Space-time modelling of a Quorum Sensing system

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Chapter 1

Modelling a toggle switch

1.1 Biological models

1.1.1 Basic model

The basic model of a Toggle switch features two transcription ways. After traduction of the ARNm, the proteins produced in each way repress the promoter of the opposing way. This double repression system ensures the basic function of a toggle switch : When a way is followed in the first time - in our example, by putting some IPTG or aTc molecules in the medium - the system will remain stable in the chosen way. It would then require a much more important concentration of the other protein to switch into the opposing way.

1.1.2 Our model

The biological system we are trying to implement is more complex, on both biological and physical side.
However, the toggle switch model is basically the same. In the study of the toggle switch itself, the system can be reduced to a simple two-ways subsystem that we will then use for the rest of our modelling. The toggle switch itself is not influenced by the rest of the system, if we do not consider the rsma regulatory system that will be modelized at the very end of our work. Thus we will be able to modelize the toggle switch independantly and then build the rest of the model on this basis.

1.2 Mathematical models

1.2.1 Simple toggle switch model

A common model that can be used for toggle switch modelling is as follow :

$$\frac{d[TetR]}{dt} = \frac{\alpha_1}{1+[lacI]^\beta} - [TetR] \tag{1.1}$$

$$\frac{d[lacI]}{dt} = \frac{\alpha_2}{1+[TetR]^\gamma} - [lacI] \tag{1.2}$$

For better understanding of this model we demonstrated it.
The differential equation describing the production of xR is as follow :

$$\frac{d[TetR]}{dt} = k_{plac}[P_{lac\ avail}] - \delta_{TetR}[TetR]$$

With $[P_{lacavail}]$ being the concentration of available binding sites - i.e. not repressed by lacI molecule.
$P_{lacavail}$ is of course related to the total number of promoters plac :

$$[P_{lac\ avail}] + [P_{lac\ -\ lacI}] = [P_{lac\ total}]$$

with $[P_{lac\ -\ lacI}]$ being the concentration of promoters repressed by lacI.
If we set $K_{plac} = \frac{[P_{lac\ avail}][lacI]}{[P_{lac\ -\ lacI}]}$ we get :

$$[P_{lac\ avail}] = \frac{[P_{lac\ total}]}{1+\frac{lacI}{K_{plac}}}$$

We then try to get $[lacI]$:

$$[lacI_{IPTG}] + [lacI] + [lacI_{plac}] = [lacI_{total}]$$

With $[lacI_{IPTG}]$ the concentration of lacI repressed by IPTG and $[lacI_{Plac}]$ the concentration of lacI linked to the promoter. If we set $K_{lacI\ -\ IPTG} = \frac{[lacI][IPTG]}{[lacI_{IPTG}]}$ we get :

$$[lacI] = \frac{[lacI_{total}]}{1 + \frac{[IPTG]}{K_{lacI\ -\ IPTG}}}$$

Which finally gives us our differential equation for TetR :

$$\frac{d[TetR]}{dt} = \frac{k_{plac}[P_{lac\ total}]}{1 + (\frac{[lacI]}{K_{P1}(1+\frac{[IPTG]}{K_{lacI\ -\ IPTG})})^{n_{plac}}} - \delta_{TetR}[TetR] \tag{1.3}$$

With similar calculation we get the differential equation for lacI :

$$\frac{d[lacI]}{dt} = \frac{k_{pTet}[P_{Tet\ total}]}{1 + (\frac{[TetR]}{K_{pTet}(1+\frac{[aTc]}{K_{TetR-aTc}})})^{n_{pTet}}} - \delta_{lacI}[lacI] \tag{1.4}$$

These two equations can be easily computed with a differential solver. With this model we can get a good model of our system with good knowledge of all the factors. We can precisely estimate the effects of each parameter. We get a similar equation to the usual model.

Chapter 2

Quorum Sensing Modelling - Through Space and Time

2.1 Mathematical models

2.1.1 Bangalore 2007 models

Our work mainly refers to the models set up by the 2007 iGem Bangalore team. On the basis of their work we set up models adapted to our own system.
The main difference between our models is that their model is designed for a whole medium, in which the concentrations of quorum sensing molecules are considered for a whole fixed volume of a medium. Our system, however, is supposed to describe the spacial diffusion of quorum sensing molecules as well, and therefore needs to be designed for an infinitesimal volume of medium containing bacteries and outside medium.
A few other differences exist between our model and theirs, mainly due to the fact that the system we intend to describe is made of other different parts. For example the production rate of our Quorum Sensing enzymes are directly linked to the previously described toggle switch model.

For these reasons we strongly recommend getting familiar with the works of the 2007 Bangalore team for an easier understanding of the models we used.

2.1.2 Our Models

Bangalore 07 modelized the behaviour of quorum sensing for a simple quorum sensing system. With the input of the toggle switch model taken into account, we can adapt their equations to our system.

Equations for cinI and cinR

With our toggle switch system the production would be ruled by the regulatory network of lacI and TetR :

$$\frac{d[cinI]}{dt} = \frac{k_{pTet}[P_{Tet\ total}]}{1+(\frac{[TetR]}{K_{pTet}(1+\frac{[aTc]}{K_{TetR-aTc}})})^{n_{pTet}}} - \delta_{cinI}[cinI] \tag{2.1}$$

$$\frac{d[cinR]}{dt} = \frac{k_{plac}[P_{lac\ total}]}{1+(\frac{[lacI]}{K_{P1}(1+\frac{[IPTG]}{K_{lacI\ -\ IPTG}})})^{n_{plac}}} - \delta_{cinR}[cinR] - V_{complexation} \tag{2.2}$$

We can therefore describe the production of cinI and cinR inside the cells. $V_{complexation}$ is the rate of complexation of the cinR molecule in terms of concentration. As a matter of fact cinR will be transformed into cinR* after being complexed with the Quorum Sensing molecules entering the cell. It is now taken into account via this complexation rate.
A simple way to write this rate would be as follow :

$$V_{complexation} = k_{comp}Q_i^n[cinR]$$

with Q_i being the concentration in QS molecule inside the cell. If we consider that only one QS molecule would bind to a cinR molecule, we obtain the following equation for cinR :

$$\frac{d[cinR]}{dt} = \frac{k_{pTet}[P_{Tet\ total}]}{1+(\frac{[TetR]}{K_{pTet}(1+\frac{[aTc]}{K_{TetR-aTc}})})^{n_{pTet}}} - \delta_{cinR}[cinR] - k_{comp}Q_i[cinR] \tag{2.3}$$

Equations for Quorum sensing molecules inside and outside the cells

For the following equations the physical volume considered is an infinitesimal volume of medium along x - i.e. we only consider an $l * dx$ volume of cell, l being the width of our plate and dx an infinitesimal portion of length. In this infinitesimal volume we set a fixed number of non-growing cells and take into account the diffusion from one portion to the next ones.

$$\frac{d[Q_i]}{dt} = \eta([Q_e] - [Q_i]) - \delta_{Qi}[Q_i] + f([cinI]) \tag{2.4}$$

$$\frac{d[Q_e]}{dt} = \rho v_c \eta([Q_i] - [Q_e]) - \delta_{Qe}[Q_e] + D_{diff}\frac{\partial^2[Q_e]}{\partial x^2} \tag{2.5}$$

- With $f([cinI])$ being a mathematical function describing the production of QS molecule by cinI enzyme. Basically this fonction would be as follow :

  $$f([cinI]) = k_{QSp}[substrate]^n[cinI]$$

  But if we consider the reaction as Michaelian, from equation (3.4) we obtain :

  $$\frac{d[Q_i]}{dt} = \eta([Q_e] - [Q_i]) - \delta_{Qi}[Q_i] + k'_{QSp}[cinI] \tag{2.6}$$

- With D_{diff} being the diffusion coefficient for our Quorum sensing molecule in our medium along spatial dimension x.
- In our case ρv_c is a constant (we consider the cells do not grow in our time scale)

With the equations set $(3.1); (3.3); (3.5); (3.6)$ we have, we can not use solvers like matlab ODE because of their space and time dependancies. To solve our problem we have to use a space-time derivation matrix we will describe in the next chapter.

2.2 Solvation ot the set of equations $(3.1); (3.3); (3.5); (3.6)$

2.2.1 The Matrix

To solve this set of equations we have to use a matrix that will describe our system in both space and time. for example for the QS molecule outside of the cell :

$$M_{Qe}(m, n) = [Q_e](x, t)$$

$$M_{Qe}(m+1, n+1) = [Q_e](x + dx, t + dt)$$

$$M_{Qe} = \begin{pmatrix} 0 & \cdots & 0 \\ Q_e(0, dt) & \cdots & Q_e(L, dt) \\ & \ddots & \\ \vdots & Q_e(m \times dx, n \times dt) & \vdots \\ & & \ddots \\ Q_e(0, T) & \cdots & Q_e(L, T) \end{pmatrix}$$

- On the spatial point of view, we only consider the x dimension, as the IPTG gradient will be only evolving along this dimension. Thus we consider the state of our cells is the same along the width of our plate.
- With this Matrix, and after computation of all the terms, we can get the entire behaviour of cinI, cinR, QS inside and outside the cells.

- The first line of the Matrix equals 0. These are the initial conditions we set to 0 at time t = 0s.
- On the borders of the plate (x = 0 and x = L) the model used has to be different, limit conditions will be set.
- Of course, Qi, cinI and cinR matrices will be similarly implemented.

2.2.2 Discretization of the equations set

With our continuous equations set, we want to obtain discrete definition of each of the matrices. The interdependancies of the equations imply that the computation of the matrices will be performed on the entire cinI matrix first, then each line of the Qi and Qe matrices will be computed alternatively. Finally cinR matrix computation will be performed.
Parallel computation of all the matrices without proper control is not possible indeed, as the terms of Qi matrix will depend on the Qe terms of the preceding line (and vice-versa).
Discretization is obtained with first order taylor series :

$$M_{Qi}(m,n+1) = \Delta t(\eta(M_{Qe}(m,n) - M_{Qi}(m,n)) - \delta_{Qi}M_{Qi}(m,n) + k_{QSp}M_{cinI}(m,n)) + M_{Qi}(m,n) \tag{2.7}$$

$$M_{Qe}(m,n+1) = \Delta t(D_m + D_{diff}\frac{M_{Qe}(m+1,n) - 2M_{Qe}(m,n) + M_{Qe}(m-1,n)}{\Delta x^2}) + M_{Qe}(m,n) \tag{2.8}$$

$$with\ D_m = \rho v_c \eta M_{Qi}(m,n) - M_{Qe}(m,n)(\delta_{Qe} + \rho v_c \eta)$$

$$M_{cinR}(m,n+1) = \Delta t(\frac{k_{pTet}[P_{Tet\ total}]}{1 + (\frac{[TetR]}{K_{pTet}(1+\frac{[aTc]}{K_{TetR-aTc}})})^{n_{pTet}}} - M_{cinR}(m,n)(\delta_{cinR} - k_{comp}M_{Qi}(m,n))) + M_{cinR}(m,n) \tag{2.9}$$

With these discrete equations the 4 matrices can be computed through simple calculation loops over each line. The cinI matrix does not depend on space dimension, it is then possible to compute it without discretization with a differential solver.