Physics of Behavior

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Exercise 3

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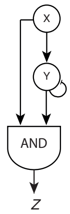
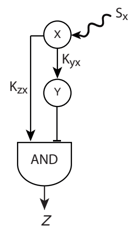
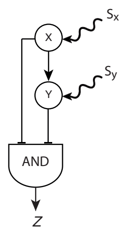
1 *A decoration on the FFL*. The regulator Y in C1-FFLs in transcription networks is often negatively auto-regulated. How does this affect the dynamics of the circuit, assuming that it has an AND input function at the Z promoter? Consider both an On step and an OFF step.



2 *Amplifying intermediate stimuli*. This problem highlights an additional function of incoherent type-1 FFLs for sub-saturating stimuli Sx. Consider an I1-FFL, such that the activation threshold of Z by X, Kzx, is smaller than the activation threshold of Y by X, Kyx. That is, Z is activated when X*>Kzx, but it is repressed by Y when X*>Kyx. Schematically plot the steady-state concentration of Z as a function of X*. Note that intermediate values of X* lead to the highest Z expression. When might such a design be useful?



3 *Type three.* Consider a type-3 coherent FFL with AND - logic at the Z promoter with Sx activates X and Sy activates Y. More precisely the promoter logic is ((NOT X*) AND (NOT Y*)). Sketch the dynamics in response to ON step and OFF step of Sx in the presence of Sy. Are there sign sensitive delays?



4. *Shaping the pulse*. Consider a situation where X in an I1-FFL with an AND–logic begins to be produced at time t=0, so that the level of protein X gradually increases. The input signal Sx is present throughout.

a) How does the pulse shape generated by the I1-FFL depend on the thresholds Kxz, Kxy and Kyz and on β, the production rate of protein X?

b) Analyze a set of genes Z1, Z2, … , Zn, all regulated by the same X and Y in I1-FFLs.

c) Design thresholds such that the genes are turned ON in the rising phase of the pulse in a certain temporal order and turned OFF in the declining phase of the pulse with the same order.

d) Design thresholds such that the turn-off order is opposite to the turn-on order.

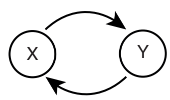
e) Plot the resulting dynamics.

5. *Nullclines for lock-on switch*: Nullclines are a useful concept for analyzing dynamical systems. To define nullclines, consider a two-component dynamical system defined generally by the equations

$$\frac{dx}{dt} = f_1(x, y), \qquad \frac{dy}{dt} = f_2(x, y)$$

The system two nullclines are the curves at which $dx/dt = 0$ and $dy/dt = 0$. Thus the two nullclines are defined by the equations $f_1(x, y) = 0$ and $f_2(x, y) = 0$. Their important feature is their crossing points. The crossing points are fixed points of the system (steady states), because both x and y do not change ($dx/dt = 0$ and $dy/dt = 0$). Here we will use nullclines to show that a double positive feedback loop (DPFL) can be mono-stable or bi-stable. We will show that Bi-stability requires cooperative input functions. The DPFL is defined by two increasing input functions, f and g, that describe the mutual repression:

$$\frac{dx}{dt} = f(y) - \alpha_1\, x, \qquad \frac{dy}{dt} = g(x) - \alpha_2\, y$$



Thus, the nullclines in this case are $x = f(y)/\alpha_1$ and $y = g(x)/\alpha_2$.
(a) Show that if f and g are non-cooperative with a basal expression level (Michaelis-Menten functions $f \sim a + b\, y/(k + y)$, $g \sim c + d\, x/(k + x)$), there is only one fixed point (Hint: how many solution a quadratic equation has? How many solution do we need for bi-stability)
(b) Explain why this means there is no switching.
(c) Show graphically that bi-stability, with three fixed points, a high a low and a middle unstable fixed point, can occur if f and g are sigmoidal (S-shaped).