Dynamic Models in Biology
Computer Lab: Oscillatory gene expression

With so much physiology operating in an oscillatory manner, it should not be surprising to learn that, in many physiological systems, gene expression operates in an oscillatory manner, because rhythmic gene expression has to be coordinated to, and in some cases actually drive, these rhythmic processes. Therefore, cells have evolved mechanisms to produce oscillatory gene expression. Most of these mechanisms depend on some kind of negative feedback, where the gene produces a product that inhibits that very gene. A good example is the tumor suppressor gene called p53. It has been called "the guardian of the genome", "the guardian angel gene", and the "master watchman", referring to its role in conserving stability by preventing genome mutation.

In this lab, based on work from Uri Alon's group at the Weizmann Institute and described in part by Alan Garfinkel at UCLA, you will investigate a model of p53 dynamics that produce oscillations.

p53 model

After damage to DNA (by radiation, in this case), p53 levels are known to rise. p53 induces the production of another protein called Mdm2, and Mdm2 actually inhibits p53 and increases p53 degradation.

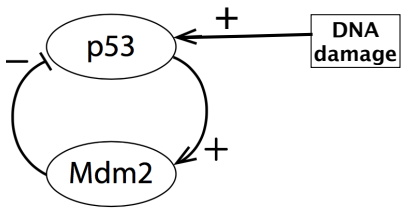

Figure 1: p53 and Mdm2 feedback loop.

This is clearly a negative feedback loop. However, the function of this negative feedback loop was not immediately clear to scientists. Some speculated that its function was to ensure "stability" of this critical protein, by providing a kind of thermostat-like control of its level.

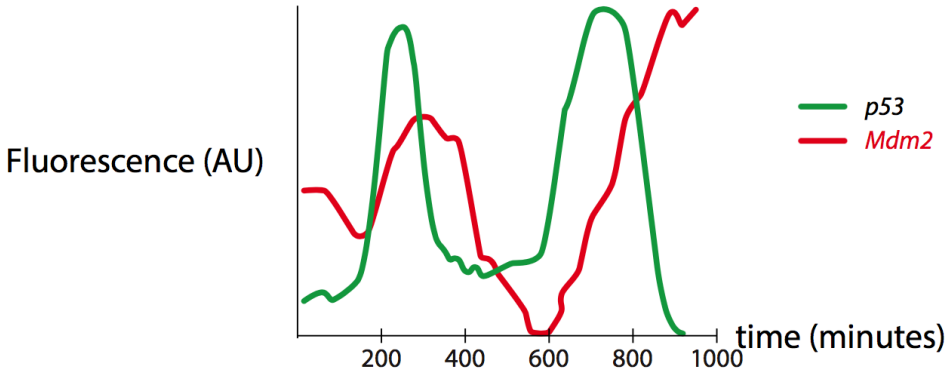

Figure 2: p53 and Mdm2 oscillations. Garfinkel et al. Modeling Life: Redrawn from G. Lahav, N. Rosenfeld, A. Sigal, N. Geva-Zatorsky, A. J. Levine, M. B. Elowitz, and U. Alon, Dynamics of the p53-mdm2 feedback loop in individual cells, Nature Genetics, 36(2):147-150; 2004.

Then, one group actually followed the expression of the two genes over time. They found that "p53 was expressed in a series of discrete pulses after DNA damage". The two genes were expressed in an oscillatory manner, with p53 expression always leading that of Mdm2 (Fig. 2).

They developed a model which postulates an upstream activator of p53, which they call S, and could therefore be a protein that is produced by damaged DNA.[1]

- S then activates p53 ($= X$) in a sigmoidal manner, which then activates Mdm2 ($= Y$) after a time delay τ. This is the primary event post-DNA damage.
- Mdm2 then combines with p53 to degrade it, resulting in a XY term in the $\dot{X}$ equation.
- Mdm2 is degraded at a rate proportional to its concentration.
- The S protein is assumed to be produced at a constant rate β_S, and then Mdm2 combines with S to degrade it, producing the SY term in the $\dot{S}$ equation.

[1] N. Geva-Zatorsky, N. Rosenfeld, S. Itzkovitz, R. Milo, A. Sigal, E. Dekel, T. Yarnitzky, Y. Liron, P. Polak, G. Lahav, and U. Alon, Oscillations and variability in the p53 system, Molecular Systems Biology 13; 2006

This results in a set of differential equations:

$$\text{p53} \qquad \dot{X} = \beta_x \frac{S^n}{1+S^n} - \alpha_{xy} XY$$

$$\text{Mdm2} \qquad \dot{Y} = \beta_y X(t-\tau) - \alpha_y Y$$

$$\text{DNA damage molecule} \qquad \dot{S} = \beta_s - \alpha_s Y S$$

Matlab file
In the Matlab program `p53_lab4.m`, numerical integration of this model is implemented. Because the model contains a delay differential equation, we use a special solver in Matlab, called `dde23`. The call to this solver is mostly similar to the call to the `ode45` solver, in that you give the equations as a function, you specify the time interval over which the integration will take place, and you can define optional settings such as error tolerances. An important difference is in the initial conditions. Whereas for ordinary differential equation systems you specify one initial value for each state variable, for a delay differential equation, a function of values are required, specifying the value of the state variable back to τ time units ago. In the `p53_lab4.m` program, the `p53hist` function specifies constant function initial conditions. Finally, the `dde23` needs the lag τ as a parameter.

Oscillations
Run the `p53_lab4.m` program and confirm the existence of oscillations in gene expression in the p53 model system.

What is the period of oscillation? How does that correspond to the period seen in the experiments? 6 hours? quite close

Effects of initial conditions
Vary the initial conditions to see if there are other stable attractors. Are there? No

Increased DNA damage
Simulate increased DNA damage by doubling the value of the parameter β_S. How are the dynamics changed? What is the period of the oscillation now? near 5.6 hours

decrease T
decrease amplitude

Stop the oscillation
Can you make the oscillations go away by changing the value of a model parameter? Identify two different model parameters, for which changes (increase or decrease) might kill the oscillation. Try these modifications out in simulations. Were you right?

I suppose tao, betax and n.

for decrease the tao(0.45) by half: it works

for decrease the betax(0.3): it works

for decrease the n(2): it works

or to minimize the influence of I equation
as if just two equation, it would probably no oscillation

betay = 0.2 works

increase alphay to 3 works

increase alphaxy to 10

decrease betas to 0.2

increase alphas to 20 works

A different model

The group actually developed a series of models reflecting various hypotheses about the mechanism producing the oscillatory gene expression. The models all produce oscillations, but each has its own characteristic frequency, amplitude, and waveform, which can be used to choose one model over another. One of these models did not include the unknown S protein but assumed a production of p53 set by a constant parameter. The differential equations for this model are:

$$\dot{X} = \beta_x - \alpha_{xy} XY$$
$$\dot{Y} = \beta_y X(t - \tau) - \alpha_y Y$$

The parameter values of this model are: $\tau = 6.3$ hrs, $\beta_x = 2.3$ hrs^{-1}, $\beta_y = 24$ hrs^{-1}, $\alpha_{xy} = 120$ hrs^{-1}, and $\alpha_y = 24$ hrs^{-1}.

Implement this model in Matlab. (You will probably want to copy the `p53_lab4.m` into a new file, e.g., `p53_lab4_alternative_model.m`, and edit the new file).

Model comparison

Run the new (alternative) model. How are the dynamics different from those of the first model? phase shift and amplitude T = 12.66

Based on the phase shift between p53 and Mdm2 (i.e., the time difference between their peaks) in the experiments shown in Fig. 2, which of the two models do you think is best? time difference for peak is 6.3 the first one is the best

Simulate increased DNA damage in the new model by doubling the value of the parameter β_x. What happens with this change? Is there a change in the period of the oscillation? T = 12.4, change in period

The researchers found that in their experiments, the frequency of p53 oscillations would increase with increased DNA damage. Based on this finding, which of the two models would you pick as the one that best reproduces the experimental data? both frequency would increase

High cellular levels of p53 can easily be toxic, and it is thought that increasing the frequency of p53 oscillations, rather than increasing the p53 amplitude, in response to increased DNA damage, protects the cells.