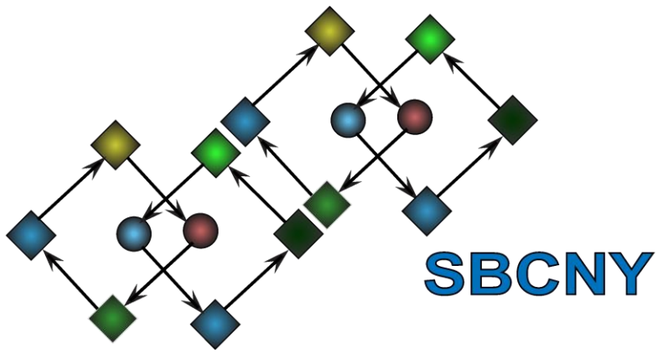
Computational modeling of the cell cycle

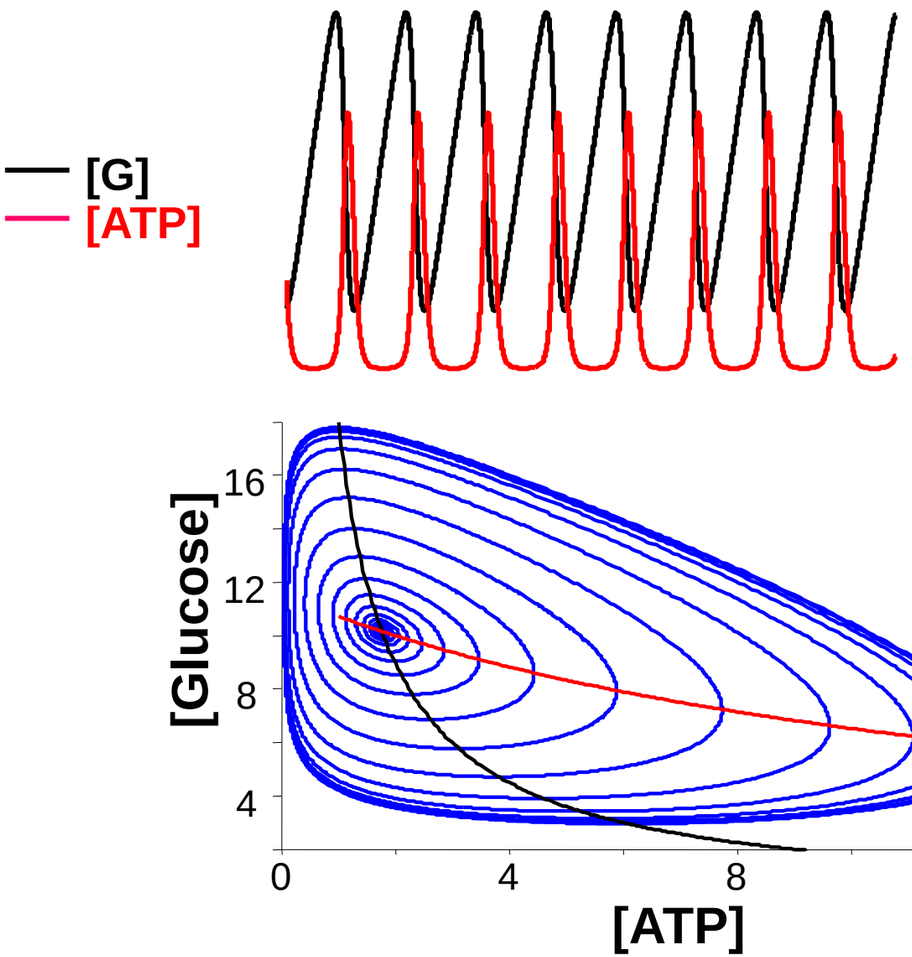
Part 1

Icahn School of Medicine at Mount Sinai



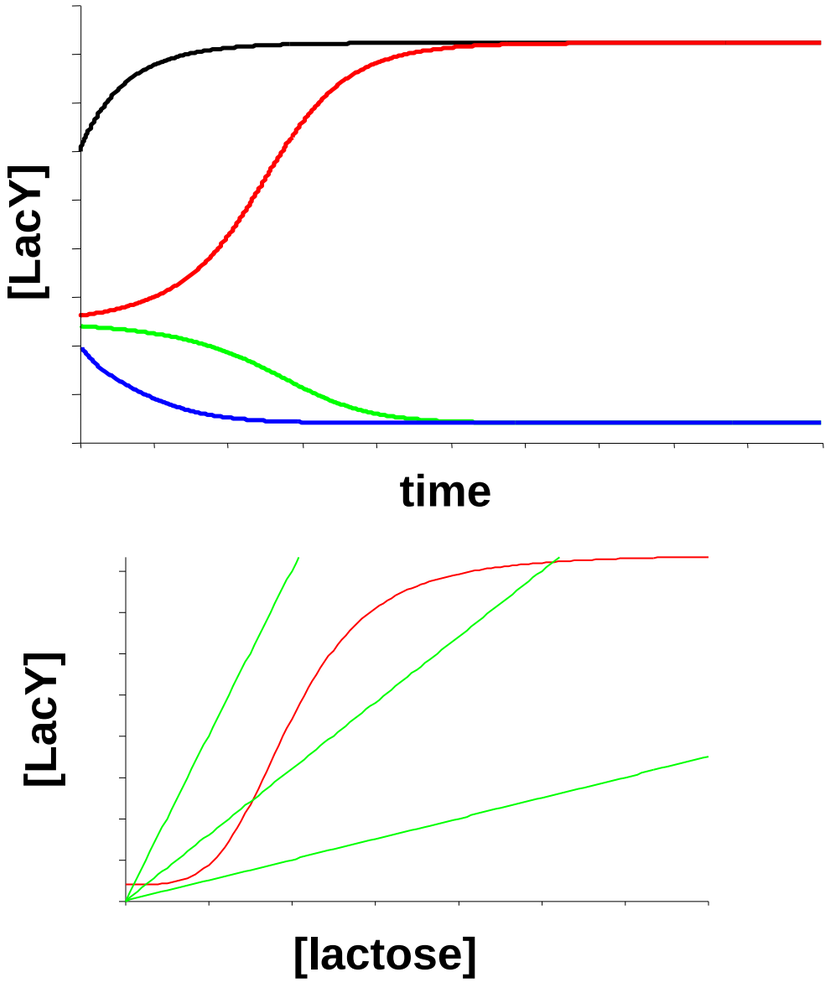
Review from previous lectures

Yeast glycolysis model



System could oscillate or settle to stable values

Lac operon model

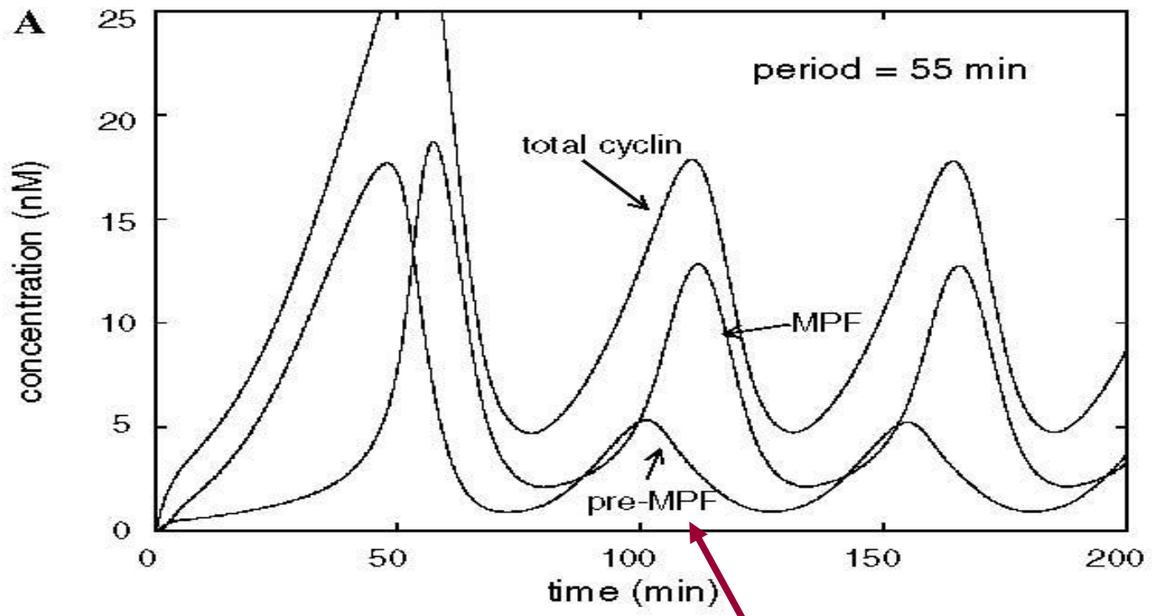


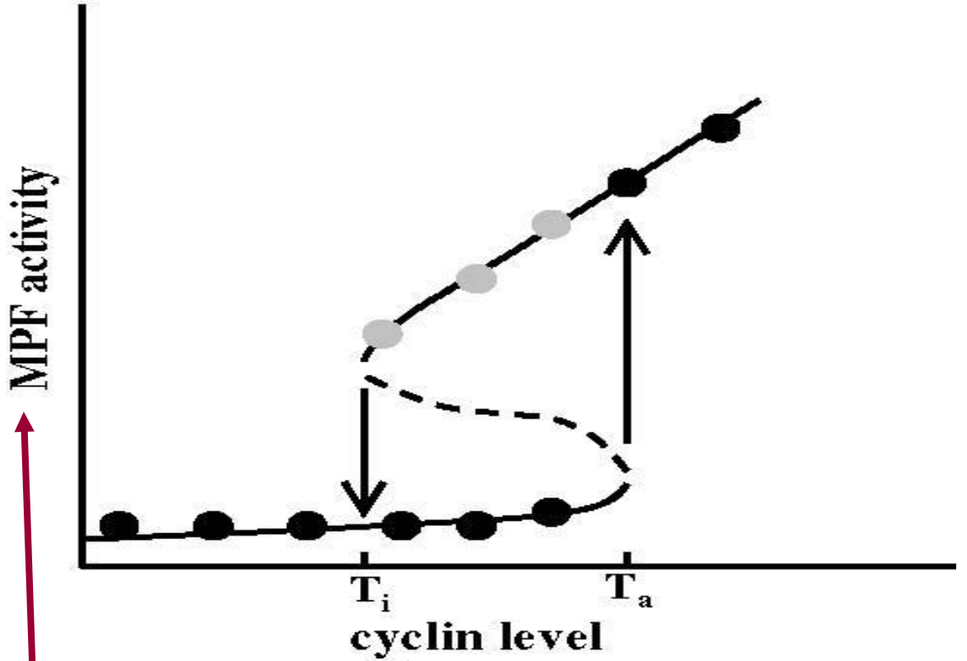
System could be monostable or bistable

What is different about the cell cycle?

Now we consider more than 2 variables

This allows the system to exhibit BOTH stable oscillations and bistability





Sible & Tyson (2007) *Methods* 41:238-247

MPF, pre-MPF, cyclin, etc. will be defined

Outline: Part 1

Biological background

Importance of “Maturation-Promoting Factor” (MPF)

(aka mitosis-promoting factor, M-phase promoting factor)

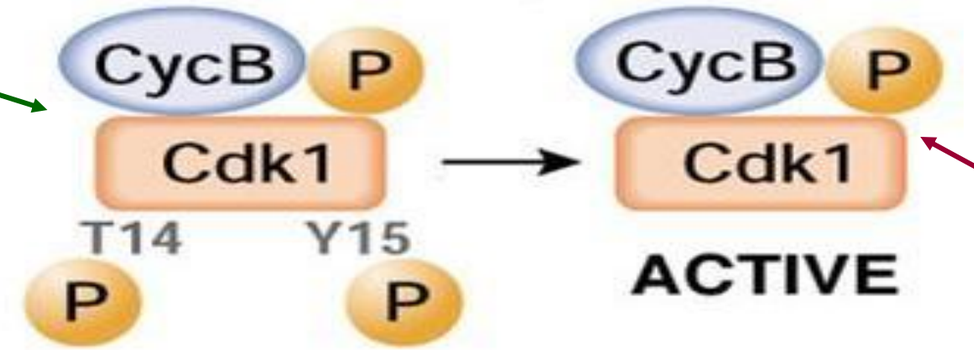
Regulation of MPF activation

Basics of the cell cycle

G2→M transition driven by increase in MPF

MPF = Maturation Promoting Factor

pre-MPF



Activated MPF

Alberts et al. *Molecular Biology of the Cell* 4th edition.

Cyc = cyclin

Cdk = cyclin-dependent kinase

Two obvious ways to regulate Cdk/MPF activity:

1) synthesis/degradation of cyclin
2) Phosphorylation/dephosphorylation of Cdk

Basics of the cell cycle

cyclin is alternately synthesized and degraded

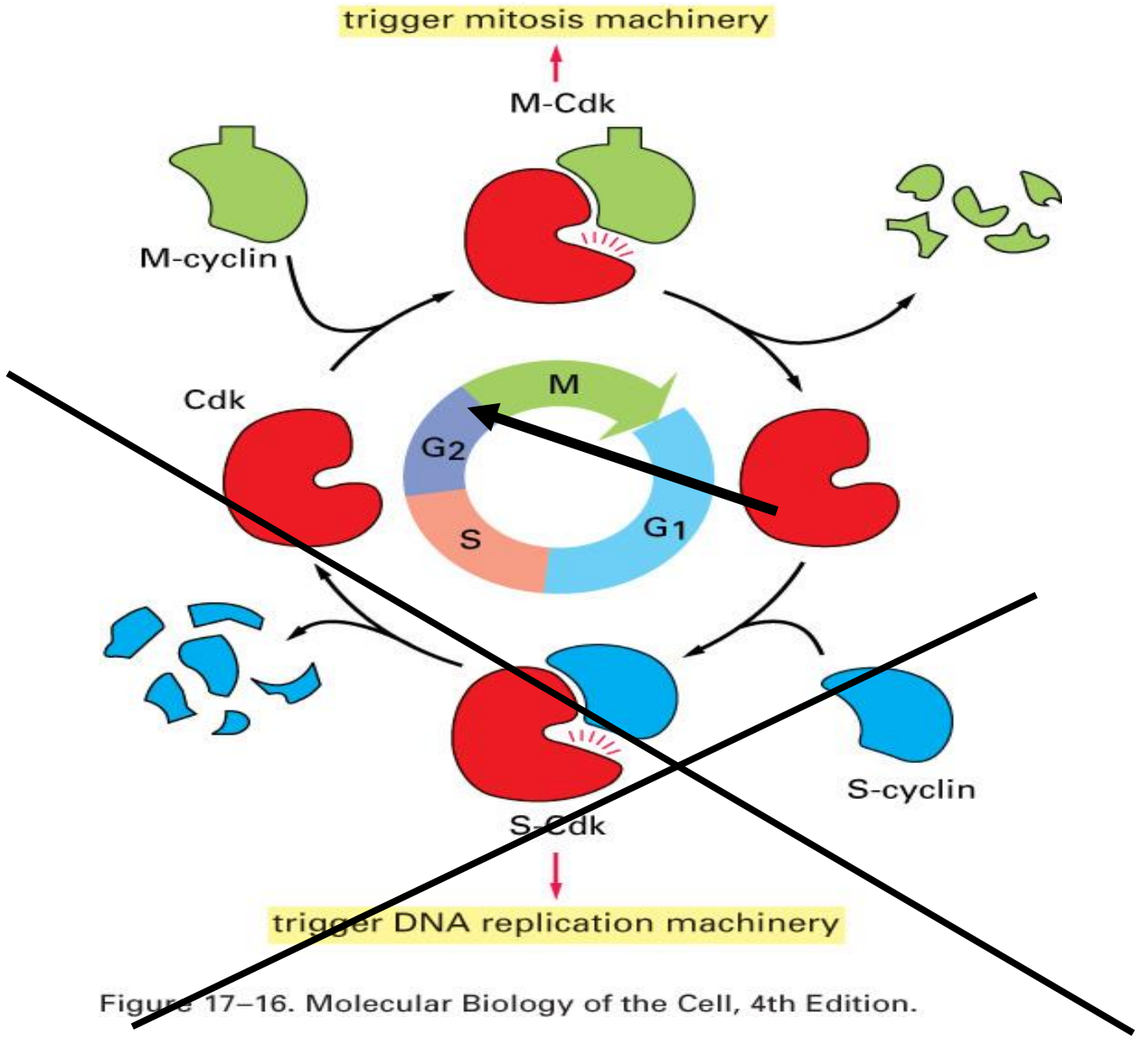
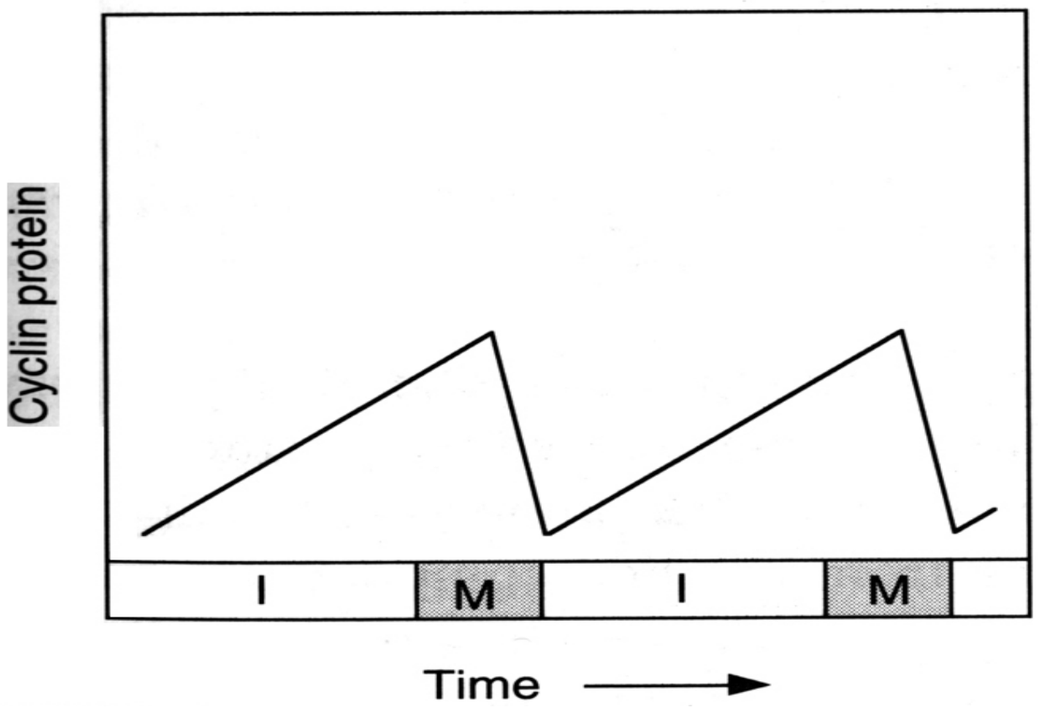


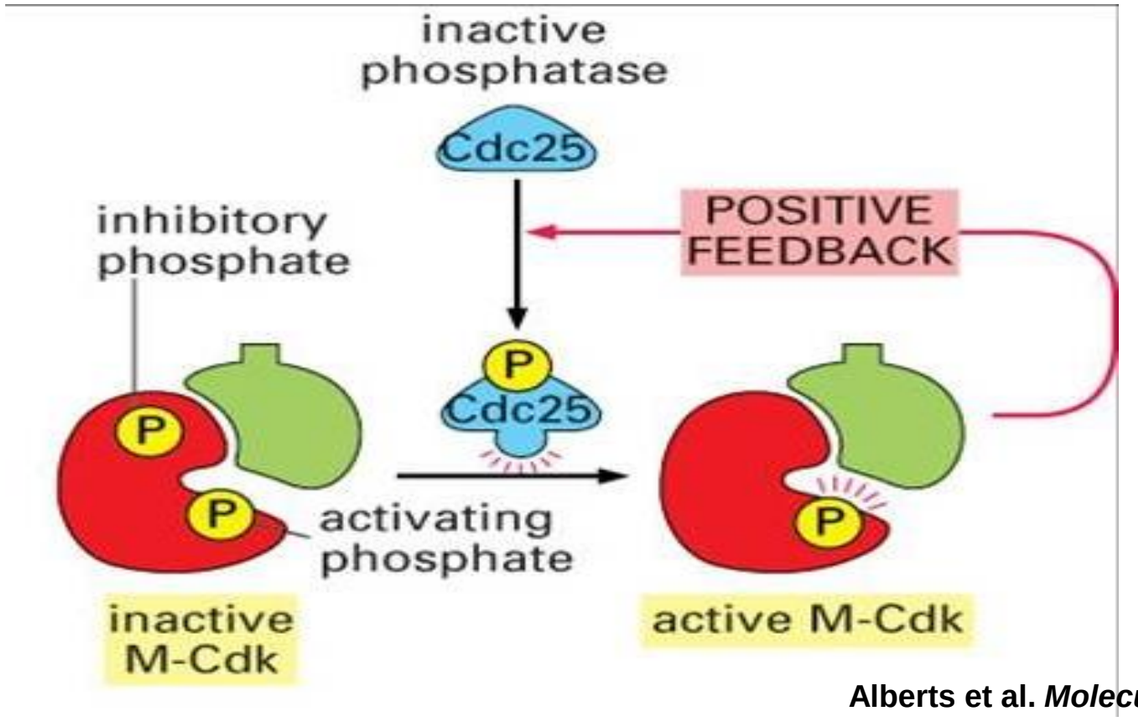
Figure 17–16. Molecular Biology of the Cell, 4th Edition.



We will only consider M-type cyclins (aka cyclinB), not others

Basics of the cell cycle

Positive feedback in activation of MPF



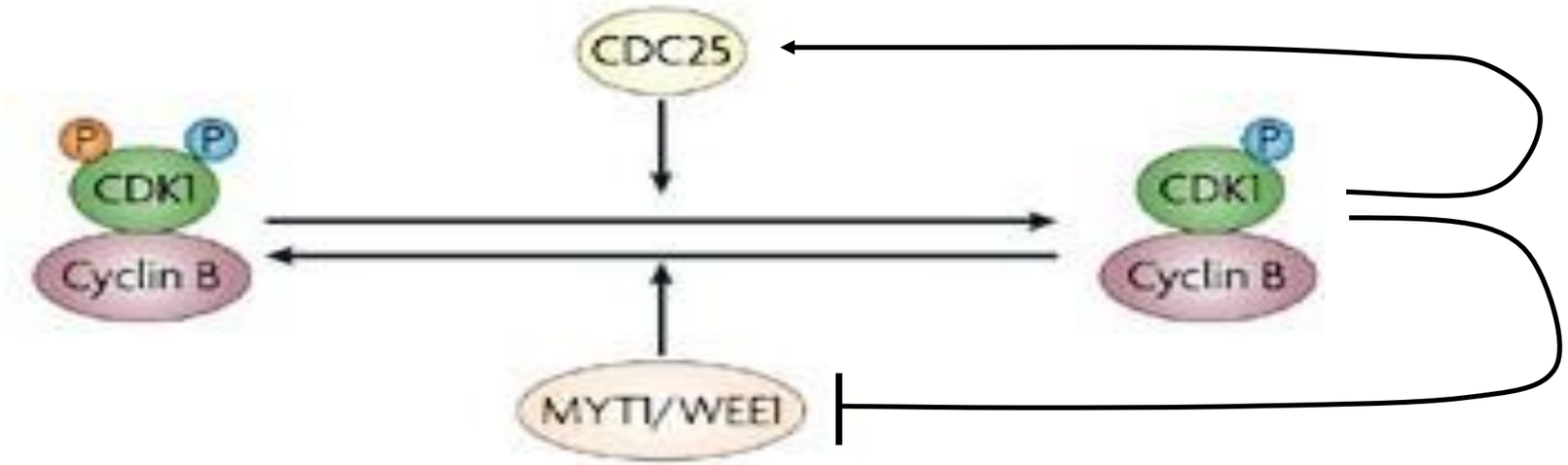
Alberts et al. *Molecular Biology of the Cell* 4th edition.

Greater MPF activity → Greater cdc25 activity
Greater cdc25 activity → Greater MPF activity

Mutual activation can lead to: bistability

Basics of the cell cycle

wee1 opposes MPF activation



Boutros et al. (2007) *Nature Reviews Cancer* 7:495-507

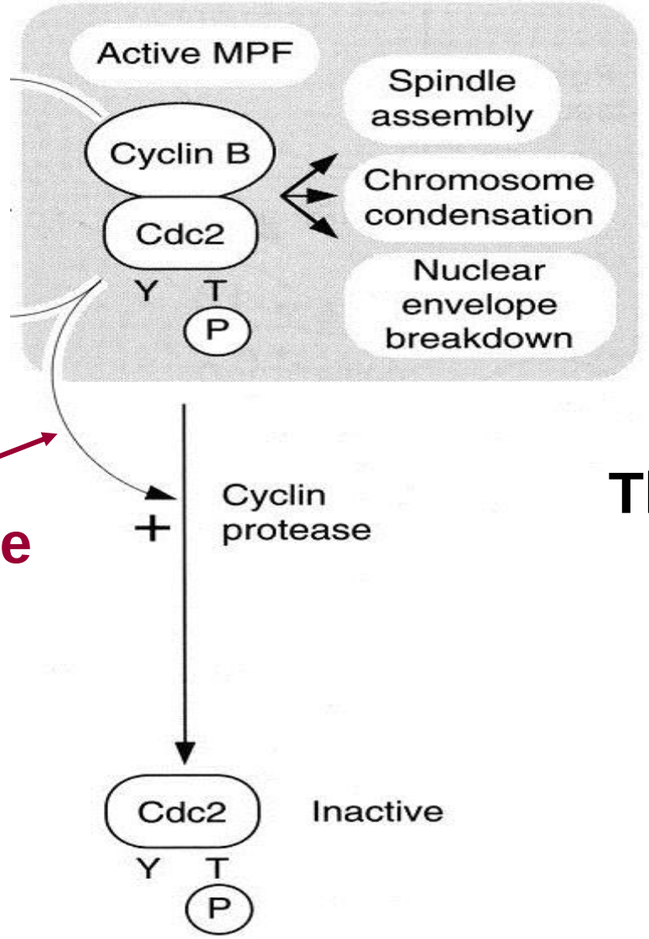
Even more complicated because MPF inhibits wee1

Therefore MPF regulates both:

1) **activation of MPF (de-phosphorylation of CDK)**
2) **inactivation of MPF (phosphorylation of CDK)**

Basics of the cell cycle

MPF triggers cyclin degradation



Alberts et al. *Molecular Biology of the Cell* 4th edition.

Through anaphase promoting complex, APC

Thus, MPF:

1) **+ regulates MPF activation (cdc25)**
2) **- regulates MPF de-activation (wee1)**
3) **+ regulates MPF destruction (APC)**

It is difficult (or impossible) to make predictions using only intuition

A brief, possibly confusing aside

Multiple phosphorylation sites on Cdk

-P on T161/167 is activating, but this step not regulated

-P on T14 and Y15 are inhibitory, these are the regulatory steps

The model only considers the latter, treats these as a single site

T161 vs. T167
yeast vs. vertebrates

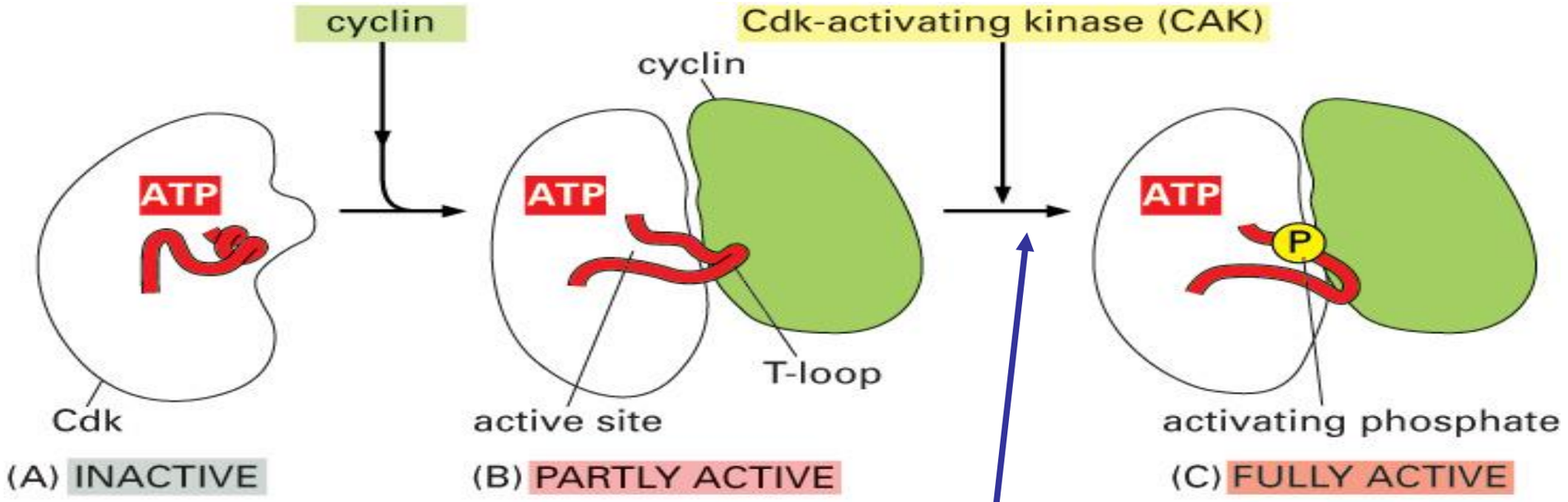


Figure 17–17. Molecular Biology of the Cell, 4th Edition.

This –P on T-161/167
Required for function, but not regulated

Summary

MPF is the most important regulatory element in the cell cycle

MPF activity can be regulated by:

- **synthesis of cyclin**
- **dephosphorylation of cdk by cdc25**
- **phosphorylation of cdk by wee1**
- **cyclin degradation, initiated by MPF itself**

Mathematical models can help to make sense of these complex regulatory interactions.