**Modelling gene circuits using DDE simulations**

In this example we will compare simulations of the Repressilator system using both ODE and DDE models.

**DDE models**

Typically analysis of synthetic circuits uses ODE models in which rates of production/loss/transport are calculated using the current state of the system.

This neglects the time delays inherent in gene regulatory systems, in particular the time taken for mRNA transcription and protein translation. Here we will assume both processes require around ~1 min to complete.

To fully account for these delays we can use delayed differential equation DDE models.

In the case of the repressilator, the standard ODE model involves mRNA production terms like:

However at a given time point the amount of mRNA produced will depend upon the level of the repressor at the time that transcription began (~1 min previously). To account for this we can modify the equation into the delay differential equation:

Here the term means that in the calculation we do not use the current level of protein ), but instead use the level present in the system a time in the past (where is the delay that exists between initiation of transcription to release of completed mRNA).

Similarly the delay differential equation for protein production is:

Here the term means we do not use the current level of but the level that was present at a time in the past (where is the delay that exists between initiation of translation to release of completed protein).

Note: Because the terms involved in delay differential equations combine variable values from different time-points they are more difficult to analyse and solve mathematically.

They are also harder to work with computationally, as standard libraries for solving ODEs cannot be used, and dealing with past simulation values can cuase difficulties when adapting standard algorithms for numerical integration. Methods must also record and store a record of the past states of the system as the simulation progresses.

**Tasks**

**1) Examine the Python code file provided**

Open file repressilator\_dde.py

At the top of this file (lines 8 to 80) there are some functions needed to be able to work with DDE models.

Below these functions there is code that can be used to generate a comparison of the ODE and DDE simulations.

The function sdot\_ODE contains the standard ODE model for the Repressilator, which can be simulated using odeint in the standard way, e.g.

s\_obs1=odeint(sdot\_ODE,s0,t\_obs,args=(param,))

The function sdot\_DDE contains part-modifed code that will form the basis of our DDE model. To simulate this we can use a similar command ddeint:

s\_obs2=ddeint(sdot\_DDE,s0,t\_obs,args=(param,))

To use this method we need to adapt our sdot function so that references to the state vector s are be replaced by calls to return the state at a given timepoint.

e.g. s(t) returns state vector containing current levels of species

s(t-T) returns state vector containing past levels of species

In the sdot\_DDE function we need to work with both the current protein/mRNA levels, and the levels as existed 60 seconds previously (we assume transcription and translation both take 1 minute).

# load current levels of proteins/mRNA

(p\_LacI, p\_TetR, p\_CI, m\_LacI, m\_TetR, m\_CI) = s(t)

# transcription / translation delay both set as 60 seconds

delay = 60

# load past levels of proteins/mRNA present 60 seconds previously

(pd\_LacI, pd\_TetR, pd\_CI, md\_LacI, md\_TetR, md\_CI) = s(t-delay)

**2) Complete the code.**

At the moment the DDE model has not been updated to utilise the past levels of protein / mRNA loaded.

Complete the code by editing the expressions for protein and mRNA production, so that where appropriate they refer to the past mRNA/protein levels (at initiation of transcription/translation) rather than current values (i.e. replace p\_LacI by pd\_LacI in the calculations etc.)

**3) Examine the result.**

Compare the results of the ODE and DDE simulations (you should find they are non-identical but broadly similar).

In particular we are most interested in considering how the behaviour of the limit cycles reached change.

Generally when simulating and analysing the behaviour of the Repressilator an ODE model is used. How does this figure you created validate this approach?