

Ordinary differential equations

Introduction to Synthetic Biology

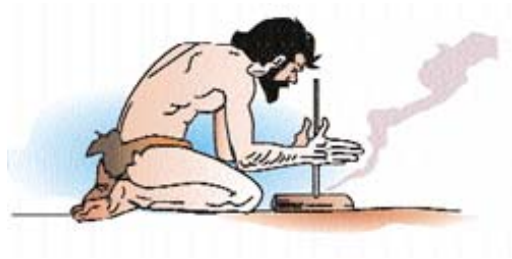
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Overview

- Introduction-Modelling
- Basic concepts to understand an ODE.
- Description and properties of ODE.
- Solving ODE.
- Vector spaces.
- Dynamic systems.



Modelling



Modelling

- Describing the behavior of a system.

Understand it.

Predict its future behaviour.

Be able to manipulate the system

What to take into account and what not.

How to do this?

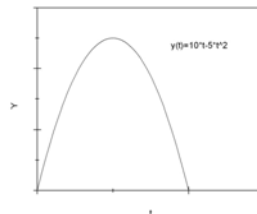
Having knowledge of the system

Knowing physical laws

Using math as a working language to describe the system

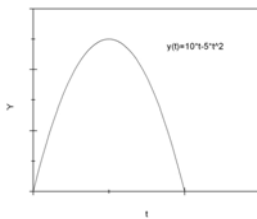
Simulation

- A simulation is a set of equations that describes a system
- They do not need to have a solid conceptual background.
- The grade of trust of a simulation is not known when you try to apply it to different conditions



Modelling

- By using some knowledge of physical processes involved in the system, a modeling strategy tries to describe the system.
- Could be less exact than a simulation.
- It is adaptable to different situations

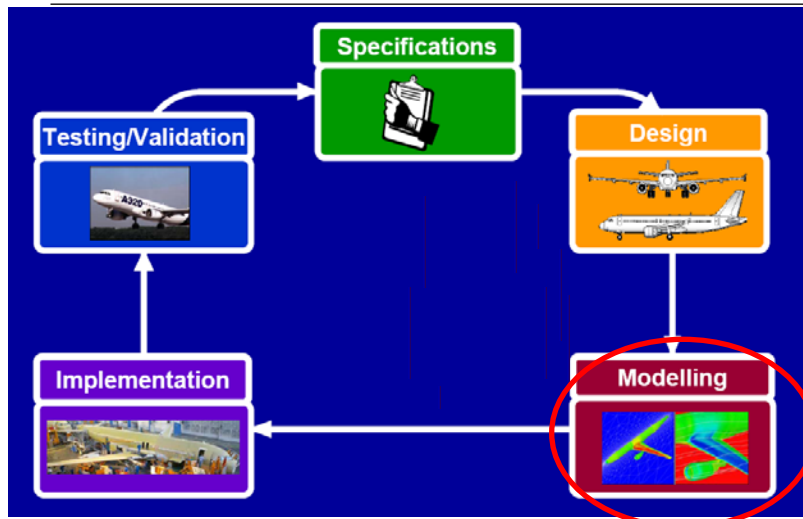


$$F = m\ddot{y} \rightarrow y(t) = x_0 + v_0 t + \frac{g t^2}{2}$$

Why is a model useful?

- It allows a better understanding of a system.
- It makes a system more predictable
- It allows engineering the system
- It could drive the experiments
- It allows the control of a system.

Engineering cycle



http://openwetware.org/images/5/5b/Vincent_Rouilly_SynBio_Course_Topic_1.pdf

Ordinary differential equations



Introduction

Why should we use differential equations?

Whenever a deterministic relationship involving some continuously changing quantities (modeled by functions) and their rates of change (expressed as derivatives) is known or postulated.



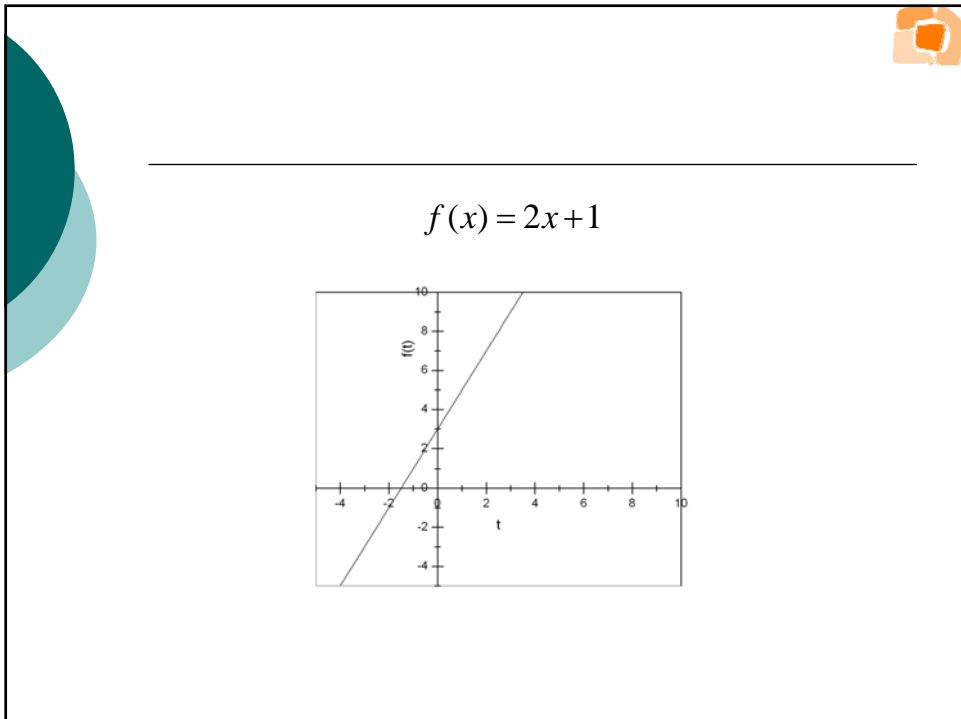
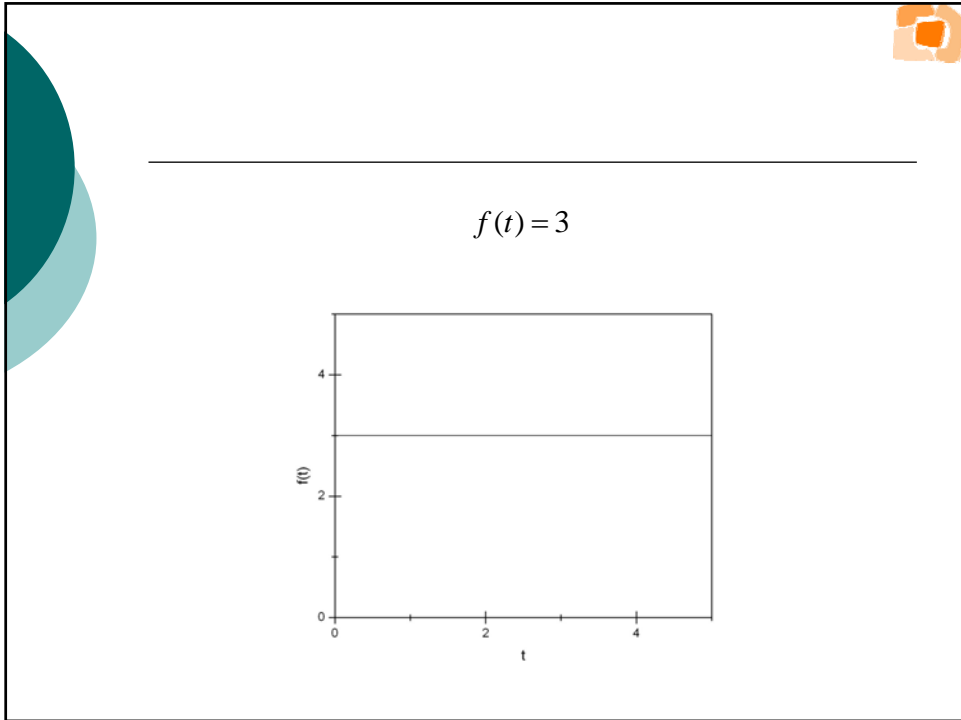
Previous concepts

What is a function?

A function is a relation between two sets of elements

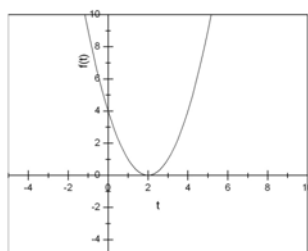
How is it represented in math?

$$f : x \rightarrow f(x)$$

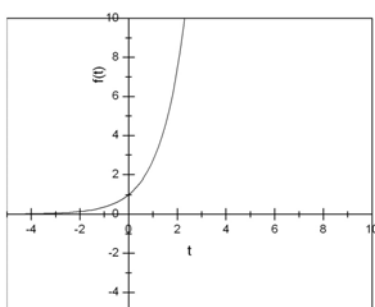


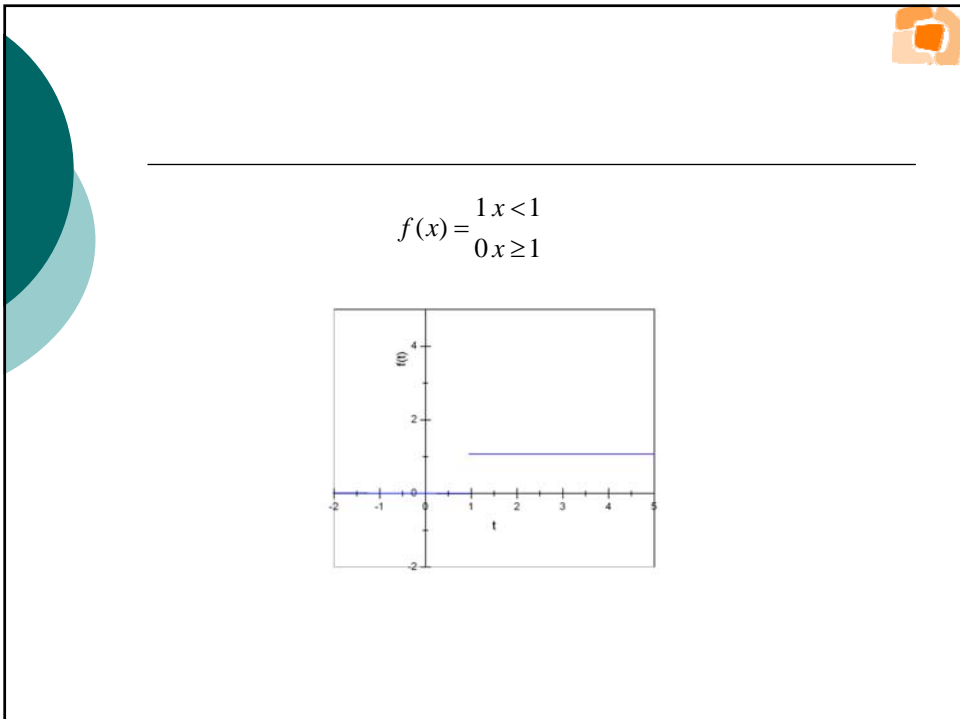
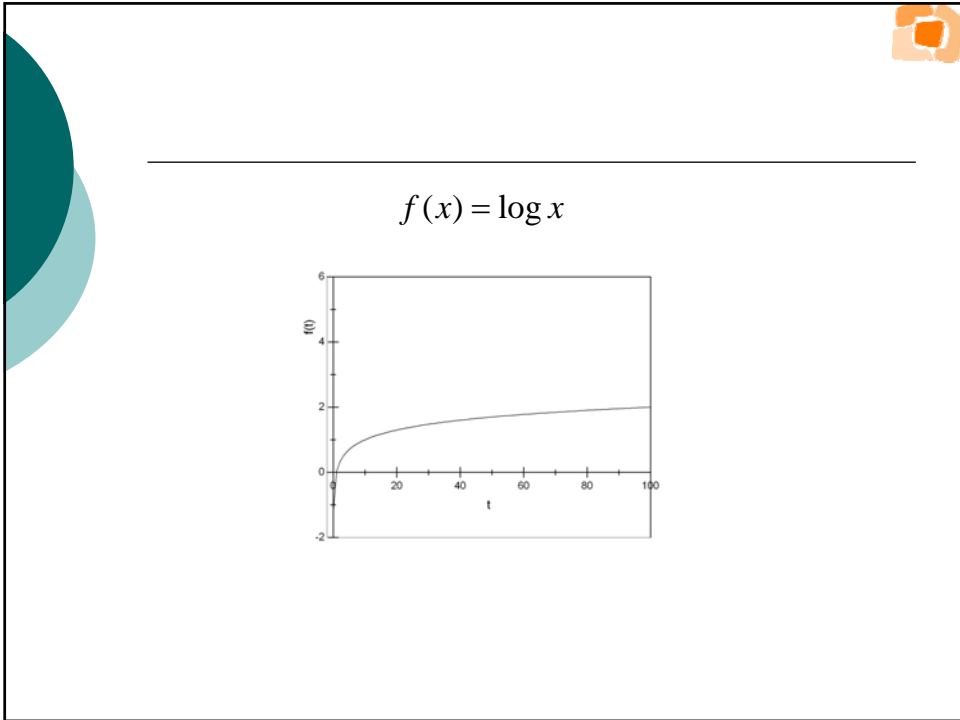


$$f(x) = (x-2)^2$$



$$f(x) = e^x$$

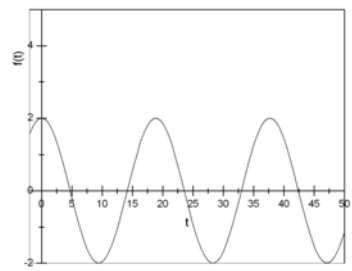
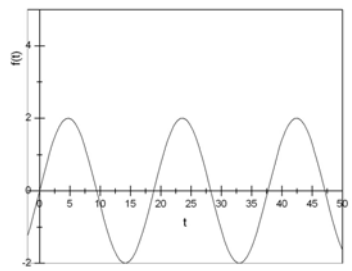






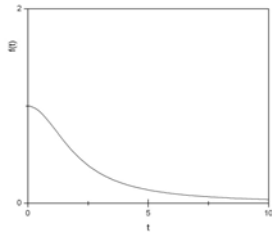
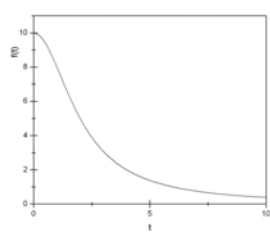
$$f(x) = A \sin\left(\frac{x}{T}\right)$$

$$f(x) = A \sin\left(\frac{x}{T} + \varphi\right)$$



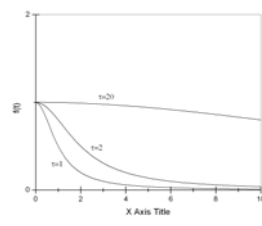
$$f(t) = \frac{k}{1 - \left(\frac{t}{\tau}\right)^n}$$

K=10;τ=2;n=2

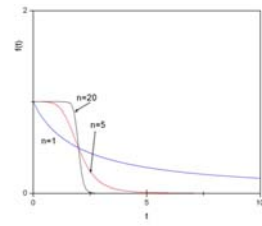


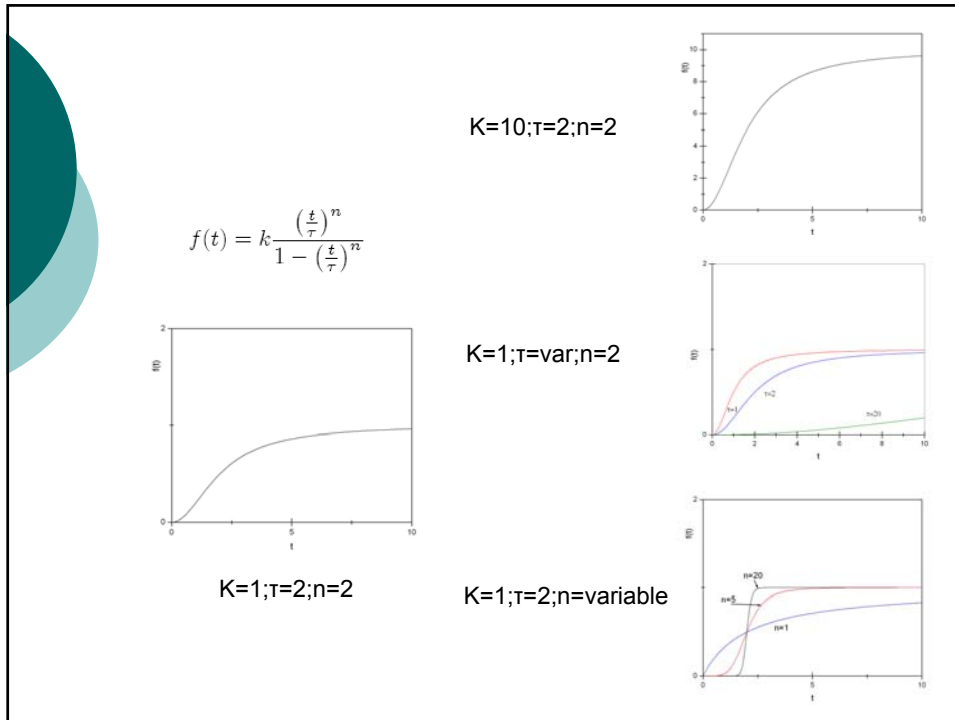


K=1;τ=2;n=2

K=1;τ=var;n=2



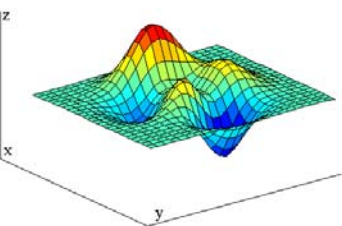
K=1;τ=2;n=variable

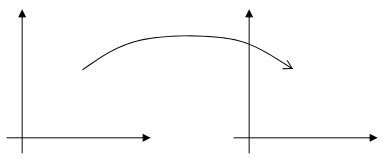


Functions of several variables

- It is a function which depends on several variables:
 - Scalar: $z=F(x,y)$
 - Vectorial: $y_i=F_i(x_j)$



$$\mathbb{R}^n \xrightarrow{f^m(x_i)} \mathbb{R}^m$$




Linear function

- A linear function is a function which fulfills:

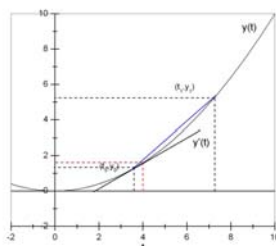
$$f(ax + by) = af(x) + bf(y)$$



What is a derivative?

Having two variables, related by a function, the derivative gives the variation of one of them when the remaining is changed

$$\lim_{t \rightarrow 0} \frac{f(t + \Delta t) - f(t)}{\Delta t} = \frac{df(t)}{dt}$$

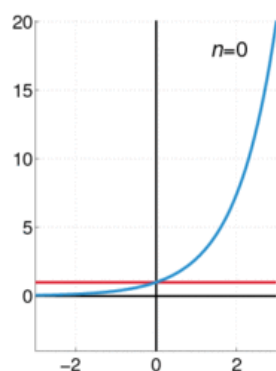


Taylor series development

- A serie is a summation of terms.
- The Taylor serie development of a function $f(x)$ is the approximation of this function by a power serie:

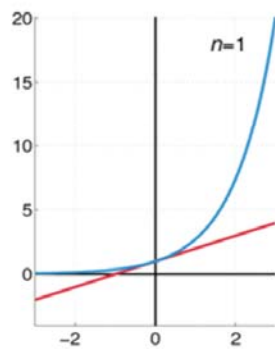
$$f(x) \approx f(a) + \frac{f'_a(t)}{1!}(t-a) + \frac{f''_a(t)}{2!}(t-a)^2 + \dots + \frac{f^{(n)}_a(t)}{n!}(t-a)^n + (t-a)^{n+1}$$

The error of a function is of $n+1$ order if we develop the power serie up to the n power.



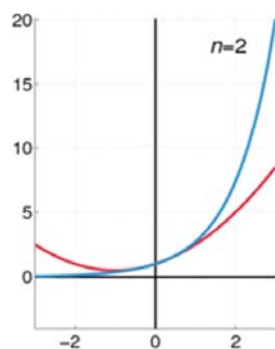
$$f(t) = e^t$$

$$\frac{de^t}{dt} = e^t$$



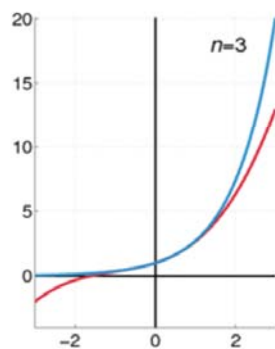
$$f(t) = e^t$$

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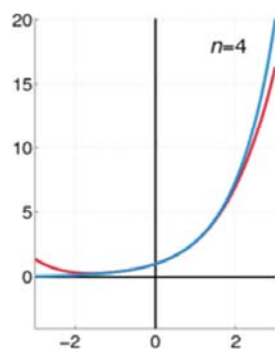
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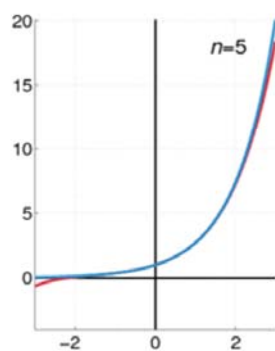
$$f(t) = e^t$$

$$\frac{de^t}{dt} = e^t$$



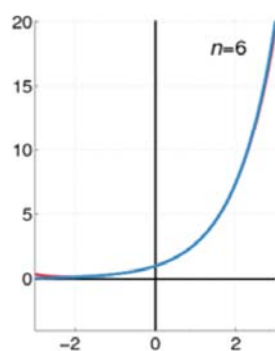
$$f(t) = e^t$$

$$\frac{de^t}{dt} = e^t$$



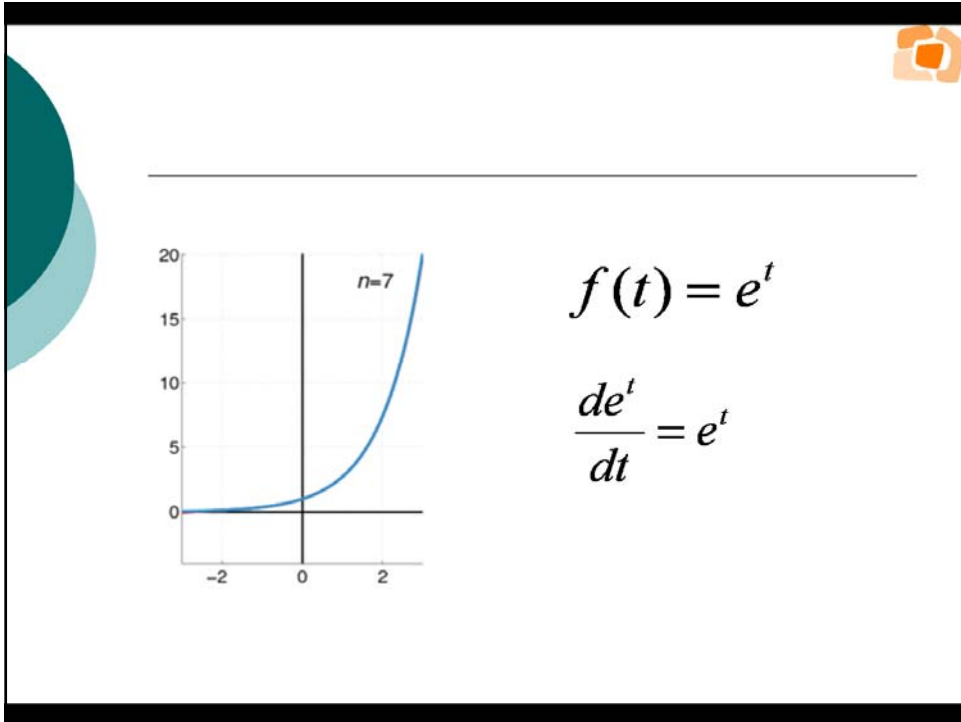
$$f(t) = e^t$$

$$\frac{de^t}{dt} = e^t$$



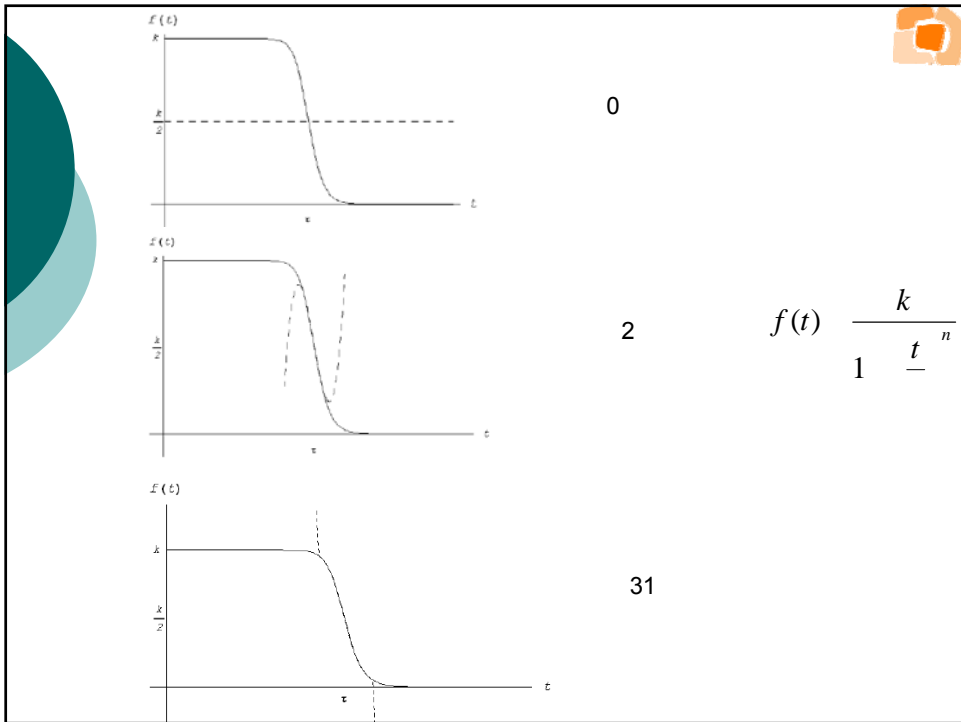
$$f(t) = e^t$$

$$\frac{de^t}{dt} = e^t$$



$$f(t) = e^t$$

$$\frac{de^t}{dt} = e^t$$



0

2

$$f(t) = \frac{k}{1 + \frac{t^n}{\tau^n}}$$

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-
- Remark

$$e^{i\alpha} = \cos \alpha + i \sin \alpha$$

The Taylor development makes to conclude that the complex exponential is equivalent to the sum of a sinus and a cosinus.



What is a differential equation?

What is an equation?



Having a variable x , an equation express a mathematical relation between that variable and some other which are known.

What is a differential equation?

Equation which relates a function with its derivatives.

t : variable

x : variable dependent

λ_i : parameters of the function

$$\frac{dx}{dt} = f(t, x, \{\lambda_1, \lambda_2, \dots\})$$

If the function f depends on more than one variable then the differential equation is called partial differential equation (PDE)



In order to solve a differential equation, we should transform the problem in a problem in which we can integrate a function.

Integration is the opposite to derivation. If we subtract infinitesimal terms in a derivative we perform sum of infinitesimal terms in an integral.

When we solve an indefinite integral, there is a constant of integration that we should fix using the conditions of the defined problem:

$$\int f(x) dx = g(x) + K$$

The solution of an ODE is a function $x(t)$ which is defined but a constant and is unique.

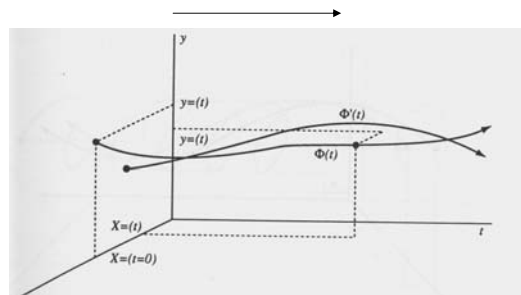
Solution of a differential equation



- The solution of a differential equation is an equation which allows to know the value of the dependent variable as a function of the independent ones given the value of the dependent variable for a defined value of the independent one.
 - Initial conditions of the problem: the independent variable is the time.
 - Contour conditions of the problem: the independent variable is another one.

$X(t=0)$

$Y(t=0)$



$X(t)$

$Y(t)$

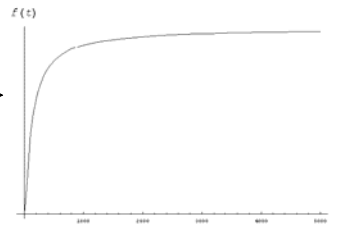
Simple examples

$$\frac{df}{dt} \longrightarrow f(t) \quad t \quad K$$

$$\frac{df(t)}{dt} \quad f(t) \longrightarrow f(t) \quad e^t \quad K$$

$$\frac{d^2 f}{dt^2} \quad f(t) \longrightarrow f(t) \quad K_1 \sin(\omega t) \quad K_2$$

$$\frac{df}{dt} \quad \frac{f(t)}{\left(1 - \frac{t}{K}\right)^2} \longrightarrow$$



Types of differential equations

$$\frac{dx}{dt} = kx \quad \text{1st order}$$

$$\frac{dx}{dt} = kx \quad \text{Linear}$$

$$\frac{d^2 x}{dt^2} + \frac{dx}{dt} = kx \quad \text{2nd order}$$

$$\frac{dx}{dt} = kx^2 \quad \text{Non linear}$$

$$\frac{dx}{dt} = kx \quad \text{Autonomous}$$

$$\frac{d^2 x}{dt^2} + \frac{dx}{dt} = kx \quad \text{ODE}$$

$$\frac{dx}{dt} = kx + \sin(t) \quad \text{Non Autonomous}$$

$$\frac{\partial^2 y(x,t)}{\partial t^2} - c^2 \frac{\partial y(x,t)}{\partial x} = ky \quad \text{PDE}$$

How to solve a differential equation?

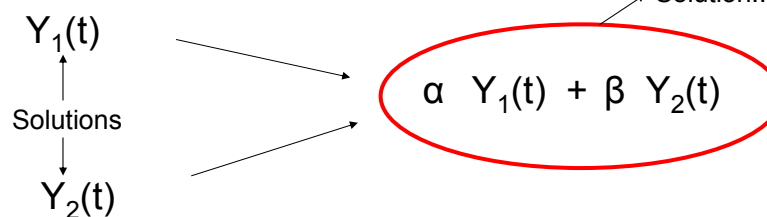
- In some cases there is a possibility of solving analytically the differential equation.
- In most of the cases this is not possible and several techniques have been developed to solve the problem in an approximated way.
- Some of these techniques are included in the branch of mathematics known as numerical methods

Linear differential equations

- A linear differential equation is:

$$a_n \frac{d^n f(t)}{dt^n} + a_{n-1} \frac{d^{n-1} f(t)}{dt^{n-1}} + \dots + a_0 f(t) = g(t)$$

Linear \longrightarrow Superposition principle



Linear differential equations

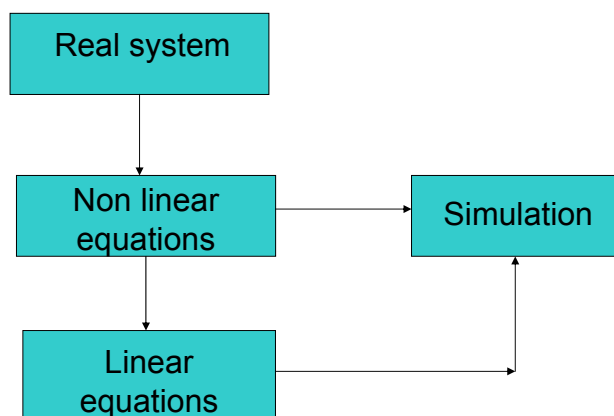
The problem is reduced to solve the characteristic equation

$$a_n z^n + a_{n-1} z^{n-1} + \dots + a_0 z = 0$$

The general solution of the system will have the form:

$$f(t) = \sum_i e^{z_i t}$$

Non linear $\xrightarrow{\text{Linearization}}$ Linear





Linearization method

A function $f(x)$ could be approximated by:

$$f(x) \approx f(a) + \frac{f'_a(t)}{1!}(t-a) + \frac{f''_a(t)}{2!}(t-a)^2 + \dots + \frac{f^{n'}_a(t)}{n!}(t-a)^n + \dots$$

First order approximation or linearization:

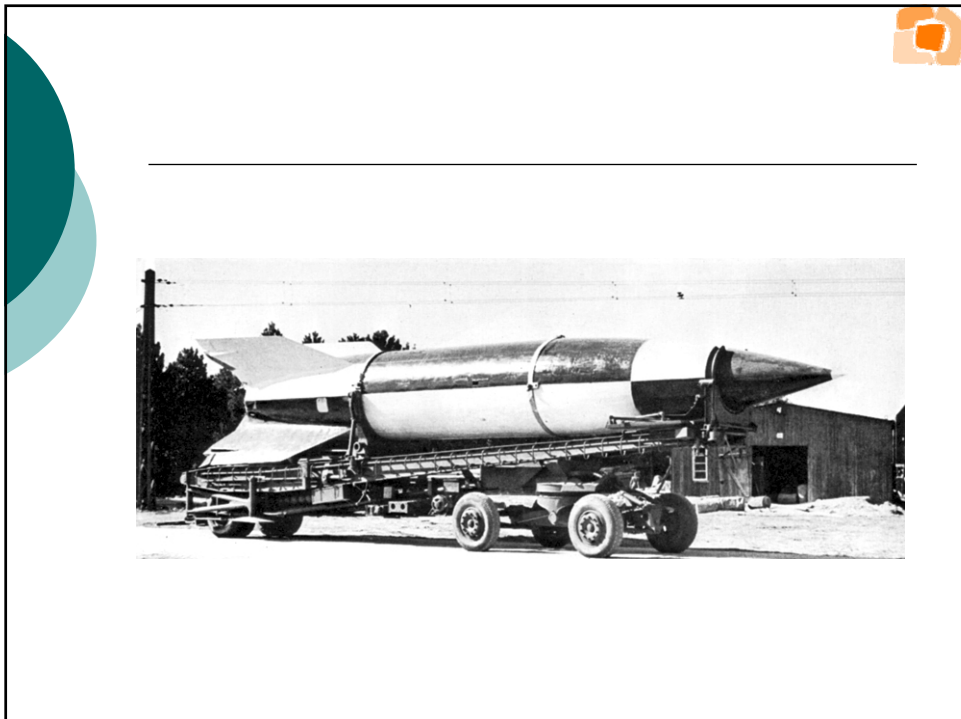
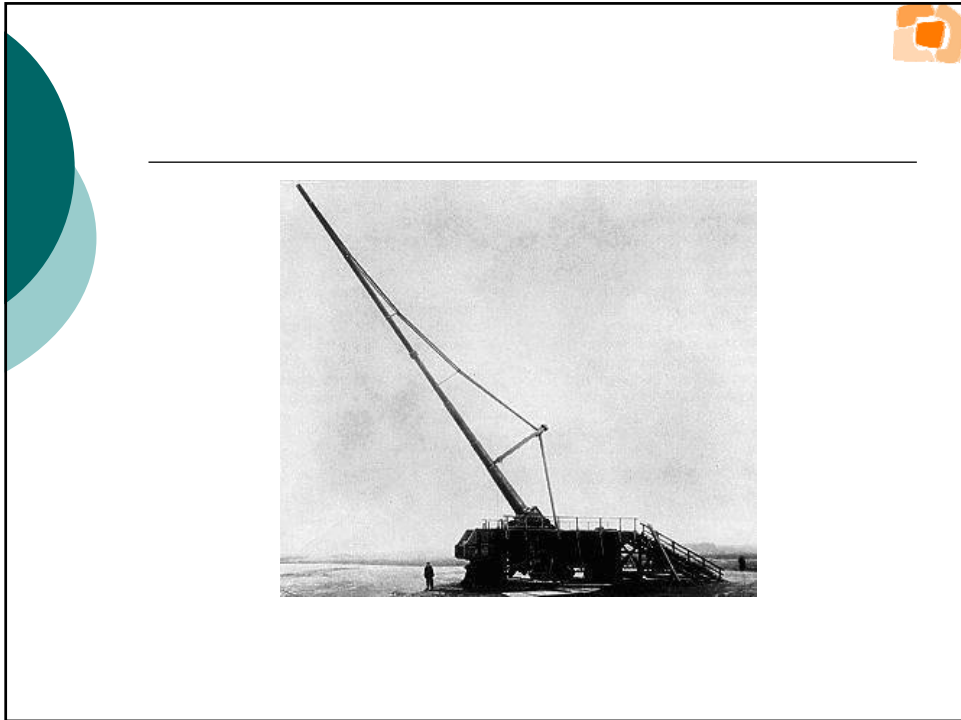
$$f(x) \approx f(a) + \frac{f'_a(t)}{1!}(t-a) + \theta(t^2)$$

Based on this there is a procedure to obtain a linear equation which has a similar behavior to the equations we want to solve, around some special points.



Practical issues of the LP

- The working point should be close to an equilibrium point in such a way that the first order derivatives will be 0.
- The linear model will be more accurate near the equilibrium point.
- The equilibrium point should be selected as close as possible to the working point.



Numerical solution of ODE

- We have come to know that there are solutions just for a few ODE.
- The meaning of a derivative is the subtraction of very close terms.
- If we do not have an exact solution of a differential equation, we can try to obtain an approximated solution of it, subtracting by hand these terms time and again.



Very stupid devices can perform very stupid operation but with an incredible speed

Numerical solution of ODE

- Later on an example of a very simple algorithm to solve numerically an ODE is given

$$y'(t) = f(t; y(t)) \quad y(t_0) = y_0$$

We substitute the derivative term by its approximated value:

$$y'(t) \approx \frac{y(t+h) - y(t)}{h} \rightarrow y(t+h) \approx y(t) + hf(t, y(t))$$

Selecting a proper value for h, we have a time step with the value $t_0=t_0, t_1=t_0+h, \dots, t_n=t_{n-1}+h$

$$y_{n+1} = y_n + hf(t_n; y_n)$$

Numerical solution of ODE

- This method is called explicit Euler method and it is one of the simplest methods to obtain the solution of ODE.
- The obtained solution is only an approximation to the real solution, and the goodness of the solution depends on the kind of the problem and on the selection of the different model parameters like h .
- Although the power of computing has increased a lot in the last years, there are too many problems which require many computing time to be solved.
- Always you should take care when you solve a problem numerically!!

Usefulness of differential equations

- When describing systems, it is usually very useful to know not only the value of the variable but also the evolution of it.

AAM \longrightarrow $\frac{d^2 x}{dt^2} + b \frac{dx}{dt} + kx = 0$



$$\text{Div } \mathbf{E} = 4 \pi \rho$$

$$\text{Div } \mathbf{B} = 0$$

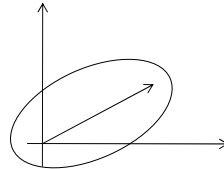
$$\text{Rot } \mathbf{E} = -\frac{1}{c} \frac{\partial \mathbf{B}}{\partial t}$$

$$F = m \frac{d^2 x}{dt^2}$$

$$i\hbar \frac{\partial \Psi(t, \vec{r})}{\partial t} = -\frac{\hbar^2}{2m} \nabla^2 \Psi(t, \vec{r}) + V(\vec{r}, t) \Psi(t, \vec{r})$$

An introduction to vectors and matrix

○ What is a vector?



1. Any mathematic set of “things” whose sum gives us another “thing” of the set.
2. It is defined multiplication property between these “things” and numbers.

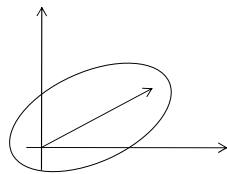
In a more rigorous way $\longrightarrow v_3 \quad v_1 \quad v_2$

Base of a vector space

Minimum number of vectors which generate all the space

Dimension of the space

The number of vectors of the base



Matrix

Roughly, it is a set of numbers

$$\begin{array}{ccc} 3 & 2 & 1 \\ 1 & 3 & 2 \\ 2 & 1 & 3 \end{array} \quad \left(\begin{array}{ccc} 1 & 2 & 3 \\ 3 & 1 & 2 \end{array} \right)$$

Determinant of a square matrix

$$|A| = \varepsilon_{ijk} a_1^i a_2^j a_3^k$$

Some matrix properties

$$\begin{array}{cc} a & b \\ c & d \end{array} \quad \begin{array}{cc} a & b \\ c & d \end{array}$$

$$\begin{pmatrix} e & f \\ g & h \end{pmatrix} + \begin{pmatrix} a & b \\ c & d \end{pmatrix} = \begin{pmatrix} e + a & f + b \\ g + c & h + d \end{pmatrix}$$

$$\begin{array}{cccc} e & f & a & b \\ g & h & c & d \end{array} \quad \begin{array}{cccc} ea & fc & eb & fd \\ ga & hc & eb & fd \end{array}$$

Linearity

$$\begin{array}{ccccc} a & b & x & ax & by \\ c & d & y & cx & dy \end{array}$$

Eigenvalues and eigenvectors

$$\begin{array}{ccccc} a & b & x & x & 0 \\ c & d & y & y & 0 \end{array}$$

Calculation of eigenvalues

$$A\vec{v} = \lambda\vec{v} \rightarrow (A - \lambda I)\vec{v} = 0$$

$$\downarrow$$
$$\det[A - \lambda I] = 0$$

Systems of linear differential equations

- As in standard algebraic equations, there can be problems in which instead of a ODE we have a system of differential equations.
- If the system is linear we can apply all the developed algebraic methods for vectorial spaces.
- A system of n ODE of n order is equivalent to a system of $n+1$ ODE of $n-1$ order

Example

$$\begin{array}{ccc}
 \begin{array}{l} \frac{df_1}{dt} \\ \frac{df_2}{dt} \end{array} \begin{array}{cc} a_1 f_1 & a_2 f_2 \\ a_3 f_1 & a_4 f_2 \end{array} & \longrightarrow & \begin{array}{l} \frac{df_1}{dt} \\ \frac{df_2}{dt} \end{array} \begin{array}{ccc} a_1 & a_2 & f_1 \\ a_3 & a_4 & f_2 \end{array} \\
 & & \downarrow & \\
 \begin{array}{l} \frac{df'_1}{dt} \\ \frac{df'_2}{dt} \end{array} \begin{array}{c} {}_1 f'_1 \\ {}_2 f'_2 \end{array} & \longleftarrow & \begin{array}{l} \frac{df'_1}{dt} \\ \frac{df'_2}{dt} \end{array} \begin{array}{ccc} {}_1 & 0 & f'_1 \\ 0 & {}_2 & f'_2 \end{array}
 \end{array}$$



Dynamical system

- A system that evolves with time is a dynamical system.
 - State variable: magnitudes whose evolution in time we want to know.
 - Evolution variable: the state variables evolution as a function of them.
 - Parameters: constant magnitudes of the system under certain conditions
 - Evolution laws: the relation between the state variables and the evolution variables.



Example

$$\frac{d[Y]}{dt} = \alpha \frac{1}{1 + \left(\frac{[U]}{K}\right)^n} - \beta[Y] + \gamma$$

Dynamical systems

- We are going to describe autonomous systems, which fulfill the following form:

$$\frac{df_i}{dt} = F_i(f_i; \dots)$$

Autonomous means not explicit dependence in time

Any ODE of order higher than 1 can be changed in an equivalent system of equations of first order

$$k_2 \frac{d^2 y}{dt^2} + k_1 \frac{dy}{dt} + k_0 y = C$$

Change of variables

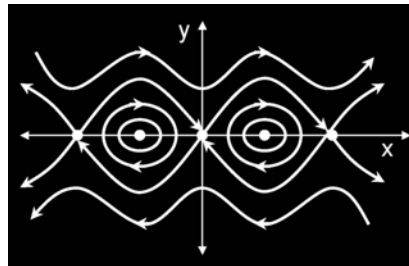
$$x_1(t) = y$$

$$\frac{dx_1}{dt} = x_2(t)$$

$$x_2(t) = \frac{dy}{dt}$$

$$\frac{dx_2}{dt} = \frac{C - k_0 x_1(t) - k_1 x_2(t)}{k_2}$$

- Phase space: It is a representation of the solution of a ODE in which f' is represented against f .
- It represents all the possible states of the system.



Stability

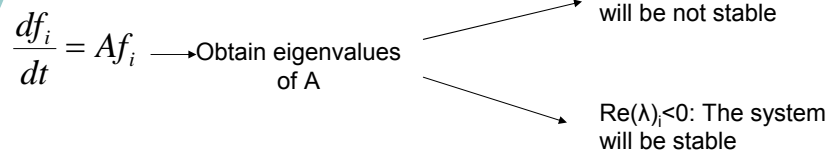
- At this point a fundamental concept is the fix point or equilibrium point

$$\frac{df_i}{dt} = 0 \rightarrow F_i(f_i; \alpha_i) = 0$$

Stability \longrightarrow If all the solutions of a dynamical system which start out near an equilibrium point x_e remain near x_e , then x_e is Lyapunov stable. Even more, if all the solutions which start out near x_e converge to x_e , then x_e is asymptotically stable .

Stability

Linear systems



Stability

Linearizable systems

$$\frac{df_i}{dt} = F_i(f_i; \alpha) \longrightarrow \frac{df_i}{dt} = F(f_{ie}; \alpha) + J\Delta f_i \rightarrow \Delta f_i = f_i - f_{ie}$$

$$J = \begin{pmatrix} \frac{\partial F_1}{\partial f_1} & \dots & \frac{\partial F_1}{\partial f_n} \\ \dots & \dots & \dots \\ \frac{\partial F_n}{\partial f_1} & \dots & \frac{\partial F_n}{\partial f_n} \end{pmatrix} \longrightarrow \text{Jacobian matrix}$$

As we are in a stable point $F=0$, the equation could be written as

$$\frac{df_i}{dt} = J\Delta f_i$$

The criteria are the same ones as for linear systems



Stability

- All these procedures are quite simple but here they are explained for very particular cases.
- An study of the stability of a system is usually not so simple.
- Several mathematically more accurate definitions have been done by mathematicians:
 - Stability in the sense of Liapunov
 - Stability in the sense of Lagrange
- If we are working with nonlinear systems, the analysis turns into a more complicated one.



Sensibility

- Sensibility analysis is related not only to the dependence of the results of the model in the initial conditions but also in the value of the parameters.
- A sensitive analysis of a problem could give us information about:
 - The influence in the system of the different parameters.
 - The care we should take when determining the initial conditions of a problem.
 - If a model of a system is useful to predict it or not.
 - The influence of external perturbations.

Non linearity and Chaos

Why could Non linear systems be so complicated?

The linear property $\longrightarrow f(ax + by) = af(x) + bf(y)$

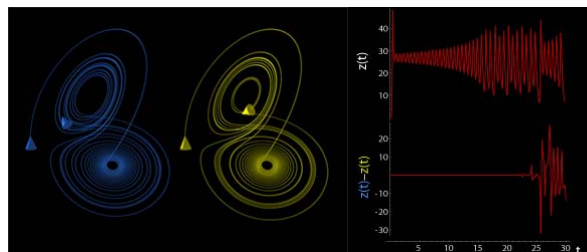
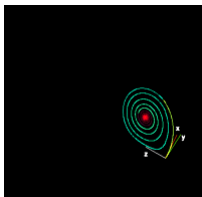
This property states that if we introduce a small variation in the system the system, in principle, do not change too much

But if we introduce other kind of dependences like product or power laws, this property is not valid. Consequently, small changes could produce very different behaviours of the system.

Non linearity and Chaos

Chaos does not mean randomness in a system, chaos means a determined system but very difficult to be predicted.

$$\begin{aligned} dx/dt &= s(y - x) \\ dy/dt &= r x - y - xz \\ dz/dt &= xy - b z \end{aligned}$$



http://to-campos.planetaclix.pt/fractal/lorenz_eng.html



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