\bar{P} & -s + ab\bar{V} \end{pmatrix}$$

where $\bar{V} = \frac{s}{ab}$ and $\bar{P} = \frac{r(abK-s)}{a^2bK}$. Hence the characteristic equation is of the form

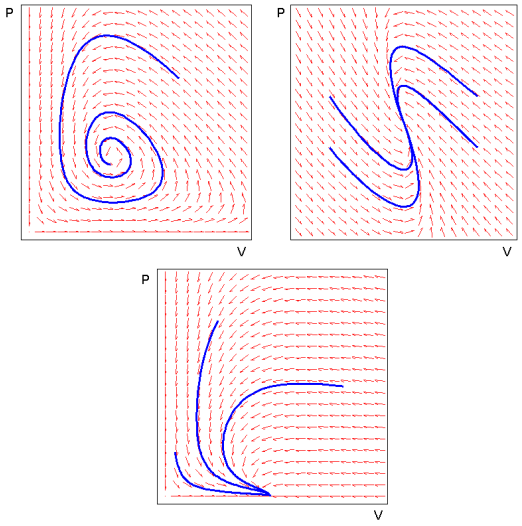
$$\lambda^2 abK + \lambda rs + rsabK - rs^2 = 0$$

with the discriminant

$$\Delta = -4a^2b^2rsK^2 + 4abrs^2K + r^2s^2$$

and we see that

- if K is sufficiently large, then $\Delta < 0$ yielding the steady state is a focus,
- if $K \to \frac{s}{ab}^+$, then $\Delta \to s^2r^2 > 0$ and the steady state is a node.



Competition model

Now, we turn to the case when there are two or more species competing for the same environmental resources as food, place for living and so on.

In the model we would like to reflect the well-know ecological principle of competitive exclusion called also Gause principle.

It states that if two species occupy the same ecological niche, then one of them should become extinct.

What does it mean? The same ecological niche means that the species have the same ecology, that is they require the same food and other nutrients, interact in the same way with other species, live in the same habitat and so on.

Therefore, we need to assume that both species have the same underlying dynamics, and due to the experience with Lotka-Volterra model, this underlying dynamics is assumed to be logistic:

$$\dot{N}_i = r_i N_i \left(1 - \frac{N_i}{K_i}\right),$$

where N_i reflects the size of species i, $i = 1, \ldots, n$, r_i is the growth rate, while K_i reflects carrying capacity for the species i and $\frac{N_i}{K_i}$ represents intraspecific competition in the per capita growth $\frac{\dot{N}_i}{N_i}$.

Assume at the beginning $n = 2$. The most straightforward way of including competitive interactions between species is to include the term of interspecific competition proportional to N_j with $j \neq i$ for the species i.

Hence, we study the system of equations

$$\begin{aligned} \dot{N}_1 &= r_1 N_1 \left(1 - \tfrac{N_1 + \beta_{12} N_2}{K_1}\right), \\ \dot{N}_2 &= r_2 N_2 \left(1 - \tfrac{N_2 + \beta_{21} N_1}{K_2}\right), \end{aligned} \tag{22}$$

where β_{ij}, $i \neq j$, is the coefficient of interspecific competition.

Notice, that the change of variables $u_i = \frac{N_i}{K_i}$ gives

$$\begin{aligned} \dot{u}_1 &= r_1 u_1 \left(1 - u_1 - \alpha_{12} u_2\right), \\ \dot{u}_2 &= r_2 u_2 \left(1 - u_2 - \alpha_{21} u_1\right), \end{aligned} \tag{23}$$

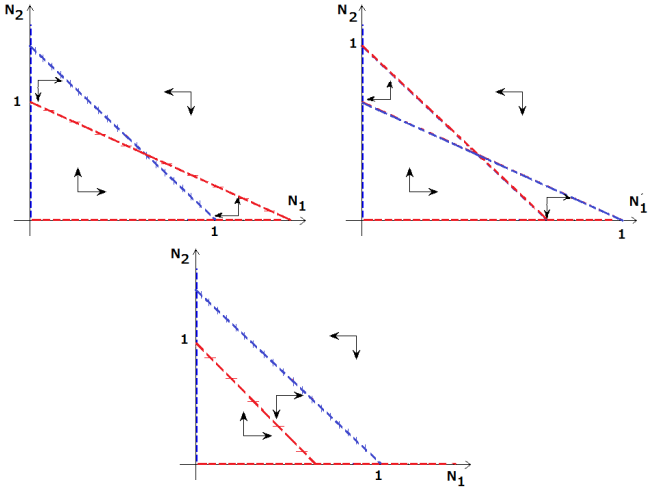
where $\alpha_{ij} = \beta_{ij} \frac{K_j}{K_i}$, and the dynamics of Eq. (23) depends on the magnitude of both coefficients α_{ij}.

Analysing Eq. (23) we easily see that existence, uniqueness, positivity and prolongation of solutions can be shown as before, as the right-hand side is bi-linear and can be approximated by the linear function.

Moreover, for both equations we have $\dot{u}_i <= r_i u_i (1 - u_i)$ which yields $u_i <= \max\{u_i(0), 1\}$.

Therefore, we can restrict our analysis to the invariant set $[0, 1]^2$ and we can use Poincaré-Bendixson Theorem.

Possible dynamics is suggested by the vector field and its null-clines:



We see that there is one case when the coexistence of both competing species is possible, in other cases only one species can stay alive.

Moreover, it is easy to see that in the co-existence case the positive steady state is globally stable in $(\mathbb{R}^+)^2$, as the direction of the vector field is such that the periodic orbit cannot occur.

In other cases one of the steady states $(1,0)$ or $(0,1)$ is either globally stable, or stable in the region over/under stable manifold of the positive steady state being a saddle in this case.

This stable manifold is then called separatrix, as it separates basins of attraction of both steady states.

The positive steady state $(\bar{u}_1, \bar{u}_2) = \left(\frac{1-\alpha_{12}}{1-\alpha_{12}\alpha_{21}}, \frac{1-\alpha_{21}}{1-\alpha_{12}\alpha_{21}}\right)$ exists if

- either $\alpha_{12} < 1$ and $\alpha_{21} < 1$,
- or $\alpha_{12} > 1$ and $\alpha_{21} > 1$.

Calculating Jacobi matrix for this state we obtain

$$\begin{pmatrix} -r_1\bar{u}_1 & -r_1\bar{u}_1\alpha_{12} \\ -r_2\bar{u}_2\alpha_{21} & -r_2\bar{u}_2 \end{pmatrix},$$

and the characteristic polynomial reads

$$W(\lambda) = \lambda^2 + (r_1\bar{u}_1 + r_2\bar{u}_2)\lambda + r_1r_2\bar{u}_1\bar{u}_2(1 - \alpha_{12}\alpha_{12}).$$

It is easy to see that if $\alpha_{ij} > 1$, then the free term of W is negative, and therefore the positive steady state is a saddle.

If $\alpha_{ij} < 1$, then $(\bar{u}_1, \bar{u}_2)$ is a stable node. Clearly, the discriminant od W reads

$$(r_1^2\bar{u}_1 - r_2\bar{u}_2)^2 + 4r_1r_2\bar{u}_1\bar{u}_2\alpha_{12}\alpha_{21} > 0$$

yielding positive eigenvalues.

To conclude

- if $\alpha_{ij} < 1$, then stable coexistence occurs;
- if $\alpha_{ij} > 1$, then the system is bistable and the winner depends on initial data,
- if $\alpha_{21} < 1 < \alpha_{12}$, then the second species is the winner, and we call it superior competitor,
- if $\alpha_{12} < 1 < \alpha_{21}$, then the first species is the winner.

Let us interpret the conditions above in terms of original model coefficients.

From the point of view of the first species it is good to minimize $\alpha_{12} = \beta_{12}\frac{K_2}{K_1}$, that is to enlarge its carrying capacity comparing to competitor.

On the other hand, there is no advantage from increasing the growth rate r_1.

Notice, that increase of K_1 can be a consequence of decrease of an individual of this species.

Hence, smaller species should be preferred in such a case.

However, for the species occupying the same ecological niche there is $\alpha_{12}\alpha_{21} = \beta_{12}\beta_{21} = 1$. Clearly, imagine two species with individual of different size eating some seeds, and

let an individual of species 1 needs 100 seeds per day, while an individual of species 2 needs 200. Then $\beta_{12} = 2$, as one individual of the second species is equivalent to two individuals of the first one, and $\beta_{21} = 0.5$, as one individual of the first species is equivalent to a half of individual of the second species. Therefore, there is always $\alpha_{ij} < 1$ and $\alpha_{ji} > 1$ in such a case, and this implies the competitive exclusion.

Mutualism

Mutualism is a type of symbiosis in which two species have benefits from co-existence. This is the inverse relation comparing to competition.

Mutualism is more common than we can expect, e.g. more than 48% of land plants rely on mycorrhizal relationships with fungi.

As we have an experience in studying bi-linear systems, the simplest way to describe two mutualistic species is to use the same framework of the logistic equation as underlying model and include mutualistic relations similarly as competition, that is we study

$$\begin{aligned} \dot{u}_1 &= r_1 u_1 \left(1 - u_1 + \alpha_{12} u_2\right), \\ \dot{u}_2 &= r_2 u_2 \left(1 - u_2 + \alpha_{21} u_1\right), \end{aligned} \tag{24}$$

where $u_i = \frac{N_i}{K_i}$ as for the competition model, while α_{ij} reflects the mutualism coefficient.

Studying the dynamics of Eq. (24) we easily show existence, uniqueness and positivity of solutions. However, prolongation for all $t > 0$ is not so obvious. In fact, for this model we can expect blow up, as for quadratic function.

The positive steady state $(\bar{u}_1, \bar{u}_2) = \left(\frac{1+\alpha_{12}}{1-\alpha_{12}\alpha_{21}}, \frac{1+\alpha_{21}}{1-\alpha_{12}\alpha_{21}}\right)$ exists only for $\alpha_{12}\alpha_{21} < 1$.

We are able to prove its global stability using the same Lyapunov function as for Lotka-Volterra model.

Let

$$L(u_1, u_2) = A\left(u_1 - \bar{u}_1 - \bar{u}_1 \ln \tfrac{u_1}{\bar{u}_1}\right) + u_1 - \bar{u}_2 - \bar{u}_2 \ln \tfrac{u_2}{\bar{u}_2},$$

with $A > 0$ to be chosen.

Calculating the derivative of L along trajectories of Eq. (24) one gets

$$\begin{aligned} \frac{d}{dt}L =& A r_1 (u_1 - \bar{u}_1)\left(1 - u_1 + \alpha_{12} u_2\right) + r_2 (u_2 - \bar{u}_2)\left(1 - u_2 + \alpha_{21} u_1\right) \\ =& A r_1 (u_1 - \bar{u}_1)\left(\bar{u}_1 - u_1 + \alpha_{12}(u_2 - \bar{u}_2)\right) + r_2 (u_2 - \bar{u}_2)\left(\bar{u}_2 - u_2 + \alpha_{21}(u_1 - \bar{u}_1)\right) \end{aligned}$$

and we see that this derivative can be written as a quadratic form of $x_1 = u_1 - \bar{u}_1$ and $x_2 = u_2 - \bar{u}_2$.

Clearly,

$$-\frac{d}{dt}L = A r_1 x_1^2 - (A r_1 \alpha_{12} + r_2 \alpha_{21}) x_1 x_2 + r_2 x_2^2,$$

and the matrix of the right-hand side reads

$$M = \begin{pmatrix} A r_1 & -\frac{A r_1 \alpha_{12} + r_2 \alpha_{21}}{2} \\ -\frac{A r_1 \alpha_{12} + r_2 \alpha_{21}}{2} & r_2 \end{pmatrix}.$$

To have this matrix positive definite we require $\det M > 0$, that is

$$A r_1 r_2 - \frac{(A r_1 \alpha_{12} + r_2 \alpha_{21})^2}{A} > 0$$

which is equivalent to the quadratic inequality

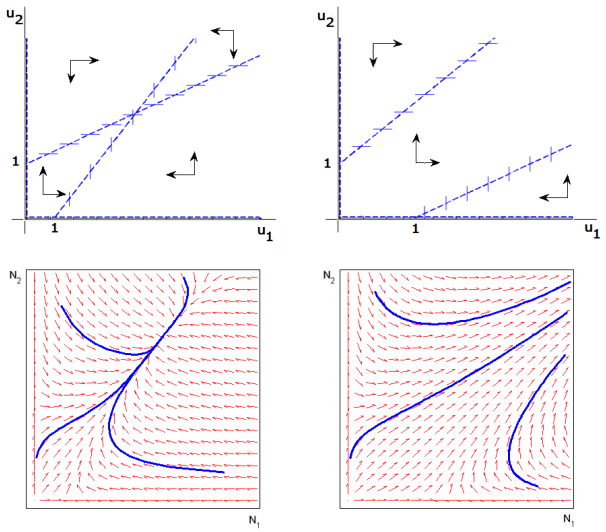
$$A^2 r_1^2 \alpha_{12}^2 - 2r_1 r_2 (2 - \alpha_{12}\alpha_{21})A + r_2^2 \alpha_{21}^2 < 0$$

with the discriminant

$$\Delta = 4r_1^2 r_2^2 (2 - \alpha_{12}\alpha_{21})^2 - 4r_1^2 r_2^2 \alpha_{12}^2 \alpha_{21}^2 = 16 r_1^2 r_2^2 (1 - \alpha_{12}\alpha_{21}) > 0.$$

Hence, there exists $A > 0$ such that M is positive definite; we can take $A = \frac{A_1 + A_2}{2}$, where A_1 and A_2 are the roots, that is

$$A = \frac{2r_2(2 - \alpha_{12}\alpha_{21})}{r_1 \alpha_{12}^2}.$$



Corollary 2. *If* $\alpha_{12}\alpha_{21} < 1$*, then the unique positive steady state of Eq.* (24) *is globally stable.*

In other cases positive impact of mutualism is so large that the size of species growths boundlessly, which is sometimes called “orgy of mutualistic licentiousness”.

It is obvious that such unbounded growth is impossible in reality and will lead to some catastrophe.

Lecture VI:
Food-chain model
Lorenz attractor

Food chain model

Next, we consider an example of three species model.

Let us assume that species 1 is a prey for species 2, while species 2 is a prey for species 3.

In such a case species 3 is called super predator.

This model belong to the class of food-chains.

Let y_0, y_1 denote N_i/K_i, $i = 0, 1$, where N_0 and N_1 are sizes of the first and second species, while K_i are their carrying capacities.

We assume that the underlying dynamics of both species is logistic. This means that although the second species is a predator for the first one, it can survive alone (that is there is another source of food not included into the model).

The model reads

$$\begin{aligned} \dot{y}_0 &= a_0 y_0(1 - y_0) - \mu_1 y_0 y_1 \,, \\ \dot{y}_1 &= a_1 y_1(1 - y_1) - \mu_2 y_1 y_2 + \eta_1 y_0 y_1 \,, \\ \dot{y}_2 &= -y_2 + \eta_2 y_1 y_2 \,, \end{aligned} \tag{25}$$

with the time scaled such the the death rate for super predator is 1. Other model coefficients have the same interpretation as before.

Notice, that existence, uniqueness, non-negativity and prolongation of solutions can be proved as for two-dimensional models discussed before.

Moreover,

$$\dot{y}_0 <= a_0 y_0(1 - y_0) \quad \Longrightarrow \quad y_0 <= y_0^{\max} := \max\{y_0(0), 1\} \,,$$

hence

$$\dot{y}_1 <= a_1 y_1(1 - y_1) + \eta_1 y_0^{\max} y_1 \quad \Longrightarrow \quad y_1 <= y_1^{\max} := \max\left\{ y_1(0), 1 + \frac{\eta_1 y_0^{\max}}{a_1} \right\},$$

and

$$\dot{y}_2 <= -y_2 + \eta_2 y_1^{\max} y_2 .$$

The last inequality implies that if $\eta_2 y_1^{\max} < 1$, then y_2 is decreasing for all $t > 0$.

It is easy to check that Eqs. (25) has from 3 up to 6 steady states.

1. The trivial steady state $A = (0, 0, 0)$ exists and is a saddle point independently of the model parameters.

2. The semi-trivial steady state $B = (0, 1, 0)$ exists independently of the model parameters and is a stable node for $a_0 < \mu_1$ and $\eta_2 < 1$. It reflects the case when the second species alive, while the first and third become extinct.

3. The semi-trivial steady state $C = (1, 0, 0)$ exists and is a saddle independently of the model parameters. It reflects ecosystem without both predators.

4. The semi-trivial steady state $D = \left(a_1 \frac{a_0-\mu_1}{a_0 a_1+\eta_1\mu_1}, a_0 \frac{a_1+\eta_1}{a_0 a_1+\eta_1\mu_1}, 0\right)$ exists for $a_0 > \mu_1$. It bifurcates at $a_0 = \mu_1$ from B and is stable (node or focus) for $\eta_2 < \frac{a_0 a_1+\eta_1\mu_1}{a_0(a_1+\eta_1)} =: \eta_2^I$. It reflects ecosystem without super predator.

5. The semi-trivial steady state $E = \left(0, \frac{1}{\eta_2}, a_1 \frac{\eta_2-1}{\eta_2\mu_2}\right)$ exists for $\eta_2 > 1$. It bifurcates at $\eta_2 = 1$ from B and is stable for $\eta_2 < \frac{\mu_1}{a_0} =: \eta_2^{II}$. We also see that if E exists, then D is unstable.

6. The positive steady state $F = \left(\frac{a_0\eta_2-\mu_1}{a_0\eta_2}, \frac{1}{\eta_2}, \frac{a_0 a_1(\eta_2-1)+\eta_1(a_0\eta_2-\mu_1)}{a_0\eta_2\mu_2}\right)$ exists and is stable for $\eta_2 > \max\left\{\eta_2^I, \eta_2^{II}\right\}$. Notice that

   - if $\eta_2^{II} > \eta_2^I \Leftrightarrow \mu_1 > a_0$, then there is no D, while E exists;
   - if $\eta_2^{II} < \eta_2^I \Leftrightarrow \mu_1 < a_0$, then either there is no E (for $\eta_2 < 1$) or both D and E exist (for $\eta_2 > 1$).

Now, we check the properties described above.

Jacobi matrix for Eqs. (25) at any point $y = (y_0, y_1, y_2)$ reads

$$MJ(y_0, y_1, y_2) = \begin{pmatrix} a_0(1-2y_0) - \mu_1 y_1 & -\mu_1 y_0 & 0 \\ \eta_1 y_1 & a_1(1-2y_1) - \mu_2 y_2 + \eta_1 y_0 & -\mu_2 y_1 \\ 0 & \eta_2 y_2 & \eta_2 y_1 - 1 \end{pmatrix}. \quad (26)$$

For the trivial steady state A we have

$$MJ(A) = \begin{pmatrix} a_0 & 0 & 0 \\ 0 & a_1 & 0 \\ 0 & 0 & -1 \end{pmatrix}$$

yielding that eigenvalues for the steady state A are equal to $\lambda_1 = a_0 > 0$, $\lambda_2 = a_1 > 0$, $\lambda_3 = -1 < 0$, and therefore A is a saddle.

For the semi-trivial steady state B we have

$$MJ(B) = \begin{pmatrix} a_0 - \mu_1 & 0 & 0 \\ \eta_1 & -a_1 & -\mu_2 \\ 0 & 0 & \eta_2 - 1 \end{pmatrix}$$

implying the characteristic quasi-polynomial reads

$$W_B(\lambda) = (a_0 - \mu_1 - \lambda)(a_1 + \lambda)(1 - \eta_2 + \lambda).$$

Therefore, this state is stable for $\eta_2 < 1$ and $a_0 < \mu_1$. On the other hand, if $\eta_2 > 1$ or $a_0 > \mu_1$, then B is a saddle.

For the next semi-trivial state D the characteristic matrix reads

$$MJ(D) = \begin{pmatrix} -a_0 y_0^D & -\mu_1 y_0^D & 0 \\ \eta_1 y_1^D & -a_1 y_1^D & -\mu_2 y_1^D \\ 0 & 0 & \eta_2 y_1^D - 1 \end{pmatrix},$$

where y_0^D and y_1^D are positive coordinates of D. This yields the characteristic quasi-polynomial of the form

$$W_D(\lambda) = \left(\eta_2 y_1^D - 1 - \lambda\right)\left(\lambda^2 + \alpha\lambda + \beta\right),$$

where $\alpha = a_0 y_0^D + a_1 y_1^D > 0$ and $\beta = (a_0 a_1 + \mu_1\eta_1)\, y_0^D y_1^D > 0$.

It is easy to see that the quadratic term has no influence on the stability.

Hence, D is stable for $\eta_2 < \eta_2^I$.

For E we have

$$MJ(E) = \begin{pmatrix} a_0 - \mu_1 y_1^E & 0 & 0 \\ \eta_1 y_1^E & -a_1 y_1^E & -\mu_2 y_1^E \\ 0 & \eta_2 y_2^E & 0 \end{pmatrix},$$

and hence

$$W_E(\lambda) = \left(a_0 - \frac{\mu_1}{\eta_2} - \lambda\right)\left(\lambda^2 + \frac{a_1}{\eta_2}\lambda + \frac{a_1(\eta_2 - 1)}{\eta_2}\right).$$

Because E exists for $\eta_2 > 1$, the quadratic term has no influence, again.

Therefore, E is stable for $\eta_2 < \eta_2^{II}$.

For the positive steady state F we have

$$MJ(F) = \begin{pmatrix} -a_0 y_0^F & -\mu_1 y_0^F & 0 \\ \eta_1 y_1^F & -a_1 y_1^F & -\mu_2 y_1^F \\ 0 & \eta_2 y_2^F & 0 \end{pmatrix},$$

and we can check that F is stable whenever exists.

Now, we turn to the global stability analysis.

Assume that F exists and define

$$L(y_0, y_1, y_2) = \sum_{i=0}^{2} A_i \left(y_i - y_i^F - y_i^F \ln \frac{y_i}{y_i^F}\right).$$

Calculating derivative along solutions of Eq. (25) we obtain

$$\begin{aligned} \frac{d}{dt} L(y_0, y_1, y_2) = {} & A_0(y_0 - y_0^F)\,(a_0(1 - y_0) - \mu_1 y_1) \\ & + A_1(y_1 - y_1^F)\,(a_1(1 - y_1) - \mu_2 y_2 + \eta_1 y_0) \\ & + A_2(y_2 - y_2^F)\,(\eta_2 y_1 - 1)\,. \end{aligned}$$

Because $a_0(1 - y_0^F) - \mu_1 y_1^F = 0$, $a_1(1 - y_1^F) - \mu_2 y_2^F + \eta_1 y_0^F = 0$ and $\eta_2 y_1^F - 1 = 0$, we can rewrite this derivative as

$$\begin{aligned} \frac{d}{dt} L(y_0, y_1, y_2) = {} & A_0(y_0 - y_0^F)\left(-a_0(y_0 - y_0^F) - \mu_1(y_1 - y_1^F)\right) \\ & + A_1(y_1 - y_1^F)\left(-a_1(y_1 - y_1^F) - \mu_2(y_2 - y_2^F) + \eta_1(y_0 - y_0^F)\right) \\ & + A_2(y_2 - y_2^F)\eta_2(y_1 - y_1^F). \end{aligned}$$

We need to have this derivative at least non-positive definite. Choosing

$$A_2\eta_2 = A_1\mu_2, \quad A_0\mu_1 = A_1\eta_1 \quad \Longrightarrow A_2 = \frac{1}{\eta_2}, \quad A_1 = \frac{1}{\mu_2}, \quad A_0 = \frac{\eta_1}{\mu_1\mu_2}$$

we obtain

$$\frac{d}{dt}L(y_0,y_1,y_2) = -\left(A_0a_0(y_0-y_0^F)^2 + A_1a_1(y_1-y_1^F)^2\right),$$

and therefore the derivative is non-positive, implying global stability of F.

To obtain global asymptotic stability we need something more.

We have $\frac{d}{dt}L(y_0,y_1,y_2) = 0$ for every $(y_0,y_1,y_2) = (0,0,y_2)$. Let the point $(0,0,y_2(\bar{t}))$ lies on the trajectory of Eq. (25) for some $\bar{t} > 0$. Then calculating the second derivative we obtain

$$\begin{aligned}\frac{d^2}{dt^2}L(y_0,y_1,y_2)\Big|_{(0,0,y_2(\bar{t}))} &= -2\Big(A_0a_0(y_0-y_0^F)\left(a_0y_0(1-y_0)-\mu_1y_0y_1\right)\\ &\quad + A_1a_1(y_1-y_1^F)\left(a_1y_1(1-y_1)-\mu_2y_1y_2+\eta_1y_0y_1\right)\Big)\Big|_{(0,0,y_2(\bar{t}))} = 0.\end{aligned}$$

The next derivative can be calculated as

$$\frac{d^3}{dt^3}L(y_0,y_1,y_2)\Big|_{(0,0,y_2(\bar{t}))} = -\mu_2^2(y_1^F)^2y_2^2(\bar{t}) < 0.$$

This shows that it is a point of inflection. Hence, L is strictly decreasing, and therefore F is globally asymptotically stable.

It occurs that if F does not exists, then one of the semi-trivial steady states is globally stable.

Assume that there is no F but E exists and define

$$\bar{L}(y_0,y_1,y_2) = B_0y_0 + \sum_{i=1}^{2} B_i\left(y_i - y_i^E - y_i^E\ln\frac{y_i}{y_i^E}\right).$$

Calculating derivative along solutions we obtain

$$\begin{aligned}\frac{d}{dt}\bar{L}(y_0,y_1,y_2) &= B_0y_0\left(a_0(1-y_0)-\mu_1y_1\right)\\ &\quad + B_1(y_1-y_1^E)\left(a_1(1-y_1)-\mu_2y_2+\eta_1y_0\right)\\ &\quad + B_2(y_2-y_2^E)\left(\eta_2y_1-1\right)\\ &= -B_0\left(\frac{\mu_1}{\eta_2}-a_0\right)y_0 - B_0a_0y_0^2 - B_1a_1y_1^2\\ &\quad - B_0\mu_1y_0y_1 + B_1\eta_1y_0y_1 - B_1\mu_2y_1y_2 + B_2\eta_2y_1y_2\end{aligned}$$

and choosing $B_0\mu_1 = B_1\eta_1$ and $B_1\mu_2 = B_2\eta_2$ we have this derivative non-positive.

Similarly to the case of F we show global asymptotic stability of E.

Next, if there is no F and E but D exists, then it is stable, while if D does not exists, then B is stable.

Appropriate Lyapunov functions can be constructed similarly as for E.

Lorenz model

In 1963 Edward Lorenz, a meteorologist at MIT, analyzed the problem of weather prediction in his article "Deterministic Nonperiodic Flow" published in Journal of the Atmospheric Sciences.

He proposed a system of ODEs basing on the Saltzman model (1962), which describes idealized thermal convection in the EarthŠs atmosphere.

Lorenz showed that for a certain range of physical parameters this simple model has very complicated behaviour and it is extremely sensitive to initial conditions.

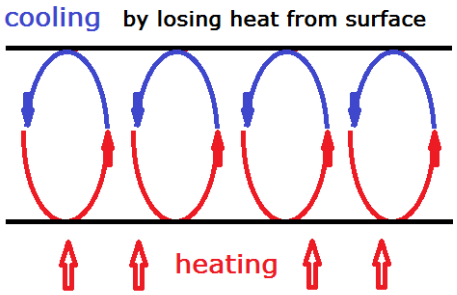
This sensitivity is considered as the foundation of chaos and led Lorenz to coin the term "butterfly effect" during his talk "Does the flap of a butterflyŠs wings in Brazil set off a tornado in Texas?"

This suggests the prediction of the future of the system is impossible.

Lorenz pointed out that if the future prediction in a simple atmospheric convection model is impossible, then long term prediction of a complicated system such as weather, would be impossible.

The physical process described by Lorenz model is a 2-D thermal convection.

Such type of convection can be represented schematically as one convective "roll" moving between two plates.



The driving force is the temperature difference between the two plates in the fluid.

No motion is observed at low temperature value.

The transfer of heat necessary to maintain the temperature difference is achieved solely by conduction of heat.

For two dimensional flow the Navier-Stokes equations can be simplified into the following two convective equations:

$$\frac{\partial}{\partial t}\nabla^2\psi = -\frac{\partial\left(\psi,\nabla^2\psi\right)}{\partial(x,z)} + \nu\nabla^4\psi + g\alpha\frac{\partial\theta}{\partial x},$$
$$\frac{\partial}{\partial t}\theta = -\frac{\partial\left(\psi,\theta\right)}{\partial(x,z)} + \frac{\Delta T}{H}\frac{\partial\psi}{\partial x} + \kappa\nabla^2\theta,$$

where:

- ψ – stream function whose components are tangent to fluid velocity vectors;
- θ – function of temperature departure (deviation from average);
- g, α, ν, κ – gravitational acceleration, buoyancy, kinematic viscosity, thermal conductivity, respectively;
- ΔT – change in temperature from top to bottom;
- H – depth of fluid cell.

In the early 20th century lord Rayleigh found the solutions to the convective equations that read

$$\psi = \psi_0 \sin\left(\frac{\pi\alpha x}{H}\right)\sin\left(\frac{\pi z}{H}\right), \quad \theta = \theta_0 \cos\left(\frac{\pi\alpha x}{H}\right)\sin\left(\frac{\pi z}{H}\right),$$

and such solutions exists when the Rayleigh number

$$R_a = \frac{g\alpha H^3 \Delta T}{\nu\kappa}$$

exceeds the critical value $R_c = \frac{\pi^4(1+a^2)^3}{a^2}$, where a is proportional to the length of the convective cell.

Mathematician and meteorologist Barry Saltzman used these solutions to formulate a complex system of differential equations for the weather model.

Using these equations Lorenz made his famous discovery on sensitivity to initial conditions.

Moreover, he noticed that over time, all but three variables tended to zero.

He introduced the terms x, y, and z in the following way:

- x is proportional to convective intensity;
- y – to the temperature difference between descending and ascending currents,
- z – to the difference in vertical temperature profile.

Lorenz formulated a simple system of three nonlinear differential equations:

$$\begin{aligned} \dot{x} &= \sigma(y - x), \\ \dot{y} &= x(r - z) - y, \\ \dot{z} &= xy - bz, \end{aligned} \tag{27}$$

where

- $\sigma = \frac{\nu}{\kappa}$ – Prandtl number (equal to 10 in Lorenz numerical analysis);
- $r = \frac{R_a}{R_c}$ – ratio of Rayleigh number (R_a) to critical Rayleigh number (R_c);
- $b = \frac{4}{1+a^2}$ – geometric constant (equal to 8/3).

Model properties

It is easy to see that solutions exists and are unique.

Eqs. (27) are symmetric with respect to x and y. Clearly, taking $-x$ and $-y$ instead of x and y we obtain the same system of equations.

The z-axis is invariant with respect to Eqs. (27). Moreover, $z \to 0$ in this axis.

Global existence of solution is a consequence of its boundedness.

The easiest way to show boundedness is to look at the motion of the solution in phase space, (x, y, z), as the flow of a fluid, with velocity $(\dot{x}, \dot{y}, \dot{z})$.

Divergence of this flow measures how the volume of a fluid particle or parcel changes:

- positive divergence means that the fluid volume is increasing locally,
- negative divergence means that the fluid volume is shrinking locally;
- zero divergence signifies an incompressible fluid.

The divergence of the vector field $F = (F_1, F_2, F_3)$ is defined by

$$\mathrm{div}F = \frac{\partial F_1}{\partial x} + \frac{\partial F_2}{\partial y} + \frac{\partial F_3}{\partial z}.$$

For Eqs. (27) let F denote the right-hand side, and the divergence reads

$$\mathrm{div}F = \frac{\partial}{\partial x}(\sigma(y-x)) + \frac{\partial}{\partial y}(x(r-z)-y) + \frac{\partial}{\partial z}(xy - bz) = -(\sigma + 1 + b) < 0.$$

Turning to steady states, let $(\bar{x}, \bar{y}, \bar{z})$ denote a steady state.

It is obvious that we have the trivial steady state which represents non-convective state.

For the non-trivial state we have:

$$\bar{x} = \bar{y}, \quad \bar{y} = \bar{x}\,(r - \bar{z})\,, \quad \bar{x}\bar{y} = b\bar{z},$$

and therefore $r - \frac{\bar{x}^2}{b} = 1$ yielding $\bar{x} = \pm\sqrt{b(r-1)}$ and $z = r - 1$, and we see that the convective steady state exists for $r > 1$, that is if Rayleigh number exceeds the critical value.

It is obvious that we have two non-zero steady states due to symmetricity of Eqs. (27).

Linearizing Eqs. (27) around the trivial steady state we obtain:

$$\begin{aligned}\dot{x} &= \sigma(y - x),\\ \dot{y} &= rx - y,\\ \dot{z} &= -bz,\end{aligned}$$

with the Jacobi matrix

$$\begin{pmatrix} -\sigma & \sigma & 0\\ r & -1 & 0\\ 0 & 0 & -b\end{pmatrix},$$

implying that eigenvalues satisfy $\lambda_3 = -b$ and $\lambda^2 + (\sigma + 1)\lambda + \sigma(1 - r) = 0$ and we easily see that for $r < 1$ this state is stable, while for $r > 1$ is unstable.

For non-trivial steady states the Jacobi matrix reads

$$\begin{pmatrix} -\sigma & \sigma & 0\\ r - \bar{z} & -1 & -\bar{x}\\ \bar{y} & \bar{x} & -b\end{pmatrix},$$

and the characteristic equation has the form

$$\lambda^3 + (\sigma + b + 1)\lambda^2 - (\sigma r - b - \sigma b + \bar{x}^2 - \sigma - \sigma\bar{z})\lambda - (-\sigma b + \bar{x}\bar{y}\sigma + \sigma r b + \sigma\bar{x}^2 - \sigma\bar{z}b) = 0,$$

and because $\bar{x}^2 = \bar{x}\bar{y} = b(r-1)$ and $\bar{z} = r - 1$, we obtain

$$\lambda^3 + (\sigma + b + 1)\lambda^2 - (-\sigma b + br - 2b)\lambda - 2b(r-1)\sigma = 0,$$

and whenever $r > 1$ these states are unstable.

Hence, for $r > 1$ all three steady states are unstable!

Now, to check global behaviour of Eqs. (27), we use the property called dissipativity of the system.

We say that the system (of n equations) is dissipative if there exists a function $W : \mathbb{R}^n \to \mathbb{R}^+$ such that the derivative of W along the trajectories of the system satisfies the inequality

$$\frac{d}{dt}W(x_1, x_2, \ldots, x_n) <= A - \delta W,$$

for some positive constants A and δ.

It is known that if the system is dissipative, then there exists compact global attractor.

For Eqs. (27) we can define

$$W(x, y, z) = \frac{1}{2}\left((x)^2 + y^2 + (z - \sigma - r)^2\right)$$

and calculating the derivative along trajectories we obtain:

$$\begin{aligned}\frac{d}{dt}W(x, y, z) &= \sigma x(y - x) + y(x(r - z) - y) + (z - \sigma - r)(xy - bz) \\ &= -\sigma x^2 - y^2 - \frac{b}{2}(z - \sigma - r)^2 + \frac{b}{2}(\sigma + r)^2 - \frac{b}{2}z^2.\end{aligned}$$

Choosing $A = \frac{b}{2}(\sigma + r)^2$ and $\delta = \min\{2\sigma, 2, b\}$ we get

$$\frac{d}{dt}W(x, y, z) <= A - \delta W,$$

which yields dissipativity of Eqs. (27).

This means that for every parameter values the system has a global attractor.

But this attractor can have a complicated structure.

Consider the sphere $R_0 = \{(x, y, z) : (x)^2 + y^2 + (z - \sigma - r)^2 <= c^2\}$ for sufficiently large c.

If the ellipsoid $\left\{(x, y, z) : \sigma x^2 + y^2 + b\left(z - \frac{\sigma}{2} - \frac{r}{2}\right)^2 = b\left(\frac{\sigma}{2} + \frac{r}{2}\right)^2\right\}$ lies inside the sphere R_0, then the left-hand side of Eqs (27) is negative.

Therefore, R_0 is an invariant set for our system.

Moreover, on the boundary of R_0 the right-hand side of Eqs. (27) is negative. If we consider the discrete dynamical system generated by $X(n)$, where $X = (x, y, z)$, $n \in \mathbb{N}$, then $R_1 = X(1)(R_0)$ is the smaller set, than original R_0, and so on.

Let V_n denotes the volume of R_n.

Then $V_n = \exp(-n(\sigma + 1 + b))\, V_0$.

It is obvious that the volume of the limit set is equal to 0.

This limit set is called the strange Lorenz attractor.

Lecture VII: Biochemical reactions

Biochemical kinetics describes concentrations of chemical substances in biological systems as functions of time.

Such processes are often controlled by enzymes.

Enzymes are present in very low concentrations, but have a large effect on the final result.

Therefore, chemical reactions may take place on very different time scales.

One of the methods that can give good approximations to the solution is the method of asymptotic expansions.

Michaelis-Menten kinetics

Now, we give the simplest example of such a system, called Michaelis-Menten kinetics.

Modelling of biochemical reactions is based on the law of mass action.

It states that if chemical A reacts with chemical B to produce chemical C, then the rate of reaction is given by kAB, where A and B are concentrations of chemicals A and B.

Such reaction is typically described diagrammatically in the following way

$$\mathrm{A} + \mathrm{B} \xrightarrow{k} \mathrm{C}$$

According to the lwa of mass action we have

$$\frac{dC}{dt} = -\frac{dA}{dt} = -\frac{dB}{dt} = kAB,$$

where k is called the rate constant or propensity of the reaction.

In fact, due to thermodynamic principles reactions can take place in both directions:

$$\mathrm{A} + \mathrm{B} \underset{k_-}{\overset{k_+}{\rightleftharpoons}} \mathrm{C}$$

Hence,

$$\frac{dC}{dt} = -\frac{dA}{dt} = -\frac{dB}{dt} = k_+AB - k_-C.$$

Let us consider a reaction catalysed by an enzyme.

Enzymes are proteins, crucial in biochemistry, that catalyse a biochemical reaction by lowering the activation energy.

Enzymes are specific to substrates and catalyse their conversion to a product.

They are unchanged by the reaction.

In the simplest Michaelis-Menten kinetics, they accomplish this in two steps:

- first forming a complex with the substrate,
- then breaks down to the product and the enzyme.

This reaction reads

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

because the back reaction $P + E \to C$ is so slow, that we neglect it.

The system of equations reflecting this channel has the form

$$\begin{aligned} \frac{dS}{dt} &= k_{-1}C - k_1 S E, \\ \frac{dE}{dt} &= (k_{-1} + k_2)\, C - k_1 S E, \\ \frac{dC}{dt} &= k_1 S E - (k_{-1} + k_2)\, C, \\ \frac{dP}{dt} &= k_2 C. \end{aligned} \tag{28}$$

It is obvious that $\frac{d}{dt}(E + C) = 0$, yielding

$$E + C = E_0 = \text{const}.$$

E_0 is the total amount of enzyme, free and bound, and is conserved, obviously, as the enzyme is only a catalyst of the reaction.

There is also another conservation equation $\frac{d}{dt}(S + C + P) = 0$, and therefore

$$S + C + P = S_0,$$

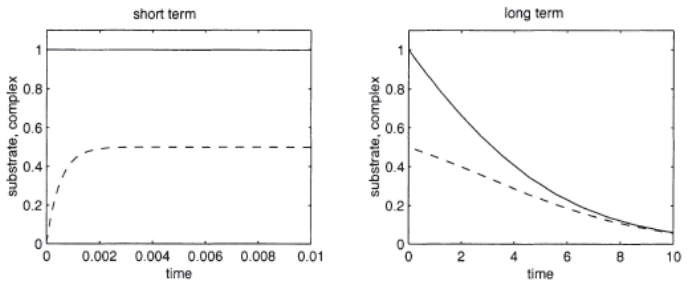
as substrate appears in its original form, or bound to the enzyme, or converted to its product.

Finally, we have

$$\begin{aligned} \frac{dS}{dt} &= k_{-1}C - k_1 S E, \\ \frac{dC}{dt} &= k_1 S E - (k_{-1} + k_2)\, C, \\ E &= E_0 - C, \\ P &= S_0 - S - C. \end{aligned}$$

Initial conditions typically reflect the situation where free enzyme is added to its substrate:

$$S(0) = S_0, \quad E(0) = E_0, \quad C(0) = 0, \quad P(0) = 0.$$



We see that for typical solution there are two distinct parts:

- first the concentration of the complex increases quickly, while the substrate concentration remains almost unchanged, then both concentrations change on a much slower time scale as the substrate is converted to the product by the enzyme;
- the second part is where all the action is (in terms of converting substrate to product), and it may be analysed using the approximation $\frac{dC}{dt} \approx 0$.

This approximation is called the quasi-steady-state hypothesis.

We obtain $k_1 S\,(E_0 - C) = (k_{-1} + k_2)\,C$, and therefore

$$C = \frac{k_1 S\, E_0}{k_{-1} + k_2 + k_1 S} = \frac{S\, E_0}{K_m + S},$$

and

$$\frac{dS}{dt} = -k_2 C = -\frac{V_m S}{K_m + S}, \tag{29}$$

where $V_m = k_2 E_0$ and $K_m = \frac{k_{-1}+k_2}{k_1}$ is the Michaelis constant.

Eq. (29) is an equation with separated variables

$$\int_{S_0}^{S(t)} \frac{K_m + S}{S}\, dS = -V_m \int_0^t dt \quad \Longrightarrow \quad K_m \ln \frac{S(t)}{S_0} + S(t) - S_0 = -V_m t.$$

However, this solution is not informative, as we are not able to write explicit formula on $S(t)$.

The fraction of binding sites on the enzyme that are occupied can be calculated as

$$Y(S) = \frac{C}{E + C} = \frac{C}{E_0} = \frac{S}{K_m + S}.$$

The function $Y(S)$ is the saturation function – half of the site is occupied for $S = K_m$.

From biological point of view it is important to know the overall velocity V of the reaction.

This is the rate at which product is formed.

Using this approximation this rate is the same as the rate at which substrate is consumed.

Hence,

$$V = \frac{dP}{dt} = V_m Y(S) = \frac{V_m S}{K_m + S}. \tag{30}$$

Eq. (30) is called the Michaelis-Menten rate equation.

It highlights the importance of the saturation function.

In general, similar equations can be formulated if conditions of the quasi-steady-state hypothesis holds. For example, when dimers must be formed to produce the final product, then S^2 appears instead of S in the saturation function.

The saturation function is then calculated by putting the right-hand sides of the enzyme equations equal to zero, including the enzyme conservation equation, and solving the system of algebraic equations.

What can we do in the case when we are not sure about the quasi-steady-state hypothesis?

The intuition of this hypothesis is based on the observation that there are two time scales in the system – a fast and a slow time scale.

This suggests to apply the method of asymptotic expansions.

We can obtain expressions for each time scale, and then match them smoothly together.

To precise the notion of fast and slow time scales one needs to make undimensionalisation of the system first.

Let

$$s = \frac{S}{S_0}, \quad c = \frac{C}{E_0}, \quad e = \frac{E}{E_0}, \quad p = \frac{P}{S_0}, \quad \tau = k_1 E_0 t.$$

The choice of undimensionalisation for the chemical concentrations is rather obvious.

The undimensionalisation for t depends on a careful examination of the equations to determine possible time scales.

Looking at the first equation of Eq. (28) we see that the maximal rate at which S may be taken up for $C = 0$ equals $k_1 E_0$.

Looking at the second equation of Eq. (28) we see that the maximal rate at which E may be taken up for $C = 0$ equals is $k_1 S_0$.

Both these time scales are important.

Let us choose the first one called the outer time scale.

Our equations now read

$$\begin{aligned} \frac{ds}{d\tau} &= k_e c - s(1-c), \\ \varepsilon \frac{dc}{d\tau} &= s(1-c) - k_m c, \end{aligned} \tag{31}$$

where

$$\varepsilon = \frac{E_0}{S_0}, \quad k_e = \frac{k-1}{k_1 S_0} = \frac{K_e}{S_0}, \quad k_m = \frac{k_{-1} + k_2}{k_1 S_0} = \frac{K_m}{S_0}.$$

Here the constant $K_e = \frac{k_{-1}}{k_1}$ is the equilibrium constant between S and E, k_e is its non-dimensional version, while k_m is a non-dimensional version of the Michaelis constant K_m.

Initial conditions are

$$s(0) = 1, \quad e(0) = 0.$$

Typically, $\varepsilon << 1$ and we can try to solve this problem by looking for s and c as power series:

$$s(\tau) = \sum_{n=0}^{\infty} \varepsilon^n s_n(\tau), \quad c(\tau) = \sum_{n=0}^{\infty} \varepsilon^n c_n(\tau).$$

Using these expansions we obtain equations for the leading order in the following form

$$\begin{aligned} \frac{ds_0}{d\tau} &= k_e c_0 - s_0(1-c_0), \\ 0 &= s_0(1-c_0) - k_m c_0, \end{aligned}$$

yielding

$$\frac{ds_0}{d\tau} = -\frac{ks_0}{k_m + s_0}, \quad c_0 = \frac{s_0}{k_m + s_0},$$

with $s_0(0) = 1$, $c_0(0) = 0$, $k = k_m - k_e$.

Integrating the first equation we obtain

$$k_m \ln s_0 + s_0 = A - kt \tag{32}$$

with A being an integration constant.

Higher order corrections may easily be found.

However, we see that there is a problem with the solution we have got.

Choosing $A = 1$, for which the initial condition for s is satisfied, we obtain the initial value of c_0 equal to $\frac{1}{k_m+1}$, so the initial condition for c is not satisfied.

This problem comes from the implicit assumption that s and c are analytic functions of ε – which we need to assume for proposed power series.

However, this is not true, as the original problem (the system of differential equations) is quite different from the resulting problem which consists of a single differential equation and an algebraic equation.

Clearly, we cannot expect to satisfy two initial conditions with only one differential equation.

This is called a singular perturbation problem.

What can we do with this problem?

We use the method of matched asymptotic expansions.

Notice, that better approximations may be found by using higher order expansions.

To leading order Eq. (32) with $c_0 = \frac{s_0}{k_m+s_0}$ defines a solution of the problem P_ε, which is good except:

- it does not satisfy the initial conditions – so is not valid near $\tau = 0$,
- it contains an unknown constant of integration A.

Let us call it the outer solution.

Now, near $\tau = 0$ we need to find another solution, called the inner solution, to satisfy the initial conditions.

Moreover, we require that these solutions match together smoothly.

Therefore, they satisfy some matching conditions, which will determine the constant of integration.

We define a new independent (time) variable T and dependent variables S and C (not to be confused with the original dimensional variables) in the following way

$$T = \frac{\tau}{\varepsilon}, \quad S(T) = s(\tau), \quad C(T) = c(\tau)$$

and obtain the system of equations

$$\frac{dS}{dT} = \varepsilon(k_w C - S(1 - C)),$$
$$\frac{dC}{dT} = S(1 - C) - k_m C,$$

with initial data $S(0) = 1, C(0) = 0$.

Now, expanding S and C as power series we obtain the leading order approximation that reads

$$S_0(T) = 1, \quad C_0(T) = \frac{1}{1+k_m}\left(1 - \mathrm{e}^{-(1+k_m)T}\right).$$

We see that

$$\lim_{T\to\infty}(S_0(T), C_0(T)) = \left(1, \frac{1}{1+k_m}\right).$$

As we need to match the two forms of solutions, it is necessary to assume that the common apart of both solution is equal, that is

$$\lim_{\tau\to 0}(s_0(\tau), c_0(\tau)) = \lim_{T\to\infty}(S_0(T), C_0(T)).$$

The conditions above are called the matching conditions.

They are satisfied for $A = 1$.

The condition $\varepsilon << 1$ is crucial in the method.

It is equivalent to the quasi-steady-state hypothesis, the requirement that after an initial short time period the right-hand side of the equation describing C can be neglected.

It is very often satisfied because enzymes are so efficient that they need to be present in very small concentrations, that is $E_0 << S_0$.

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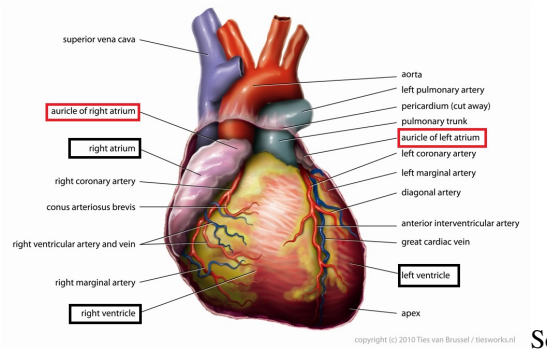
Lecture VIII: Zeeman model for the heartbeat

Human heart is a four chamber organ:

- the two upper chambers are called the left atrium and the right atrium;
- the two lower chambers are called the right and the left ventricle.



Scheme of heart from Wikipedia

It works as a pump.

Normally with each heartbeat, the right ventricle pumps the same amount of blood into the lungs that the left ventricle pumps out into the body.

During the lecture we will describe simple models of the heart beat, starting from the linear description and ending with the Zeeman model which involves a dynamics called cusp catastrophe.

In the simplification we use for the model description, heart is a chamber being either in a systole or diastole (called also relaxation of the heart).

We will use two variables of time describing the heart beat:

- x – measures the myocardial fiber length (the length of fiber of the heart muscles)
- b – measures the electrochemical stimulus.

Physically b can be measured as the difference between potential on the membrane surrounding the fiber and the interior potential of the fiber.

If the heart is in diastole, then electrochemical stimulus causes myocardial contraction.

The process is slow at the beginning and leads to pumping of blood from the atria to the ventricles.

Next this process rapidly accelerates leading to systole and pumping of blood from the ventricles to arteries.

The revers process is similar.

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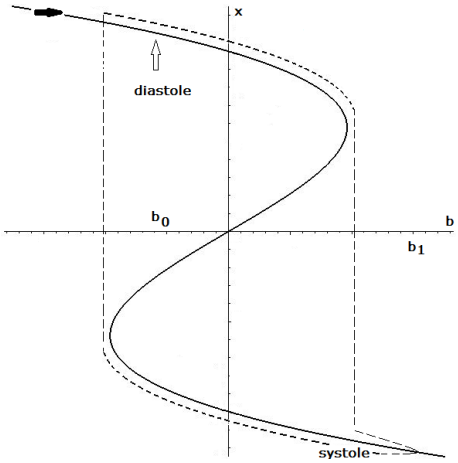


In general, the model is described by some system of differential equations

$$\begin{aligned} \dot{b} &= g(b, x), \\ \dot{x} &= f(b, x), \end{aligned} \tag{33}$$

and we assume that f and g are sufficiently smooth.

To describe the heart beat the model should satisfies the following hypotheses.

- (W1) It should have a stable equilibrium reflecting diastole, to which the system comes back periodically.
- (W2) There should exists some threshold of the stimulus exceeding which causes rapid systole.
- (W3) After the action of stimulus the system should come back to equilibrium.

According to (W1) there should be some point (b_0, x_0) such that

$$f(b_0, x_0) = g(b_0, x_0) = 0.$$

Linearizing Eqs. (33) around this point one gets

$$\begin{aligned} \dot{y}_1 &= y_1 \frac{\partial g}{\partial b}(b_0, x_0) + y_2 \frac{\partial g}{\partial x}(b_0, x_0), \\ \dot{y}_2 &= y_1 \frac{\partial f}{\partial b}(b_0, x_0) + y_2 \frac{\partial f}{\partial x}(b_0, x_0), \end{aligned}$$

where $y_1 = b - b_0$ and $y_2 = x - x_0$ are the deviations from the equilibrium.

Let

$$J = \begin{pmatrix} \frac{\partial g}{\partial b}(b_0, x_0) & \frac{\partial g}{\partial x}(b_0, x_0) \\ \frac{\partial f}{\partial b}(b_0, x_0) & \frac{\partial f}{\partial x}(b_0, x_0) \end{pmatrix}$$

be the matrix of this system.

According to the hypothesis that the equilibrium is stable, we require

$$\det J > 0 \quad \text{and} \quad \operatorname{tr} J < 0$$

Of course, to describe the heart beat, it is not enough to assume these inequalities.

Let us pose more hypotheses.

- (W4) The rate of change of electrochemical stimulus in time is proportional to the deviation of myocardial fiber length.
- (W5) The rate change of contraction of the cardiac muscle fiber is dependent on fiber strain and electrochemical stimulus.

According to (W5) we obtain

$$\dot{b} = x - x_0$$

(assuming the proportionality constant equal to 1).

Therefore,

$$\frac{\partial g}{\partial b}(b_0, x_0) = 0 \quad \text{and} \quad \frac{\partial g}{\partial x}(b_0, x_0) = 1,$$

and furthermore,

$$\det J = \frac{\partial g}{\partial b}(b_0, x_0)\frac{\partial f}{\partial x}(b_0, x_0) - \frac{\partial g}{\partial x}(b_0, x_0)\frac{\partial f}{\partial b}(b_0, x_0) = -\frac{\partial f}{\partial b}(b_0, x_0) \Rightarrow \frac{\partial f}{\partial b}(b_0, x_0) < 0$$

and

$$\operatorname{tr} J = \frac{\partial g}{\partial b}(b_0, x_0) + \frac{\partial f}{\partial x}(b_0, x_0) \Rightarrow \frac{\partial f}{\partial x}(b_0, x_0) < 0.$$

Now, according to (W2), as there should be rapid action of stimulus after the threshold, the absolut value $\left|\frac{\partial f}{\partial x}(b_0, x_0)\right|$ should be large.

Moreover, as the rate $\dot{b}$ is proportional to x, the absolut value $\left|\frac{\partial f}{\partial b}(b_0, x_0)\right|$ should be large as well.

This leads to some small parameter $\varepsilon > 0$ such that

$$\frac{\partial f}{\partial b}(b_0, x_0) = -\frac{1}{\varepsilon}, \quad \frac{\partial f}{\partial x}(b_0, x_0) = -\frac{a}{\varepsilon},$$

where $a > 0$ is some constant.

Eventually we have the linear system

$$\begin{aligned} \dot{b} &= x - x_0, \\ \varepsilon\dot{x} &= -(b - b_0) - a(x - x_0), \end{aligned} \tag{34}$$

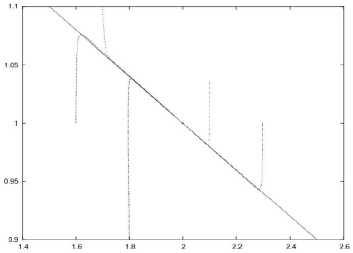
which is our first approximation of the model.

Clearly, the characteristic polynomial for Eqs. (34) takes the form

$$P(\lambda) = \lambda^2 + \frac{a}{\varepsilon}\lambda + \frac{1}{\varepsilon}$$

with the discriminant $\Delta = \frac{1}{\varepsilon}\left(\frac{a^2}{\varepsilon} - 4\right) > 0$, and as $\varepsilon << a^2$.

Hence, we have two real, negative eigenvalues and the equilibrium (b_0, x_0) forms a stable node.



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On the exemplary phase portrait we see that trajectories are almost vertical.

Our first approximation model is not able to reflect the threshold values of the stimulus, as the rate of change for linear models cannot change rapidly.

Now, we would like to include the threshold value of the stimulus to our model.

The idea is based on the van der Pol system

$$\begin{aligned} \dot{b} &= x, \\ \varepsilon \dot{x} &= -(x^3 - x + b), \end{aligned} \tag{35}$$

where the original van der Pol equation was devised as a model in the electronic circuit theory and is a prototype of the nonlinear oscillator.

However, the original system (35) has another disadvantage, that the only equilibrium $(0, 0)$ is obviously unstable.

Zeeman proposed a modification, which combines the idea of Eqs. (34) and (35):

$$\begin{aligned} \dot{b} &= x - x_0, \\ \varepsilon \dot{x} &= -(x^3 - x + b), \end{aligned} \tag{36}$$

and it occurs that this can lead to stabilisation of the equilibrium.

Clearly, for Eqs. (36) the equilibrium takes the form $x = x_0$ and $b = x_0 - x_0^3$. Calculating the Jacobi matrix of Eqs. (36) one gets

$$J(b, x) = \begin{pmatrix} 0 & 1 \\ -1 & -3x^2 + 1 \end{pmatrix}$$

and it is obvious, that for $x_0^2 > 1/3$ there is $\operatorname{tr} J(b_0, x_0) < -3x_0^2 + 1 < 0$, while $\det J(b_0, x_0) = 1 > 0$.

Moreover, in Eqs. (36) the threshold mechanism appears.

Clearly, if the stimulus increases from b_0 to some $b_1 > b_0$, then rapid contraction of myocardial fiber appears leading to the change from diastole to systole.

Next, as the stimulus disappears, the myocardial muscle first gently, then suddenly, returns to the equilibrium.

Succeeding change of the electrochemical potential leads to the next contraction and so on...

It occurs that this simple model can be also used in interpretation of many specific behaviours in the heart beat, both normal and pathological.

During experiments it was observed that the heart beat occurs when the myocardial muscle is subjected to a tension from blood pressure (the heart without blood does not beat).

Zeeman proposed to include the additional parameter a reflecting the effect of blood pressure.

$$\begin{aligned} \dot{b} &= x - x_0, \\ \varepsilon \dot{x} &= -(x^3 - ax + b), \end{aligned}$$

and still for $x_0 > \sqrt{\frac{a}{3}}$, $a > 0$, the system has stable equilibrium.

Moreover, the additional modification is necessary to have the possibility of switch between two different steady states.

Eventually we consider the model

$$\begin{aligned} \dot{b} &= x - x_0 + u(x_0 - x_1), \\ \varepsilon \dot{x} &= -(x^3 - ax + b), \end{aligned} \tag{37}$$

where u is the switch parameter defined in the following way.

$u = 1$ if

- $||(b, x) - (b_0, x_0)|| < \delta$;
- or $||(b, x) - (b_0, x_0)|| >= \delta$ and $b \in [b_0, b_1]$ and $x^3 - ax + b > 0$ or $b > b_1$;

otherwise $u = 0$.

It is obvious, that the dynamics of Eqs. (37) depends on a crucially:

- $a = 0$ can be interpreted as a lack of pressure (e.g. for heart bypass). Fiber contracts and relax slowly – there is no sudden contractions reflecting heart beat and blood pumping.
- $a > 0$ (small) – weak heartbeat, the atria contracts slowly, causing the return of blood to the veins via valves.
- $a > 0$ (large) – myocardial fiber contracts beyond the equilibrium sucking blood into the ventricles; with increasing pressure the time of relaxation increases, while the time of contraction decreases; the heart beats hard and fast.
- $a > \sqrt[3]{\frac{27b_1^2}{3}}$ – due to the high blood pressure the threshold causing contraction moves beyond b_1, and therefore there is no contraction and the heart does not beat.

This last case reflects so called Starling law which states that longer myocardial fiber yields stronger heart beat and this reflects the heart action during stress situation.

Stress causes the increase of the secretion of adrenaline, overflow of adrenaline causes narrowing of arteries, which leads to the increase of blood pressure and can cause cardiac arrest.

Now, we discuss the original
van der Pol model (35)
as an interesting example of the oscillatory dynamics.

Studying the phase portrait we look for null-clines first.

For b the null-cline is defined by $x = 0$, which means that whenever x is positive, b increases and vice versa.

The null-cline for x is $b = -x^3 + x$ and above this line x decreases, while increases below.

As we know, the only equilibrium $(0, 0)$ is unstable.

We would like to show that there exists a periodic orbit.

In fact, we are able to show that property for a wider class of Liénard equations that read

$$\ddot{l} + kf'(l)\dot{l} + (\omega_0)^2 l = 0. \tag{38}$$

This equation describes an electrical circuit: k – inductiveness of this circuit, ω_0 – constant reflecting a frequency of vibrations.

Liénard proved the following theorem.

Theorem 3. *Let f be of class $\mathbf{C}^1$ and satisfies:*

- *(Z1) f is an odd function;*
- *(Z2) $|f(l)| \to \infty$ as $|l| \to \infty$ and there exists $\beta > 0$ such that for $l > \beta$ the function f is positive and monotonic;*
- *(Z3) there exists $\alpha > 0$ such that $f(l) < 0$ for $0 < l < \alpha$.*

Then f has a periodic orbit. Moreover, if $\alpha = \beta$, then this orbit is unique.

Clearly, van der Pol model is an example of Liénard equation for $f(x) = x^3 - x$.

For this function $\alpha = \beta = 1$.

Now, we give the sketch of the proof of Theorem 3.

Assume $k = \omega_0 = 1$, for simplicity, and rewrite Eq. (38) in the form

$$\begin{aligned} \dot{x} &= -b - f(x), \\ \dot{b} &= x. \end{aligned} \tag{39}$$

To simplify approximations below we also assume that $\alpha = \beta$, such that we can use $f(x) = x^3 - x$ as an exemplary function.

It is obvious that Eqs. (39) have unique solution for any initial data.

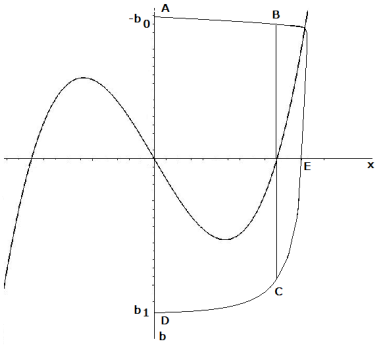
Let us take the solution $(x(t), b(t))$ starting at $(0, -b_0)$ for sufficiently large b_0.

Then both functions $x(t)$, $f(t)$ are increasing until the solution crosses the nul-cline $b = -f(x)$.

Due to (Z2), if b_0 is sufficiently large, then this cross-section appears for $x(t) > \beta$.

Now, $x(t)$ decreases, while $b(t)$ still increases.

Therefore, the solution must cross the axis at some point $(0, b_1)$.



On the other hand, from (Z1) we know that if $(x(t), b(t))$ is the solution, then $(-x(t), -b(t))$ is the solution too.

This means that the trajectory starting from $(0, -b_0)$ goes to $(0, b_1)$ through the second and first quadrant, while the trajectory starting from $(0, b_0)$ goes to $(0, b_1)$ through the fourth and third quadrant.

If $b_0 > b_1$, then the trajectory starting from $(0, b_1)$ goes to $(0, -b_2)$, such that $b_2 < b_0$, meaning that the trajectory starting from $(0, -b_0)$ is bounded.

According to the Poincaré - Bendixson Theorem we know that such trajectory must tend to a periodic orbit.

Now, it is enough to show that for sufficiently large b_0 the trajectory starting from $(0, -b_0)$ goes to the point $(0, b_1)$ such that $b_1 < b_0$.

Let us consider the auxiliary function

$$V(x, b) = \frac{1}{2}\left(x^2 + b^2\right)$$

and calculate

$$\frac{dV}{dt} = x\dot{x} + b\dot{b} = -f(x)x$$

implying

$$\frac{dV}{dx} = \frac{dV}{dt} \cdot \frac{dt}{dx} = \frac{xf(x)}{b + f(x)}, \quad \text{for} \quad b = b(x)$$

$$\frac{dV}{db} = \frac{dV}{dt} \cdot \frac{dt}{db} = -f(x), \quad \text{for} \quad x = x(b).$$

We can calculate the integral along the trajectory shown in the picture

$$\int_{ABECD} dV = V(D) - V(A)$$

using the fact that the curves AB and CD can be parametrizes by x, while BEC by b.

Hence

$$V(D) - V(A) = \int_{AB} \frac{xf(x)}{b + f(x)} dx + \int_{BEC} (-f(x))db + \int_{CD} \frac{xf(x)}{b + f(x)} dx.$$

Knowing that on AB there is $x \in [0,\beta]$ we have $|xf(x)| <= \beta \max_{[0,\beta]} |f|$.

Moreover, $|b + f(x)| <= |b| <= b_0$ on AB, as b and f have different signs.

Letting $b_0 \to \infty$ we obtain that the integrand $\frac{xf(x)}{b+f(x)} \to 0$.

Therefore,

$$\int_{AB} \frac{xf(x)}{b + f(x)} dx \to 0 \quad \text{as} \quad b_0 \to \infty.$$

If we assume that $b_1 > b_0$, then the third integral also tends to 0.

Let us denote

$$G(b_0) = \int_{BEC} (-f(x))db.$$

The function $-f(x)$ is negative along the open arch BEC, because $x > \beta$ on it. Therefore, we have

$$G(b_0) < \int_{KE} (-f(x))db,$$

where K is any point inside the arch BE.

Denote $K = (\beta + \delta, -b^*)$, with small $\delta > 0$.

As f is monotonic for $x > \beta$, we have $-f(\beta + \delta) < -c < 0$ for some $c > 0$.

Hence,

$$G(b_0) < -cb^*$$

and $b^* \to \infty$ as $b_0 \to \infty$.

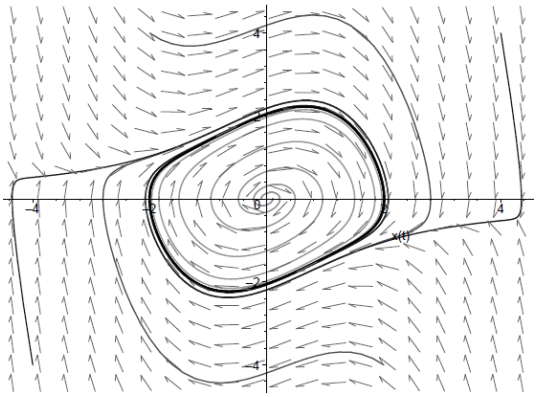
This yields $G(b_0) \to -\infty$, and therefore

$$V(D) - V(A) < 0 \quad \Longrightarrow \quad b_1 < b_0$$

for sufficiently large b_0 and this contradicts the assumption.

Therefore, $b_0 >= b_1$ and the solution is bounded.

We can also show that for $\alpha = \beta$ this orbit is unique and is asymptotically stable.



PhD STUDIES
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Catastrophe theory is a method proposed by Rene Thorn of using singularities of smooth maps to model nature.

We describe this notion on a simplest example of one-dimensional model of a pest outbreak.

There are many various kind of pests being a huge problem for forest managing all over the world.

The outbreaks typically appear regularly for several years and mean the huge number of pests in the sezon.

The model describing such population is based on the logistic equation with predation term that reads

$$\frac{dN}{ds} = r_B N\left(1 - \frac{N}{K_B}\right) - p(N), \tag{40}$$

where

- $N(s)$ reflects the pest population size at time s;
- r_B is the reproduction coefficient;
- K_B is the carrying capacity connected with the amount of available food;
- $p(N)$ is the predation function.

One of the possibility to describe predation is to use the Hill function.

Here, to include the possibility of bistability, that is the existence of two stable steady states, we use this function with the coefficient $n = 2$, that is

$$p(N) = \frac{BN^2}{A^2 + N^2},$$

where A and B are positive constants.

To make the analysis easier we change variables

$$u = \frac{N}{A}, \quad r = \frac{Ar_B}{B}, \quad k = \frac{K_B}{A}, \quad t = \frac{Bs}{A}$$

and obtain the undimensional form of the model (40)

$$\dot{u} = ru\left(1 - \frac{u}{k}\right) - \frac{u^2}{1 + u^2}. \tag{41}$$

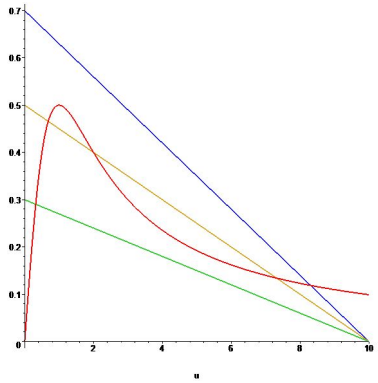
Let $f(u; r, k)$ denote the right-hand side of Eq. 41

Notice that f depends on two parameters r and k.

Looking for positive steady states we obtain the relation

$$r\left(1 - \frac{u}{k}\right) = \frac{u}{1 + u^2}$$

and keeping constant k while increasing r we can obtain one, three and again one positive steady state.

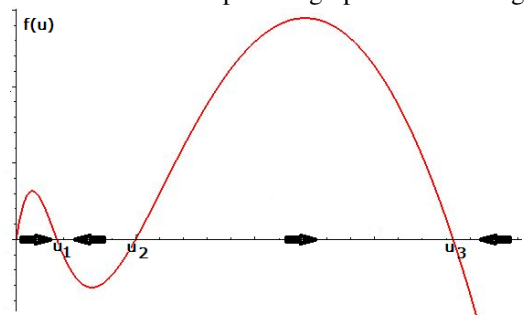


There are also two threshold values for which two positive steady states exist.

The same picture can be obtained keeping constant r and changing k.

It is easy to check that whenever three positive steady states exist (that is we have $u_0 = 0$ and $0 < u_1 < u_2 < u_3$), then u_1 and u_3 are stable, while u_0 and u_2 are unstable.

Clearly, treating f as a function of u we plot the graph of u obtaining the phase portrait



Now, we are on the position to explain the loop of hysteresis and cusp catastrophe.

We show that the threshold curves for the existence of three steady states are parametrized by

$$r(a) = \frac{2a^2}{(1+a^2)^2}, \quad k(a) = \frac{2a^3}{a^2-1}, \quad \text{for} \quad a >= \sqrt{3}.$$

Clearly, non-trivial steady state lies on the cross-section of two curves

$$g_1(u) = r\left(1 - \frac{u}{k}\right), \quad g_2(u) = \frac{u}{1+u^2}$$

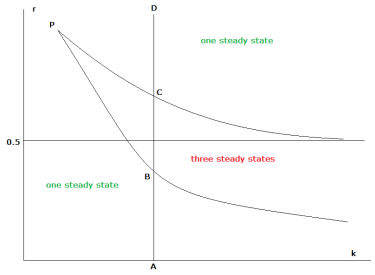
and the threshold values of r and k appear when the solutions are double.

Let us fix $u = a$ and solve the system of two equations describing double solutions:

$$g_1(a) - g_2(a) = 0, \quad g_1'(a) - g_2'(a) = 0$$

with respect to r and k.

The corresponding curves are sketched below.



If we fix k and change r from 0 along the interval ABCD, then we see that the positive steady state u_1 bifurcates at $r = 0$ from u_0 and increases to the maximal value that is reached in C.

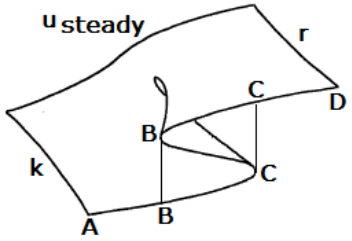
When C is exceeded, then this positive steady state disappears and the equilibrium switches to u_3.

Now, decreasing r we have that u_3 is the steady state until the point B is reached.

Exceeding B the equilibrium again changes to u_1.

Corollary 4. *If r increases along ABCD, then there is a switch at the point C, while if r decreases from D to A, then a switch appears at B.*

The loop of hysteresis appears in 3D picture drawn in the space $(u_{\text{steady}}, r, k)$. This 3D picture corresponds to the projection onto the plane (r, k) above.



When r increases the solution goes along the path ABCCD, while when it decreases it goes along DCBBA.

The fold of the surface corresponds to three positive steady state.

Now, let us look at this features from the point of view of the pest dynamics.

Typically, this dynamics is in the range of parameter values with three positive steady states.

The first state u_1 is a kind of refuge for the population, while in the second one outbreak is observed.

We want to control the population such that the first steady state is kept.

Now, we should come back to the original model parameter.

For example, whenever leaves are sprayed against the pest, then k decreases, that is the carrying capacity K_B for pests decreases as well.

If k decreases sufficiently, then only one steady state is present.

However, it is easy to calculate the parameters only when there is no predators.

In the presence of predators the problem of control (optimal control) is not an easy task.

Lecture IX: Simple models of immune reaction

Now, we focus on the modelling of immune reactions.

We start from simple models described in the framework of prey-predator equations.

In the simple models we take into account only two main players, that is antigens and antibodies.

Antigen is a common notion covering all substances that can trigger the immune reaction.

We distinguish between two main types of antigen:

- active antigen that is able to reproduce in the host body, such as bacteria, virus, parasite, tumor/cancer cells;
- passive antigen that is not able to reproduce in the host body, such as poison, venom, vaccine;
- antigen produced in the body, as auto-antigen or transplantation antigen.

Let us denote the concentration of antigen by $V(t)$.

Depending on the type of antigen, different governing law should be used in the description of the change of V in time.

As the simple description we can use:

- Malthus law for the active antigen:

$$\dot{V} = rV,$$

  where $r > 0$ is the antigen reproduction rate;

- "death"/clearance process for the passive antigen:

$$\dot{V} = -sV,$$

  with $s > 0$ reflecting clearance rate, which describes how fast this substances is removed from the host body (it is sometimes described by so-called half-disintegration time, that is the time $\bar{t}$ such that $V(\bar{t}) = \frac{V_0}{2}$; we see that $\bar{t} = \frac{\ln 2}{s}$);

- "migration process" for the antigen produced in the body:

$$\dot{V} = p - sV,$$

  where $\bar{V} = \frac{p}{s} > 0$ for $p, s > 0$, reflects some equilibrium, which is a level of antigen present in the organism.

Appearance of the antigen should cause some immune reaction.

Typically there are two main types of immune response:

- humoral immune response during which antibodies are produced by plasma cells and released into the blood and lymph; antibodies are proteins which main role is to bind the antigen and removed it from the organism;
- cellular or cell-mediated immune response during which natural killers and then specific T-lymphocytes are produced to kill antigens.

In most of infections both types of immune response is involved.

Clearly, both types of the reaction can be described in a similar way, so we focus on the humoral response during this lecture.

Let $F(t)$ denotes the concentration of antibodies.

During the immune reaction antibodies bind to the antigen, which can lead not only to the destruction of the antigen, but also to the destruction of antibodies, the simples way of reflecting this fact is to include the term $-V(t)F(t)$ with some proportionality constant to both equations on V and F.

Clearly, the proportionality constant for V depends on the number of binding site present on the surface of the antigen, while for F it depends on the final result of the immune reaction (meaning how many from binding antibodies is destroyed).

Now, we can propose the equation for the change of the active antigen as

$$\dot{V} = \beta V - \gamma_1 VF.$$

So we see that the first proposed equation is the same as for the Lotka-Volterra model.

What can be the simplest stimulation term in the equation of antibodies dynamics?

As immune reaction is triggered due to the presence of the antigen, it seems that we can use just the term proportional to $V(t)$ as the stimulation.

Therefore, for the active antigen we obtain the system

$$\begin{aligned} \dot{V} &= \beta V - \gamma_1 VF, \\ \dot{F} &= \alpha V - \gamma_2 VF. \end{aligned} \tag{42}$$

It is obvious that unique positive solutions exist for every positive V_0, F_0.

Moreover, the solution is defined for every $t > 0$, as the right-hand side of Eqs. (42) has a linear estimation $\dot{V} <= \beta V$ and $\dot{F} <= \alpha V$.

Notice, that any point $(0, F)$ is a steady state of Eqs. (42).

This means that we are not able to use the standard linearization method, however the method of phase portrait still works.

The dynamics of Eqs. (42) depends on the sign of

$$a_1 - a_2, \quad a_1 := \frac{\beta}{\gamma_1}, \quad a_2 := \frac{\alpha}{\gamma_2}.$$

Looking for null-clines we obtain

$$\dot{V} = 0 \quad \Longleftrightarrow V = 0 \quad \text{or} \quad F = a_1,$$

and

$$\dot{F} = 0 \quad \Longleftrightarrow V = 0 \quad \text{or} \quad F = a_2.$$

We see that the null-cline $F = a_1$ is the solution, because

$$\dot{F}(t)\Big|_{F=a_2} = 0$$

and then

$$\dot{V} = (\beta - \gamma_1 a_2)V \quad \Longrightarrow \quad V(t) = V_0 \exp\Big((\beta - \gamma_1 a_2)t\Big)$$

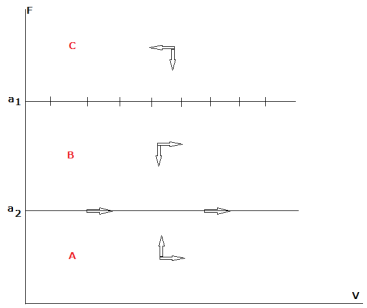
We easily see that

- $\dot{V} > 0$ for $F < a_1$ and $\dot{V} < 0$ for $F > a_1$;
- $\dot{F} > 0$ for $F < a_2$ and $\dot{F} < 0$ for $F > a_2$.

Let us assume that $a_1 > a_2$.

Therefore, we have three regions in the phase space

- C for $F > a_1$, in which both variables are decreasing;
- B for $F \in (a_2, a_1)$, in which F decreases and V increases;
- A for $F \in (0, a_2)$, in which both variables increases.



We see that the solution starting in A remains in A, as $F = a_2$ is the solution.

The solution remaining in A is monotonic.

The variable F is bounded, so $F \to F_g > F_0$ and $F_g <= a_2$.

Assume that $V \to V_g < \infty$, and $V_g > V_0$, obviously.

If both variables are bounded, then $\dot{V} \to 0$ and $\dot{F} \to 0$.

This means that the solution must tend to the steady state.

However, $V = 0$ is the only possibility of achieving the steady state in this region.

Therefore, $V \to \infty$. This implies that $F \to a_2$.

Clearly, if F does not tend to a_2, then $\dot{F} \to 0$ gives $V \to 0$, which is impossible.

Therefore, all trajectories in A has the property $F \to a_2$ and $V \to \infty$ monotonically.

Similarly, we show that the trajectories starting in B have the same properties.

If the trajectory starts in C, then it either remains in C (and then it tends to one of the steady states $(0, F)$ for $F > a_1$), or it enters B and then remains in B.

We are able to find explicit formula for solutions of our system.

Clearly,

$$\frac{dV}{dF} = \frac{\gamma_1(a_1 - F)}{\gamma_2(a_2 - F)}, \quad \text{for} \quad F \neq a_2.$$

One can integrate this equation and obtain

$$V(t) = V_0 + \frac{\gamma_1}{\gamma_2}\left(F(t) - F_0 - (a_1 - a_2)\ln\frac{F(t) - a_2}{F_0 - a_2}\right).$$

If $V \to 0$ and $F \to F_g$, then

$$V_0 = \frac{\gamma_1}{\gamma_2}\left(F_0 - F_g + (a_1 - a_2)\ln\frac{F_g - a_2}{F_0 - a_2}\right).$$

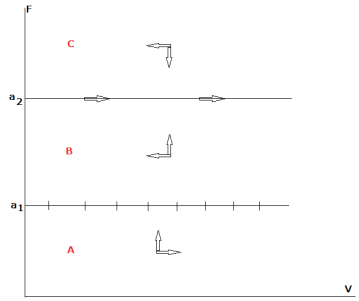
In this case $F_0 > F_g >= a_1$, and therefore

$$V_0 <= \frac{\gamma_1}{\gamma_2}\left(F_0 - a_1 + (a_1 - a_2)\ln\frac{F_g - a_2}{a_1 - a_2}\right) \tag{43}$$

and for such (V_0, F_0) solutions remain in C.

Corollary 5. *For Eqs.* (42) *with* $a_1 > a_2$ *(that is* $\beta > \alpha\frac{\gamma_1}{\gamma_2}$*), either* $V \to \infty$ *and then* $F \to a_2$*, or, if* V_0 *is sufficiently small (satisfies* (43)*) and* $F_0 > a_2$*, then* $V \to 0$*.*

On the other hand, if $a_2 > a_1$, then the dynamics of Eqs. (42) is completely different.



We also have three regions, but now the solution remains in B and C, while always leave A.

Clearly, if the solution remains in A, then $F \to F_g < a_1$ and $\dot{F} \to 0$, but this means $V \to 0$, which is impossible as V is increasing in A.

Solutions in B and C are monotonic with decreasing V, so $V \to 0$, and therefore all solutions tend to some $(0, F_g)$.

Corollary 6. *For Eqs.* (42) *with* $a_2 > a_1$ *(that is* $\beta < \alpha\frac{\gamma_1}{\gamma_2}$*), the solution tends to one of the steady state* $(0, F_g)$*, where* F_g *depends on the initial data.*

It is obvious that the model dynamics depends crucially on the model parameters.

If the immune system is strong comparing to the antigen, that is

$$\alpha\gamma_1 > \beta\gamma_2,$$

meaning the the immune system stimulation coefficient α is large, while the antigen reproduction rate β is small, not so many antibodies are destroyed during the immune reaction (small γ_2) and the effectiveness of immune reaction γ_1 is large, then the organism always wins the battle against the antigen.

Otherwise, if the organism is in poor condition that reflects in small immune coefficients, then only for specific initial data the recovery is possible.

This initial data reflect large initial number of antibodies and sufficiently small initial number of antigens.

This small number is called the immune barrier.

Note that recovery means here that $V \to 0$, while $F \to F_g$, depending on initial data.

For any other initial data $V \to \infty$, which is just mathematical artifact, while in nature, if V exceeds some threshold level (maximal for given host body), then it always leads to the lethal outcome of the disease.

Lecture X: Immune reaction against tumor: Kuznetsov model

Now we describe the model of immune reaction against tumour.

We again use simple mathematical structure to reflect some features from nature, mainly so-called sneaking through mechanism reflecting the escape of tumor from the immune control.

In 1994, V.A. KUZNETSOV, I.A. MAKALKIN, M.A. TAYLOR and A.S. PERELSON presented a mathematical model of the cytotoxic T lymphocyte response to the growth of an immunogenic tumor.

The immune response to a tumor is usually cell-mediated with cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells playing a major role.

The anti-tumor immune response in vivo is complicated and not well understood.

Spontaneously arising tumors are known to be of low immunogenicity and usually grow out of control.

The escape from immune surveillance can be associated with a number of different mechanisms, including:

- the selection of tumor clones resistant to cytolytic mechanisms;
- the loss or masking of tumor antigens;
- the loss of Major Histocompatibility Complex (MHC) class I molecules;

and tumor induced disorders in immunoregulation.

Nevertheless, cancer cells are attacked and killed by cells of the immune system, so the immune surveillance of spontaneous tumors may be effective and important in keeping cancer incidence low.

On the other hand, the majority of immunotherapy attempts are not effective.

One of the main reasons for this lies in the fact that even after a so-called “successful” and “clinically” complete removal of a tumor, a small quantity of tumor cells stay in an organism, which can grow into secondary tumors or “dormant” metastases.

Tumor dormancy is a term used to describe a state in which potentially lethal tumor cells persist for a prolonged period of time with little or no increase in the tumor cell population.

Dormant states emerge not only after a radical treatment of a tumor, but also at early stages of tumor progression.

In fact, there is general agreement that in the human, neoplastic cells escape from a primary tumor very early in its development.

The fate of these escaping neoplastic cells will determine whether the patient lives or dies of cancer.

Small dormant tumors, which after a long time begin uncontrolled growth, may escape from immune surveillance by the so-called “sneaking through mechanism”.

It refers to a phenomenon in which animals:

- with a low dose of tumor cells fail to generate a successful anti-tumor immune response and progressive tumor growth results;
- with medium doses of tumor cells generate the response leading to tumor rejection;
- while large doses break through the immune defence and successfully generate tumors.

This effect has been reproduced in different experimental models.

It has been found in numerous studies both in vivo and in vitro that the growth of a tumor cell population is exponential for small numbers of tumor cells but is slowed at large population sizes.

The inhibition of growth may be caused by the competition of cells for metabolites and/or growth factors, or by inhibiting factors produced by the tumor cells.

In many cases of non-exponential tumor growth, the kinetics are well described by the logistic or Gompertz equation.

Consider tumor cells being "immunogenic", and therefore subject to immune attack by cytotoxic effector cells, that is CTLs or NK cells.

The model involves tumor cells $T(t)$, effector cells $E(t)$, tumor-effector cells complexes $C(t)$, inactivated effector cells $E_*(t)$, and "lethally hit" (programmed to die) tumor cells $T_*(t)$.

It is assumed that T and E can form complexes but the complexes can break down again to form tumor and effector cell.

Moreover, complexes can break down into:

- effector cell and lethally hit tumor cell (interactions irreversibly program TC for lysis);
- or into inactivated effector cell and "normal" tumor cell (interactions inactivate EC).

The interactions are described by the following system of equations

$$\begin{aligned}
\dot{E} &= s + F(C,T) - d_1 E - k_1 ET + (k_{-1} + k_2)C, \\
\dot{T} &= aT(1 - bT_{\text{tot}}) - k_1 ET + (k_{-1} + k_3)C, \\
\dot{C} &= k_l ET - (k_{-1} + k_2 + k_3)C, \\
\dot{E}_* &= k_3 C - d_2 E_*, \\
\dot{T}_* &= k_2 C - d_3 T_*,
\end{aligned} \tag{44}$$

where

- s is the "normal" (non-enhanced by TC presence) rate of flow of mature EC into the region of TC localization;
- $F(C,T)$ characterizes the rate at which cytotoxic EC accumulate in the region of TC localization due to the presence of the tumor;

- k_1 and k_{-1} are kinetic constant describing the rates of binding of EC to TC and detachment of EC from TC without damaging cells;
- k_2 is the rate at which EC-TC interactions irreversibly program TC for lysis;
- k_3 is the rate at which EC-TC interactions inactivate EC;
- a and b are logistic parameters of TC growth;
- $T_{\text{tot}} = T + C$ is the total number of non-hit tumor cells;
- d_1, d_2 and d_3 are death rates of EC and TC, respectively.

The analysis of Kuznetsov suggests the following explicit form for this stimulated accumulation of effector cells:

$$F(C,T) = \frac{fC}{g+T},$$

where f and g are positive constants.

This functional form is consistent with a model in which one assumes that the accumulation of effector cells is due to signals, such as released cytokines, generated by effector cells in conjugates.

Moreover, the rate of stimulated accumulation has some maximum value as T gets large.

This is consistent with limitations in the rate of transport of effector cells to the tumor.

Notice, that the last two equations on E_* and T_* have no influence on the dynamics of the other three equations.

The formation and dissociation of cellular complexes occurs on a time scale of several tens of minutes to a few hours.

A time interval of this order is also observed before the lysis of lethally hit TCs.

On the other hand, the multiplication as well as influx of effector cells into the spleen occurs on a much slower time scale.

This motivates the application of a quasi-steady-state approximation for the third equation, that is $\dot{C} \approx O$, which yields the following relation:

$$C \approx KET, \quad K = \frac{k_1}{k_{-1} + k_2 + k_3}.$$

Experimental observations indicate that EC-TC complexes usually comprise a small portion of the total number of effector or tumor cells (up to 1-10%).

This motivates the approximation $T_{\text{tot}} \approx T$ which finally allows to simplify Eqs. (44) to the following system

$$\begin{aligned} \dot{E} &= s + \frac{pET}{g+T} - dE - mET, \\ \dot{T} &= aT(1-bT) - nET, \end{aligned} \tag{45}$$

with parameters $p = fK$, $m = Kk_3$, $n = Kk_2$ and $d = d_1$.

This parameters were estimated by Kuznetsov at all as:

$$p = 0.1245 \text{ day}^{-1}, \quad g = 2.019 \cdot 10^7 \text{ cells},$$

$m = 3.422 \cdot 10^{-10}$ day^{-1}cells^{-1}, $n = 1.101 \cdot 10^{-7}$ day^{-1}cells^{-1}, $d = 0.0412$ day^{-1}.

Moreover, as suggested by experiments $E_0 = T_0 = 10^6$ cells.

These initial values were used in the undimensionalization procedure.

Time is scaled relative to the rate of tumor cell deactivation; i.e. $\tau = nT_0 t$.

Then the model can be rewritten as:

$$\begin{aligned} \dot{x} &= \sigma + \frac{\rho xy}{\eta + y} - \mu xy - \delta x, \\ \dot{y} &= \alpha y(1 - \beta y) - xy, \end{aligned} \tag{46}$$

where $\dot{x} = \frac{dx}{d\tau}$, $\dot{y} = \frac{dy}{d\tau}$, and

$$x = \frac{E}{E_0}, \quad y = \frac{T}{T_0}, \quad \sigma = \frac{s}{nE_0T_0}, \quad \rho = \frac{p}{nT_0}, \quad \eta = \frac{g}{T_0},$$

$$\mu = \frac{m}{n} = \frac{k_3}{k_2}, \quad \delta = \frac{d}{nT_0}, \quad \alpha = \frac{a}{nT_0}, \quad \beta = bT_0$$

with the specific values:

$\sigma = 0.1181$, $\rho = 1.131$, $\eta = 20.19$, $\mu = 0.00311$, $\delta = 0.3743$, $\alpha = 1.636$, $\beta = 2.0 \cdot 10^{-3}$.

Looking for the null-clines we see that

- $\dot{x} = 0$ only if $x = \frac{\sigma}{\mu y + \delta - \frac{\rho y}{\eta + y}} =: f(y)$;
- $\dot{y} = 0$ if $y = 0$ or $x = \alpha(1 - \beta y) =: g(y)$.

As $\beta > 0$, $g(y)$ is simply a straight line with a negative slope.

Semi-trivial steady state with coordinates $\left(\frac{\sigma}{\delta}, 0\right)$ is given by the intersection of $f(y)$ and $y = 0$.

Stability of this steady state depends on the relative values of the system parameters.

Depending on the relation of $f(y)$ and $g(y)$ there can be from zero to three additional steady states.

Setting $f(y) = g(y)$ yields a third-order polynomial:

$$C_3 y^3 + C_2 y^2 + C_1 y + C_0 = 0,$$

with

$$C_0 = \eta\left(\frac{\sigma}{\alpha} - \delta\right), \; C_1 = \frac{\sigma}{\alpha} + \rho - \mu\eta + (\delta\eta - 1)\beta, \; C_2 = \beta(\mu\eta + \delta - \rho) - \mu, \; C_3 = \mu\beta.$$

To have three real roots, it follows from Descartes' rule of signs that there must be three sign changes among the coefficients.

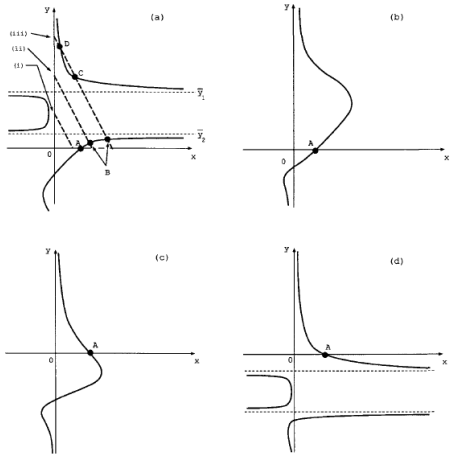
The Descartes' rule of signs states that

Theorem 7. *If the terms of a single-variable polynomial with real coefficients are ordered by descending variable exponent, that is*

$$p(x) = c_n x^n + c_{n-1} x^{n-1} + \ldots + c_1 x + c_0,$$

then the number of positive roots of the polynomial is either equal to the number of sign differences between consecutive nonzero coefficients, or is less than it by an even number. Multiple roots of the same value are counted separately.

It occurred that for the parameters estimated by Kuznetsov there are four steady states of the model.



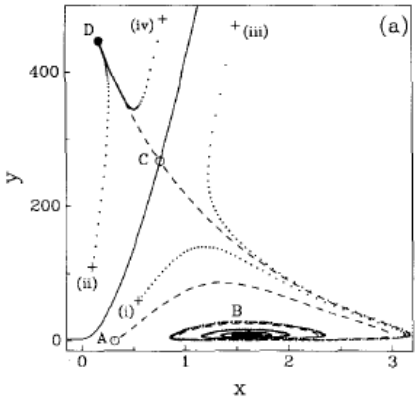
Four qualitatively different graphs of f:

- (a) $\rho >= \left(\sqrt{\eta\mu} + \sqrt{\delta}\right)^2$;
- (b) $\left(\sqrt{\eta\mu} - \sqrt{\delta}\right)^2 < \rho < \left(\sqrt{\eta\mu} + \sqrt{\delta}\right)^2$ and $\rho > \eta\mu$;
- (c) $\left(\sqrt{\eta\mu} - \sqrt{\delta}\right)^2 < \rho < \left(\sqrt{\eta\mu} + \sqrt{\delta}\right)^2$ and $\rho < \eta\mu$;
- (d) $\rho <= \left(\sqrt{\eta\mu} - \sqrt{\delta}\right)^2$.

The Dulac-Bendixson Criterion can be used to show that there is no periodic orbits for Eqs. (46).

Clearly, taking standard $B = \frac{1}{xy}$ we obtain

$$\frac{d}{dx}\left(\frac{\sigma}{xy} + \frac{\rho}{\eta + y} - \mu - \frac{\delta}{y}\right) + \frac{d}{dy}\left(\frac{\alpha(1-\beta y)}{x} - 1\right) = -\left(\frac{\sigma}{x^2 y} + \frac{\alpha\beta}{x}\right) < 0.$$



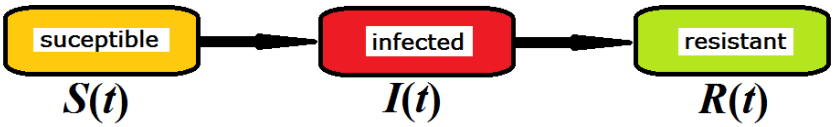
Phase portrait in logarithmic scale

We see that an external stimulation to the immune system, which may seem intuitively to aid the immune response (immunostimulation, e.g. perturbing from initial condition (i) to (ii)) can actually be detrimental – this is the illustration of sneaking through mechanism.

Lecture XI: Hybrid models: modeling of vaccination as impulsive equations.

During this lecture we will focus on the modeling of infection transmission and prevention of it by vaccination.

We describe the model of SIR type, that is after the disease individuals become resistant to it.



The first model of that type was proposed by Kermack and McKendrick in 1927.

In this model it is assumed that:

- the size of the whole population N is constant in time; if S, I, R denote the ration of susceptible, infected and resistant individual, respectively, then $S(t) + I(t) + R(t) = 1$;
- only the transmission of infection is described, other processes like reproduction, migration etc. are omitted;
- disease is transmitted by personal contacts between individuals of S and I classes; this is called horizontal transmission;
- contacts between individuals are random, so the number of infections is proportional to both ratios S and I;
- after the infection individuals recover and become resistant to that disease.

Therefore, the model is described by the system of equations:

$$\begin{aligned} \dot{S} &= -\beta S I, \\ \dot{I} &= \beta S I - \gamma I, \\ \dot{R} &= \gamma I, \end{aligned} \tag{47}$$

where:

- β – infection coefficient, describing probability of infection after the contact of healthy individual with infected one;
- γ – recovery coefficient, $1/\gamma$ describes the mean time of infection for an individual.

Basic properties like existence, uniqueness and non-negativity of solutions are a simple consequence of the right-hand side of Eqs. (47).

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Let us denote $N(t) = S(t) + I(t) + R(t)$. Then

$$\dot{N} = 0,$$

meaning that the whole population is kept on the constant level, that is if $N(0) = 1$, then $N(t) = 1$ for all $t \in \mathbb{R}$.

As solutions are bounded, $S(t), I(t), R(t) \in [0, 1]$ for all t, we obtain boundedness of solutions and their derivatives, so all solutions exists for all $t > 0$.

Because $R(t) = 1 - S(t) - I(t)$ for all t, we can reduce Eqs. (47) to the system of two equations describing the dynamics of S and I in the following phase space:

$$\mathcal{D} = \{(S, I) : S >= 0, \;\; I >= 0, \;\; S + I <= 1\}.$$

We easily see that non-negativity implies monotonicity of S, while I is increasing for $S > \frac{\gamma}{\beta}$ and decreasing for $S < \frac{\gamma}{\beta}$.

Corollary 8. *If $\mathcal{R}_0 = \frac{\beta}{\gamma} <= 1$, then there is no point with the coordinate $S > \frac{1}{\mathcal{R}_0}$ in $\mathcal{D}$, implying that I is decreasing.*

From the monotonicity of both variables S and I we obtain

Corollary 9. *If $\mathcal{R}_0 = \frac{\beta}{\gamma} <= 1$, then any solution $(S(t), I(t), R(t))$ of Eqs. (47) has a limit as $t \to +\infty$.*

However, in this model steady states are not isolated, the whole line $I = 0$ consists of steady states. This means that existing limits depends on the initial data.

On the other hand, if $\mathcal{R}_0 > 1$, then also the model dynamics depends on the initial data.

- If $S_0 > 1/\mathcal{R}_0$, then I increases at the beginning. Let us notice that the upper border of $\mathcal{D}$, that is the line $S + I = 1$, is repelling:

  $$\dot{S} = \beta S(S - 1) \;\text{ on }\; S + I = 1$$

  and we see that for any $S \in (0, 1)$ there is $\dot{S} < 0$. This means that I achieves its maximum in $\mathcal{D}$ for some $\bar{t}$, such that $S(\bar{t}) = 1/\mathcal{R}_0$, and I decreases for $t > \bar{t}$.

- If $S_0 > 1/\mathcal{R}_0$, then I decreases for all $t > 0$.

The number $\mathcal{R}_0$ is called basic reproduction number/ratio, and the value $\mathcal{R}_0 = 1$ is the threshold for the spread of infection in the population.

The dynamics of Kermack-McKendrick model is not typical among the epidemic models, as the outbreak of the epidemic (that is the increase of the number of infected individuals $I(t)$ comparing to the initial number $I(0)$) depends not only on the basic reproduction number but also on the initial data.

At the end let us notice that

$$\frac{dI}{dS} = -1 + \frac{1}{\mathcal{R}_0 S}$$

and integrating this identity we obtain the limit value S_∞.

Clearly,

$$I(t) - I_0 = -S(t) + S_0 + \frac{1}{\mathcal{R}_0} \ln \frac{S(t)}{S_0},$$

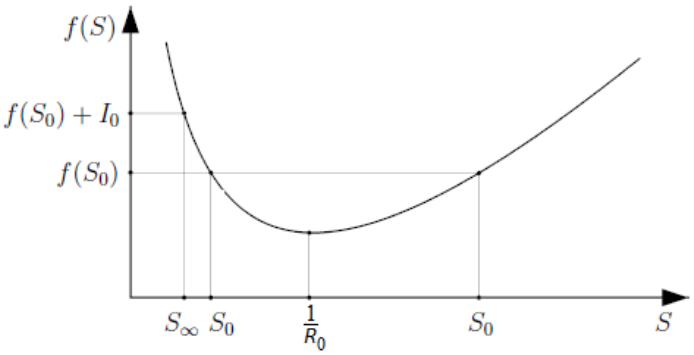
and for $I(t) \to 0$ we obtain

$$S_\infty = I_0 + S_0 + \frac{1}{\mathcal{R}_0} \ln \frac{S_\infty}{S_0}. \tag{48}$$

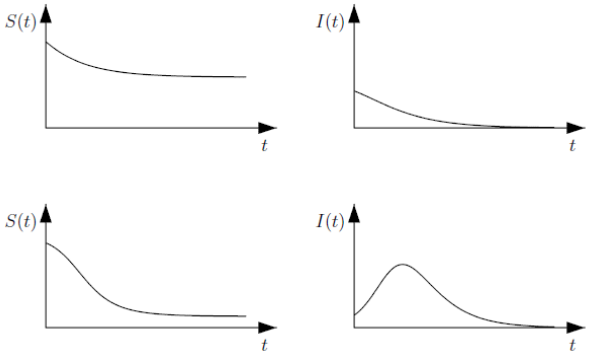
Denoting $f(S) = S - \frac{1}{\mathcal{R}_0} \ln S$, we get the relation

$$I(t) - I_0 = f(S_0) - f(S(t)),$$

and analyzing the graph of f we see that there are two values satisfying (48).



It is obvious, however, that the limita value satisfies $S_\infty < 1/\mathcal{R}_0$.



Solutions: upper graphs for $S_0 < 1/\mathcal{R}_0$, lower graphs for $S_0 > 1/\mathcal{R}_0$.

We see that for larger initial I_0 the value of S stabilizes on the higher level (upper graphs) S_∞ than for smaller I_0 (lower graphs).

Now, we include the processes of birth and death into the model proposed by Kermack and McKendrick.

Although we include these processes, we still would like to keep the whole population size constant.

Therefore, we need to describe reproduction in the simplified manner.

We assume that birth and death are in balance, such that both coefficients are equal.

Hence, for the population without infection we propose the simple linear equation:

$$\dot{N} = \mu - \mu N,$$

where $N(t)$ represents the population size and μ is the birth/death coefficient.

It is obvious that $N = 1$ is the only stable steady state for this equation.

Moreover, we assume that there is no vertical transmission, that is the transmission from parents to children, which means that all new born individuals are susceptible.

Therefore, instead of Eqs. (47) we obtain the modified model

$$\begin{cases} \dot{S} &= \mu - \beta IS - \mu S, \\ \dot{I} &= \beta IS - \gamma I - \mu I, \\ \dot{R} &= \gamma I - \mu R, \end{cases} \tag{49}$$

where:

- S, I, R – proportions of healthy susceptible, infected and healthy resistant individuals, $S + I + R = 1$;
- μ – birth/death coefficient, with $1/\mu$ reflecting mean life-time of an individual;
- β – infection coefficient;
- γ – recovery coefficient.

Dynamics of Eqs. (49) depends on $\mathcal{R}_0$, obviously.

For this model it reads

$$\mathcal{R}_0 = \frac{\beta}{\mu + \gamma}.$$

If

- $\mathcal{R}_0 <= 1$, then Eqs. (49) has only one semi-trivial steady state $(1, 0, 0)$ reflecting healthy population and this state is globally stable;
- $\mathcal{R}_0 > 1$, then Eqs. (49) has two steady states; additional positive steady state

$$(S^*, I^*, R^*) = \left(\frac{1}{\mathcal{R}_0}, \mu\frac{\mathcal{R}_0 - 1}{\beta}, 1 - S^* - I^*\right)$$

describes endemic state and is globally stable if exists.

We see the main difference between Eqs. (49) and (47): dynamics of the modified model depends only on the basic reproduction number $\mathcal{R}_0$.

This gives better biological interpretation, as epidemic does not depend on the initial data, but on the model parameters only.

Clearly, the model described by Eqs. (49) has also better mathematical properties as there are isolated steady states.

Analysis of Eqs. (49)

Moreover, for $S(0)+I(0)+R(0)=1$ we obtain $S(t)+I(t)+R(t)=1$ for any $t\in\mathbb{R}$.

This means that we again can reduce the analysis of Eqs. (49) to the system of two equations

$$\begin{cases} \dot{S} &= \mu-\beta IS-\mu S,\\ \dot{I} &= \beta IS-\gamma I-\mu I, \end{cases} \tag{50}$$

in $\mathcal{D}$.

Let us find steady states first.

- If $I=0$, then from the first equation we obtain $S=1$, which gives the semi-trivial steady state $(1,0)$ reflecting healthy population.
- If $I\neq 0$, then $S^*=\frac{\mu+\gamma}{\beta}$.

  Hence, if $S^*=1/\mathcal{R}_0<1$, then from the first equation we obtain $I^*=\mu\frac{1-S^*}{\beta S^*}=\mu\frac{\mathcal{R}_0-1}{\beta}$, giving the positive steady state (S^*,I^*) describing epidemic.

Now, we check local stability of these states.

Jacobi matrix of Eqs. (50) reads

$$M_J(S,I)=\begin{pmatrix} -\mu-\beta I & -\beta S\\ \beta I & \beta S-\gamma-\mu \end{pmatrix}.$$

For the semi-trivial steady state we have

$$M_J(1,0)=\begin{pmatrix} -\mu & -\beta\\ 0 & \beta-\gamma-\mu \end{pmatrix}$$

and we see that for $\beta<\gamma+\mu$, which is equivalent to $\mathcal{R}_0<1$ both eigenvalues are real negative, yielding stability.

For the positive steady state (S^*,I^*) we have

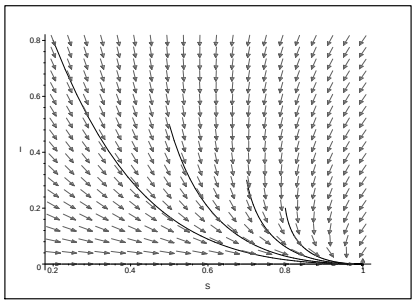
$$M_J(S^*,I^*)=\begin{pmatrix} -\mu-\beta I^* & -\beta S^*\\ \beta I^* & \beta S^*-\gamma-\mu \end{pmatrix}=\begin{pmatrix} -\frac{\mu}{S^*} & -\beta S^*\\ \beta I^* & 0 \end{pmatrix},$$

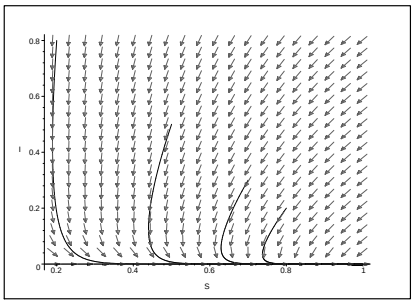
so

$$\operatorname{tr} M_J(S^*,I^*)=-\mu/S^*<0 \quad\text{and}\quad \det M_J(S^*,I^*)=\beta^2 I^*S^*>0,$$

yielding stability of this state whenever exists (that is for $\beta>\gamma+\mu$), and moreover the state $(1,0)$ is unstable in this case.

Analysing phase portraits we easily see that the positive steady state is globally stable if exists, while if it does not exist, then the semi-trivial steady state is globally stable in $\mathcal{D}$.





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$$\beta <= \mu \qquad\qquad \mu < \beta <= \gamma + \mu.$$

Case $\beta <= \mu$

If $I <= 1 - S$, then

$$\dot{S} >= \mu - \mu S - \beta S(1 - S) = \beta S^2 - (\mu + \beta)S + \mu,$$

and the right-hand side of this equation has two zeros: $S_1 = \mu/\beta <= 1$ and $S_2 = 1$, implying $\dot{S} >= 0$.

Moreover,

$$\dot{I} <= \beta I - \gamma I - \mu I = (\beta - \gamma - \mu)I <= 0.$$

Corollary 10. *For $\beta <= \mu$ both variables in Eqs. (50) are monotonic, hence any solution tends to the unique steady state, $(S(t), I(t)) \to (1, 0)$ as $t \to \infty$.*

Case $\mu < \beta <= \gamma + \mu$

Both inequalities presented above are fulfilled, but now $S_2 < 1$, so S is not necessarily monotonic.

The null-cline for S reads

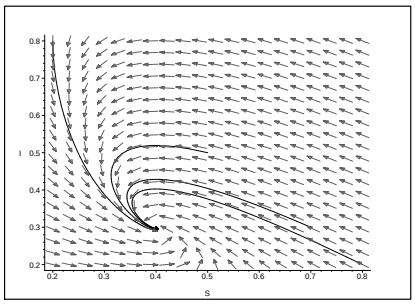
$$I = \frac{\mu}{\beta}\left(\frac{1}{S} - 1\right)$$

and crosses the border $I = 1 - S$ at the points S_2 i S_1.

If the orbit starts at the point above this null-cline, then S is decreasing, as well as I, so the solution must cross this null-cline.

Below the null-cline both variables are monotonic, as in the previous case, hence the solution tends to $(1, 0)$.

Case $\beta > \gamma + \mu$



In this case, to show global stability we need to exclude the possibility of periodic orbits.

We use the Dulac-Bendixson Criterion with the standard function $B(S, I) = \frac{1}{SI}$ for $S > 0, I > 0, S + I \ 1$.

We obtain

$$BF_1(S, I) = \frac{1}{SI}(\mu - \mu S - \beta S I),$$

$$BF_2(S,I) = \frac{1}{SI}(\beta SI - (\gamma+\mu)I)$$

implying

$$\operatorname{div} BF = -\frac{\mu}{S^2 I} < 0.$$

Corollary 11. *For Eqs.* (50) *there are no closed orbits, and hence the positive steady state is globally stable if exists.*

Modeling of vaccinations

We will discuss the strategies of vaccinations against measles and polio in Central and South Africa and against measles and rubella in Great Britain on the basis of Eqs. (49).

In standard mathematical analysis we typically assume constant vaccination strategy, which means that we vaccine the constant fraction p of new born individuals.

According to this assumption we need to change the birth coefficient in Eqs. (49).

Hence, we obtain

$$\dot{S} = (1-p)\mu - \beta IS - \mu S$$

and those who are immunized become resistant, so the third equation reads

$$\dot{R} = p\mu + \gamma I - \mu S.$$

We can made the analysis for new birth coefficient and obtain the conclusion that

- threshold value of vaccination is

$$p_c = 1 - \frac{1}{\mathcal{R}_0};$$

- for $p > p_c$ the new steady state $(1-p, 0, p)$ reflecting the healthy population is stable;
- for $p < p_c$ endemic state

$$(S^*, I^* - \frac{\mu}{\mu+\gamma}p, R^* + \frac{\mu}{\mu+\gamma}p)$$

is stable.

Notice, that using this vaccination strategy the number of susceptible at equilibrium does not change.

For measles the following parameter values was estimated:

$$\mu = 0,02, \quad \beta = 1800, \quad \gamma = 100$$

which gives the critical ratio of vaccine $p_c \approx 95\%$.

This means that almost all new born individuals should get the vaccine.

Therefore, another strategy, which seems to be more rational, has been proposed.

This strategy consists of series of vaccinations which we call "impulsive vaccine".

From mathematical point of view this strategy is described by
impulsive differential equations.

Such type of equations appear as an external influence on the dynamical systems, mainly in the context of fishery/hunting in population dynamics and treatment/vaccines in the context of infections.

In general we study the following mathematical structure:

$$\begin{cases} \dot{x} &= F(t, x(t)), \\ x(t_i) - x(t_i^-) &= g(t_i, x(t)), \quad i \in \mathbb{N}, \\ x(t_0) &= x_0, \end{cases}$$

where:

- $\dot{x} = F(t, x(t))$ with initial data $x(t_0) = x_0$ is the dynamical system under the external influence;
- $x(t_i^-)$ – left-hand limit of the solution at t_i;
- t_i, $i \in \mathbb{N}$ – moments at which impulses appear;
- $g(t_i, x(t))$, $i \in \mathbb{N}$ – magnitude of impulses.

Typically $g(t_i, x(t)) = g(t_i, x(t_i^-)) \sim x(t_i^-)$, that is the magnitude of impulses is proportional to the present state of the system.

In the case of vaccines:

$$g(t_i, x(t)) = -c_i x(t_i^-),$$

where $c_i \in [0, 1]$ reflects the fraction of individuals vaccinated.

Now, we include vaccines into the basic model (49).

The strategy assumes giving a vaccine for constant fraction p of susceptibles every T years.

We obtain

$$S(t_n) = (1 - p)S(t_n^-), \quad t_{n+1} = t_n + T.$$

It occurs that for fixed p we can choose T such that the infection becomes extinct.

Assume first that $I \equiv 0$ and let us study the dynamics of S between two impulses t_n and t_{n+1}.

Under the assumption $I = 0$ we have

$$\dot{S} = \mu(1 - S), \quad S(t_n) = (1 - p)S(t_n^-), \quad t_{n+1} = t_n + T, \tag{51}$$

and hence

$$S(t) = \begin{cases} Q(t) = 1 + (S(t_n) - 1)\,\mathrm{e}^{-\mu(t - t_n)}, & t \in [t_n, t_{n+1}), \\ (1 - p)Q(t), & t = t_{n+1}. \end{cases} \tag{52}$$

Let $S(t_n) = S_n$ and define the map

$$S_{n+1} = F(S_n),$$

reflecting the number of susceptible individuals just after the vaccine at time t_n.

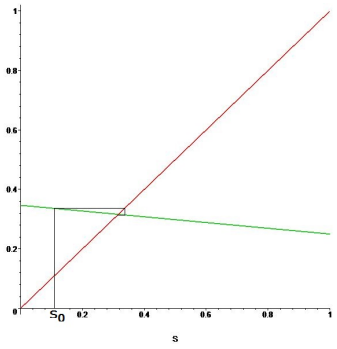
From the formula (52) we obtain

$$F(S) = (1-p)\left(1 + (S-1)\,\mathrm{e}^{-\mu T}\right).$$

Notice, that the map F has a constant point that reads

$$S_F^* = F(S_F^*) = \frac{(1-p)(\mathrm{e}^{\mu T}-1)}{p-1+\mathrm{e}^{\mu T}}.$$

Moreover, it is easy to see (e.g. using the cob-webbing method) that S_F^* is globally stable in $[0,1]$.



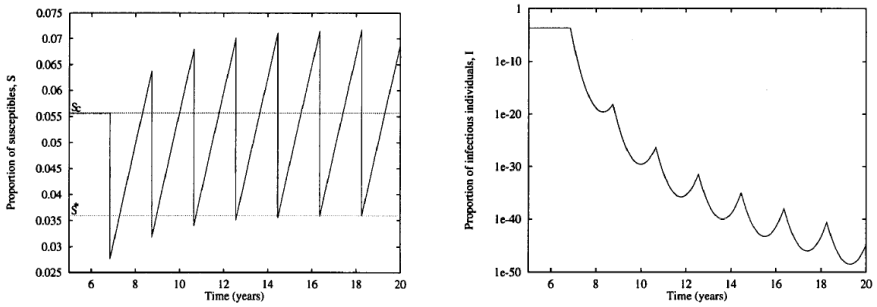
Let us notice, that if the orbit of the discrete dynamical system generated by the map F tends to S_F^*, then the population of susceptibles goes to the limit cycle of period T.

In this way the periodic solution reflecting healthy population under the impulsive vaccination is constructed.

However, to get the periodic solution we need to assume $S(t_n) = S_F^*$.

Eventually, the periodic solution reads

$$\begin{cases} \bar{S}(t) = \begin{cases} 1 + \frac{p\mathrm{e}^{\mu T}}{1-\mathrm{e}^{\mu T}-p}\mathrm{e}^{-\mu(t-t_n)}, & t \in [t_n, t_{n+1}), \\ S_F^*, & t = t_{n+1}, \end{cases} \\ \bar{I}(t) = 0. \end{cases}$$



(a) The proportion of susceptibles S when pulse vaccination is applied ($p = 0.5$, and $T = 2$) to the SIR model. The susceptibles are attracted to a periodic "infection-free" solution. The line at $S_c \approx 0.0556$ marks the "epidemic threshold". (b) Time-series for the corresponding rapidly decreasing infectious population I. Note the logarithmic scale employed.

Now, we would like to study stability of this periodic solution.

Let us denote

$$s(t) = S(t) - \bar{S}(t), \qquad j(t) = I(t) - 0$$

and linearize the system.

We obtain

$$\begin{cases} \dot{s} &= -\mu s - \beta \bar{S}\, j, \\ \dot{j} &= j(\beta \bar{S} - \mu - \gamma), \\ s(t_n) &= (1-p)s(t_n^-), \qquad t_{n+1} = t_n + T. \end{cases} \tag{53}$$

Notice that local stability of the point $(0,0)$ for linearized system Eqs. (53) implies local stability of the periodic solution.

The equation for j can be easily integrated in any interval $[t_n, t_{n+1}]$:

$$j_{n+1} = j(t_{n+1}) = j_n \mathrm{e}^{\int_{t_n}^{t_{n+1}} (\beta \bar{S}(t) - \mu - \gamma) dt}.$$

If the integral in the exponent is negative, then j_n decreases exponentially.

Moreover, if $j(t) \to 0$, then the first equation of Eqs. (53) implies that $s(t) \to 0$, as asymptotically

$$\dot{s} = -\mu s \quad \Longrightarrow \quad s(t) = s(t_n)\, \mathrm{e}^{-\mu(t-t_n)}$$

and we easily see that on each interval $[t_n, t_(n+1))$ the function $s(t)$ is decreasing, and moreover the sequence $s(t_n)$ is a geometric progression with the quotient $\mathrm{e}^{-\mu T} < 1$, implying $s(t_n) \to 0$ as $t \to \infty$.

Eventually, if

$$S_{\text{mean}} = \frac{1}{T} \int_{t_n}^{t_{n+1}} \bar{S}(t) dt < \frac{\mu + \gamma}{\beta} = S_c,$$

then the periodic solution is locally stable.

Coefficient S_c is called the epidemic threshold.

We see that $S_c = 1/\mathcal{R}_0$.

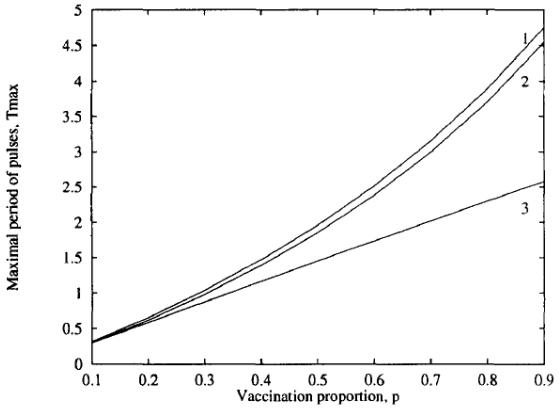
Calculating the mean value S_{mean} we obtain the sufficient condition of local stability:

$$\frac{(p - \mu T)(1 - \mathrm{e}^{\mu T}) + \mu p T}{\mu T (p - 1 + \mathrm{e}^{\mu T})} <= \frac{\mu + \gamma}{\beta},$$

which allows to estimate $T_{\max}$, e.g. expanding the left-hand side into Taylor series.

Assuming that $T << 100$ and $\mu << \gamma$ it can be shown that

$$T_{\max} \approx \frac{p\gamma}{\beta\mu} \frac{1}{1 - p/2 - \gamma/\beta}.$$



The maximum interpulse interval T_{max} as a function of vaccination proportion, p. Curve 1: approximation; Curve 2: exact result; Curve 3: the approximation proposed earlier

Lecture XII:
Simple signaling pathway of p53: the guardian of genome.

Tumour-suppressor genes are necessary to keep cells under control.

Just like a car brakes regulate its speed, tumour-suppressor genes act as brakes to the cell cycle, DNA replication and division into two new cells.

If these genes does not act properly, uncontrolled growth, which is a defining feature of cancer cells, can appear.

The p53 gene, discovered in 1979, was the first tumour-suppressor gene to be identified.

However, at the beginning, it was believed to be an oncogene, that means a cell-cycle accelerator.

Genetic and functional data obtained ten years after its discovery showed it to be a tumour suppressor.

Moreover, it was found that the p53 protein does not act correctly in most human cancers.

In about half of these tumours, p53 is inactivated directly as a result of mutations in the p53 gene.

In many others, it is inactivated indirectly through binding to viral proteins, or as a result of alterations in genes whose products interact with p53 or transmit information to or from p53.

In 2000, Vogelstein et al. called the p53 tumour suppressor protein
"guardian of the genome".

In general, it constitutes the core in a network of molecular interactions regulating the cellular response to stresses.

Stresses promote tumour formation, often resulting in cancer.

The main role of p53 is to guard cells against malignant transformations.

When DNA is damaged (by ionizing radiation or chemicals), the appropriate p53-mediated pathways are activated.

This yields the arrest of the cell cycle, which prevents the proliferation of cells containing damaged DNA leading to tumour formation.

Next, biochemical processes involved in DNA repair are triggered.

If it is successful, the cell resumes its progression and cell division can take place.

If repair is not possible due to excessive damage, the p53-mediated apoptotic pathway becomes functional, leading to apoptosis, which is programmed cell death.

The p53 pathway is switched off in normal cells, that is its activity is kept low, such that the cell cycle is not disrupted.

This is caused by a negative feedback loop consisting of the p53 and MDM2 genes.

The p53 protein acts as a transcription factor and regulates the expression of several target genes.

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The MDM2 gene is one of the target genes the transcription of which is activated by the p53 proteins.

However, the MDM2 proteins inhibit the p53 activity, forming a negative feedback loop.

The ability of MDM2 to keep p53 under control is essential for normal cell function.

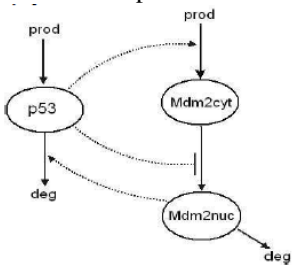
The repression operates via three mechanisms:

- MDM2 binds p53 at its DNA binding domain such that the latter cannot function as a transcription factor;
- MDM2 on binding p53 labels it for degradation;
- MDM2 is responsible for the export of p53 from the nucleus to the cytoplasm changing its transcriptional activity.

In mammalian cells, if DNA is damaged, a protein called ATM kinase is activated, which phosphorylates the p53 protein at a specific site, preventing the binding of the MDM2 protein to p53.

In the absence of MDM2 mediated degradation of p53, the protein stabilizes at a higher level, that is in the "active" state.

On the other hand, a positive feedback loop was later found in this signaling pathway.



The negative feedback arises since p53 positively regulates production of Mdm2, and in turn Mdm2, when in nucleus, enhances p53 degradation.

In addition p53 inhibits nuclear import of Mdm2, and since nuclear Mdm2 induces p53 degradation, this leads to positive feedback.

In the model the role of gene copies in the dynamics of this pathway is considered, since experiments suggest that it can play a role in oscillatory dynamics in p53-Mdm2 regulation.

The pathway can be described by the system of three ordinary differential equations for p53, cytoplasmic and nuclear Mdm2 levels

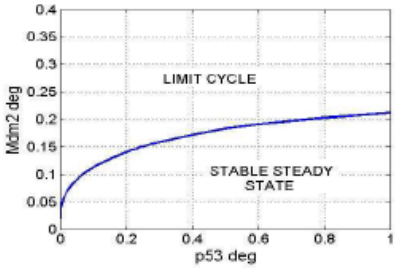
$$\begin{aligned} \dot{x} &= ms_1 - d_1 x y_n^2, \\ \dot{y}_n &= \frac{k_1}{x + k_2} y_c - d_2 y_n, \\ \dot{y}_c &= n\left(s_2 + \frac{x^3}{x^3 + k_3}\right) - \frac{k_1}{x + k_2} y_c, \end{aligned} \tag{54}$$

where m and n are the numbers of p53 and Mdm2 gene copies, respectively.

As transcription is regulated by p53 tetramers we assumed that p53 induces Mdm2 transcription following a Hill function, with exponent 3.

The nonlinear p53 degradation results from the fact that nuclear Mdm2 must attach several ubiquitines to p53, to initiate its degradation.

DNA damage is modeled here by a rapid change in p53 and Mdm2 degradation coefficients. It is known that DNA damage leads to p53 phosphorylation enhancing its stability and increases Mdm2 degradation.



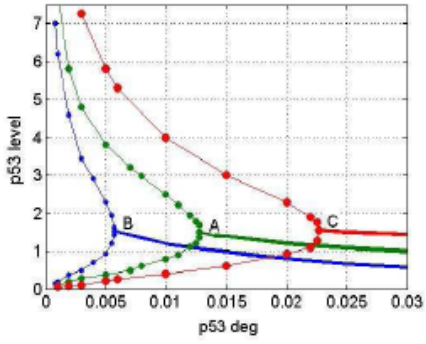
Bifurcation for normal cells $m = n = 2$

We see that the model has the required property, that is the transition from stable steady state to limit cycle results both from increased Mdm2 degradation (d_2) or decreased p53 degradation (d_1).

Finally, we analyze bifurcation diagrams to investigate how the transition from stable point to limit cycle (due to Hopf bifurcation) depends on the number of p53 or Mdm2 copies.

Hopf bifurcation is a local bifurcation in which a fixed point of a dynamical system loses stability as a pair of complex eigenvalues of the linearization around the fixed point cross the imaginary axis of the complex plane with increasing bifurcation parameter.

Under reasonably generic assumptions about the dynamical system, we can expect to see a small-amplitude limit cycle branching from the fixed point.



A, B and C denote, respectively, diagrams for normal cells ($m = n = 2$), p53 haploidal cells ($m = 1$, $n = 2$) and cells with p53 transfection ($m = 4$, $n = 2$).

The bifurcation point moves towards higher p53 degradation coefficients as number of p53 gene copies increases.

On the other hand, the increase in number of Mdm2 copies results in narrowing of oscillatory region (data not shown).

It shows that the change in gene copy number due to transfection or missing allele may

induce oscillations even when DNA is intact, or it may inhibit oscillations when DNA is damaged.

On the other hand, when one of p53 copies is missing, the system may remain in stable state even when DNA is damaged.

This may lead to haploinsufficiency and results in tumor, as the oscillations of p53 and Mdm2 are needed to initiate transcription of p53 dependent genes involved in cell cycle arrest, DNA repair or apoptosis.

The analysis implies also that behavior of transfected cells can be qualitatively different from normal cells and that observed oscillations could be an artifact of experimental setup.

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Lecture XIII: Simple compartmental models of hemodialysis.

Kidneys are paired organs which main role is to produce urine.

Urine takes waste metabolic products outside an organism and regulates amount of water, to keep proper osmolarity of body fluids.

Complete loss of kidney function causes death within few weeks.

However, with an adequate care a person can survive even if there is only about 5% of normal kidney functionality.

It is estimated that milder forms of chronic kidney disease (CKD) affect $5-7\%$ of the world population.

At the end of 2004:

- 1 783 000 people worldwide were undergoing treatment for end stage renal disease (ESRD, the last stage of CKD);
- 1 371 000 (77%) people were on dialysis treatment;
- 412 000 (23%) people were living with a functioning renal transplant.

It is also estimated that the number of patients receiving renal replacement therapy (RRT) increases about $6-7\%$ per year.

Hemodialysis is a renal replacement therapy, which is typically conducted in a hospital or a dedicated clinic.

It uses a designated hardware called the dialyzer.

Dialyzer filters the blood flowing in the extracorporeal circuit.

Blood filtration occurs by solutes diffusion through a semi-permeable membrane that separates the blood and dialysate (special sterilized solution).

To maintain concentration gradient and thus higher solutes removal rate (higher therapy efficacy) dialysate flows in the opposite direction to the blood flow.

Water removal called ultrafiltration (UF) is achieved by altering the hydrostatic pressure of the dialysate compartment.

The hemodialysis efficacy can be controlled by:

- using different membranes,
- altering the flow rates in the dialyzer.
- altering the hydrostatic pressure in the dialysate compartment.

Compartment models of hemodialysis

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In the compartment models of hemodialysis we assume that the solutes to remove from the system are dissolved in body water which can be divided into several compartments.

In the model one needs to make a proper division of water into compartments and to correctly describe the possible flow of solutes between those compartments.

We assume that the change of the total water volume in the body is described by the linear relationship

$$V(t) = V(0) + (G_w - UFR)t,$$

where

- G_w describes the water intake,
- ultrafiltration rate (UFR) is non-zero (positive) only during the HD interval.

In some cases it is convenient to assume that the changes in the amount of water have small impact on the overall amount of the removed solute, and therefore

$$V(t) = \text{const.}$$

In the first attempt to model the effect of HD, it was assumed that there is only one compartment, i.e. all body fluids and plasma water are considered as one volume of distribution.

The dynamics imposed on the total solute mass in the considered compartment reads

$$\frac{d}{dt}(V(t)C(t)) = -KdC(t) + G - KrC(t),$$

where

- $C(t)$ is the solute concentration,
- G is the generation rate of the solute,
- Kr is the residual kidney clearance (equal to zero when there is complete renal failure),
- Kd is the dialyzer clearance (non-zero and positive only during HD session).

Simplifying the model by assuming constant volume during the HD session ($V(t) \equiv V$) we can easily calculate the solute concentration achieved after time T of the treatment:

$$C(T) = \frac{1}{Kd + Kr}\left(G + (C(0)(Kd + Kr) - G)\exp\left(-\frac{Kd + Kr}{V}T\right)\right).$$

Let C_{end} be the solute concentration which should be achieved at the end of the HD session.

Using the model we may calculate the time needed to reach C_{end} starting from the initial concentration $C(0)$:

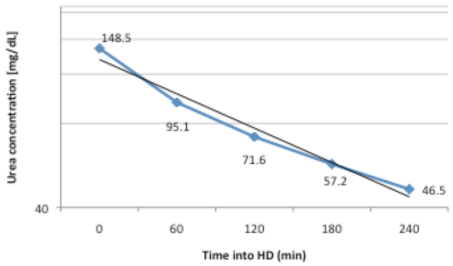
$$T = \frac{V}{Kd + Kr}\ln\frac{G - C(0)(Kd + Kr)}{G - C_{\text{end}}(Kd + Kr)}.$$

If we further assume that the solute generation rate G and kidneys residual clearance Kr are negligible, we obtain

$$T = \frac{V}{Kd} \ln \frac{C(0)}{C_{\text{end}}}.$$

This simplified formula is used to calculate the necessary treatment duration.

Comparison of experimentally measured urea concentration during hemodialysis (diamonds) and exponential decrease predicted by one-compartment model (black, solid line); Y-axis plotted in logarithmic scale:

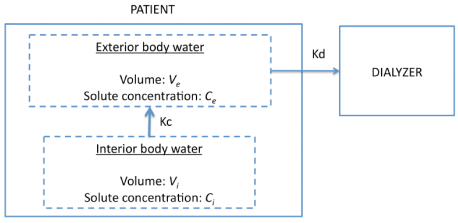


We see that the one-compartmental model poorly agrees with the experimental data concerning the dynamic of solute removal during the HD session.

The experimental concentration profiles show that initial fast decline in the concentration is slowed down further into the HD session more than the one-compartment model predicts.

In order to increase the accuracy of the model one needs to consider introduction of additional compartments for the body water and propose the mechanism of solute exchange between those compartments.

In the two-compartment model it is assumed that the body fluids are divided into two compartments: directly and indirectly accessible for the dialyzer.



A two-compartment model for the transport of solute from the extracellular compartment of the body during HD is described by the following set ordinary differential equations:

$$\begin{aligned} \frac{d}{dt}(V_e(t)C_e(t)) &= Kc(C_i(t) - C_e(t)) - KdC_e(t) + G - KrC_e(t), \\ \frac{d}{dt}(V_i(t)C_i(t)) &= -Kc(C_i(t) - C_e(t)), \end{aligned} \tag{55}$$

where:

- where Kc is the inter-compartmental clearance rate,
- the volumes of extracellular (V_e) and intracellular (V_i) compartments are related

to total body volume V as:

$$V = V_e + V_i, \quad V_e = \alpha V.$$

In Eqs. (55) the solute generation G is incorporated into the extracellular compartment, which is a valid assumption for urea.

However, for creatinine it seems more appropriate to incorporate it into intracellular compartment as most of the creatinine is generated in muscles, and hence one should assume that G is incorporated into the equation describing intracellular concentration.

If, as before, we assume the constant volume $V = \text{const}$, then Eqs. (55) can be solved as a non-autonomous linear system of equations.

Moreover, if, again as before, we assume no kidney function $Kr = 0$ and no generation of solute $G = 0$, then the simplified system reads

$$\begin{aligned} \alpha V \frac{d}{dt}(C_e(t)) &= Kc(C_i(t) - C_e(t)) - KdC_e(t), \\ (1-\alpha V)\frac{d}{dt}(C_i(t)) &= -Kc(C_i(t) - C_e(t)), \end{aligned} \tag{56}$$

and we can solve it easily.

Clearly, the matrix of this system has the form

$$\begin{pmatrix} -\frac{Kc+Kd}{\alpha V} & \frac{Kc}{\alpha V} \\ \frac{Kc}{(1-\alpha)V} & -\frac{Kc}{(1-\alpha)V} \end{pmatrix}$$

implying the characteristic equation of the form

$$\alpha(1-\alpha)V^2\lambda^2 + (Kc + (1-\alpha)Kd)V\lambda + KcKd = 0.$$

Assume further $\alpha = 0.5$. Then the characteristic equation simplifies to

$$V^2\lambda^2 + 2(2Kc + Kd)V\lambda + 4KcKd = 0,$$

yielding eigenvalues

$$\lambda_1 = \frac{-(2Kc + Kd) + \sqrt{4Kc^2 + Kd^2}}{V}, \quad \lambda_2 = \frac{-(2Kc + Kd) - \sqrt{4Kc^2 + Kd^2}}{V}.$$

In general, solutions can be calculated as linear combinations of the exponential functions

$$\exp(\lambda_1 t), \quad \exp(\lambda_1 t)$$

with eigenvectors constituting the relation between both coordinates C_e and C_i of the solution.

More precisely, let us denote by $[v_1, v_2]^T$ the eigenvector for λ_1.

Then

$$\begin{pmatrix} -2\frac{Kc+Kd}{V} - \lambda_1 & 2\frac{Kc}{V} \\ 2\frac{Kc}{V} & -2\frac{Kc}{V} - \lambda_1 \end{pmatrix}\begin{pmatrix} v_1 \\ v_2 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$$

yielding

$$2Kcv_1 + (Kd - \omega)v_2 = 0, \quad \omega = \sqrt{4Kc^2 + Kd^2},$$

and therefore $[\omega - Kd, 2Kc]^T$ is the eigenvector.

Hence, $[(\omega - Kd)\,\mathrm{e}^{\lambda_1 t}, 2Kc\,\mathrm{e}^{\lambda_1 t}]$ is one of the two independent solutions of Eqs. (56).

The other solution can be obtained similarly, looking for eigenvector for λ_2.

We have

$$\begin{pmatrix} -2\frac{Kc+Kd}{V} - \lambda_2 & 2\frac{Kc}{V} \\ 2\frac{Kc}{V} & -2\frac{Kc}{V} - \lambda_2 \end{pmatrix}\begin{pmatrix} v_1 \\ v_2 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix} \Longleftrightarrow \begin{pmatrix} \frac{\omega - Kd}{V} & 2\frac{Kc}{V} \\ 2\frac{Kc}{V} & \frac{Kd+\omega}{V} \end{pmatrix}\begin{pmatrix} v_1 \\ v_2 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$$

so $[\omega + Kd, -2Kc]^T$ is the eigenvector, and hence, $[(\omega + Kd)\,\mathrm{e}^{\lambda_2 t}, -2Kc\,\mathrm{e}^{\lambda_2 t}]$ is the other independent solution of Eqs. (56).

Eventually, if we assume equilibrated initial concentrations ($C_e(0) = C_i(0)$), then we obtain the following expression for the extracellular concentration after time T of the treatment:

$$C_e(t) = \frac{C_e(0)}{\omega}\exp\left(-\frac{2Ks + Kd + \omega}{V}T\right)\left(\omega + 2Kc\left(\mathrm{e}^{\frac{2\omega T}{V}} - 1\right) + \mathrm{e}^{\frac{2\omega T}{V}}(\omega - Kd) + Kd\right).$$

The formula above shows that the first exponential decrease term, which is analogous to the one-compartment model, is compensated by the increasing value of the second term.

Hence, the compartmental model is capable to reflect the slowdown in the solute concentration decrease rate.

However, due to the form of the solution, we are unable to obtain closed form expression for the time of therapy needed to reach the specified concentration, as it was possible for one compartment model.

Moreover, we have mentioned, that different equations should be assumed for urine and creatinine.

Therefore, we propose more complex, four-compartmental model.

In general, the N-compartment model with time dependent volumes, $V_n(t)$, and concentrations of the solute, $C_n(t)$, can be described by the following set of differential equations:

$$\frac{d}{dt}\left(V_n(t)C_n(t)\right) = \sum_{i=1}^{N} k_{ni}C_i(t) + G_i, \quad n = 1, \ldots, N,$$

where:

- coefficients k_{ni} describe the solute exchange or removal in terms of solute clearance,
- G_i models solute mass input to the ,th compartment in terms of generation rate.

Let us define

$$b_{ni} = \begin{cases} k_{ni} & \text{for } n \neq i, \\ k_{nn} - \dfrac{d}{dt}V_n(t) & \text{for } n = i. \end{cases}$$

Then the model reads

$$V_n(t)\frac{d}{dt}C_n(t) = \sum_{i=1}^{N} b_{ni}C_i(t) + G_i, \quad n = 1, \ldots, N,$$

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which can be rewritten in the matrix form

$$\mathbf{V} \cdot \frac{d}{dt}\mathbf{C} = \mathbf{B}\mathbf{C} + \mathbf{G},$$

with $\mathbf{V} = [V_1, \ldots, V_N]^T$, $\mathbf{C} = [C_1, \ldots, C_N]^T$, $\mathbf{G} = [G_1, \ldots, G_N]^T$, and $\mathbf{B}$ is the matrix of the coefficients b_{ni}.

Assume that the volume changes are described by linear functions of time:

$$\mathbf{V}(t) = (V_0 + Qt)\mathbf{r}, \quad \mathbf{r} = [r_1, \ldots, r_N], \ \sum_{i=1}^{N} r_i = 1,$$

where:

- V_0 is the total volume of all compartments at time $t = 0$,
- Q refers to the negative ultrafiltration rate, $Q < 0$, during hemodialysis (HD), or to the positive fluid accumulation rate, $Q > 0$, during the interdialytic interval (ID),
- r_n refers to the fractional volume of each compartment.

Next, let us normalize the volume to the initial value

$$\omega := \frac{V_0 + Qt}{V_0},$$

and notice, that ω is a linear function of t.

Using the definition of ω we again rewrite the system in the form

$$\frac{V_0}{Q}\omega \cdot \frac{d}{dt}\mathbf{C} = \mathbf{A}\mathbf{C} + \mathbf{g}, \tag{57}$$

where

$$\mathbf{A} = (a_{ni})_{ni=1}^{N}, \quad a_{ni} = \frac{b_{ni}}{r_n Q}, \quad \mathbf{g} = [g_1, \ldots, g_N], \quad g_n = \frac{G_n}{r_n Q}.$$

We will prove the following theorem about solutions of Eqs. (57).

Theorem 12. *The analytical expressions for the concentrations defined by Eqs.* (57)*, assuming that matrix* $\mathbf{A}$ *has* N *distinct eigenvalues, have the form*

$$C_n(t) = \sum_{i=1}^{N} x_{ni}\omega^{\lambda_i}(t) + d_n, \quad n = 1, \ldots, N. \tag{58}$$

To prove Theorem 12 we will need the following lemma:

Lemma 13. *Consider the general system of equations of the form*

$$(p + qt)\frac{d}{dt}\mathbf{C}(t) = \mathbf{A}\mathbf{c}(t) + \mathbf{B}, \quad p + qt \neq 0 \tag{59}$$

with $\mathbf{A}$ *having* N *distinct eigenvalues. If* $\mathbf{B}$ *belongs to the image of the linear transformation defined by* $\mathbf{A}$*, then solutions of Eqs.* (59) *have the form*

$$\mathbf{C}(t) = \left(\frac{p + qt}{p}\right)^{\mathbf{A}/q} (\mathbf{C}(0) - \mathbf{d}) + \mathbf{d}, \tag{60}$$

where $\mathbf{d}$ *satisfies* $\mathbf{B} = -\mathbf{A}\mathbf{d}$.

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Proof: Let us notice first that

$$\mathbf{A}u^{\mathbf{A}} = u^{\mathbf{A}}\mathbf{A}$$

for any scalar $u > 0$. This is a consequence of one of the possible definitions of the function $\mathrm{e}^{\mathbf{A}}$.

We have

$$\mathrm{e}^{\mathbf{A}} = \sum_{n=0}^{\infty} \frac{\mathbf{A}^n}{n!}, \tag{61}$$

and it is obvious that $\mathbf{A}$ is commutative with $\mathrm{e}^{\mathbf{A}}$.

Let us notice that for any $u > 0$ we have

$$u^{\mathbf{A}} = \mathrm{e}^{\ln u^{\mathbf{A}}} = \mathrm{e}^{\ln u\mathbf{A}}$$

giving the required commutativity property.

Let us take $\mathbf{C}$ of the form (60). Then

$$\mathbf{AC} + \mathbf{B} = \mathbf{A}\left(\frac{p+qt}{p}\right)^{\mathbf{A}/q}(\mathbf{C}(0) - \mathbf{d}) + \mathbf{Ad} + \mathbf{B} = \mathbf{A}\left(\frac{p+qt}{p}\right)^{\mathbf{A}/q}\mathbf{C}(0) + \left(\frac{p+qt}{p}\right)^{\mathbf{A}/q}\mathbf{B}.$$

Moreover, calculating the derivative of $\mathbf{C}(t)$ one gets

$$\frac{d}{dt}\mathbf{C} = \frac{\mathbf{A}}{p+qt}\left(\frac{p+qt}{p}\right)^{\mathbf{A}/q}(\mathbf{C}(0) - \mathbf{d})$$

(the result of calculating the derivative for this matrix function is exactly the same as for any scalar function due to Formula (61)).

Comparing the last two formulas we see that Eq. (60) solves (59).

For any matrix $\mathbf{A}$ with distinct eigenvalues we can also use Lagrange-Sylvester formula

$$f(A) = \sum_{n=1}^{N} f(\lambda_n) \prod_{\substack{k=1 \\ k \neq n}}^{N} \frac{\mathbf{A} - \lambda_k \mathbb{I}}{\lambda_n - \lambda_k} \tag{62}$$

Using (62) for $f(\mathbf{A}) = u^{\mathbf{A}}$ we also easily see that

$$u^{\mathbf{A}}\mathbf{x}_n = \mathbf{x}_n u^{\lambda_n}$$

for any eigenvector $\mathbf{x}_n$ corresponding to the eigenvalue λ_n.

As it is always possible to represent the N-dimensional vector in the relevant basis, we can write the following:

$$\mathbf{C}(0) - \mathbf{d} = \sum_{n=1}^{N} \mathbf{y}_n s_n,$$

where $\mathbf{y}_n$ is the normalized eigenvector.

Therefore, the analytical solution of (59) reads

$$\mathbf{C}(\mathbf{t}) = \mathbf{d} \sum_{n=1}^{N} \mathbf{y}_n s_n \, \mathrm{e}^{\lambda_n}(t).$$

For the model of hemodialysis we have

$$p + qt = \frac{V_0}{Q}\omega(t) = \frac{V_0 + Qt}{Q} \implies q = 1,\ p = \frac{V_0}{Q},$$

hence

$$\mathbf{C}(t) = \omega^{\mathbf{A}}(t)(\mathbf{C}(0) - \mathbf{d}) + \mathbf{d}$$

is the solution of Eqs. (57).

Notice, that due to the knowledge of analytic solutions we are able to predict the duration of hemodialysis period T, however exact values of T cannot be calculated for more than one compartment model.

On the other hand, we are able to make some approximations to calculate T.

Lecture XIV: Role of Hill coefficient: Mackey-Glass model of haematopoiesis.

There are many acute physiological diseases where the initial symptoms are manifested by an alteration or irregularity in a control system which is normally periodic, or by the onset of an oscillation in a hitherto non-oscillatory process.

Such physiological periodic diseases have been termed dynamical diseases by Glass and Mackey (1979) who have made a particular study of several important physiological examples.

In this lecture we will focus on haematopoiesis, which is connected with the formation of blood cell elements in the body.

White and red blood cells, platelets and so on are produced in the bone marrow from where they enter the blood stream.

When the level of oxygen in the blood decreases this leads to a release of a substance which in turn causes an increase in the release of the blood elements from the marrow.

This forms a feedback from the blood to the bone marrow.

Abnormalities in the feedback system are considered major suspects in causing periodic haematological diseases in general and this one is no exception.

Now, we describe a simple model of haematopoiesis.

Let $c(t)$ be the concentration of cells (the population species) in the circulating blood (the units of c are, say, cells/mm^3).

We assume that the cells are lost at a rate proportional to their concentration, that is, like gc, where the parameter g has dimensions (day)$^{-1}$.

After the reduction in cells in the blood stream there is about a 6-day delay before the marrow releases further cells to replenish the deficiency.

Therefore, we assume that the flux F of cells into the blood stream depends on the cell concentration at an earlier time, namely, $c(t-T)$, where T is the delay.

Such assumptions suggest a model that reads

$$\dot{c}(t) = F\big(c(t-T)\big) - gc(t). \tag{63}$$

Eq. (63) is an example of delay differential equation (DDE).

Delay equations such as Eq. 63 describe systems in which a stimulus has a delayed response.

There are many practical examples from physics, economics, biology and other fields in which such type of equations are useful.

Mackey and Glass (1977) proposed two possible forms for the function $F(\cdot)$.

We consider the following one:

$$F(x) = \frac{\alpha a^m x}{a^m + x^m}, \tag{64}$$

where α, a, m are positive constants.

Using the function F of the form (64) and defining new variable

$$x(t) = \frac{c(t)}{a}$$

we obtain the final model

$$\dot{x}(t) = \alpha \frac{x(t-T)}{1+x^m(t-T)} - gx(t), \quad \alpha,\ g > 0. \tag{65}$$

Eq. (65) has become popular in chaos theory, especially as a model for producing high dimensional chaos to test various methods of chaotic time series analysis.

In such studies one keeps usually the parameters α, m, and g fixed at

$$\alpha = 0.2, \quad m = 10, \quad g = 0.1, \tag{66}$$

and varies the delay time T.

On the other hand, it is also interesting to vary the Hill coefficient m.

Notice, that to solve Eq. (65) we need to know the function x on the whole interval of the length T.

Therefore, initial data reads

$$t_0 = 0, \quad x(t) = \phi(t) > 0,\ t \in [-T, 0].$$

Having such initial function ϕ we are able to solve Eq. (65) on the interval $[0, T]$.

Clearly, let $t \in [0, T]$. Then Eq. (65) takes the form

$$\dot{x}(t) = \alpha \frac{\phi(t-T)}{1+\phi^m(t-T)} - gx(t),$$

which is a non-autonomous ordinary differential equation.

Solving it we obtain

$$x(t) = \phi(0)\,\mathrm{e}^{-gt} + \mathrm{e}^{-gt} \int_0^t \frac{\alpha\phi(s-T)}{1+\phi^m(s-T)}\,\mathrm{e}^{gs}\,ds = \phi(0)\,\mathrm{e}^{-gt} + \int_{-T}^{t-T} \frac{\alpha\phi(s)\,\mathrm{e}^{g(s-t+T)}}{1+\phi^m(s)}\,ds, \tag{67}$$

and it is obvious that it is enough to assume that the function

$$\frac{\phi(s)\,\mathrm{e}^{gs}}{1+\phi^m(s)}$$

is integrable.

However, we typically take continuous initial function ϕ.

We see that continuing this procedure of solving Eq. (65) on the intervals $[n(T-1), nT]$, $n \in \mathbb{N}$, we can define the solution for all $t >= 0$.

This procedure of solving DDEs is called the step method.

Moreover, Formula (67) implies positivity of the solution for positive initial data.

Corollary 14. *For any non-negative initial function ϕ the solution of Eq.* (65) *exists, is unique and non-negative.*

The number of parameters in Eq.(65) can be reduced more by dividing this equation by g and changing the time scale $tg \longrightarrow t$.

The parameters T and α are transformed as follows:

$$Tg \longrightarrow T \quad \text{and} \quad \frac{\alpha}{g} \longrightarrow \alpha.$$

As a result, the given set of the parameters becomes $\alpha = 2$, $m = 10$, $g = 1$, and T is ten times smaller than before scaling, which is important from the computational point of view.

The changes in the qualitative behaviour of the attractor as the parameter T is varied are as follows:

- instability occurs at $T = T_1 \approx 0.471$,
- for $0.471 < T < 1.33$, there is a stable limit cycle attractor,
- period doubling bifurcation sequence is observed at $1.33 < T < 1.68$,
- for $T > 1.68$, numerical simulations show chaotic attractors at most parameter values.

Looking for steady states of Eq. (65) we observe that steady states are the solutions independent of time, that is they are the same for the system with delay and the corresponding non-delayed system

$$\dot{x}(t) = \alpha \frac{x(t)}{1 + x^m(t)} - g x(t), \quad \alpha,\ g > 0. \tag{68}$$

We easily see that there is the trivial steady state $\bar{x}_0 \equiv 0$, while a positive steady state satisfies

$$\frac{\alpha}{1 + x^m(t)} = g.$$

Therefore,

$$\bar{x}_1 = \sqrt[m]{\frac{\alpha - g}{g}}$$

exists if $\alpha > g$.

For the specific parameter values $\bar{x}_1 = 1$.

Studying local stability of steady states we use the same framework as for ODEs, that is we look for the solution of the linearized system in the exponential form.

Let $y = x - \bar{x}$ be a small deviation from the steady state.

Using Taylor expansion we obtain

$$\begin{aligned} \dot{y} &= \alpha \frac{y(t-T) + \bar{x}}{1 + (y(t-T) + \bar{x})^m} - g(y(t) + \bar{x}) \\ &= \alpha \frac{1 - (m-1)\bar{x}^m}{(1 + \bar{x}^m)^2} y(t-T) - g y(t) + \dots \end{aligned} \tag{69}$$

In general, we have to analyse linear equation of the form

$$\dot{x} = ax(t) + bx(t-T), \quad a,\ b \in \mathbb{R}. \tag{70}$$

Depending on the signs and magnitude of a and b we observe different dynamics of Eq. (70).

Looking for solutions of Eq. (70) in the exponential form $x(t) = e^{\lambda t}$ one gets

$$\lambda e^{\lambda t} = a e^{\lambda t} + b e^{\lambda(t-T)}$$

yielding the characteristic quasi-polynomial reads

$$W(\lambda) = \lambda - a - b e^{-\lambda T} \tag{71}$$

Zeros of W are called eigenvalues and determine stability of the trivial solution of Eq. (70).

However, there are infinitely many zeros of W, which makes the analysis more difficult than for the case without delay.

One can use so-called Mikhailov Criterion which considers quasi-polynomial of the general form

$$W(\lambda) = P(\lambda) + Q(\lambda) e^{-\lambda T},$$

where P and Q are polynomials, $p = \deg P > \deg Q = q$, and P, Q hes no zeros on the imaginary axis.

In such a case Mikhailov Criterion implies that:

Theorem 15. *The trivial solution of corresponding linear system of DDEs is asymptotically stable if and only if the increase of the argument of the vector $W(i\omega)$ in the complex plane equals to $\frac{p\pi}{2}$ when ω increases from 0 to ∞.*

For Eq. (71) we have $p = 1$ and $q = 0$.

Let us calculate what can be the change of the argument of the vector $W(i\omega)$ for Eq. (71).

We have:

$$W(i\omega) = i(\omega + b\sin(\omega T)) - (a + b\cos(\omega T)),$$

and hence

$$W(0) = -(a + b).$$

Therefore, if $a + b \neq 0$, we obtain

- $\arg W(0) = 0$ if $a + b < 0$,
- $\arg W(0) = \pi$ if $a + b < 0$.

Moreover,

$$\sin\big(\arg W(i\omega)\big) = \frac{\mathrm{Im} W(i\omega)}{|\arg W(i\omega)|}, \quad \cos\big(\arg W(i\omega)\big) = \frac{\mathrm{Re} W(i\omega)}{|\arg W(i\omega)|},$$

yielding

$$\sin\big(\arg W(i\omega)\big) = \frac{\omega + b\sin(\omega T)}{\sqrt{\omega^2 + o(\omega^2)}}, \quad \cos\big(\arg W(i\omega)\big) = \frac{-a - b\cos(\omega T)}{\sqrt{\omega^2 + o(\omega^2)}},$$

where $o(\omega^2)$ is a function having the property

$$\frac{o(\omega^2)}{\omega^2} \to 0 \text{ as } \omega \to \infty.$$

We easily see that

$$\sin\Big(\arg W(i\omega)\Big) \to 1 \quad \text{and} \quad \cos\Big(\arg W(i\omega)\Big) \to 0 \quad \text{as } \omega \to \infty.$$

Hence,

$$\arg W(i\omega) \to \frac{\pi}{2} + 2k\pi, \ k \in \mathbb{Z}.$$

It is obvious that the change of the argument of the vector $W(i\omega)$ can be equal to $\frac{\pi}{2}$ only when $W(0) > 0$ and $k = 0$, that is the Mikhailov hodograph which is the curve drawn by the vector $W(i\omega)$ does not make any loop around the origin.

Notice, that $a + b < 0$ is equivalent to the case when the trivial steady state of Eq. (70) is stable for $T = 0$.

Therefore, for one DDE with one delay it is not possible to have stability for positive delay if we have instability in the case without delay.

Now, let us assume that $a + b < 0$.

To have the change of stability for some critical T_{crit} one needs to have such ω, for which the vector $W(i\omega)$ crosses the imaginary axis in the negative half-line.

Therefore, we look for ω and T such that

$$\mathrm{Re}W(i\omega) = 0 \quad \text{and} \quad \mathrm{Im}W(i\omega) < 0,$$

that is

$$\cos(\omega T) = -\frac{a}{b} \quad \text{and} \quad \sin(\omega T) = -\frac{\omega}{b}. \tag{72}$$

Notice first that to have such value of cos one requires $|a| <= |b|$.

Hence, taking together both inequalities on a and b we obtain

- if $|a| > |b|$, that is the term with delay is dominated by the one without delay, then the change of stability with increasing delay is not possible, and therefore the stability is preserved for all $T > 0$ whenever it is for $T = 0$,
- if the term with delay dominates, then the change of stability is possible.

From Eqs. (72) we also have

$$\sin^2(\omega T) + \cos^2(\omega T) = 1 \quad \Longrightarrow \quad a^2 + \omega^2 = b^2,$$

and therefore

$$\omega = \omega_0 = \sqrt{b^2 - a^2},$$

so to have $\omega_0 > 0$ one needs $|b| > |a|$, that is the strict inequality.

The formula for ω_0 yields

$$\sin(\omega_0 T) = -\frac{\sqrt{b^2 - a^2}}{b}, \quad \cos(\omega_0 T) = -\frac{a}{b}.$$

As we know the value of ω_0, we are able to calculate $\omega_0 T$ as

- $\omega_0 T = \arccos\left(-\frac{\sqrt{b^2-a^2}}{b}\right)$ if both a and b are negative or $a = 0$, $b < 0$;
- $\omega_0 T = \arccos\left(\pi + \frac{\sqrt{b^2-a^2}}{b}\right)$ if $ab < 0$.

Hence, $T = T_{crit}$ equals

- either $T_{crit} = \frac{\arccos\left(-\frac{\sqrt{b^2-a^2}}{b}\right)}{\omega_0}$,
- or $T_{crit} = \frac{\arccos\left(\pi+\frac{\sqrt{b^2-a^2}}{b}\right)}{\omega_0}$.

Now, let us come back to Eq. (69).

For $\bar{x} = \bar{x}_0 = 0$ we obtain:

$$\dot{y} \approx \alpha y(t-T) - g y(t)$$

Notice, that for $T = 0$ we obtain the characteristic polynomial

$$W(\lambda) = \lambda + g - \alpha,$$

and therefore $W = 0$ for $\lambda = \alpha - g$.

Hence, the trivial steady state:

- is stable for $g > \alpha$, that is when the positive steady state does not exist,
- is unstable for $g < \alpha$, that is when the positive steady state exists.

Moreover, if the positive steady state exists, then the trivial steady state cannot gain stability, according to our analysis.

For our study stability of the positive steady state is of the main interest.

Making linearization we obtain

$$\dot{y} = g^2 \frac{m - \frac{\alpha}{g}(m-1)}{\alpha} y(t-T) - g y(t). \tag{73}$$

In fact, depending on α, g and m we are able to obtain various stability possibilities.

For the specific parameter values (66) the linearized scaled system reads:

$$\dot{y}(t) = -4y(t-T) - y(t)$$

for which the steady state is stable for $T = 0$ and loses stability for some critical value T_{crit} as $a = -1$ and $b = -4$ yield $a + b = -5 < 0$ and $4 = |b| > |a| = 1$.

For this parameter values we observe the change of the model dynamics with increasing delay.

One manifestation of leukaemia is the periodic oscillations observed in, for example, the white cell count.

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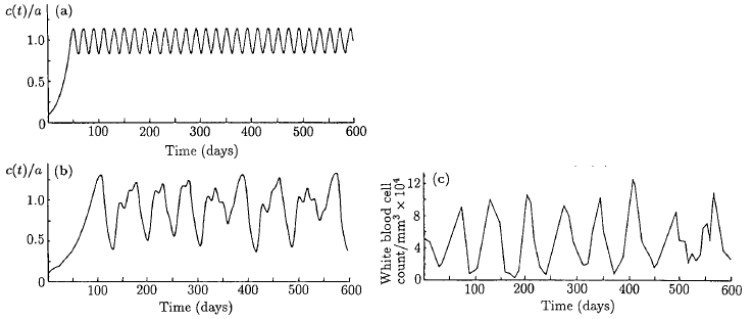
Below is an example from a 12-year-old patient with chronic myelogenous leukaemia. Although the overall character is quasi-periodic, it is in fact aperiodic.



(a) For $T = 6$ days the low amplitude oscillation has a period of about 20 days.

(b) For $T = 20$ days we observe the aperiodic behaviour of the solution which can be compared with (c).

(c) Circulating blood count of a 12-year-old girl suffering from chronic leukaemia. The rough period of the oscillation is about 72 days.

The qualitative change in the solution behaviour as the delay is increased is indicative of what is now referred to as chaos.

Basically chaos is when the solution pattern is not repetitive in any regular way.

An indication of periodic behaviour and of the onset of chaos can be obtained from the plot of $c(t - T)$ against $c(t)$ for various values of the parameters.

As we would like to study the role of Hill coefficient, we present the results of simulations for $m = 7, 7.5, 8, 10, 12$ and 19 (other parameter values for the original model with function (64) are $g = a = 1$, $\alpha = 2$ and the value of delay $T = 2$).

The behaviour in graph (a), where the phase plane trajectory is a simple closed curve, implies the solution is a simple periodic solution.

If we now look at graph (b), it looks a bit like a double loop trajectory of the kind in (a); you have to go round twice to return to where you started.

As before the solution is still periodic of course, but its appearance is like a mixture of two solutions of the type (a) but with different periods and amplitudes.

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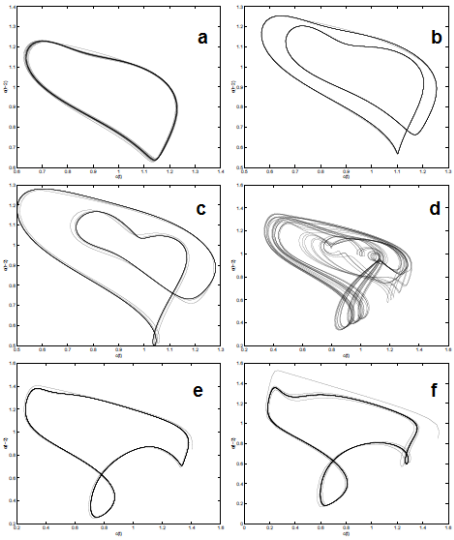

As m increases, the "phase plane" trajectories become progressively more complex suggesting quite complex solution behaviour for $c(t)$.

For the case in graph (d) the solution undergoes very many loops before it possibly returns to its starting point. In fact it never does!

This is an example of chaotic behaviour.

Although we have shown that the model solutions exhibit similar aperiodic behaviour as in the case of leukemia, it is dangerous to presume that this model is therefore the one governing white cell behaviour in leukaemia patients.

However, what this modelling exercise has demonstrated, among other things, is that delay can play a significant role in physiological pattern disruption.

In turn this suggests that a deficiency in bone marrow cell production could account for the erratic behaviour in the white cell count.

So although such a model can highlight important questions for a medical physiologist to ask, for it to be of practical use it is essential that close interdisciplinary collaboration is maintained so that realism is retained in making suggestions and drawing conclusions, however plausible they may be.

Summary.

During this course we have learned about various models of natural phenomena, mainly described by ordinary differential equations (ODEs).

Although the last model of Mackey-Glass was described as delay differential equation (DDE), it can be also studied in the framework of non-autonomous ODEs.

What is important from the modeling point of view?

- Checking whether the model is properly definite.
- Making as full as possible mathematical analysis to be sure that results obtained in computer simulations are not numerical artifacts.
- If it is possible, comparizon with real data can restrict parameter values that may be used to reflect the process we study.

We always should check the existence, uniqueness and prolongation of solutions, and if it is justified, non-negativity (if, for instance, the variable describe the size of population or other quantity measured in positive numbers).

What kind of the dynamics can be expected?

Using one autonomous differential equation of the form

$$\dot{x} = F(x)$$

we are not able to obtain oscillations.

Oscillatory dynamics can be produced by:

- including the dependance of time in one ODE, it can be also included as a delayed argument $x(t - T)$, $T > 0$ is a delay;
- describing the process using at least two ODEs.

Chaotic dynamics can be expected in:

- non-linear discrete models, even if the model is one-dimensional;
- at least three autonomous ODEs are needed;
- non-linear delay equation can also exhibit it.

Notice hear similarities between DDE and discrete system!

The main way to obtain chaos is a sequence of period doubling bifurcations.

Chaotic dynamics is also connected with strange attractors.

What type of attractors can appear?

- single steady state can be always an attractor, both local and global;

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- bi-stability appears when we have two stable steady states and the whole space (except trajectories connected with unstable state that separates two stable ones) is divided into two basins of attraction of the positive steady states;
- in more complex models there can be more stable steady states separated by unstable states;
- periodic orbit can attract other solutions as well, in this case non-autonomous equation or systems of equations are needed;
- more than one periodic orbit can attract solutions and in this case two periodic attractors must be somehow separated – if we consider the system of two equations, then two periodic attractors must be separated by another unstable periodic orbit;
- combination of periodic orbits and stable steady states is possible in complex models;
- strange attractors appear in the context of chaotic dynamics, when solutions have aperiodic structure.

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Proposition of questions on the exam:

1. Formulate the logistic equation. Explain the variable, parameters and terms appearing on the right-hand side of the equation.

2. Explain the role of coefficients r and K in the dynamics of the logistic equation.

3. Explain the difference between the dynamics of the logistic and Gompertz equation.

4. Explain the difference between the dynamics of the logistic equation and the model with Alee effect.

5. Explain the notion of bistability on some example of the population model with predation term.

6. Explain the notions of cusp catastrophe and hysteresis loop on some example.

7. Consider single autonomous differential equation dx/dt = f(x), where f has a continuous derivative. Explain why periodic dynamics is not possible in this model.

8. Consider the discrete logistic equation. Explain the way from stable steady state to chaotic dynamics.

9. Describe the classic Lotka-Volterra model (variables, parameters, terms).

10. Explain the rule of mean values preservation in the Lotka-Volterra model.

11. Explain the influence of hunting/fishing on the dynamics of predator in the Lotka-Volterra model.

12. What is the main feature of the pray-predator system?

13. Explain the rule of competitive exclusion in the context of competition model.

14. What are the possible behaviours in the competition model?

15. What is the influence of mutualism on the population dynamics?

16. Explain why the strange attractor appears in the Lorenz model.

17. Explain the Michaelis-Menten kinetics using quasi-stationary approach.

18. Describe one example of the immune reaction model.

19. What are the underlying equations for different types of antigens?

20. What is the mathematical explanation of sneaking through mechanism in tumour-immune system model?

21. Explain the idea of impulsive equations on the example of vaccinations.

22. Explain the idea of hemodialysis on some simple model.

23. Explain the role of the Hill coefficient in the description of any dynamics.

24. Give two examples of interesting dynamics connected with non-linearities in two dimensional models.

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