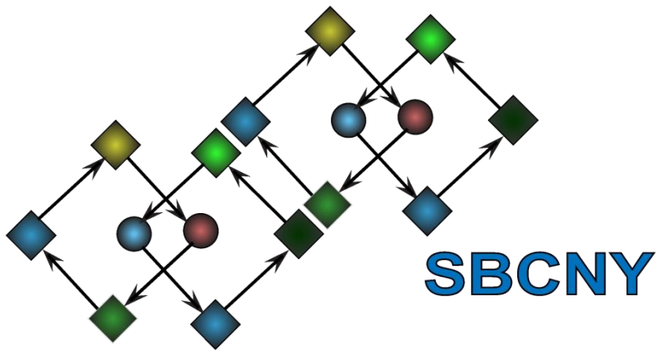
Computational modeling of the cell cycle

Part 3

Icahn School of Medicine at Mount Sinai



Theme

Phenomenology versus Mechanism in Mathematical models

Sometimes models describe biochemical/molecular mechanisms,

sometimes they just describe an observed phenomenon

Examples

1993 Novak-Tyson model versus 1991 Tyson model

1993 Novak-Tyson model versus contemporary models

Models generally become more mechanistic and more complex, but they occasionally get simpler

The 1993 Novak-Tyson cell cycle model

Journal of Cell Science 106, 1153-1168 (1993)
Printed in Great Britain © The Company of Biologists Limited 1993

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

Bela Novak* and John J. Tyson†

Department of Biology, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24060-0406, USA

*Permanent address: Department of Agricultural Chemical Technology, Technical University of Budapest, 1521 Budapest Gellert Ter 4, Hungary
†Author for correspondence

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

The 1991 Tyson cell cycle model

Proc. Natl. Acad. Sci. USA
Vol. 88, pp. 7328–7332, August 1991
Cell Biology

Modeling the cell division cycle: cdc2 and cyclin interactions

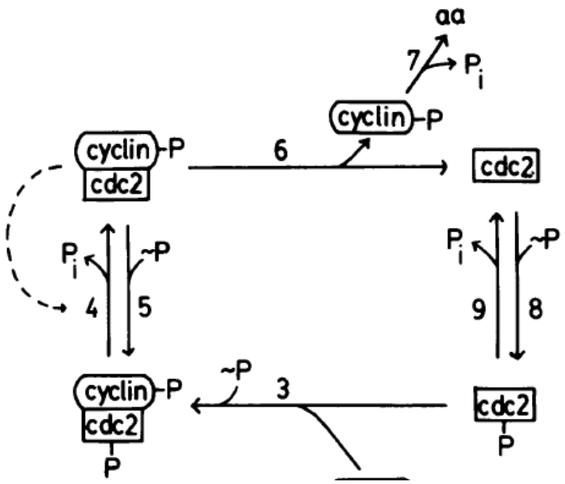
(maturation promoting factor/metaphase arrest/*wee1*/*cdc25*)

JOHN J. TYSON

Department of Biology, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061

Communicated by David M. Prescott, May 20, 1991 (received for review January 23, 1991)

ABSTRACT **The proteins cdc2 and cyclin form a heterodimer (maturation promoting factor) that controls the major events of the cell cycle. A mathematical model for the interactions of cdc2 and cyclin is constructed. Simulation and analysis of the model show that the control system can operate in three modes: as a steady state with high maturation promoting factor activity, as a spontaneous oscillator, or as an excitable switch. We associate the steady state with metaphase arrest in unfertilized eggs, the spontaneous oscillations with rapid division cycles in early embryos, and the excitable switch with growth-controlled division cycles typical of nonembryonic cells.**

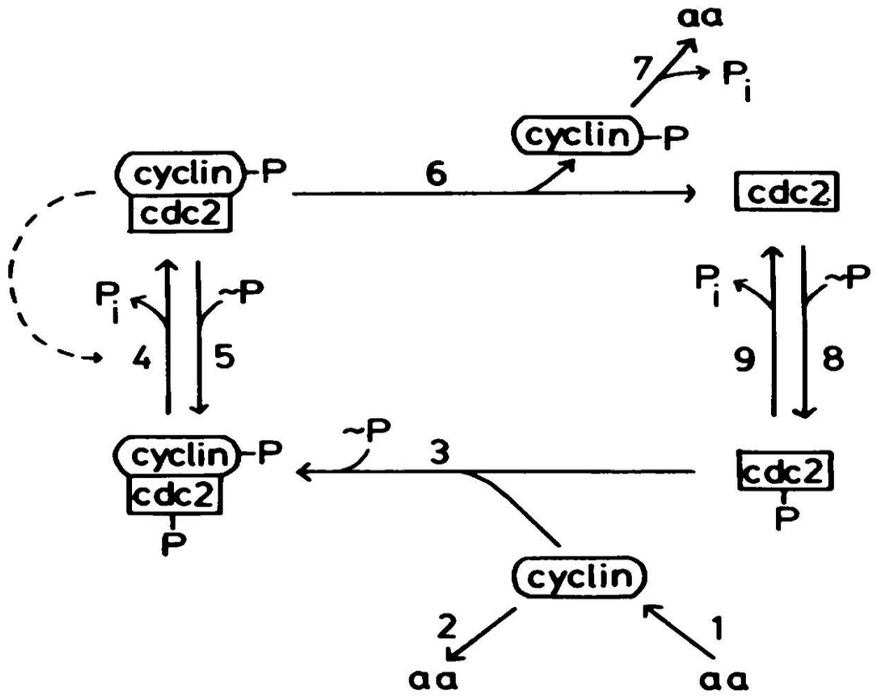


Tyson (1991) *PNAS* 88:7328-7332.

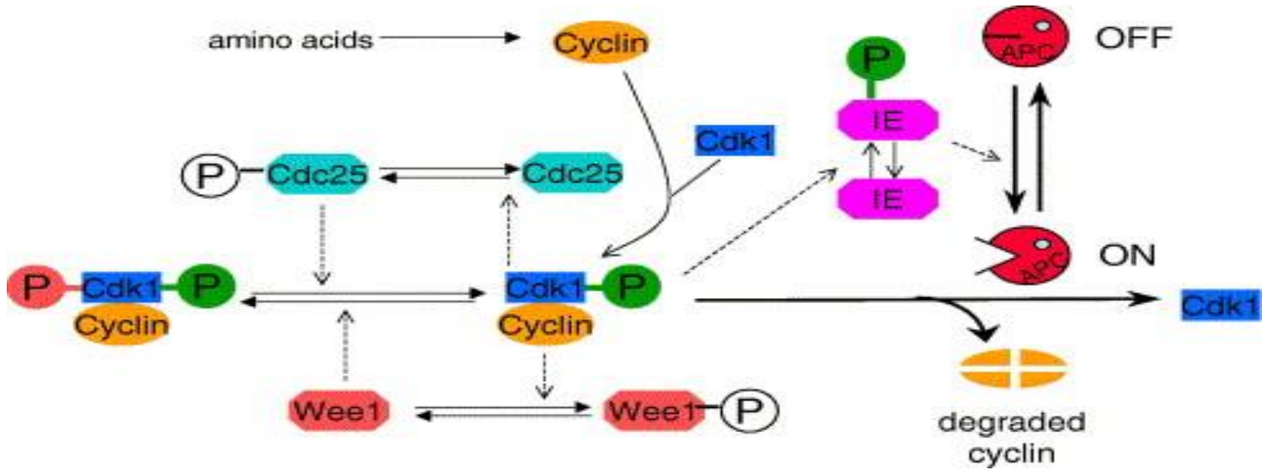
Comparing these two models can illustrate phenomenology vs. mechanism

Phenomenology versus Mechanism

Compare 1991 model with 1993 model



Tyson (1991) *PNAS* 88:100:7328-7332



Novak & Tyson (1993) *J. Cell Science* 106:1153-1168
diagram from Sible & Tyson (2007)

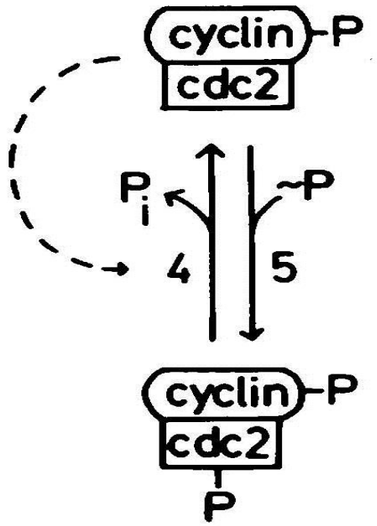
Between 1991 and 1993, new processes added to the model

1991 model versus 1993 model

Autocatalytic activation of MPF

Tyson (1991)

Active MPF

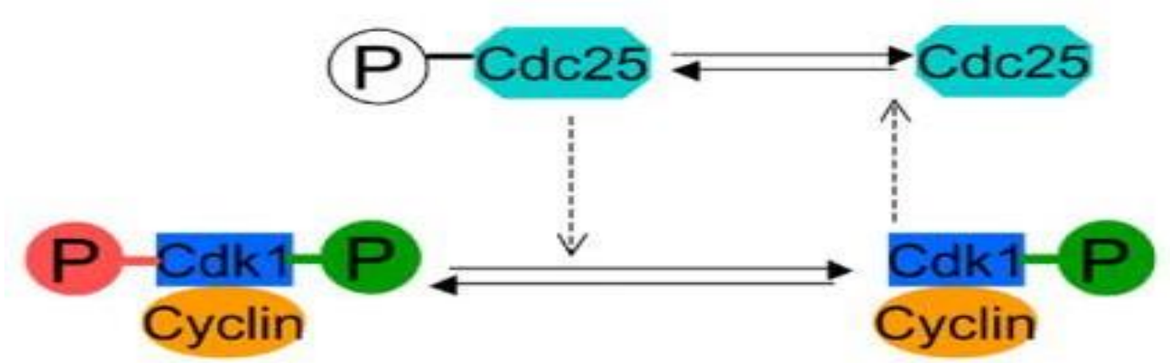


Inactive MPF

Direct effect of [MPF]

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

Novak & Tyson (1993)



Inactive MPF **Active MPF**

Occurs through cdc25

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

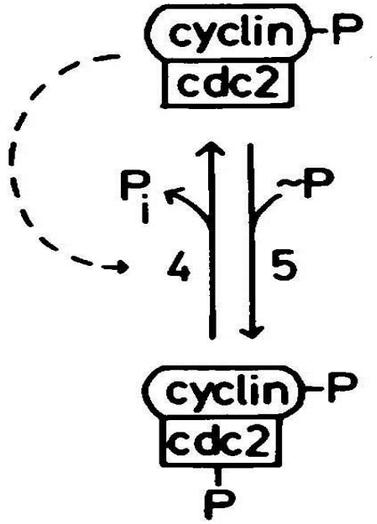
$$Rate_{CDC25 \to CDC25-P} = \frac{k_a[MPF][CDC25]}{[CDC25] + K_a}$$

1991 model versus 1993 model

Conversion of Active back to Inactive MPF

Tyson (1991)

Active MPF



Inactive MPF

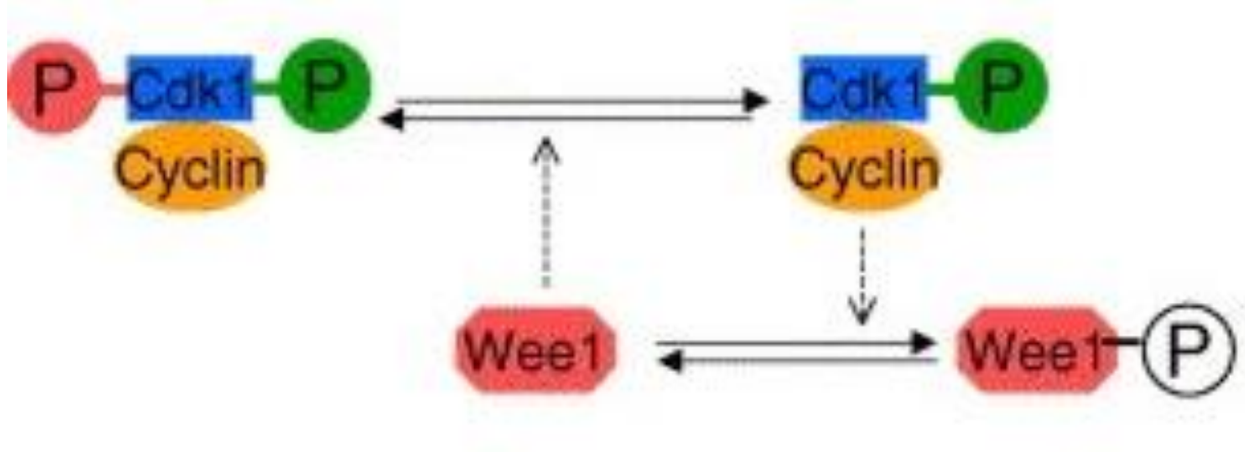
Rate constant k_5 is constant

wee1 not included

Novak & Tyson (1993)

Inactive MPF

Active MPF

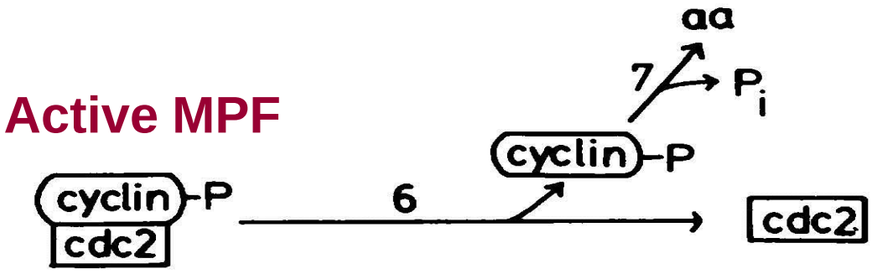


Phosphorylation occurs through wee1

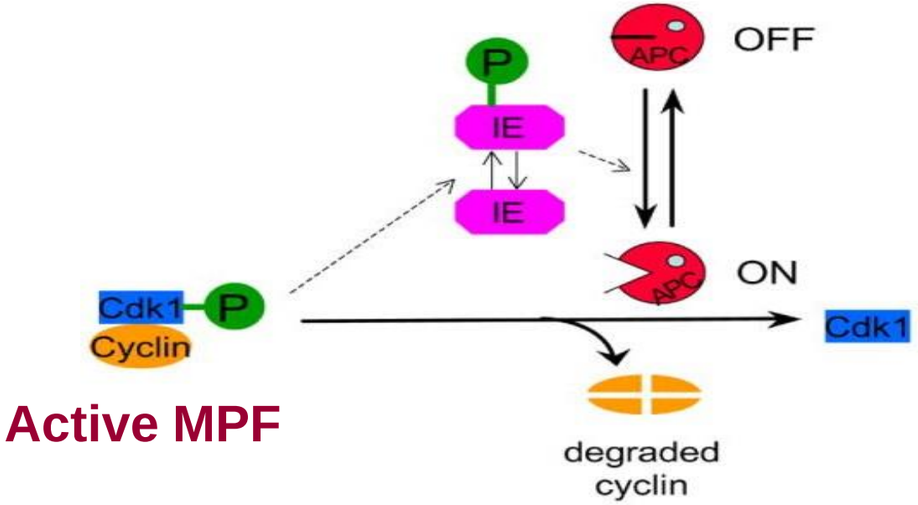
1991 model versus 1993 model

Degradation of cyclin

Tyson (1991)



Novak & Tyson (1993)



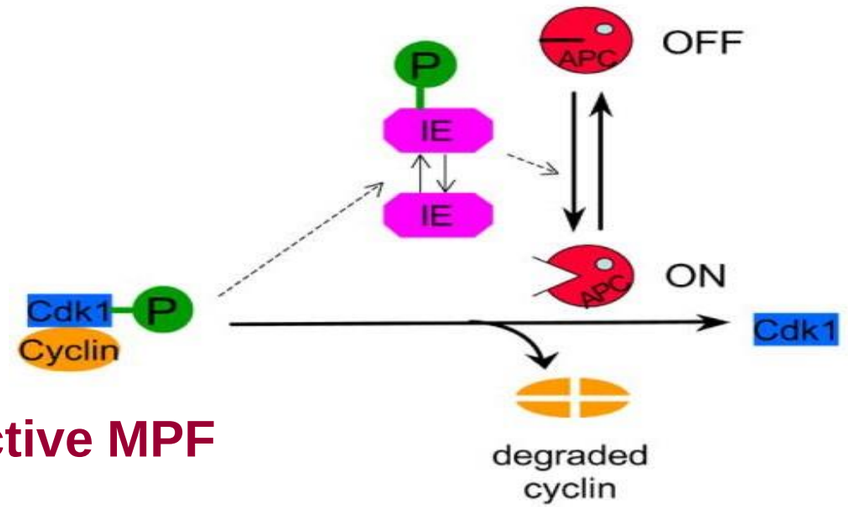
Degradation occurs at a constant rate (k_6 = constant)

[MPF] indirectly activates APC

1993 model versus contemporary knowledge

Degradation of cyclin

Novak & Tyson (1993)



Active MPF

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

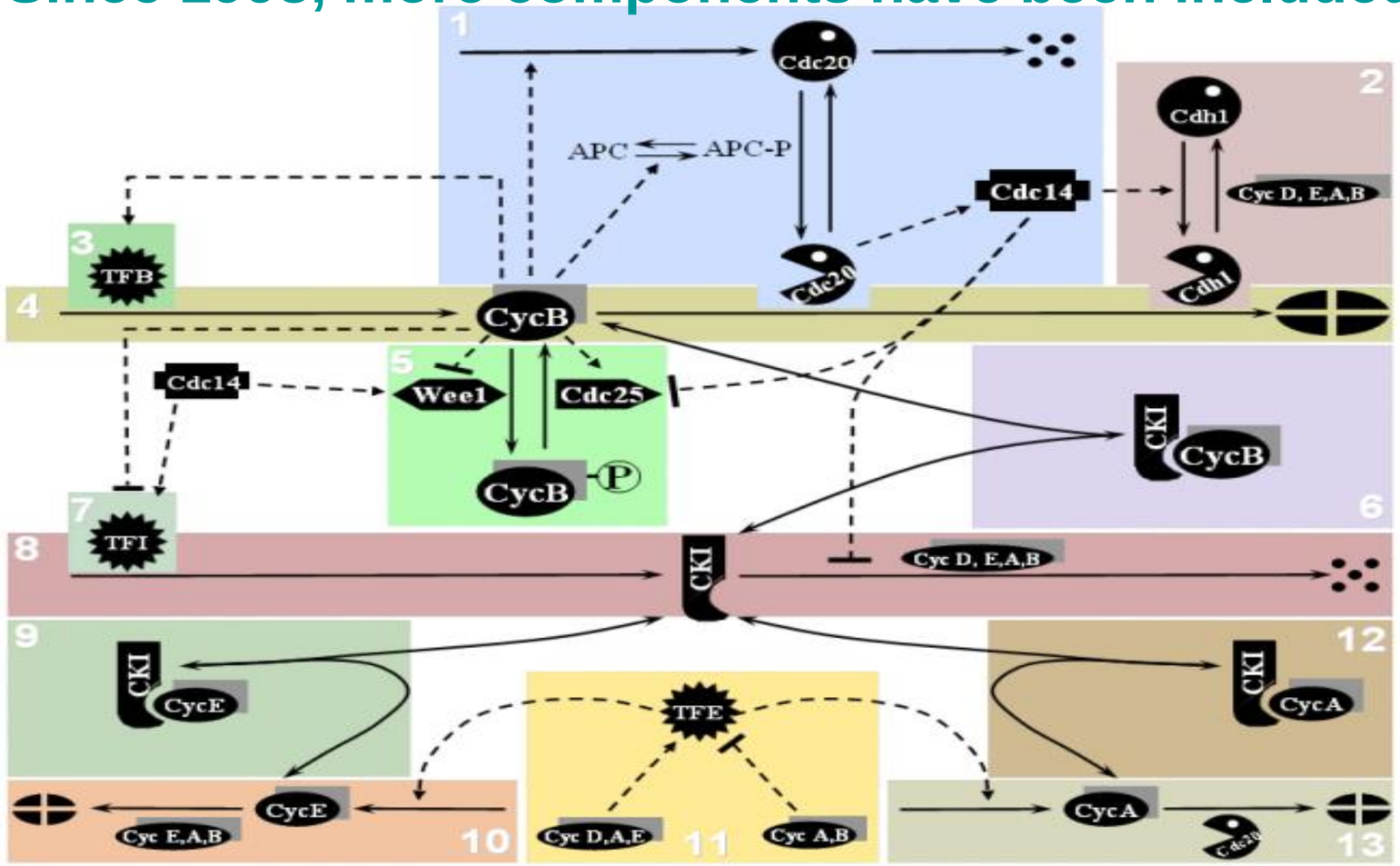
Overall Theme

Several processes modeled in a phenomenological way in 1991 were described more mechanistically in 1993.

This is how dynamical models typically evolve.

How dynamical models evolve

Since 1993, more components have been included

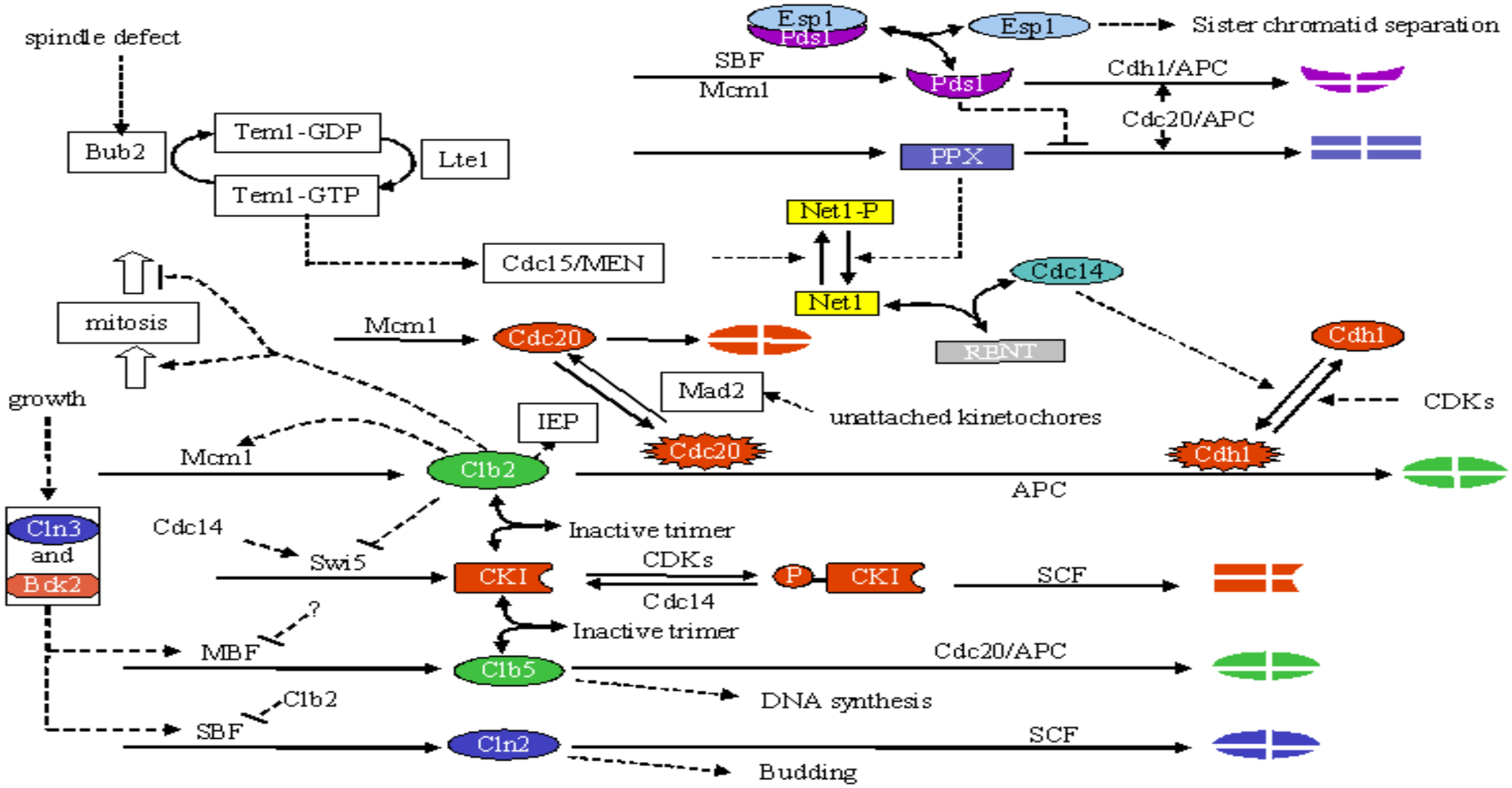


Generic model of cell cycle regulation

Csikász-Nagy et al. (2006) *Biophysical Journal* 90:4361 – 4379.

Phenomenology versus Mechanism

Since 1993, more components have been included



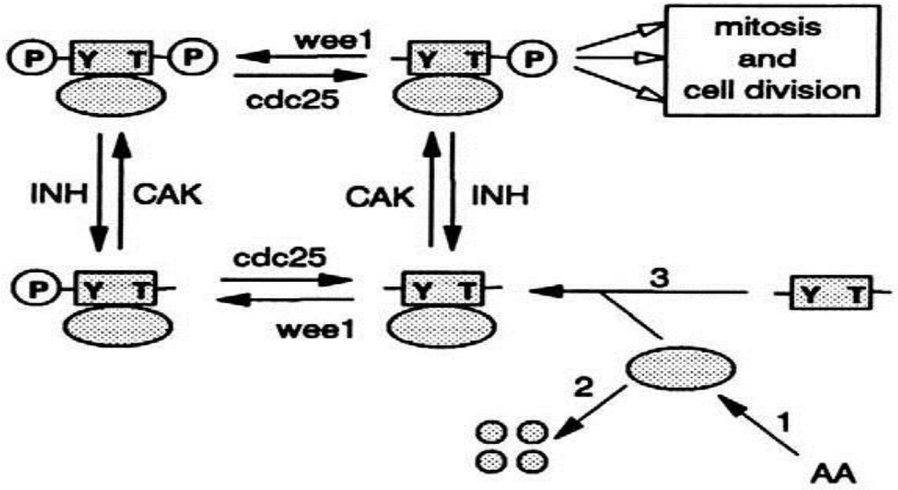
A model specific to budding yeast

Chen et al. (2004) *Mol. Biol. Cell* 15:3841-3862.

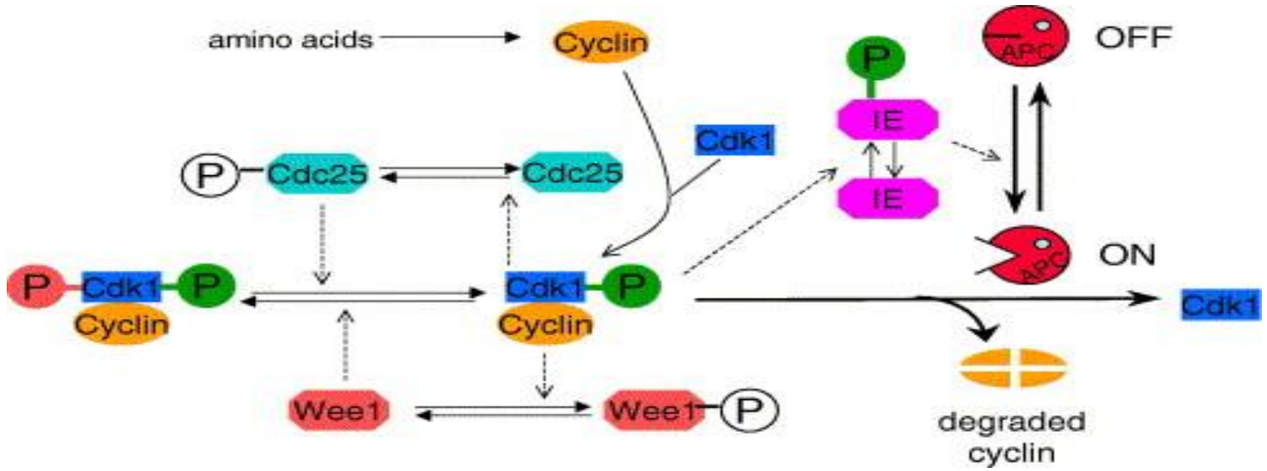
Phenomenology versus Mechanism

Occasionally things get simpler rather than more complicated

Novak & Tyson (1993)



Sible & Tyson (2007)



Phosphorylation on T161 by CAK no longer included in model

Simulations showed that T161 was almost always phosphorylated, so it was safe to exclude the unphosphorylated form from the model

Summary

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.