Université Libre de Bruxelles

Modélisation des rythmes du vivant

CHIM-F-422

Dynamics of small signaling modules

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Contents

1 Introduction

Regulatory networks, or circuits, can be found everywhere in all organisms. To understand the mechanisms behind these complex circuits, we were tasked to simulate several subnetworks, analyse their behaviour and characteristics and understand how they can be combined to form more complex systems.

2 Simple networks

2.1 Regulatory network a

$$\frac{dR}{dt} = k_0 + k_1 S - k_2 R \tag{1}$$

Where k_0 is the term for the constant supply of R, $k_1 S$ is the term expressing the added supply of R in the presence of S and $k_2 R$ is the term of degradation of R.

$$\begin{aligned}\frac{dR}{dt} &= 0\\ k_2 R &= k_0 + k_1 S\\ R &= \frac{k_0 + k_1 S}{k_2}\end{aligned} \tag{2}$$

The steady state is obtained in function of the supply rate (obtained by the constant supply or the additional supply in function of S) on the degradation rate. The steady state is thus proportional to the signal S (Fig 1).

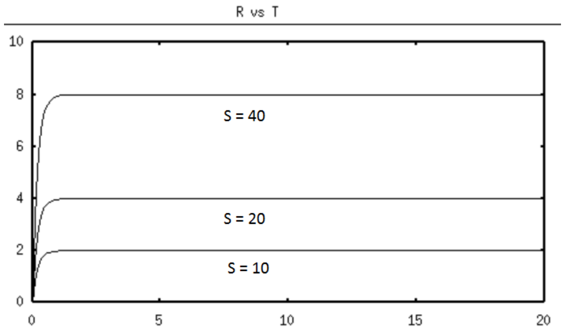


Figure 1: Response with different signal intensities. We can observe the steady state obtained is proportional to the signal.

2.2 Regulatory network b

$$\frac{dR_P}{dt} = \frac{k_1 S(R_T - R_P)}{K_{m1} + (R_T - R_P)} - \frac{k_2 R_P}{K_{m2} + R_P} \quad (3)$$

Where the signal S promotes the conversion of R ($= R_T - R_P$) into R_P for the first term and the second term represents the reconversion of R_P into R.

The curve of response follow an hyperbolic allure until a specific value of signal S where the response curve adopts a sigmoid allure (Fig 2. The latter is linked to a ultrasensitivity, only obtained under saturation conditions. The saturation conditions are met because we have a limited amount of total R and we increase the amount of signal until all R is converted into R_P.

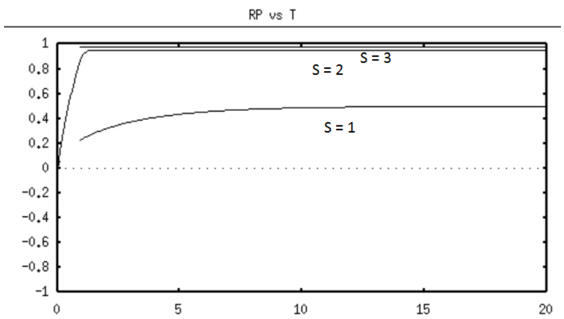


Figure 2: Response with different signal intensities. We can observe first curve with signal equal to 1 is an hyperbole, whereas the curve for signal equal to 2 and 3 are sigmoid.

3 Positive networks

3.1 Regulatory network c

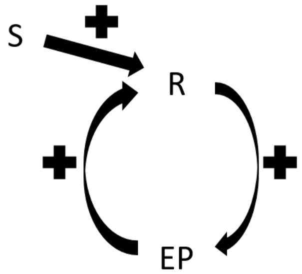
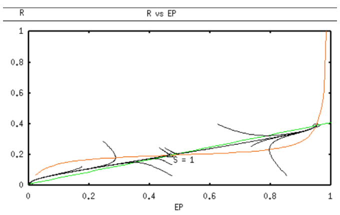


Figure 3: Schema of the regulatory network c

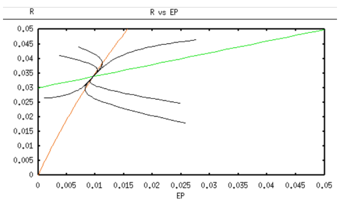
We can observe in the figure 3 that the circuit is ultimately positive.

$$\frac{dR}{dt} = k_0 E_P + k_1 S - k_2 R \tag{4}$$
$$\frac{dE_P}{dt} = \frac{k_3 R(E_T - E_P)}{J_3 + (E_T - E_P)} - \frac{k_4 E_P}{J_4 + E_P}$$

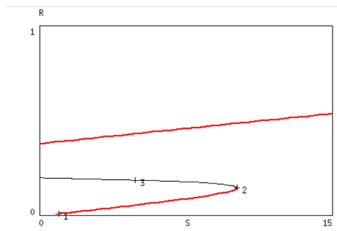
In the phase space, we observed the behaviour of the system with different initial conditions. When the signal is small, we distinguished three steady states : two stable nodes and one saddle (Fig 4a). Once the signal is high enough, we observe the disappearance of the saddle point and one of the stable node (Fig 4b). This observation is confirmed by the bifurcation diagram of the response R in function of the signal S where we observed bistability until a specific value of S (Fig 4c).



(a) Phase space with a signal intensity of 1



(b) Phase space with a signal intensity of 3



(c) Bifurcation diagram of the response in function of the signal intensity

Figure 4: Pictures of the simulation of the regulatory network c

3.2 Regulatory network d

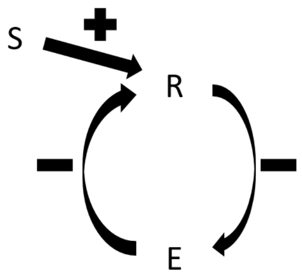


Figure 5: Schema of the regulatory network d

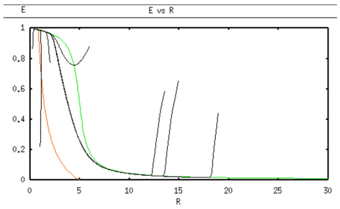
According the the schema realized in the figure 5, we observed that the network is positive because the number of the inhibitory interactions is even.

$$\begin{aligned}\frac{dR}{dt} &= k_0 + k_1 S - k_2 R - k_2' E.R \\ \frac{dE}{dt} &= k_3 \frac{E_T - E}{J_3 + (E_T - E)} - \frac{k_4 R.E}{J_4 + E}\end{aligned} \tag{5}$$

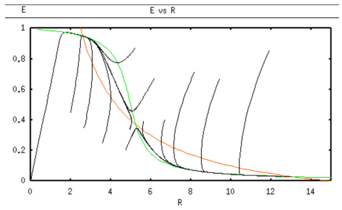
In the phase space, we observed four different behaviour :

1. at small signal intensities until a certain threshold, you have only one steady state, a stable node, (Fig 6a)
2. beyond the previous threshold to another one, we can observe three steady states, two stable nodes and a saddle point, (Fig 6b)
3. beyond the final threshold, you only have a steady state of a stable node, similar to the first behaviour,
4. above a signal intensity of 3, we observe a chaotic behaviour of the system, with no apparent steady state (Fig 6c)

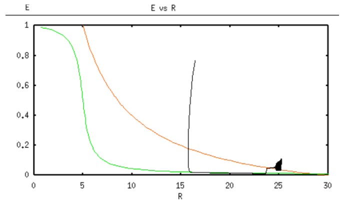
These observations are confirmed by looking in the phase space with different signal intensities, the bifurcation diagram of the response in function of the signal where we can observe a bistability (Fig 6d), and the time plot of R with different S and initial conditions.



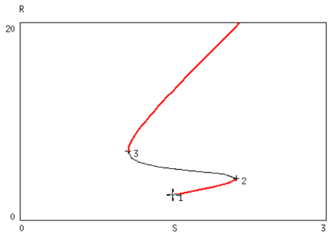
(a) Phase space with a signal intensity of 0.5



(b) Phase space with a signal intensity of 1.5



(c) Phase space with a signal intensity of 3



(d) Bifurcation diagram of the response in function of the signal intensity

Figure 6: Pictures of the simulation of the regulatory network d

4 Negative networks

4.1 Regulatory network e

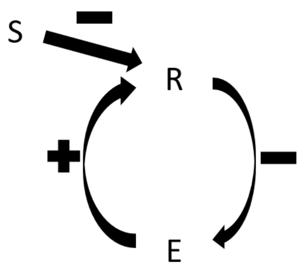


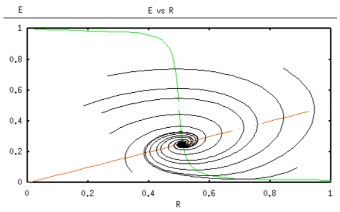
Figure 7: Schema of the regulatory network e

We observe that the circuit is negative as the number of negative reactions is odd. (Fig 7)

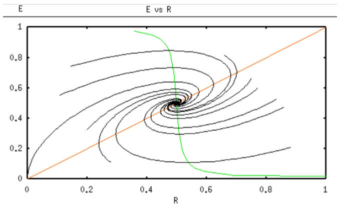
$$\frac{dR}{dt} = k_0 E - k_2 S.R \tag{6}$$
$$\frac{dE}{dt} = k_3 \frac{E_T - E}{J_3 + (E_T - E)} - \frac{k_4 R.E}{J_4 + E}$$

During the simulation, we observed only one steady state, always stable (Fig 8). The time plot of the response shows some damped oscillations until we reach the steady state. Another behaviour of the time plot for the response with higher signal intensity was to reach the steady state without oscillations. This two behaviours were confirmed by study of the phase space at different signal intensities : the damped oscillations correspond to a stable focus (Fig 8a and fig 8b) and the other one to a stable node (Fig 8c).

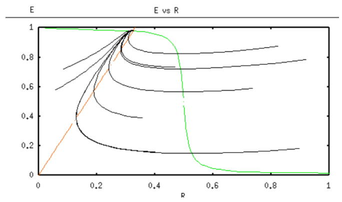
When we studied the bifurcation diagram of the response in function of the signal intensity, we took note of an interesting range of the signal intensity where the response does not change. This is the phenomena of *homeostasis*. We simulated a change in the signal intensity inside the range found in the bifurcation diagram. We confirmed that after some damped oscillations we returned to the steady state observed at the previous signal (Fig 8e).



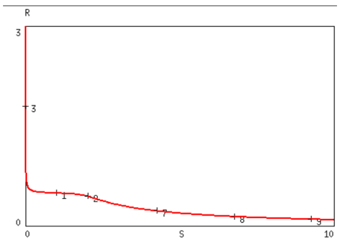
(a) Phase space with signal intensity of 0.5



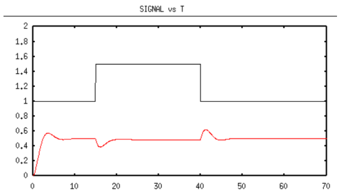
(b) Phase space with signal intensity of 1



(c) Phase space with signal intensity of 3



(d) Bifurcation diagram of the response in function of the signal intensity



(e) Time plot of the response with a pulse of signal (black), showing the homeostasis of the system

Figure 8: Pictures of the simulation of the regulatory network e

4.2 Regulatory network f

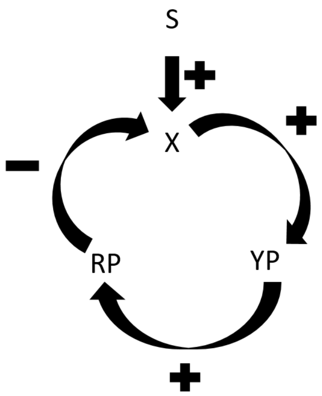
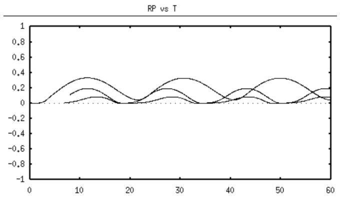


Figure 9: Schema of the regulatory network f

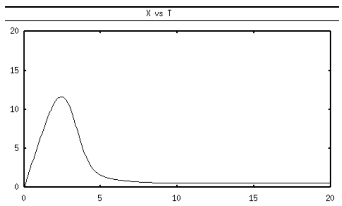
The number of the negative reactions is odd, so the circuit is negative.(Fig 9)

$$\begin{aligned}\frac{dX}{dt} &= k_0 + k_1 S - k_2 X - k_2' R_P.X \\ \frac{dY_P}{dt} &= k_3 X \frac{(Y_T - Y_P)}{K_{m3} + (Y_T - Y_P)} - \frac{k_4 Y_P}{K_{m4} + Y_P} \\ \frac{dR_P}{dt} &= k_5 Y_P \frac{(R_T - R_P)}{K_{m5} + (R_T - R_P)} - \frac{k_6 R_P}{K_{m6} + R_P}\end{aligned} \tag{7}$$

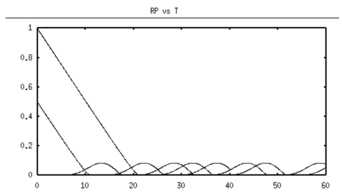
Two behaviours were observed : oscillations (Fig 10a), not damped as observed in the previous network, and for the higher intensities we reached the steady state after a peak (Fig 10b. Within the range of the oscillations, we observe that a change of signal intensities impacts on the amplitude an the phase of the oscillations (Fig 10a) and a change in the other variables modifies only their phase (Fig 10c). The study of the bifurcation diagram confirms that a low signal intensity we observe limit cycle and for higher values, a stable node (Fig 10d).



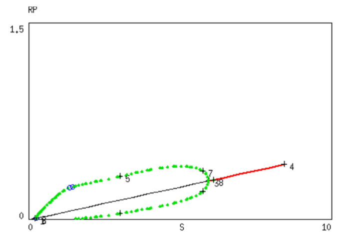
(a) Time plots of the response with signal intensity of 0.5, 1 and 3



(b) Time plot of the response with signal intensity of 6



(c) Time plots of the response with a signal intensity of 0.5 and initial R_P of 0, 0.5 and 1.



(d) Bifurcation diagram of the response in function of the signal intensity

Figure 10: Pictures of the simulation of the regulatory network f

4.3 Regulatory network g

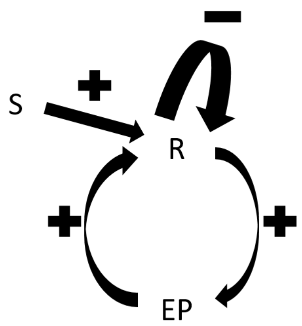


Figure 11: Schema of the regulatory network g

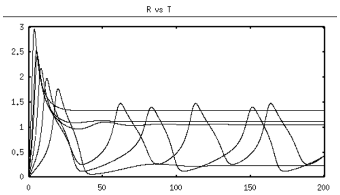
The main circuit is positive, but the compound of interest is itself involved in a negative circuit, resulting into a negative network for both circuits (Fig 11).

$$\frac{dR}{dt} = k_0 E_P + k_1 S - k_2 R - k_2' X.R \tag{8}$$

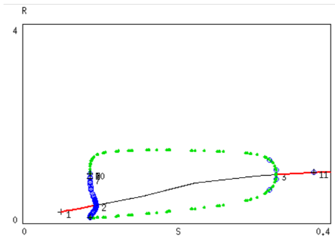
$$\frac{dE_P}{dt} = k_3 R \frac{(E_T - E_P)}{J_3 + (E_T - E_P)} - \frac{k_4 E_P}{J_4 + E_P}$$

$$\frac{dX}{dt} = k_5 R - k_6 X$$

We encountered the same two behaviours as in the previous network : oscillations not damped and a peak before reaching a steady state (Fig 12a). However, when we studied the bifurcation diagram of the response in function of the signal, we observed a different Hopf Bifurcation (HP) than in the previous network. Here, the HP is sub-critical (in blue in the Fig 12b), which means there is a coexistence of a stable steady state and a stable limit cycle, separated by an unstable limit cycle. This means we need a great change in signal intensities to leap from the steady state to the stable limit cycle.



(a) Time plots of the response with different signal intensities



(b) Bifurcation diagram of the response in function of the signal intensity

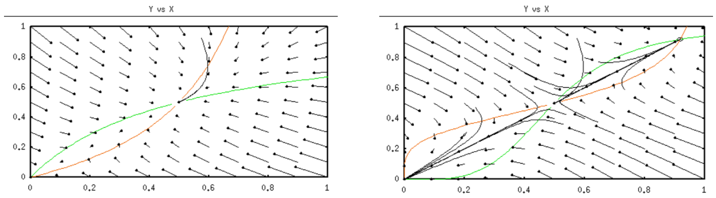
Figure 12: Pictures of the simulation of the regulatory network g

5 Validation with two compounds systems

5.1 Regulatory network h

$$\frac{dX}{dt} = k_1 \frac{Y^n}{\theta^n + Y^n} - X$$
$$\frac{dY}{dt} = k_2 \frac{X^n}{\theta^n + X^n} - Y \tag{9}$$

This is a positive circuit similar to the regulatory network c (Fig 4). We can observe the same phenomena that in the c circuit, meaning : a bistability depending on the n parameter, n being the Hill coefficient. When n is equal to one (Fig 13a), we observe only a stable node. However, when n is equal to 4 (Fig 13b), we observe three steady states : one saddle, and two stable nodes.



(a) Phase space with n equal to 1

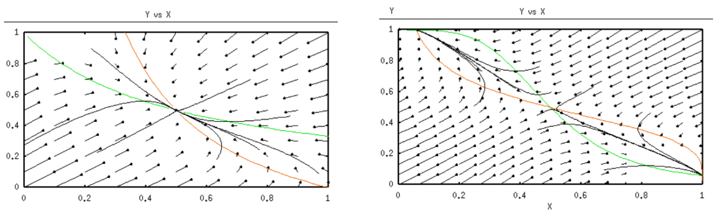
(b) Phase space with n equal to 4

Figure 13: Pictures of the simulation of the regulatory network h

5.2 Regulatory network i

$$\begin{aligned}\frac{dX}{dt} &= k_1 \frac{\theta^n}{\theta^n + Y^n} - X \\ \frac{dY}{dt} &= k_2 \frac{\theta^n}{\theta^n + X^n} - Y\end{aligned} \tag{10}$$

This is a positive circuit similar to the regulatory network d (Fig 5). We can observe the same phenomena that in the previous circuit, despite the fact that the system is composed of negative reactions.



(a) Phase space with n equal to 1

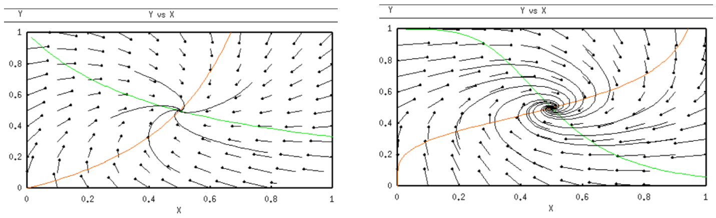
(b) Phase space with n equal to 4

Figure 14: Pictures of the simulation of the regulatory network i

5.3 Regulatory network j

$$\begin{aligned}\frac{dX}{dt} &= k_1 \frac{Y^n}{\theta^n + Y^n} - X \\ \frac{dY}{dt} &= k_2 \frac{\theta^n}{\theta^n + X^n} - Y\end{aligned} \tag{11}$$

This is a positive circuit similar to the regulatory network e (Fig 6). We observe the same two behaviours found in this network e : stable focus when n is equal to 4 and a stable node when n is equal to 1. The system does oscillate under specific circumstances.



(a) Phase space with n equal to 1

(b) Phase space with n equal to 4

Figure 15: Pictures of the simulation of the regulatory network j

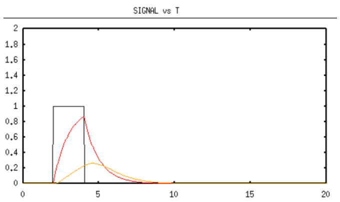
6 A switch network : regulatory network k

$$\frac{dX}{dt} = S - kX \tag{12}$$
$$\frac{dY_1}{dt} = \frac{X}{K_x + X} + \frac{Y_2^n}{K_2^n + Y_2^n} - Y_1$$
$$\frac{dY_2}{dt} = \frac{X}{K_x + X} + \frac{Y_1^n}{K_1^n + Y_1^n} - Y_2$$

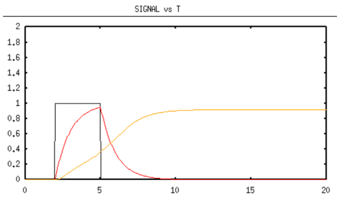
The network here is positive, as all the reactions are positive. The system here is controlled by the presence of signal which will increase the concentration of X, which in turn activates the concentration of Y_1 and Y_2. Interestingly, Y_1 and Y_2 also activates each other.

We used a pulse function to have a signal of 1 during a specific range of time, from t_1=2 to t_2=4, 5 and 8. We observed for all the expositions, X decays as soon as the signal is gone. Another observation is that Y_1 and Y_2 follows the exact same plot, which is logical as their evolution equations are symmetrical.

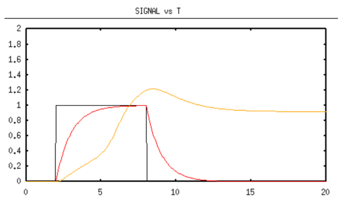
For the shortest exposition (Fig 16a), Y_1 and Y_2 decays shortly after the the disappearance of the signal. However, for the two other expositions (Fig 16b and 16c), even after the disappearance of the signal, Y_1 and Y_2 do not decay and seem to be at a steady state. When we studied this phenomena further with the phase space of Y_1 and Y_2 (Fig 16d), we could observe a phase space similar to the regulatory network h (Fig 13b), with two stable nodes and a saddle point, which is logical as Y_1 and Y_2 follows the same equations as this network (see equations (9) and (12)). This suggest the system has some proprieties of bistability.



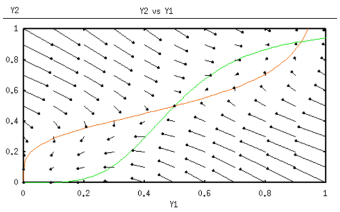
(a) Time plot of X (red), Y_1 and Y_2 (both in yellow) with t_2 equal to 4. The signal is in black.



(b) Time plot of X (red), Y_1 and Y_2 (both in yellow) with t_2 equal to 5. The signal is in black.



(c) Time plot of X (red), Y_1 and Y_2 (both in yellow) with t_2 equal to 8. The signal is in black.



(d) Phase space of Y_1 and Y_2

Figure 16: Pictures of the simulation of the regulatory network k

7 Summary of the regulatory networks

We could see that to observe bistability, the minimum condition is to have a positive network. With two compounds system, another condition was to have a Hill coefficient superior to 1, meaning that you need several molecules of the compound to affect the other compound.

To observe oscillations, damped or not, the minimal condition is to have a negative network.

Damped oscillations can be observed in systems with only two reactions (regulatory network e and j). As with the bistability, you need to have a Hill coefficient superior to 1 to observe damped oscillations in two-compound systems. We found this behaviour linked to the phenomena of homeostasis, where change of the signal was not accompanied by a change in the steady state of the response.

The harmonic oscillations (translated by limit cycle in the phase space) were found in negative networks with more than two reactions.