Working one model through

Goldbeter, 1991 modified

What we will do

- Brief intro to biology: cell cycle
- Work in groups not from same discipline
- Hands on exercise
- Examine Stella version of Goldbeter model.

Done at Beloit and we will do

- Research Course
- Students perform as scientists
- Introduced 4-5week module on modeling the cell cycle
- Students worked in groups not from same year
  - on first exercise only

- Hands on exercise
- Perform as science students
  - New to topic
  - Some understanding
  - Different skills
- First modeling exercises
- Work in groups with multiple disciplines.

Cell Cycle/ Cell division

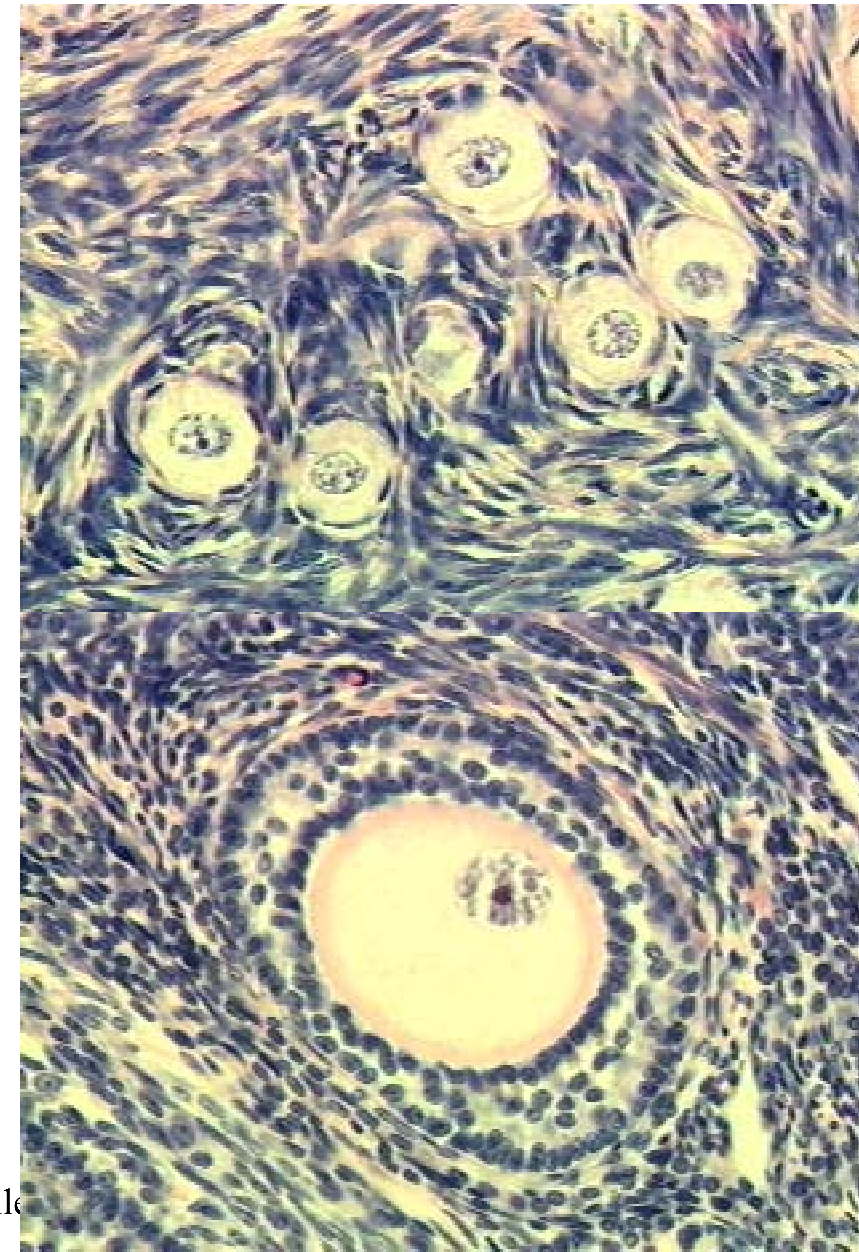
- What do we know?
  - A collective version/story

- Why do we care?
  - A collective version/story

Group sharing or improvisation

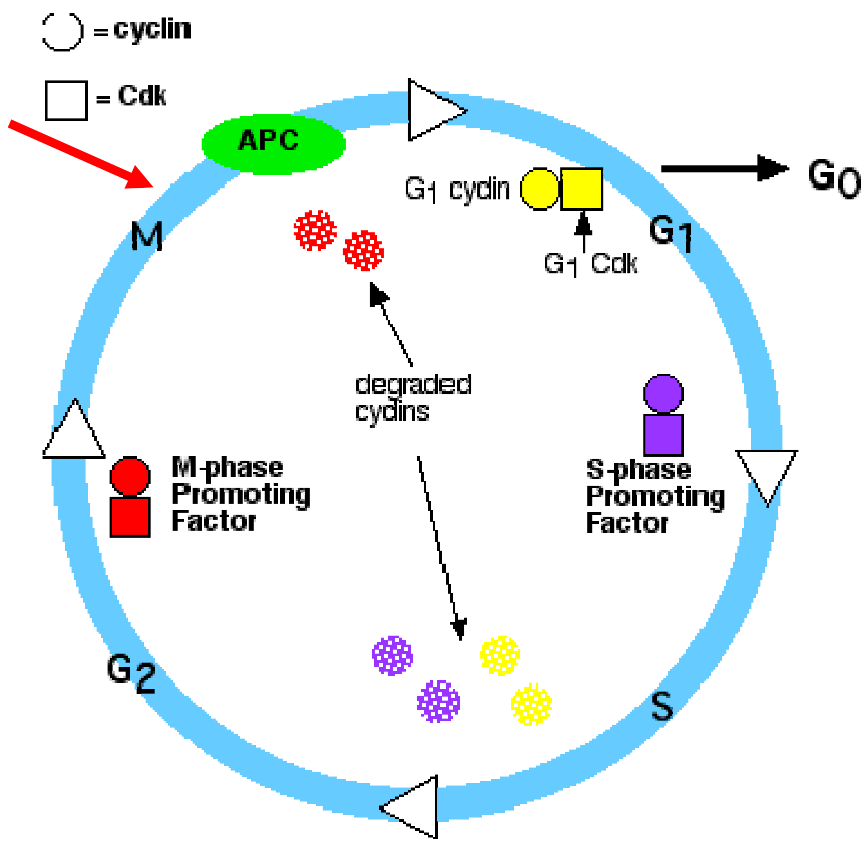
Cell: Cycles and Growth

Cells in the tip of an onion root



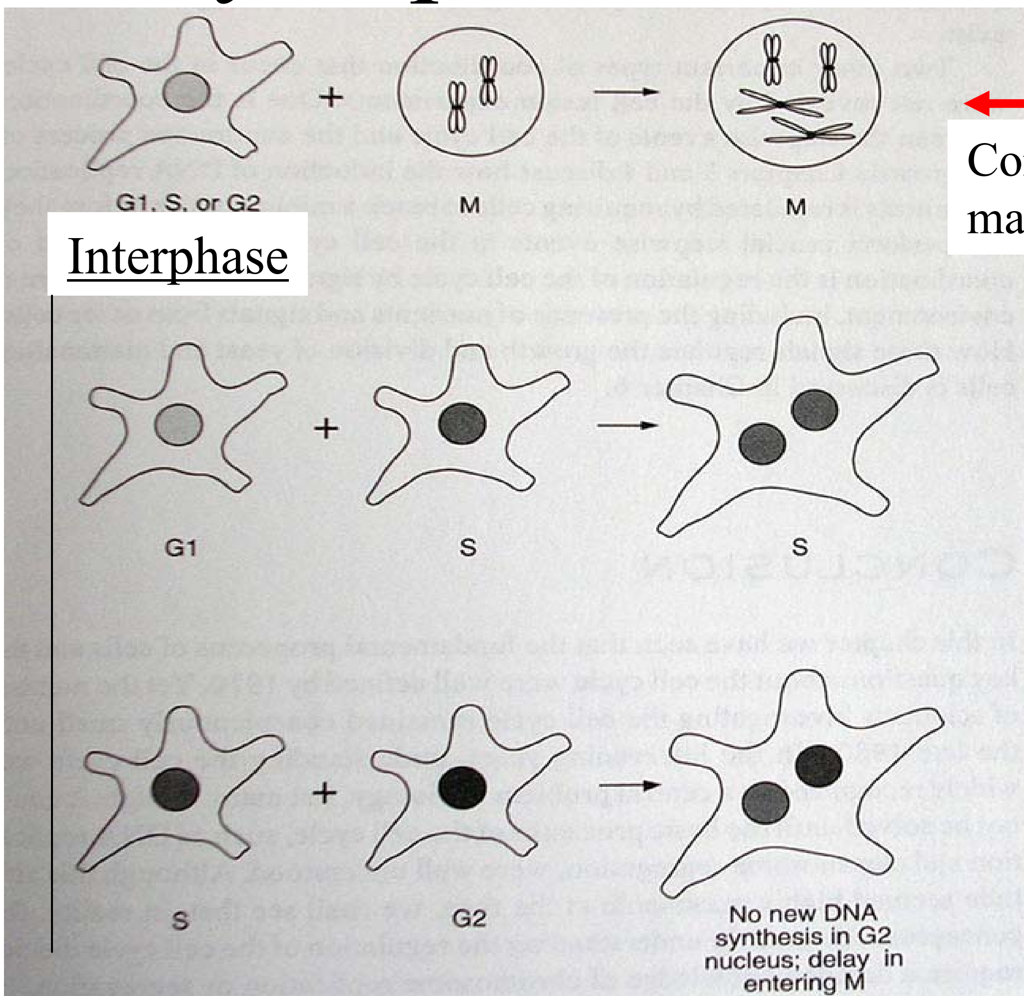
Gap phases (G1, G2)
Synthesis (S phase)
Mitosis (M phase)

Cell Cycle and Phases



Interphase (G1, S, G2)
M-phase (M)

Key experiments identify MPF



Condensed DNA is marker for mitotic state

Interphase

FIGURE 1-10 Cell fusion experiments. Fusing mammalian cells at different stages of the cell cycle revealed the logic of the cycle. Fusing cells at any stage of the cell cycle to mitotic cells produced hybrid cells in which all the nuclei entered mitosis (M). Fusing G1 cells to S phase cells induced the G1 nucleus to enter DNA synthesis. By contrast, fusing G2 cells to S phase cells did not induce the G2 nucleus to replicate its DNA, demonstrating a block to rereplication. References: Rao, P. N., & Johnson, R. T. *Nature* **225**, 159–164 (1970); Johnson, R. T., & Rao, P. N. *Nature* **226**, 717–722 (1970).

Murray and Hunt, 1993. The Cell Cycle

Key experiments contd.

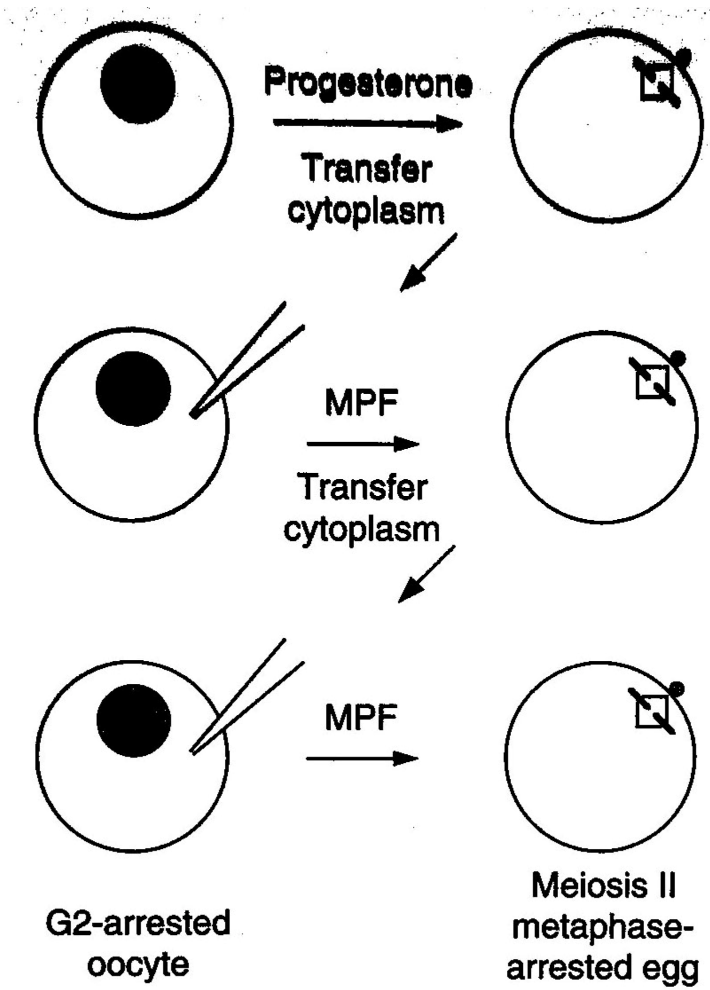
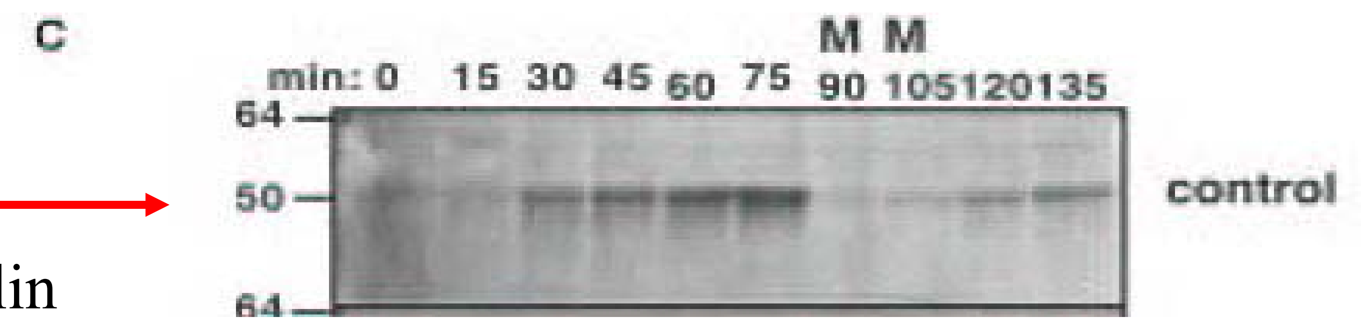


FIGURE 2-5 Discovery of MPF. Oocytes induced to mature into unfertilized eggs by treatment with progesterone are used to donate cytoplasm to untreated oocytes. The transferred cytoplasm contains active MPF which induces the recipient oocytes to enter meiosis. Maturation induces the activation of MPF in the recipient oocyte, allowing it to act as a cytoplasmic donor that can induce meiosis in a fresh round of recipient oocytes. Reference: Masui, Y., & Markert, C. L. *J. Exp. Zool.* **177**, 129–145 (1971).

Murray and Hunt, 1993. The Cell Cycle

Cyclin levels trigger M-phase



cyclin

- Took a very long time to discover cyclins.
  - Columns indicate “amount” of cyclin
  - M indicates M-phase of the cell cycle

Figure excerpt from Sha et. al., 2003; PNAS

What is MPF?

- What characteristics does it have or have to have?
  - How can this function be regulated?

What is MPF?

- What characteristics does it have or have to have?
  - Temporally regulated function
    - "On" during M-phase, "off" during interphase
      - Biological assay
    - In embryos must cycle, show periodicity

  - How can this function be regulated?
    - Regulated synthesis*
    - Regulated degradation*
    - Regulated form (phosphorylation, protein complexes)

What we believe/know…

- Cyclin synthesis is constant
- MPF activity is turned "on" and "off"
- MPF activity is turned on by cyclin
- Cyclin is degraded

Creating a Computational Model

- Concept Map
- Factors and relationships between factors
- Describe relationships mathematically

- Solve equations: using computer tools
- View and interpret results

To be performed:
See First Lab Ex.

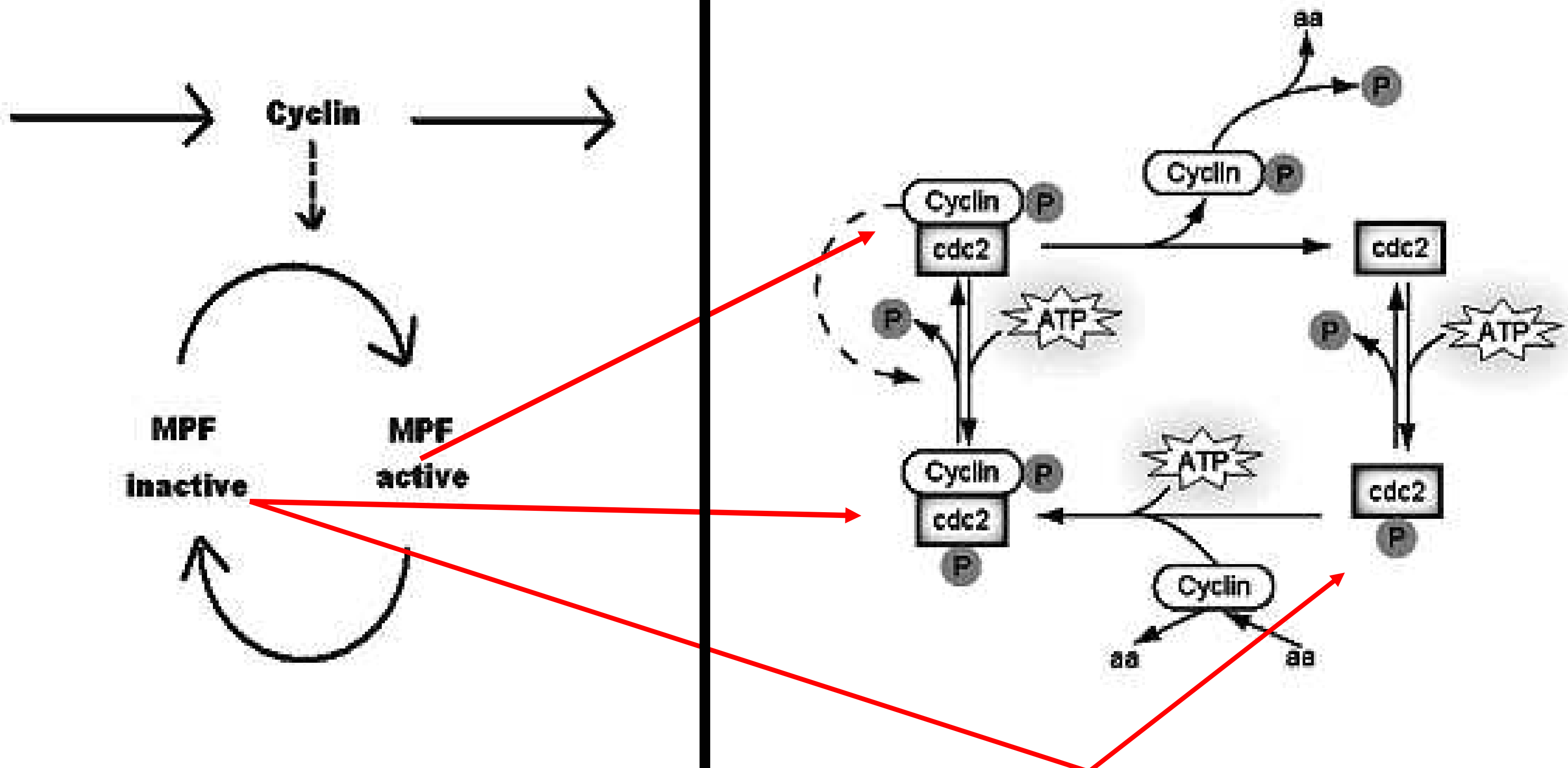
Draw flow diagrams/concept map for the statements

1. System statements
   - inactive MPF **becomes** active MPF
   - Active MPF **becomes** inactive MPF
   -
2. System statements
   - Cyclin is **synthesized** and **degraded**
   - Cyclin **stimulates** inactive MPF **to become** active MPF

Pen and paper will do

Current conceptual models of the cell cycle

System statements | Additional detail (Tyson, 1991)



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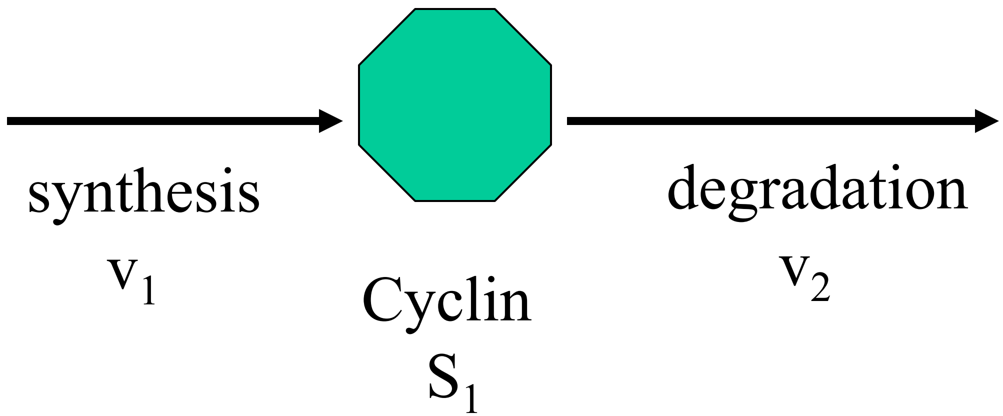
We are looking at the dynamics

- Kinetics~Dynamics~Behaviors over time

- How do we mathematically describe behaviors?
  - <u>ODE</u>, Stochastic, Boolean, Rules
    - Initial concentrations, rate equations, rate constants.

- Describing relationship mathematically

Representations



<u>Difference equations</u>

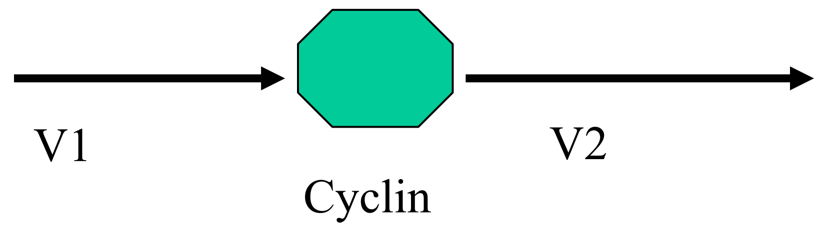
Cyclin= synthesis -degradation

<u>Ordinary differential equation</u>

$$\frac{dS_1}{dt} = v_1 - v_2$$

Parameter values

Cyclin	conc	0.01 $\mu moles$
M*	conc	0.01 unitless
X*	conc	0.01 unitless



Process Rate equation	**Velocity**	**Parameter**	**Value**
Cyclin synthesis k1	V1	k1	0.025 $\mu moles/\min$
Cyclin degradation vmax2*Xa*Cyclin/(Km2+cyclin)	V2	vmax2	0.25 $\mu moles/\min$
		Km2	0.02 $\mu moles$

Creating a Computational Model

- Concept Map
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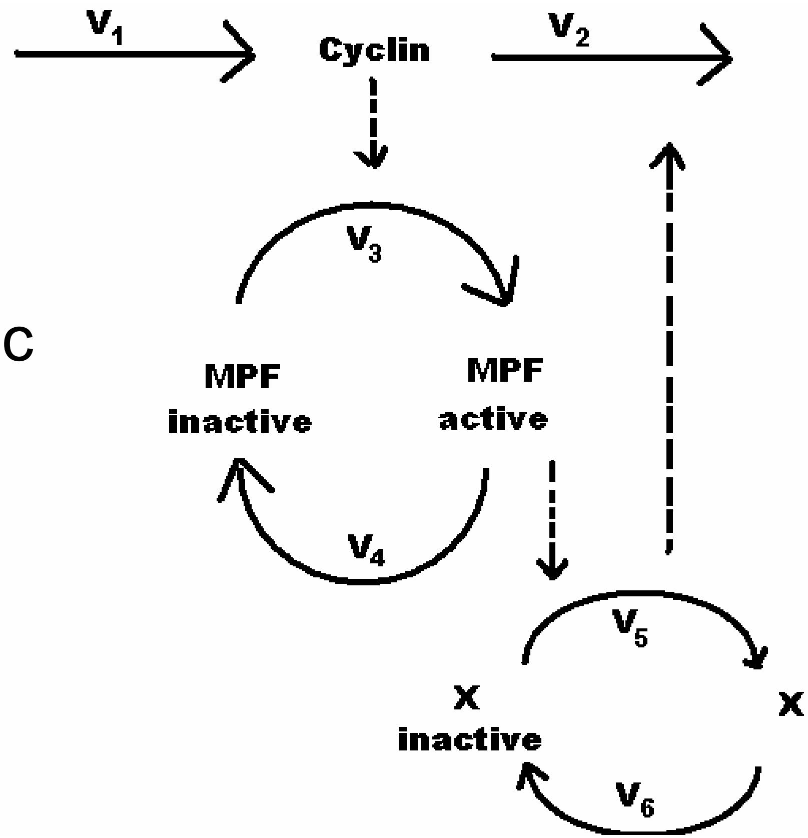
We’re using Stella

- Stella Demo
  - Create models, no saving
- Stella Player
  - View existing model
  - No changing

- Stella Research
  - Full fledged
  - Many available models

Modified Goldbeter, 1991

Goldbeter proposed negative feedback loops and enzymatic thresholds as sufficient for embryonic cell cycles (oscillations)



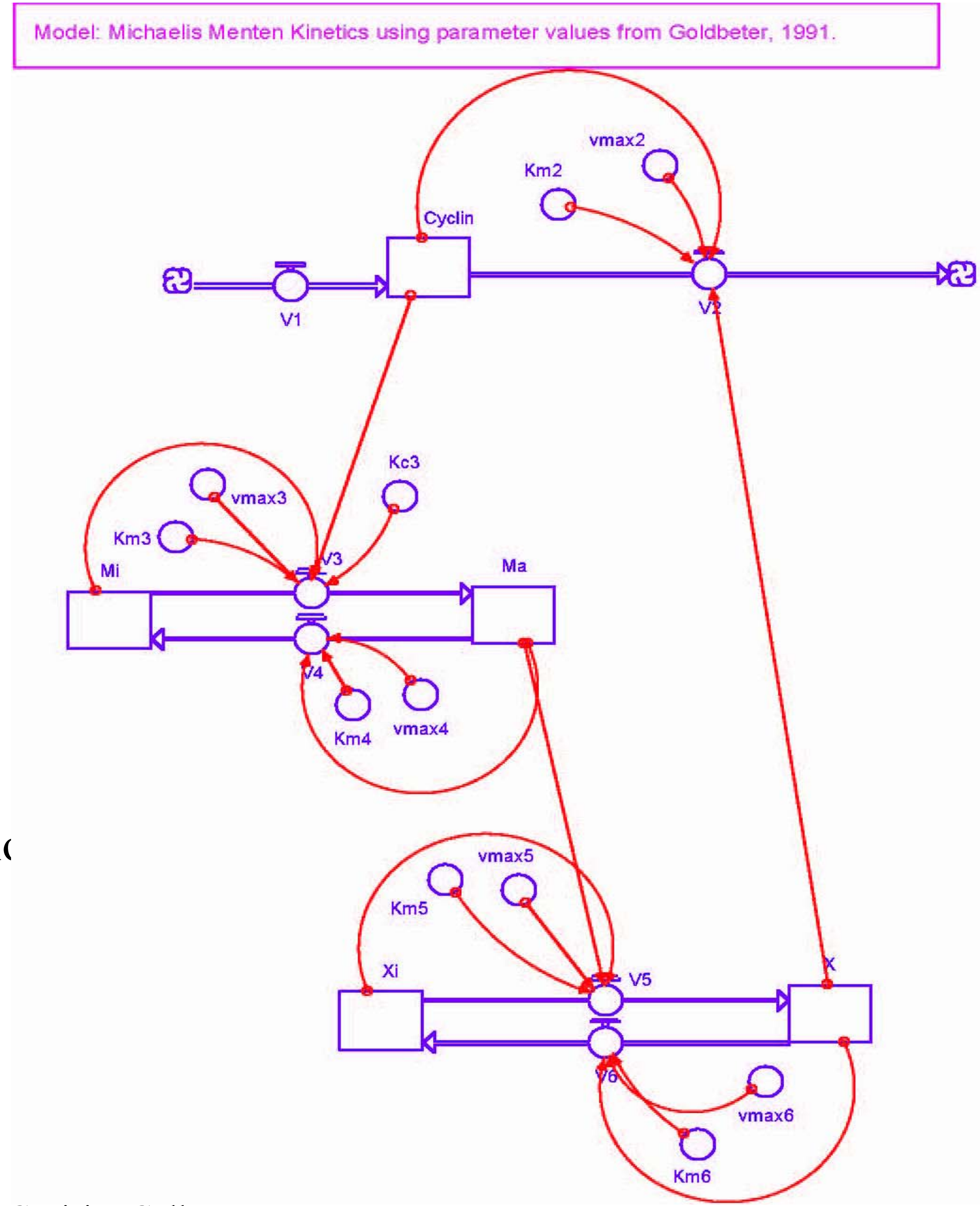
Exercise contd.

B. Create your concept maps in Stella Demo.

C. Assume the following for reactions and variables:

1. All **reactions** are flat rate or based on the law of mass action (rate constant x substrate).
2. Examine different **rate constants** and **amounts**
3. No writing ODE’s they are created for you

Goldbeter in Stella Player



Refer to print out for initial exploratic

Research Projects for Students: A three week assignment

Models of cell cycle taking into account the following:

1. Cell size in yeast

2. MPF self-activation of MPF in mammalian or amphibian cells

3. Binding rates of cyclin to cdc2 in yeast, mammalian or amphibian cells

4. Phosphorylation rates of cdc2/MPF in yeast, mammalian or amphibian cells

5. Mechanisms of threshold generation: Michaelis-menten models

6. Ubiquitination and cyclin degradation mechanisms yeast, mammalian or amphibian cells

7. Additional regulators of activation or inactivation of MPF yeast, mammalian or amphibian cells

Student models

Wee1 and Cdc25 regulation of Cell Cycle

Eq. 1

$2.3\log [S]_0/[S] = kt$

S=Substrate

k=Rate Constant

t=Time

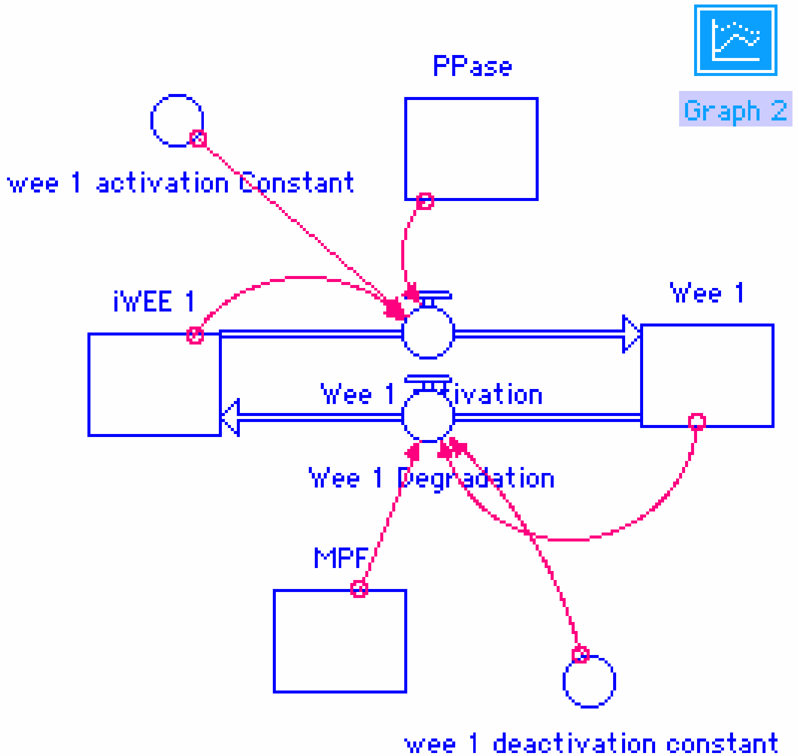
Ex. Wee1 activation constant

$[S]= 100 \quad [S] = 50 \quad t = 7.5$

$2.3\log (100/50) = 7.5k$

$k = 0.092\ nM^{-1}\ min^{-1}$

Figure 2. Wee1 model



Chung, Morgan-Wesiburg and Murphy

Goldbeter model in EBI Database