Modelling complexe biological systems in the context of genomics

# Ordinary Differential Equations (ODEs) and the biological switch

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# Plan

- ODEs and biology: Why?
- Biological Switch
- Biological switch and ODEs
- Geometrical representation of ODEs
- Geometrical interpretation of ODEs
- Geometrical interpretation of the switch
- Conclusion

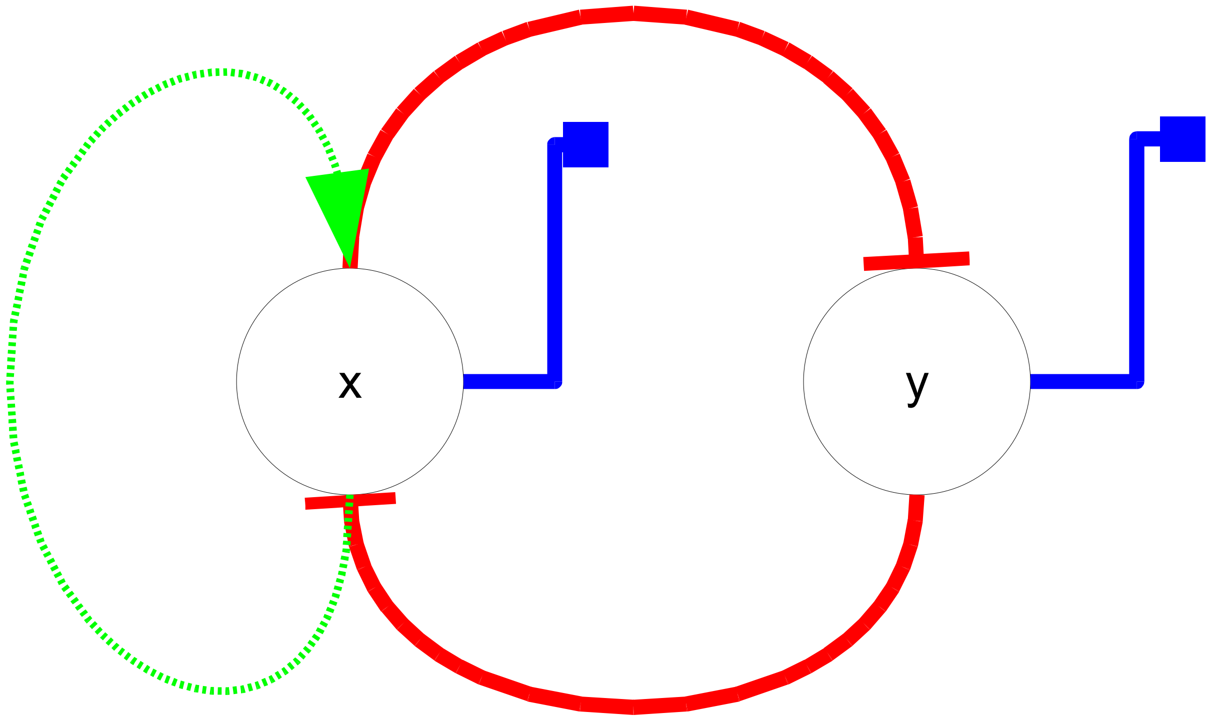
# ODEs and Biology

- Assumptions for ODEs:
  - Deterministic system
  - No uncertainity
  - Populational level of description
  - ***dynamics (***or time evolution***)of a system***
- Why ODEs:
  - Strong mathematical history and background
  - Historical relationships between ODEs and biology (bio)chemistry, enzymology, ecology, epidemiology
  - Well accepted formalism in biological communities
  - Software for *in silico* experiments for biologists

# A first ODE tour for biologists

- Our aim in this tutorial is:
  - To present fundamental notions in analysing ODEs
  - Illustrate our to model a biological system (Switch)
  - To to understand the biological switch with these notions.

# Biological Switch : schematic




- Two biological species: *x* and *y*
- *x* repress *y*
- *y* repress *x*
- *x,y* : *degradation*
- *x* : *auto-activation*

# Modelling the Biological Switch using ODE formalism

- Fundamental idea:
  - We want the time evolution of $x$ and $y$, that is $x(t)$
  - We don't know how to obtain a formula for $x(t)=???$
  - We know how to describe a small variation of the concentration of $x$ and $y$ during a small time interval $dt$
- Procedure (for each biological entity):
  - Identify each mechanism where $x$ is involved
  - For each mechanism, give an equation describing a small variation of the concentration ($dx$) for a small time interval ($dt$)
  - Sum up to obtain $dx/dt = f(x,...)$

# From *dx/dt* to *x(t)*

- dx/dt = f(x,...)
- One can compute *x(t)* using *dx/dt*:
  - By definition :

    $x(t+dt) = x(t)$ + small variation of $x(t)$ during the small time interval $dt$.

    $x(t+dt) = x(t) + dt.( dx(t)/dt )$

# From *dx/dt* to *x(t)*

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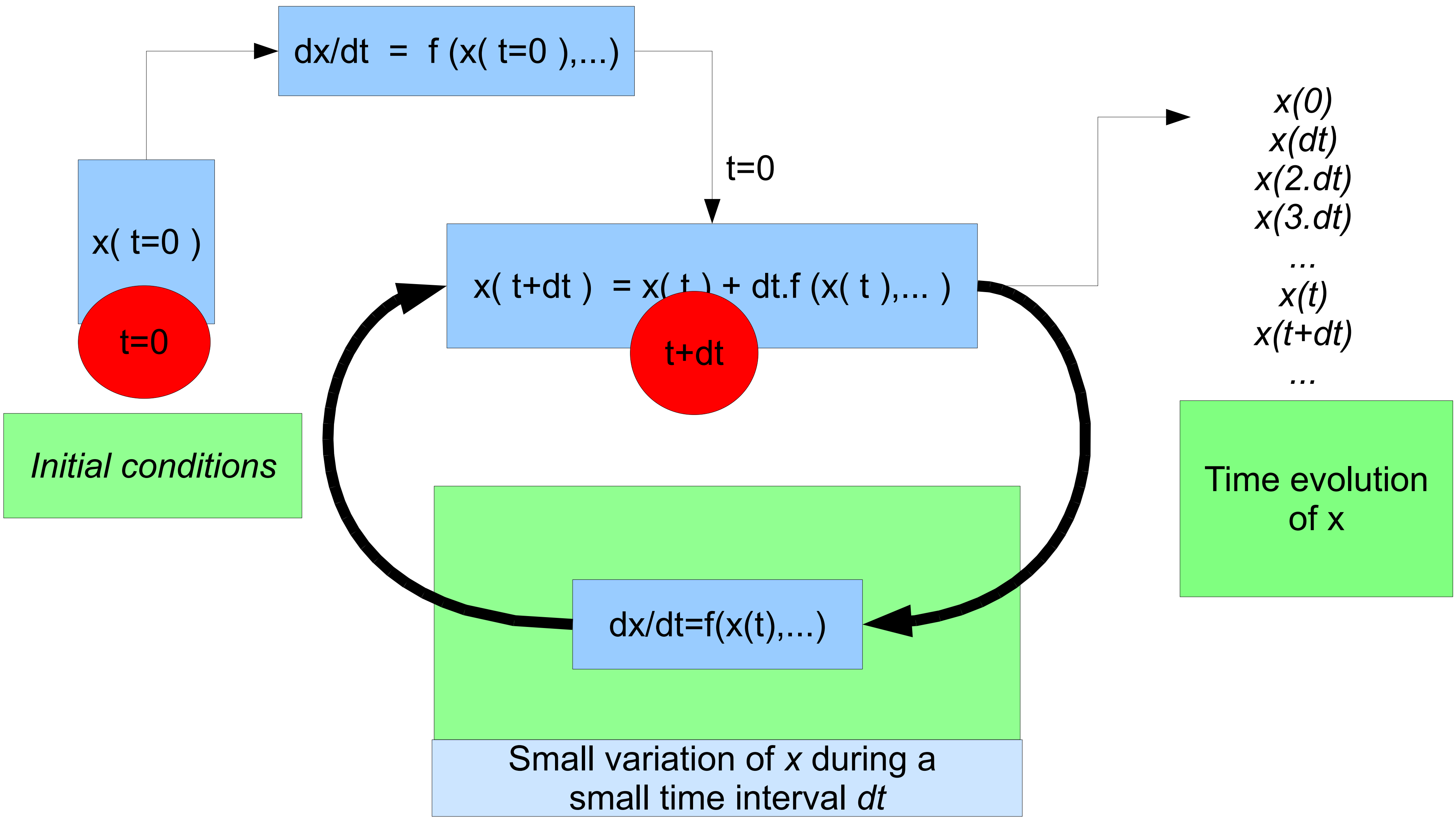
    *x(t+dt)* = *x(t)* + small variation of *x(t)* during the small time interval *dt*.

    $x(t+dt) = x(t) + dt.(\boxed{dx(t)/dt})$

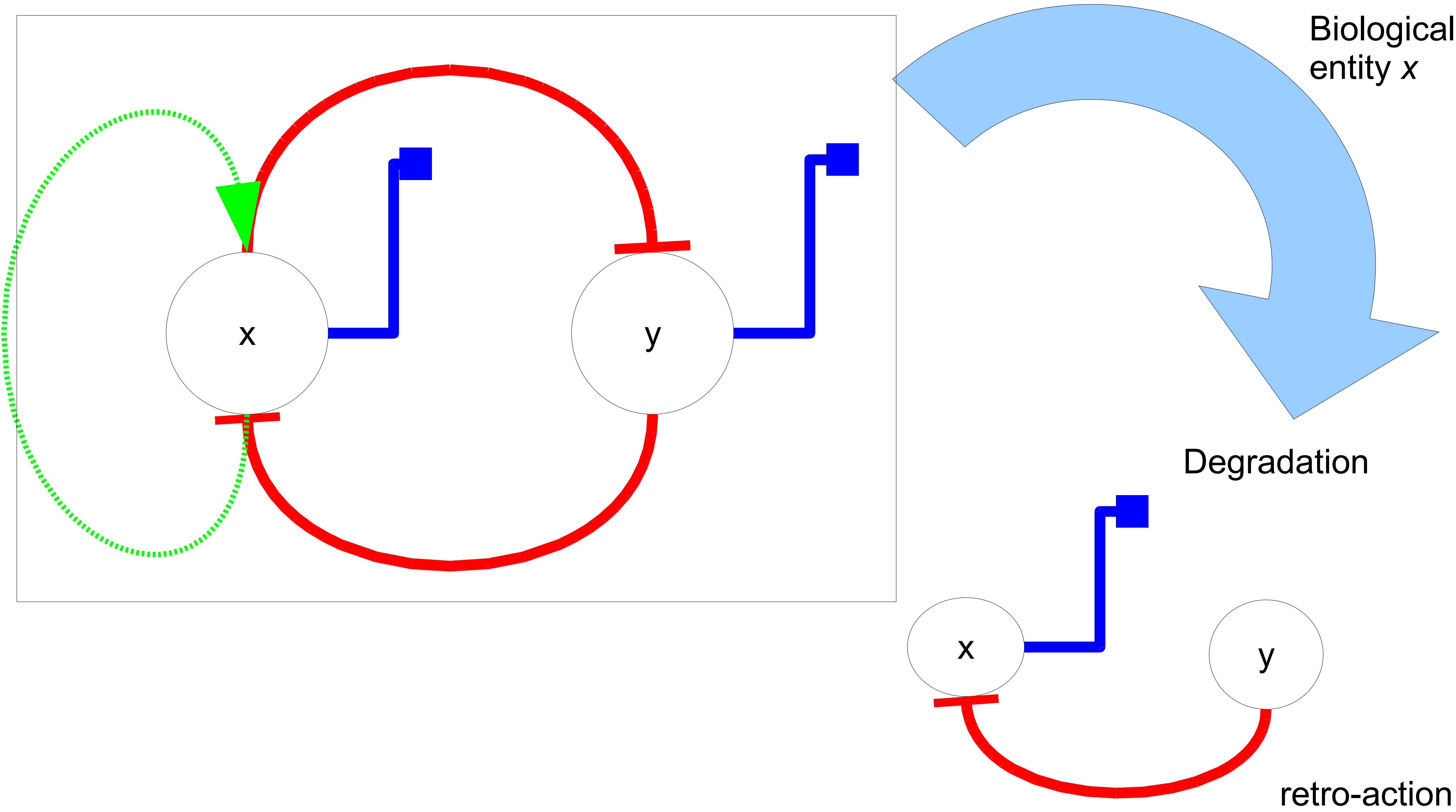
  - We know how to compute *dx/dt* for a given *x(t)*
  - Then:

# Simple numerical integration scheme



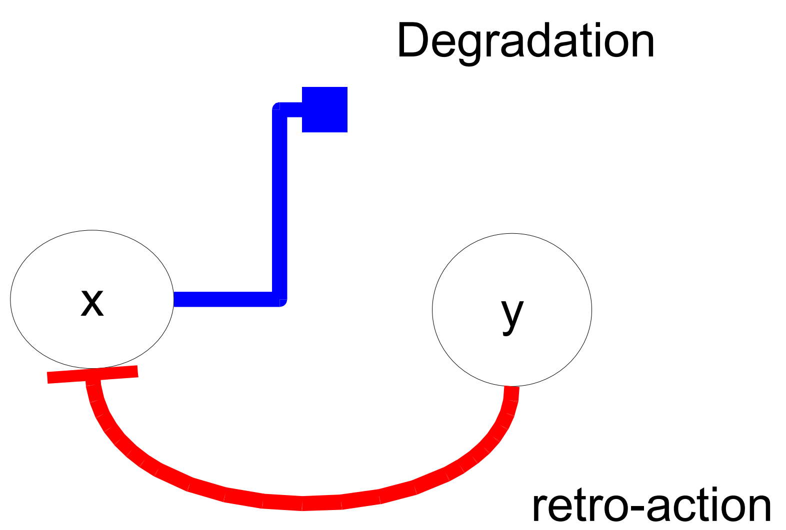

Explicit Euler scheme

# Building the biological switch ODE model



# Biological switch : *x* proteins

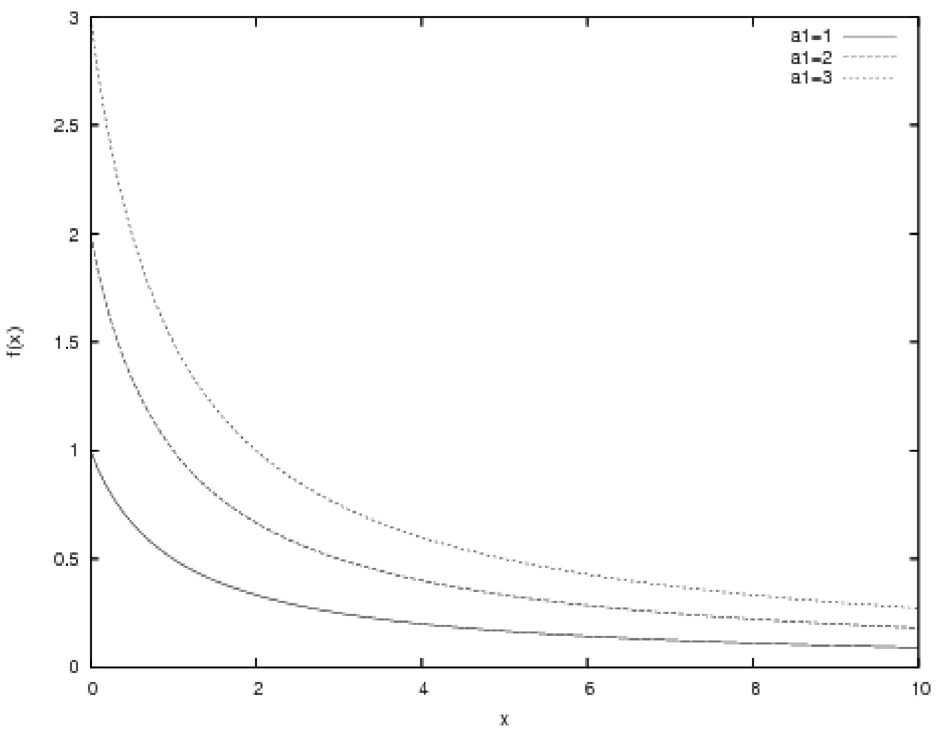
- Mechanism involving *x*:
  - Residual synthesis
  - Retro-inhibition by *y*
  - Degradation
  - Auto-activation : not included here for simplicity

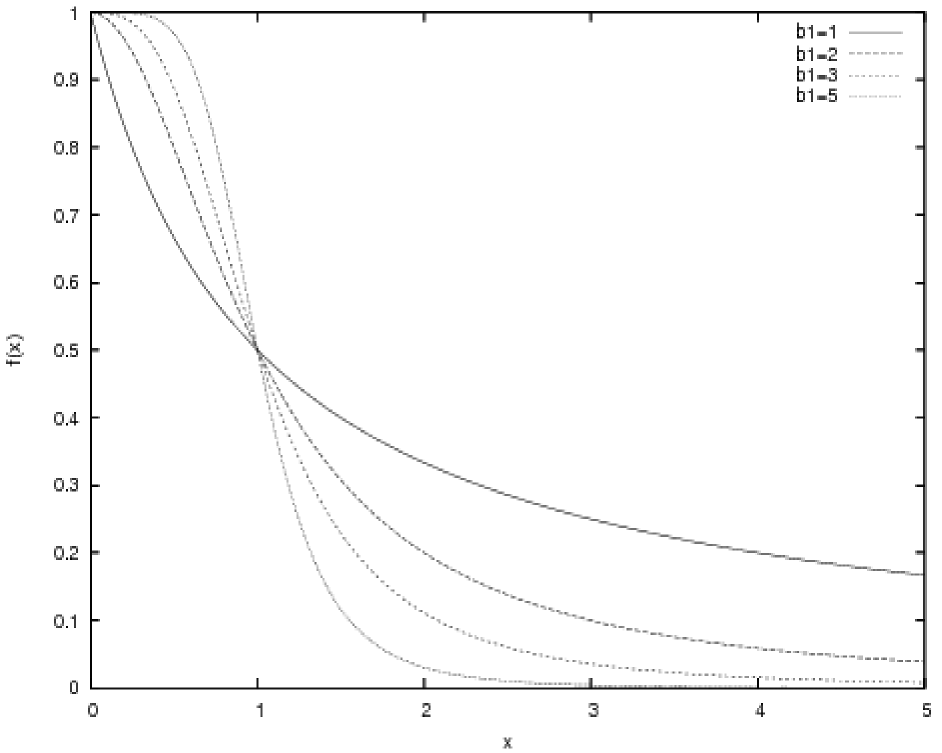


# Biological switch : x proteins

- Residual synthesis of *x* and inhibition by *y*:
  - Classical Hill function:

$$dx/dt = a1 / ( 1 + y^{b1} )$$



# Biological switch : *x* proteins

- Degradation:

  $dx/dt = -\, c1.x$

- Summing all the terms:

  $$dx/dt = \boxed{a1 \,/\, (\, 1 + y^{b1}\, )} - \boxed{c1.x}$$

  degradation

  synthesis

- *Same reasoning for y :*

  $dy/dt = a2 \,/\, (\, 1 + x^{b2}\, ) - c2.x$

# Time evolution of the model: example

dx/dt = f(x,y)

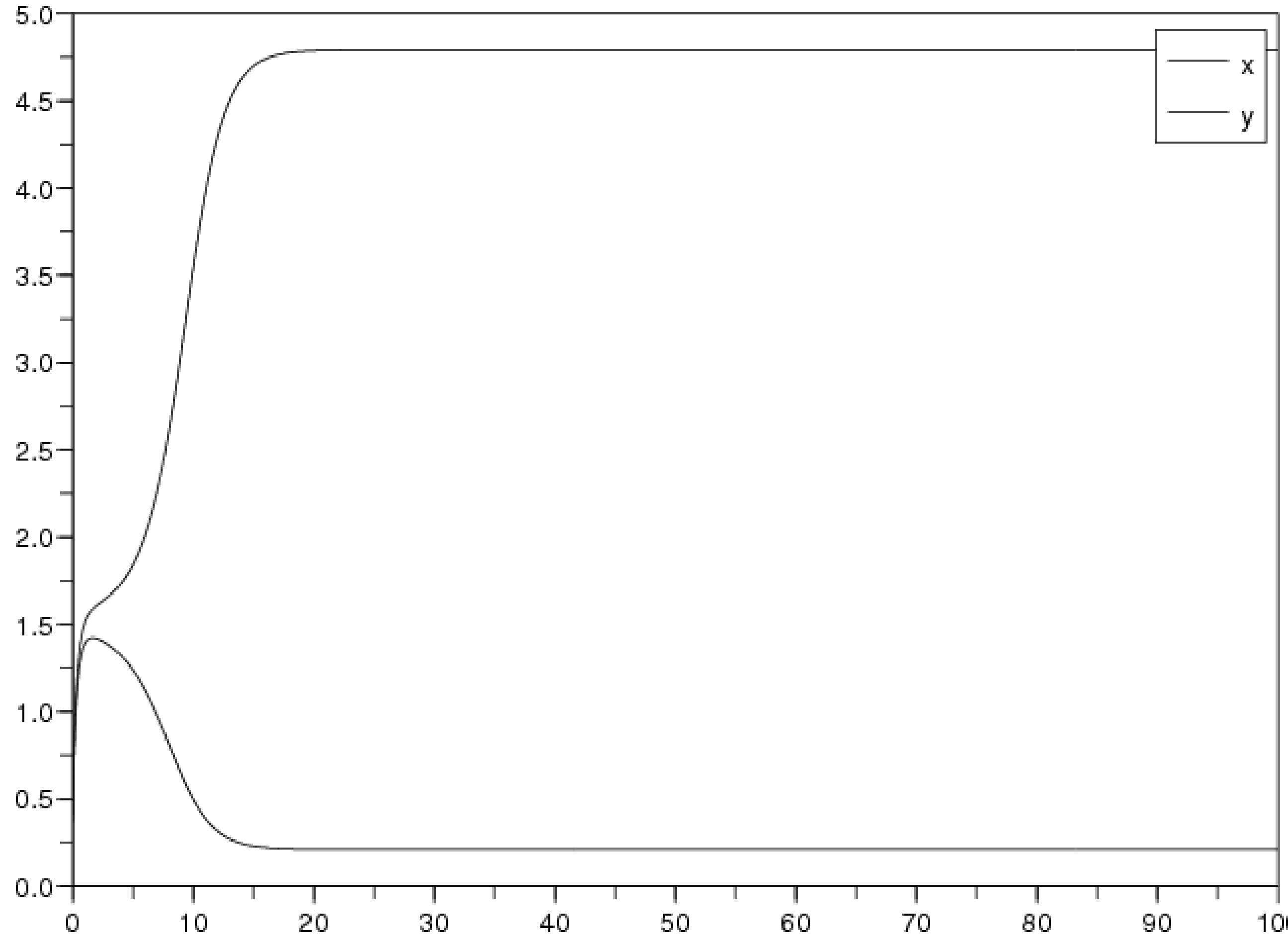
dy/dt = g(x,y)

x(0), x(dt), x(2.dt), ... x(t), x(t+dt),..,x(tmax)

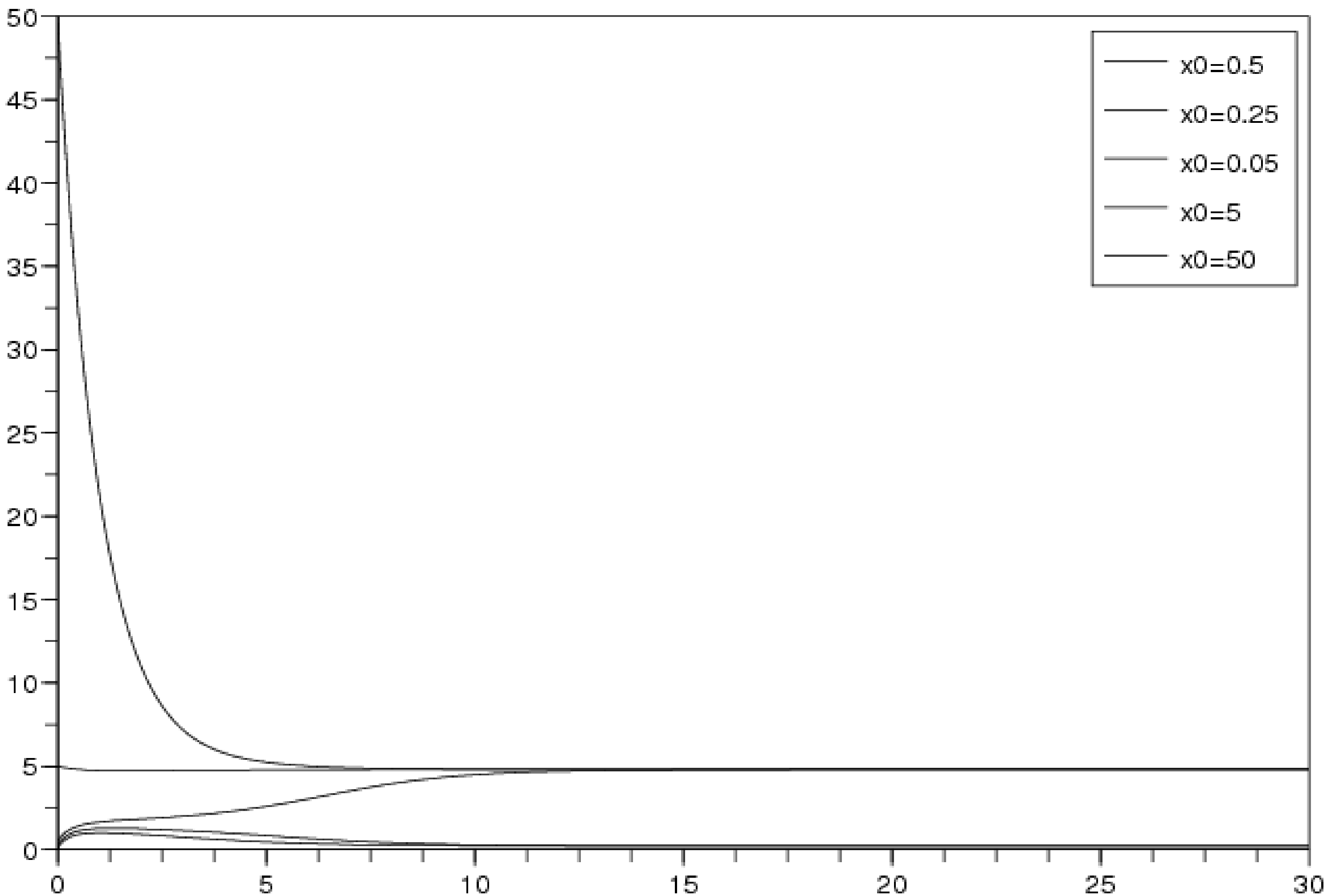
x(t=0), y(t=0): initial conditions

dt: integration step

Tmax: time of simulation



# Time evolution of *x*: different initial conditions




Equilibrium state

X do not change in time

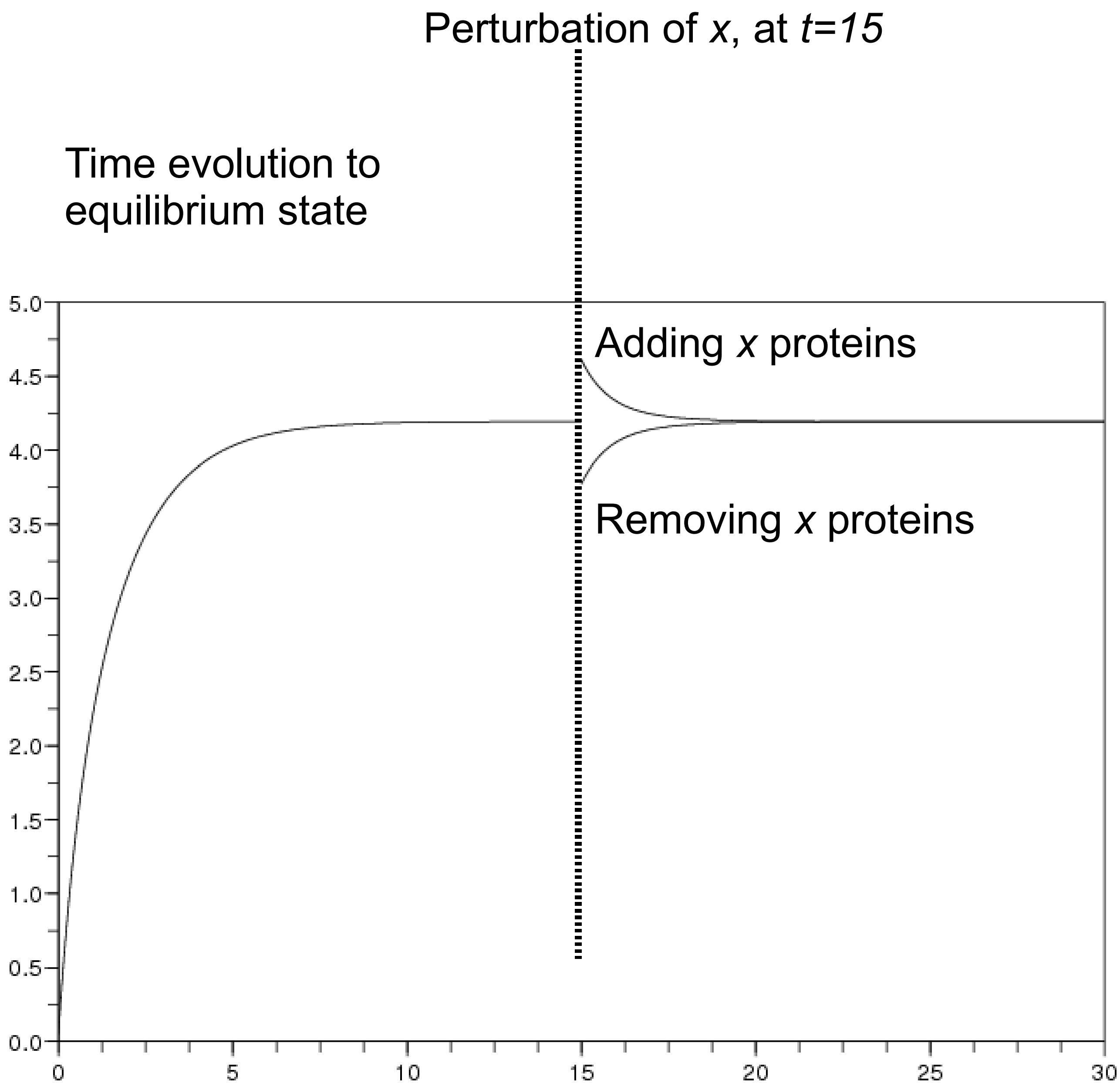
# From biology to ODEs: equilibrium state

- Biological fact:
  - the concentration of the *x* (and *y*) proteins do not change in time
- ODEs « translation »:
  - A small variation of the concentration, *dx* (and dy), over a small time interval, *dt*, is null.

Equilibrium state <=> $dx/dt=0$ and $dy/dt=0$

- Analytically: $f(x,y)=0$ / $g(x,y)=0$ *(Fixe point)*
- What about a small perturbation of this point?

# Stability of the equilibrium state?




The concentration of the x protein return to its equilibrium state

The equilibrium state is ***stable***.

# Geometrical representation of ODEs

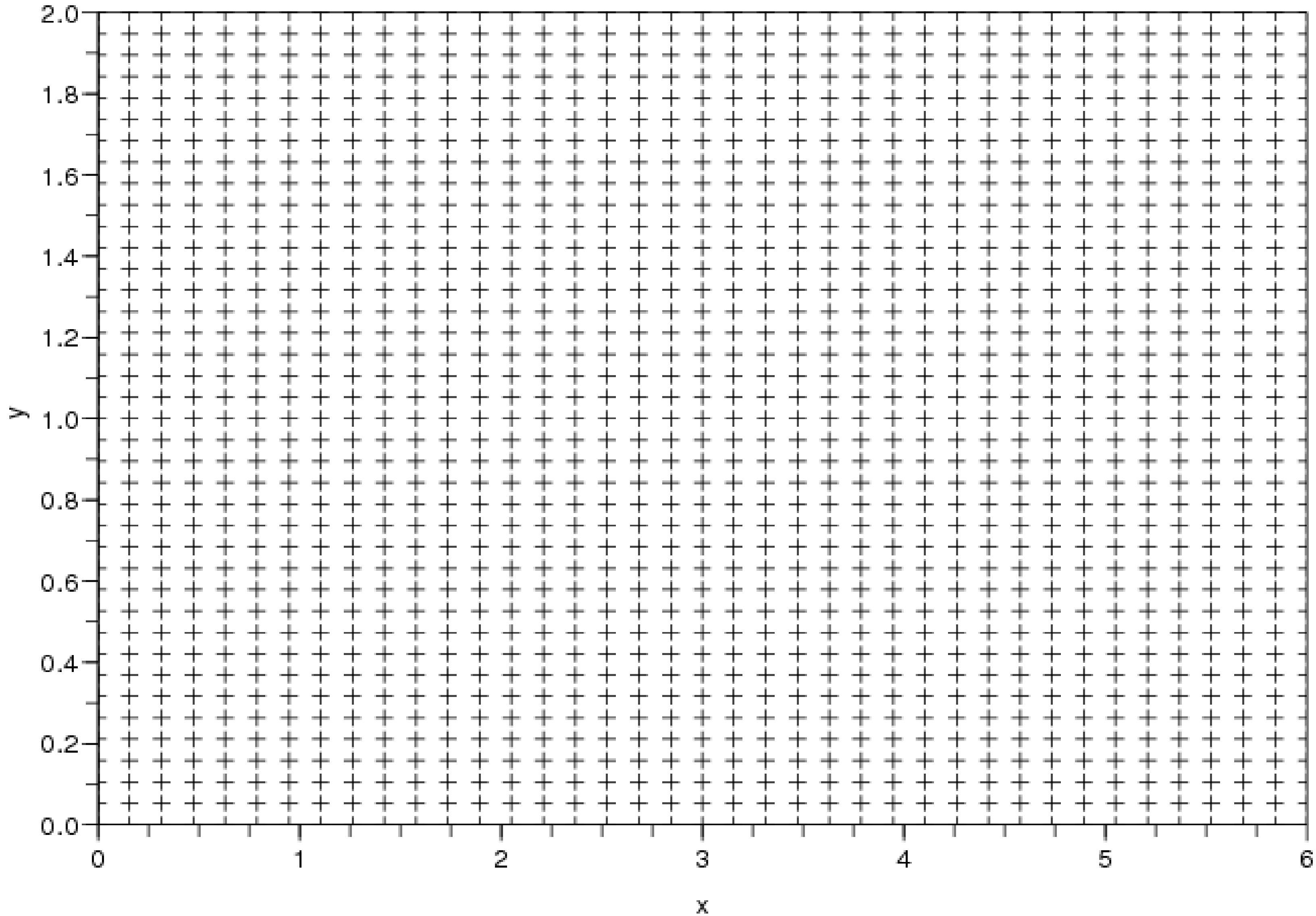
- All analytical calculus can be formulated into geometry
- Geometrical representation is « visual » and more intuitive
- We restrict this tutorial to the geometrical aspects in order to present notions of ODEs.

# Geometrical representation of ODEs: Phase Plane

- We adopt a numerical point of view here
- Select a domain of values for *x* and *y*
- Select a space of *n* coordinates:
    - one coordinates for each variables (*n=2: x* and *y*)
- Each couple (*x(t),y(t)*) represent the state of the system at time t
- A point this space = the state of the system

***PHASE SPACE***

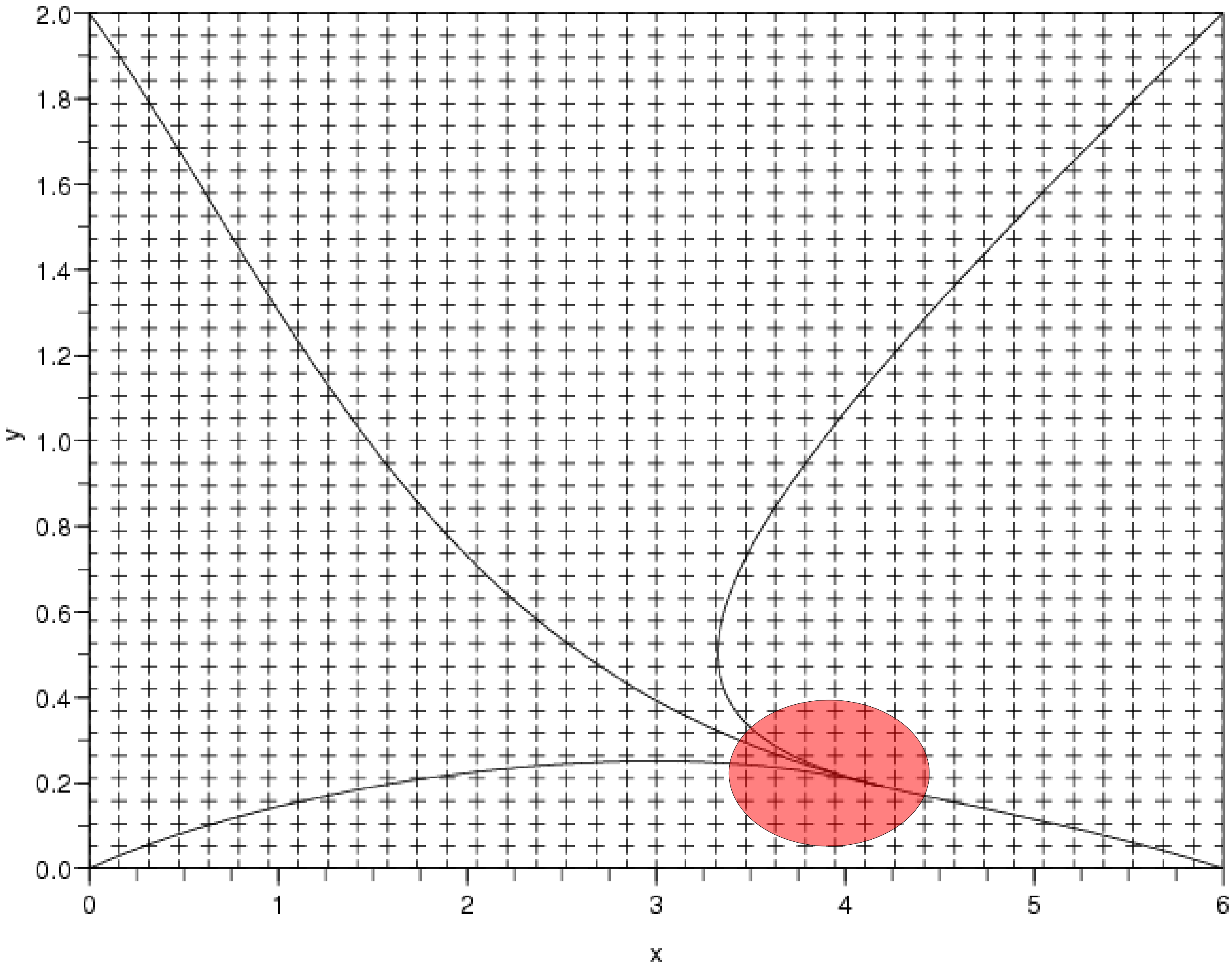
# Geometrical representation of ODEs: Phase Plane



# Phase trajectory

- Starting for one initial condition, one can compute the sequence of $x(t)$ and $y(t)$
- This is a sequence of states = a sequence of point in the phase plane
- Phase trajectory

# Phase trajectory: 4 examples



# Nullclines

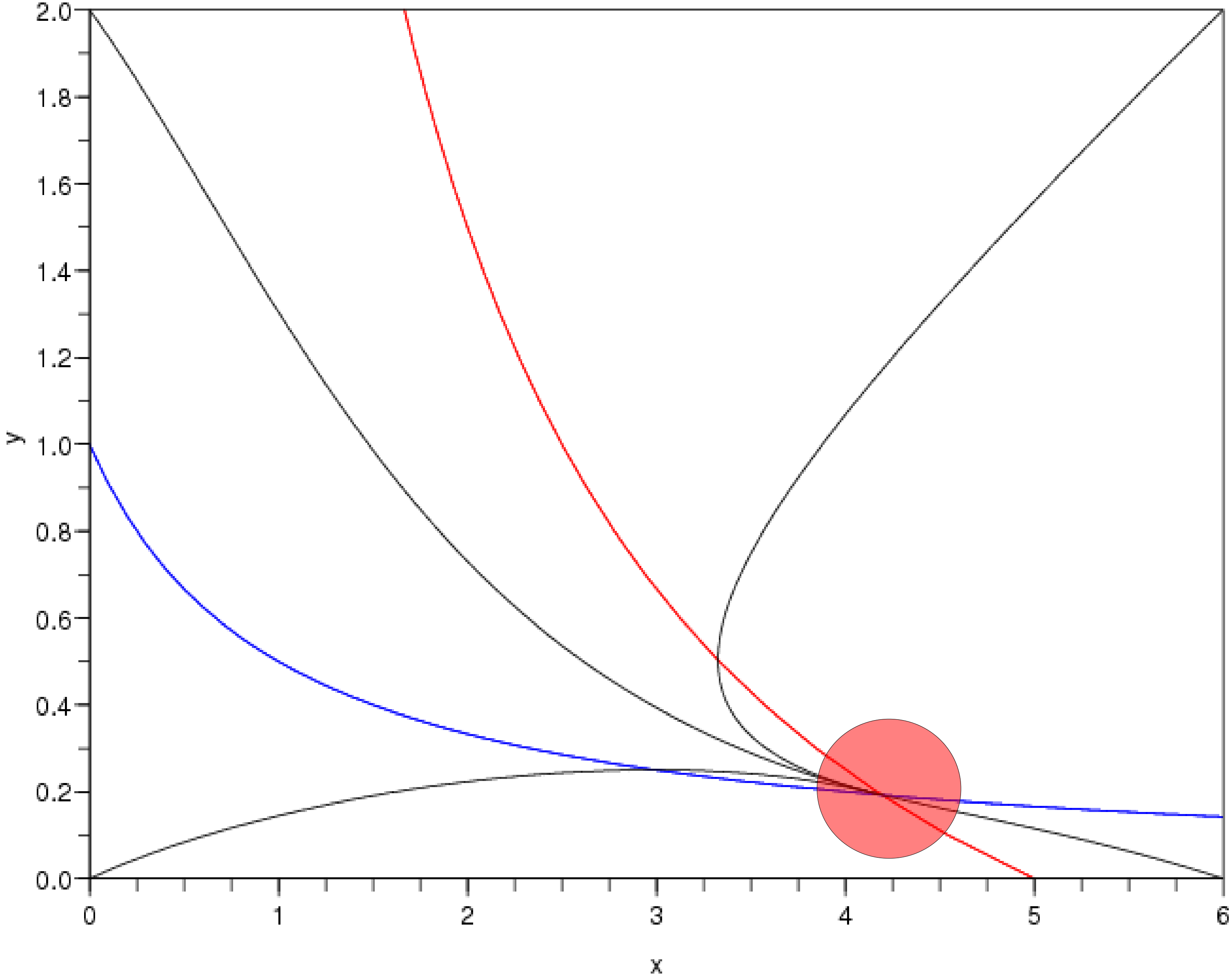
- We show an equivalence:
  - equilibrium state <=> $dx/dt=0$ and $dy/dt=0$
- We can draw each couples ($x,y$) where $dx/dt=0$
  - $x$-nullcline
- Same for $y$: $y$-nullcline
- The intersection points of $x$- and $y$-nullclines definies a equilibrium point.
- Geometrical criteria = biological fact

# Nullclines

Red: x-nullcline

Blue: y-nullcline

Black: phase traj.

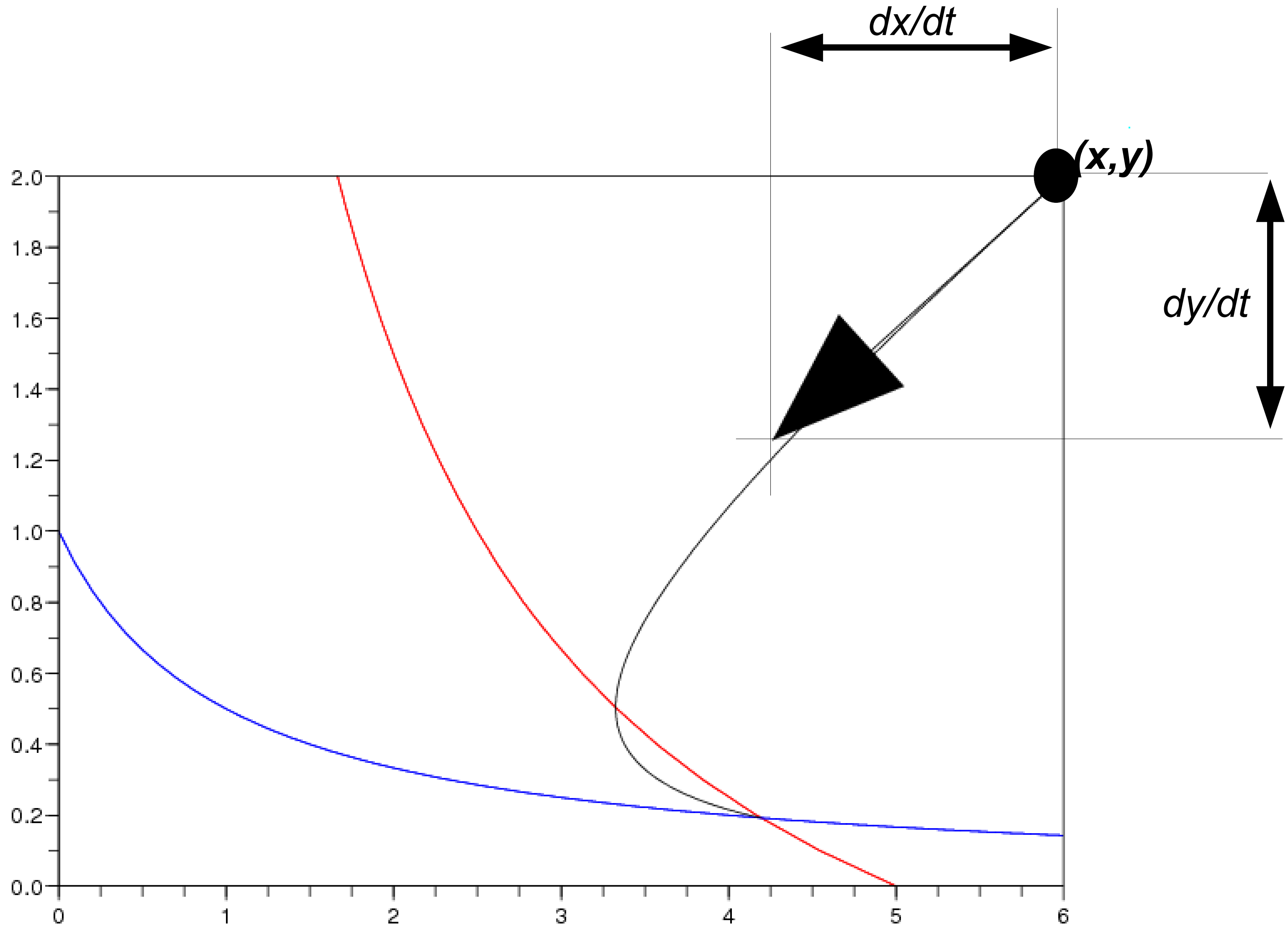


# Vector field

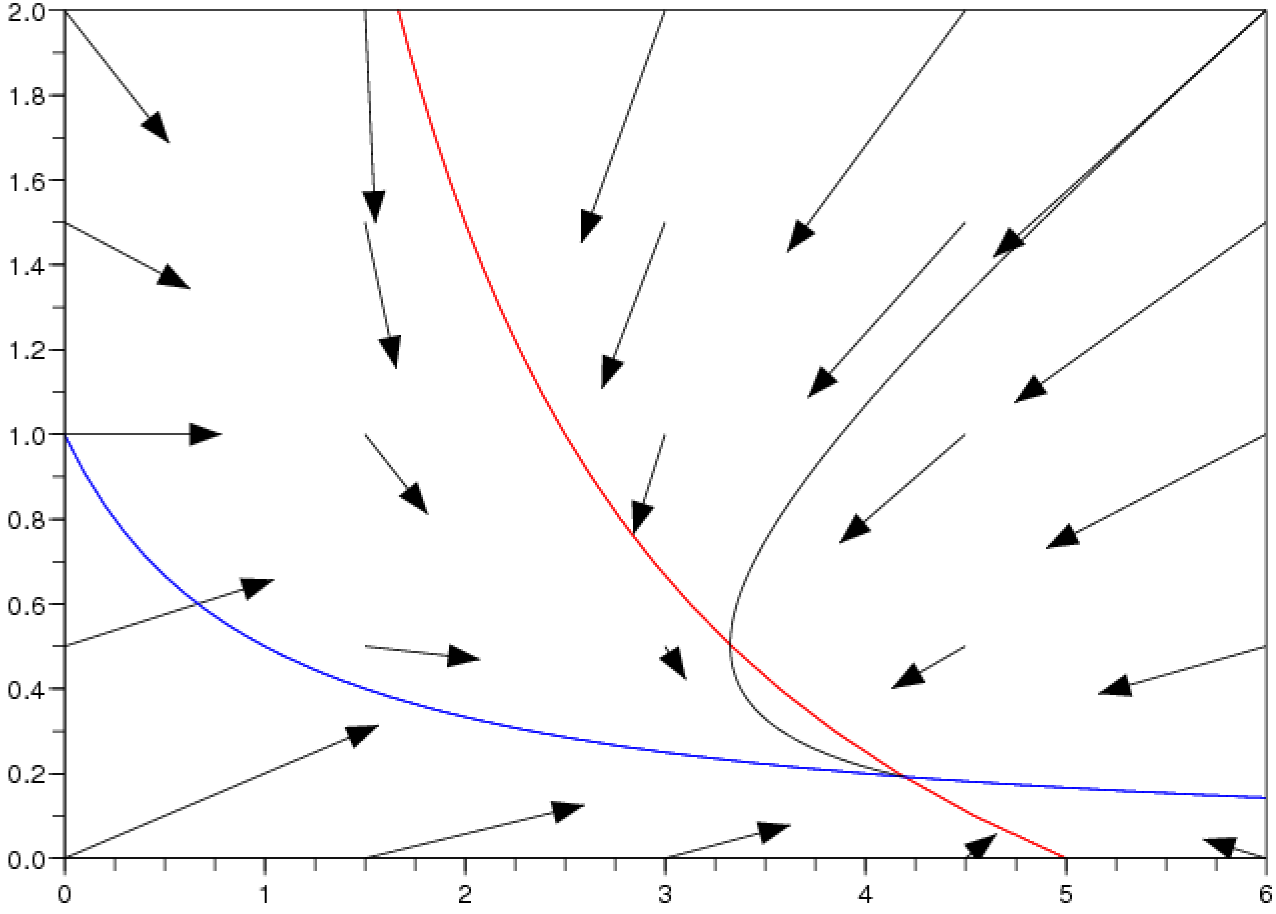
- Last informations: *derivatives*
- We can compute *dx/dt* and *dy/dt* for each couple (*x,y*)
  - Used (for example) in the numerical integration scheme
- We can represent these two values using an « arrow », *i.e.* a vector (here in 2D)
- 
- For each couples (x,y) of the phase space

***VECTOR FIELD***

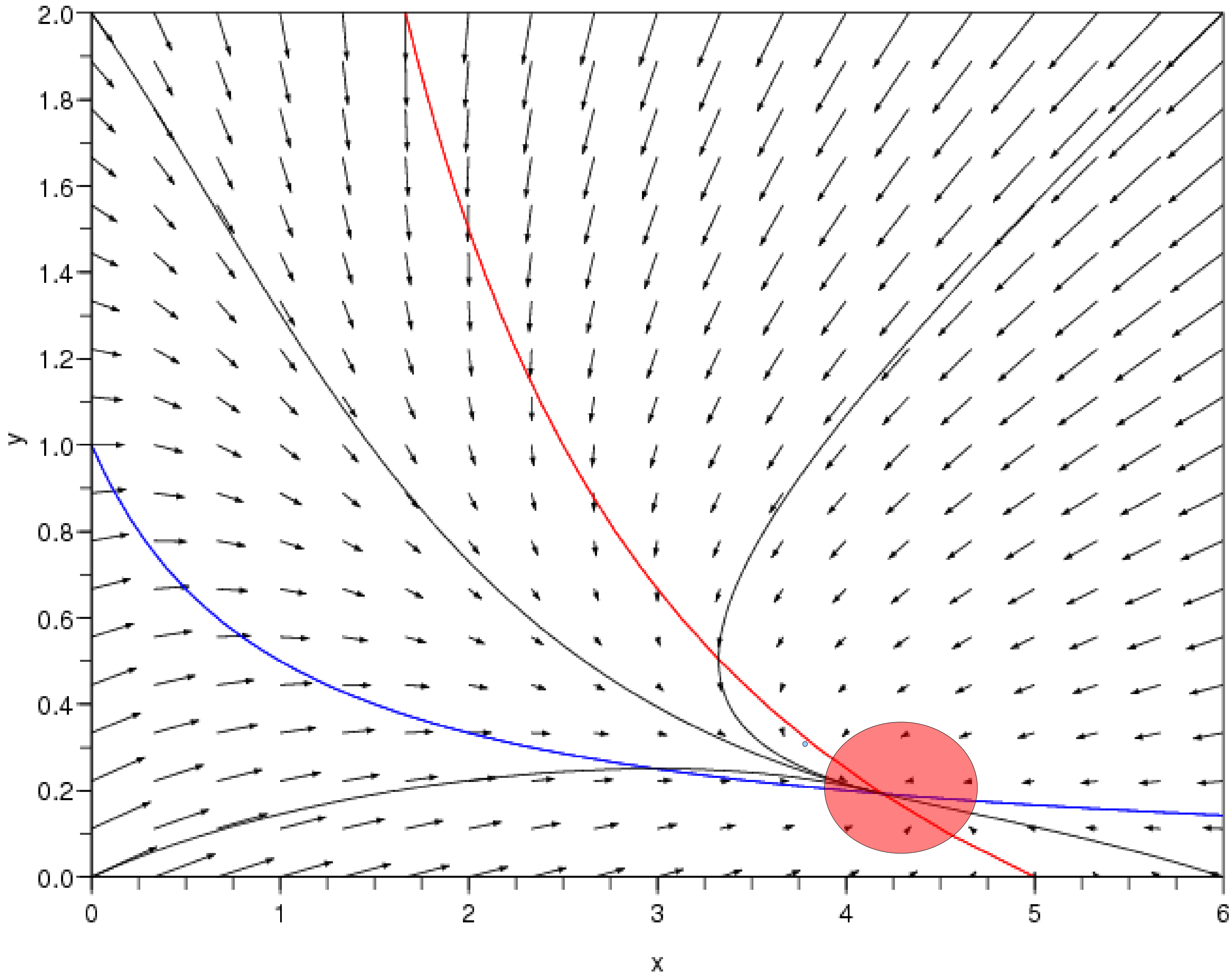
# Vector field: example of computation



# Vector field: example



# Phase plane and vector field

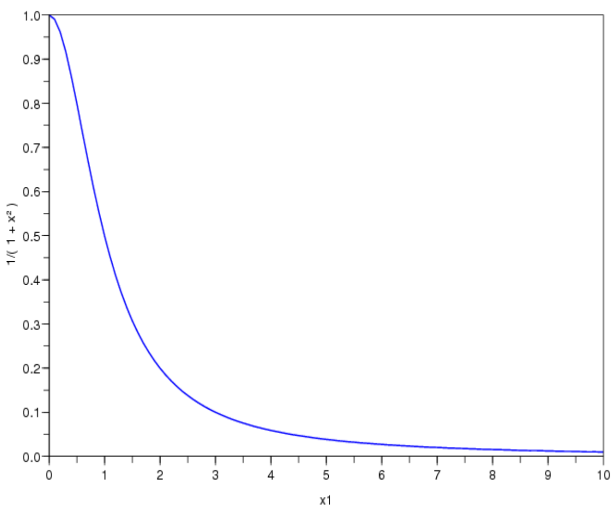


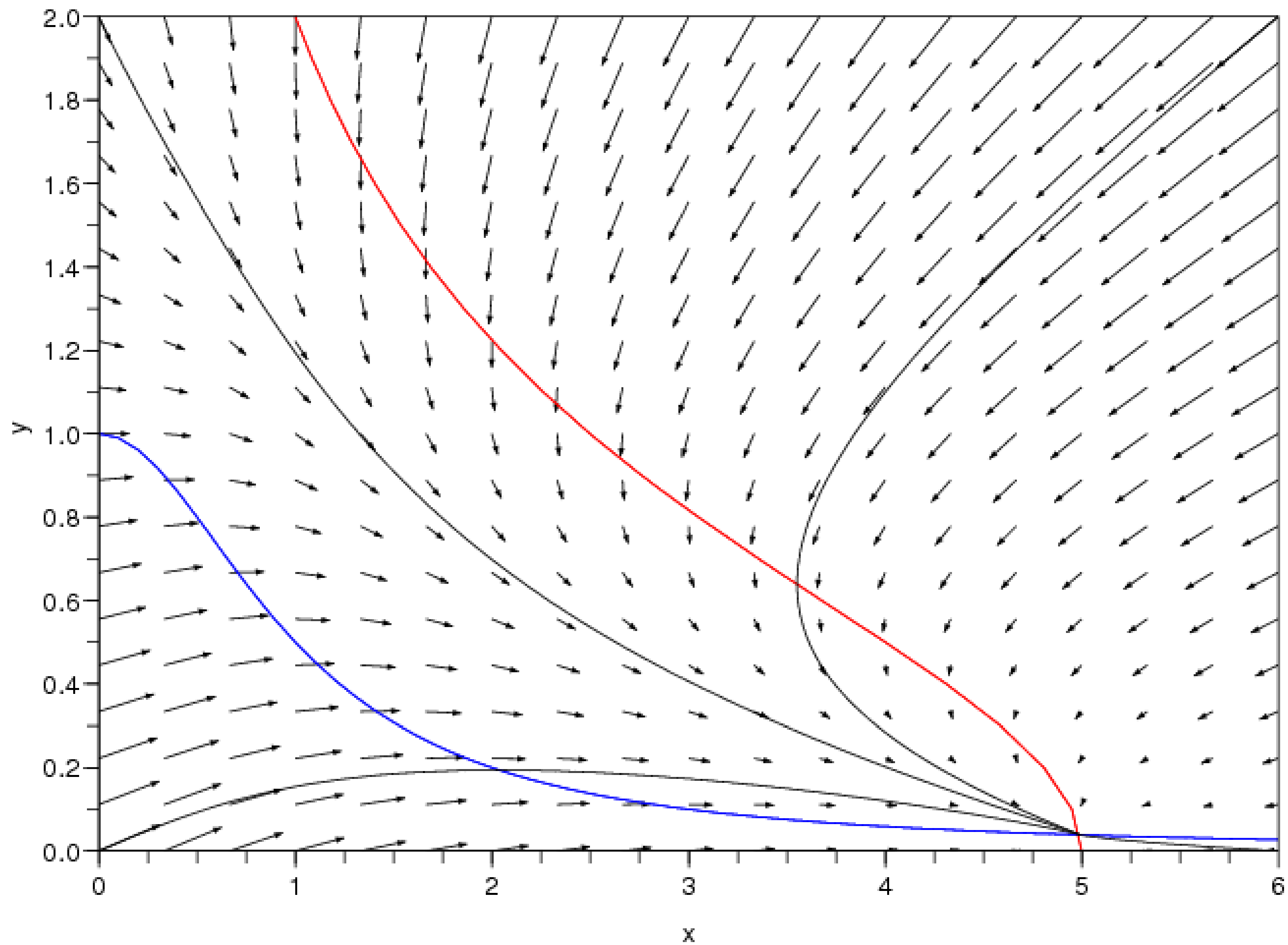
# Geometry, ODEs and biology

- Phase plane: plane of each possible states of the system
- Phase trajectory: a time evolution starting from one initial contition
- Nullcline: location where derivatives are null
- Vector field: « *direction/intensity* » of small variations of the proteins concentration over a small time interval

# The biological switch and ODEs: cooperativity, a2=1

dy/dt=a2/(1+x$^{b1}$)-c2.y



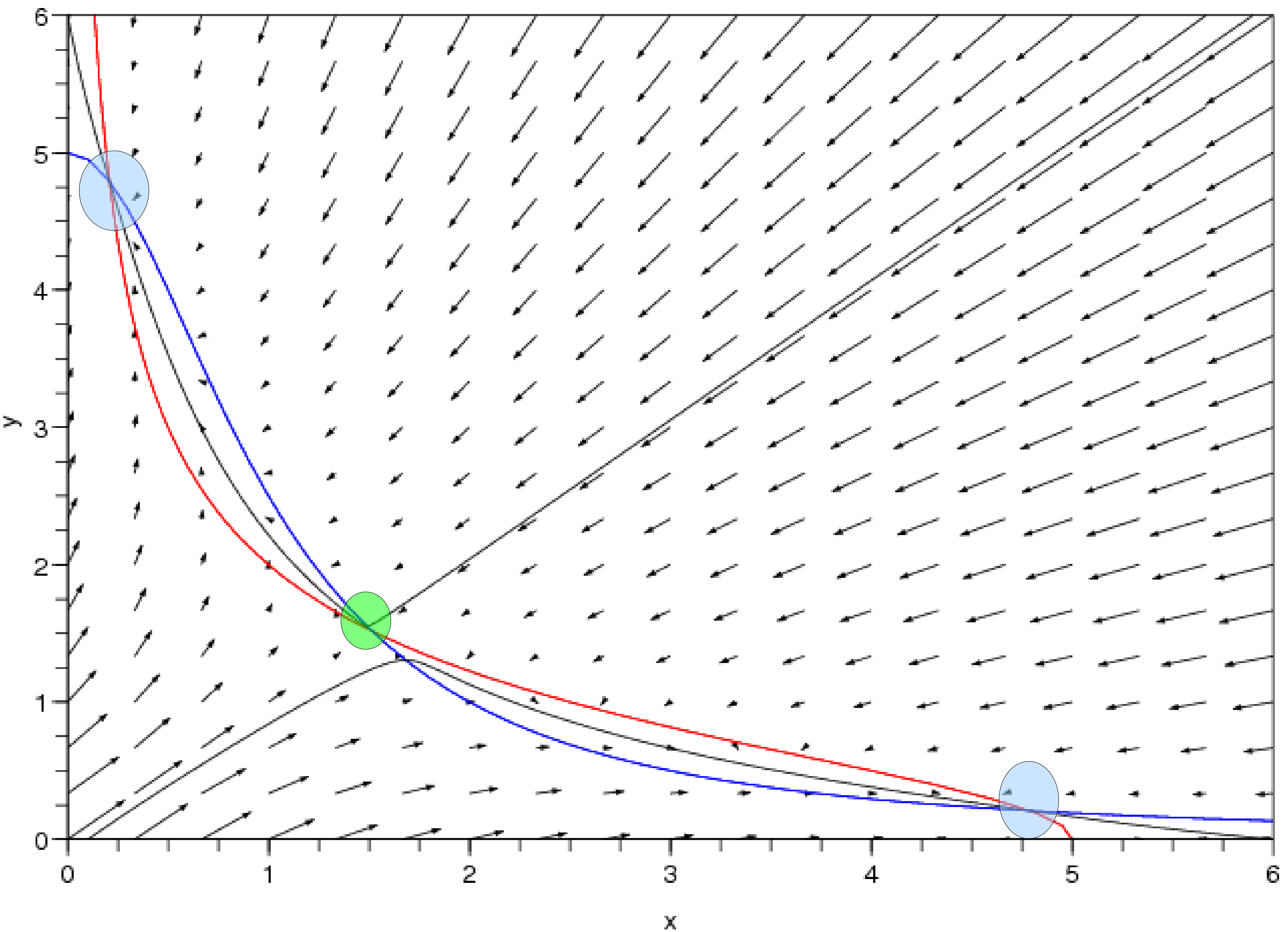
# The biological switch and ODEs: cooperativity, a2=5

x- and y-nullclines intersect at 3 points

Three equilibrium states

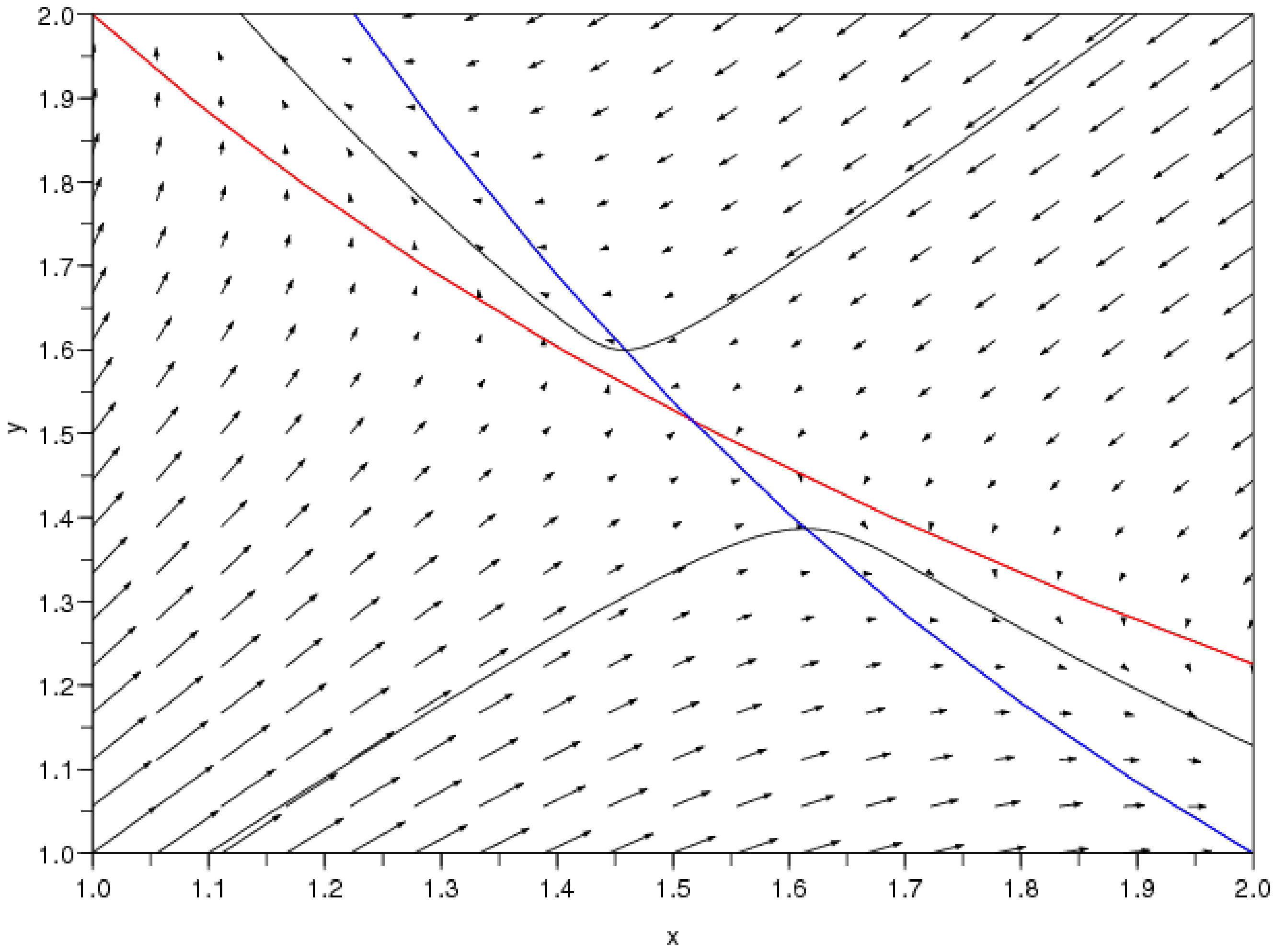
Two stables

One instable

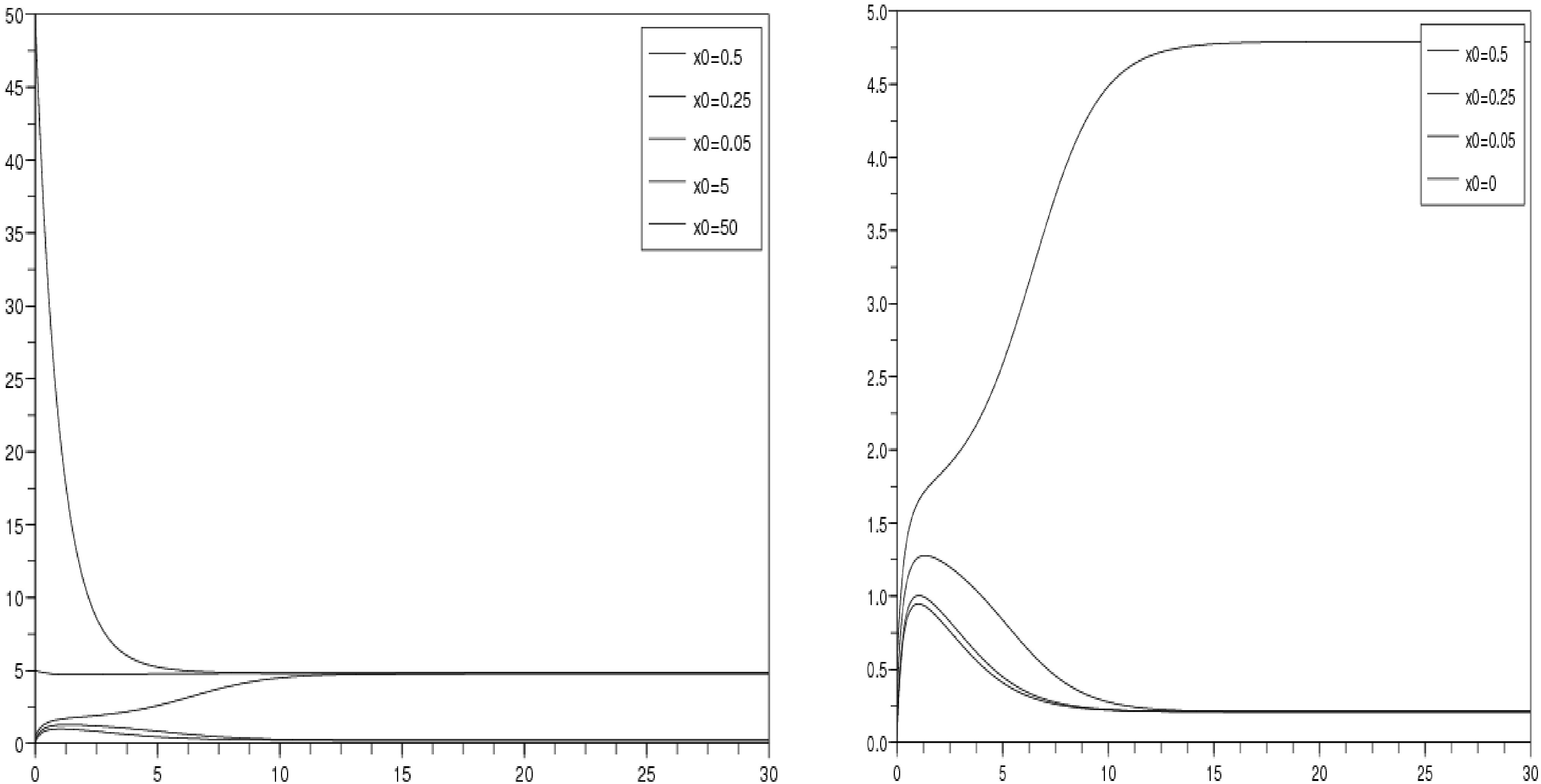


# The biological switch and ODEs: cooperativity, a2=5 -ZOOM

Unstable equilibrium state



# Dynamical time evolution



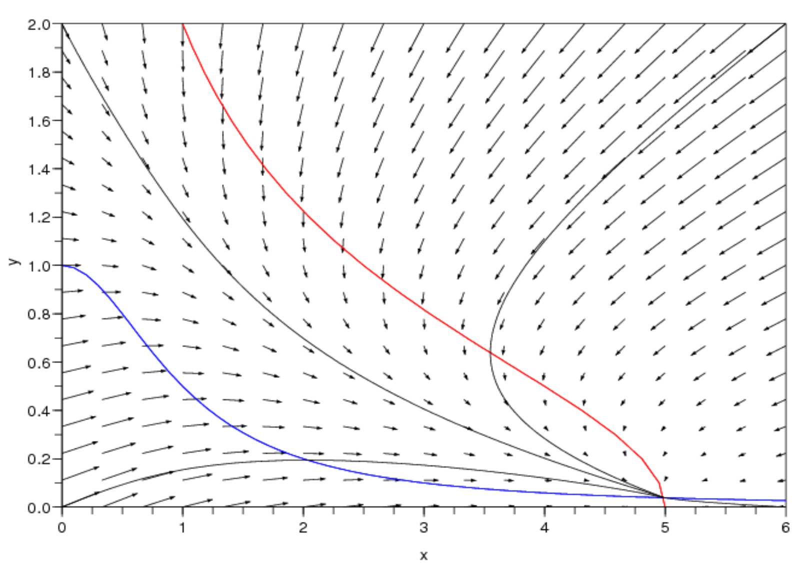

Bistable system: depending on initial conditions = one different equilibrium state

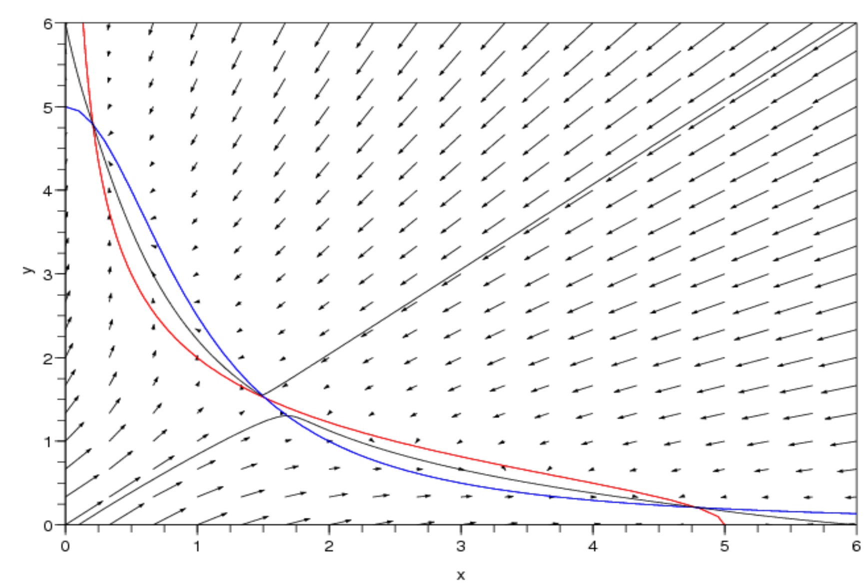
# Understanding the biological switch using ODEs notions

- For specific values of parameters, the system has three equilibrium states:
  - Two *stable* equilibrium states : bi-stability
  - One *unstable* equilibrium state
- The unstable equilibrium state is very important:
  - it prevent one stable equilibrium state to switch to the other
  - It divide the phase plane into two domains: one domain (i.e. Initial conditions) is attracted by one point and the other domain is attracted to the other equilibrium point.

# Understanding the biological switch using ODEs notions

- Thus, the unstable point has a structural rôle in the dynamic of the system.
- When we change parameters (*a2: 5 -> 1*), the nullclines intersect only once: the unstable point disappear, and the system had only on equilibrium state.



# Understanding the biological switch using ODEs notions

- The structural change in the geometrical properties reflect a structural change in the dynamical properties of the system.
- The biological switch is then sustained when we switch back and forth, from one geometry (3 equilibrium states) to the other (1 equilibrium state).
- We can hypothesis that if we introduced a « correct » variation of the *a2* parameter, the system will switch between these two situations, and oscillations will occur

# Designing a biological switch

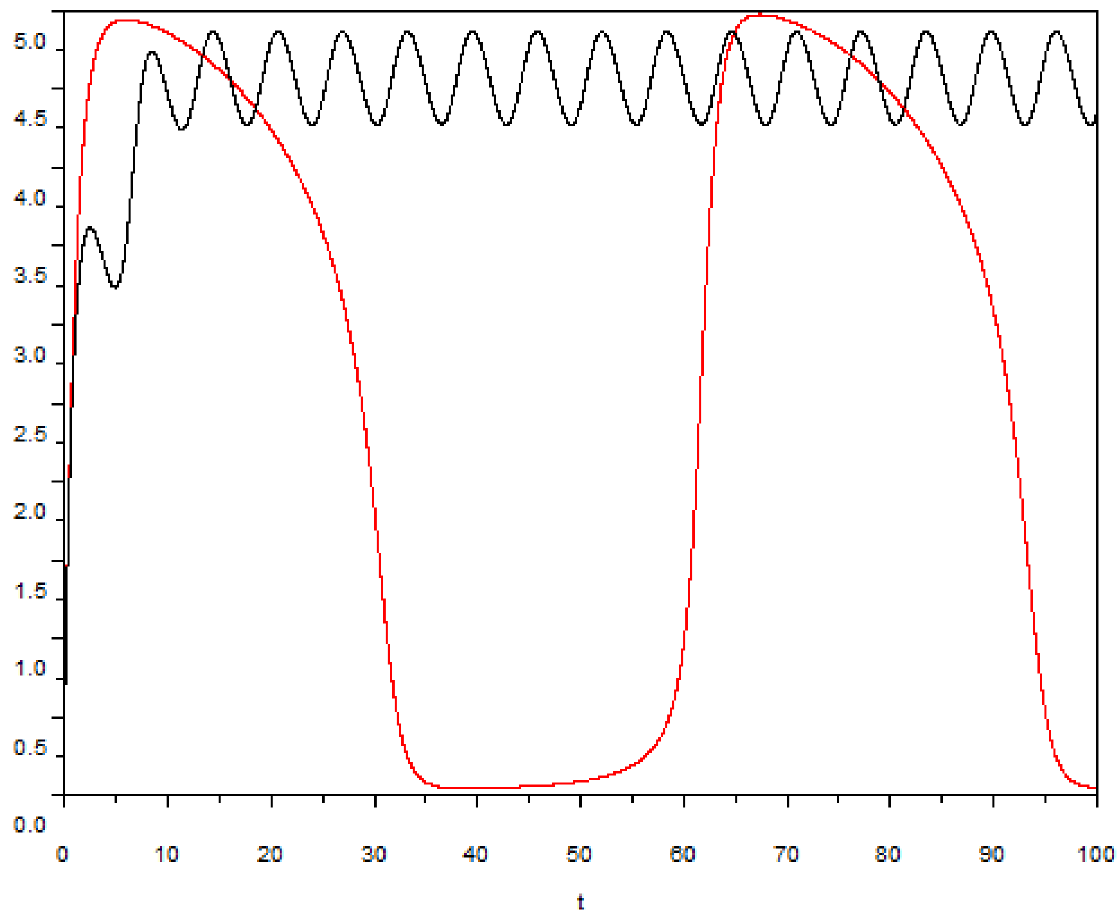
*dx/dt = a1/( 1 + $y^2$ ) - c1.x*

*dy/dt = a2*sin(w.t)/( 1 + $x^2$ ) - c2.y*

a2=15

Black: *w=0.5*, fast variations of parameter *a2.*

Red: *w=0.05*, slow variations of parameter *a2*



# Conclusions

- ODEs are a well developped mathematical formalism
- « Transcribing » a biological system into ODEs open the door to vast mathematical literature, and an active community
- Biologists can developp their model, and do some « *in silico* » experiments thanks to software
- ... provided that they understand fundamental notions
- A geometrical view of an ODEs system is a first step

In this tutorial, we use Scilab (*http://www.scilab.fr*)

# Conclusions

- ODEs can be extended:
  - Take into account stochastic variations in the derivatives: Stochastic Differential Equations
  - Take into accound space: Partial Differential Equations

- For biological applications:
  - Constructing biological switch: Gardner et al. (2000)
  - Understanding transition during Cell Cycle: Tyson and Novak.