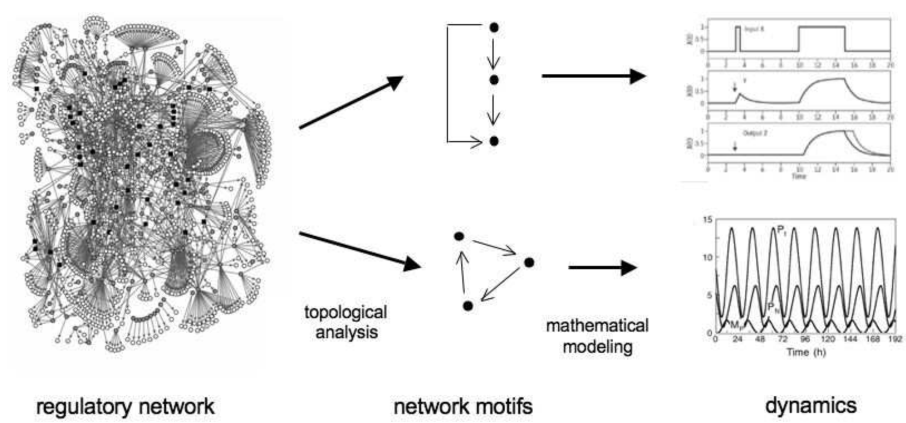
Dynamics of small signalling modules

The function of living cells is controlled by complex regulatory networks, involving various types of components and interactions: gene regulation, protein-protein interactions, protein modifications, etc.

Although the dynamics of relatively large networks can be simulated, a deep understanding of the design principles underlying these networks requires a bottom-up approach. This approach consists of analyzing, in a first step, well-characterized small regulatory networks (building blocks). The next step is to understand how these subnetworks can be combined together to provide the system with more elaborated properties.

Topological analyses of large gene networks highlight their modularity and help to identify basic regulatory motifs. Mathematical modeling is then needed to decipher the links between the structure, logic, and function of these small regulatory circuits. Due to the non-linearities of the kinetics of gene regulation and enzymatic reactions, the repertoire of non-trivial dynamical behaviours is very large.



In these practicals, we will analyze, through mathematical modeling and numerical simulations, a couple of basic motifs and to assess their response to an external signal. The goal is to establish relationships between motif architecture (in term of "circuits") and dynamical properties (behaviour, bifurcation, etc). This analysis will highlight the "design principles" of regulatory networks.

References

- Alon U (2007) Network motifs: theory and experimental approaches. Nat Rev Genet. 8:450-61.
- Lim WA, Lee CM, Tang C (2013) Design principles of regulatory networks: searching for the molecular algorithms of the cell. Mol Cell. 49:202-12.
- Sneppen K, Krishna S, Semsey S (2010) Simplified models of biological networks. Annu Rev Biophys. 39:43-59.
- Tyson JJ, Novak B (2010) Functional motifs in biochemical reaction networks. Annu Rev Phys Chem. 61:219-40.

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1. For the regulatory networks (a) and (b):

   - Explain the evolution equations.

   - Compute the steady state of the response R as a function of the signal S. What is the major difference between the two signal-response curves?

2. For the regulatory networks (c), (d), and (e):

   - Draw the nullclines in the phase space for different values of the signal intensity S, indicate the direction of the trajectories starting from different initial conditions, and deduce the stability and nature of the steady state(s).

   - Draw a time plot starting from different initial conditions.

   - Draw a bifurcation diagram with the response of the system as a function of the signal intensity S. Describe what happens at different signal intensities.

3. For the regulatory networks (f) and (g):

   - Draw a time plot for different values of S, starting from different initial conditions.

   - Draw a bifurcation diagram with the response of the system as a function of the signal intensity S. Describe what happens at different signal intensities.

4. For the regulatory networks (h), (i), and (j):

   - Draw the nullclines in the phase space, indicate the direction of the trajectories starting from different initial conditions, and deduce the stability and nature of the steady state(s). Compare the results for $n = 1$ and $n = 4$.

5. Consider module (k). Transcription factor X activates the transcription factors Y_1 and Y_2, which mutually activate each other cooperatively. Y_1 is activated when either X or Y_2 binds to the promoter. Similarly Y_2 is activated when either X or Y_1 binds to the promoter. The production of X is under the control of a signal S.

   At time $t = 0$, $X = Y_1 = Y_2 = 0$. S is switched on ($S = 1$) at time $t = t_1 = 2$, and switched off at time $t = t_2$.

   - Plot the dynamics of X, Y_1, and Y_2 for $t_2 = 4$, $t_2 = 5$, $t_2 = 8$.

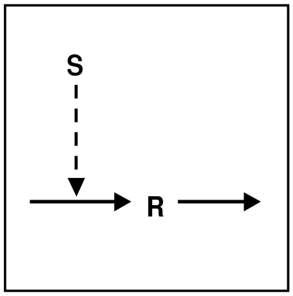
   - What happens to Y_1 and Y_2 after X decays away?

   - How would we characterize this type of behavior?

6. Compare the behavior of the different systems and discuss the results in the framework of the general properties of positive and negative circuits.

Dynamics of small signalling modules

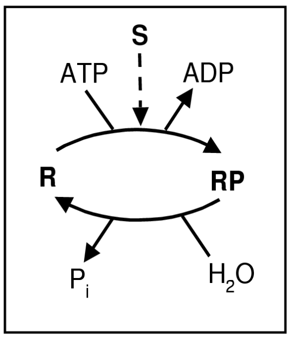
(a)



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

Parameters: $k_0 = 0.01$, $k_1 = 1$, $k_2 = 5$.

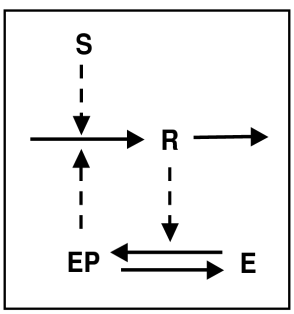
(b)



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

Parameters: $k_1 = 1$, $k_2 = 1$, $R_T = 1$, $K_{m1} = 0.05$, $K_{m2} = 0.05$.

(c)

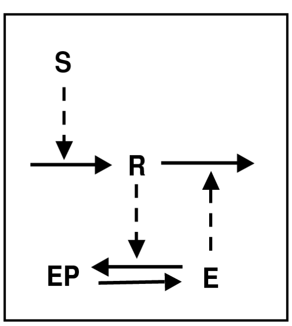


$$\frac{dR}{dt} = k_0 E_P + k_1 S - k_2 R$$

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

Signal: $S = 1$.
Parameters: $E_T = 1$, $k_0 = 0.4$, $k_1 = 0.01$, $k_2 = 1$, $k_3 = 1$, $k_4 = 0.2$, $J_3 = 0.05$, $J_4 = 0.05$.

(d)

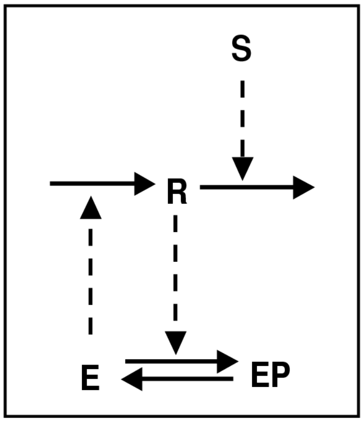


$$\frac{dR}{dt} = k_0 + k_1 S - k_2 R - k_2' E.R$$

$$\frac{dE}{dt} = k_3 \frac{E_T - E}{J_3 + (E_T - E)} - \frac{k_4 R.E}{J_4 + E}$$

Signal: $S = 1.5$.
Parameters: $E_T = 1$, $k_0 = 0$, $k_1 = 1$, $k_2 = 0.1$, $k_2' = 0.5$, $k_3 = 1$, $k_4 = 0.2$, $J_3 = 0.05$, $J_4 = 0.05$.

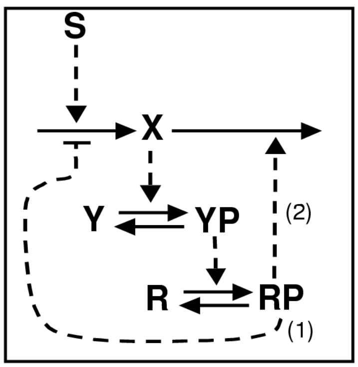
(e)



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

Signal: $S = 1$.
Parameters: $E_T = 1$, $k_0 = 1$, $k_2 = 1$, $k_3 = 0.5$, $k_4 = 1$, $J_3 = 0.01$, $J_4 = 0.01$.

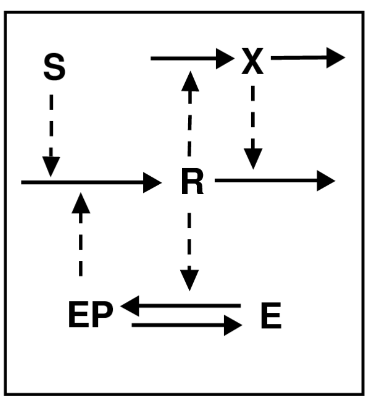
(f)



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

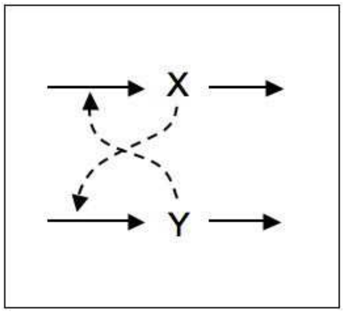
Signal: $S = 1$.
Parameters: $k_0 = 0$, $k_1 = 1$, $k_2 = 0.01$, $k_2' = 10$, $k_3 = 0.1$, $k_4 = 0.2$, $k_5 = 0.1$, $k_6 = 0.05$, $Y_T = 1$, $R_T = 1$, $K_{m3} = 0.01$, $K_{m4} = 0.01$, $K_{m5} = 0.01$, $K_{m6} = 0.01$.

(g)



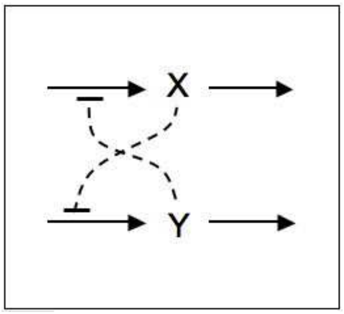
$$\frac{dR}{dt} = k_0 E_P + k_1 S - k_2 R - k_{2p} X.R$$
$$\frac{dE_P}{dt} = k_3 R \frac{(E_T - E_P)}{J_3 + (E_T - E_P)} - \frac{k_4 E_P}{J_4 + E_P}$$
$$\frac{dX}{dt} = k_5 R - k_6 X$$

Signal: $S = 0.2$.
Parameters: $E_T = 1$, $k_0 = 4$, $k_1 = 1$, $k_2 = 1$, $k_{2p} = 1$, $k_3 = 1$, $k_4 = 1$, $k_5 = 0.1$, $k_6 = 0.075$, $J_3 = 0.3$, $J_4 = 0.3$.

(h) 

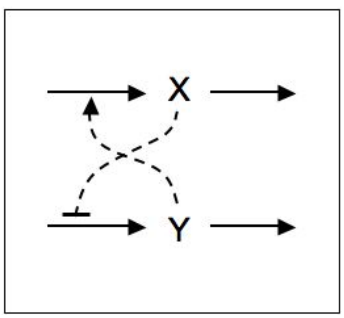
$$\frac{dX}{dt} = k_1 \frac{Y^n}{\theta^n + Y^n} - X$$
$$\frac{dY}{dt} = k_2 \frac{X^n}{\theta^n + X^n} - Y$$

Parameters: $\theta = 0.5,\ k_1 = 1,\ k_2 = 1,\ n = 1$ or $n = 4$.

(i) 

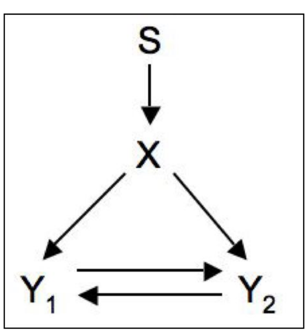
$$\frac{dX}{dt} = k_1 \frac{\theta^n}{\theta^n + Y^n} - X$$
$$\frac{dY}{dt} = k_2 \frac{\theta^n}{\theta^n + X^n} - Y$$

Parameters: $\theta = 0.5,\ k_1 = 1,\ k_2 = 1,\ n = 1$ or $n = 4$.

(j) 

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

Parameters: $\theta = 0.5,\ k_1 = 1,\ k_2 = 1,\ n = 1$ or $n = 4$.

(k) 

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

Parameters: $k = 1,\ K_x = 2,\ K_1 = K_2 = 0.5$, and $n = 4$.