Differential Equations in Mathematical Biology

- Anatomy of some applications -

Jorge Duarte

Engineering Superior Institute of Lisbon - Portugal

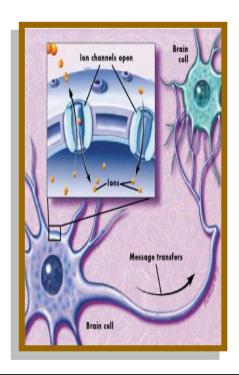


MatRIC

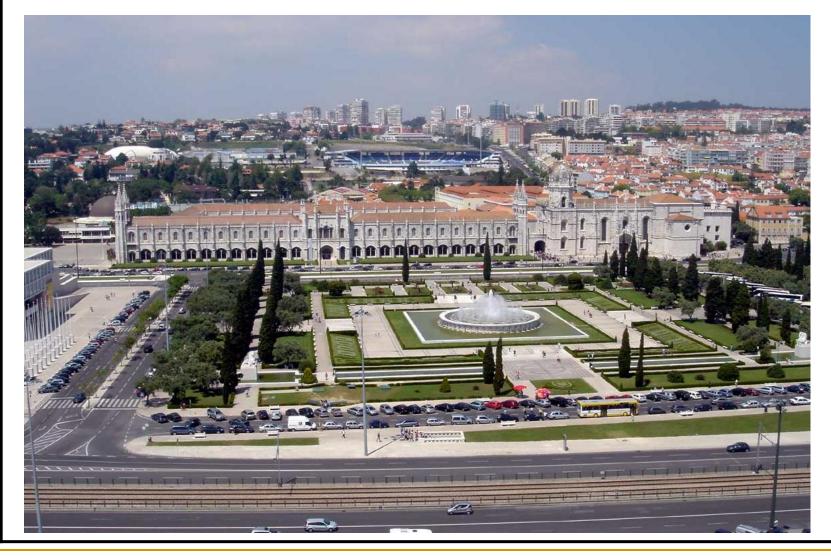
Modelling Colloquium

2016

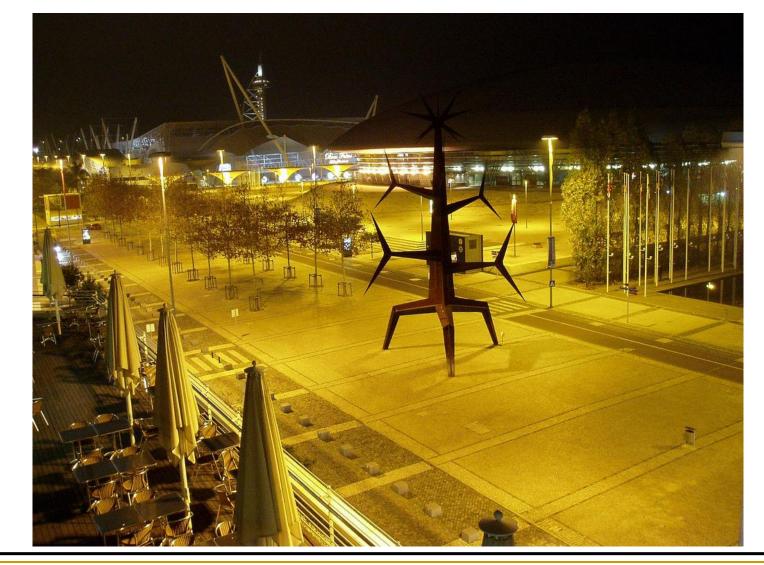




Lisbon by day...

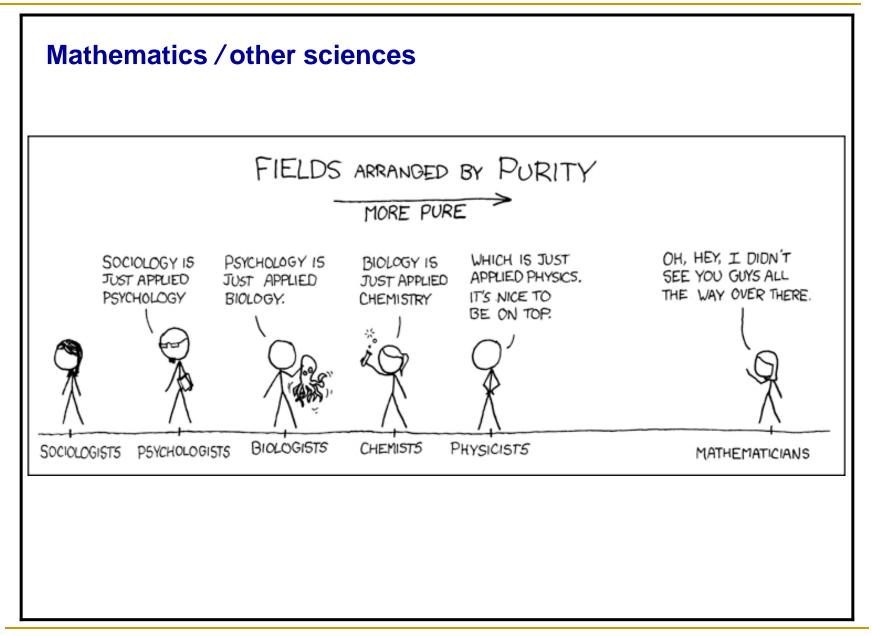


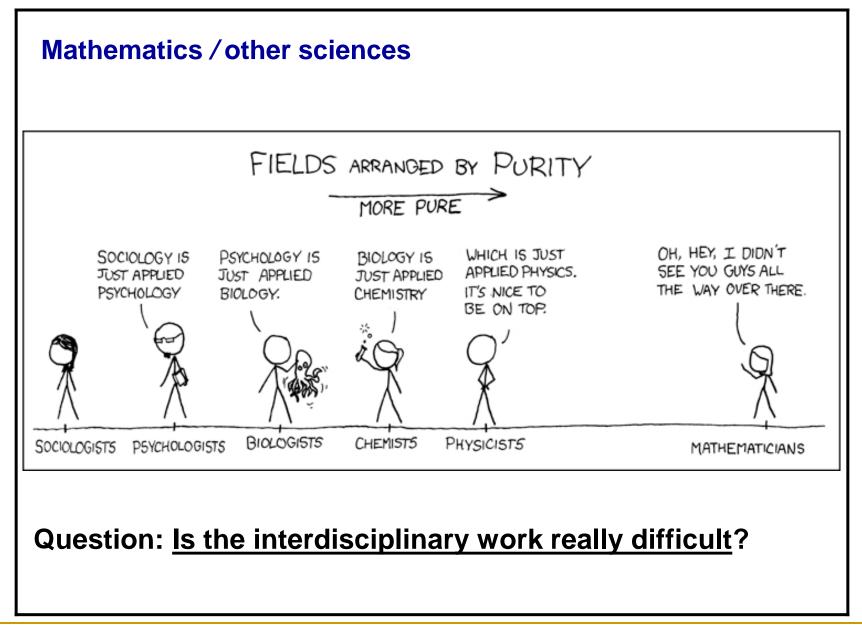
and by night...



Aims for this talk

- Mathematics / other sciences
- Differential equations and biological rhythms
- Wonders of the nonlinear world
- Mathematical concepts in use
- Teaching / research a multidisciplinary approach
 - Key encouraging aspects / Maths matters





Our body in numbers

- We have around 42 billion blood vessels.
 (about 160,000 km: 4 times around the Earth's equator, half way to the moon).
- The heart pumps 8,000 liters of blood each day (800 buckets). (During a lifetime around 88 Olympic swimming pools).
- Most of us will cry 68 liters of tears (7 buckets). Certainly there will be gender differences :)
- We are constantly replacing our bones.
 The equivalent of 12 skeletons of new bone during a lifetime.
- We take 500 million breaths and inhale around 300 million liters of air during our lifetime.

And many more...

Our body in numbers

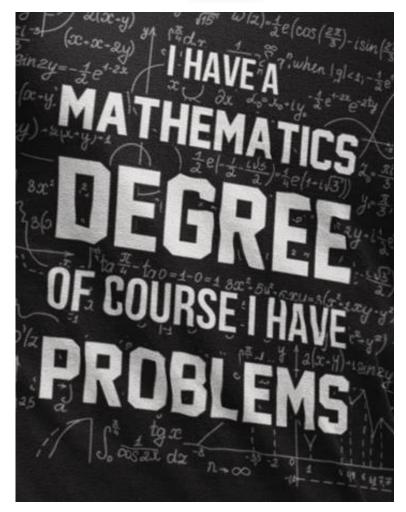
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Quite impressive, isn't it?

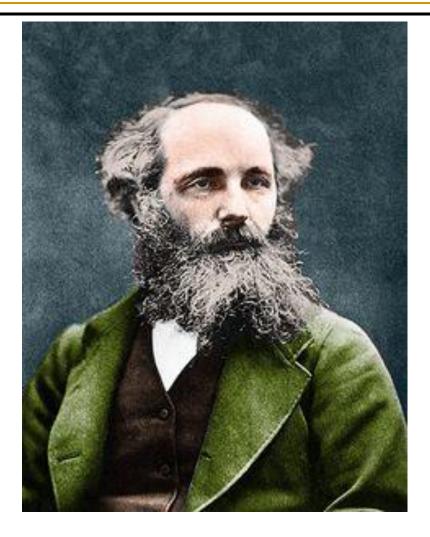






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Jorge Duarte (jduarte@adm.isel.pt)



"There is nothing more practical than a good theory."

(James Clerk Maxwell (1831-79))

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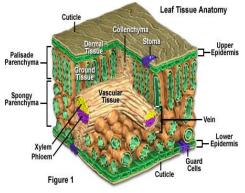
Differential equations and biological rhythms

The cellular growth

"Cells are matter that dance."

(Uri Alon, An Introduction to Systems Biology)

- Suppose that the cell maintains a cubic shape.
- Starting from a certain volume v_0 at instant t = 0, the cell absorve continuously nutrients through the exterior membrane, which determines the increasing of the volume. This volume is v(t), at each instant t ($t \ge 0$).
- We identify the cellular growth per unit of time with the area of the exterior membrane of the cell (that is, the total area of the six faces of the cube).



• We express the total area of the cubic surface as a function of the volume

Let l be the length of the cube's side, so the volume v is

$$v = l^3 \Rightarrow l = v^{\frac{1}{3}}.$$

Since the total area of the six faces of the cube is given by $a = 6 l^2$ we have $a = 6 v^{\frac{2}{3}}$.

Thus, for
$$t \ge 0$$
 and $\Delta t > 0$ we will have

$$v(t + \Delta t) \approx v(t) + 6 [v(t)]^{\frac{2}{3}} \Delta t$$
$$v(t + \Delta t) - v(t) \approx 6 [v(t)]^{\frac{2}{3}} \Delta t$$
$$\frac{v(t + \Delta t) - v(t)}{\Delta t} \approx 6 [v(t)]^{\frac{2}{3}}$$

Taking the limite when $\Delta t \rightarrow 0$,

 Δt

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Taking the limite when $\Delta t \rightarrow 0$,

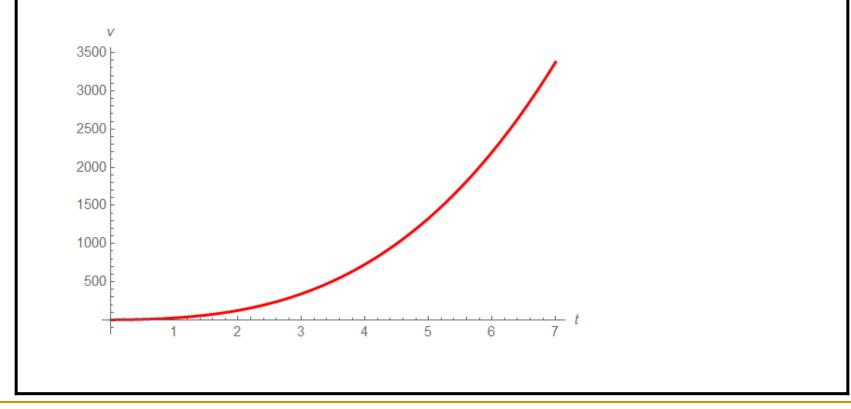
we obtain

$$v' = 6 v^{\frac{2}{3}}$$

A particular solution of this differential equation is

 $v(t) = (2 t + 1)^3$

The graph of this function is



A story of a detective

There are problems, solved using differential equations, where information seems to be missing. The following situation is just an example of that...

"A body of a victim was found at 23:30 in a office which temperature we suppose constant and equal to 8,2° C.

At the moment the body was found, its temperature was 32,8° C, and after one hour was 31,6° C.

Considering that the normal temperature of the body is 36,8° C and that it is valid the Newton's law of cooling, i. e., the variation of the temperature of a body is proportional to the difference between the temperature of the body and the environment,

what time did the crime occur?

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Let x(t) be the temperature of the body at time t and t₀ the instant when the crime was commited.
 So, we have

$$x(t_0) = 36, 8^{\circ} C.$$

Being $t_1 = 23,50$ the instant when the body was found, we know that

 $x(t_1) = 32, 8^{\circ} C$ and $x(t_2) = 31, 6^{\circ} C$, where $t_2 = t_1 + 1 = 24, 5$.

Now, let us consider $t \ge 0$ and $\Delta t \ge 0$.

Since the variation of the temperature per unit of time is equal to *k* times the difference between the temperature of the body and the temperature of the environment,

(x(t) - 8, 2) at instant t,

in Δt units of time, the variation of the temperature will be multiplied by Δt and we write

 $x(t + \Delta t) \approx x(t) - k (x(t) - 8, 2) \Delta t$, for some k > 0,

that is,

 $\frac{x(t+\Delta t)-x(t)}{\Delta t} \simeq -k \ (x(t)-8,2).$

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that is,

$$\frac{x(t+\Delta t)-x(t)}{\Delta t} \simeq -k \ (x(t)-8,2).$$

With $\Delta t \rightarrow 0$, we obtain the differencial equation (model of our problem)

$$x'(t) = -k (x(t) - 8, 2)$$
, for some $k > 0$.

• Taking in consideration the given initial conditions, the solution of the differential equation is

$$x(t) = 24, 6 e^{-0.05(t-23,5)} + 8, 2.$$

Since the temperature of the body, at the moment of the crime, was $x(t_0) = 36, 8^{\circ} C$,

 $36,8 = 24,6 e^{-0.05(t-23,5)} + 8,2$ $28,6 = 24,6 e^{-0.05(t-23,5)}$ $t_0 \cong 20,4868.$ • Taking in consideration the given initial conditions, the solution of the differential equation is

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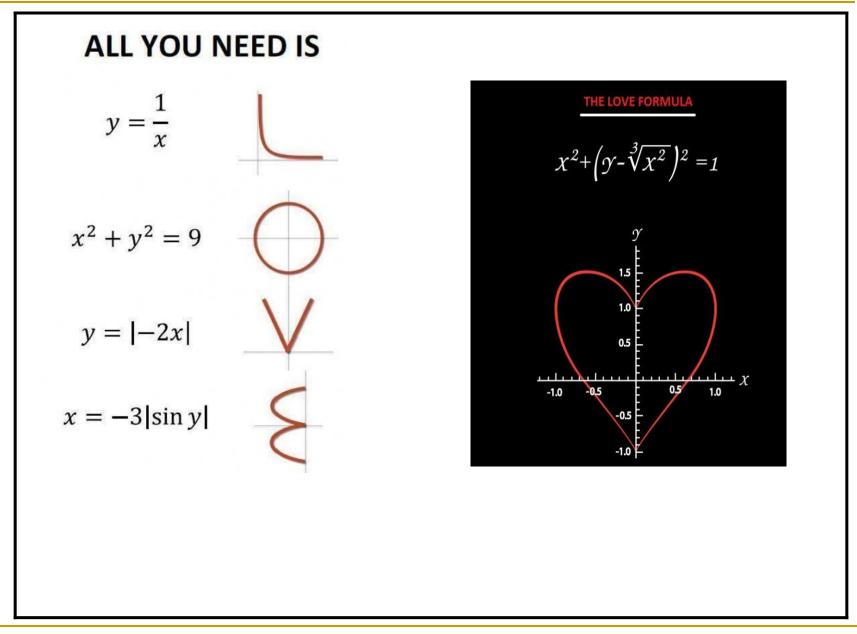
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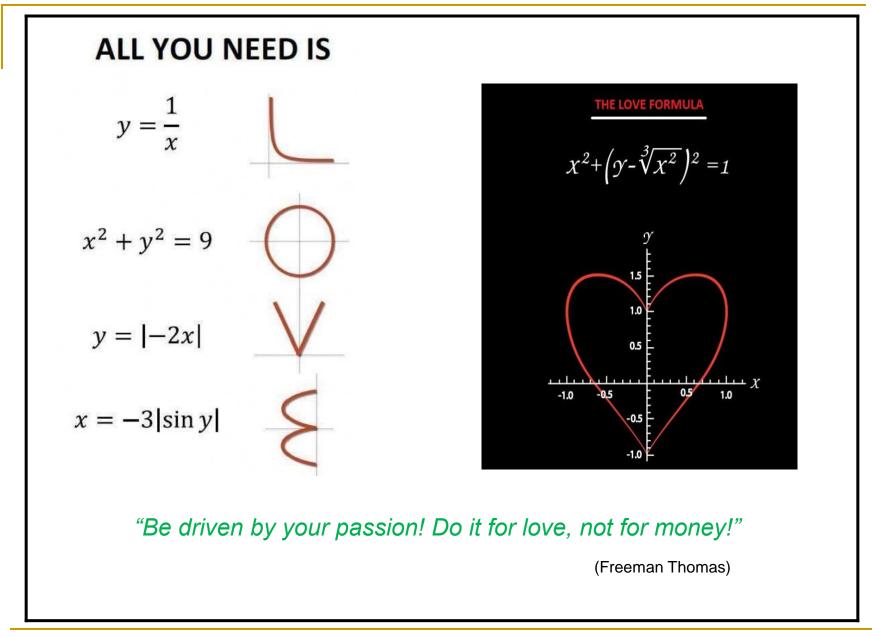
$$28,6 = 24,6 e^{-0.05(t-23,5)}$$

$$t_0 \cong 20,4868.$$

So, our victim died around 20 : 29.

Mystery solved!...





Love dynamics

To arouse the interest of students for linear systems of ODEs, Steven Strogatz (1988) discussed a simple model of the *love affairs*.

"Romeo is in love with Juliet, but in our version of this story, Juliet is a fickle lover.

The more Romeu loves her, the more Juliet wants to run away and hide.

But when Romeo gets discouraged and backs off, Juliet begins to find him strangely attractive.

Romeo, on the other hand, tends to echo her: he warms up when she loves him, and grows cold when she hates him."

- R(t) = Love of Romeo (positive values of R(t)) / hate for Juliet (negative values of R(t)) at instant t
- J(t) = Love of Juliet (positive values of J(t)) / hate for Romeo (negative values of J(t)) at instant t

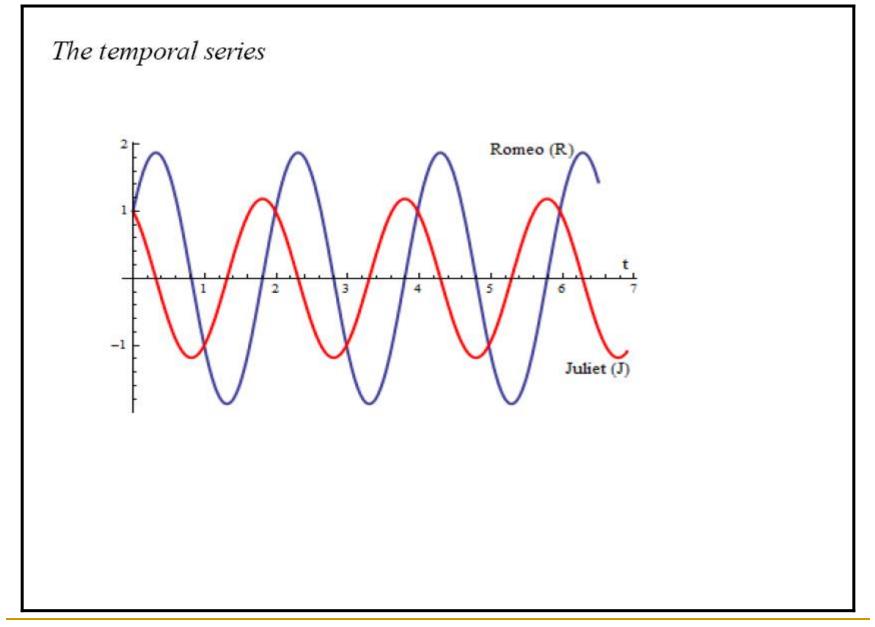
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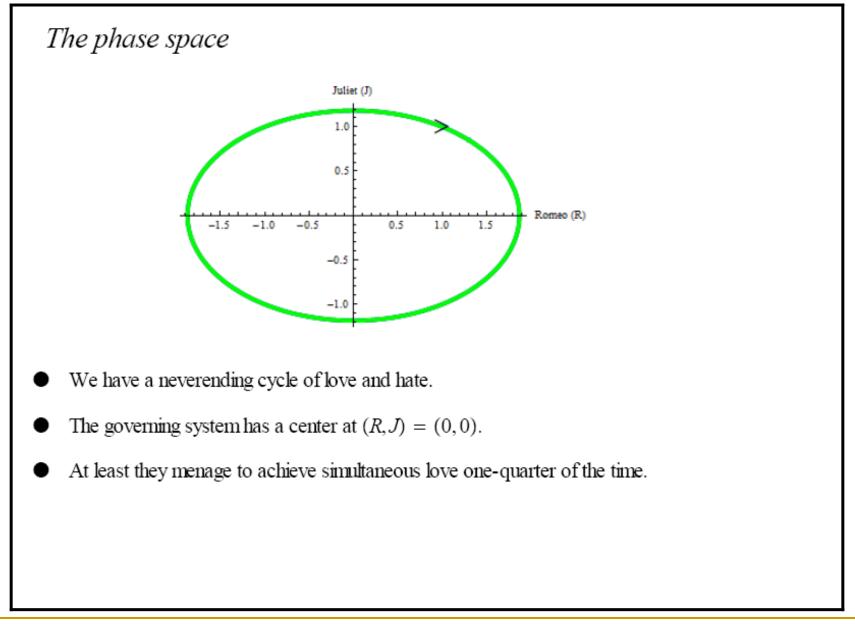
J(t) = Love of Juliet (positive values of J(t)) / hate for Romeo (negative values of J(t)) at instant t

The model for this romance is

$$\begin{cases} R' = a J \\ J' = -b R \end{cases}$$

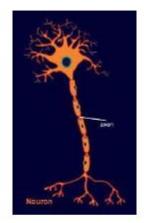
where the parameters a and b are positive, to be consistent with the story.

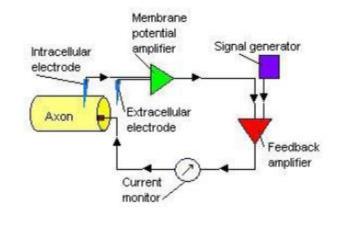


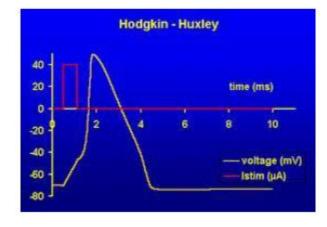


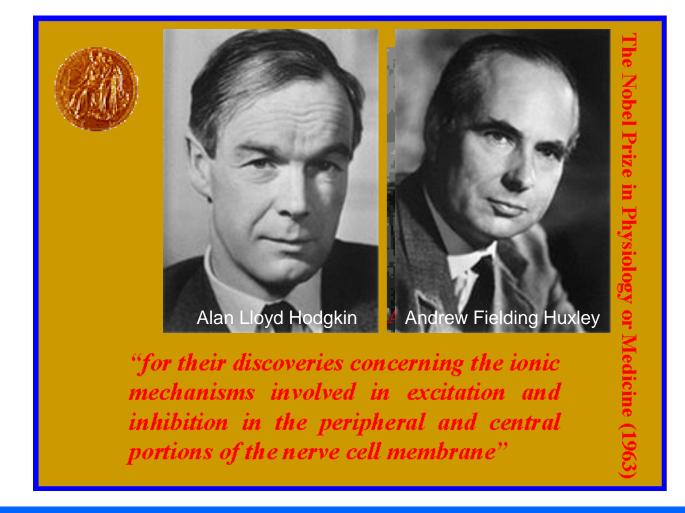
The Hodgkin-Huxley model for excitable cells

$$\begin{cases} C_M \frac{\partial v}{\partial t} = D_M \frac{\partial^2 v}{\partial x^2} - g_{Na} m^3 h(v - v_{Na}) - g_K n^4 (v - v_K) - g_L (v - v_L) \\\\ \frac{dm}{dt} = (m_\infty(v) - m) / \tau_m(v) \\\\ \frac{dn}{dt} = (n_\infty(v) - n) / \tau_n(v) \\\\ \frac{dh}{dt} = (h_\infty(v) - h) / \tau_h(v). \end{cases}$$









Hodgkin, A.L. and A.F. Huxley, *A quantitative description of membrane current and its application to conduction and excitation in nerve,* J. Physiol. 117(1952), pp.500--544.

The FitzHugh-Nagumo model

$$\begin{cases} \frac{dv}{dt} = f(v) - w + I \equiv g_1(v, w) \\ &, \text{ with } f(v) = v(1 - v)(v - a). \end{cases}$$
$$\frac{dw}{dt} = bv - \gamma w \equiv g_2(v, w) \end{cases}$$

- I depolarized current
- v voltage
- w recovery variable



Richard FitzHugh in his Lab (National Institute of Health Maryland CA (1960)

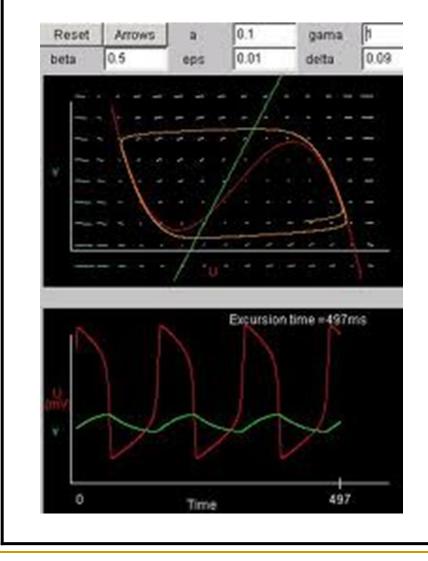


Jin-ichi Nagumo

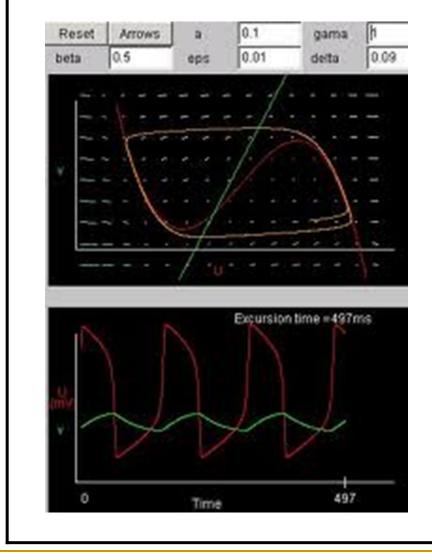


The Nagumo's original circuit (Tokyo University)

Phase space and time series

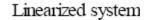


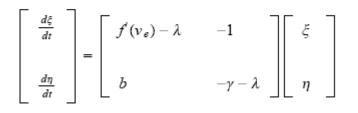
Phase space and time series



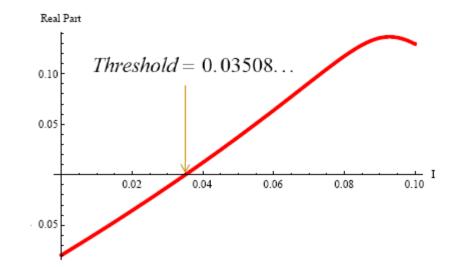
Fixed points of the system (v_e, w_e)

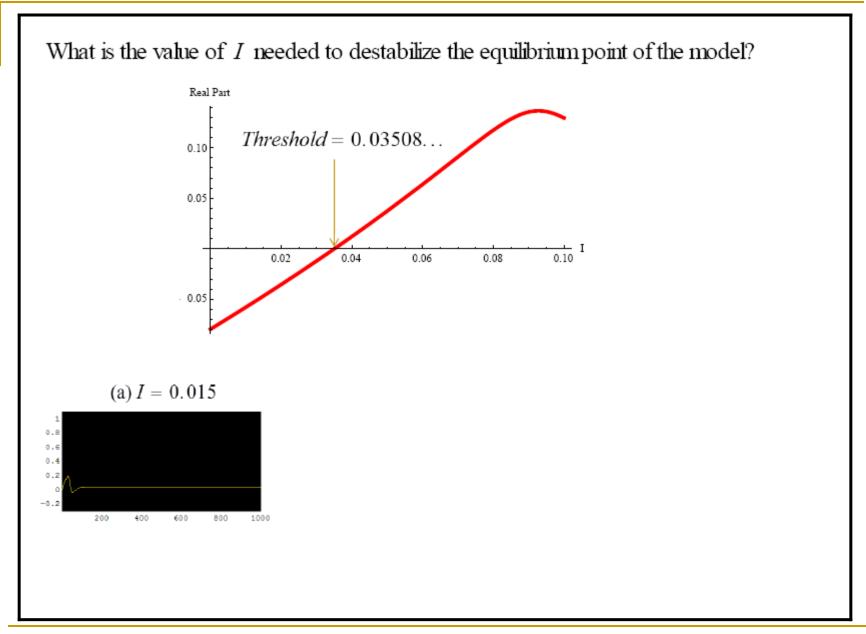
$$\begin{cases} \frac{dv}{dt} = 0\\ \frac{dw}{dt} = 0 \end{cases} \iff \begin{cases} w = v(1-v)(v-a)\\ w = \frac{b}{\gamma}v \end{cases}$$

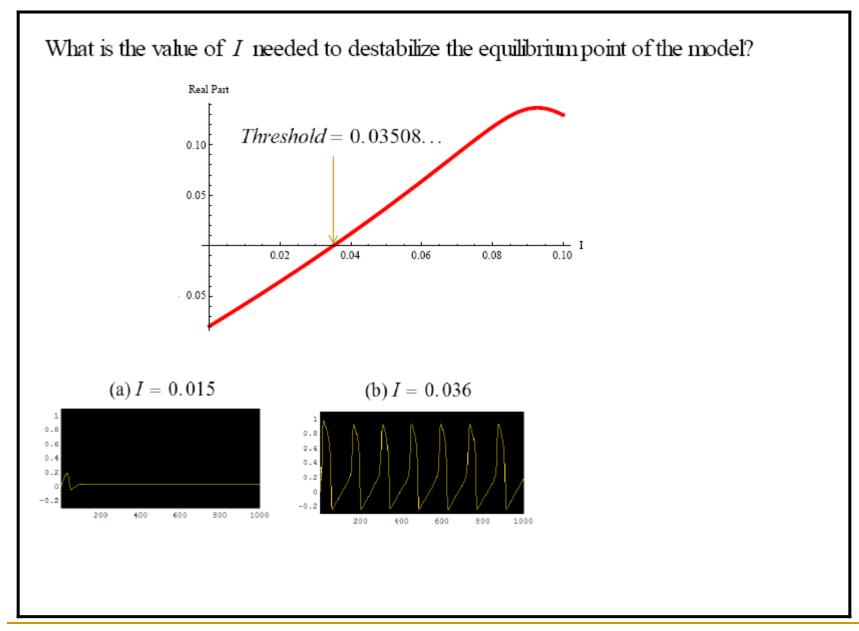


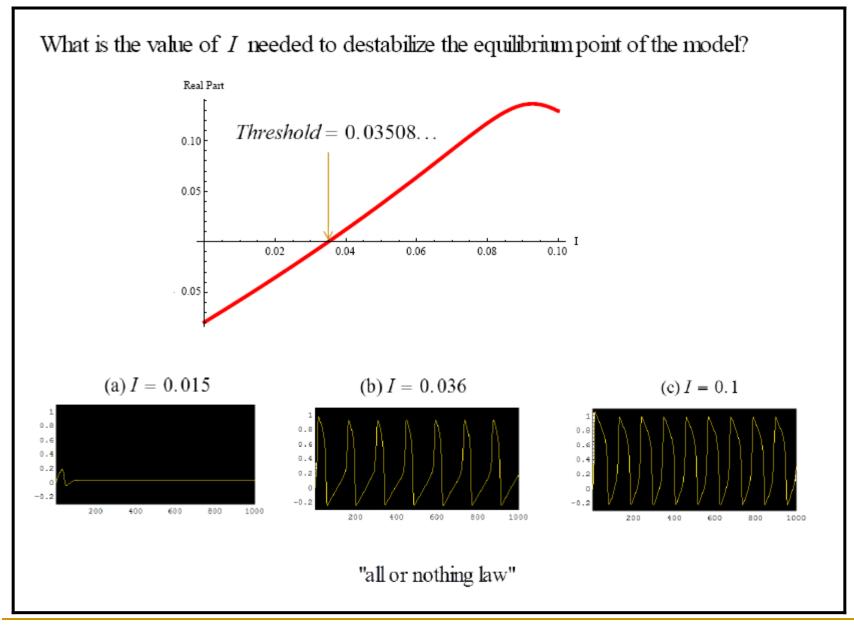


What is the value of I needed to destabilize the equilibrium point of the model?



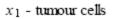


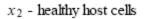




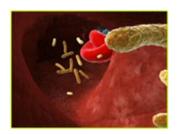
Mathematical model of tumour growth

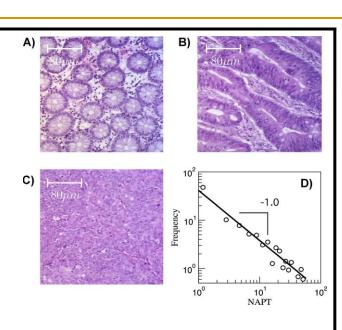
$$\begin{cases} \frac{dx_1}{dt} = x_1(1-x_1) - a_{12}x_1x_2 - a_{13}x_1x_3, \\\\ \frac{dx_2}{dt} = r_2x_2(1-x_2) - a_{21}x_1x_2, \\\\ \frac{dx_3}{dt} = \frac{r_{3}x_1x_3}{x_1+k_3} - a_{31}x_1x_3 - d_3x_3. \end{cases}$$

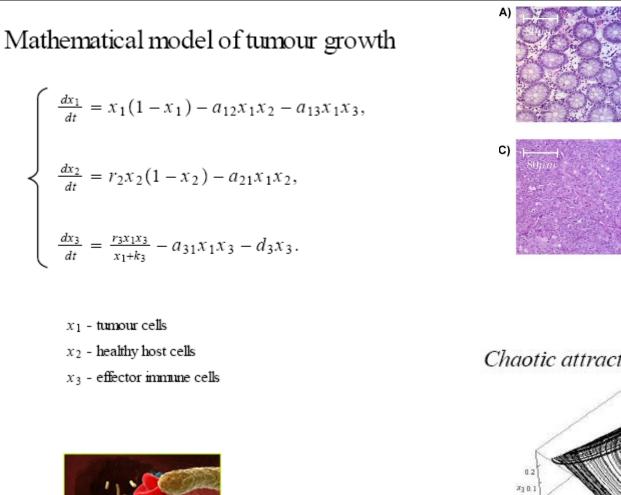


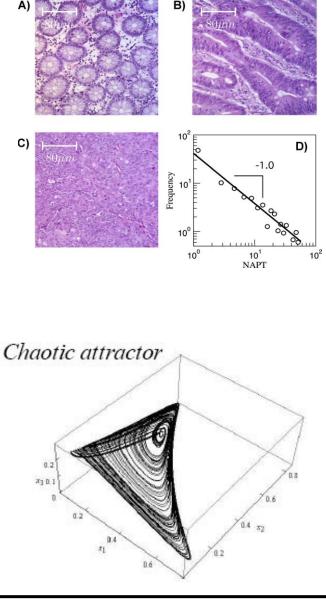


 x_3 - effector immune cells









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Wonders of the nonlinear world...

The studied dynamical systems are sets of deterministic rules, represented by differential equations, that describe the behavior of certain magnitudes evolving in time.

Depending on the initial conditions, and on specific choice of parameters, these dynamical variables can evolve in time towards some asymptotic behavior - *chaotic attractor*.

Dynamics - A Capsule History

1666	Newton	Invention of calculus, explanation of planetary motion
1700s		Flowering of calculus and classical mechanics
1800s		Analytical studies of planetary motion
1890s	Poincaré	Geometric approach, nightmares of chaos
1920–1950		Nonlinear oscillators in physics and engineering, invention of radio, radar, laser
1920–1960	Birkhoff Kolmogorov Arnol'd	Complex behavior in Hamiltonian mechanics
	Moser	
1963	Lorenz	Strange attractor in simple model of convection
1970s	Ruelle & Takens	Turbulence and chaos
	May	Chaos in logistic map
	Feigenbaum	Universality and renormalization, connection between chaos and phase transitions
		Experimental studies of chaos
	Winfree	Nonlinear oscillators in biology
	Mandelbrot	Fractals
1980s		Widespread interest in chaos, fractals, oscillators, and their applications

Chaos

• The word *chaos* was coined in 1975, by Tien-Yien Li and James Yorke, to designate a long term behavior:

(i) aperiodic

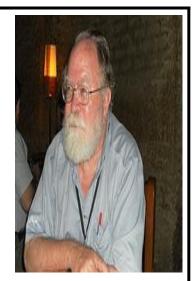
(solutions with irregular behavior when $t \to \infty$)

(ii) in a *deterministic* system

(the irregular behavior appears from the nonlinearities of the system)

(iii) which exhibits *sensitivity to initial conditions*

(the nonlinearities amplify exponentially tiny variations of the initial conditions)



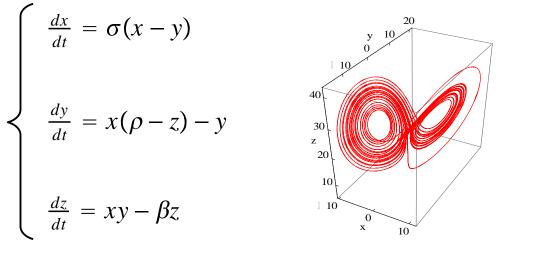
Attractor

- An **attractor** is a set to which all neighboring trajectories converge.
- A chaotic attractor exhibits *sensitive dependence on initial conditions*.

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The Lorenz system



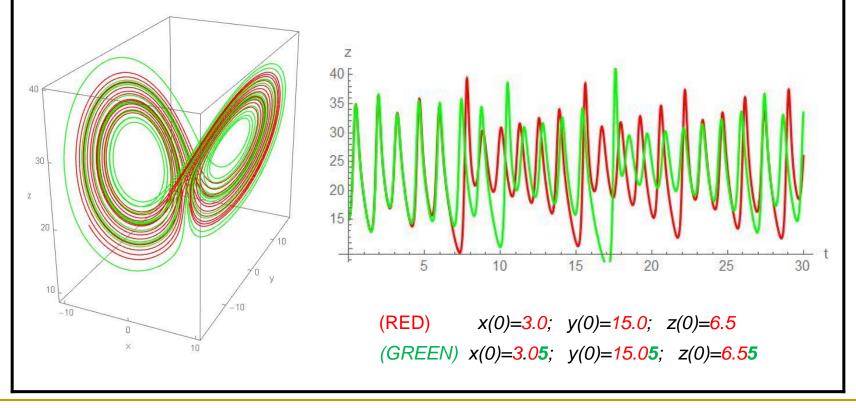


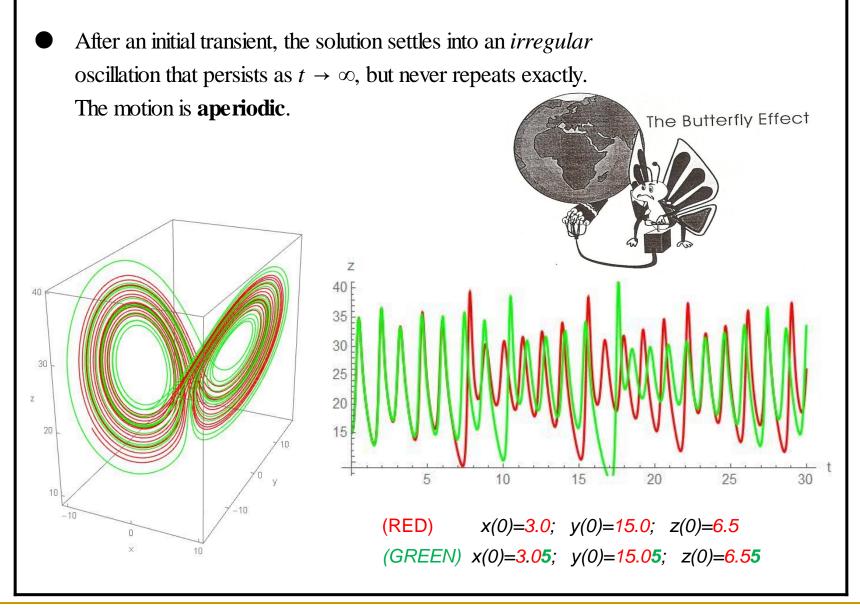
(Inspired by investigations in atmospheric dynamics, 1963)

Edward N. Lorenz

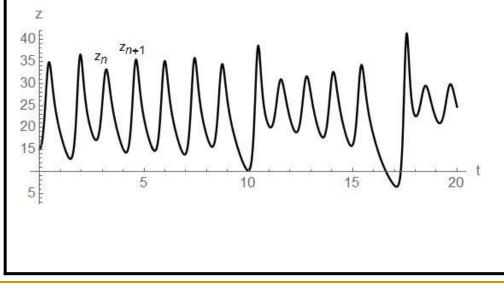
• Lorenz discovered that a wonderful structure with the dynamical property of *sensitive dependence on initial conditions* emerges, if the solution is vizualized in phase space.

The chaotic attractor has a *butterfly pattern*.

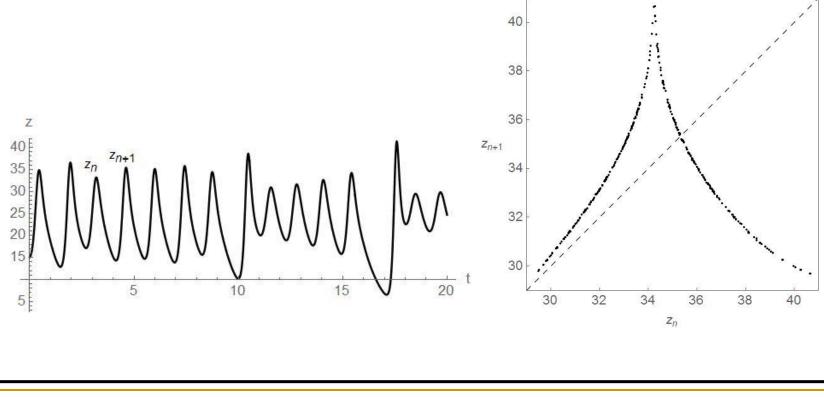


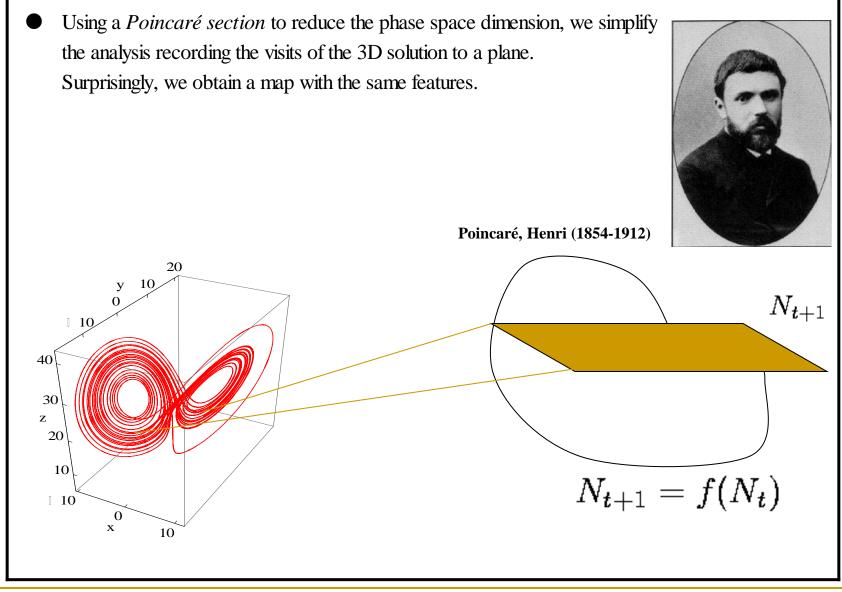


- Lorenz (1963) found a remarkable way to analyze the dynamics of a chaotic attractor. He directs our attention to a particular view of the attractor.
- Recording the successive *n*th local maxima of z(t), in the form (z_n, z_{n+1}) , we obtain



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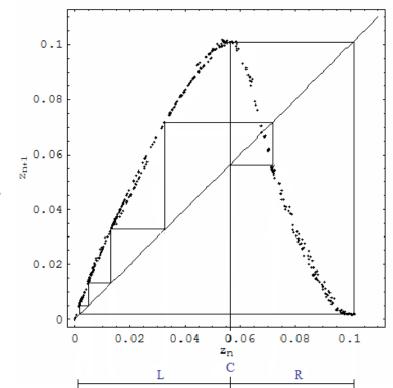


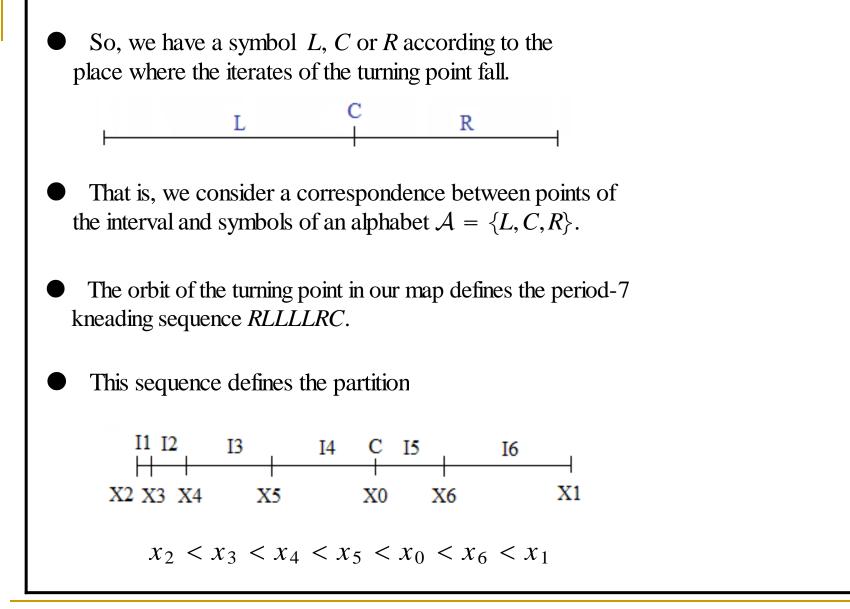
Using a Poincaré section to reduce the phase space dimension, we simplify the analysis recording the visits of the 3D solution to a plane. Surprisingly, we obtain a map with the same features. 0.08 0.06 Zn+1 0.04 Poincaré, Henri (1854-1912) 0.02 20 0.02 0.04 0.06 0.08 Zn y 10 N_{t+1} 0 10, 40 30 z 20 10 $N_{t+1} = f(N_t)$ 10 0 х 10

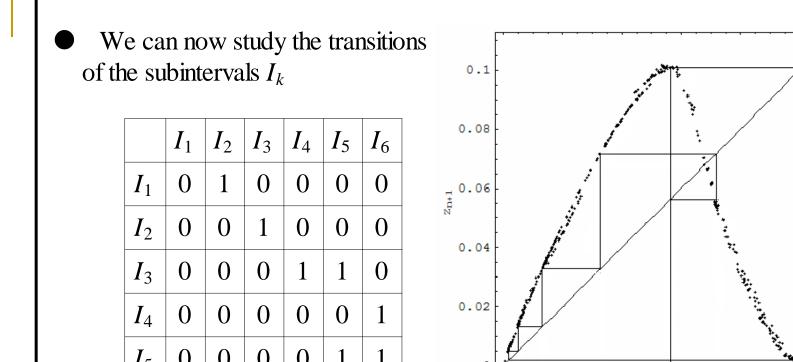
Unimodal maps

Let us consider the map

- The point C at which the family of maps has a maximum is called a turning point.
- The dynamics is characterized by the symbolic sequences associated to the orbit of the point *C*.
- We associate to the orbit a sequence of symbols. Each symbol corresponds to a new iteration.







0.02

0

I1 I2

X2 X3 X4

0.02

I3

X5

0.04

I4

0.06

C 15

zn

X0

RLLLLRC

0.08

X6

I6

0.1

X1

0

0

1

 I_4

 I_5

 I_6

0

0

1

0

0

1

0

0

1

0

1

0

1

1

0

Therefore, the corresponding transition matrix is

$$M(f) = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 1 & 1 \\ 1 & 1 & 1 & 1 & 0 & 0 \end{bmatrix}$$

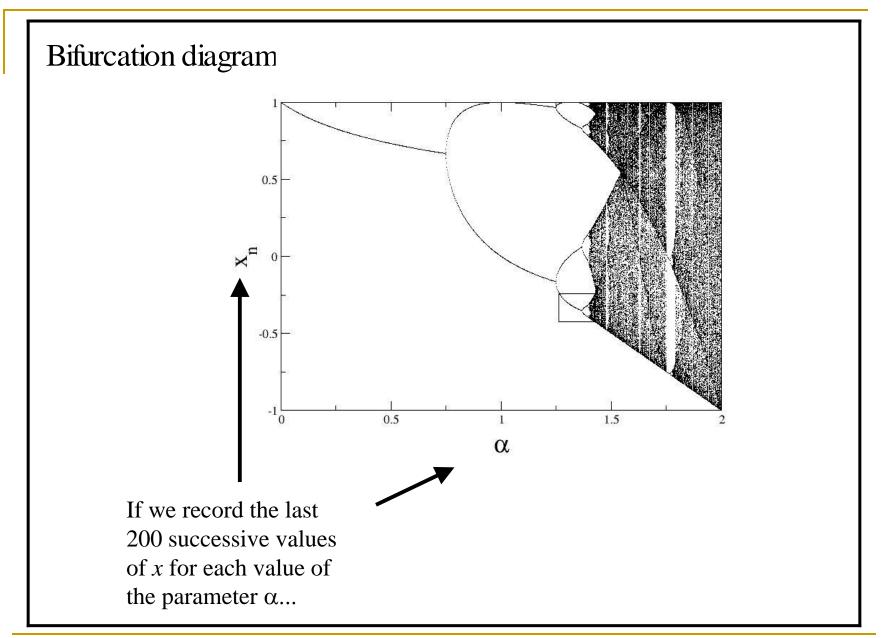
wich has the characteristic polynomial

$$p(\lambda) = \det[M(f) - \lambda I] = 1 - \lambda - \lambda^2 - \lambda^3 - \lambda^4 - \lambda^5 + \lambda^6.$$

The growth number s(f) (the spectral radius of matrix M(f)) is 1.94686....

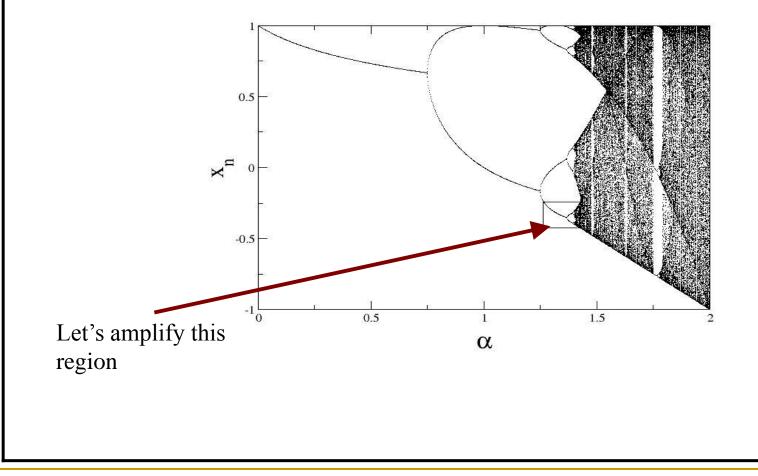
So, the value of the topological entropy can be given by

$$h_{top}(f) = \log s(f) = 0.675975...$$

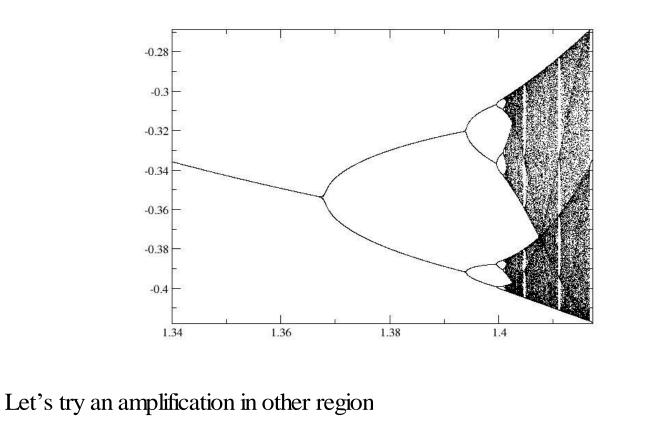


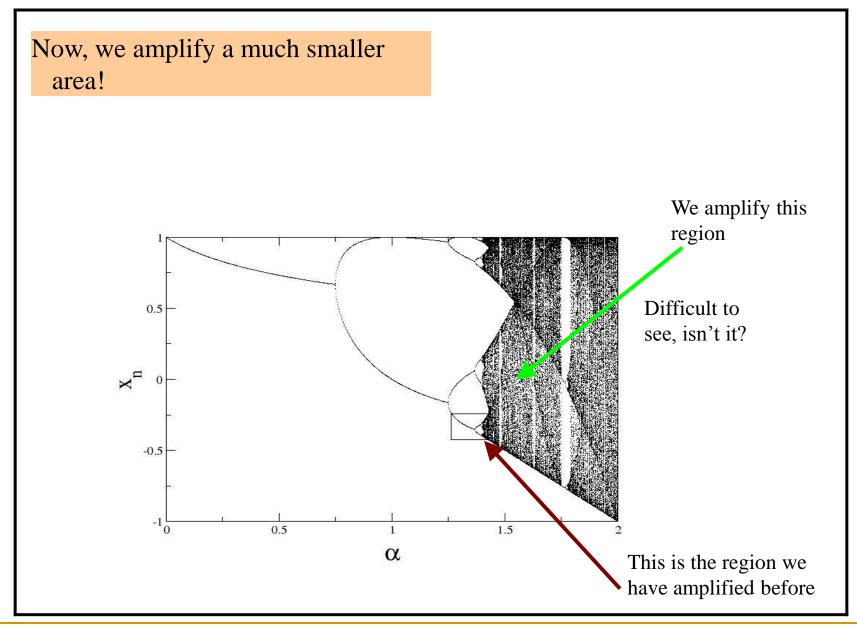
What special feature does this diagram have?

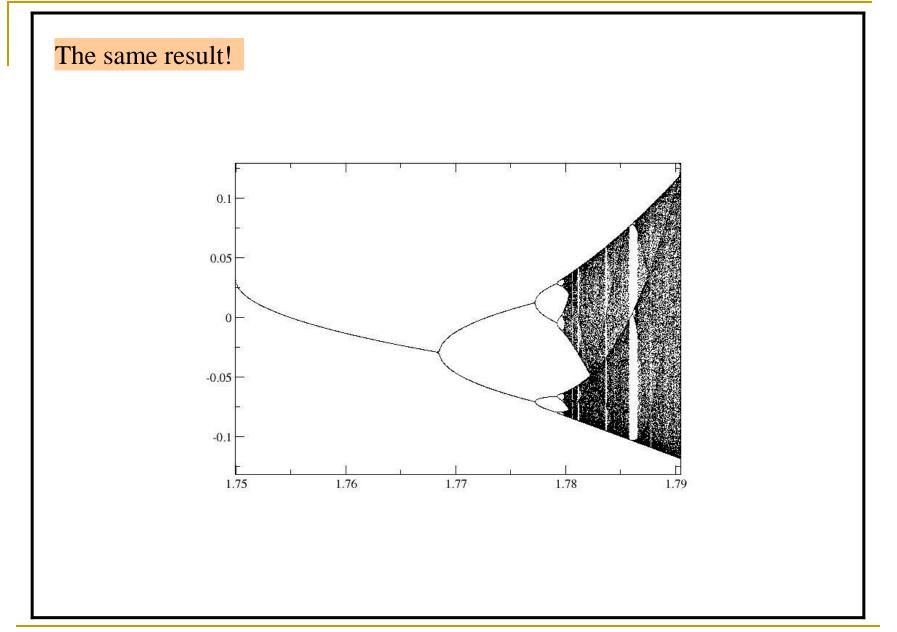
Let's take a closer look...



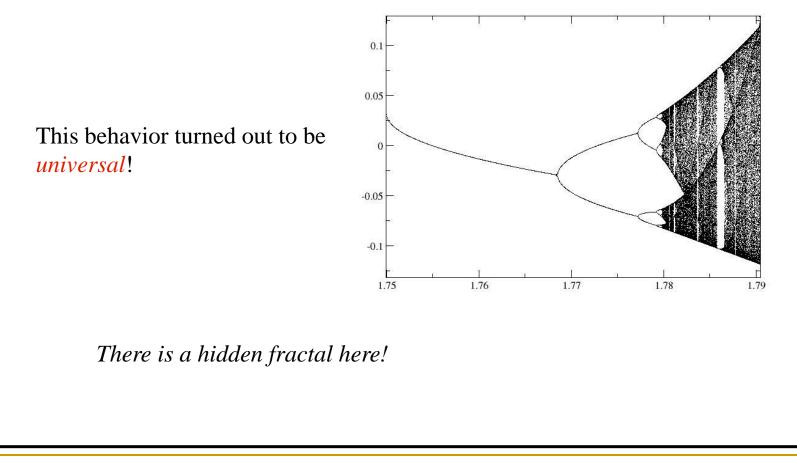
And... We obtain something very similar!



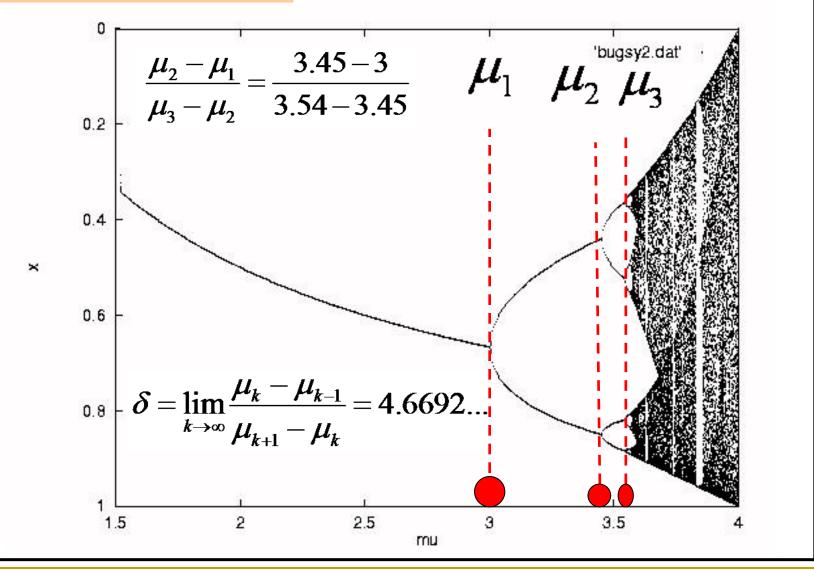




In fact, the bifurcation diagram repeats itself successively in smaller and smaller scales...



Moreover, check this out!...



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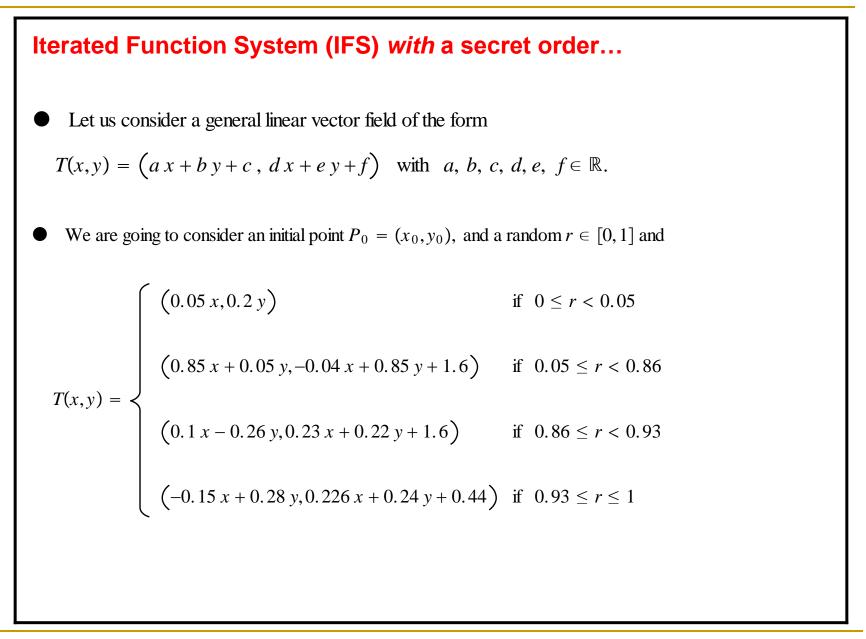
In 1975, Feigenbaum discovered this regularity, truly unexpected, in the period-doubling cascade.

 $\delta = \lim_{k \to \infty} \frac{\mu_k - \mu_{k-1}}{\mu_{k+1} - \mu_k} = 4.6692...$



This universal value, δ , is called **Feigenbaum constant**.

Quite impressive, isn't it?



Iterated Function System (IFS) with a secret order...

$$T(x,y) = \begin{cases} (0.05 \ x, 0.2 \ y) & \text{if } 0 \le r < 0.05 \\ (0.85 \ x + 0.05 \ y, -0.04 \ x + 0.85 \ y + 1.6) & \text{if } 0.05 \le r < 0.86 \\ (0.1 \ x - 0.26 \ y, 0.23 \ x + 0.22 \ y + 1.6) & \text{if } 0.86 \le r < 0.93 \\ (-0.15 \ x + 0.28 \ y, 0.226 \ x + 0.24 \ y + 0.44) & \text{if } 0.93 \le r \le 1 \end{cases}$$

Let's start with
$$P_0 = (0.5, 0.5)$$

1st iteration

For example, if r = 0.55, we use the second branch to compute the image of the initial point $P_0 = (0.5, 0.5)$.

The result is T(0.5, 0.5) = (0.45, 2.005).

Consequently, we represent in the plane the point $P_1 = (0.45, 2.005)$

Iterated Function System (IFS) with a secret order...

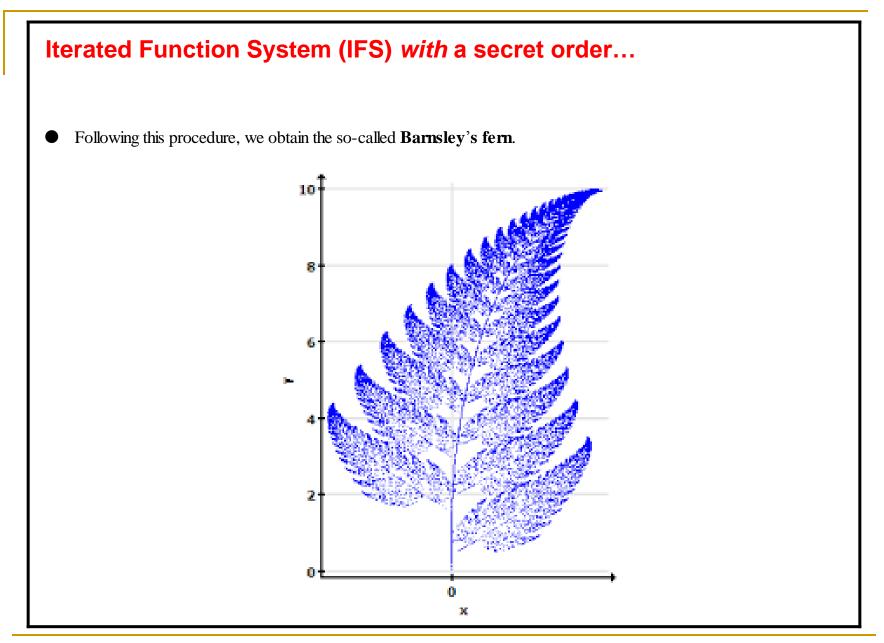
$$T(x,y) = \begin{cases} (0.05 x, 0.2 y) & \text{if } 0 \le r < 0.05 \\ (0.85 x + 0.05 y, -0.04 x + 0.85 y + 1.6) & \text{if } 0.05 \le r < 0.86 \\ (0.1 x - 0.26 y, 0.23 x + 0.22 y + 1.6) & \text{if } 0.86 \le r < 0.93 \\ (-0.15 x + 0.28 y, 0.226 x + 0.24 y + 0.44) & \text{if } 0.93 \le r \le 1 \end{cases}$$

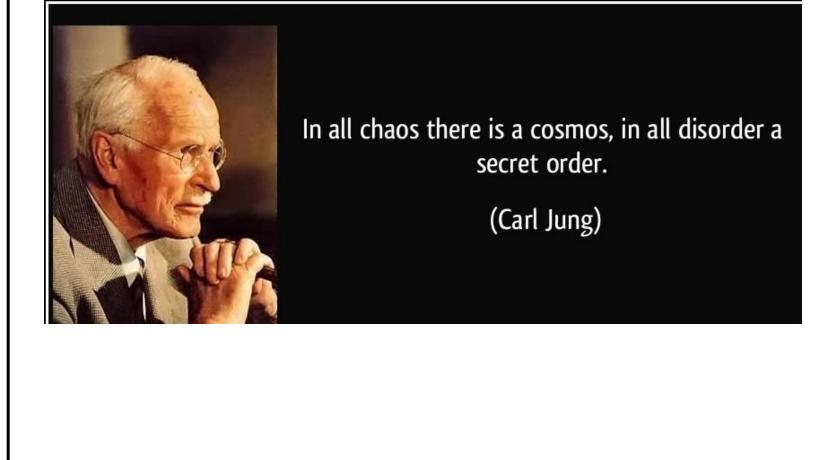
 2^{st} iteration

For example, if r = 0.9, we use the third branch to compute the image of the previous point $P_1 = (0.45, 2.005)$.

The result is T(0.45, 2.005) = (-0.4763, 2.1446)

Consequently, we represent in the plane the point $P_2 = (-0.4763, 2.1446)$





"It is the nature of chaotic systems to surprise."

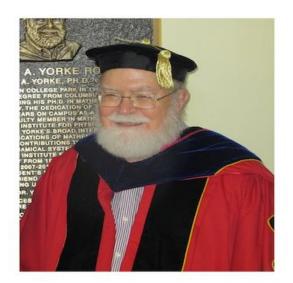
"The **most successful people** are those who are good at plan B."

"...this means that life can plan ahead, but you have to be prepared to change plans . It is a basic principle of chaos."

And an advice offered to new generations of scientists...

"<u>It is not the same</u> to be a <u>good student</u> and to be a <u>good researcher</u>, often the two come into conflict.

You're a **good student** if you do what you are told to, while you will be a **good researcher** if you seek to find what you do not understand."



Prof. James A. Yorke University of Maryland at College Park

Doctor Honoris Causa, January 28th, 2014 (Universidad Rey Juan Carlos)



Prof. Miguel A. Sanjuán (Universidad Rey Juan Carlos)

Mathematics in use (some aspects)

Analysis and application of different concepts

Boundedness of the dynamical orbits

```
\begin{split} \Psi &= x_1 + x_2 + x_3 \\ \frac{d\Psi}{dt} + \varepsilon \Psi &\leq L. \\ \Psi(t) &\leq \Psi(0) e^{-\varepsilon t} + \frac{L}{\varepsilon} (1 - e^{-\varepsilon t}) \leq \max(\frac{L}{\varepsilon}, \Psi(0)). \end{split}
```

Observability

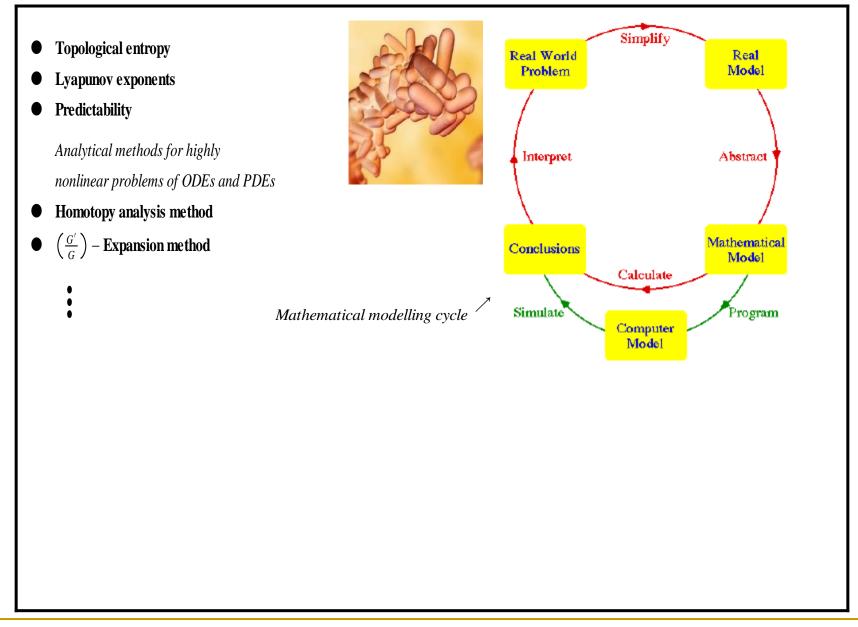
The observability indices estimate the coupling complexity

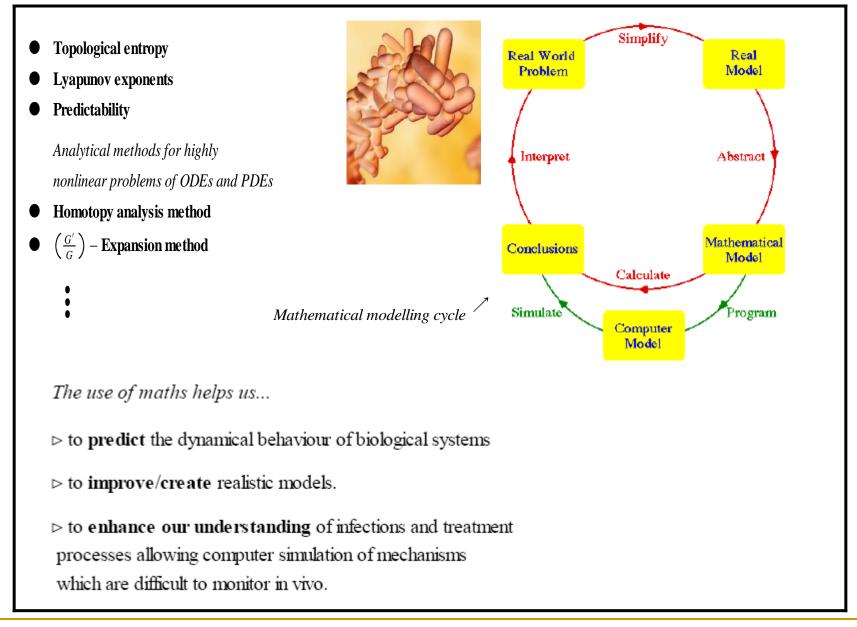
$$\delta_{s} = \frac{1}{T} \sum_{t=0}^{T} \frac{|\lambda_{\min}[O_{s}^{T}O_{s}, \mathbf{x}(t)]|}{|\lambda_{\max}[O_{s}^{T}O_{s}, \mathbf{x}(t)]|},$$

$$\delta_{x_{1}} = 0.015..., \ \delta_{x_{2}} = 0.021... \text{ and } \delta_{x_{3}} = 0.0001...$$

The variables can be ranked in descending degree of observability

 $x_2 \triangleright x_1 \triangleright x_3$



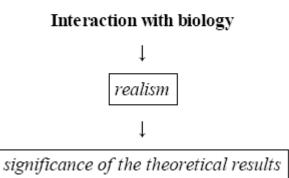


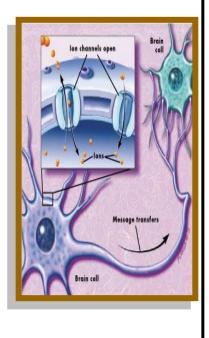
Research work...

... collaborative and interdisciplinary.









Network of collaborators

Biomedical Research Park - Barcelona

Evolutionary Systems Virology Group - Valencia



Santiago Elena



Collaboration

is key!...







J. Duarte Svitlana and Yuriy Rogovchenko



N. Martins

C. Januário

Josep Sardanyés

BI

C L C C Y

IST - Lisbon



ISEL - Lisbon



Univ. of Agder - Kristiansand

MatRIC Modelling Colloquium, Kristiansand - August 9th to 11th, 2016

- The keyword in the science of the early twenty-first century is **multidisciplinary**.
- Along the history of science, nature has been splitted into many parts for better understanding.

- The keyword in the science of the early twenty-first century is **multidisciplinary**.
- Along the history of science, nature has been splitted into many parts for better understanding.

- Now, the different areas *must* interact to complete their descriptions and better comprehend the surrounding reality.
- Every time that science sheds light into nature, revealing its hidden shapes, the shadow of our ignorance gets longer.



"Nature imagination far surpasses our own."

(Richard P. Feynman, The character of physical law)

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Jorge Duarte (jduarte@adm.isel.pt)

Teaching / research – a multidisciplinary approach

- ▷ Teaching and working interaction with students are definitely major and compelling reasons for pursuing an academic career.
- My academic qualifications and some years of experience make me agree with the famous quote of E. T. Bell
 - 'Obvious' is the most dangerous word in Mathematics.

Teaching / research – a multidisciplinary approach

- ▷ Teaching and working interaction with students are definitely major and compelling reasons for pursuing an academic career.
- My academic qualifications and some years of experience make me agree with the famous quote of E. T. Bell
 - 'Obvious' is the most dangerous word in Mathematics.
- We must be always very careful with the level of motivation and curiosity of our students, especially at the undergraduate level.
- When designing a mathematical course in Math Bio Education, do it FOR and WITH biologists.

MatRIC Modelling Colloquium, Kristiansand – August 9th to 11th, 2016

Teaching / research – a multidisciplinary approach

- Mathematics, in particular the study of differential equations, gives students an holistic perspective which integrates in a special way key areas such as: *calculus* and *numerical methods*, *algebra*, *geometry*.
- One of the major benefits of nonlinear dynamics is that it can be used in a wide variety of scientifically relevant situations.
- It's truly important for a professor to have the willingness to learn, pay attention, and change.

Unique and distinctive features of Maths...

▷ One thing should be clear:

While our perception of the physical world can always be distorted, our perception of the **mathematical truths** can't be. They **are objective**, **persistent**, **necessary truths**.

A mathematical formula means the same thing to anyone anywhere
 no matter what gender, ethnicity, religion; it will mean the same thing to
 anyone a thousand year from now. And that's why mathematics is going
 to play an increasingly important role in science and technology.



(Edward Frenkel, author of *Love & Mathematics*)

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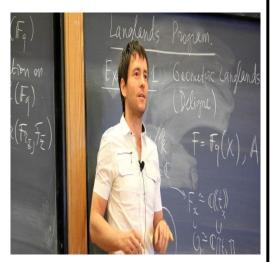
- A mathematical formula means the same thing to anyone anywhere
 no matter what gender, ethnicity, religion; it will mean the same thing to
 anyone a thousand year from now. And that's why mathematics is going
 to play an increasingly important role in science and technology.
- It might still be possible to be "bad in math" and be a good scientist
 in some areas, and probably not for too long.
 But this is a handicap and nothing to be proud of.
- Granted, some areas of science currently use less math than others.
 But then professionals in those fields stand to benefit even more from learning mathematics.



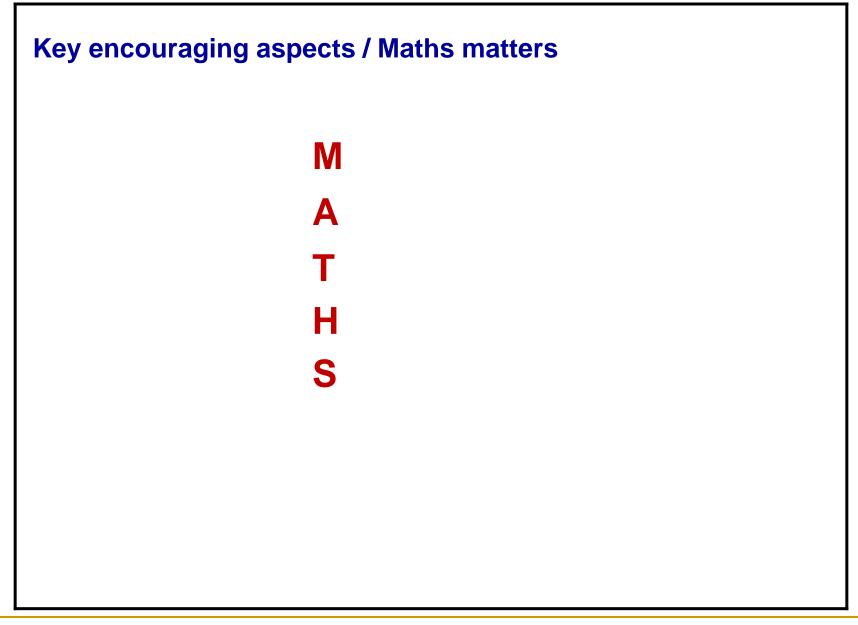
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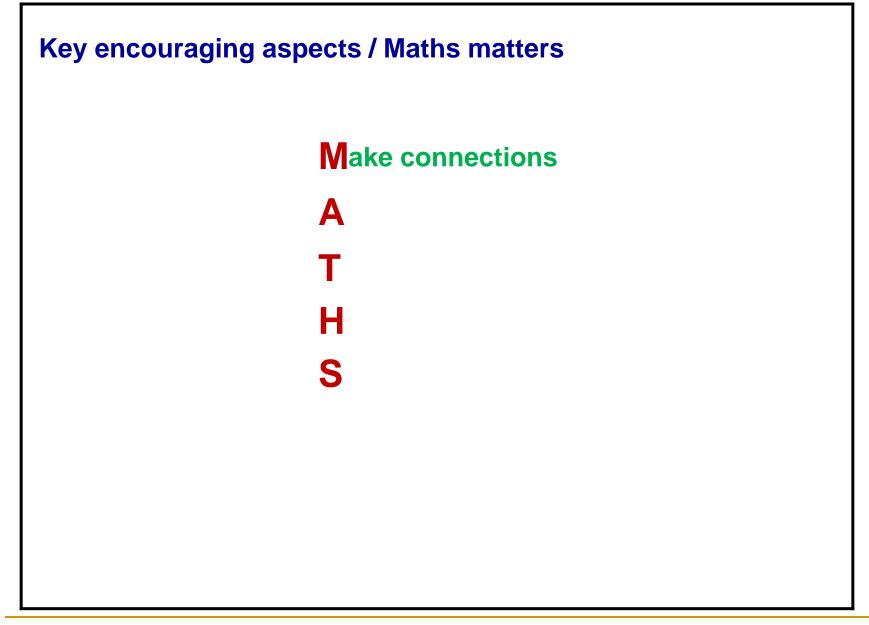
Unique and distinctive features of Maths...

- ▷ We should discuss the real question, which is how to improve our math education and to eradicate *the fear of mathematics*.
- The fear of Mathematics, among the next generation and future scientists, it's not just counterproductive;
 - it is a DISGRACE, SELF-EXTINGUISHING strategy!

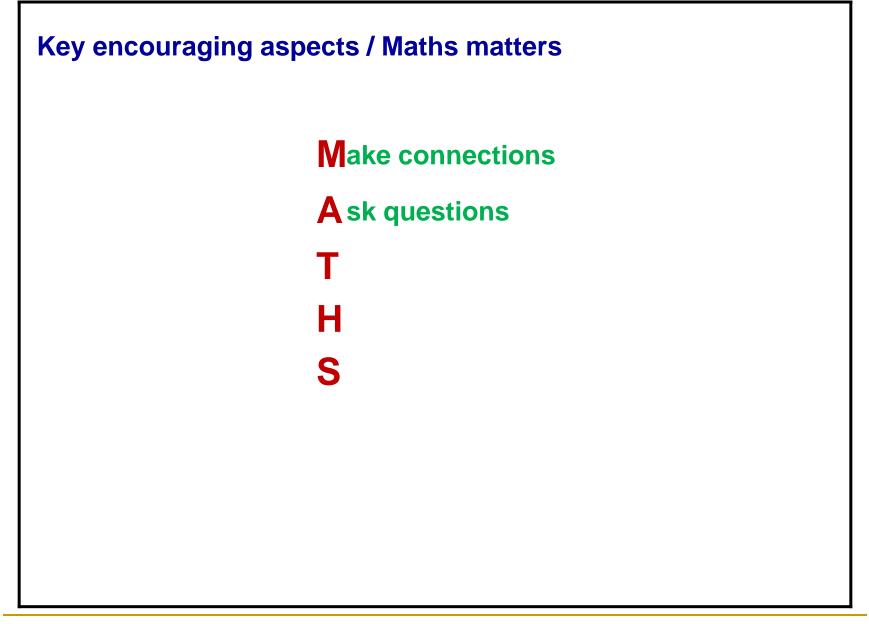


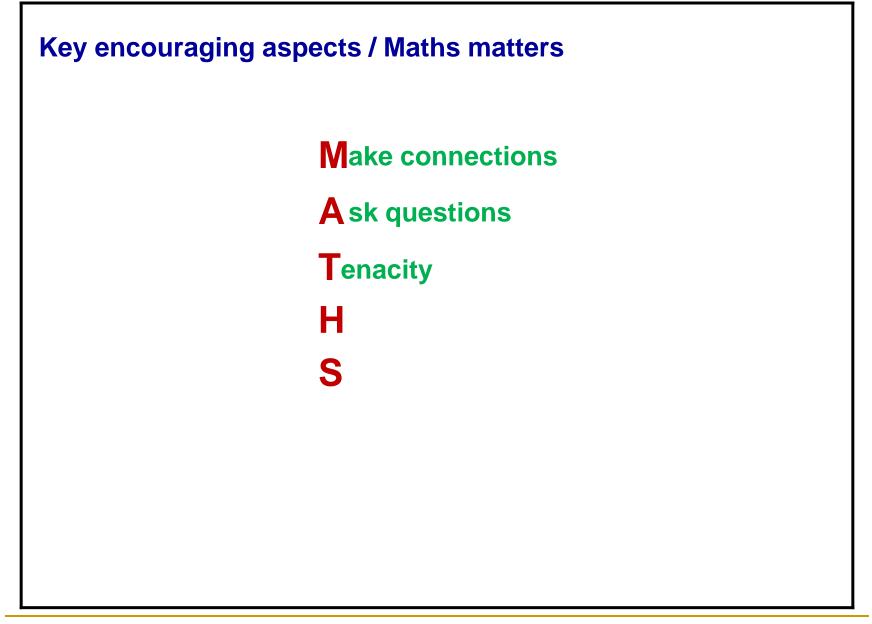
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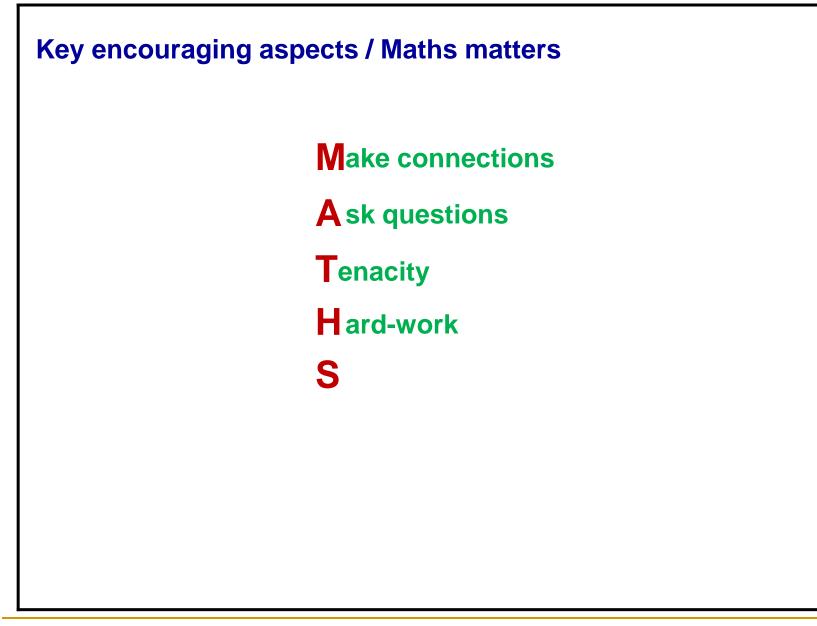




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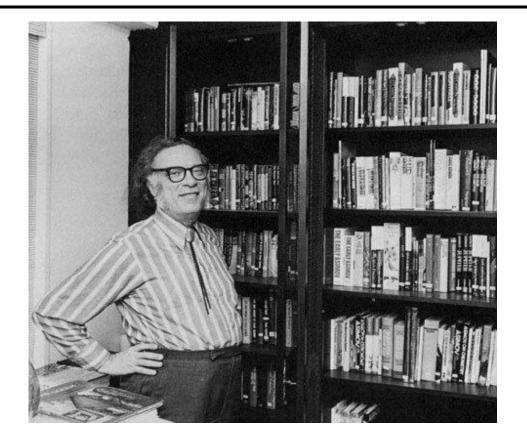








Make connections A sk questions Tenacity H ard-work Skills



"Call it the satisfaction of curiosity. I understand a little of it today, perhaps a little more tomorrow. That's a victory in a way."

(Isaac Asimov, Profession)

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Jorge Duarte (jduarte@adm.isel.pt)

Jusen takk!



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