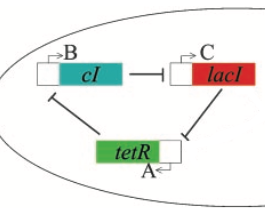
**Building Quorum Sensing into the Repressilator**

**Model adapted from:**

Jordi Garcia-Ojalvo, Michael B. Elowitz, and Steven H. Strogatz

***Modeling a synthetic multicellular clock: Repressilators coupled by quorum sensing*** PNAS 2004 101 (30) 10955-10960; published ahead of print July 15, 2004, doi:10.1073/pnas.0307095101

**Model Equations**

You should be familiar with the Repressilator oscillator system. This involves a plasmid that includes genes to encoding three proteins cI, LacI, TetR which are inhibit each other in a cyclic arrangement:

The model uses the following ODEs:

***mRNA production / degradation***

***protein production / degradation***

Garcia-Ojalvo et. al. propose a modification of the Repressilator to study how cells can behave collectively when quorum sensing is added into the system.

They suggest using an additional plasmid that contains genes to encode LacI and AI with promoter regions designed so that:

* expression of AI is repressed by LacI
* expression of LacI is activated by AI

Let’s adapt our equations to build a model for this.

**Including AI**

The expression of AI can be modelled in the same ways as LacI, CI and TetR:

**LacI production**

In addition to this we must note that the new plasmid produces LacI mRNA when activated by AI. This can be modelled using the following modification:

**Diffusion terms**

As well as production and degradation, we need to model the diffusion processes that enable protein AI to diffuse in and out of cells. This allows cells to influence each other’s gene expression levels.

To include this we need to add variable into the model to track the extracellular concentration of protein AI, and include the process of diffusion between the cell and extracellular space:

Here new parameters are:

rate of diffusion of protein AI into/out of cell

V accounts for the larger volume of the extracellular space

rate at which AI in the extrcellular space is lost

The resulting model for the modified Repressilator is therefore:

***mRNA production / degradation***

***protein production / degradation / diffusion***

***extracellular protein diffusion / degradation***

Open file repressilator\_quorum\_template.py.

This contains the basic code to model a two cell repressilator system, but does not yet include the diffusion processes.

**Tasks**

**1) Run the code.**

The plot produced displays the observations of protein levels in cell 1 (red) cell 2 (blue) and extracellular volume (black).

Note:

* the top plot shows the LacI protein level,
* the middle plot shows LacI mRNA,
* the bottom plot shows cellular and extracellular AI protein levels.

You should see that:

* on the bottom plot external level of AI (black line) stays at zero as no diffusion is included yet.
* the cells oscillate but are out of time with each other.

The cells are out of step because the code specifies different initial conditions for each cell:

* cell 1 starts with LacI mRNA =4 (all other levels zero)
* cell 2 starts with TetR mRNA=4 (all other levels zero)

This means that although the cells oscillate they are not synchronised.

**2)** **Edit the model to include diffusion.**

Hint. edit lines: 35, 69, 40, 74, 83

You should find that when AI is allowed to diffuse into/out of the extracellular space, the cells couple so that their oscillations synchronise and fall into step with each other.

**3) Produce plots showing the system behaviour, with and without quorum sensing** (e.g. set k\_diff=0 to prevent cell-to-cell interaction)