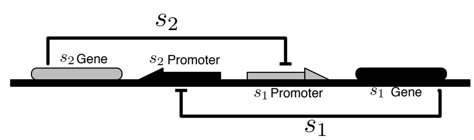


Figure 1: Schematic representation of the Gardner's Genetic Toggle Model [1]. The species $s_1$ represses the gene that transcribes $s_2$ and vice versa.

Gardner's genetic toggle switch [1] is an excellent example of a system where small populations and noise have great importance. The system is comprised of two promoters, each of whose product inhibits the other; if species $s_1$ gains a slight edge it will shut off $s_2$, and vice versa. Fig. 2 illustrates this genetic regulatory system. The signals of the network are the populations of the two repressors, $s_1$ and $s_2$. We assume that these repressors react according to the simple production and degradation reactions:

$$\emptyset \underset{\gamma_1}{\overset{k_1}{\rightleftarrows}} s_1$$

$$\emptyset \underset{\gamma_2}{\overset{k_2}{\rightleftarrows}} s_2$$

where the degradation reactions (left arrows) of $s_1$ and $s_2$ are monomolecular reactions with propensity functions $\gamma_1 x_1$ and $\gamma_2 x_2$, respectively, and the synthesis rates (right arrows) of $s_1$ and $s_2$ depend upon the populations $[s_2]$ and $[s_1]$, respectively, and are given by:

$$k_1([s_2]) = \frac{\alpha_1}{1+[s_2]^\beta}, \text{ and } k_2([s_1]) = \frac{\alpha_2}{1+[s_1]^\delta},$$

respectively.

Consider the following set of parameters for the switch:

$$\gamma_1 = \gamma_2 = \delta = 1, \alpha_1 = 50, \alpha_2 = 16, \beta = 2.5, \tag{1}$$

and begin with an initial condition of zero for both species $s_1$ and $s_2$. Define the system to be in an ON state when $x_1 > 15$. Define the system to be OFF when $x_2 > 5$. Otherwise the switch is indeterminate.

(1) Simulate this problem many times using the SSA.

(a) Plot one such trajectory ($x_1$ and $x_2$ vs. $t$).

(b) For each run, record the times at which the switch first turns ON and the time at which the switch first turns OFF.

(c) What are the median times at which the system first turns ON/OFF?

(d) What portion of runs first turns OFF then turns ON?

(2) Use an Finite State Projection approach to examine this system. For your projection use the set of configurations such that $x_1 \leq 100$, $x_2 \leq 40$ and $x_1 x_2 \leq 260$. (Hint: It may be easiest to first find **A** for a projection such that $x_1 \leq 100$ and $x_2 \leq 40$. Then remove all of the rows and columns such that $x_1 x_2 > 260$. See the sample code below.)

(a) Plot the probability distributions for $x_1$ and $x_2$ first separately and then as a contour plot. (Hint: you may wish to scale the axis in the contour plot).

(b) Change the projection to include all configurations such that $x_1 \leq 15$ and $x_2 \leq 40$. Use this projection to find the times at which 50 % and 99 % of trajectories will turn ON.

(c) Change the projection to include all configurations such that $x_1 \leq 100$ and $x_2 \leq 5$. Use this projection to find the time at which 50 % and 99 % of trajectories will turn OFF.

(d) Use another projection to compute the probability that a cell will turn OFF before it turns ON.

(e) Compare your results to those found with the SSA.

# 1 Matlab Code to remove rows and columns from A

First form the A matrix according to a simple rectangular section of the configurations space, then apply the following:

```
Iin=[]; %initialize vector including indices of the states we wish to keep
for i=0:N(1) %from x1 min to x1 max
for j=0:N(2) %from x2 min to x2 max
ix = i*(N(2)+1)+j+1; %this is the index of the state (x1,x2)=(i,j). This enumeration is not unique, but it is quite simple to use.
if (i*j < 260) % if we want to include this state
Iin=[Iin,ix]; %append current state to Iin
end
end
end
Asmall = A(Iin,Iin); %find the principle submatrix of A.
```

Once you have solved the system with Asmall, you can easily lift the solution back to the original coordinates of A with the line:

```
q(Iin) = qsmall;
```

# References

[1] T. Gardner, C. Cantor, and J. Collins. Construction of a genetic toggle switch in escherichia coli. *Nature*, 403:339–242, 2000.