A Mutual Division

Regulation of the Eukaryotic Cell Cycle: Molecular Antagonism, Hysteresis, and Irreversible Transitions

A paper by John Tyson and Bela Novak

Presented by Marie Wilkening

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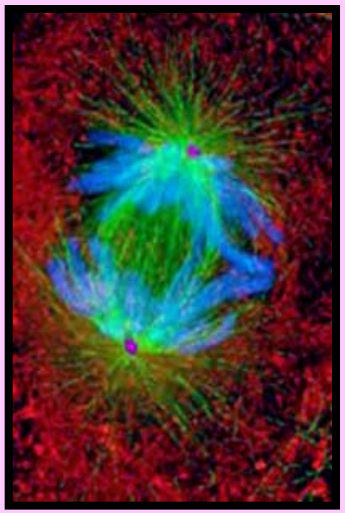
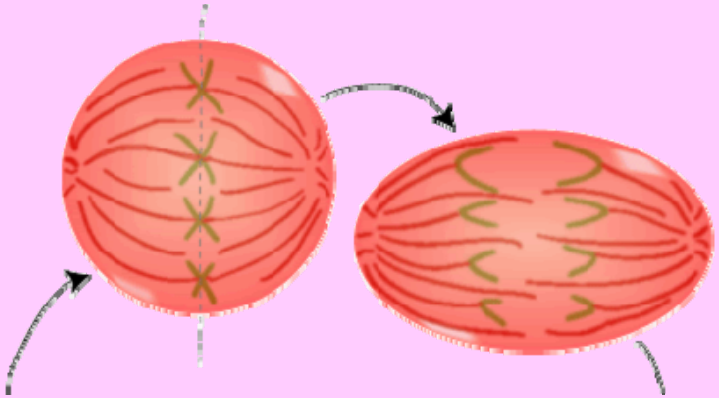
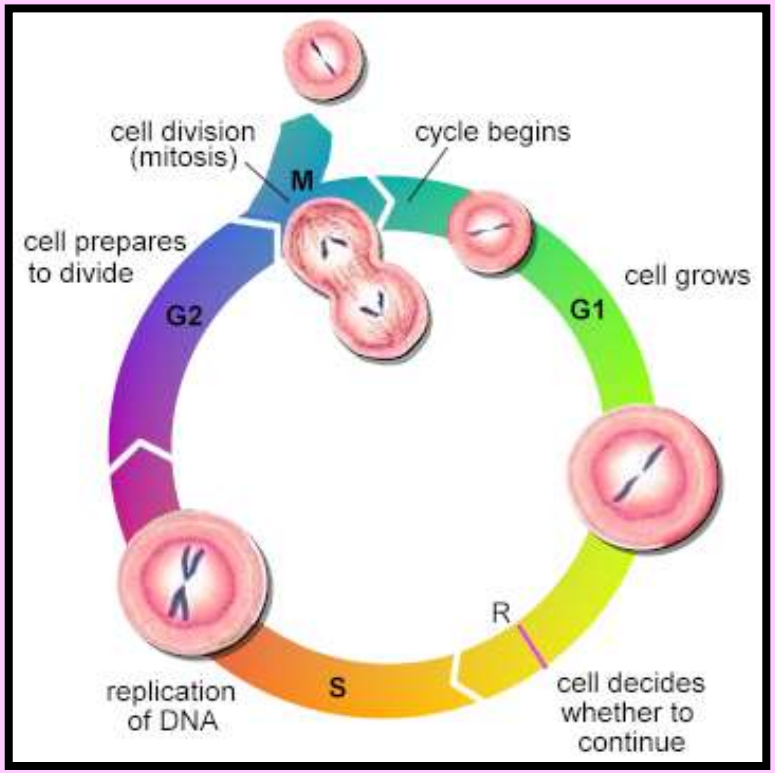


Mitotic Cell Cycle

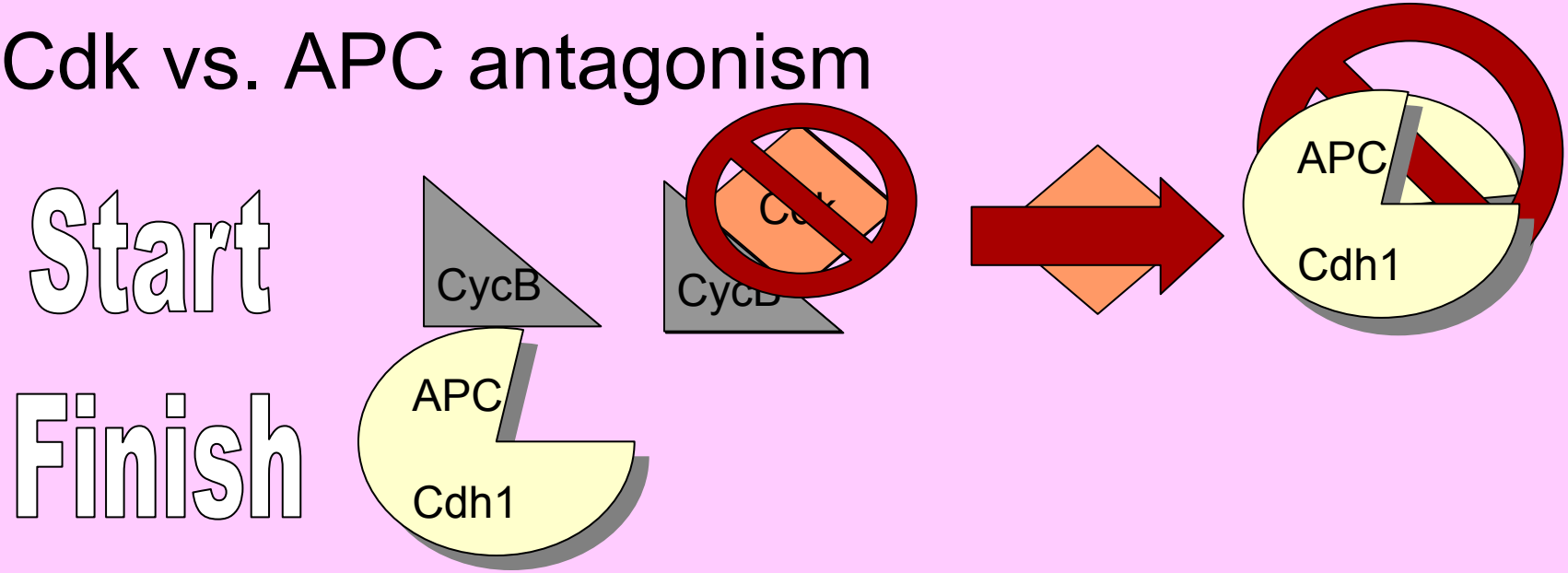
- Temporal stages
  - Growth (G1 & G2)
  - Chromosome (S & M)
- Occur at same rate!





Core Model Principles

- Cell size drives
- G1 vs. S, G2, M
  - Irreversible
  - Stable States
- Cdk vs. APC antagonism



The Model: Part 1

$$\frac{d[CycB]}{dt} = k_1 - (k_2' + k_2'' [Cdh1])[CycB],$$

Rate of change of CycB concentration

Synthesis

Degradation

Degradation Due to Cdh1

Concentration of CycB

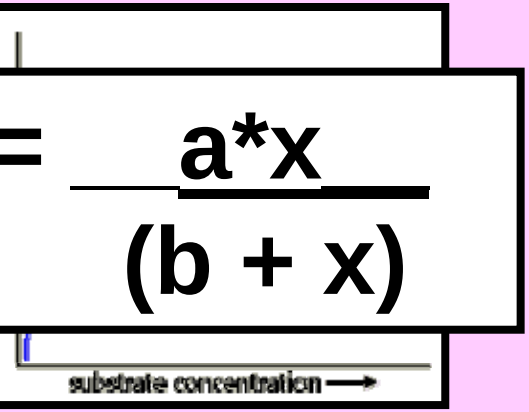
The Model: Part 2a

- Cdh1 is Michaelis-Menton Enzyme

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + \text{products}$$

$$v = \frac{V_{max}[S]}{K_M + [S]}$$

$$y = \frac{a*x}{(b + x)}$$



The Model: Part 2b

$$\frac{d[Cdh1]}{dt} = \frac{(k_3 + k_3'' A)(1 - [Cdh1])}{J_3 + 1 - [Cdh1]} - \frac{k_4 m [CycB][Cdh1]}{J_4 + [Cdh1]}.$$

Rate of change of Cdh1 Activation

Activation

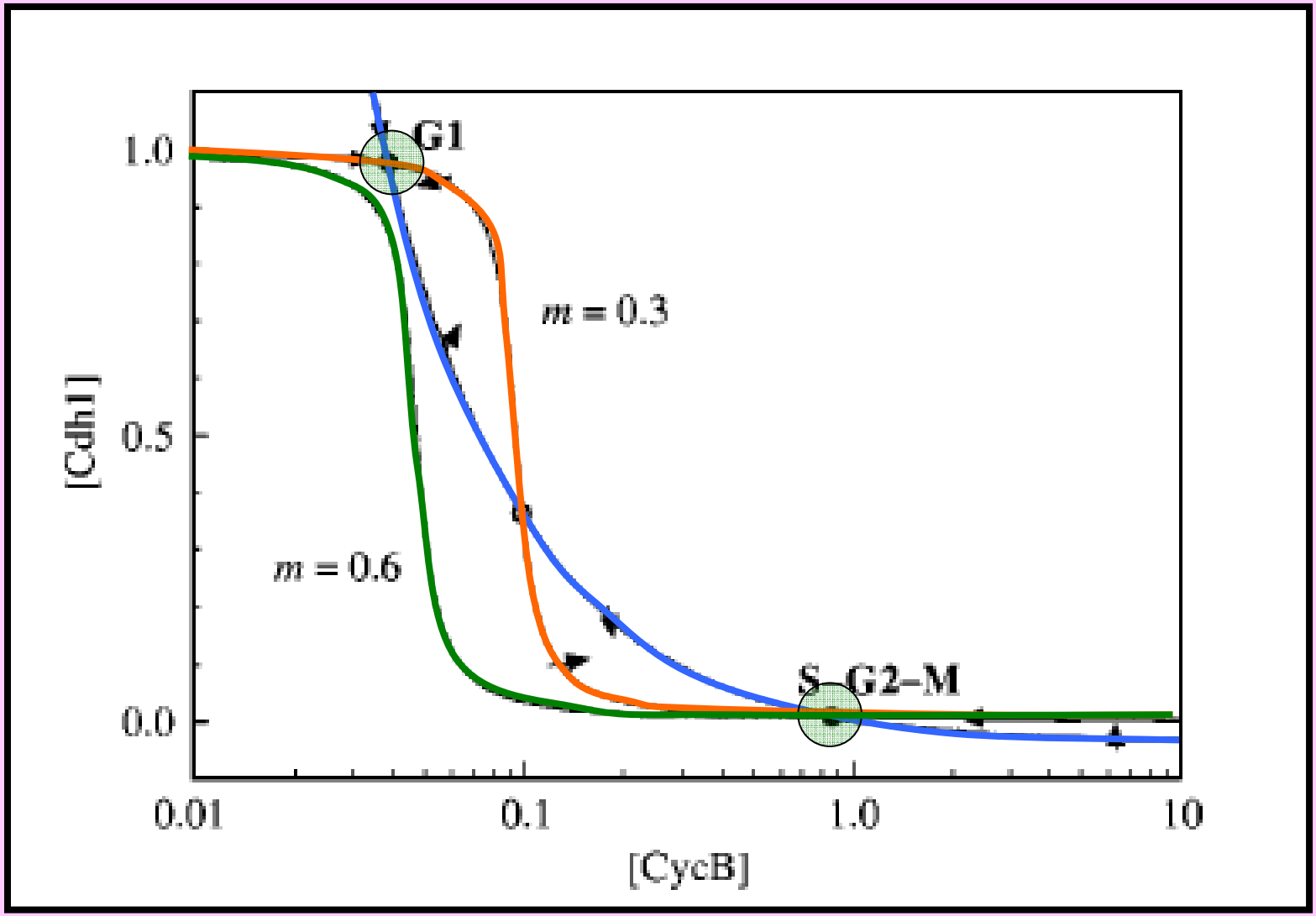
Deactivation

$$y = \frac{a*x}{(b + x)}$$

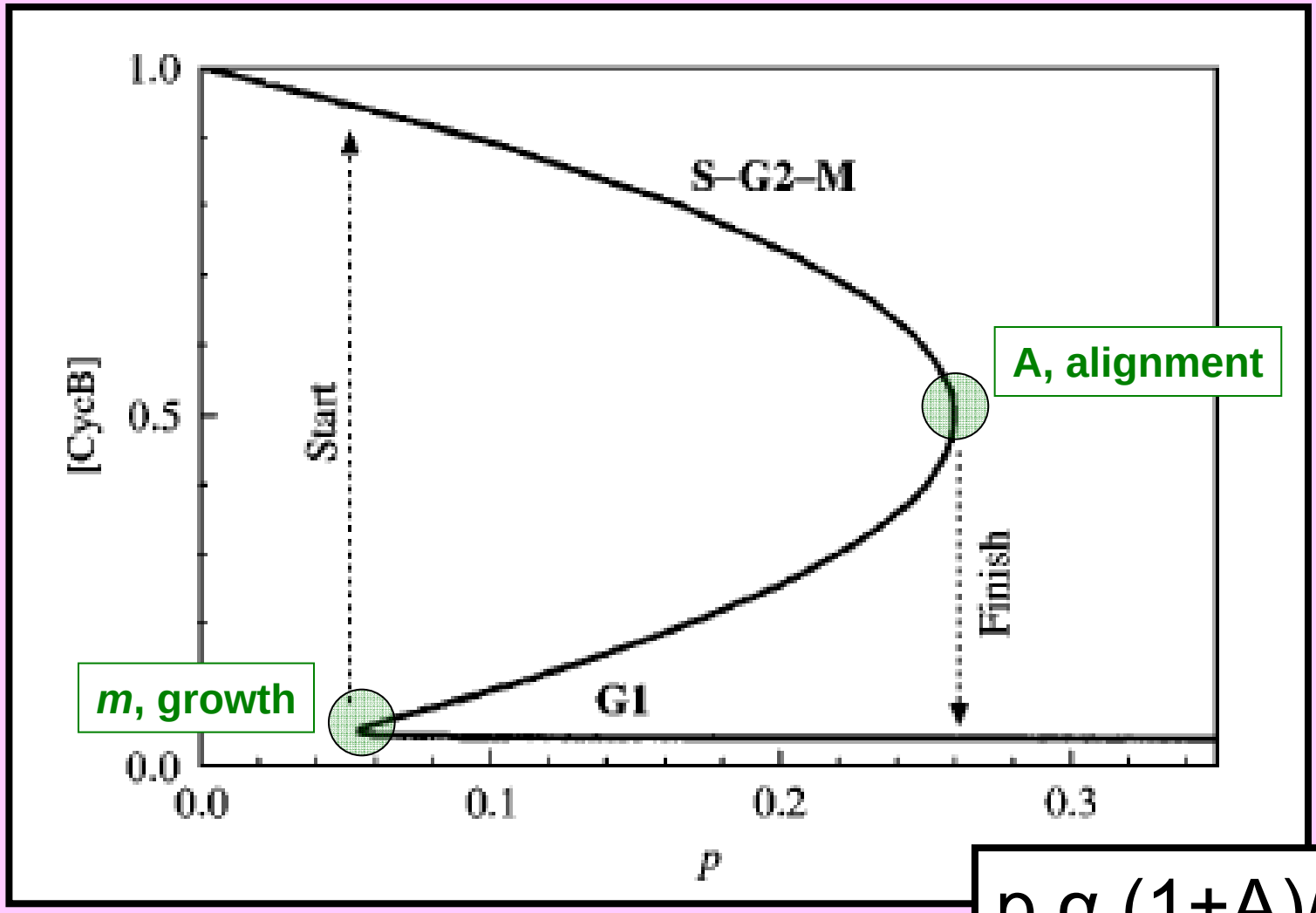
Assumptions

- J3 & J4 << 1
- APC cores in excess
- CycB/Cdk1 inactivates Cdh1 in nucleus
- CycB combines rapidly with excess Cdk
- Cdh1 Concentration is constant

What it Means:



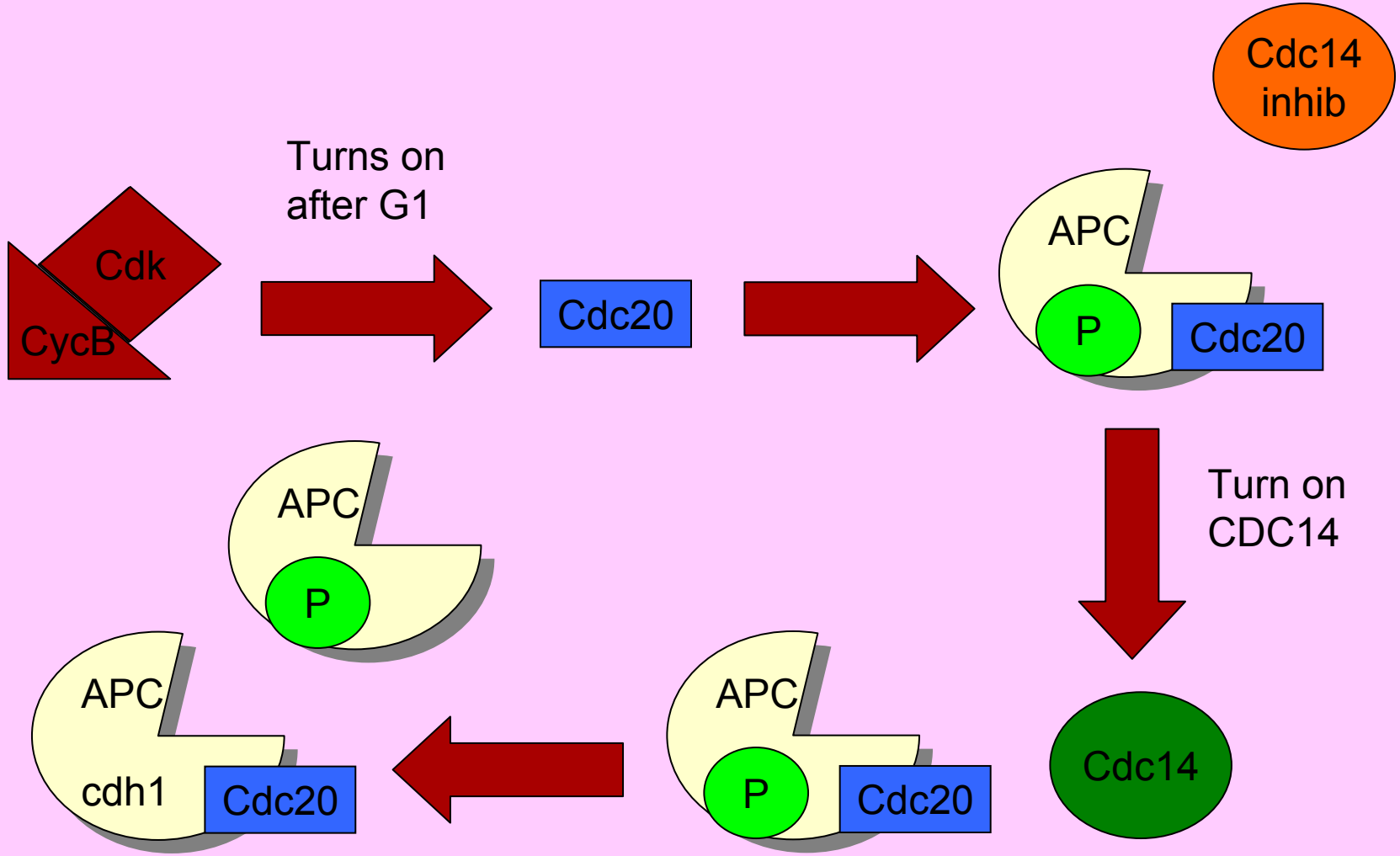
Bifurcation Diagram



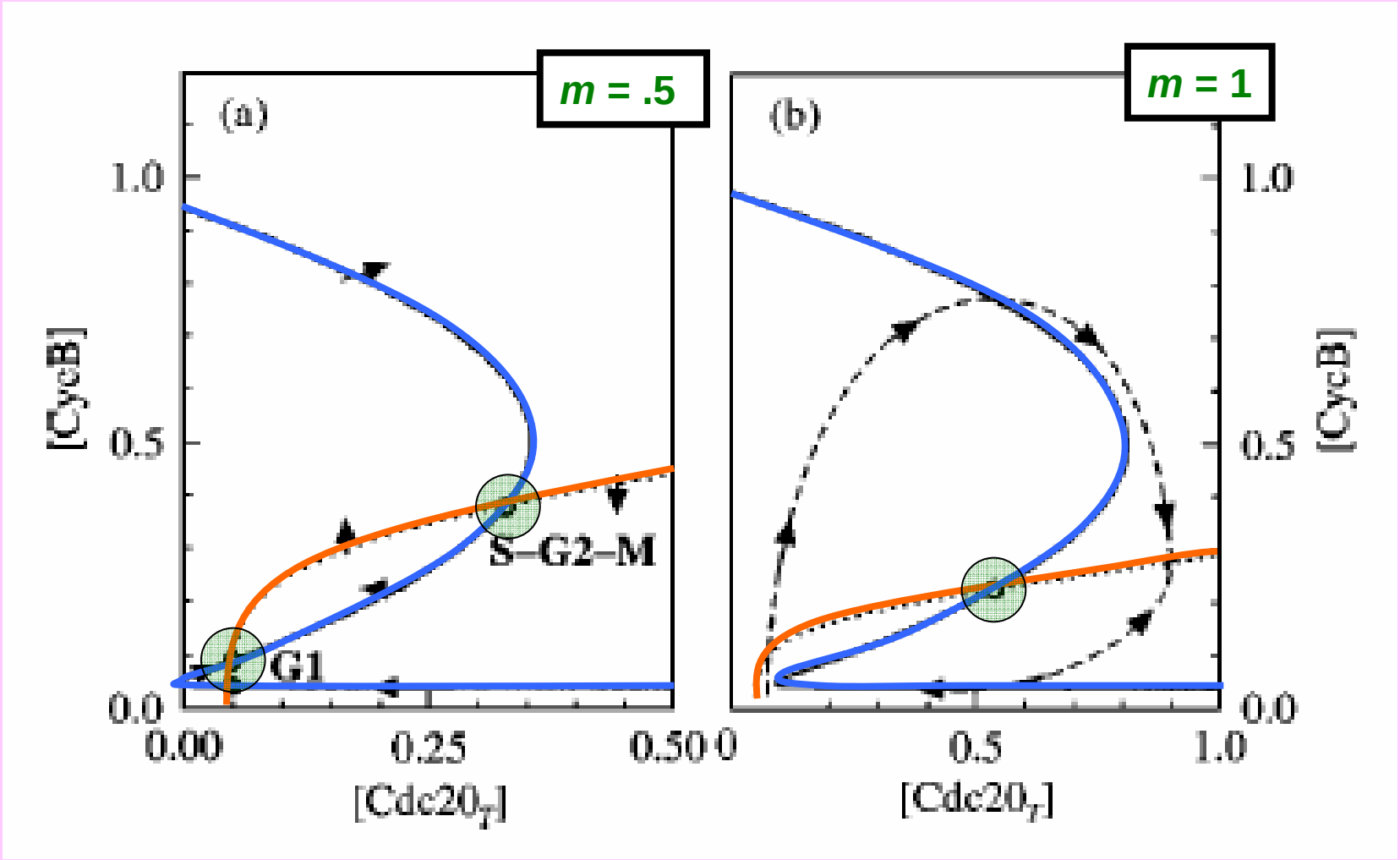
p α (1+A)/*m*

Give me an A!

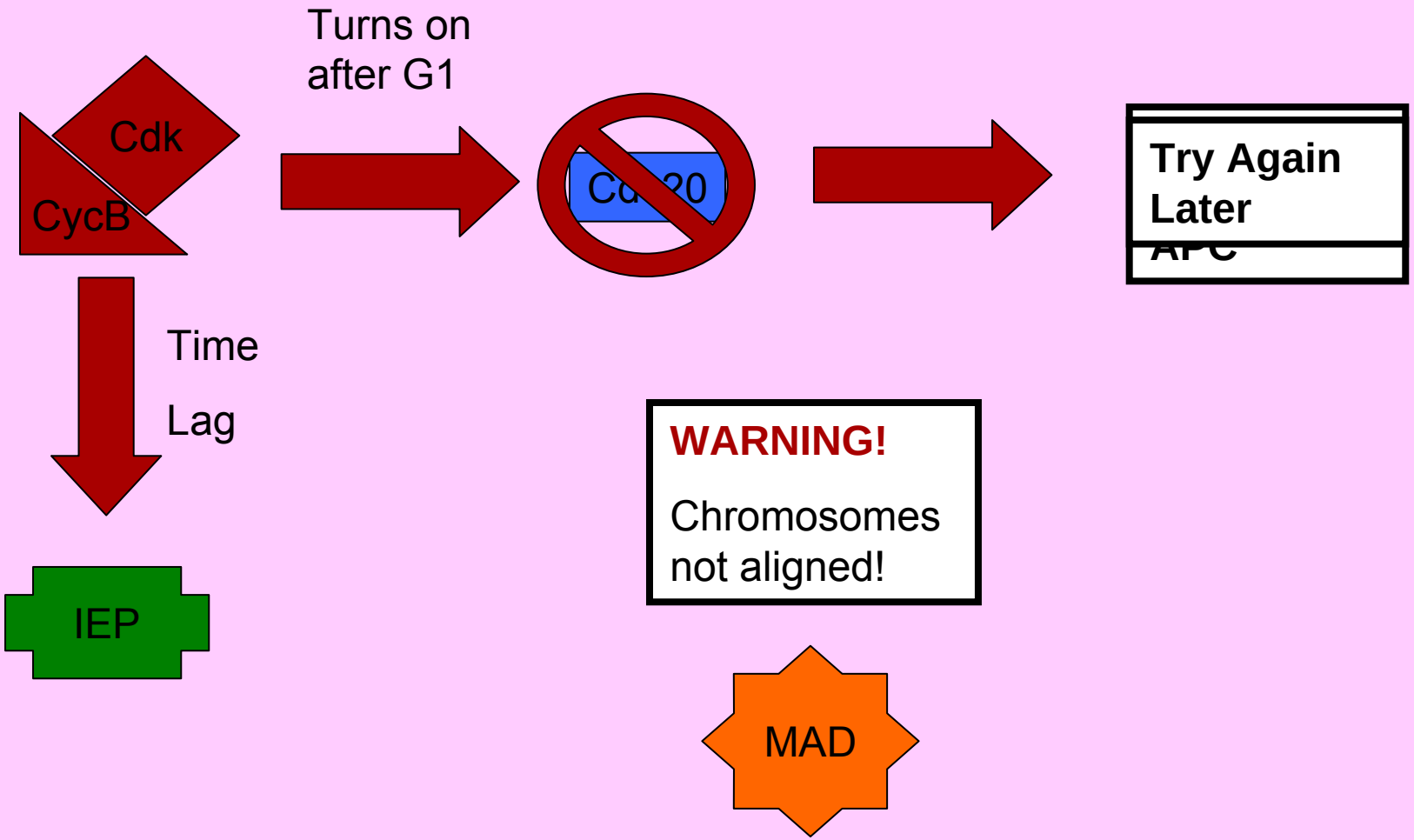
- Activating APC, not metaphase dependant



New Nullclines



Metaphase Controls



What Causes it to Rise?

- Base for eukaryotic cells
- Adjustments for budding and fission yeast
- Model accurate for mutants
- Limit-Cycle Oscillators?

References

- (1) Banner www.extrabyte.de/.../ ref/cell-division.jpg
- (1) Anaphase http://www.healthsystem.virginia.edu/internet/microscopy
- (2) Cell Cycle Pic learninglab.co.uk/headstart/cycle3.htm
- Gale Rhodes,Chemistry Department,University of Southern Maine “A simple Model of Enzyme Action” http://www.usm.maine.edu/~rhodes/Goodies/DeriveMMEqn.html
- John J. Tyson, Bela Novak. “Regulation of the Eukaryotic Cell Cycle: Molecular Antagonism, Hysteresis, and Irreversible Transitions”. J. theor. Biol. (2001) 210, 249-263. Online at www.idealibrary.com, figures (4,6,8,9,11)
- Animations by Marie Wilkening