PRINCIPLES OF MATHEMATICAL MODELLING

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Lectures:

Tuesday: 9–11 (A201)

Exercises:

Tuesday: 11–13 (A201)

Consultations:

Monday: 14–16

Contents.

Mathematical models

- Exponential model
- Logistic model
- Tunor growth models (von Bertalanffy, Gompertz,...)
- Growth with limitation
- Model of bioreactor ('chemostat' model)
- Lotka-Volterra model (predator-prey model)
- Compartmental models
- Epidemiological models (SIS, SIR, ...)

Mathematical contents

- Prerequisite: derivation, integration
- Differential equations
- Solving differential equations
- Numerical solutions of differential equations
- Least squares method (determination of model parameters)
- Equilibria
- Stability of equilibria
- Partial derivative
- Eigenvalues of linear operator

Programming: 'Mathematica'

Grading

- 1. exam 50%
- 2. exam 50%
- Homework
- Repeated exam (maximal grade is 2)

GROWTH MODELS

1.1. EXPONENTIAL MODEL

1.1.1. Exponential function

Exponential function:

$$\exp : \mathbb{R} \to \mathbb{R},$$

(General) exponential function:

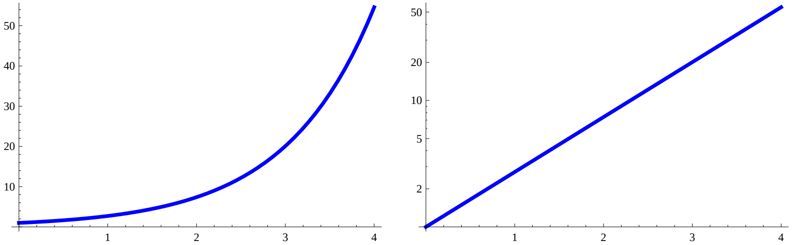
$$\exp_a : \mathbb{R} \to \mathbb{R},$$

a - base of exponential function, $a > 0$ and $a \neq 1$.

Notation:

$$\exp_a(x) = a^x$$

Graph of exponential function.



Definition of exponential function.

$$\exp(x) = \mathrm{e}^x \,.$$

NO!

Power series:

$$\exp x = \sum_{k=0}^{\infty} \frac{x^k}{k!}$$

or differential equation

$$f'(x) = f(x), \quad f(0) = 1,$$

or

$$\exp x = \lim_{n\to\infty} \left(1 + \frac{x}{n}\right)^n$$

Property:

$$\mathrm{e}^{x+y} = \mathrm{e}^x \, \mathrm{e}^y$$

Motivation for exponential function.

For $n \in \mathbb{N}$:

$$a^n = a \cdot a \cdot \ldots \cdot a$$

To extend property $f(x+y) = f(x)f(y)$ on $\mathbb{N}_0$:

$$a^n = a^{n+0} = a^n a^0 \quad \Rightarrow \quad a^0 = 1.$$

The same property we extend on $\mathbb{Z}$:

$$1 = a^0 = a^{n-n} = a^n a^{-n} \quad \Rightarrow \quad a^{-n} = \frac{1}{a^n},$$

and on $\mathbb{Q}$:

$$a = a^1 = a^{n\frac{1}{n}} = a^{\frac{1}{n}+\frac{1}{n}+\ldots+\frac{1}{n}} = \left(a^{\frac{1}{n}}\right)^n \quad \Rightarrow \quad a^{\frac{1}{n}} = \sqrt[n]{a}.$$

Property

$$f(x+y) = f(x)f(y)$$

uniquely define exponential function on $\mathbb{Q}$.
Can we this property extend on $\mathbb{R}$?

Theorem (1)

For given $a \in \mathbb{R}$, $a > 0$, there exists unique continuous function $f : \mathbb{R} \to \mathbb{R}$ satisfying $f(x+y) = f(x)f(y)$ for all $x, y \in \mathbb{R}$ and $f(1) = a$.

Theorem (2)

For given $a \in \mathbb{R}$, $a > 0$, there exists unique monotone function $f : \mathbb{R} \to \mathbb{R}$ satisfying $f(x+y) = f(x)f(y)$ for all $x, y \in \mathbb{R}$ and $f(1) = a$.

Definition

Function from Theorem 1 (2) for $a = f(1) > 0$ and $a \neq 1$ we call exponential function. Number a we call a base of exponential function.

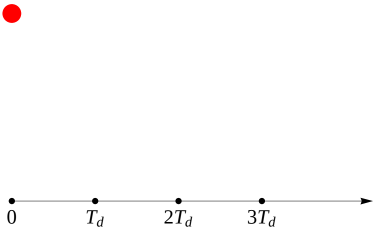
1.Homework

Prove Theorems 1. and 2.

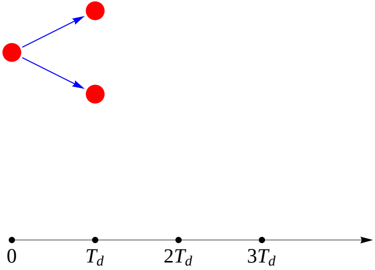
For those who want more: Show that a continuity is necessary condition for uniqueness, i.e., show that there exists a function satisfying $f(x+y) = f(x)f(y)$ for all $x, y \in \mathbb{R}$ and it is not continuosus.

1.1.2. Discrete exponential model

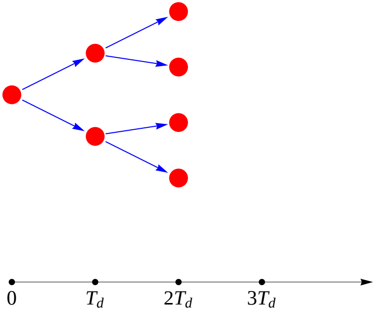
We observe cell where each cell divides after time T_d (exactly).
We start with one cell



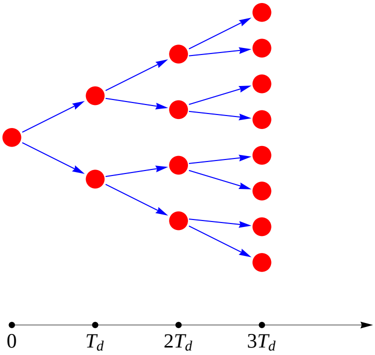
After time T_d it will divide and we will have two cells



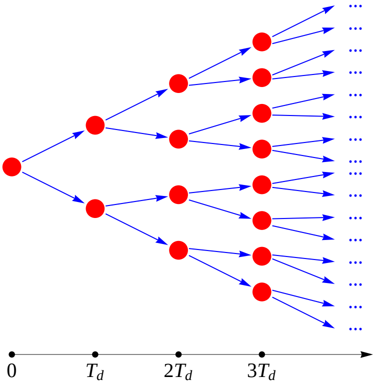
After time $2T_d$ each cell will divide and we will have 4 cells



After time $3T_d$ we will have 8 cells



etc.



Number of cells at time $t_i = i \cdot T_d$ is: $1, 2, 4, 8, 16, \ldots$.

(*Geometrical growth.*)

N - population size,

$$N_i := N(t_i) = 2^i.$$

Exponential function.
Exponential growth.

Different notation:

N_i - population size at time t_i
After period of T_d population will double:

$$N_{i+1} = 2N_i.$$

Diference equation.

Solution of diference equation:

$$N_i = 2N_{i-1} = 2^2 N_{i-2} = \ldots = N_0 2^i.$$

Solution is not unique.
With given initial value N_0 at time t_0 the solution will be unique.

Thomas Robert Malthus (1766-1834)

- English economist and demographist

- He was the first who used exponential function for the description of a population growth.

- Malthusian growth

- "An Essay on the Principle of Population" (1798)

1.1.3. Derivation of exponential model

- Assumption that all cells divide at the same time is unrealistic.

- More realistic: cells are mixed and divide at different moments.

- Time between two divisions (T_d) is not the same for all cells.

- **Doubling time** is the average time it takes for a population to double in number.

Assumption

All cells divide exactly after the same time T_d.

- Doubling time (average time for division) should not be constant with the respect on time.

- For example, it depends on availability of substrate (food).

Define gain function

$$G(N(t), h) = N(t+h) - N(t).$$

G does not depend on t explicitly.

If we start to observe population gain of size N at different time points t, after the time interval h the gain is the same.

- We consider a system that is not influenced by external factors.

Simpler notation: $N = N(t)$.

First consider dependence of gain function G on population size.

For fixed h define function

$$g_h(N) = G(N, h).$$

Divide population on two subpopulations of sizes M i N.

Each of them continues to grow under the same conditions:

$$G(N(t), h) = N(t+h) - N(t) \quad \text{i} \quad G(M(t), h) = M(t+h) - M(t).$$

On the other side, two populations can be considered as one population:

$$\begin{aligned} G(N(t)+M(t), h) &= N(t+h) + M(t+h) - N(t) - M(t)) = \\ &= G(N(t), h) + G(M(t), h), \end{aligned}$$

i.e.,

$$g_h(N+M) = g_h(N) + g_h(M).$$

Cauchy's functional equation

$$f(x+y) = f(x) + f(y).$$

$\Rightarrow$ f is linear function on $\mathbb{Q}$: $f(x) = ax$.

What about $\mathbb{R}$?

If f is monotonic (or continuous) $\Rightarrow$ f is linear function on $\mathbb{R}$.

Note: function G is monotonic (increasing) with the respect to N and h.

Larger population $\rightarrow$ larger gain

$\Rightarrow$ G is monotonic by variable N and g_h is monotonic (increasing) function.

g_h is linear function $\rightarrow$ G is linear in variable N:

$$g_h(N) = aN = a(h)N.$$

Gain function:

$$N(t+h) - N(t) = G(N(t), h) = a(h)N(t).$$

$\Rightarrow$

$$N(t+h) = a(h)N(t) + N(t) = (1 + a(h))N(t) = b(h)N(t).$$

Population increase after time $h_1 + h_2$:

$$N(t + h_1 + h_2) = b(h_1 + h_2)N(t).$$

On the other side,

$$N(t + h_1 + h_2) = b(h_2)N(t + h_1) = b(h_1)b(h_2)N(t).$$

Equalize right sides:

$$b(h_1 + h_2) = b(h_1)b(h_2).$$

G is monotonic function in variable h $\quad\Rightarrow\quad$ b is monotonic function.

b is exponential function:

$$b(h) = \mathrm{e}^{\alpha h}$$

and

$$N(t+h) = \mathrm{e}^{\alpha h} N(t).$$

Especially, for $t = 0$ and $h = t$, we obtain expresion for N:

$$N(t) = N(0)\,\mathrm{e}^{\alpha t}\,.$$

- exponential model

- model function

- $N(0)$ and α are model parameters

Instead of: cells divide after time T_d, exactly

We may consider: all cells have the same probability of splitting and this probability is time independent. $\Rightarrow$ In population of relatively large number of cells, average doubling time will be constant.

Derivation of exponential model from this assumption is the same as previous derivation. (Note: if population is divided in two parts, for both parts, assumption about the same probability of splitting holds.)

Cauchy's functional equation

$$f(x+y) = f(x) + f(y), \quad \forall x \in \mathbb{R}.$$

and f is monotonic (continuous).
Then f is a linear function.

Proof. First, we show that $f(x+y) = f(x) + f(y)$ is a linear function on $\mathbb{Q}$.

For $m \in \mathbb{N}$:

$$f(mx) = m\, f(x).$$

Now, for $n \in \mathbb{N}$:

$$f(x) = f\left(n\frac{1}{n}x\right) = n\, f\left(\frac{1}{n}x\right).$$

$$\Rightarrow \quad f\left(\frac{1}{n}x\right) = \frac{1}{n} f\left(x\right).$$

Hence, for all $r \in \mathbb{Q}$, $r = \frac{m}{n}$, we have

$$f(r\,x) = r\,f(x)\,.$$

f is linear function, but only on $\mathbb{Q}$.

Let $a \in \mathbb{R}$ is given.

$\mathbb{Q}$ is dense in the set $\mathbb{R}$ $\quad \Rightarrow$
for arbitrary $\delta > 0$ there exists $r_1, r_2 \in \mathbb{Q}$ such that $r_1 < a < r_2$, $|a - r_1| < \delta$ and $|a - r_2| < \delta$.

f is monotonic (increasing) $\quad \Rightarrow$

$$f(ay) - af(y) \leq f(r_2 y) - af(y) = r_2 f(y) - af(y) = (r_2 - a)f(y).$$

Similarly,

$$f(ay) - af(y) \geq f(r_1 y) - af(y) = r_1 f(y) - af(y) = (r_1 - a)f(y).$$

Therefore,

$$\begin{aligned} |f(ay) - af(y)| &\leq \max\{|r_1 - a|, |r_2 - a|\}|f(y)| \leq \\ &\leq \delta|f(y)| \end{aligned}$$

for all $\delta > 0$.

$$\Rightarrow \quad f(ay) - af(y) = 0,$$

i.e.

$$\Rightarrow \quad f(ay) = af(y)$$

for arbitrary $a \in \mathbb{R}$.

$$\Rightarrow \quad f(x) = f(x \cdot 1) = x\,f(1)$$

f is a linear function.

Q.E.D.

1.1.4. Taylor expansion of the gain function

Taylorov mean value theorem:

$$
\begin{aligned}
f(x+h) &= f(x) + f'(x)h + \frac{1}{2}f''(x)h^2 + \ldots + \frac{1}{k!}f^{(k)}(x)h^k + \\
&\quad + \frac{1}{(k+1)!}f^{(k+1)}(\zeta)h^{k+1}.
\end{aligned}
$$

For $k = 2$:

$$f(x+h) = f(x) + f'(x)h + \frac{1}{2}f''(x)h^2 + \mathcal{O}(h^3).$$

Function f is approximates by polinomial:

$$f(x+h) = a + bh + ch^2 + \mathcal{O}(h^3) = P_2(h) + \mathcal{O}(h^3).$$

Gain function

$$G(N(t), h) = N(t+h) - N(t)$$

depends on two variables: N i h.

$$G(N, h) = P_2(N, h) + \mathcal{O}.$$

(remainder $\mathcal{O}$ consists of third powers and higher)

'Neglect' $\mathcal{O}$:

$$G(N, h) = a + bh + cN + dh^2 + ehN + fN^2.$$

1. For $N = 0$ (no population) a gain is 0 $\quad G(0,h) = 0, \ \ \forall h \quad \Rightarrow$

$$0 = G(0,h) = a + bh + dh^2, \quad \forall h$$

$\Rightarrow a = b = d = 0$

Now,

$$G(N,h) = cN + ehN + fN^2.$$

2. For $h = 0$ (no time laps) a gain is 0 $\quad G(N,0) = 0, \ \ \forall N \quad \Rightarrow$

$$0 = G(N,0) = cN + fN^2, \quad \forall N$$

$\Rightarrow c = f = 0$

Now,

$$G(N,h) = ehN =: \alpha hN.$$

$$G(N,h) = \alpha h N.$$

$$N(t+h) - N(t) = \alpha h N(t).$$

$$\frac{N(t+h) - N(t)}{h} = \alpha N(t). \quad / \lim_{h\to 0}$$

$$N'(t) = \alpha N(t).$$

Differential equation

Function $N_0\,\mathrm{e}^{\alpha t}$ is a solution.

Is it unique?

1.1.5. Application of exponential model

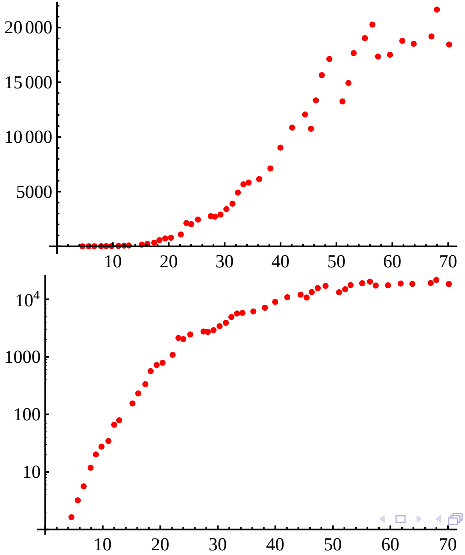
Implicit assumption: unlimited access to food

Applicable in initial phase of growth.

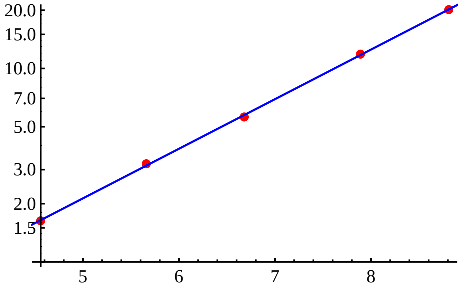
Exponential function is unbounded!

Example

Growth of tunor cells (volume is shown).



Choose first 5 data points:



Data coincide with an exponential curve!

Doubling time

Funkcija:

$$N(t) = N_0\, e^{\alpha t}$$

T_d - doubling time

$$N(t + T_d) = 2N(t)$$

$$N_0\, e^{\alpha(t+T_d)} = 2N_0\, e^{\alpha t}$$

$$e^{\alpha t}\, e^{\alpha T_d} = 2\, e^{\alpha t}$$

$$e^{\alpha T_d} = 2$$

$$\alpha = \frac{\ln 2}{T_d}$$

1.2. Differential equations
1.2.1. Definition and example

Exponential model:

$$y(t) = N_0\, e^{\alpha t}$$

or

$$y'(t) = \alpha y(t), \quad N(0) = N_0, \quad \forall t$$

Model is described by differential equation!

Interpretation of derivative:

- tangent (Leibniz)

- **velocity** (Newton)

Definition

Let $f : [a, b] \times \mathbb{R} \to \mathbb{R}$ be a given function. Then an equation of the form

$$y'(t) = f(t, y(t)) \quad \forall t \in [a, b]$$

is named **ordinary differential equation (ODE)**.
Function $y : [a, b] \to \mathbb{R}$ satisfying this equation is named a **solution of (ordinary) differential equation**.

- We will use shorter form: **differential equation**

- It is common to omit argument t in the notation of a function y

- $\forall t \in [a, b]$ is also omitted (maximal domain is assumed):

$$y' = f(t, y)$$

Examples.

Example 1.

$$y'(t) = \alpha y(t)$$

$$\Rightarrow \quad f(t, y(t)) = \alpha y(t) \quad \Rightarrow \quad f(t, y) = \alpha y$$

Shorter:

$$y' = \alpha y$$

Example 2. Check if $y(x) = \mathrm{e}^x$ is a solution of the equation

$$y' = y?$$

$$y(x) = \mathrm{e}^x \quad \Rightarrow \quad y'(x) = \mathrm{e}^x$$

$$y' = y \quad \Leftrightarrow \quad \mathrm{e}^x = \mathrm{e}^x$$

It holds for $\forall x (\in \mathbb{R})$.

Function $y(x) = \mathrm{e}^x$ is a solution of the given differential equation.

Function $y(x) = 2\,\mathrm{e}^x$ is also a solution of the differential equation $y' = y$:

$$y(x) = 2\,\mathrm{e}^x \quad \Rightarrow \quad y'(x) = 2\,\mathrm{e}^x$$

$$y' = y \quad \Leftrightarrow \quad 2\,\mathrm{e}^x = 2\,\mathrm{e}^x\,.$$

Solution is not unique!

Moreover, $y(x) = c\,\mathrm{e}^x$ is also solution for all $c \in \mathbb{R}$!

$$y(x) = c\,\mathrm{e}^x \quad \Rightarrow \quad y'(x) = c\,\mathrm{e}^x$$

$$y' = y \quad \Leftrightarrow \quad c\,\mathrm{e}^x = c\,\mathrm{e}^x\,.$$

Primjer 3. Check if function $y(x) = \mathrm{e}^{2x}$ is a solution of the equation

$$y' = y?$$

$$y(x) = \mathrm{e}^{2x} \quad \Rightarrow \quad y'(x) = 2\,\mathrm{e}^{2x}$$

$$y' = y \quad \Leftrightarrow \quad \mathrm{e}^{2x} = 2\,\mathrm{e}^{2x}$$

Does not hold $\forall x (\in \mathbb{R})$.

Function $y(x) = \mathrm{e}^{2x}$ is not solution of the given differential equation.

Differential equation $y' = f(t, y)$

- may have no solution
- if there is a solution, it should not have to be unique
- Additional condition (equation) may be implied of the form

  - $y(a) = y_0$ - initial condition $\to$ initial value (Cauchy) problem for ODE.

  - condition including behaviour in end points of some interval, for example $y(a) + \alpha y(b) = \beta \to$ boundary condition $\to$ boundary problem for ODE.

We may define differential equations of higher order (using higher order derivatives):

$$y^{(k)} = f\left(t, y, y', \ldots, y^{(k-1)}\right)$$

Example 4. Find solution of initial value problem for ODE

$$y' = y, \quad y(1) = 1.$$

One solution of the equation is of the form

$$y(x) = c\,\mathrm{e}^{x}\,.$$

Constant c is is determined from the initial condition

$$y(1) = 1.$$

$$\Rightarrow \quad 1 = y(1) = c\,\mathrm{e}^{1} = c\,\mathrm{e}$$

$$\Rightarrow \quad c = \mathrm{e}^{-1}$$

$$\Rightarrow \quad y(x) = \mathrm{e}^{-1}\,\mathrm{e}^{x} = \mathrm{e}^{x-1}$$

1.2.2. Solving differential equations

Consider differential equation

$$y' = f(t, y).$$

When function f may be written as a product

$$f(t, y) = g(t)h(y)$$

equation is

$$y' = g(t)h(y)$$

or

$$\frac{y'}{h(y)} = g(t).$$

Functions are equal $\Rightarrow$ indefinite integrals (set of all antiderivatives) are equal:

$$\int \frac{y'}{h(y)} dt = \int g(t) dt.$$

$$\int \frac{y'}{h(y)} dt = \int g(t) dt.$$

integration by substitution: $y' dt = dy$

$$\int \frac{dy}{h(y)} = \int g(t) dt.$$

Let H and G are antiderivatives:

$$H'(y) = \frac{1}{h(y)} \quad \text{i} \quad G'(t) = g(t).$$

Now,

$$H(y) = G(t) + C$$

C - generic constant.

If H is an bijection, then

$$y = H^{-1}\left(G(t) + C\right).$$

Solving differential equation $\Leftrightarrow$ calculating indefinite integral

- Method of separation of variables

Problem

Check that

$$y(t) = H^{-1}\left(G(t) + C\right).$$

is a solution of differential equation

$$y' = f(x, y).$$

Rješenje.

Derivative of inverse function:

$$\left(f^{-1}(y)\right)' = \frac{1}{f'(f^{-1}(y))}$$

The composite function rule:

$$(f(g(x)))' = f'(g(x))g'(x).$$

$$y'(t) = \left(H^{-1}\left(G(t) + C\right)\right)' = \frac{G'(t)}{H'\left(H^{-1}\left(G(t) + C\right)\right)} =$$

$$= \frac{G'(t)}{H'(y(t))} = \frac{g(t)}{\frac{1}{h(y(t))}} = g(t)h(y(t)) = f(t, y(t)).$$

Example 6.
Solve differential equation

$$y' = \alpha y.$$

Solution.

Separation of variables:

$$y' = \alpha y = g(t)h(y) \quad \Rightarrow \quad g(t) = \alpha, \quad h(y) = y$$

$$\frac{y'}{y} = \alpha \quad \Rightarrow \quad \int \frac{y'}{y} dt = \int \alpha dt \quad \Rightarrow \quad \int \frac{dy}{y} = \alpha t + C$$

$$\Rightarrow \quad \ln |y| = \alpha t + C \quad \Rightarrow \quad |y| = e^{\alpha t + C} = C_1 e^{\alpha t}, \ C_1 > 0$$

$$\Rightarrow \quad y = C_2 e^{\alpha t}, \ C_2 \in \mathbb{R}$$

In growth models differential equation does not depend explicitly on time t.

The very same argument as for gain function holds:

- If we start experiment in different times starting wit populations of the same size, growth should be the same.

Growth models:

$$y' = f(y)$$

- Autonomous differential equation

Numerical solution of differential equatioi

- Even if differential equation has a solution, it often can not be expressed explicitly.
- Method of separation of variables is just one among many methods.
- It is often the case that antiderivative can not be expressed using 'simple' functions.
- Even if we determine inverse function in the method of separation of variables, it does not mean that we will find its inverse.

New approach: calculate numerical (approximate) solution of ODE instead of exact solution.

Consider initial value problem

$$y' = f(t, y), \quad y(0) = y_0.$$

Main idea - Taylor polynomial:

$$y(t+h) = y(t) + y'(t)h + \frac{y''(\zeta)}{2}h^2.$$

Neglect quadratic term:

$$y(t+h) \approx y(t) + y'(t)h.$$

If y is a solution of differential equation $y' = f(t, y)$, then

$$y(t+h) \approx y(t) + h \cdot f(t, y(t)).$$

Initial value problem:

$$y' = f(t, y), \quad y(0) = y_0.$$

We are looking for the solution on the interval $[0, a]$.

n - given

Divide interval $[0, a]$ on n equal parts:

$$h = \frac{a}{n}, \quad t_i = i \cdot h, \; i = 0, 1, 2, \ldots, n.$$

t_0 and y_0 are known (initial conditions).
Calculate an approximation to the solution at x_1:

$$y_1 = y_0 + h \cdot f(t_0, y_0)$$

Next step:

$$y_2 = y_1 + h \cdot f(t_1, y_1)$$

etc.

Method:

$$y_{i+1} = y_i + h \cdot f(t_i, y_i), \quad i = 0, 1, \ldots$$

- Euler's method

Example

Using Euler's method approximate solution of the initial value problem

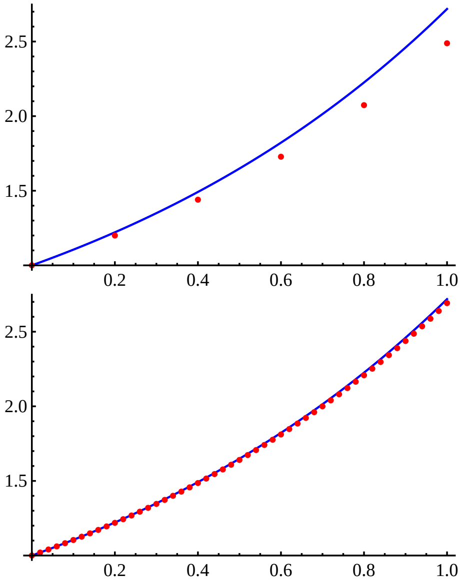
$$y' = y, \quad y(0) = 1,$$

at point $x = 1$ using subdivision on 5 subintervals.

Solution.
Interval [0, 1].

$n = 5 \quad \Rightarrow \quad h = 0.2$

i	t_i	y_i	$f(t_i, y_i)$	y_{i+1}
0	0.0	1.000	1.000	1.200
1	0.2	1.200	1.200	1.440
2	0.4	1.440	1.440	1.728
3	0.6	1.728	1.728	2.074
4	0.8	2.074	2.074	2.488
5	1.0	**2.488**		


2.5
2.0
1.5
0.2
0.4
0.6
0.8
1.0
2.5
2.0
1.5
0.2
0.4
0.6
0.8
1.0

- $y(t+h)$ is approximated by a linear term from Taylor expansion
- The simplest of all methods
- Better approximation $\rightarrow$ better method
- Well known:
  - Runge-Kutta methods
  - linear multistep methods