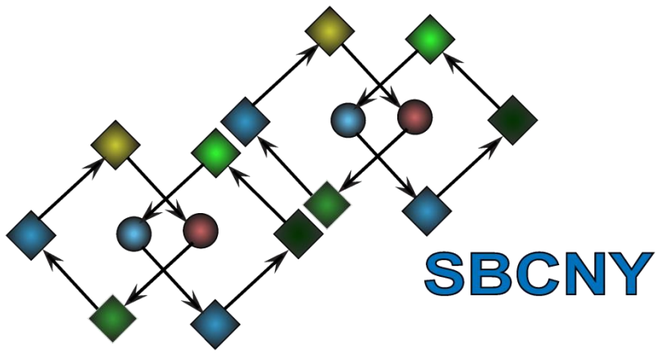
Computational modeling of the cell cycle

Part 2

Icahn School of Medicine at Mount Sinai



Outline: Part 2

The Novak-Tyson (1993) cell cycle model

Structure of the Novak-Tyson model

- Biochemical reactions
- Differential equations

Relevance of the Novak-Tyson model

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

The 1993 Novak-Tyson cell cycle model

Journal of Cell Science 106, 1153-1168 (1993)
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Numerical analysis of a comprehensive model of M-phase control in *Xenopus* oocyte extracts and intact embryos

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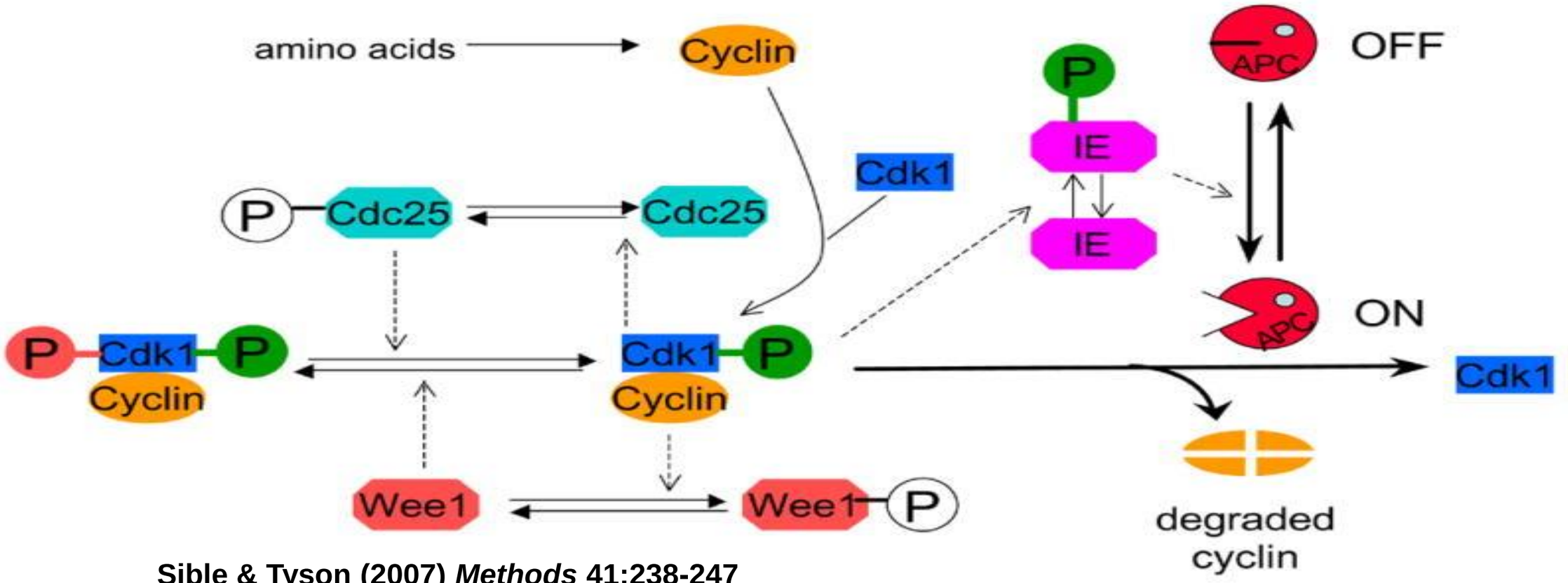
Novak & Tyson (1993) *Journal of Cell Science* 106:1153-1168

The 1993 Novak-Tyson cell cycle model

Can be divided into two “modules”

cyclin/Cdk dimer Regulation

cyclin degradation regulation



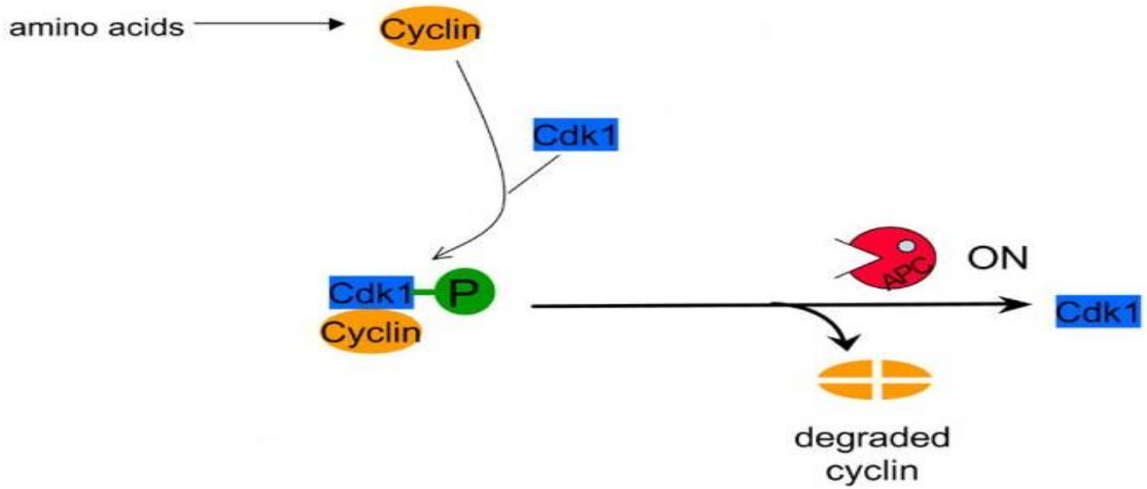
Sible & Tyson (2007) *Methods* 41:238-247

Overall “wiring diagram” combines the two

Novak-Tyson model: ODEs

Two main classes of equations

1) Those that involve synthesis/degradation of cyclin

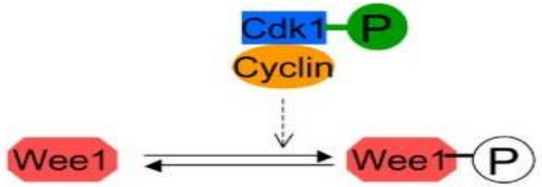


$$\frac{d[cyclin]}{dt} = k_1 - k_3[cyclin][Cdk] - k_2[cyclin]$$

$$k_2 = v_{2\_1}[APC]_{off} + v_{2\_2}[APC]_{on}$$

synthesis dimer formation degradation

2) Those that only involve phosphorylation/dephosphorylation



$$\frac{d[wee1P]}{dt} = \frac{k_e[MPF]([wee1]_{TOT} - [wee1P])}{[wee1]_{TOT} - [wee1P] + K_e} - \frac{k_f[PPase][wee1P]}{[wee1P] + K_f}$$

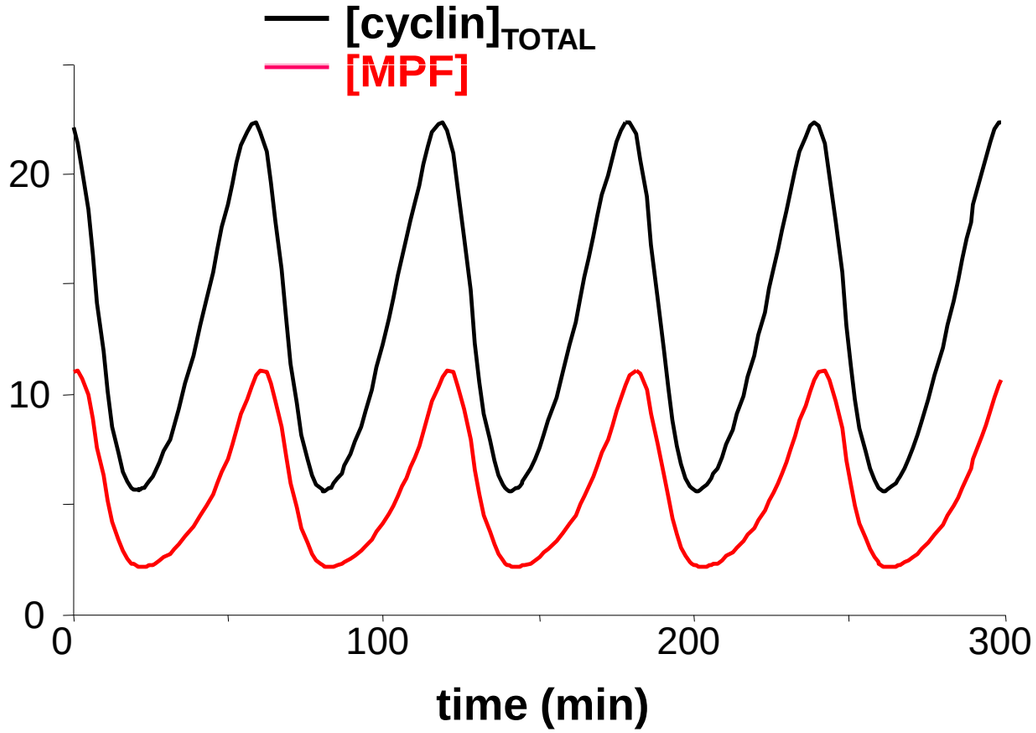
[PPase] represents generic phosphatase activity

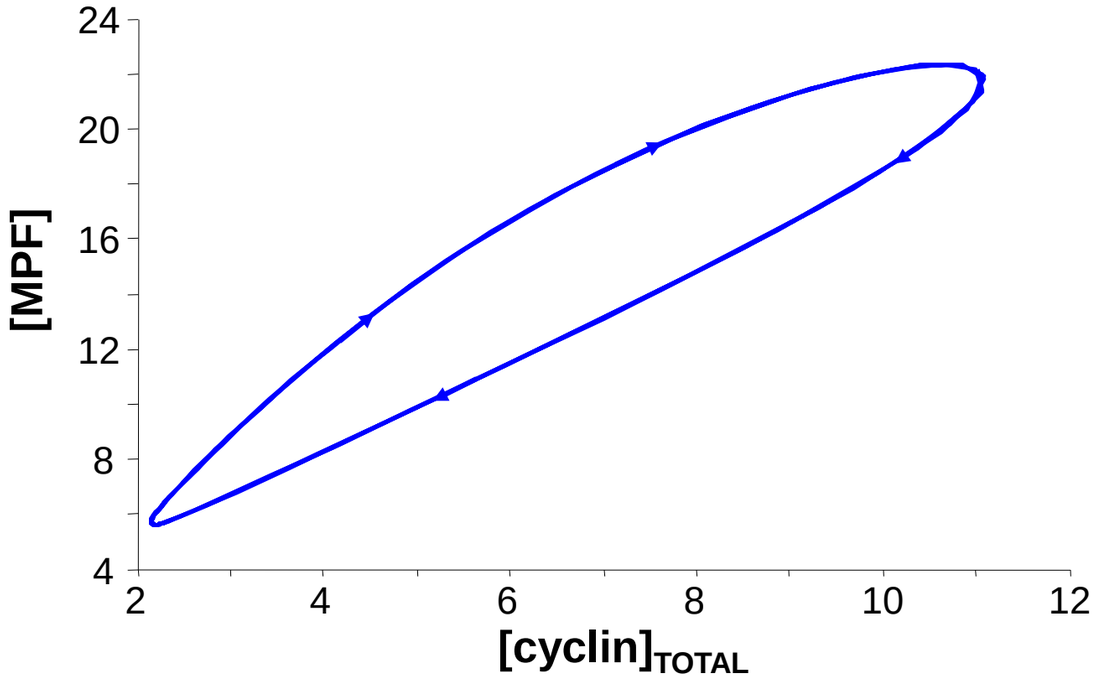
Results of the 1993 Novak-Tyson model

Spontaneous oscillations of MPF and cyclin

Analogous to rapid divisions in newly-fertilized oocyte

Similar to experimental observations



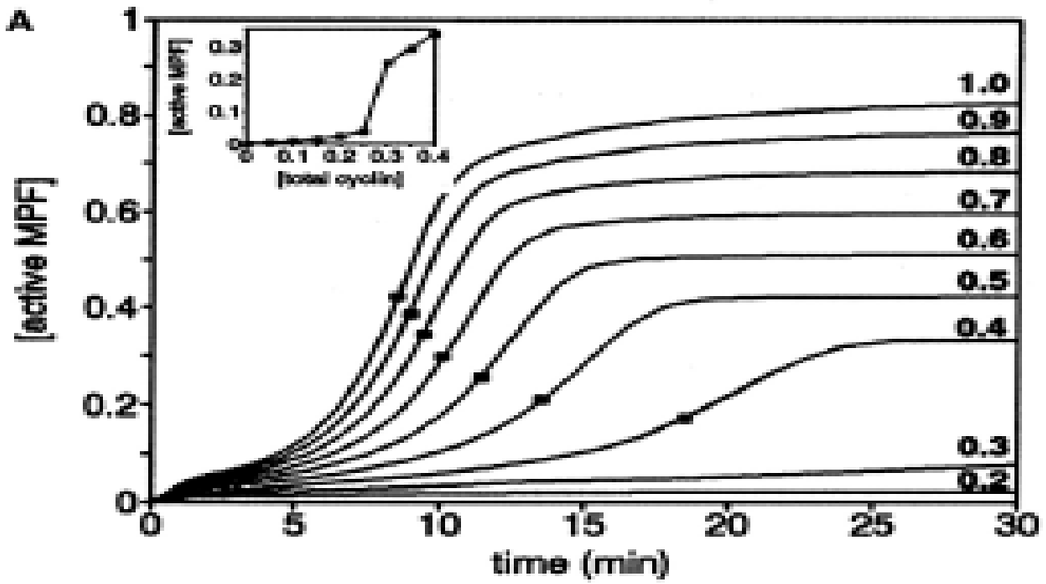


These obtained with control values of numerical parameters

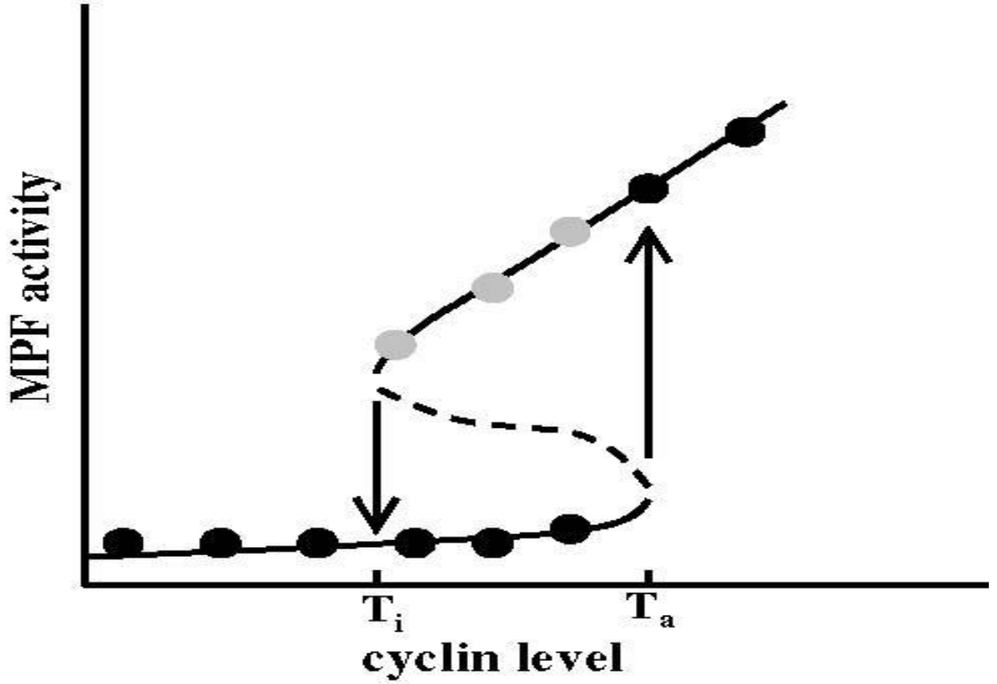
Results of the 1993 Novak-Tyson model

Bistability between $[cyclin]_{TOTAL}$ and [MPF]

To simplify, use non-degradable cyclin



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



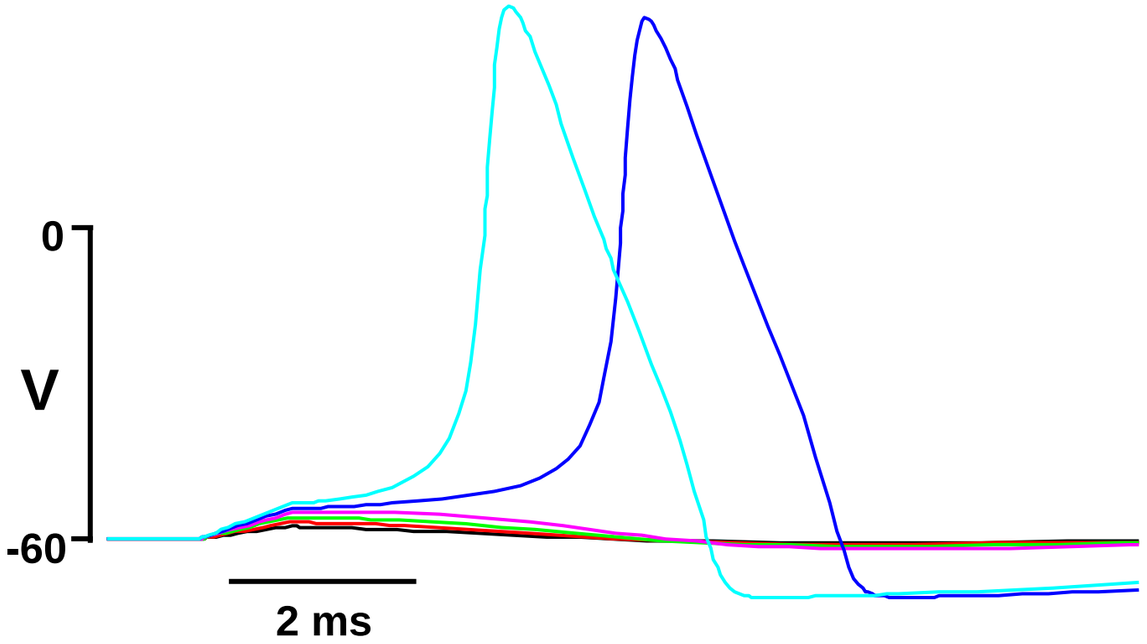
Threshold (left) was similar to experimental observations
Bistability (right) was a novel prediction

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

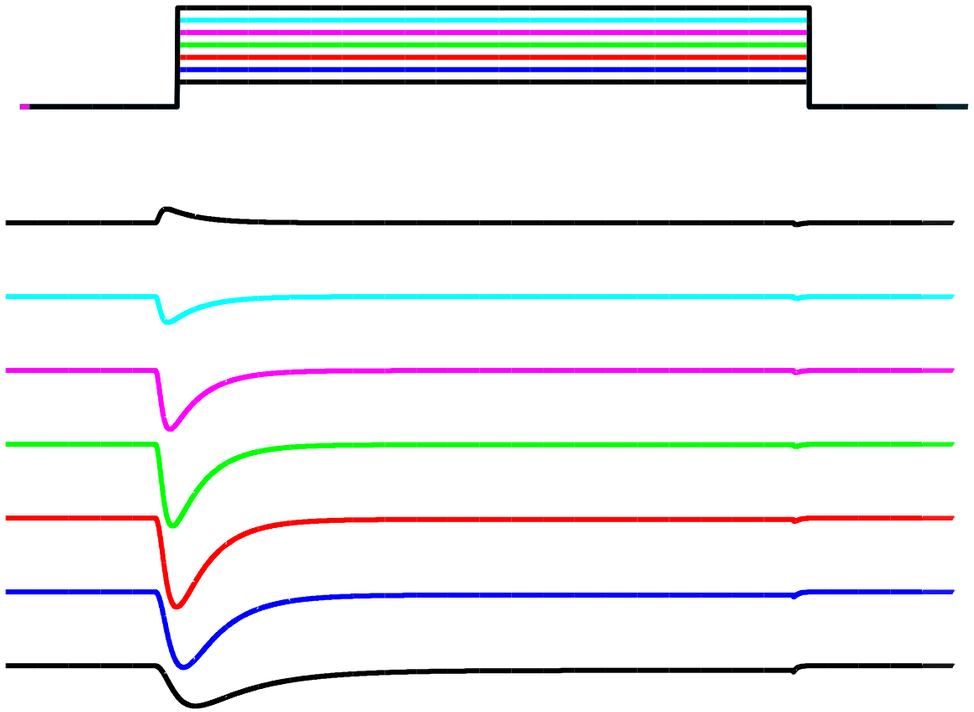
Constraining complicated systems

Experiments that remove one or more variables are extremely helpful

Everything changing at once



Fix voltage, measure only Na^+ current

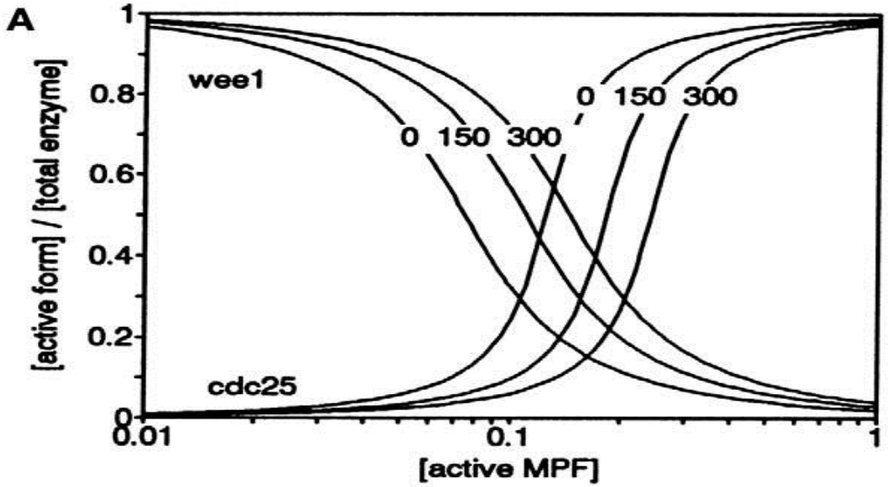


Voltage clamp was the key advance that made the Hodgkin-Huxley model possible

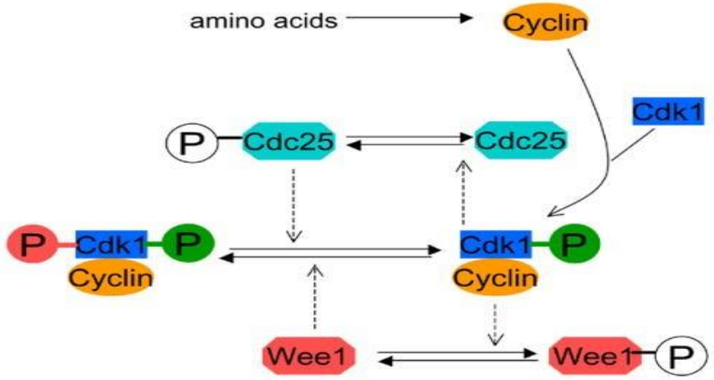
Results of the 1993 Novak-Tyson model

Effects of unreplicated DNA on cell cycle oscillations

[DNA] effects on regulation



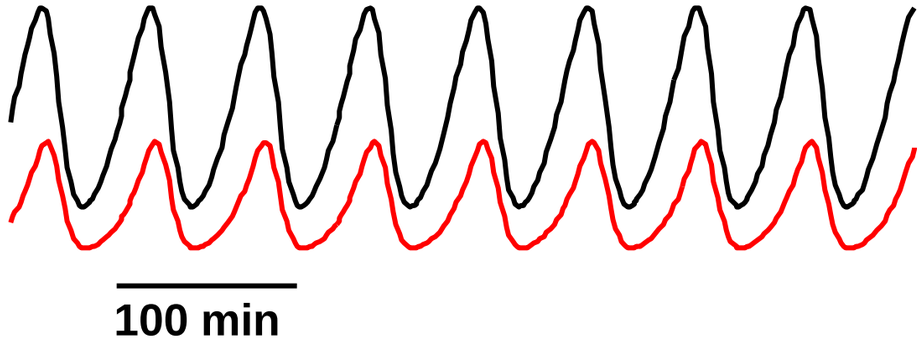
[DNA] → more wee1, less cdc25



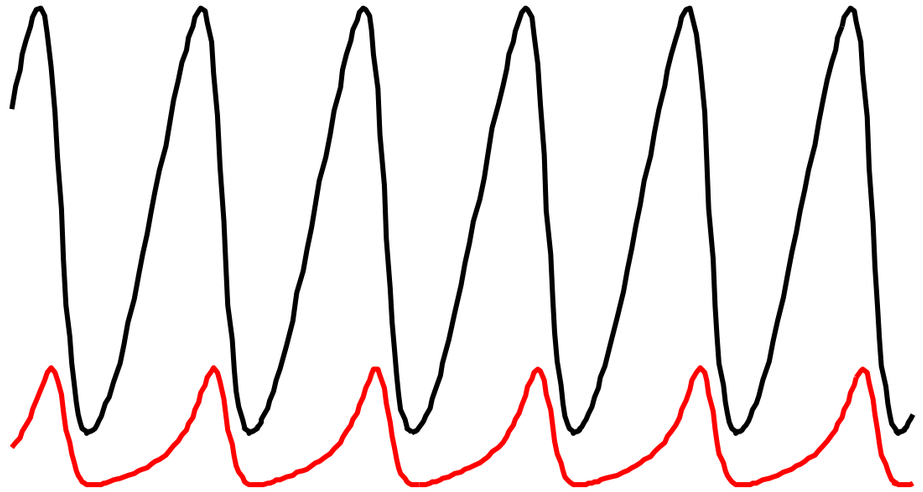
[cyclin]$_{TOTAL}$

[MPF]

Control oscillations



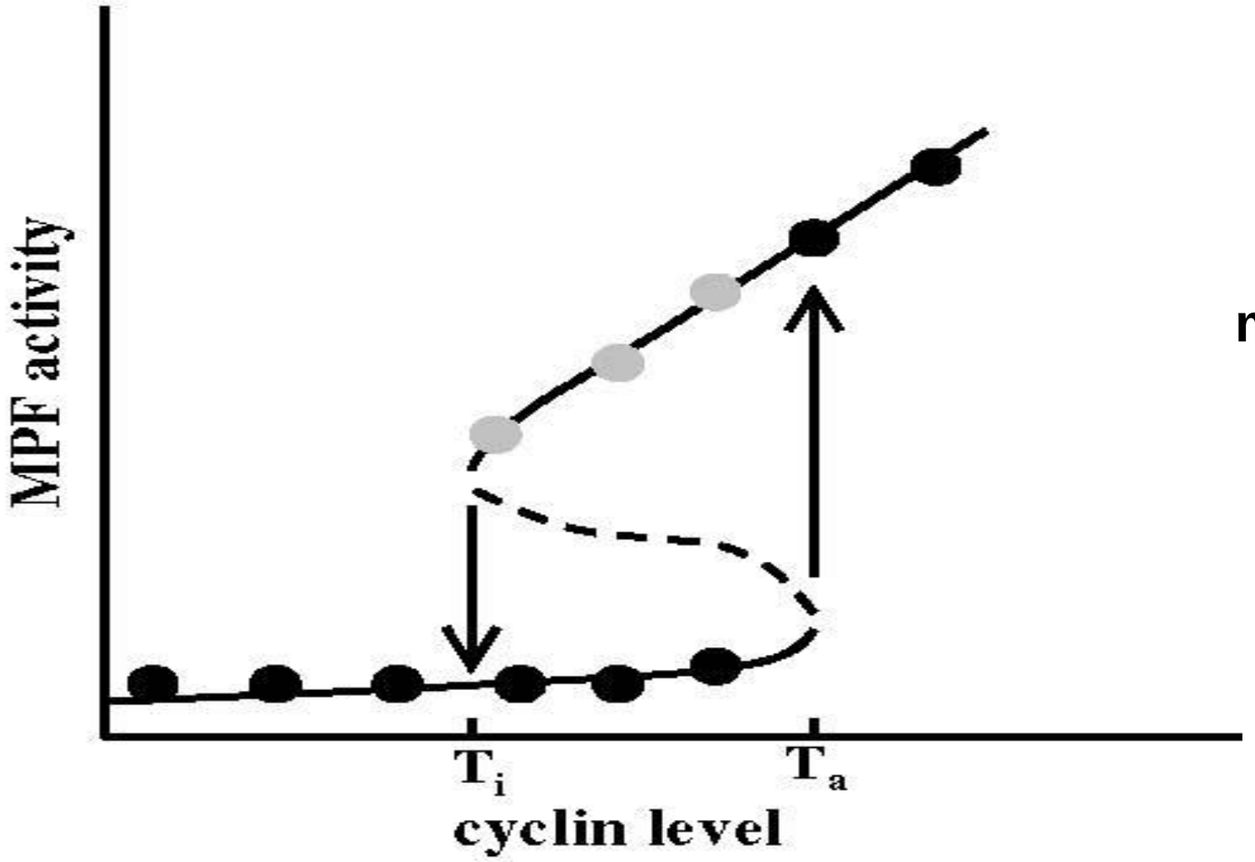
Oscillations with [DNA]



Results of the 1993 Novak-Tyson model

Model predictions were later confirmed experimentally

Hysteresis in the [cyclin]-[MPF] relationship



model prediction

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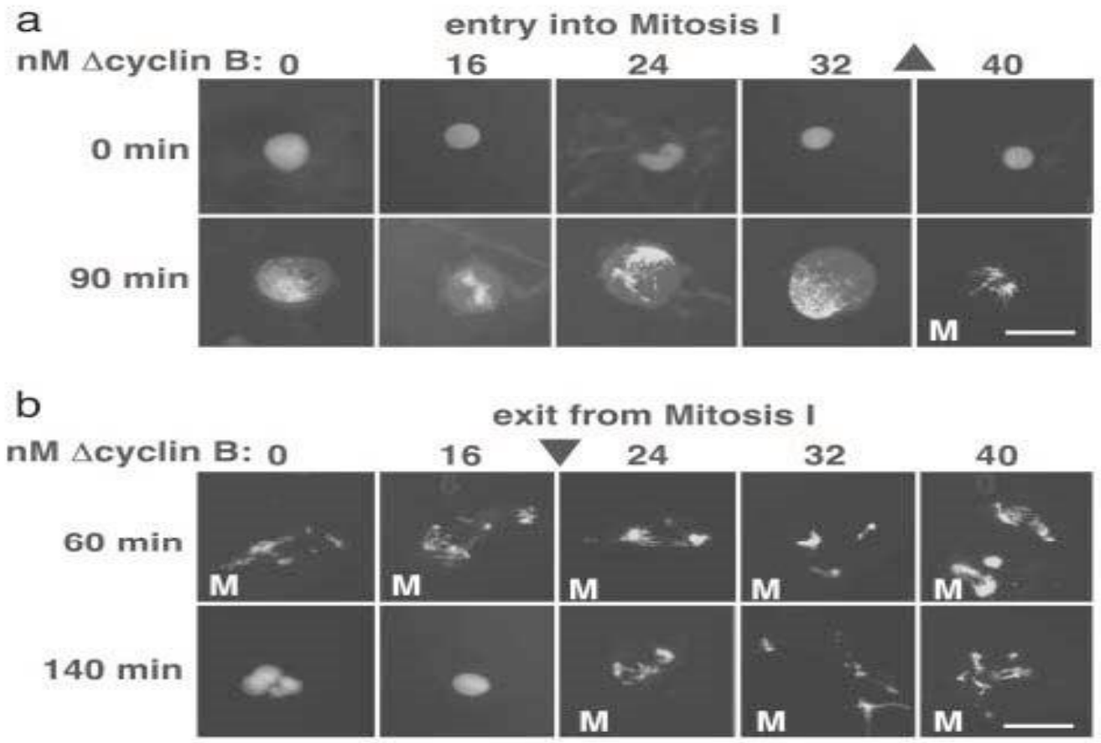
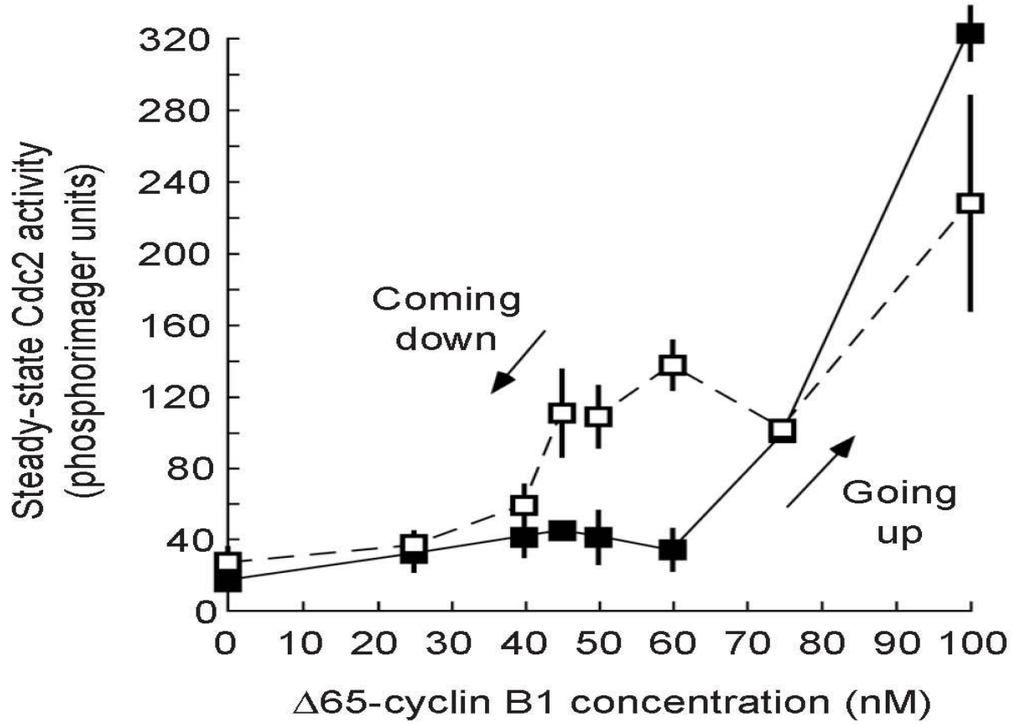


Sha et al. (2003) *PNAS* 100:975-980

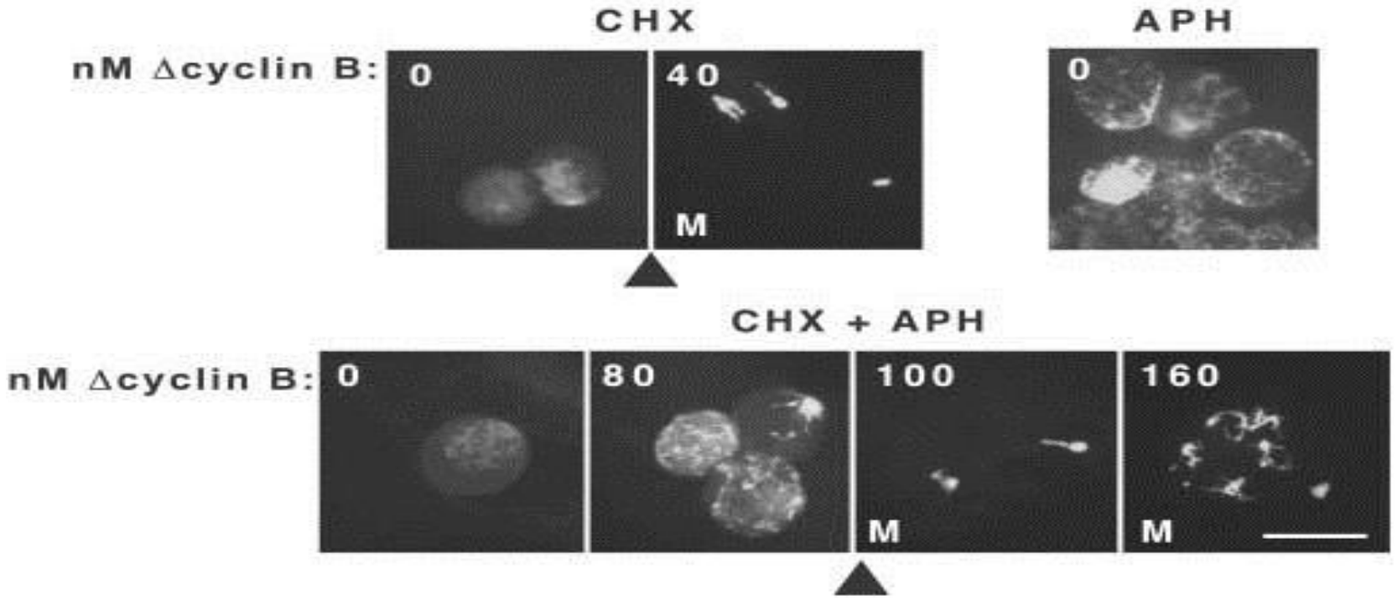


Pomerening et al. (2003) *Nature Cell Bio.* 5:346-351

Results of the 1993 Novak-Tyson model

Model predictions were later confirmed experimentally

Unreplicated DNA changes the location of the bifurcation



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

Summary

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