

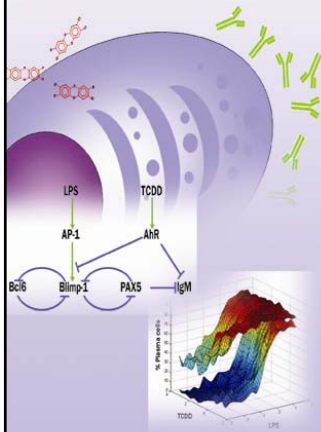
Wednesday Afternoon Exercise 1:

Modeling a Simple Cell Cycle Circuit and Checkpoint Control

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Objectives

1. Understand what types of response motifs are involved in and how they are connected into a circuit driving transitions through the eukaryotic cell cycle.
2. Understand how checkpoint control is enforced, and how DNA damage affects the cell cycle (delay, lengthening, and arrest).

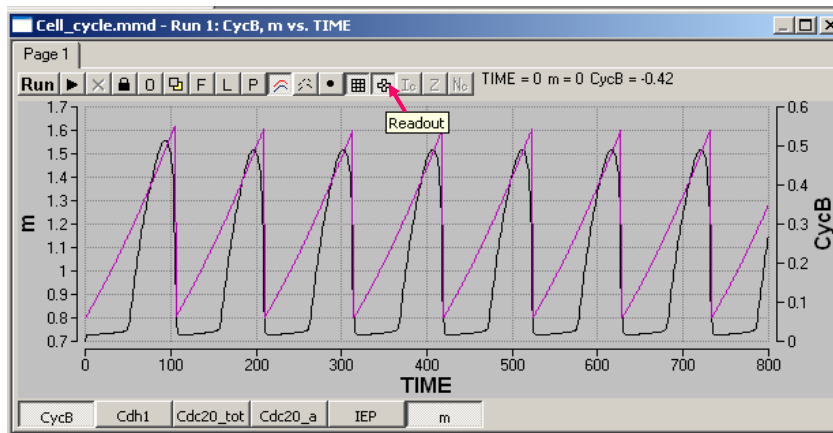
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Running the cell cycle model for the first time

1. Open Cell-cycle.mmd
(Exercises/Wednesday/Cell_cycle.mmd)
2. Examine model code
3. Run model (Click “Run” button on Equation window)

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4. Examine the oscillatory changes of variables (If a variable is not available for display as a tab, go to menu “Graph” → “Choose Variables”, then add the variable to Y axis)



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Running the cell cycle model for the first time

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5. Using “readout” tool (see the previous slide), measure the period of the cell cycle by taking the average from a few cycles (the time unit is minute).
6. Compare the phases between CycB and Cdh1. Are they opposite to each other? Why?
7. With respect to CycB and Cdh1, which part of the cycle is G1? Which part is S-G2-M? How is this related to cell mass?
8. Examine the phases between CycB, IEP, and Cdc20_a. Why does Cdc20_a look relatively delayed?
9. Examine the cell mass (m). At what point does it get halved (signifying cell division) with respect to CycB ?

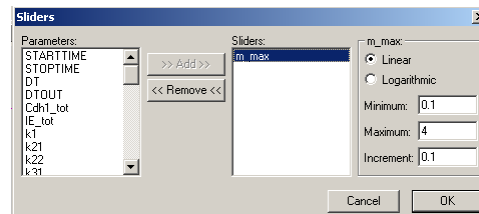
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Cell mass threshold for G1 to S-G2-M transition

Recall that the cell mass has to reach a threshold to trigger G1 to S-G2-M transition. In this exercise you will find that threshold approximately by changing the maximum mass (m_{max}) the cell is allowed to grow to.

1. Go to menu “Parameters” → “Define Sliders”
2. In the pop-up window, add m_{max} to the slider, then set values as shown at right.

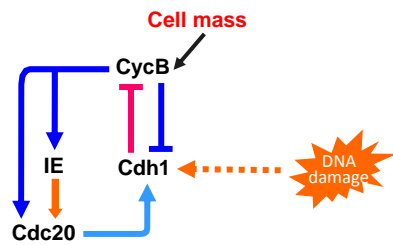
3. Click “OK”.



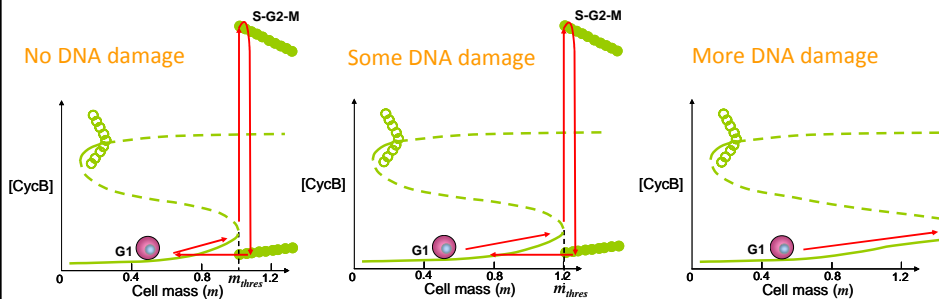
4. Use the slider to decrease m_{max} until the cell cycle is lost.
5. When the cell cycle is lost, the cell stays at G1 or S-G2-M? (Hint: look at CycB and Cdh1 levels)

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G1 DNA Damage Checkpoint Control



- By activating Cdh1, DNA damage causes an increase in the cell mass threshold for G1 to S-G2-M transition (Pinocchio effect), thus delaying and lengthening the cell cycle.
- Too much DNA damage may increase the threshold value beyond the maximal mass to which the cell can grow, resulting in cell cycle arrest at G1.



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Simulating G1 DNA damage checkpoint control

1. Go to Equation window, add "+ k33*DNA_damage" to Cdh1' equation: $Cdh1' = (k31 + k32 * Cdc20_a + k33 * DNA_damage) * (Cdh1_tot - \dots$
2. Go to the end of the Equation window, add the following code:

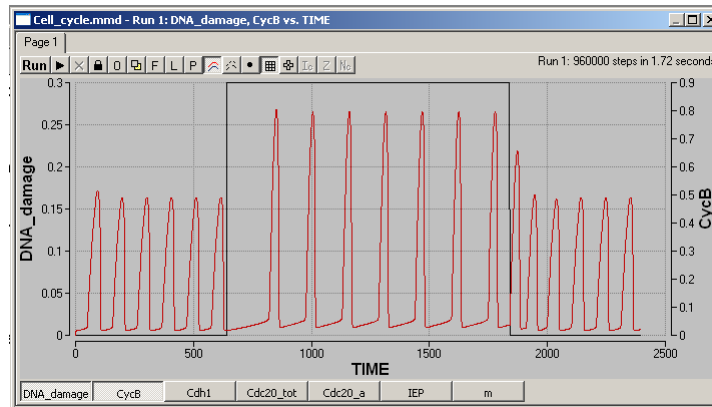

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      ;<-----DNA damage parameter----->
      k33      = 4
      ;The following 4-line code generates a pulse of DNA damage
      DNA_damage_amount    = 0.3
      DNA_damage_onset     = 640 ; in minute
      DNA_damage_duration  = 1200 ; in minute
      DNA_damage = DNA_damage_amount * SQUAREPULSE(DNA_damage_onset,
      DNA_damage_duration)
      
```
3. Go to menu "Parameters" → "Parameter Window", in the Parameter window, set STOPTIME to 2400. Hit "Run".

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Simulating G1 DNA damage checkpoint control

4. Go to menu "Graph" → "Choose Variables", in the pop-up "Choose Variable" window, add "DNA_damage" to Y-axis if not there already, click "OK". Then click button "Run" on the graph window. You should see something as shown below.



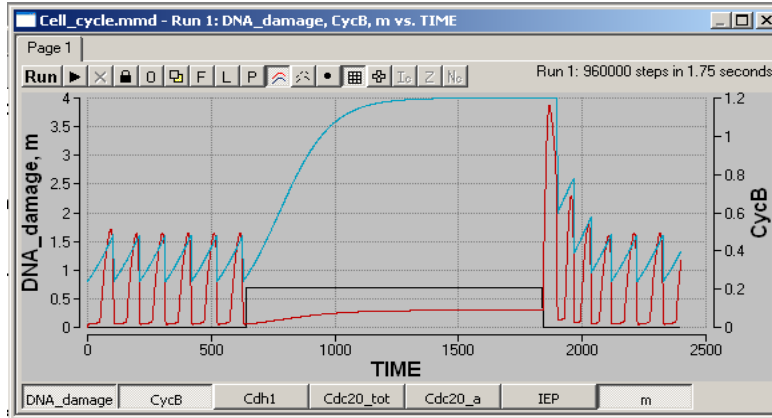
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Simulating G1 DNA damage checkpoint control

5. Observe what happens to the first cell cycle after the onset of DNA damage. How about subsequent cycles? Are they lengthened? Explain why. Observe changes in the cell mass.
6. In the Parameter window, increase DNA_damage_amount to 0.5, hit "Run", observe changes to the cell cycle.

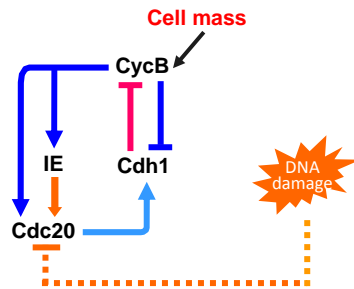
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7. In the Parameter window, increase DNA_damage_amount to 0.8, hit "Run". Is the cell still cycling? If not, is it arrested at G1 or S-G2-M phase? What happens after the offset of DNA damage? Does the cycle resume?

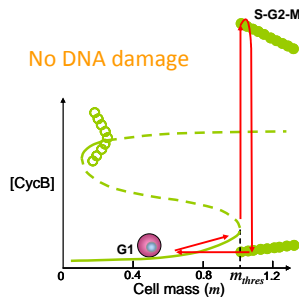


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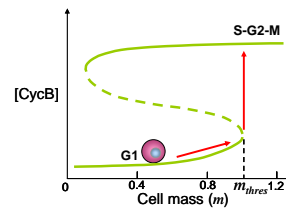
S-G2-M (Finish) DNA Damage Checkpoint Control



- DNA damage at S, G2 can inhibit Cdc20, weakening or blocking the (-) feedback loop. Without (-) feedback functioning, oscillation is lost and CycB is stabilized at high levels, leading to cell cycle arrest at S-G2-M.



DNA damage



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Simulating S-G2-M DNA damage checkpoint control

1. Go to Equation window, add “ $+k81 * DNA_damage$ ” to Cdc20_a’ equation: $Cdc20_a' = \dots + Cdc20_tot - Cdc20_a - (k8 + k81 * DNA_damage) * \dots$
2. Go to the end of the Equation window, add “ $k81=0.4$ ” in the place as shown below:
;<-----DNA damage parameter----->
k33 = 4
 $k81 = 0.4$
;The following 4-line code generates a pulse of DNA damage
3. Go to menu “Parameters” → “Parameter Window”, in the Parameter window, set “DNA_damage_amount” to 1, set “DNA_damage_onset” to 510, then hit “Run”.

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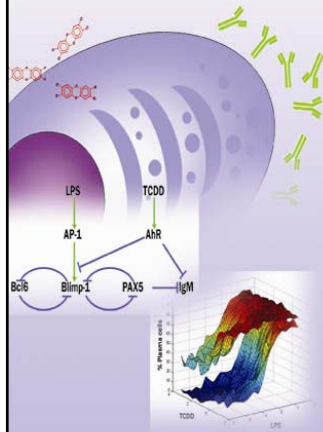
Simulating S-G2-M DNA damage checkpoint control

4. Observe what happens to the cell cycle. If the cycle is lost, it is arrested at G1 or S-G2-M? If arrested at S-G2-M, how is it related to the time of the onset of DNA damage?
5. In the Parameter window, change “DNA_damage_onset” to 450 (this shifts the onset of DNA damage to G1 phase), then hit “Run”. Observe at which phase the cell cycle is arrested.

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Exercise Summary

Modeling a Simple Cell Cycle Circuit and Checkpoint Control



- The cell cycle is highly conserved throughout biological organisms.
- These computational approaches have been used to understand cycle dynamics (see publications by Tyson and colleagues).
- The relationships of cell cycle and interactions with checkpoints are important for understanding response to DNA-damaging agents, cancer and mutational processes.