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**ADVANCED SUMMER SCHOOL ON APPLIED DYNAMICS IN SYSTEMS AND SYNTHETIC BIOLOGY**

# EXERCISES - GENE REGULATORY CIRCUITS

1. Calculate the coefficient of sensitivity for the negative feedback gene circuit studied in class with respect to the maximum expression rate $\beta$, the decay rate $\gamma$, and the repression threshold K.

2. Show graphically that adding basal expression $\alpha$ to the positive feedback gene circuit studied in class leads to an irreversible response to $\alpha$: starting from the low-expression fixed point at $\alpha$=0, an increase in $\alpha$ leads to the high-expression fixed point (the cell starts producing protein), but a subsequent decrease of $\alpha$ back down to 0 does not cause expression to turn off: the cell responds *irreversibly* to a pulse stimulus in $\alpha$.

3. Consider the following activator-repressor model discussed in class:

$$\frac{dx}{dt} = a_1 + \frac{b_1 x^n}{{K_1}^n + x^n} - gxy - d_1 x$$
$$\frac{dy}{dt} = a_2 + \frac{b_2 x^m}{{K_2}^m + x^m} - d_2 y$$

   Use the tools that you have learned in the different courses of this school to analyze this dynamical system in the plane, as the basal expression rate $a_1$ of x varies, as shown in the slides. Use these values for the other parameters to perform simulations if necessary: $a_2$=0.025 nM/s, $b_1$=15 nM/s, $b_2$=0.8 nM/s, $d_1$=$d_2$=5·10$^{-5}$ s$^{-1}$, g=2.5·10$^{-7}$ nM$^{-1}$s$^{-1}$, $K_1$=3000 nM, $K_2$=750 nM, and n=m=2.

4. The following model describes genetic competence in *B. subtilis*:

$$\frac{dK}{dt} = \alpha_k + \frac{\beta_k K^n}{k_k^n + K^n} - \frac{\gamma_k K}{1 + \frac{K}{\Gamma_k} + \frac{S}{\Gamma_s}} - \delta_k K$$
$$\frac{dS}{dt} = \alpha_s + \frac{\beta_s}{1 + (K/k_s)^p} - \frac{\gamma_s S}{1 + \frac{K}{\Gamma_k} + \frac{S}{\Gamma_s}} - \delta_s S$$

   Again, use the tools that you have learned in the different courses of this school to analyze this dynamical system in the plane, as the parameters $\alpha_k$, $\alpha_s$ and $\beta_s$ vary (one at a time or in pairs). Reproduce and study the response of the system in the different dynamical regimes studied in class. Consider the following baseline parameter values:

| Parameter | Value | Parameter | Value | Parameter | Value |
|---|---|---|---|---|---|
| $\alpha_k$ | 0.00875 molec/s | $\gamma_k$ , $\gamma_s$ | 0.001 s$^{-1}$ | $k_k$ | 5000 molec |
| $\alpha_s$ | 0.0004 molec/s | $\delta_k$ , $\delta_s$ | 10$^{-4}$ s$^{-1}$ | $k_s$ | 833 molec |
| $\beta_k$ | 7.5 molec/s | $\Gamma_k$ | 25000 molec | $n$ | 2 |
| $\beta_s$ | 0.06 molec/s | $\Gamma_s$ | 20 molec | $p$ | 5 |