W4-Note

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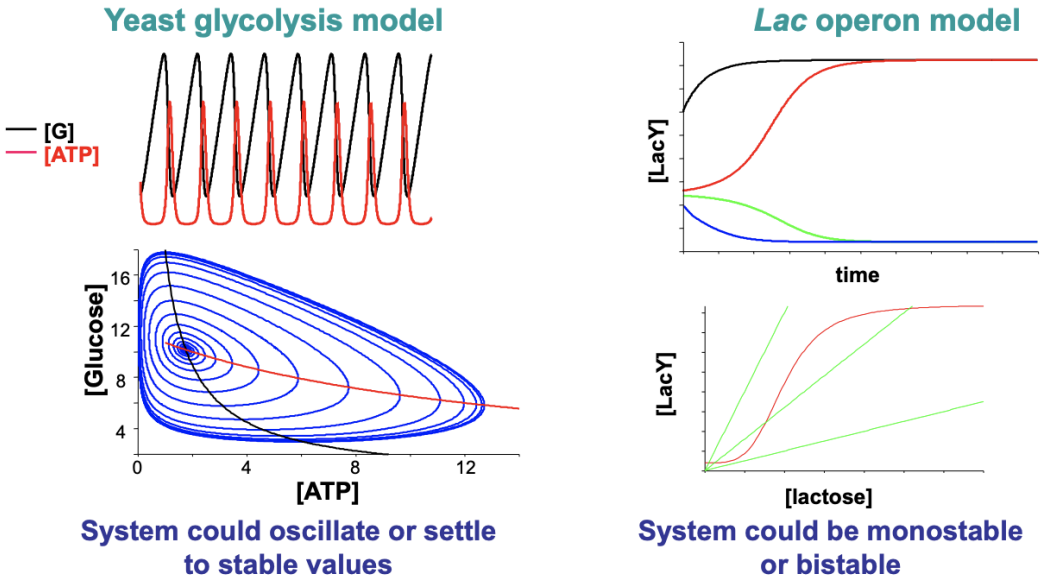
2023-08-08

W4. Computational modelling of the cell cycle

Previous examples:

1. [G] vs [ATP]: oscillation & stability
2. [LacY] vs [l] : monostablity / bistablity

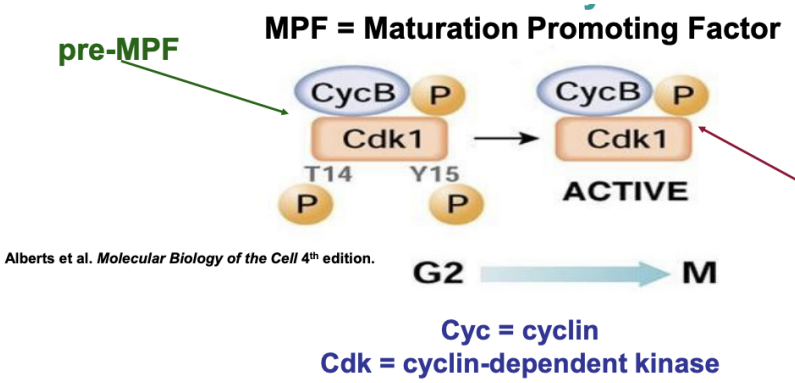


For the model more than 2 variables, the system can be considered to exhibit both stable oscillations and bistability.

Q1. Biological background

- Importance of "Maturation-Promoting Factor" (MPF)
- Regulation of MPF activation

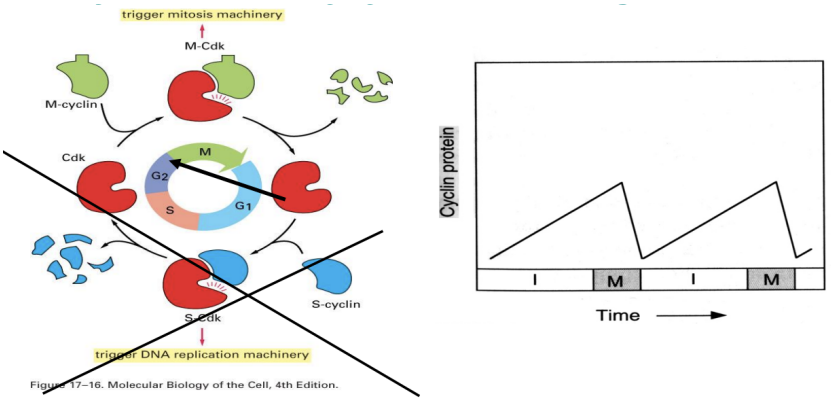
Basics of the cell cycle



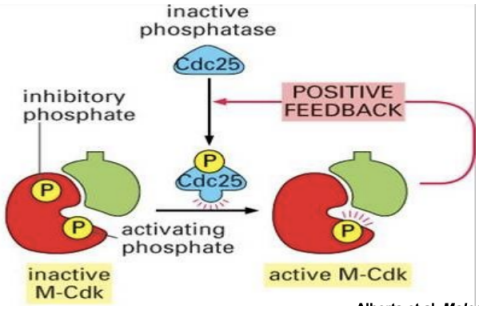
G2 -> M transition driven by increase in MPF

2 obvious ways to **regulate Cdk/MPF activity:**

1. **synthesis / degradation of cyclin**



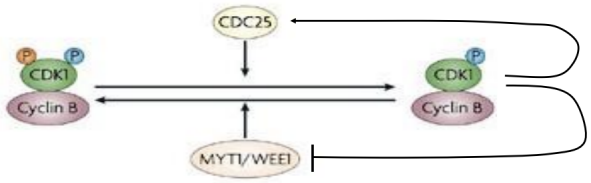
2. Phosphorylation / dephosphorylation of Cdk



Positive feedback in activation of MPF

- Greater MPF activity -> Greater cdc25 activity
- Greater cdc25 activity -> Greater MPF activity

Mutual activation can lead to: **bistability**

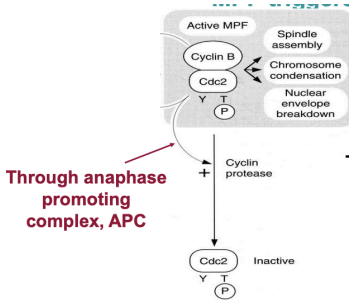


wee1 opposes MPF activation

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)

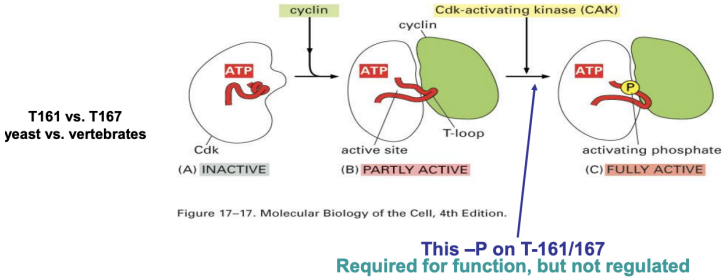


MPF triggers cyclin degradation

Thus, MPF:

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

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



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

1. MPF is the most important regulatory element in the cell cycle
2. MPF activity can be regulated by:
    1. synthesis of cyclin
    2. dephosphorylation of cdk by cdc25
    3. phosphorylation of cdk by wee1
    4. cyclin degradation, initated by MPF itself
3. Mathematical models can help to make sense of these complex regulatory interactions

Q2. The Novak-Tyson (1993) cell cycle model

Structure of the Novak-Tyson model

- Biochemical reactions

- Differential reactions

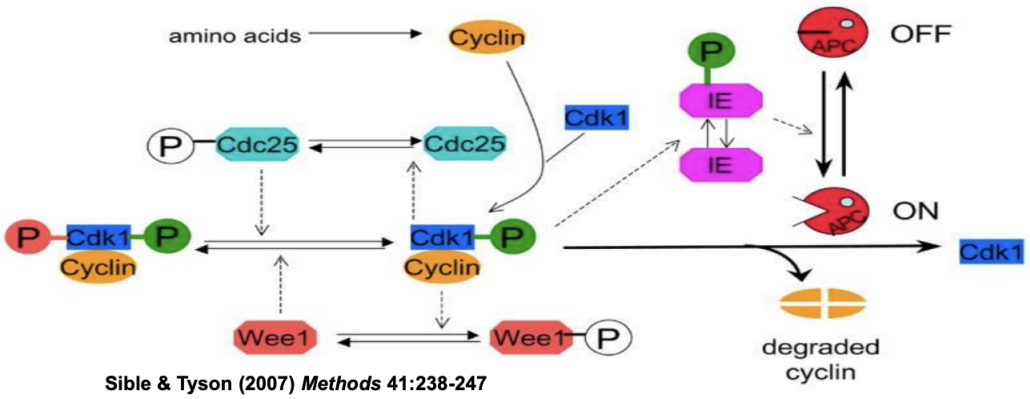
Relevance of the Novak-Tyson model

- Insight gained from the simulations
- Model predictions that were confirmed in subsequent experiments

Def Numerical analysis of a comprehensive model of M-phase control in Xenopus oocyte and intact embryos

Two Types

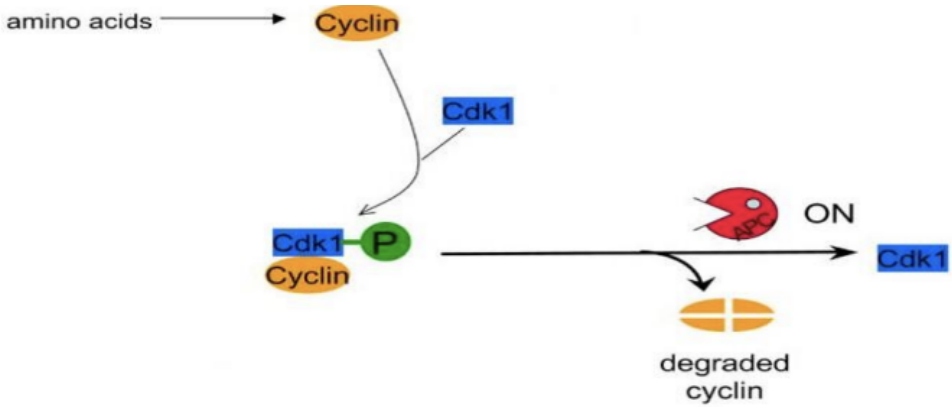
1. **cyclin/Cdk dimer Regulation**
2. **cyclin degradation regulation**



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

Two Main classes of equations

1. Those that involve **synthesis / degradation of cyclin**

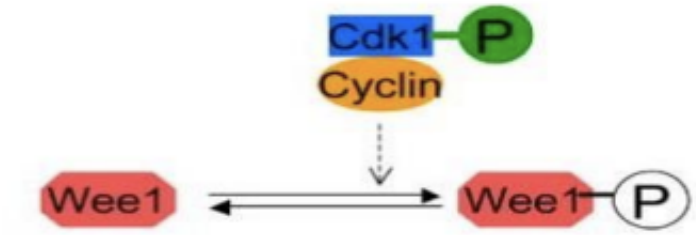


$$\frac{d[cyclin]}{dt} = k_1 - k_3[cy$$

$$k_2 = v_{2\_1}[APC$$

synthesis

2. Those that **only involve phosphorylation / dephosphorylation**



$$\frac{d[wee1P]}{dt} = \frac{k_e[MPF]([wee1]_T$$

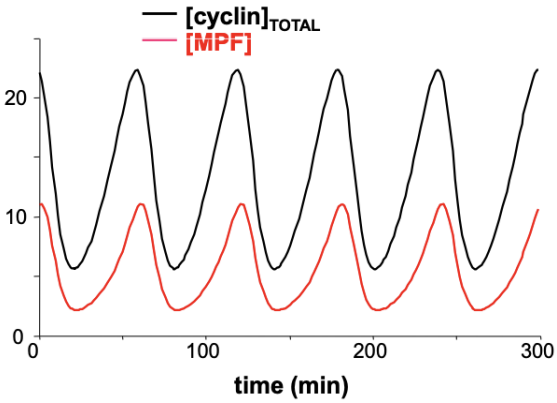
[PPase] repres

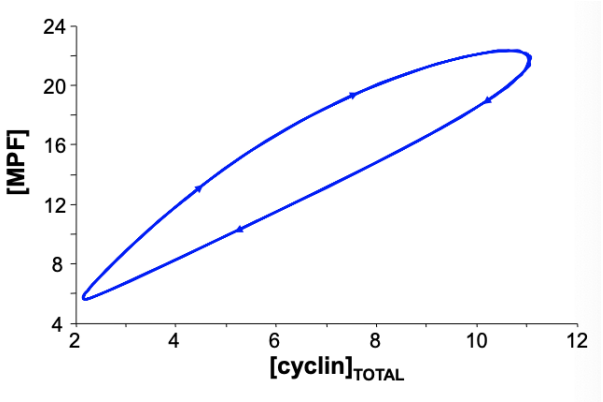
Results

1. **Spontaneous oscillations of MPF and cyclin**

   Analogous to rapid divisions in newly-fertilized oocyte

   Similar to experimental observations

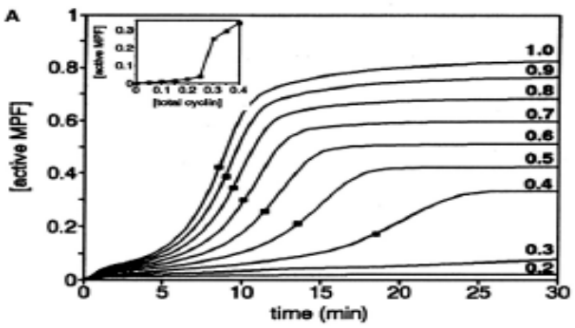




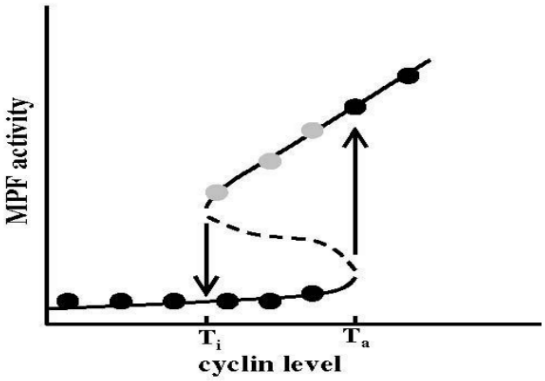
These obtained with control values of numerical parameters

2. **Bistability between [cyclin]_TOTAL and [MPF]**

   To simplify, use non-degradable cyclin



Novak & Tyson (1993) *J. Cell Science* 106:1153-1168



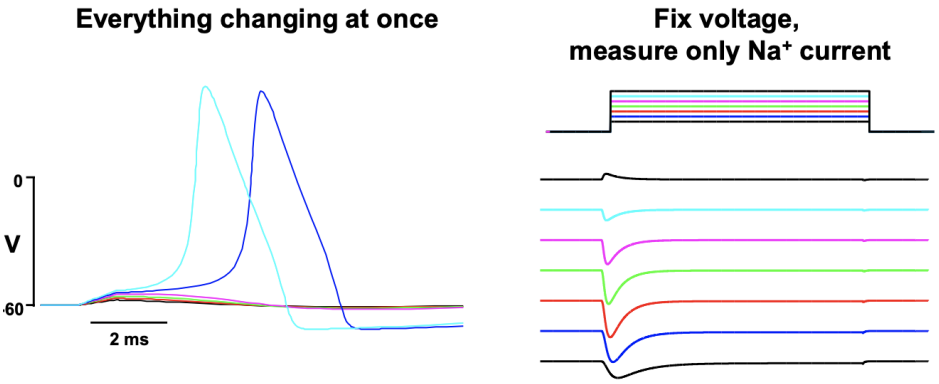
Threshold (left) was similar to experimental observations

Bistability (right) was a novel prediction

General Theme: Quantitative data in a simplified preparation are valuable for constructing a systems-level model.

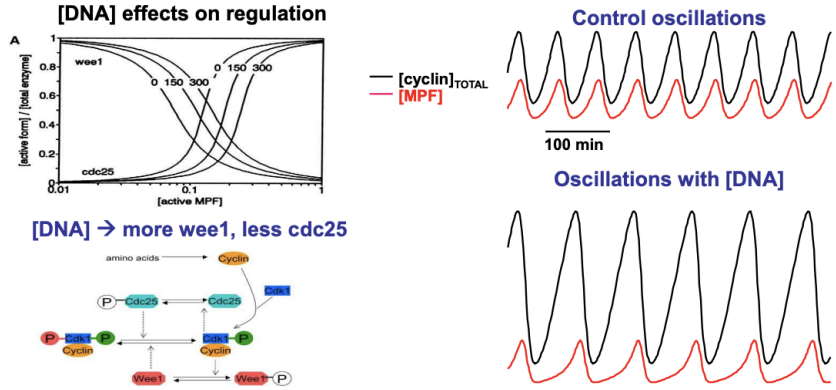
Constraining complicated systems

- **Method 1. Experiments that remove one or more variables** are extremely helpful



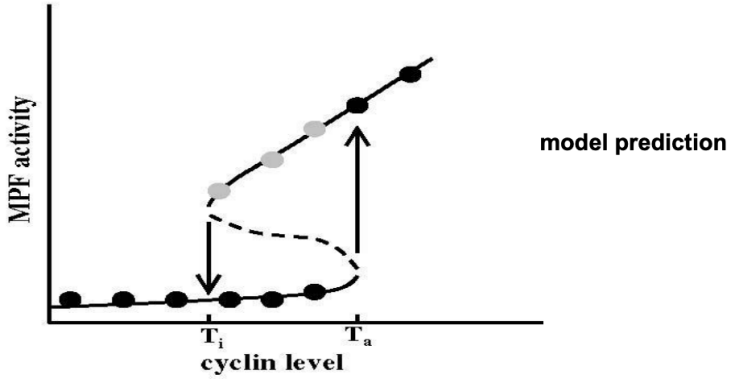
Voltage clamp was the key advance that made the Hodgkin-Huxley model possible.

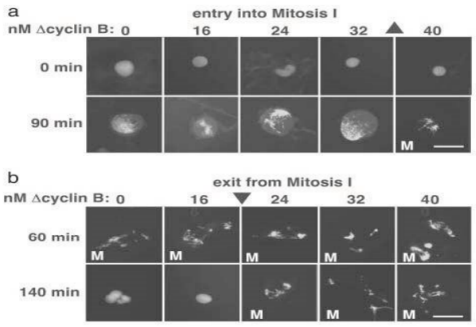
- **Method 2.** Effects of **unreplicated** DNA on cell cycle oscillations



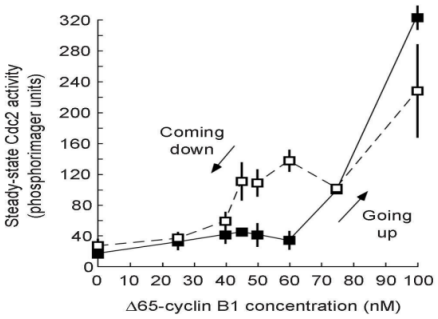
- **Method 3. Model predictions were later confirmed experimentally**

Hysteresis in the [cyclin]-[MPF] relationship

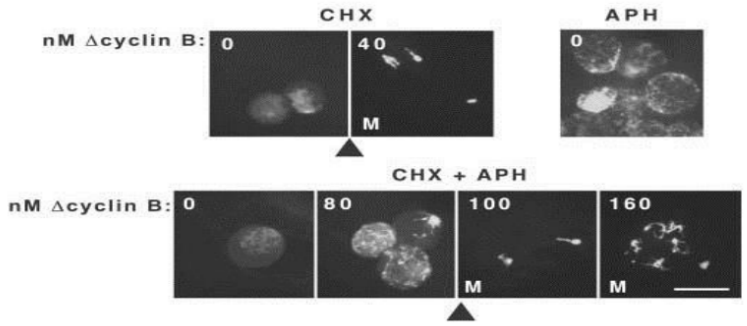




Sha et al. (2003) *PNAS* 100:975-980



Pomerening et al. (2003) *Nature Cell Bio.* 5:346-351



Sha et al. (2003) *PNAS* 100:975-980

The Novak-Tyson cell cycle model illustrates the steps involved in a dynamical modeling study:

- (1) build the model by matching data from a **simplified** system
- (2) validate by **replicating** known results
- (3) generate novel **predictions** that can subsequently be tested

Q3. Functional analysis of Novak-Tyson 1993 cell cycle model

7 ODEs for 7 molecular species

1. $\frac{d}{dt}[\text{Cyclin}] = k_1 - k_2[\text{Cyclin}] - k_3[\text{Cyclin}][\text{Cdk}]$

2. $\frac{d}{dt}[\text{MPF}] = k_3[\text{Cyclin}][\text{Cdk}] - k_2[\text{MPF}] - k_{wee}[\text{MPF}] + k_{25}[\text{preMPF}]$

3. $\frac{d}{dt}[\text{preMPF}] = -k_2[\text{preMPF}] + k_{wee}[\text{MPF}] - k_{25}[\text{preMPF}]$

4. $\frac{d}{dt}[\text{Cdc25P}] = \frac{k_a[\text{MPF}]([\text{total Cdc25}]-[\text{Cdc25P}])}{K_a + [\text{total Cdc25}]-[\text{Cdc25P}]} - \frac{k_b[\text{PPase}][\text{Cdc25P}]}{K_b + [\text{Cdc25P}]}$

5. $\frac{d}{dt}[\text{Wee1P}] = \frac{k_e[\text{MPF}]([\text{total Wee1}]-[\text{Wee1P}])}{K_e + [\text{total Wee1}]-[\text{Wee1P}]} - \frac{k_f[\text{PPase}][\text{Wee1P}]}{K_f + [\text{Wee1P}]}$

6. $\frac{d}{dt}[\text{IEP}] = \frac{k_g[\text{MPF}]([\text{total IE}]-[\text{IEP}])}{K_g + [\text{total IE}]-[\text{IEP}]} - \frac{k_h[\text{PPase}][\text{IEP}]}{K_h + [\text{IEP}]}$

7. $\frac{d}{dt}[\text{APC}] = \frac{k_c[\text{IEP}]([\text{total APC}]-[\text{APC}])}{K_c + [\text{total APC}]-[\text{APC}]} - \frac{k_d[\text{PPase}][\text{APC}]}{K_d + [\text{APC}]}$

Constant values for many model parameters

```
k1 = 1 ;
k3 = 0.005 ;
ka = 0.02 ;
kb = 0.1 ;
kc = 0.13 ;
kd = 0.13 ;
ke = 0.02 ;
kf = 0.1 ;
kg = 0.02 ;
kh = 0.15 ;
```

1. Maximal rates (usually $k'_{cat}s$)

```
Ka = 0.1 ;
Kb = 1 ;
Kc = 0.01 ;
Kd = 1 ;
Ke = 1 ;
Kf = 1 ;
Kg = 0.01 ;
Kh = 0.01 ;
```

2. Michaelis Constants

```
CDK_total = 100 ;
cdc25_total = 5 ;
wee1_total = 1 ;
IE_total = 1 ;
APC_total = 1 ;
PPase = 1 ;
```

3. Total protein concentrations

```
v2_1 = 0.005 ;
v2_2 = 0.25 ;
v25_1 = 0.0085 ;
v25_2 = 0.085 ;
vwee_1 = 0.01 ;
vwee_2 = 1 ;
```

4. Weighting parameters

9. $k_{25} = V_{25}' ([\text{Total Cdc25}] - [\text{Cdc25P}]) + V_{25}'' [\text{Cdc25P}]$

10. $k_{wee} = V_{wee}' [\text{Wee1P}] + V_{wee}'' ([\text{Total Wee1}] - [\text{Wee1P}])$

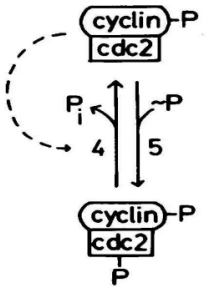
11. $k_2 = V_2' ([\text{Total APC}] - [\text{APC}]) + V_2'' [\text{APC}]$

1991 model versus 1993 model

1. **Autocatalytic activation of MPF**

Tyson (1991)

Active MPF

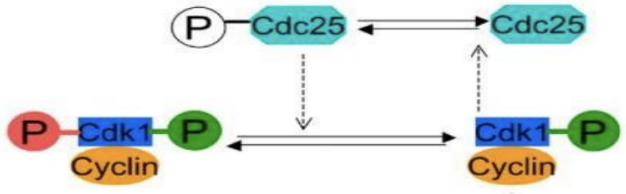


Inactive MPF

Direct effect of [MPF]

$$Rate_{pMPF\rightarrow MPF} = [pMPF]\left[k_4^{'} + k_4\left(\frac{[MPF]}{([CDC2]_{TOT})}\right)^2\right]$$

Novak & Tyson (1993)



Inactive MPF Active MPF

Occurs through cdc25

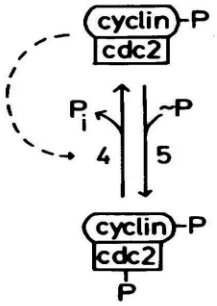
$$Rate_{pMPF\rightarrow MPF} = [pMPF](k_{25}^{'}[CDC25] + k_{25}[CDC25 - P])$$

$$Rate_{CDC25\rightarrow CDC25-P} = \frac{k_a[MPF][CDC25]}{[CDC25] + K_a}$$

2. Conversion of Active back to Inactive MPF

Tyson (1991)

Active MPF



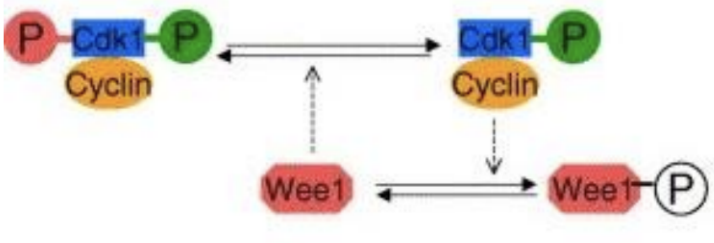
Inactive MPF

Rate constant k_5 is constant

wee1 not included

Novak & Tyson (1993)

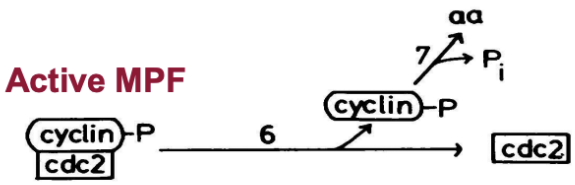
Inactive MPF Active MPF



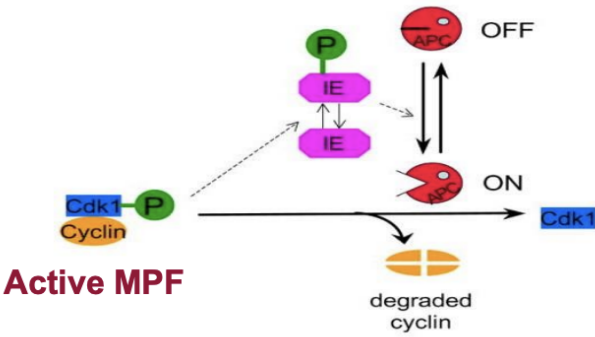
Phosphorylation occurs through wee1

3. **Degradation of cyclin**

Tyson (1991)



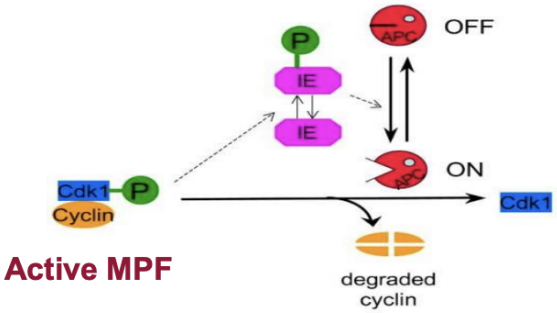
Novak & Tyson (1993)



Degradation occurs at a constant rate (k_6 = constant)

[MPF] indirectly activates A

Novak & Tyson (1993)



IE = intermediate enzyme

Included in model to account for delay between increase in MPF and activation of APC

This is now known to correspond to Fizzy/cdc20

"Intermediate enzyme" represents another experimentally-confirmed prediction

Overall, 1991 were described more mechanistically in 1993.

- Dynamical mathematical models frequently evolve by changing phenomenological descriptions into more mechanistic ones.
  - Phenomenology: B increases when A increases
  - Mechanism: A phosphorylates B
- Phenomenological representations can still be extremely useful when mechanistic detail is lacking.
- Cell cycle models developed by Tyson & coworkers provide excellent examples of such model evolution.