Modelling Biochemical Reaction Networks

Lecture 17:
Modeling the cell cycle, Part I

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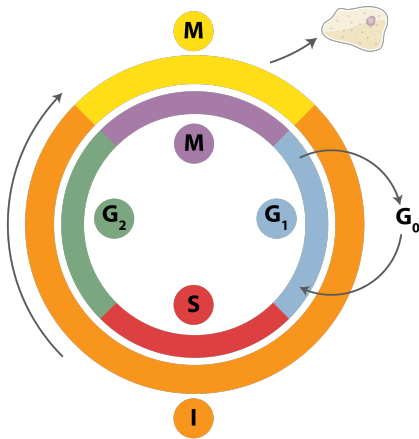
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Recommended reading

- Fall, Marland, Wagner and Tyson, sections 10.1–10.3

The cell cycle

Cell cycle phases

M: Mitosis

G_1:   1st "gap" phase

S: DNA Synthesis

G_2:   2nd "gap" phase

G_0:   resting state

Source: Richard Wheeler, Creative Commons license

Hierarchical model building

- We can treat very complex models, but there are at least two reasons to start with simple models:
  - Experimental knowledge of a system often doesn't justify a complex model.
  - We can understand small models thoroughly, and then use the intuition developed while studying small models to understand the larger models.
- This implies a hierarchical strategy, where we build larger models by adding details to smaller models.
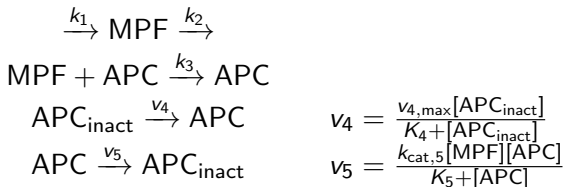
A two-variable model of the cell cycle
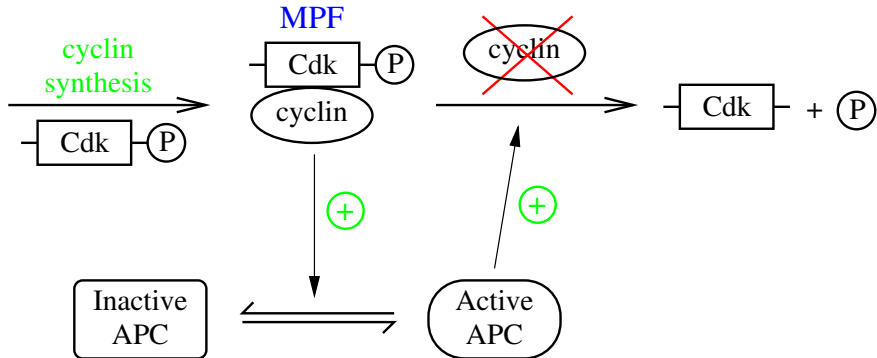
MPF (mitosis promoting factor) promotes "start"
(G$_1$ to S).

APC (anaphase promoting complex) promotes "finish"
(final events of M).

A two-variable model of the cell cycle

- A few additional facts:
    - Cyclin is synthesized at a constant rate.
    - Cdk = cyclin-dependent kinase
    - There is a roughly constant pool of Cdk.
    - MPF (Cdk/cyclin) inactivates APC by phosphorylating it at an inhibitory site.
    - There is a roughly constant pool of APC.
    - APC is activated by a phosphatase that removes the inhibitory phosphate.
    - APC tags cyclin with ubiquitin, which marks it for destruction by the cell's proteolytic machinery.
    - There will be some cyclin degradation even in the absence of APC.

A two-variable model of the cell cycle

$$\xrightarrow{k_1} \text{MPF} \xrightarrow{k_2}$$

$$\text{MPF} + \text{APC} \xrightarrow{k_3} \text{APC}$$

$$\text{APC}_{\text{inact}} \xrightarrow{v_4} \text{APC} \qquad v_4 = \frac{v_{4,\text{max}}[\text{APC}_{\text{inact}}]}{K_4 + [\text{APC}_{\text{inact}}]}$$

$$\text{APC} \xrightarrow{v_5} \text{APC}_{\text{inact}} \qquad v_5 = \frac{k_{\text{cat},5}[\text{MPF}][\text{APC}]}{K_5 + [\text{APC}]}$$

$$\frac{d[\text{MPF}]}{dt} = k_1 - k_2[\text{MPF}] - k_3[\text{MPF}][\text{APC}]$$

$$\frac{d[\text{APC}]}{dt} = v_4 - v_5$$

$$[\text{APC}] + [\text{APC}_{\text{inact}}] = [\text{APC}]_{\text{total}}$$

A two-variable model of the cell cycle
Parameters

$$k_1 = 0.04\,\text{min}^{-1} \qquad v_{4,\text{max}} = 1.5\,\text{min}^{-1}$$
$$k_2 = 0.04\,\text{min}^{-1} \qquad K_4 = 0.04$$
$$k_3 = 1\,\text{min}^{-1} \qquad k_{\text{cat},5} = 10\,\text{min}^{-1}$$
$$[\text{APC}]_{\text{total}} = 1 \qquad K_5 = 0.04$$

Sources:

- Textbook, Table 10.1
- For $[\text{APC}]_{\text{total}}$, note the term $1 - Y$ for the substrate concentration in eq. (10.2) on p. 266. This implies that the concentrations of various forms of APC are measured relative to the total size of the pool.
- Some of the parameters of this model correspond to terms involving m, the cell mass, in the textbook. I picked $m = 0.3$ because of the biologically relevant behavior near this m.

Bistability

- If you run the model from different initial conditions, you will notice that two different steady states can be reached without changing the parameters.
  This is called bistability.

- One state has a high MPF concentration, corresponding to the $S/G_2/M$ phases, while the other has a low MPF concentration, corresponding to G_1.

Investigating bistability using ***xppaut***

- Load a steady state into the initial conditions, either by running the model for a long time, then doing `Initialconds`→`Last`, or by using `Sing pts` to find a steady state, and then hitting the `Import` button in the `Equilibria` window.
- Click on `File`→`Auto`. This starts up `auto` (the `aut` part of `xppaut`), a system for automated continuation of solutions.
- Conceptually, automated continuation involves making small changes to a parameter and seeing how a solution (e.g. a steady state) changes.

Investigating bistability using $xppaut$

► We're going to vary $v_{4,\max}$. Click on the `Parameter` button in `auto` and make sure that `v4max` is one of the parameters listed there. The parameters in this window are the only ones you can vary in `auto` due to some limitations of the software. If `v4max` isn't listed, replace one of the parameters (any one) with this one. Click on the `Ok` button when you're done.

► Click on the `Axes` button, the select `hI-lo`. Set up the axes as follows, then click `Ok`:

       Y-axis: MPF
    Main Parm: v4max
         Xmin: 0
         Ymin: 0
         Xmax: 4
         Ymax: 1

Investigating bistability using ***xppaut***

▶ Click on the Numerics button in auto.

▶ There are a lot of numerical parameters, but only some of them are relevant to us:

> Par Min: 0
>
> Par Max: 4
>
> Ds: 0.001 [Suggested step size along the parameter axis]
>
> Dsmin: 0.0001 [Minimum step size]
>
> Dsmax: 0.1 [Maximum step size]
>
> Nmax: Maximum number of points to compute, i.e. the maximum number of values of the parameter to consider. Default value OK.
>
> NPr: 20. Output full information on every NPr'th point.

Investigating bistability using ***xppaut***

- ▶ Click on Run→Steady state.
- ▶ Auto will generate a branch of steady states.
- ▶ Click on Grab. You can move between labeled points in your diagram using the tab key. You should see two points of type EP (end point). These are the point you started at and the point where auto stopped the computation.
- ▶ Move to your starting point (v4max=1.5) and hit the Enter key. This sets up auto to start from this point.
- ▶ In the numerics menu, change Ds to −0.001, the click on Run.

Continuation results

▶ If all went well, you should have a diagram such as the following:
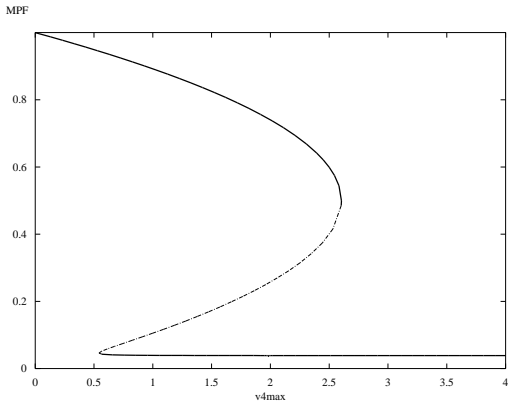
Continuation results

▶ What it means:
  ▶ There is a region of bistability between $v_{4,\max} = 0.5418$ and 2.604 (the points labeled LP—limit point—in the `auto` diagram). For values of $v_{4,\max}$ in this range, the cell cycle control system can be in either of the two states previously described.
  ▶ The two stable steady states are separated by an unstable steady state.
  ▶ Outside of this range, only one steady state exists.
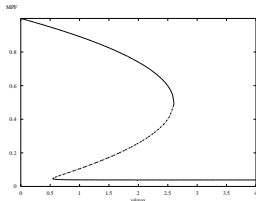
Hysteresis

- Imagine slowly increasing $v_{4,\max}$, with MPF originally on the lower steady-state branch.
- Eventually come to the end of that branch and jump up to the stable high-MPF steady state
- Now imagine slowly decreasing $v_{4,\max}$.
- Eventually jump down to the lower steady state
- Jumps occur at different values of $v_{4,\max}$: hysteresis

Hysteresis
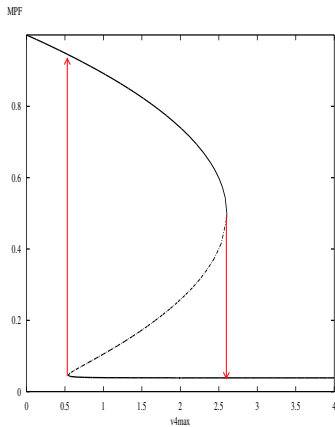
$v_{4,\max} \propto [Cdc14]$ and Cdc14 is indirectly activated by MPF...