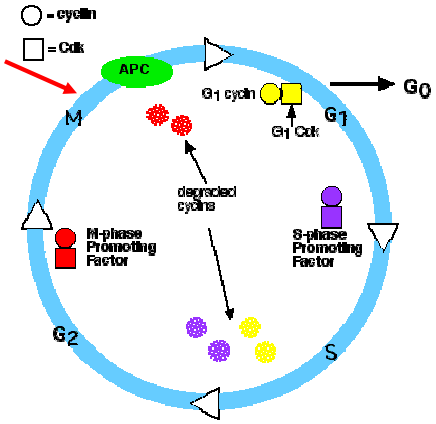
Working one model through

Goldbeter, 1991 modified

What we will do

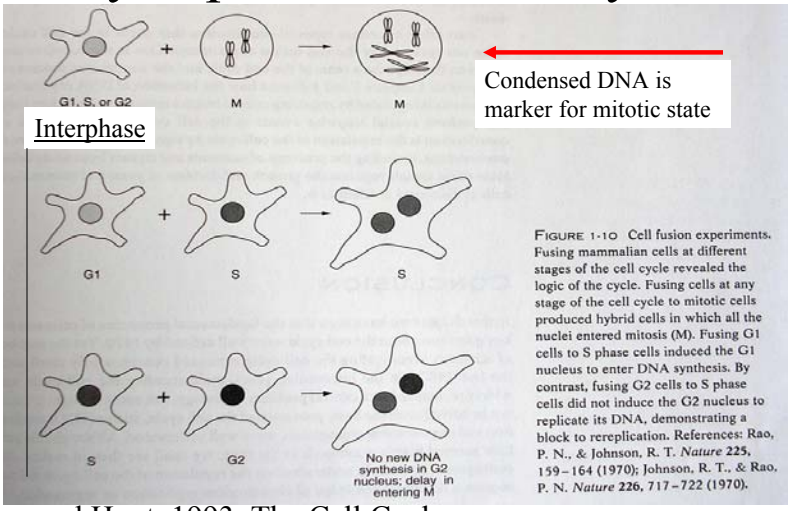
- Brief intro to biology: cell cycle
- Work in groups not from same discipline
- Hands on exercise
- Explore Stella version of Goldbeter model.

Cell Cycle and Phases



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

Key experiments identify MPF



Murray and Hunt, 1993. The Cell Cycle

Key experiments contd.

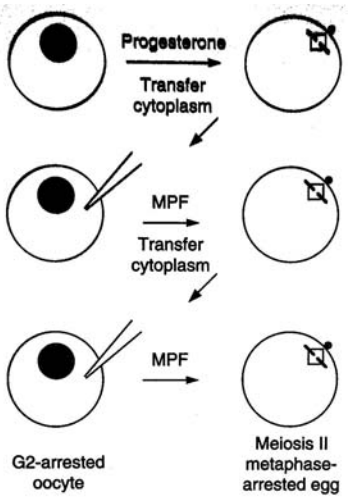
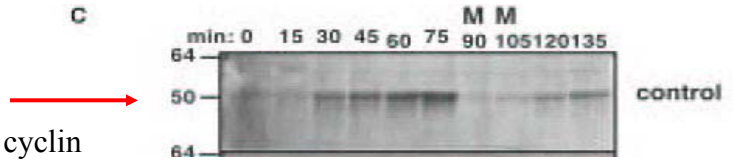


FIGURE 2-5 Discovery of MPF. Oocytes induced to mature into unfertilized eggs by treatment with progesterone are used to donate cytoplasm to untreated oocytes. The transferred cytoplasm contains active MPF which induces the recipient oocytes to enter meiosis. Maturation induces the activation of MPF 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



- 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

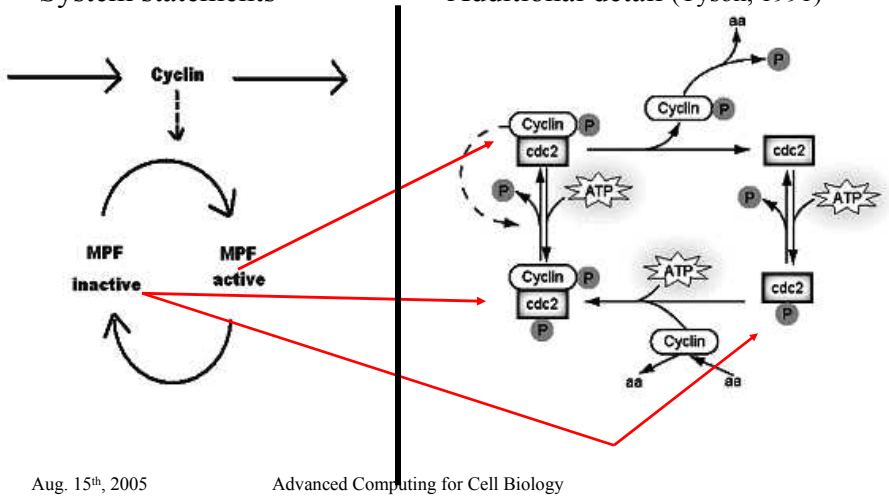
1. System statements
   - inactive MPF **becomes** active MPF
   - Active MPF **becomes** inactive MPF
   -
2. System statements
   - Cyclin is **synthesized** and **degraded**
   - Cyclin **stimulates** inactive MPF **to become** active MPF

Pen and paper will do

Current conceptual models of the cell cycle

System statements

Additional detail (Tyson, 1991)



Creating a Computational Model

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

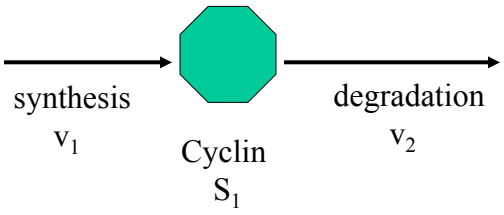
- Solve equations: using computer tools
- View and interpret results

We are looking at the dynamics

- Kinetics~Dynamics~Behaviors over time
- How do we mathematically describe behaviors?
  - ODE, Stochastic, Boolean, Rules
    - Initial concentrations, rate equations, rate constants.

- Describing relationship mathematically

Representations



Difference equations

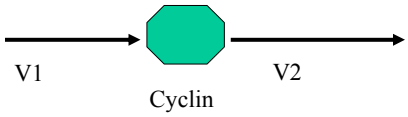
Cyclin= synthesis -degradation

Ordinary differential equation

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

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
- Factors and relationships between factors
- Describe relationships mathematically

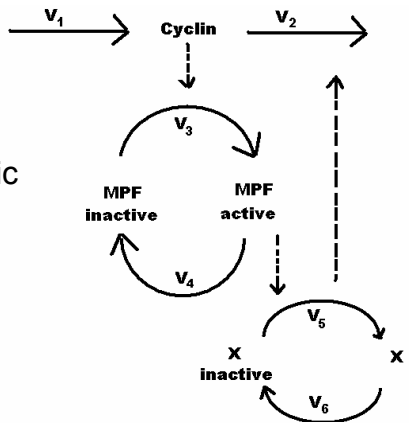
- Solve equations: using computer tools
- View and interpret results

We're using Stella

- Stella Demo
  - Create models
- Stella Player
  - View existing model
- Stella Research
  - Full fledged
  - Many available models
- Exercise for Goldbeter
- Exploration in Player

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