Model Analysis

Equilibrium concentrations

For understanding the system dynamics, following the kinetics of variable concentrations according to time may not be sufficient.

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We need to use an abstract space called the phase space or in the case of two dimensions the phase plane where the coordinates are those of the dynamic variables.
This space is used to understand how the dynamic systems evolves in time.

Lets take a simple example of two ODEs:

$$\frac{dx}{dt} = x(1-x) - xy$$

$$\frac{dy}{dt} = 2y(1-y/2) - 3xy$$

The phase plane will represent the system in (*x*,y) coordinates

Finding equilibrium concentrations: computation of nullclines.

Definition of nullcline. The *x*-nullcline is a set of points in the phase plane so that $\frac{dx}{dt} = 0$.
The *y*-nullcline is a set of points in the phase plane so that $\frac{dy}{dt} = 0$.

Equilibrium concentrations

$$\frac{dx}{dt} = x(1-x) - xy$$

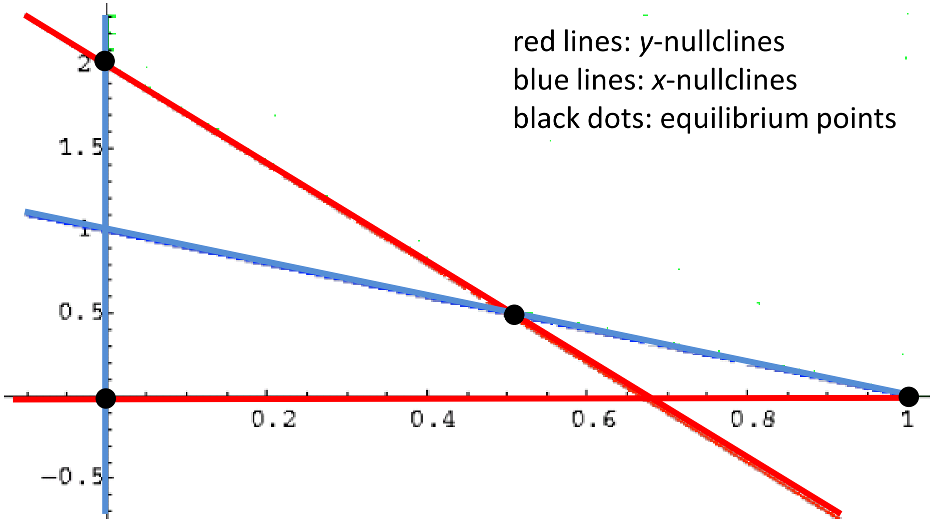
$$\frac{dy}{dt} = 2y(1-y/2) - 3xy$$

Solving the equation $\frac{dx}{dt} = 0$ implies: $x = 0$ and $x = 1 - y$

They are two *x*-nullclines: the *y*-axis and the straight-line of equation *x* = 1 - *y*

Solving the equation $\frac{dy}{dt} = 0$ implies: $y = 0$ and $y = 2 - 3x$

They are two y-nullclines: the *x*-axis and the straight-line of equation *y* = 2 - 3*x*



Equilibrium points are the points where both $\frac{dx}{dt} = 0$ and $\frac{dy}{dt} = 0$.

They correspond to the points where the *x*-nullcline and *y*-nullcline cross.

Thus, the system has four equilibrium points which coordinates are:

(0,0), (0,2), (1,0), (1/2,1/2).

Next step: establishment of stability of the equilibrium point (stable or unstable steady state?)

Equilibrium concentrations

Linear stability of the equilibrium points

It is performed by extracting the matrix of partial derivatives (the Jacobian), evaluating the components of the equilibrium points and examining the eigenvalues of the resulting matrix.
For the following system of equation:

$$\frac{dx}{dt} = f(x,y)$$
$$\frac{dy}{dt} = g(x,y)$$

the Jacobian is given by:

$$A = \begin{bmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial y} \end{bmatrix}$$

In our example:

$$\frac{dx}{dt} = f(x,y) = x(1-x) - xy$$
$$\frac{dy}{dt} = g(x,y) = 2y(1-y/2) - 3xy$$

$$A = \begin{bmatrix} 1-2x-y & -x \\ -3y & 2-2y-3x \end{bmatrix}$$

An equilibrium point will be stable if all eigenvalues have negative real parts; if at least one eigenvalue has a positive real part, then the point is unstable.
For 2x2 systems, on can show that the eigenvalues of A will have negative real parts, if and only if, the determinant of A is positive and the trace of A is negative.
det$A$ = $a_{11}a_{22} - a_{12}a_{21}$ and TrA = $a_{11} + a_{22}$

Equilibrium concentrations

$$A=\begin{bmatrix}1-2x-y & -x\\ -3y & 2-2y-3x\end{bmatrix}$$

At point (0,0), we have: $A=\begin{bmatrix}1 & 0\\ 0 & 2\end{bmatrix}$ then det*A* = 2 and Tr*A* = 3 meaning that the equilibrium point (0,0) is unstable.

At point (0,2), we have: $A=\begin{bmatrix}-1 & 0\\ -6 & -2\end{bmatrix}$ then det*A* = 2 and Tr*A* = -3 meaning that the equilibrium point (0,2) is stable.

$$A-\lambda I=\begin{bmatrix}-1-\lambda & 0\\ -6 & -2-\lambda\end{bmatrix}$$

To find the values of the two eigenvalues we have to solve:

$$\det(A-\lambda I)=(-1-\lambda)(-2-\lambda)=\lambda^2+3\lambda+2=0$$

We obtained $\Delta = 1$ and $\lambda_1 = -1$ and $\lambda_2 = -2$ Both eigenvalues are negatives.

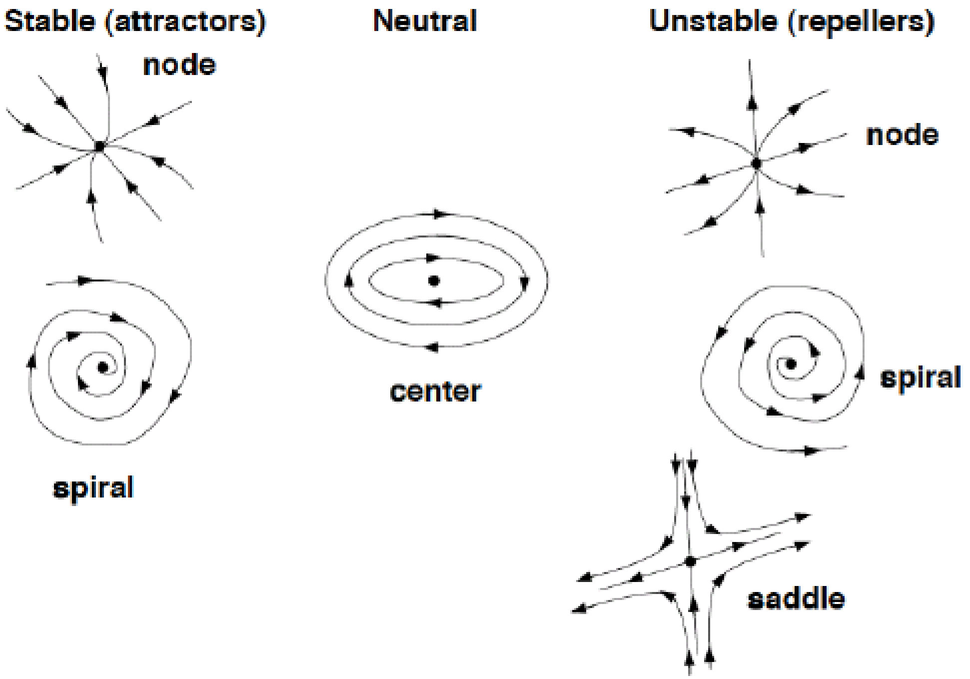
At point (1,0), we have: $A=\begin{bmatrix}-1 & -1\\ 0 & -1\end{bmatrix}$ then det*A* = 1 and Tr*A* = -2 meaning that the equilibrium point (1,0) is stable.

We have det(*A*-λ*I*) = (-1-λ)(-1-λ) = 0 thus $\Delta = 0$, only one solution $\lambda = -1$

At point (1/2,1/2), we have: $A=\begin{bmatrix}-1/2 & -1/2\\ -3/2 & -1/2\end{bmatrix}$ then det*A* = -1/2 and Tr*A* = -1 meaning that the equilibrium point (1/2, 1/2) is unstable.

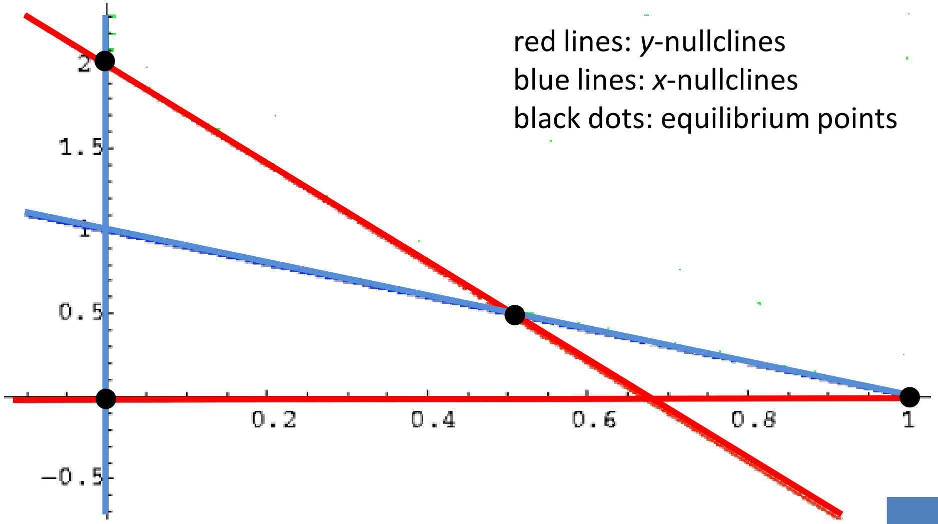
Equilibrium concentrations

Different types of equilibrium points:



Phase plane

The *x*-nullcline is the set of points in the plan where *dx/dt = 0*. Thus, it naturally divides the plan in regions where *dx/dt > 0* or *dx/dt < 0*. If *dx/dt > 0* it means that *x* is increasing which in turn means it is moving rightward in the plane. If *dx/dt < 0*, *x* is decreasing and it is moving leftward in the plane. In the same manner, the *y*-nullcline is the set of points in the plan where *dy/dt = 0*. If *dy/dt > 0*, *y* is increasing and moving upward in the plan. If *dy/dt < 0*, *y* is decreasing and moving downward in the plane

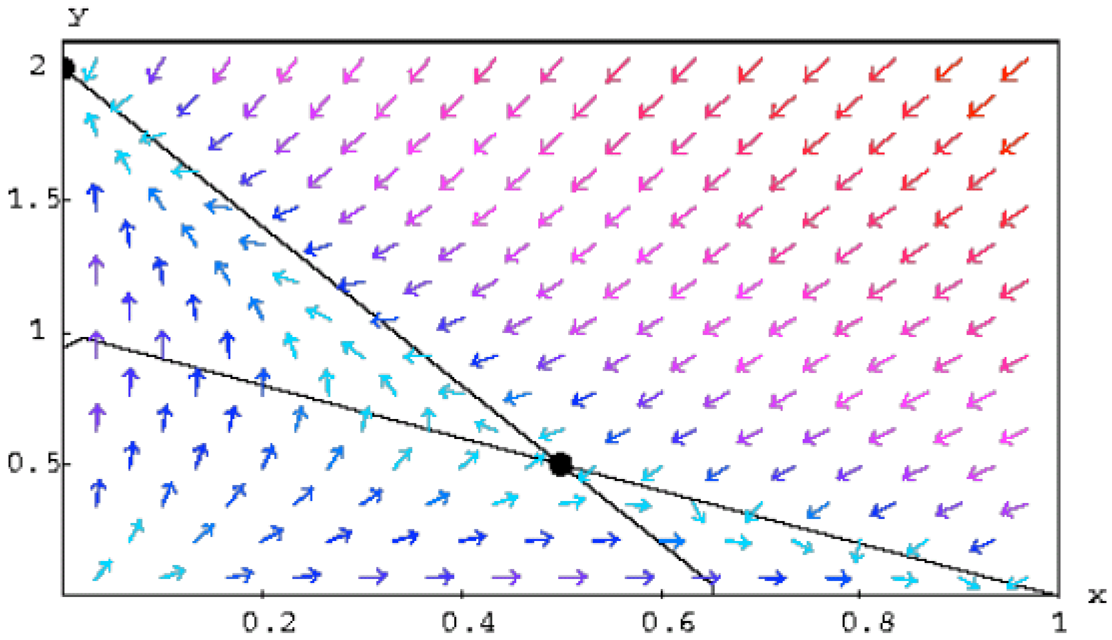


For a point (x,y), the table summarizes the possible directions of the point motion once the nullclines are known

	dx/dt > 0	*dx/dt = 0*	*dx/dt < 0*
dy/dt > 0	↗	↑	↖
dy/dt = 0	→	○	←
dy/dt < 0	↘	↓	↙

Phase plane

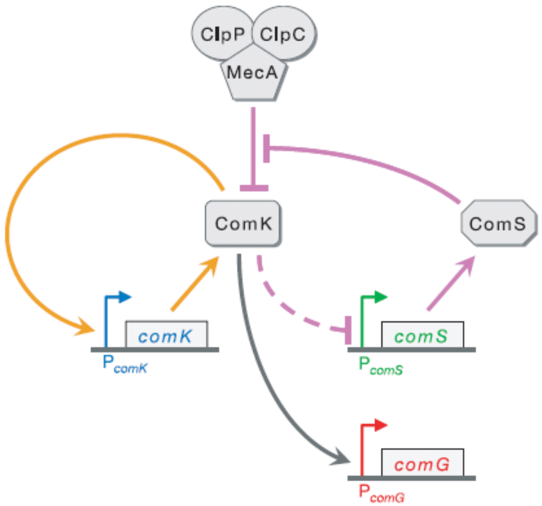
Then one can represent the vector field of the dynamic system that indicates the motions in the plane.



Afterward, we can plot the system trajectories according to its starting point.

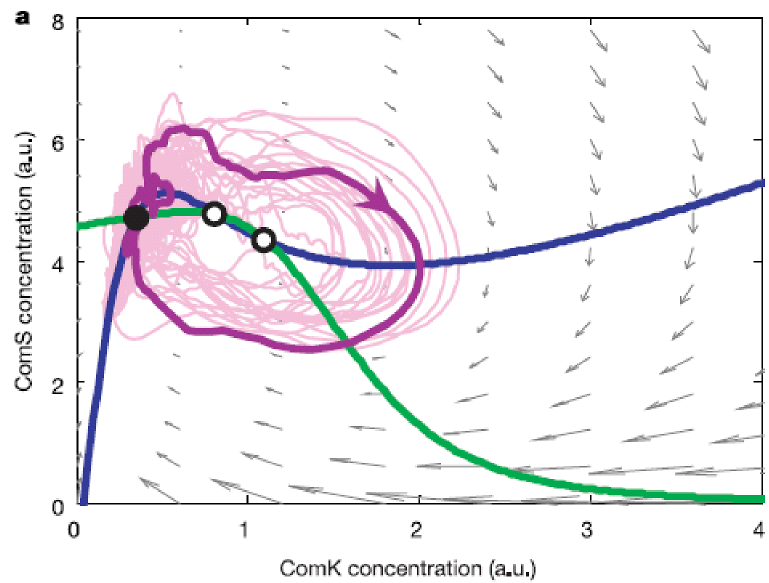
Phase plane

A biological example: Stress response in *B. subtilis* and the core competence circuit.



Extracted from Suel *et al.*, 2006, *Nature*, 440:545-550

After, modeling this regulatory network we obtained the following dynamics.



ComS-nullcline is shown in blue and ComK-nullcline in green, respectively. Grey arrows represent the vector field of the dynamical system. The stable steady-state corresponding to vegetative growth is indicated with a black filled circle. The saddle and the unstable competent fixed points are indicated with open circles. A set of excursion trajectories is shown in pink, with a single representative trajectory of the system highlighted in purple. Initiation of excursions in phase space is triggered by noise, and trajectories are determined by the phase space vector field.

Bifurcation diagram

• Stability of steady states may change when parameters are altered
• Points at which the stability of an equilibrium point changes or new steady state solutions appear or disappear are called bifurcation points
• Bifurcation diagrams are used to analyze how the values and the stability of equilibrium points depend on a regulatory control parameter, the bifurcation parameter
• In biological models, bifurcation behaviors include:

- transcritical bifurcations
- saddle-node bifurcations
- Hopf bifurcations

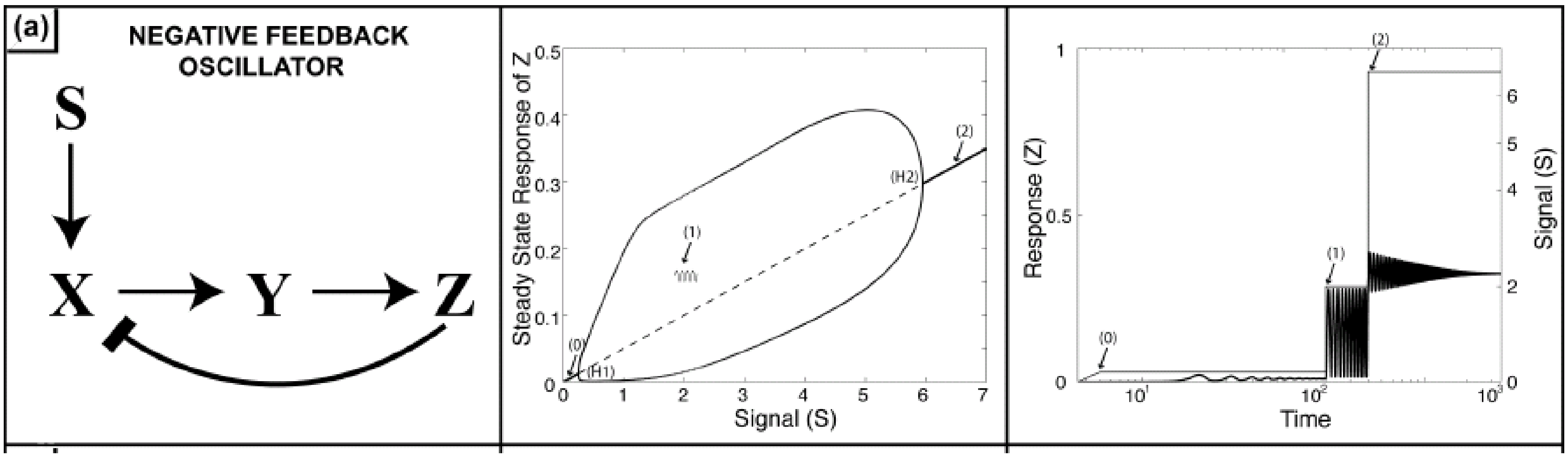
The first two bifurcations generate so-called switches: the system switches from one stable steady state solution to another stable steady state solution (for example switch from an inactive form of the system to an active form).
The Hopf bifurcation gives rise to oscillatory solutions.

Software package are available to draw bifurcation diagrams

Bifurcation diagram

Oscillations: among network topologies allowing oscillations : negative feedback oscillator

Network topology | **Bifurcation diagram** | **System behavior over time**



Extracted from a chapter book from Iber and Fengos: *Predictive models for cellular signaling networks*

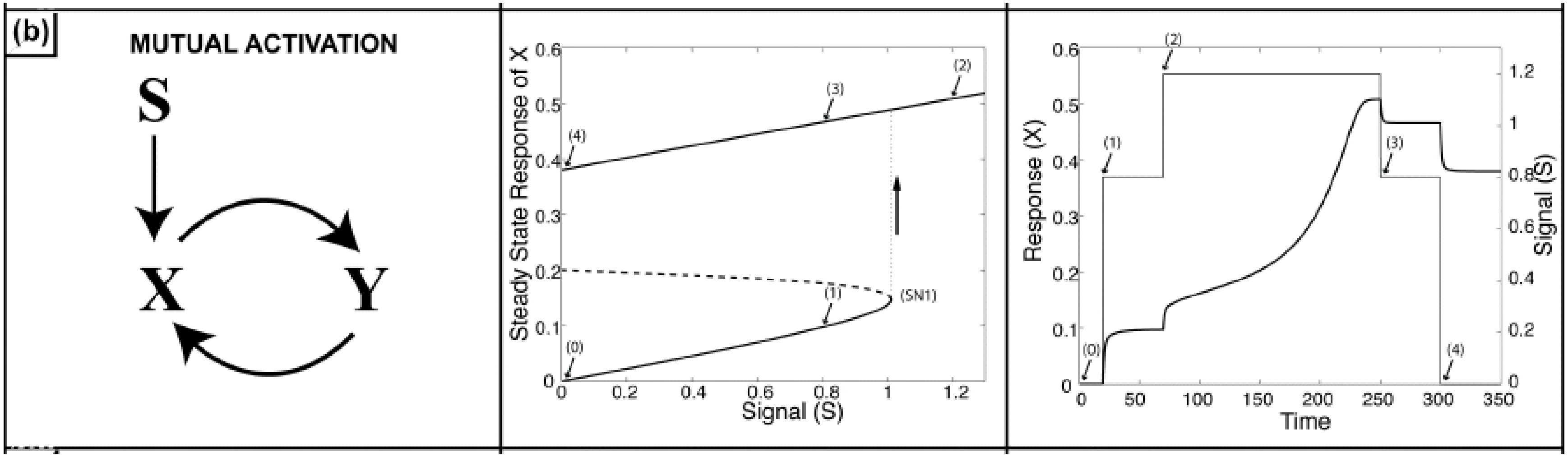
Dotted line : unstable steady state; solid line stable steady state; (H) = Hopf bifurcation points

S : the signal strength corresponds to the bifurcation parameter
Starting with *S*=0, we see that the oscillations decay quickly (region 0) to a stable equilibrium. When the strength of the signal *S* increases to fall into region (1), one obtained sustained oscillations which amplitude depends on the signal strength. If the value of *S* increases again and falls into region (2), the oscillations dampen away to the stable steady state.
There are two Hopf bifurcations (H1) and (H2).

Bifurcation diagram

Switches: one-way switches

Network topology **Bifurcation diagram** **System behavior over time**



Extracted from a chapter book from Iber and Fengos: *Predictive models for cellular signaling networks*

Dotted line : unstable steady state; solid line stable steady state; (SN) = saddle-node bifurcation points

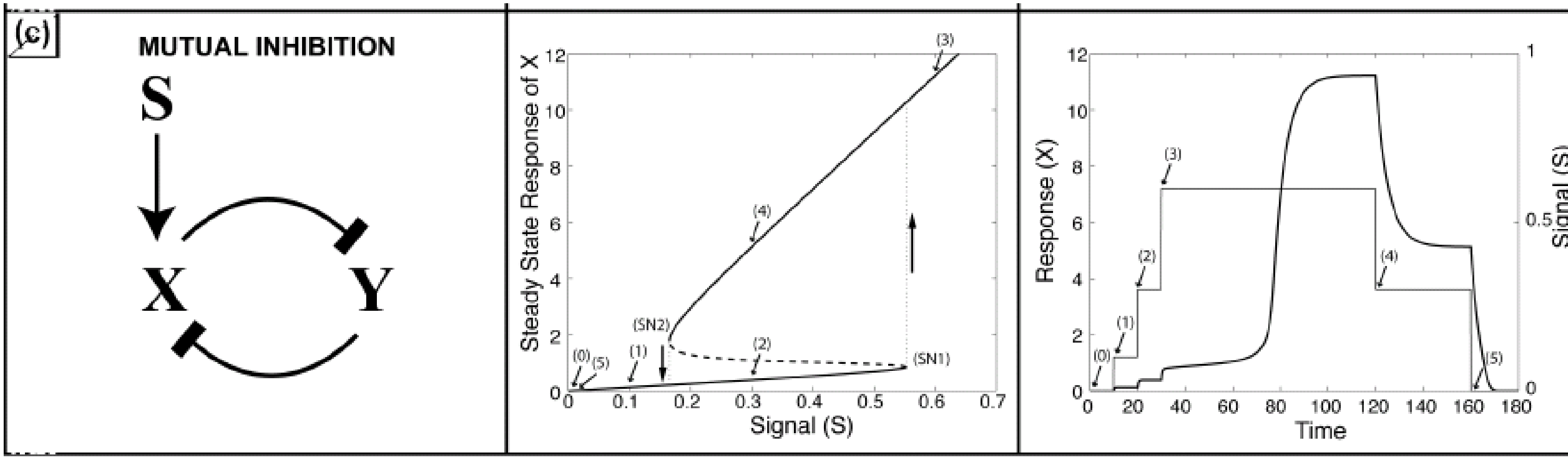
S : the signal strength corresponds to the bifurcation parameter

The system has three steady states, two stable and one unstable. If the system is started on the lower branch (low signal strength (point 0)), it will follow this branch as *S* increases (point 1) until the system reaches the saddle-node SN1 (point where the stable and unstable steady state branches collide and the two steady states are annihilated). A further increase of *S* results in a jump to a new equilibrium (point 2). If the strength of the signal is reduced, the system continues to follow the branch of this new equilibrium (point 4) and doesn't come back to the previous one. The switch is stable and is called a one-way switch

Bifurcation diagram

Switches: toggle switches

Network topology **Bifurcation diagram** **System behavior over time**



Extracted from a chapter book from Iber and Fengos: *Predictive models for cellular signaling networks*

Dotted line : unstable steady state; solid line stable steady state; (H) = (SN) = saddle-node bifurcation points

S : the signal strength corresponds to the bifurcation parameter
Same as the previous one. The system has three steady states, two stable and one unstable. If the system is started on the lower branch (low signal strength (point 0)), it will follow this branch as *S* increases until the system reaches the saddle-node bifurcation point SN1 (point where the stable and unstable steady state branches collide and the two steady states are annihilated). A further increase of *S* results in a jump to a new equilibrium (point 3). If the strength of the signal is reduced, the system continues to follow the branch of this new equilibrium (point 4). The new equilibrium branch meets a second saddle-node bifurcation point SN2. If SN2 lies in the physiological range of the bifurcation parameter (here the signal strength), the system can return to the previous steady state point (5).
In the previous case, SN2 lies out the physiological range of the bifurcation parameter and the system couldn't return to the previous steady state.

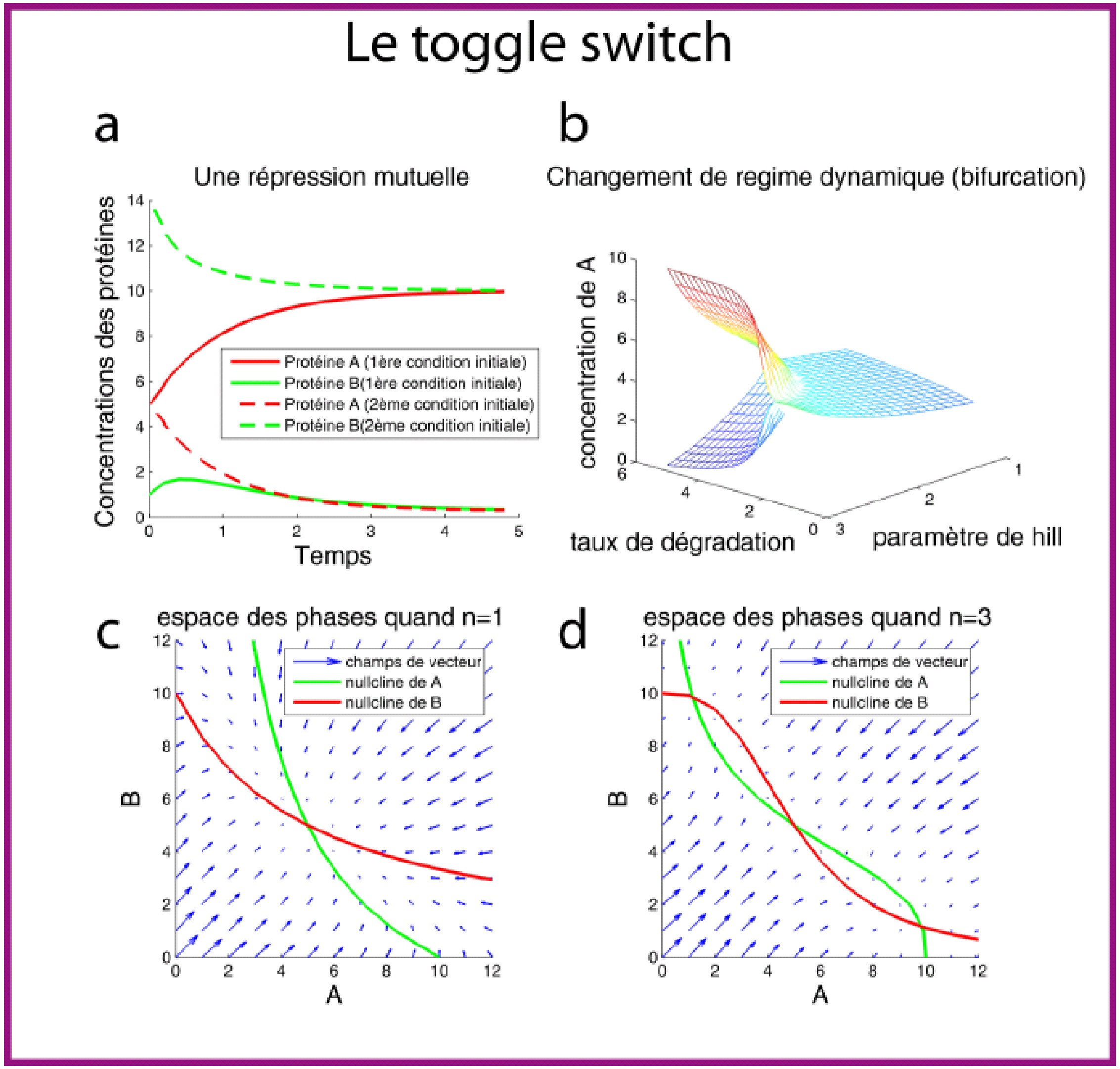
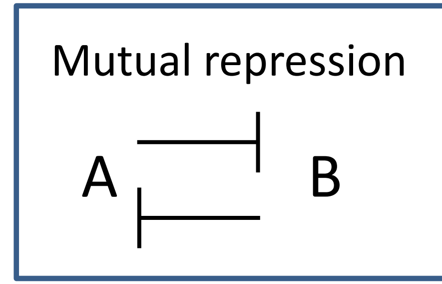


Figure V.3 – a) dynamique bistable en fonction des conditions initiales. b) bifurcation d'un régime mono-stable à un régime bistable en fonction de la valeur des paramètres. c) espace des phases avec un seul point stable. d) espace des phases avec trois points stables. Voir le code Matlab en annexe Code08ToggleSwitch.m qui génère cette figure.

Extracted from Guillaume BAPTIST's PhD manuscript (2012)

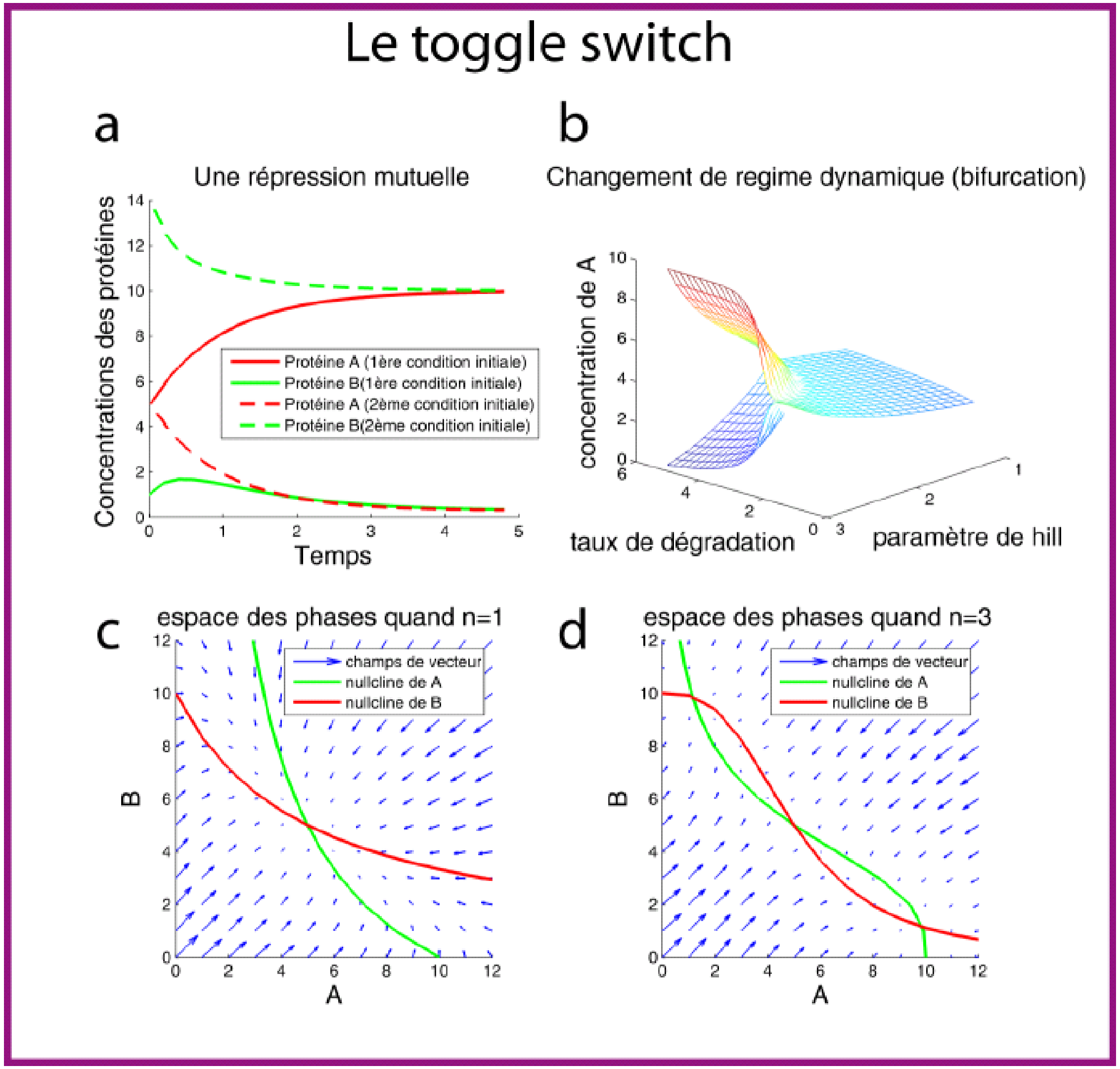


According to initial conditions, the concentrations of proteins A and B can reach two different steady states :

If A is present in high concentration at the beginning, the system reaches a steady state with a lot of proteins A and few proteins B (solid lines 3a) as A represses B expression.

If B is present in high concentration at the beginning, it is the reverse (dotted lines 3a).

It is called a toggle switch as by modifying the initial concentration of one protein (by modifying its affinity for the promoter), the system can switch from one steady state to the other.



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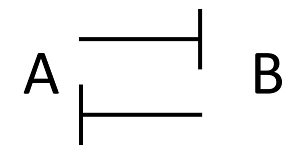
Mutual repression



$$\frac{d[A]}{dt} = \beta_{\max} \frac{K_d^n}{[B]^n + K_d^n} - \gamma [A]$$

$$\frac{d[B]}{dt} = \beta_{\max} \frac{K_d^n}{[A]^n + K_d^n} - \gamma [B]$$

Nullclines: $\frac{d[A]}{dt} = 0$ and $\frac{d[B]}{dt} = 0$

According to the value of the Hill coefficient *n*, the nullclines are different and the number of steady state points as well. For *n*=3, there are 3 equilibrium points, two stable and one unstable.

Figure 3b, the steady states of A concentration are plotted according to the degradation rate and Hill parameter. We can see the bifurcation between the two dynamic states.