Final Exam : Computational Biology

Baptiste Rouger Nicolas Senecaut Nympha Elisa Sia

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Question 1

We build the model with 3 variables : N (the density of cell in CFU), E (the concentration of the E protein) and A (the concentration of AHL).

We also have 7 parameters, defined here for pH 7 :

k	N_m	d	k_E	d_E	ν_A	d_A
0.97	$1.24 \cdot 10^9$	$4 \cdot 10^{-3}$	5	2	$4.8 \cdot 10^{-7}$	0.639

The parameter vector will be added in the following questions by the quantity of inducer, the θ and η values.

Our model is written in you_ode.m, such as

```
function xdot= you_ode(t,x,p)

  %x_names= {'N', 'E', 'A'}; -> x(1) is N, x(2) is E, x(3) is A
  %p_names= {'k', 'Nm', 'd', 'ke', 'de', 'va', 'da'}; -> p(1) is k,
                                                  % p(2) is Nm, etc
  xdot= zeros(size(x));

  xdot(1) = p(1)*x(1) * (1-x(1)/p(2)) - (p(3)*x(2)*x(1));
  xdot(2) = p(4)*x(3) - p(5)*x(2);
  xdot(3) = p(6)*x(1) - p(7)*x(3);
end
```

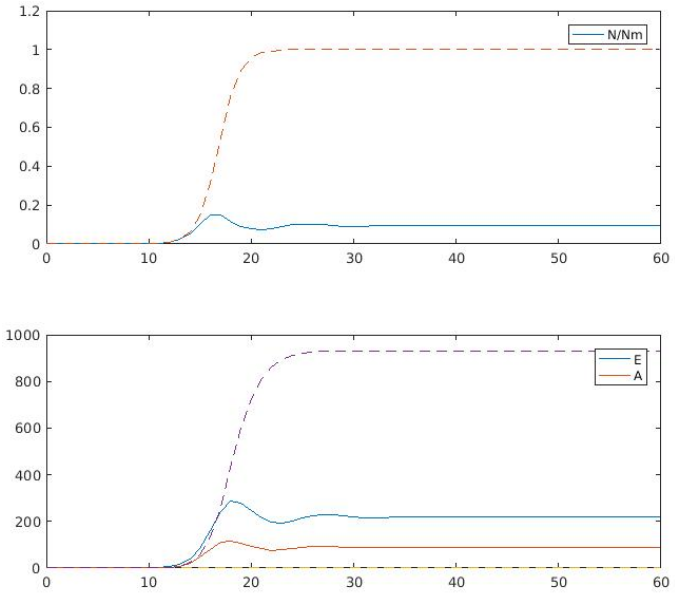

Figure 1: Cell density, E and A quantities for the You model

In FIGURE 1, we can see that the OFF system reaches a plateau as exepted (dashed lines). Though, we can also observe oscillations in the ON system, with a population stabilising its density to a far lower plateau than in the OFF system. We can see that the E quantity remains 0 in the OFF system as expected, and can observe that in the ON system, the quantity stabilises at a lower plateau than the OFF system. This allows us to say that the model describes accuratly the experiments.

Question 2

k, N_m and d_A change depending on the pH. We then have these parameter values :

	k	N_m	d	k_E	d_E	ν_A	d_A
pH 6.2	0.885	$1.25 \cdot 10^9$	$4 \cdot 10^{-3}$	5	2	$4.8 \cdot 10^{-7}$	0.274
pH 7.8	0.936	$1.20 \cdot 10^9$	$4 \cdot 10^{-3}$	5	2	$4.8 \cdot 10^{-7}$	1.19

The modulation capacity, described in the script by the fold change, is equal to 3.9477.

Question 3

We can make 3 other circuits by replacing the constitutive original promoter by an inducible promoter. Thus, we can make the following circuits :

	R promoter	I promoter
Original circuit	constitutive	constitutive
I circuit	constitutive	inducible
R circuit	inducible	constitutive
RI circuit	inducible	inducible

Question 4

To implement the 3 new circuits, we use the following template to replace the constitutive promoter :

$$(k_{basal} + k_{regulated}\frac{m^\eta}{\theta^\eta + m^\eta}) \times Inducer - degradation\ rate \times Species$$

We then get, for the you_RI circuit :

```
function xdot= you_odeRI(t,x,pe)

%n is pe(8);
%theta is pe(9);
%eta is pe(10);
xdot= zeros(size(x));
xdot(1) = pe(1)*x(1) * (1-x(1)/pe(2)) - (pe(3)*x(2)*x(1));

xdot(2) = (0.2*pe(4)
```

```
        + 5*pe(4)*((pe(8).^pe(10))/(pe(9).^pe(10) + pe(8).^pe(10))))*x(3)
        - pe(5)*x(2);

xdot(3) = (0.2*pe(6)
        + 5*pe(6)*((pe(8).^pe(10))/(pe(9).^pe(10) + pe(8).^pe(10))))*x(1)
        - pe(7)*x(3);
end
```

Question 5

We have the following steady state values for the 3 circuits and the 3 variables :

	N	E	A
circuit R	46172245.0026	233.604179309	34.6304668335
circuit I	46172245.0037	233.604179307	93.5022604502
circuit RI	17492400.9645	239.380151929	35.4726618404

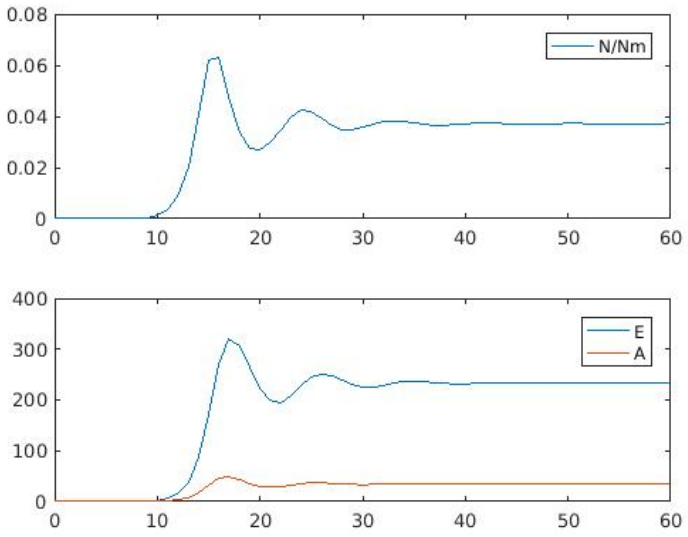

Figure 2: Cell density, E and A Quantities for the You_R model

In Figures 2, 3 and 4, we can see more or less big oscillations, with the system stabilising around the same values (except for N/N_m in Figure 4). Though, we want to control the system *via* an external inducer. In the following questions, we will use it to determine which circuit changes the most in its behaviour regarding the concentration of this inducer.

Question 6

In Figures 5, 6 and 7, we can observe the density of cells, the quantity of E and A regarding different quantities of inducer. Thus, we can see in these figures that, as expected,

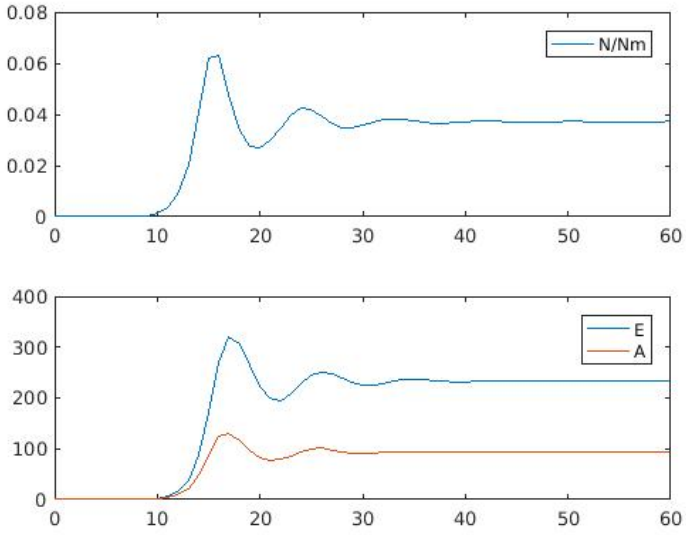

Figure 3: Cell density, E and A quantities for the You_I model

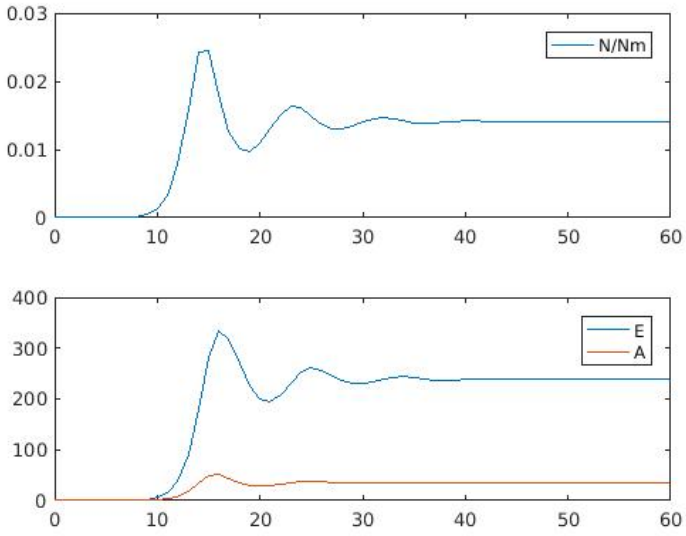

Figure 4: Cell density, E and A quantities for the You_RI model

the behaviour of the You model is not disturbed by the presence of inducer. Though, we can observe that all our new models show a behaviour that depends on the quantity of inducer.

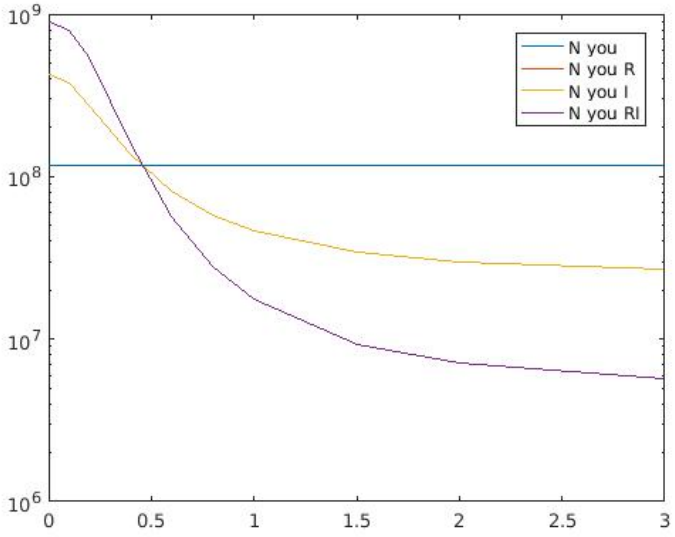

Figure 5: Cell density for all models

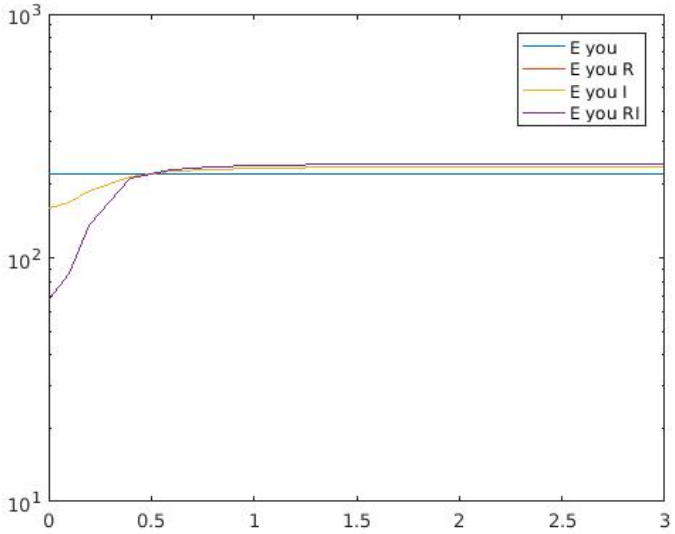

Figure 6: Concentration of E for all models

Question 7

Using the compute_msd function, we compute mean squared deviations such as :

	R : E	R : A	I : E	I : A	RI : E	RI : A
msd	4.31	16.4797	4.31004	1.72738	10.3179	10.1225

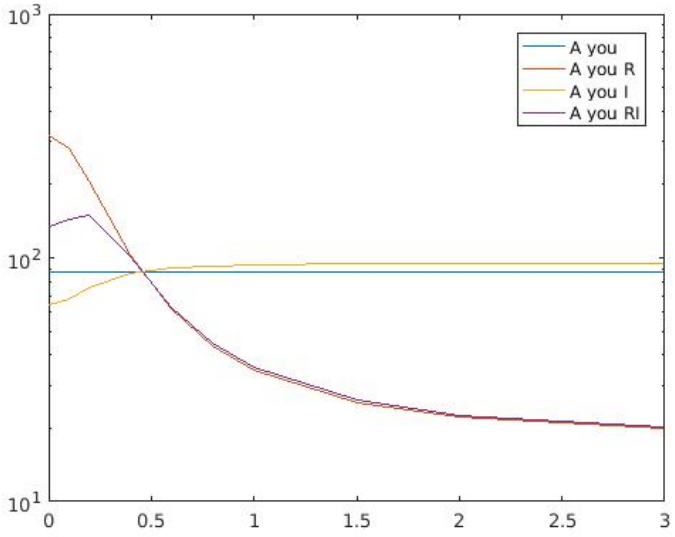

Figure 7: Concentration of A for all models

Question 8

Afterward, we compute the variance of the mean squared deviation for each circuit and observed variable, and for each θ and η combination. We get variances such as :

	R : E	R : A	I : E	I : A	RI : E	RI : A
variance	2.23808	33.0099	2.23775	0.359261	14.0975	10.4884

From this, we can see that the highest variance is the you_R model one, variable A. We then select this variable for the following computations.[1]

Question 9

In FIGURE 8, we show the experimental data and the model output after determining the values of θ and η are using cmaes. We can see in that these values are poorly caracterized for low quantities of inducer. Though, for higher quantities, the model output seems to be similar to the experimental data.

Question 10

As we can see in FIGURE 9, the highest ratio between inducer presence and absence is showed by the you_RI circuit. This circuit shows a $\frac{N_{min.\ inducer}}{N_{max.\ inducer}}$ 8 times higher than the 2 other new circuits. Thus, this is the one we have to use to get a better modulation capability.

[1] A copy/paste error in the odes, resulting in the use of wrong parameters, led to a first wrong request of data (you_RI, variable A). After correcting this mistake, we got a second data set (you_R, variable A)

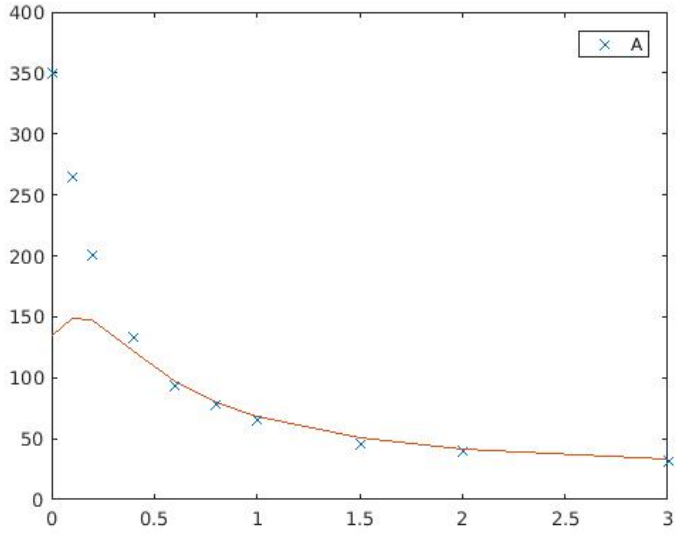

Figure 8: Concentration of A (you_R model) given the quantity of inducer

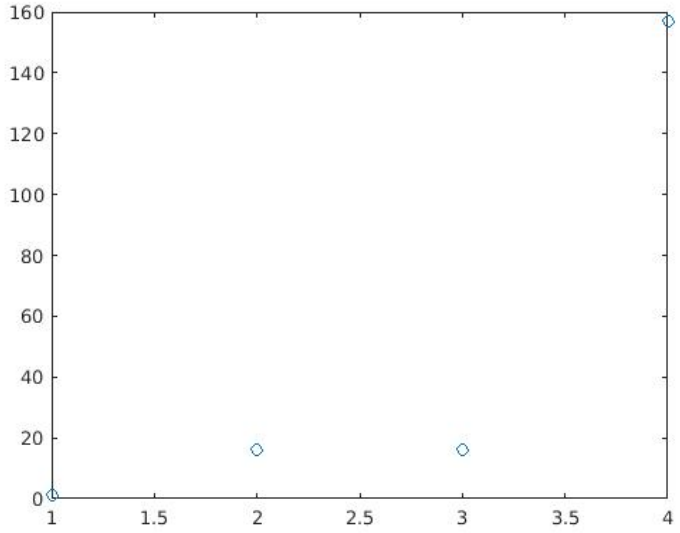

Figure 9: Plot of the $\frac{N_{min.\ inducer}}{N_{max.\ inducer}}$ for the You, you_R, you_I and you_RI models

Conclusion

We can see in FIGURE 10 that we can actually observe a modulation of the cell density using an inducer that we can add to the medium without changing its pH. Thus we can say that our goal has been reached.

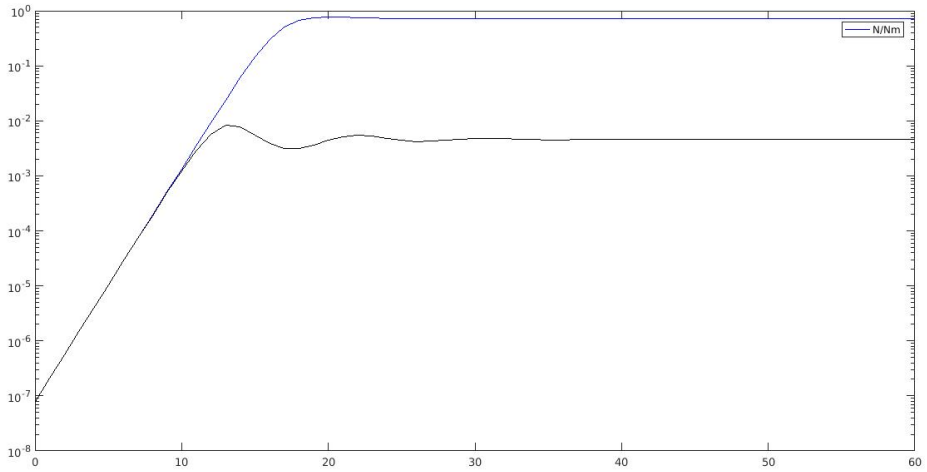

Figure 10: Plot time behaviour of the cell density with the you_RI model