Modeling the cell cycle:
New ~~Skills~~ Activities in Undergraduate Biology Education

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Goal of today's 1.5hr

- Introduce you to what was done
- Introduce you to modeling the cell cycle
- Relationship to new skills:
  - Education reform looks at engaging students in:_____
  - In biology, scientists are having to learn new ways of understanding biological systems
  - New ways are quantitative, theoretical and conceptual

The Lens

- Performance
- Co-teaching
- Cellular to biochemical view
  - Biology, math, models: conceptual, mathematical, computers

What do I mean by performance?

- Not a measure, rather an activity
- Activity of becoming:
  - students are both who they are: "students"
  - and who they are not: "scientists/mathematicians"
- Vygotsky: zones of proximal development
  - Co-learning, group, social, activity
- Performatory
  - Understanding developed in practice
  - All Stars Project, Inc. and East Side Institute

Classroom as performance

- Directors: John Jungck and Raquell Holmes
- Performers: Instructors and students
- Play: Modeling the cell cycle
- Length: Five weeks, small groups
- Props: Stella, former scripts (models) and text.
- Direction: create models and discover what you need.

Activity: Performing as scientists

- The background: biology
- The tools: computer modeling
- The challenge: take what is known and create something new
  - New understanding
  - New model

What we did 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 students/scientists
  - New to topic
  - Some understanding
  - Different skills
- Modified version of first modeling lab in class
- Work in groups not from same discipline

Today's collective performance

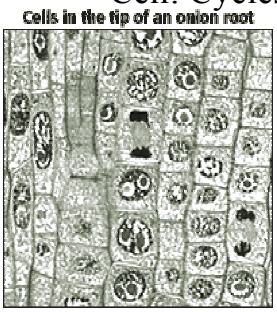
- As a large group:
  - Introduction to biology
  - Introduction to modeling
- Smaller groups (2 or 3):
  - Create models of aspects of the cell cycle

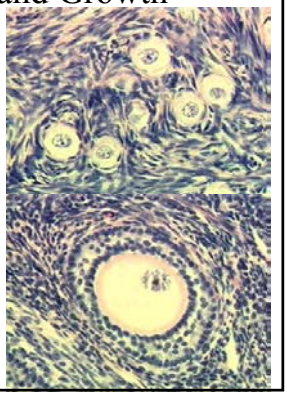
Cell Cycle/ Cell division

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

Group sharing or improvisation

Cell: Cycles and Growth





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

Key experiments

See Figure 1-10 of *The Cell Cycle* by Murray and Hunt, 1993.

Fusion of somatic cells in different cell cycle stages illustrates logic of cell cycle progression.

Murray and Hunt, 1993. The Cell Cycle

Key experiments contd.

See Figure 2-5 of *The Cell Cycle* by Murray and Hunt, 1993.

Cytoplasmic transfer experiments demonstrates presence of maturation promoting factor: MPF.

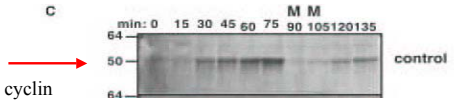
What is MPF?

- 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 form (phosphorylation, protein complexes)
    - Regulated degradation

Interesting notes



- Took a very long time to discover cyclins.
  - Discover a protein synthesized periodically
  - Discover a protein degraded periodically

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

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

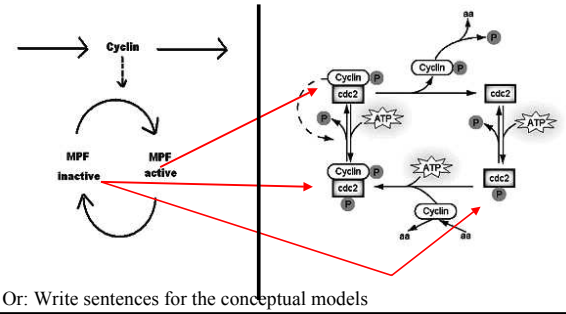
To be performed:

See First Lab Ex.

Draw flow diagrams/concept map for the statements **provided below**. Keep your hand drawings and turn them in.

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

Current conceptual models of the cell cycle

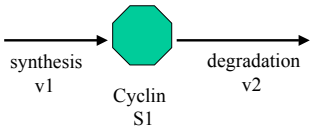


Or: Write sentences for the conceptual models

Creating a Computational Model

- Describing relationship mathematically

Representations



Difference equations
Cyclin= synthesis -degradation

Ordinary differential equation

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

Designing a dynamic experiment

- Concept Map
- Factors and relationships between factors
- Describing relationship mathematically
- What rate laws are known to describe the enzymatic reaction?
  - Types of rate laws/kinetic models
    - Constant, mass action, michaelis menten…
  - Initial conditions/values
    - Often unitless in modeling papers

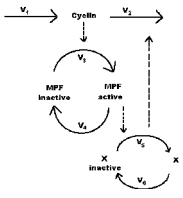
      Opportunity to work with research papers

The model we're playing with

Asks: are the minimal components of the system sufficient to account For the oscillation patterns in early embryos? Golbeter, 1991

STELLA model:
Continuous, non-stochastic, Non-spatial, population

Base model in an overview



Difference Equations

Cyclin= synthesis-degradation	= V1-V2
MPF= activation-inactivation	=V3-V4
Inactive MPF=inactivation-activation	=V4-V5
X=activation-inactivation	=V5-V6

Ordinary Differential Equations

$$\frac{dC}{dt} = V_1 - V_2$$

$$\frac{dM}{dt} = V_3 - V_4 \qquad \frac{dM_i}{dt} = V_4 - V_3$$

$$\frac{dX}{dt} = V_5 - V_6 \qquad \frac{dX_i}{dt} = V_6 - V_5$$

Mass Action Rate Equations

V1=constant	V4=k*MPF
V2=k*Cyclin*X	V5=k*MPF*iX
V3=k*iMPF*Cyclin	V6=k*X

Initial conditions in "Cell Cycle" chapter

Ex contd.

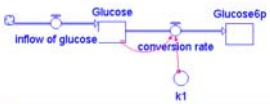
B. Create your concept maps in Stella.

C. Assume the following values for reactions and variables and enter them to your Stella model:

1. All **reactions** are linear and based on the law of mass action (rate constant x substrate).
2. Vary your **rate constants** and **amounts**

Stella

Concept Map



Rules as math

```
{ RUNTIME EQUATIONS }
Glucose(t) = Glucose(t - dt) + (inflow_of_glucose_ - conversion_rate) * dt

Glucose6p(t) = Glucose6p(t - dt) + (conversion_rate) * dt

conversion_rate = k1*Glucose
```

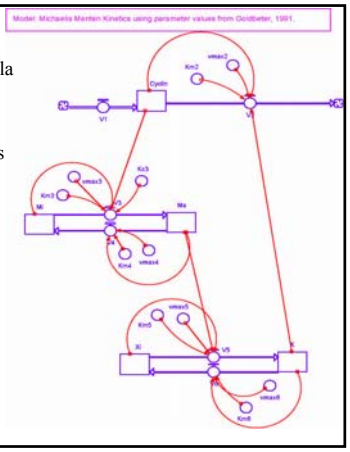
Initial Conditions

```
{ INITIALIZATION EQUATIONS }
k1 = 55{1/mM*1/min}
INIT Glucose = 0

inflow_of_glucose_ = 50{mM*1/min}
conversion_rate = k1*Glucose
INIT Glucose6p = 0
```

A version of Goldbeter in Stella

Reference model for students



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 [S] = 50 t = 7.5
2.3log (100/50) = 7.5k
$k = 0.092\ nM^{-1}\ min^{-1}$

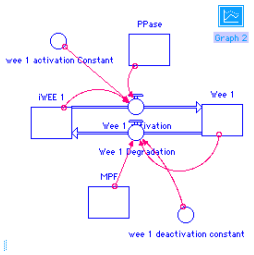
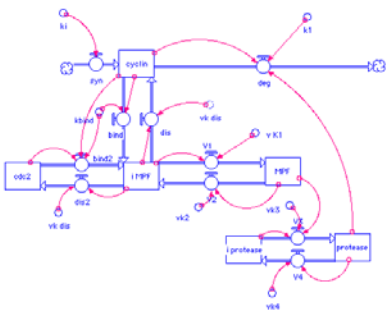


Figure 2. Wee1 model

Chung, Morgan-Wesiburg and Murphy

Student models

We believe that our results support our hypothesis that the **cycin-cdc2 binding** rate affects the cell cycle. As binding rate increases in relation to dissociation rate, oscillation frequency and amplitude increases; the reverse is true when dissociation rate is greater.



Items we hit

- What does activate, bind, turn on mean in terms of a mathematical equation (+, x, /)
- How do we construct concepts in Stella?
- My results don't look like…
- Wanted more practice with equations and stella, so that they could trust their setup decisions.
- Rarely related results to rate equations