ULB

# Modeling the cell cycle: From amphibian embryos to mammalian cells

**Albert Goldbeter**

Faculté des Sciences

Université Libre de Bruxelles (ULB)

Brussels, Belgium

*« Living Matter »*

*ICTS, Bangalore, 24 April 2018*

# Main biological rhythms

| Biological rhythm | Period |
|---|---|
| Neural rhythms* | 0.001 s to 10 s |
| Cardiac rhythm* | 1 s |
| Calcium oscillations* | sec to min |
| Biochemical oscillations* | min |
| Hormonal rhythms* | 10 min to 3-5 h (24 h) |
| Mitotic oscillator* | 10 min to 24 h |
| Circadian rhythms* | 24 h |
| Ovarian cycle | 28 days (human) |
| Annual rhythms | 1 year |
| Rhythms in ecology and epidemiology | years |

*Cellular rhythms

# Key roles of cell cycle

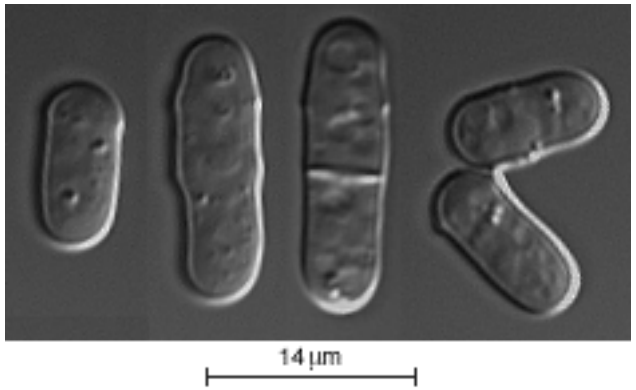
- **Developmental Biology** :
  from fertlized egg to adult organism

- **Cancer** : deregulation of cell cycle

Using mathematical models based
on experimental observations
to understand the dynamics
of the cell cycle

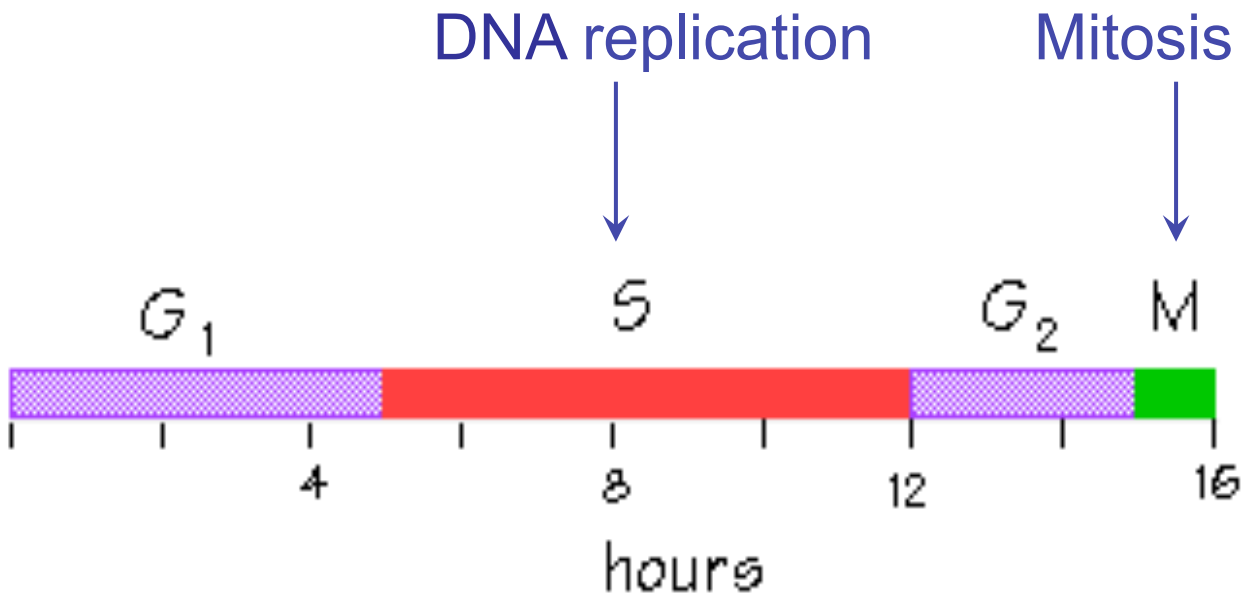
# Dynamics of the cell cycle

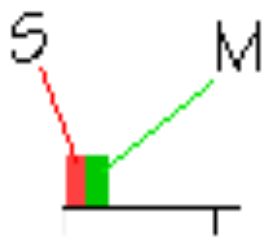
*Xenopus laevis*




Yeast *S. pombe*

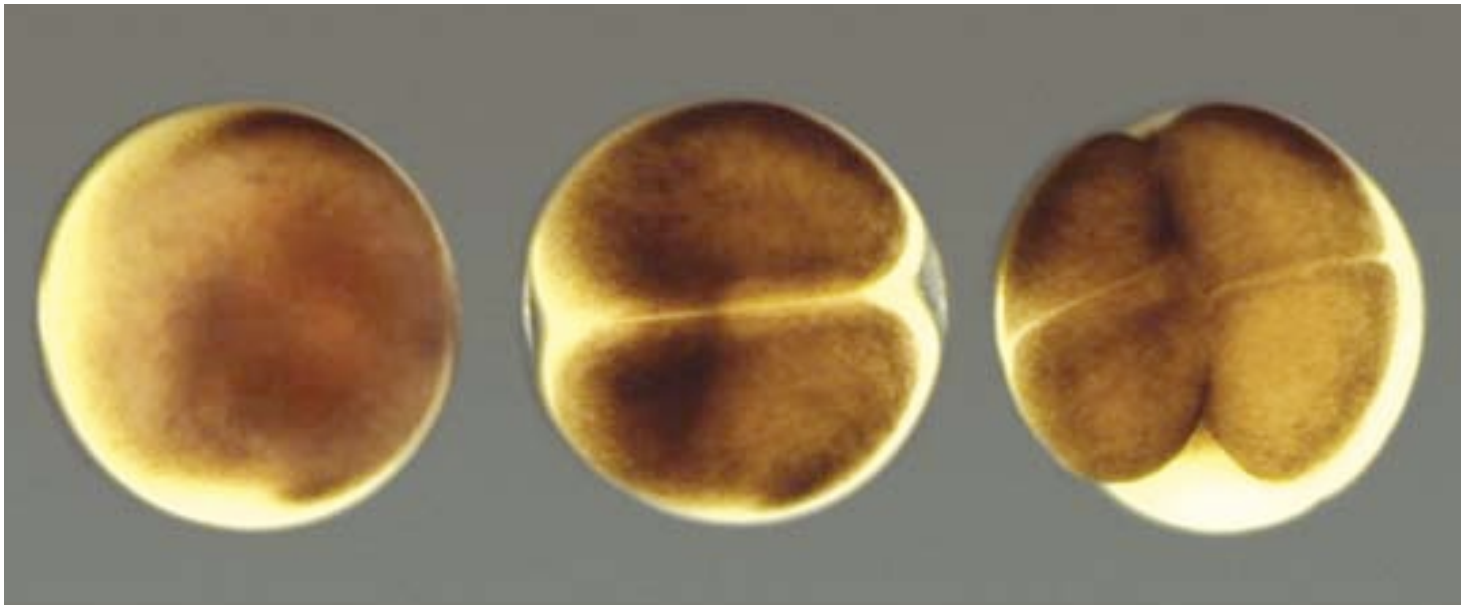
Mammal



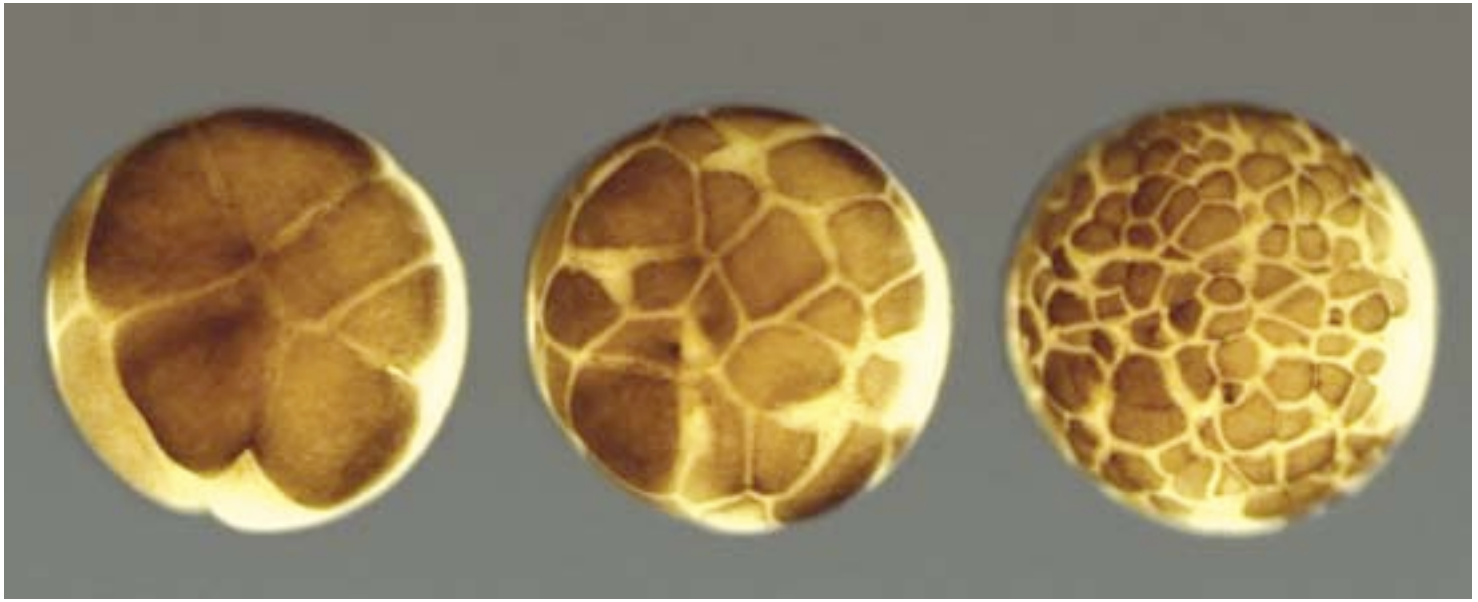




2 types of cell cycle

Frog (12 early embryonic cell cycles)

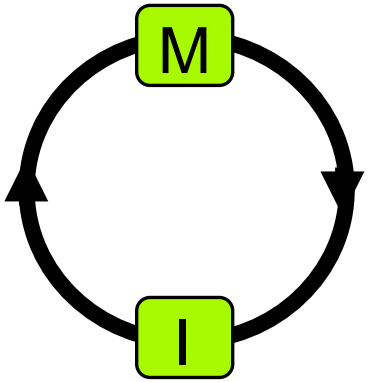


T=30min

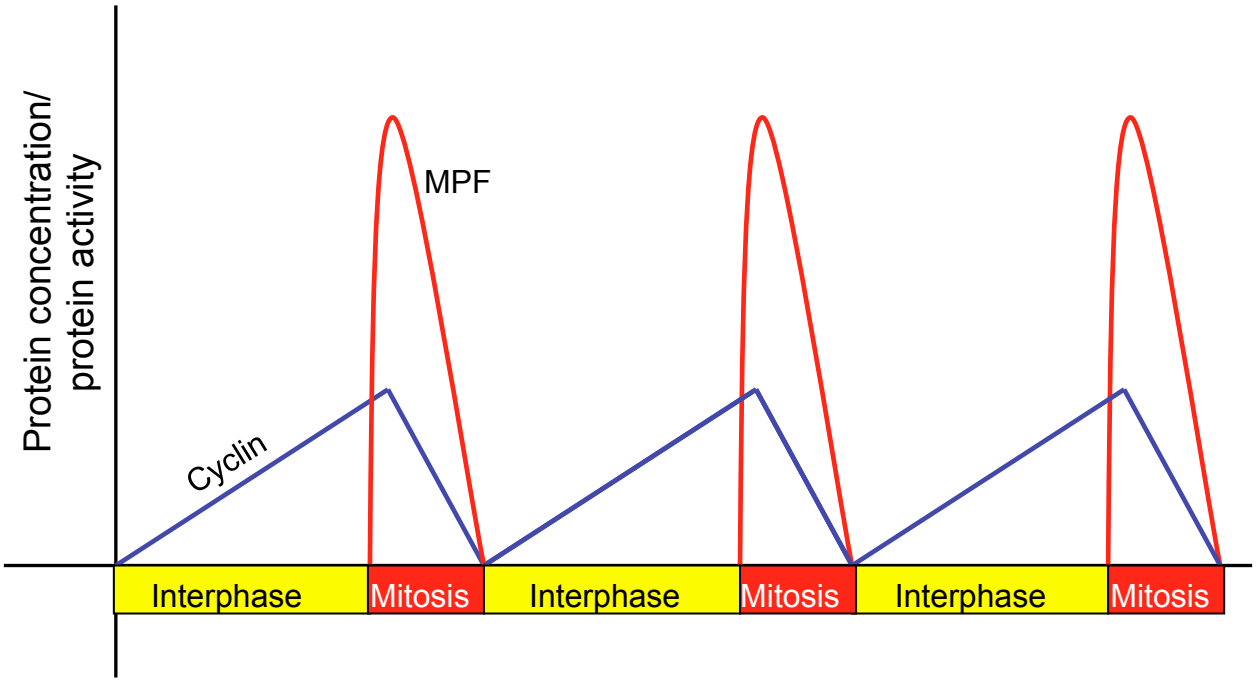


First cell divisions in the frog *Xenopus laevis*

# Cell cycle in the frog embryo




M : Mitosis
I : Interphase



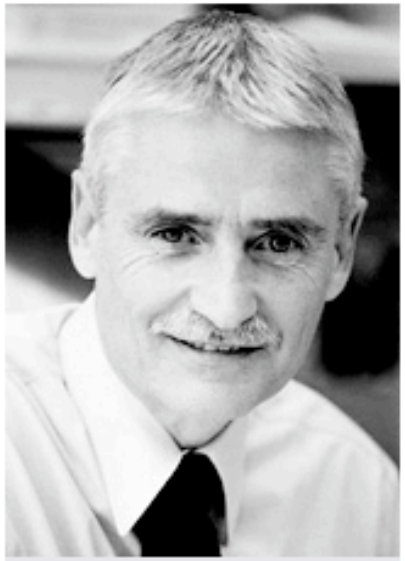

Murray AW and Kirschner MW (1989) Cyclin synthesis drives the early embryonic cell cycle. *Nature* 339, 275-80.

MPF = Kinase Cdc2 + Cyclin

Medicine

# The Nobel Prize in Physiology or Medicine 2001

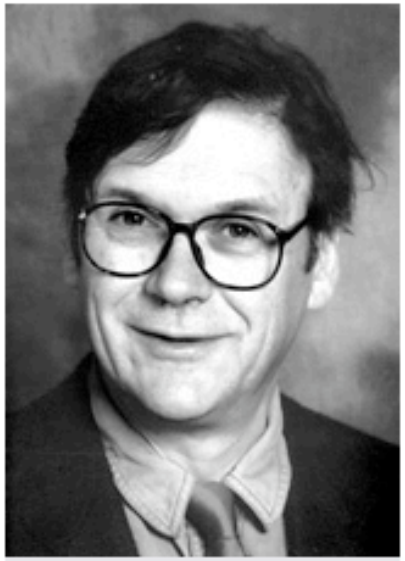
"for their discoveries of key regulators of the cell cycle"



**Leland H. Hartwell**

1/3 of the prize

USA



**Tim Hunt**

1/3 of the prize

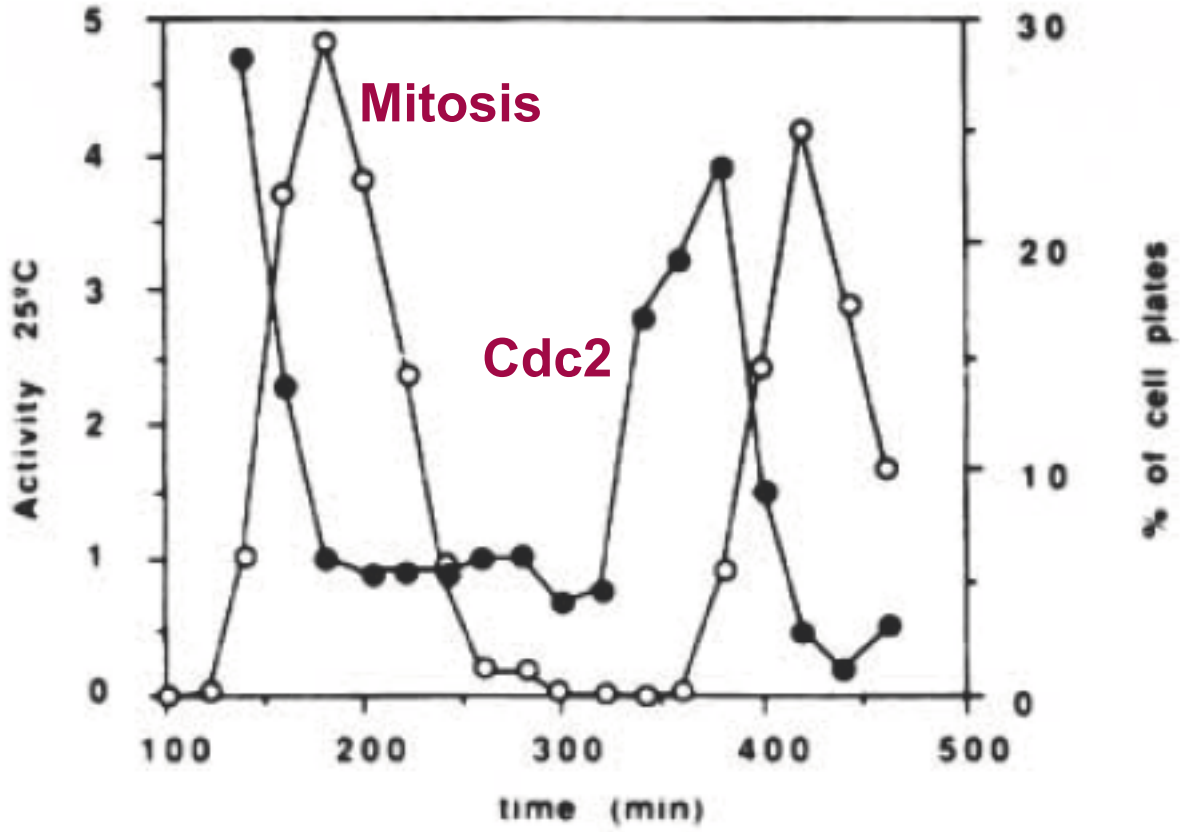
United Kingdom

**Sir Paul M. Nurse**

1/3 of the prize

United Kingdom

# Oscillations of Cdc2 and mitosis in yeast




*Nurse (2002)*

*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

*Proc. Natl. Acad. Sci. USA*
Vol. 88, pp. 9107–9111, October 1991
Cell Biology

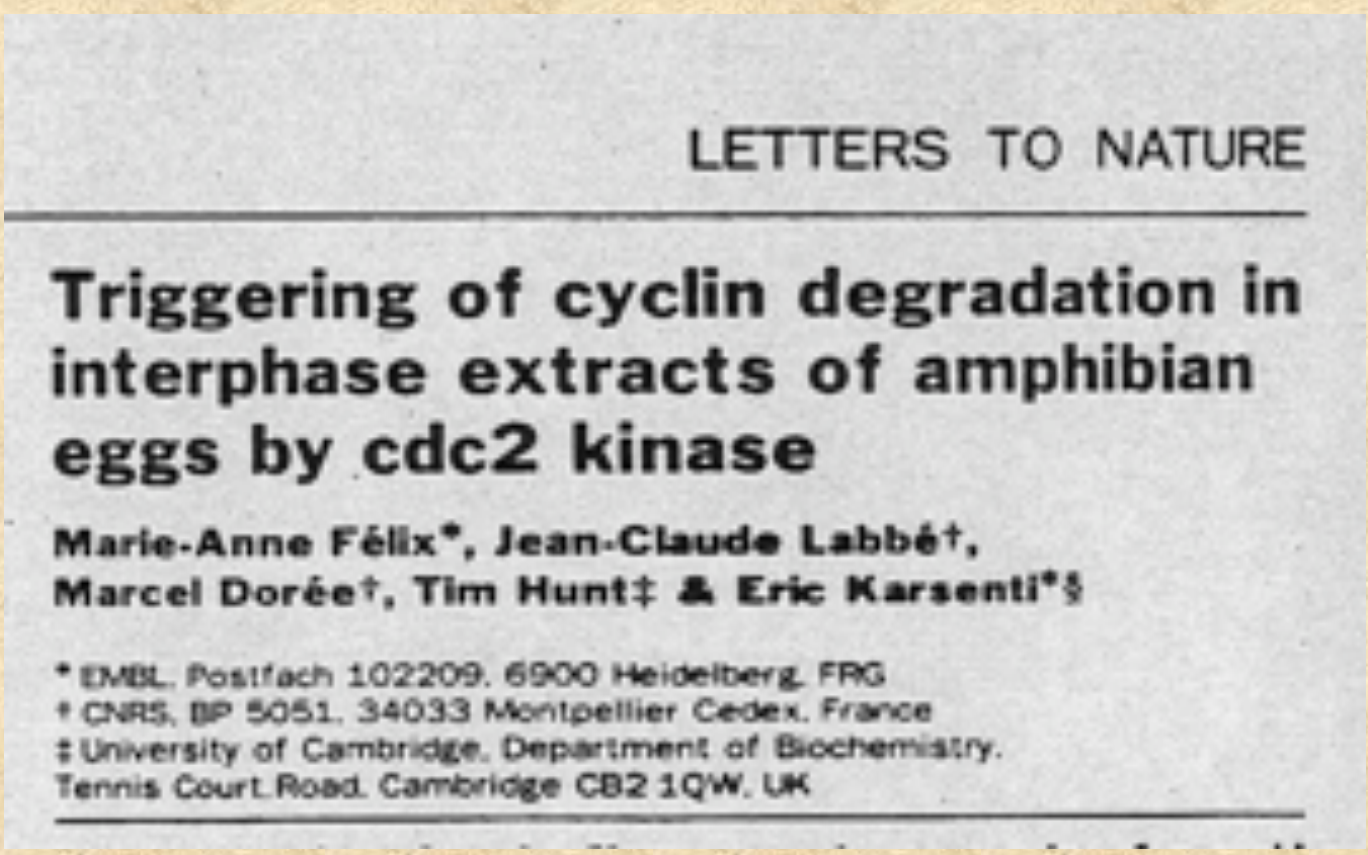
# A minimal cascade model for the mitotic oscillator involving cyclin and cdc2 kinase

(cell cycle/maturation-promoting factor/phosphorylation cascade/thresholds/biochemical oscillations)

ALBERT GOLDBETER

Faculté des Sciences, Université Libre de Bruxelles, Campus Plaine, C.P. 231, B-1050 Brussels, Belgium

*Nature* (1990)



LETTERS TO NATURE

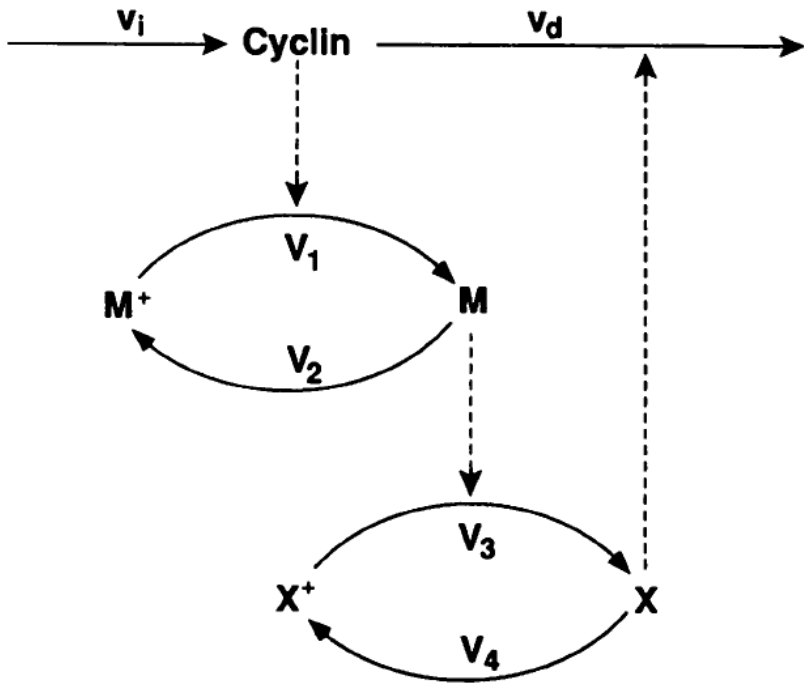
# Triggering of cyclin degradation in interphase extracts of amphibian eggs by cdc2 kinase

**Marie-Anne Félix*, Jean-Claude Labbé†, Marcel Dorée†, Tim Hunt‡ & Eric Karsenti*§**

* EMBL, Postfach 102209, 6900 Heidelberg, FRG
† CNRS, BP 5051, 34033 Montpellier Cedex, France
‡ University of Cambridge, Department of Biochemistry, Tennis Court Road, Cambridge CB2 1QW, UK

→ Negative feedback, thresholds and delays

# Model for the embryonic cell cycle




with

$$\frac{dC}{dt} = v_i - v_d X \frac{C}{K_d + C} - k_d C,$$

$$\frac{dM}{dt} = V_1 \frac{(1-M)}{K_1 + (1-M)} - V_2 \frac{M}{K_2 + M},$$

$$\frac{dX}{dt} = V_3 \frac{(1-X)}{K_3 + (1-X)} - V_4 \frac{X}{K_4 + X}$$

$$V_1 = \frac{C}{K_c + C} V_{M1}, \; V_3 = M V_{M3}.$$

Phosphorylation-dephosphorylation cascade with negative feedback



A. Goldbeter (1991) *PNAS*

*Proc. Natl. Acad. Sci. USA*
Vol. 78, No. 11, pp. 6840–6844, November 1981
Biochemistry

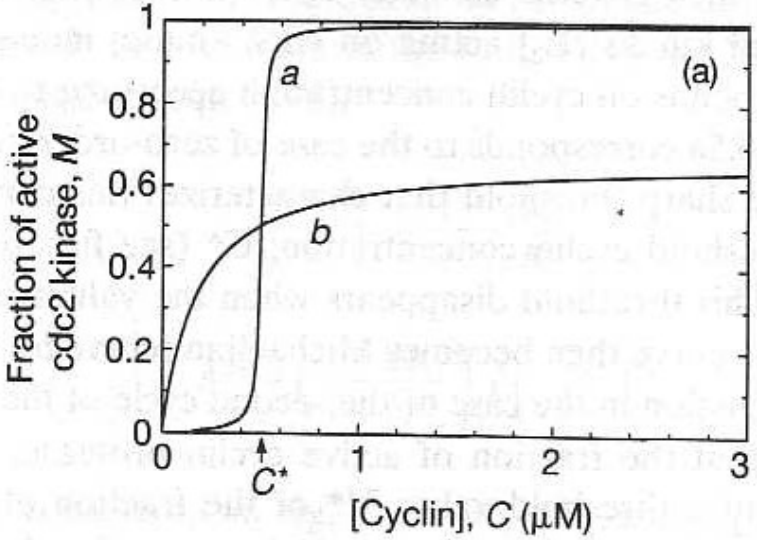
# An amplified sensitivity arising from covalent modification in biological systems

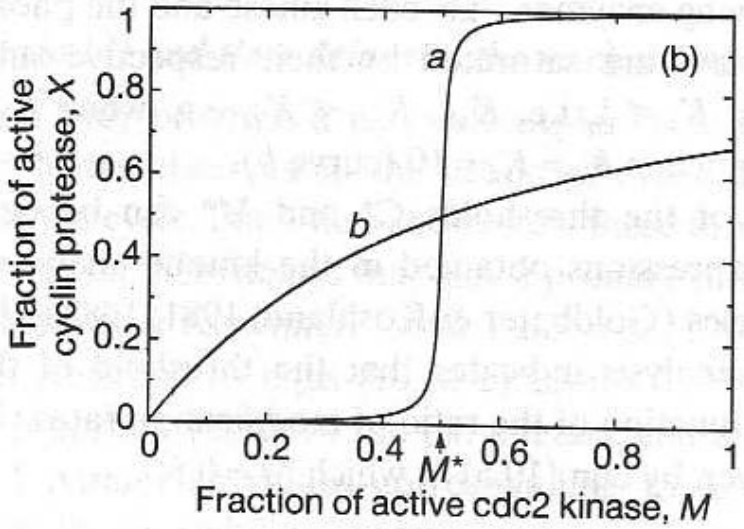
(protein modification/metabolic regulation/switch mechanism/enzyme cascades)

ALBERT GOLDBETER† AND DANIEL E. KOSHLAND, JR.

Department of Biochemistry, University of California, Berkeley, California 94720

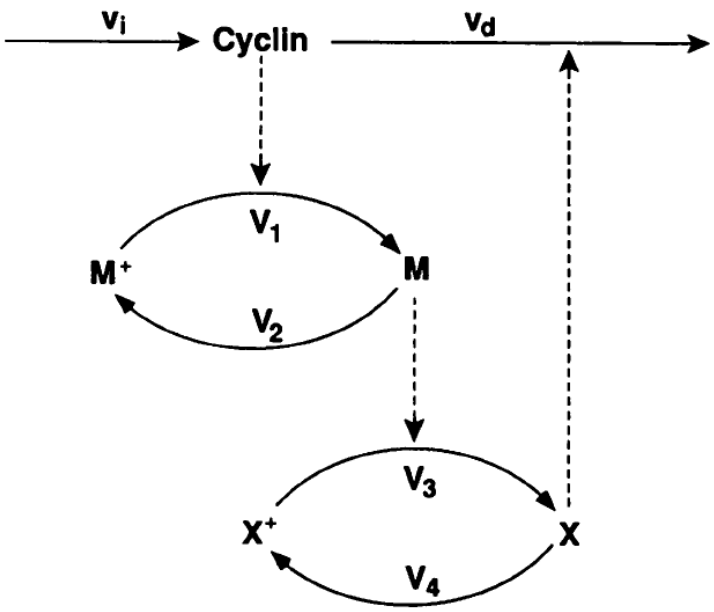
Thresholds : *zero-order ultrasensitivity*



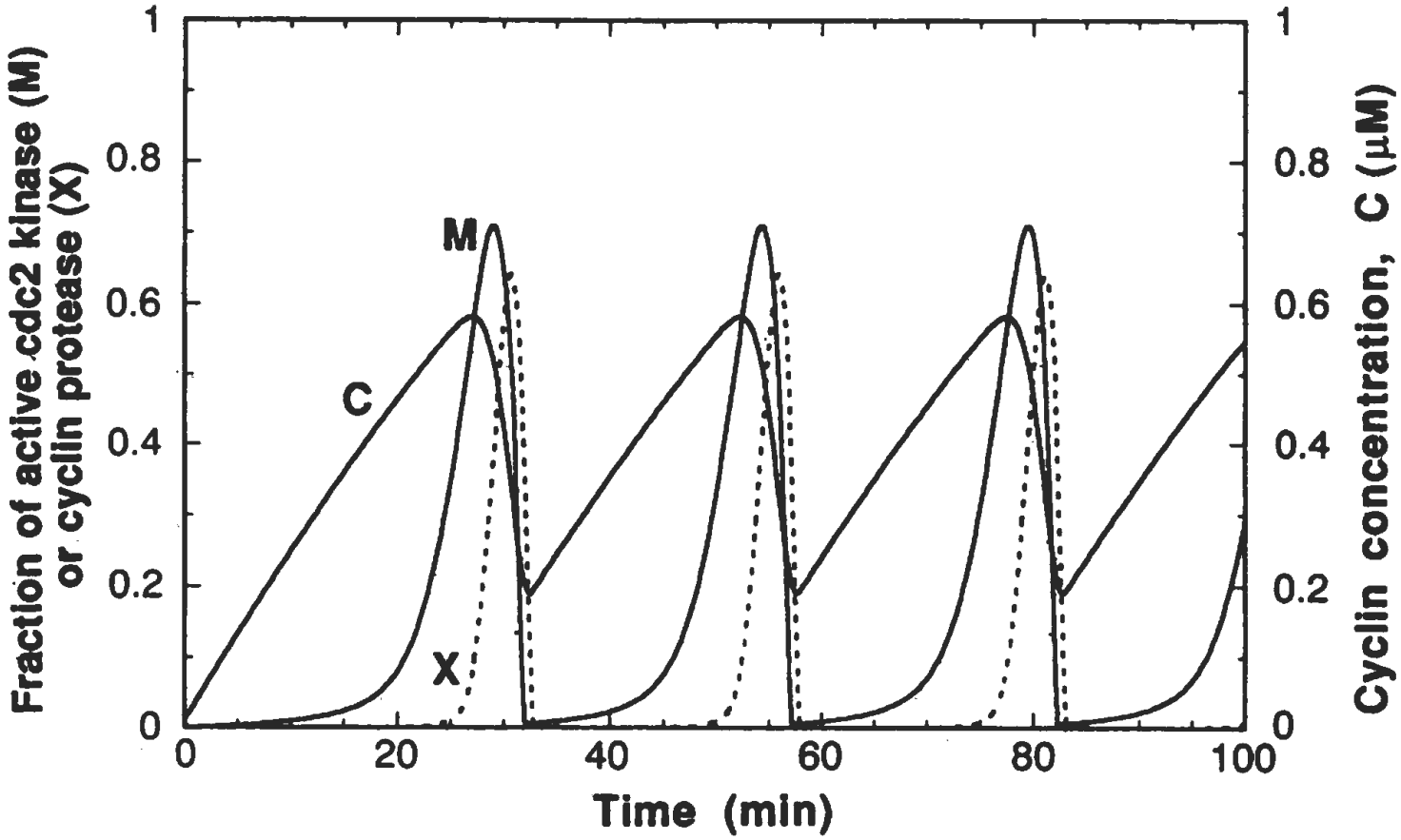

Fraction of active cdc2 kinase (M) as a function of cyclin concentration (C)

Fraction of active protease (X) as a function of active cdc2 kinase (M

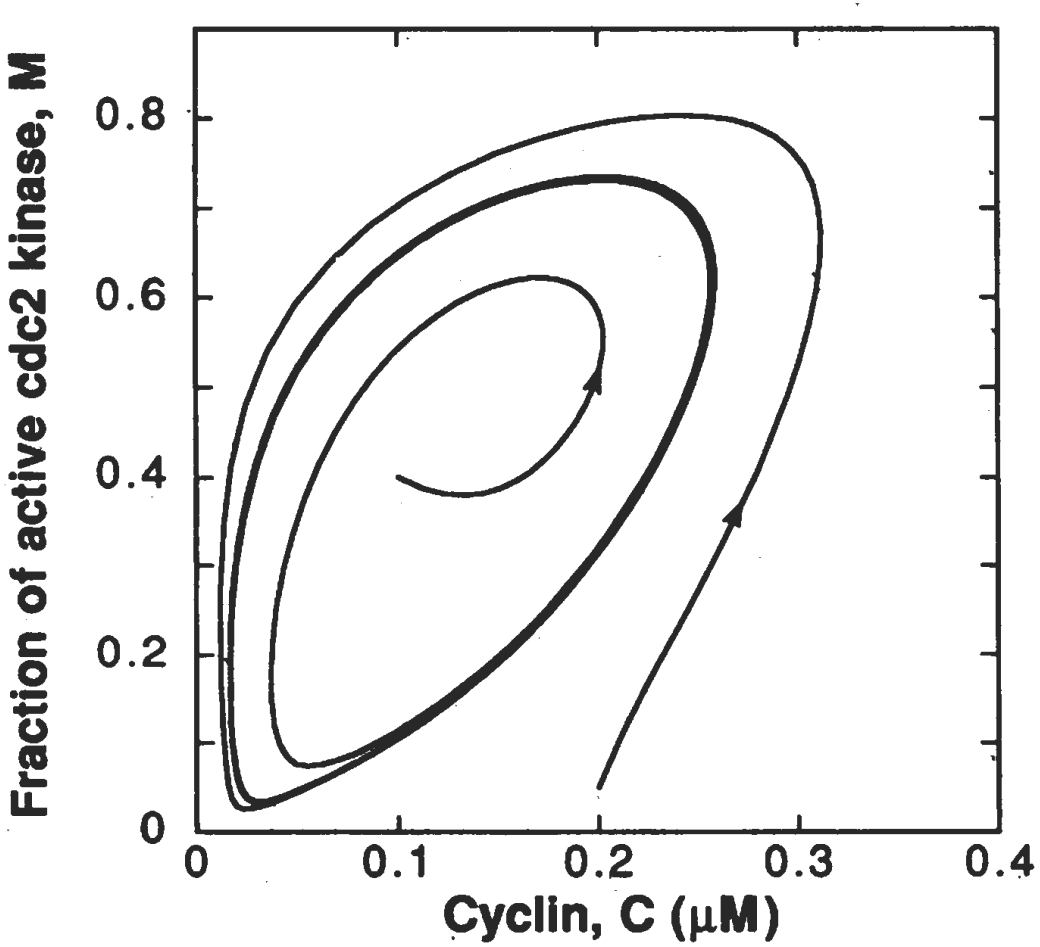



Goldbeter (1991) *PNAS*

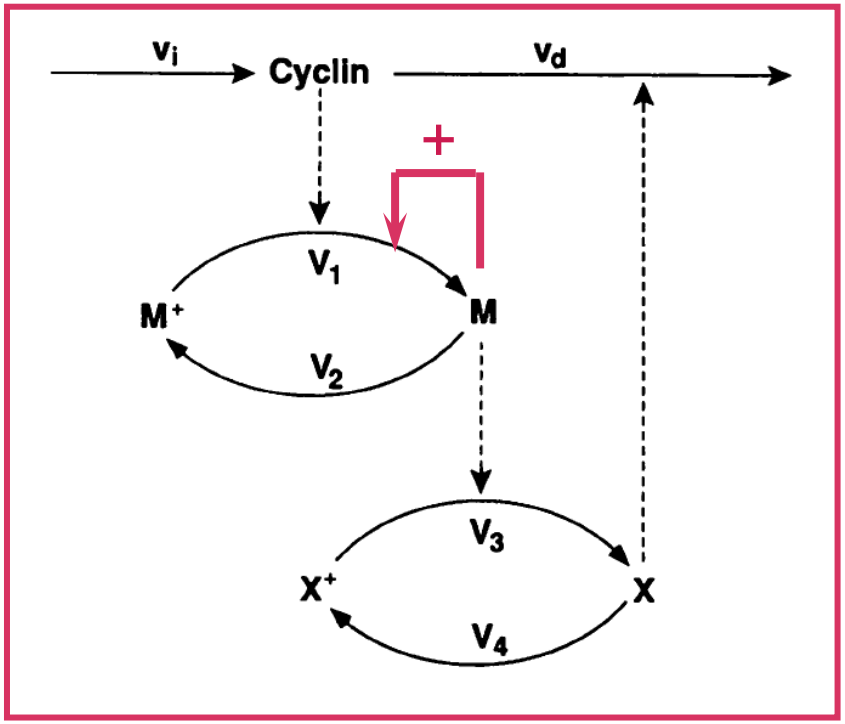
# Modeling the molecular mechanism of the cell cycle clock in frog embryos



# Sustained oscillations : Evolution toward a limit cycle



# Role of positive feedback on cdc2 kinase

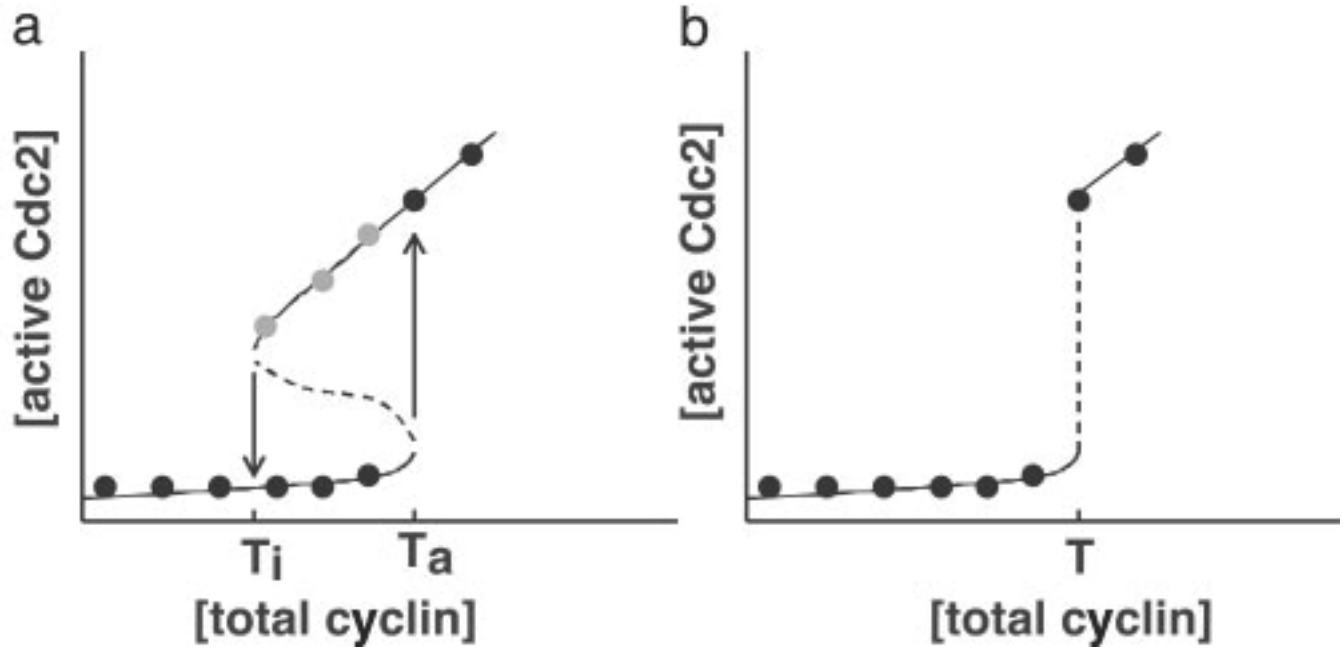



Cdc2 activates
phosphatase Cdc25
and inhibits kinase Wee1

*Bistability :*

Coexistence of two stable steady states
corresponding to two levels of activity
of cdc2 kinase

# Bistability and hysteresis




Hysteresis drives cell-cycle transitions in Xenopus laevis egg extracts
W. Sha, J. Moore, K. Chen, A.D. Lassaletta, C.S. Yi, J.J. Tyson, and J.C. Sible (2003) *PNAS* 100, 975-980.

Pomerening, Sontag & Ferrell
*Nature Cell Biology* (2003)

See also: Pommerening, Kim
& Ferrell (2005) *Cell* 122, 565-78



# Building a cell cycle oscillator: hysteresis and bistability in the activation of Cdc2

**Joseph R. Pomerening*, Eduardo D. Sontag† and James E. Ferrell Jr*‡**
**Department of Molecular Pharmacology, Stanford University School of Medicine, Stanford, CA 94305-5174, USA*
*†Department of Mathematics, Rutgers University, New Brunswick, NJ 08903, USA*
*‡e-mail: james.ferrell@stanford.edu*

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**In the early embryonic cell cycle, Cdc2–cyclin B functions like an autonomous oscillator, whose robust biochemical rhythm continues even when DNA replication or mitosis is blocked[1]. At the core of the oscillator is a negative feedback loop; cyclins accumulate and produce active mitotic Cdc2–cyclin B[2,3]; Cdc2 activates the anaphase-promoting complex (APC); the APC then promotes cyclin degradation and resets Cdc2 to its inactive, interphase state. Cdc2 regulation also involves positive feedback[4], with active Cdc2–cyclin B stimulating its activator Cdc25 (refs 5–7) and inactivating its inhibitors Wee1 and Myt1 (refs 8–11). Under the correct circumstances, these positive feedback loops could function as a bistable trigger for mitosis[12,13], and oscillators with bistable triggers may be particularly relevant to biological applications such as cell cycle regulation[14–17]. Therefore, we examined whether Cdc2 activation is bistable. We confirm that the response of Cdc2 to non-degradable cyclin B is temporally abrupt and switch-like, as would be expected if Cdc2 activation were bistable. We also show that Cdc2 activation exhibits hysteresis, a property of bistable systems with particular relevance to biochemical oscillators. These findings help establish the basic systems-level logic of the mitotic oscillator.**

It has been known for thirty years that there is an autocatalytic element to activation of the M-phase trigger. Microinjection of cytoplasm from M-phase *Rana pipiens*[4] or *Xenopus laevis*[18,19] oocytes causes G2-phase oocytes to enter M phase. Furthermore, microinjection of cytoplasm from these M-phase oocytes causes progesterone-naïve G2-phase oocytes to enter M phase, and the titre of the mature oocytes' M-phase promoting factor (MPF) activity never decreases with sequential cytoplasmic transfer[4]. The basic mechanisms of this autocatalysis were defined through experiments with *Xenopus* egg extracts treated with recombinant, non-degradable cyclins[20]. Cyclin-induced activation of Cdc2 inactivates the kinases that inhibit Cdc2 activity and activates the phosphatase that dephosphorylates the same target residues[20]. Subsequent work established that Cdc2 can activate its activator Cdc25 (refs 5–7) through the intermediacy of the Polo-like kinase Plx1 (refs 21, 22), and that Cdc2 can inactivate its inactivators Wee1 and Myt1 (refs 8–11).

It was realized that these positive feedback loops — Cdc2-mediated activation of Cdc25 and inactivation of Wee1 and Myt1 — could function as a bistable system[12,13], toggling between two discrete alternative stable steady states. Systems are termed bistable if they toggle between two discrete alternative states without being able to rest in intermediate states (Fig. 1c). In this case, the two stable states are interphase, in which Cdc2 and Cdc25 are inactive and Wee1 and Myt1 are active, and the early part of mitosis (up to anaphase), in which Cdc2 and Cdc25 are active and Wee1 and Myt1 are inactive. Bistability is not an inevitable consequence of positive feedback[23], nor is it the only useful systems-level property that can arise from positive feedback loops (for example, sensitivity amplification[24] is a more robust property of positive feedback systems than bistability is). Nevertheless, a bistable trigger could be critical for mitotic oscillator function by ensuring that a cell settles in discrete, mutually exclusive interphase and M-phase states and not in a continuum of intermediate states[12,13]. Bistability could also help keep a cell from slipping rapidly back and forth between cell cycle phases ('chattering') during transitions into and out of mitosis[13].

Moreover, bistability is one way to ensure that a mitotic oscillator will never approach a stable steady-state, but will instead oscillate indefinitely, and an oscillator that possesses a bistable trigger — a relaxation oscillator, similar in its basic mechanism to the Van der Pol oscillator from electrical engineering and the FitzHugh/Nagano oscillator from ecology—has a number of distinctive properties. A simple two-component negative feedback system, such as one in which Cdc2–cyclin B directly activates the APC and the APC in turn directly inactivates Cdc2–cyclin B, will inevitably approach a stable, intermediate steady state (Fig. 1d, e; also see Supplementary Information Part 1 for a mathematical demonstration). Some aspect of the circuit must be altered to convert it into a satisfactory oscillator. One way is to add another component to the feedback loop; for example, an intermediary, such as Plx1, between active Cdc2 and the APC (Fig. 1f). The resulting regulatory circuit can exhibit sustained negative feedback oscillations (Fig. 1g), and an oscillator of this class could in principle be the basis of the early embryonic cell cycle[12,25]. A different way of producing sustained oscillations is to add a bistable trigger to a negative feedback loop, resulting in a relaxation oscillator (Fig. 1h, i). This type of oscillator may have advantages over simple negative feedback oscillators in terms of noise rejection, reliability, self-synchronization and spatial propagation[14–16], and may be particularly suitable as a biological timer.

Therefore, we wanted to determine experimentally whether the Cdc2 system is actually bistable. We began by examining the time course of Cdc2 activation by a non-destructible *Xenopus* B-type cyclin, Δ65-cyclin B1, in undiluted, cycloheximide-treated interphase *Xenopus* egg extracts lacking endogenous cyclins (the non-destructible cyclin is not subject to APC-mediated proteolysis, allowing an examination of Cdc2 responses to specific, unchanging cyclin concentrations). If activation of Cdc2 is bistable, then the time course of Cdc2 activation in response to a constant level of non-degradable cyclin should exhibit a temporal lag that precedes an abrupt transition between low and high Cdc2 activity, as autocatalysis means that the rate of Cdc2 activation will increase as Cdc2 activity increases. The activation of Cdc2 was temporally abrupt and reached an apparent steady state within approximately 60 min (Fig. 2a), as previously reported for activation of *Xenopus* Cdc2 by a non-degradable sea urchin cyclin protein in extracts[20]. The observed temporal abruptness is consistent with the predicted

*Biophys. Chem*. (2013)

**The role of APC/C inhibitor Emi2/XErp1 in oscillatory dynamics of early embryonic cell cycles.**

Vinod, PK, Zhou, X, Zhang, T, Mayer TU, Novak, B.

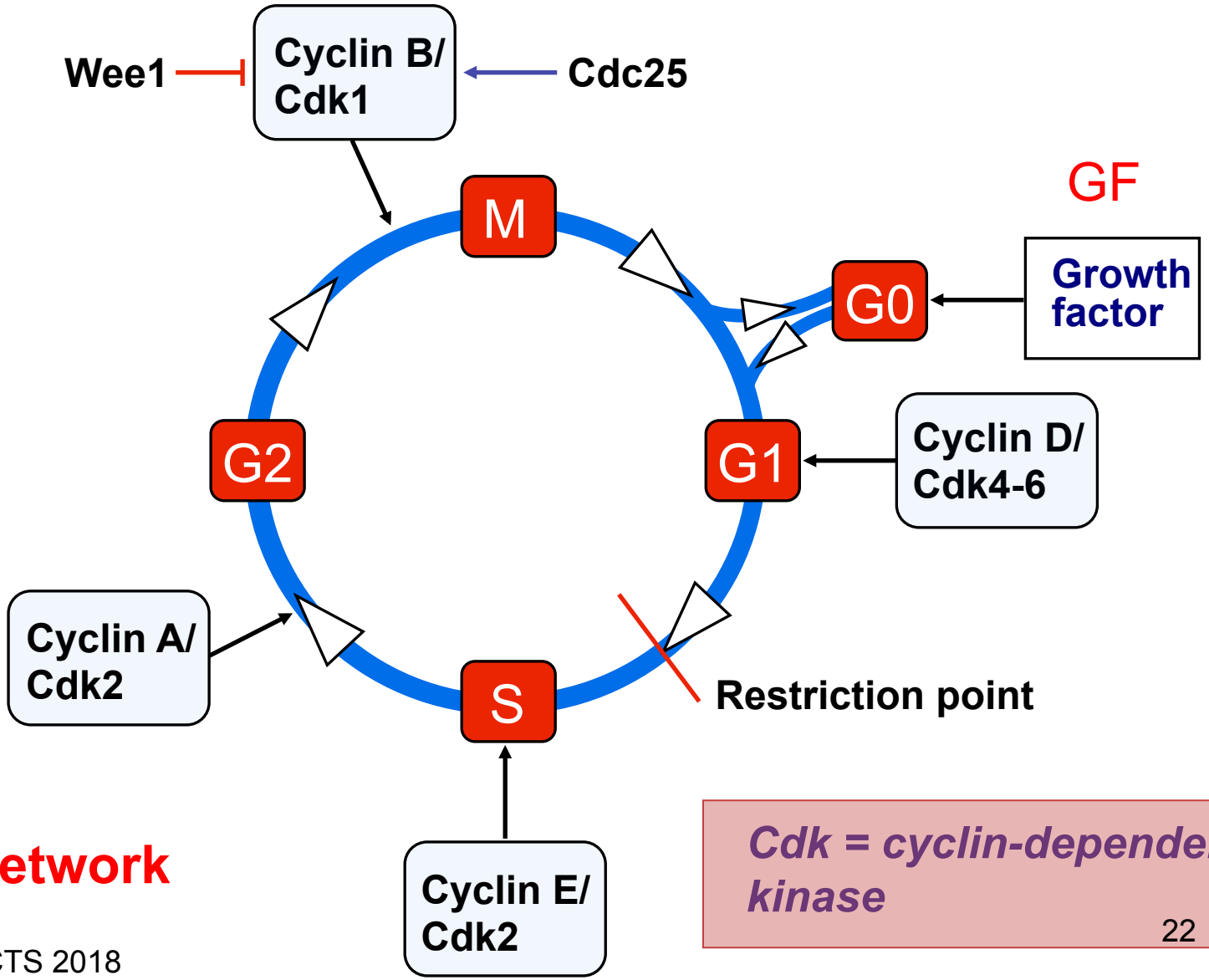
*Oxford Centre for Integrative Systems Biology, Department of Biochemistry, University of Oxford, Oxford, UK.*

## Detailed models for the yeast and embryonic cell cycle

B. Novak and J.J. Tyson

Chen KC, Calzone L, Csikasz-Nagy A, Cross FR, Novak B, Tyson JJ (2004).
Integrative analysis of cell cycle control in budding yeast.
Mol Biol Cell. 15, 3841-62.

# The mammalian cell cycle




**Cdk network**

***Cdk = cyclin-dependent kinase***

## Models for the G1/S transition in the cell cycle

Qu et al (2003)

Novak & Tyson (2004)

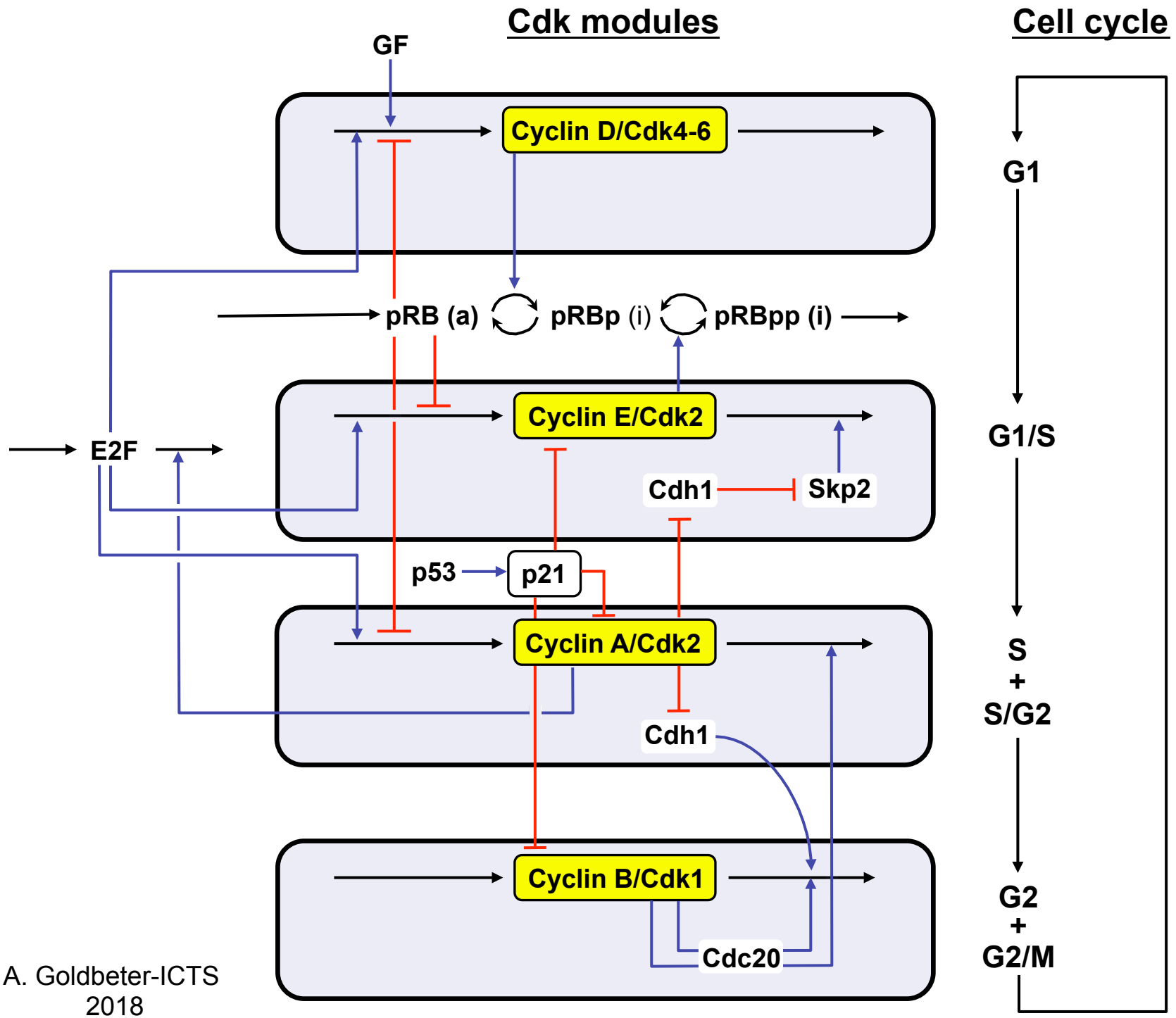
Swat, Kel & Herzel (2004)

Barberis, Klipp & Alberghina (2007) (yeast)

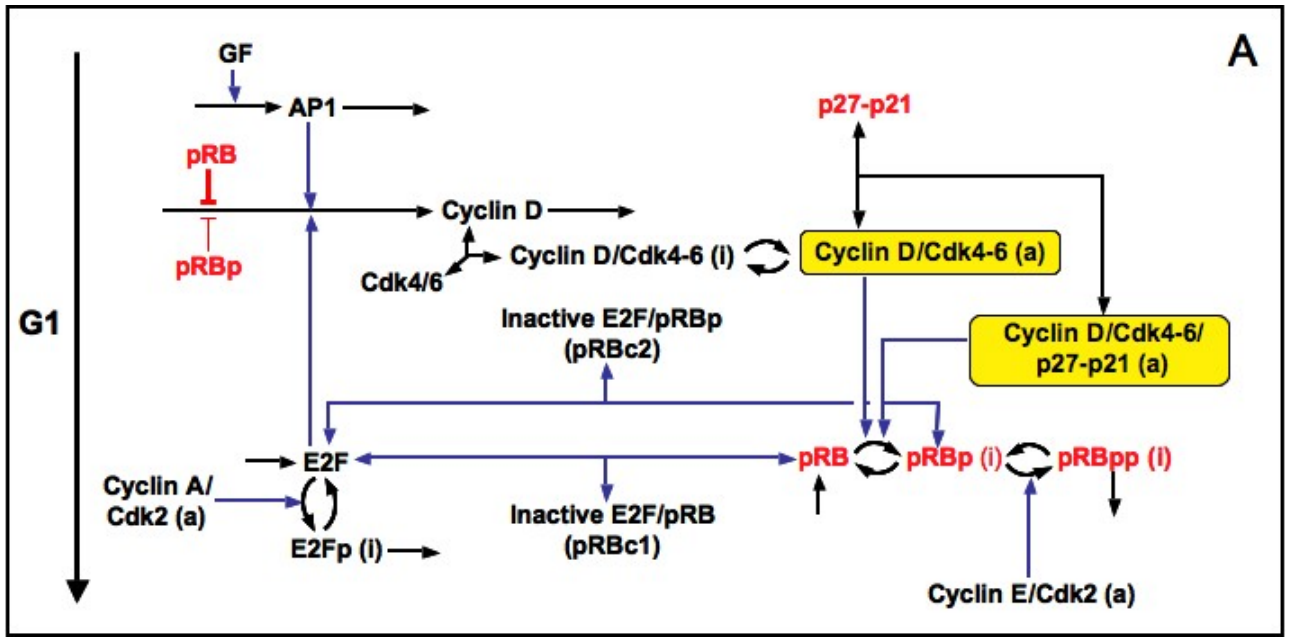
*PNAS* (2009) 106, 21643

# Temporal self-organization of the cyclin/Cdk network driving the mammalian cell cycle

Claude Gérard and Albert Goldbeter[1]


Cdk modules
Cell cycle
GF
Cyclin D/Cdk4-6
pRB (a)
pRBp (i)
pRBpp (i)
E2F
Cyclin E/Cdk2
Cdh1
Skp2
p53
p21
Cyclin A/Cdk2
Cdh1
Cyclin B/Cdk1
Cdc20
G1
G1/S
S
+
S/G2
G2
+
G2/M

# Example of Kinetic equations




Rate of synthesis

Formation and dissociation of complex between E2F and pRB

Formation and dissociation of complex between E2F and pRBp

$$\frac{dE2F}{dt} = (v_{se2f} - k_{pc1} \cdot pRB \cdot E2F + k_{pc2} \cdot pRbc1 - k_{pc3} \cdot pRBp \cdot E2F + k_{pc4} \cdot pRBc2$$

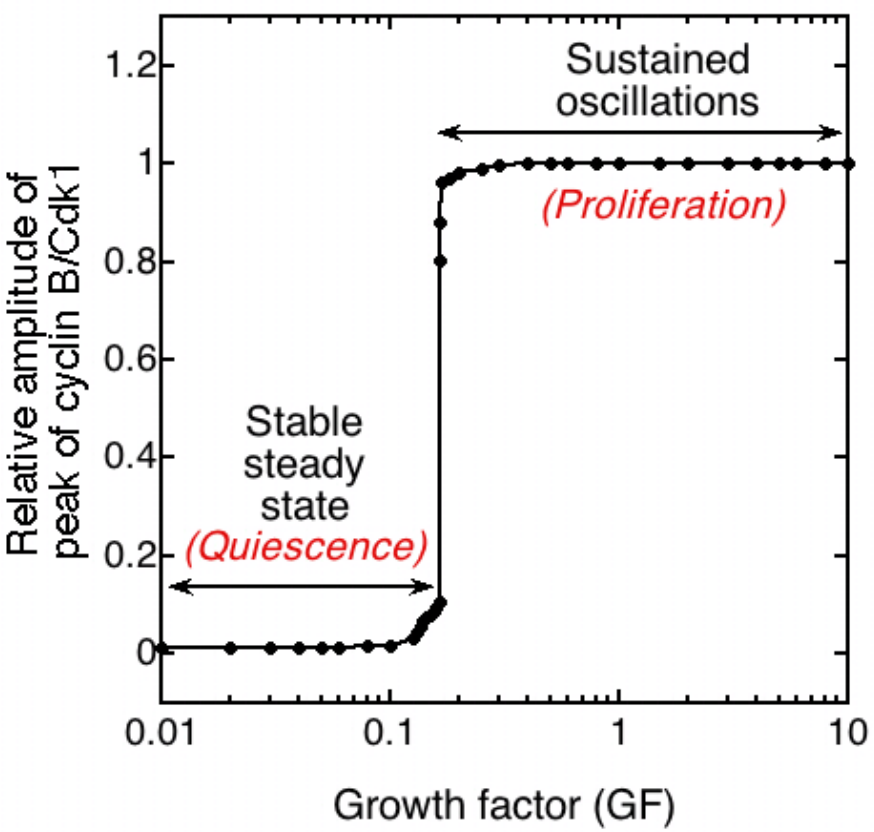
$$- V_{1e2f} \cdot Ma \cdot \left(\frac{E2F}{K_{1e2f} + E2F}\right) + V_{2e2f} \cdot \left(\frac{E2Fp}{K_{2e2f} + E2Fp}\right) - k_{de2f} \cdot E2F) \cdot eps$$

Rate of phosphorylation of E2F

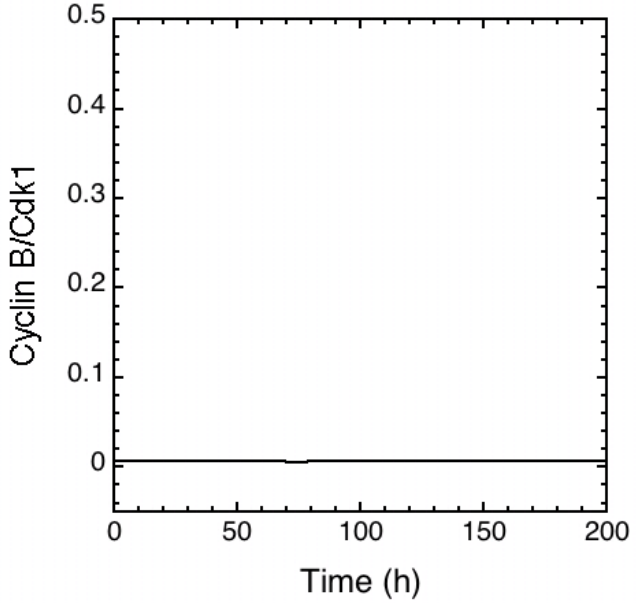
Rate of dephosphorylation of E2Fp

Rate of degradation of E2F

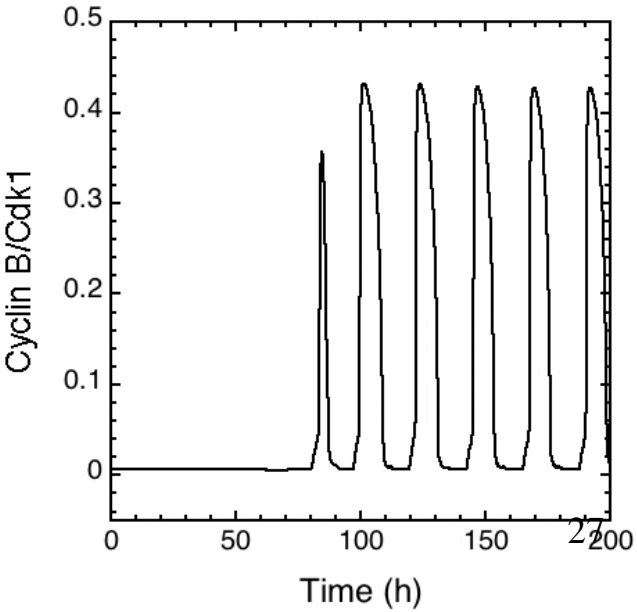
# Effect of growth factor on cell cycle progression



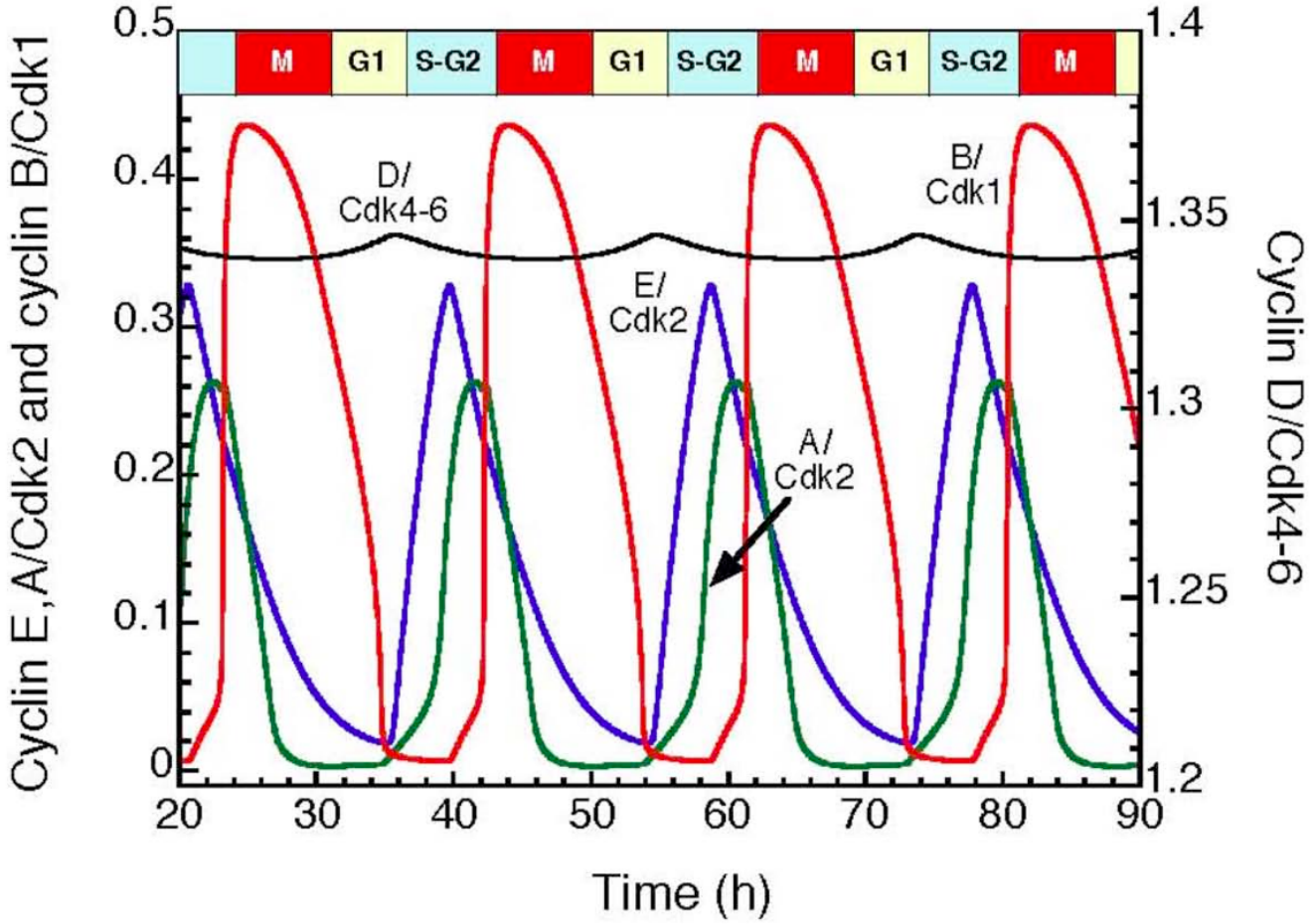

GF=0.1




GF=0.2

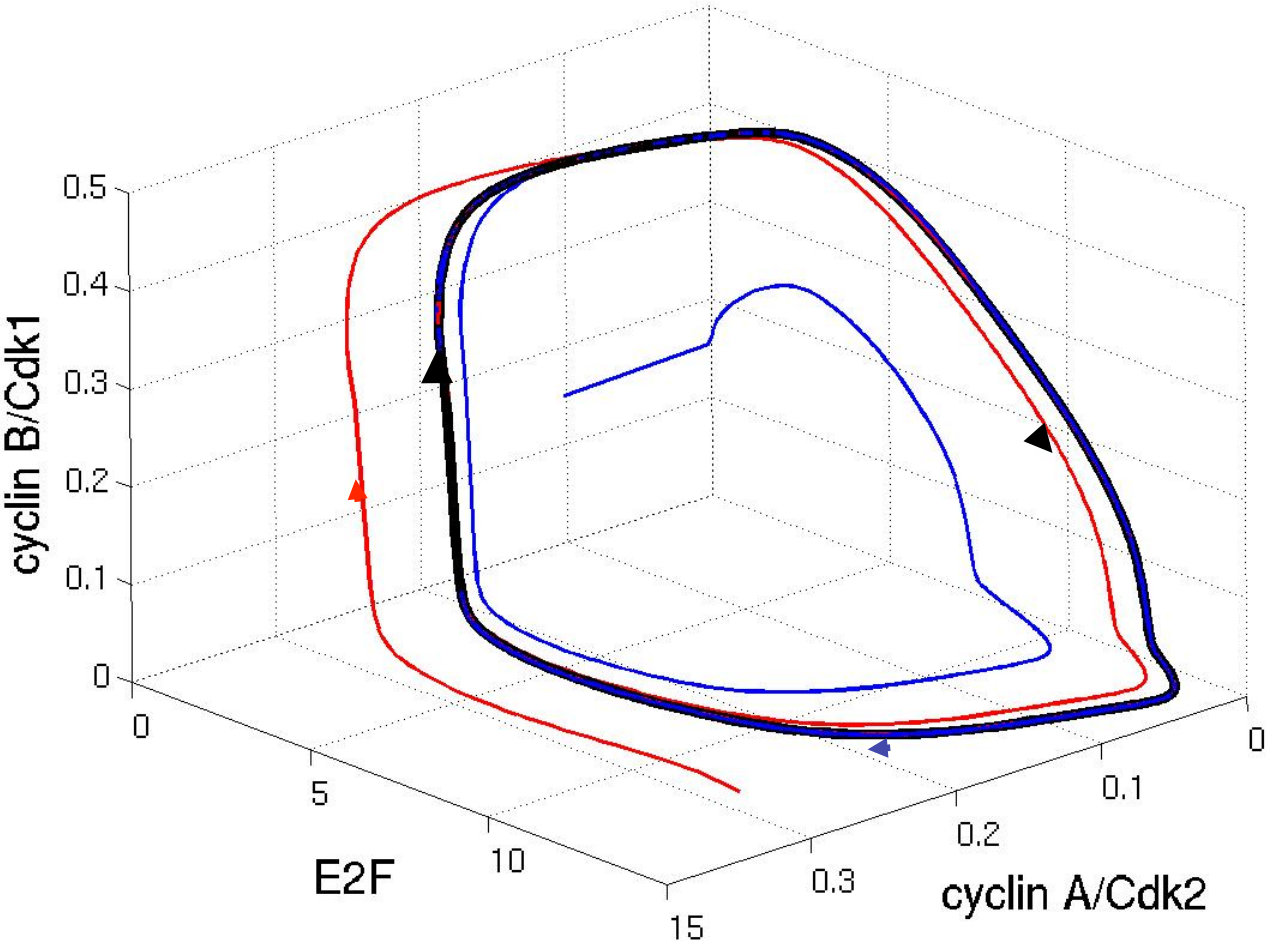


# Spontaneous oscillations in the Cdk network




Gérard & Goldbeter (2009) *PNAS*

# Oscillations in theCdk network



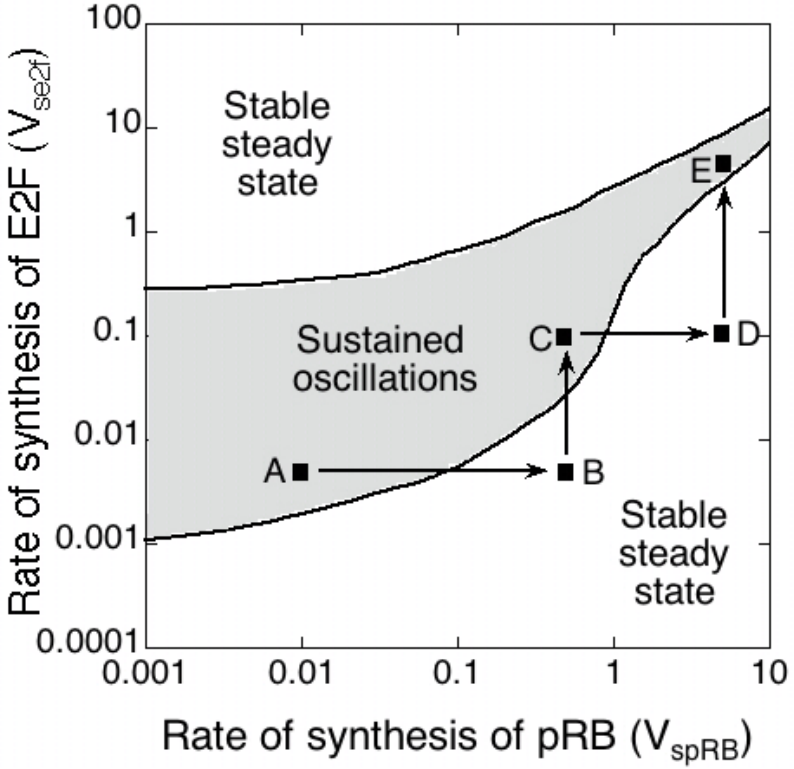

**Evolution to a limit cycle**

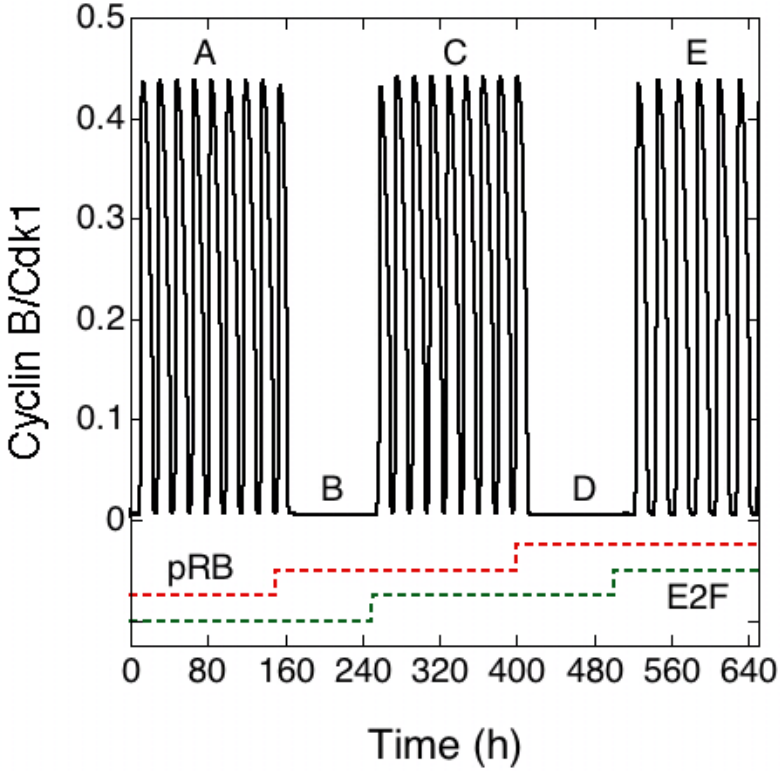
*Math. Model. Nat. Phenom.* 7, 126-66 (2012)

# The Cell Cycle is a Limit Cycle

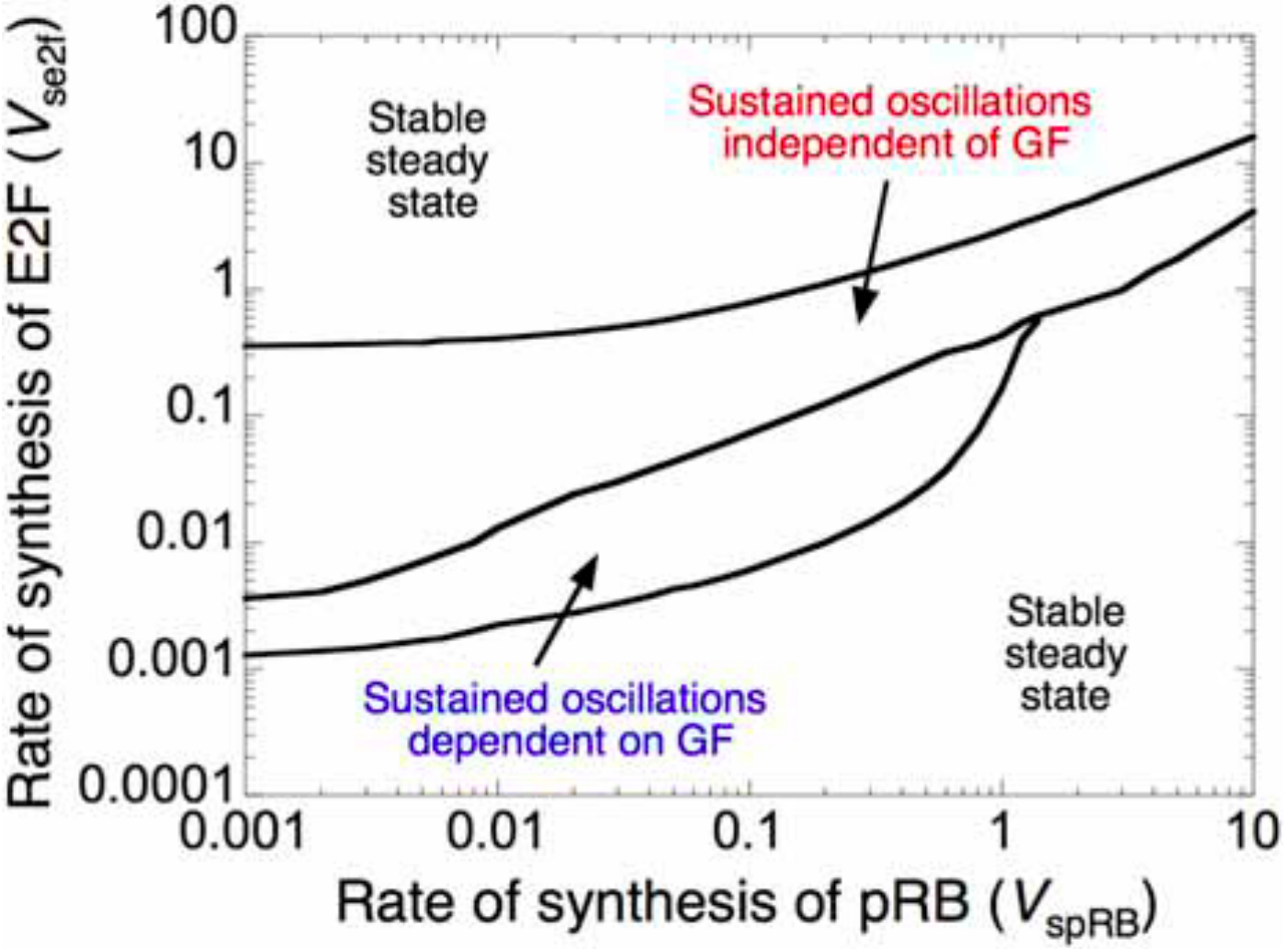
C. Gérard and A. Goldbeter

# Balance between the tumor suppressor gene pRB and the transcription factor E2F

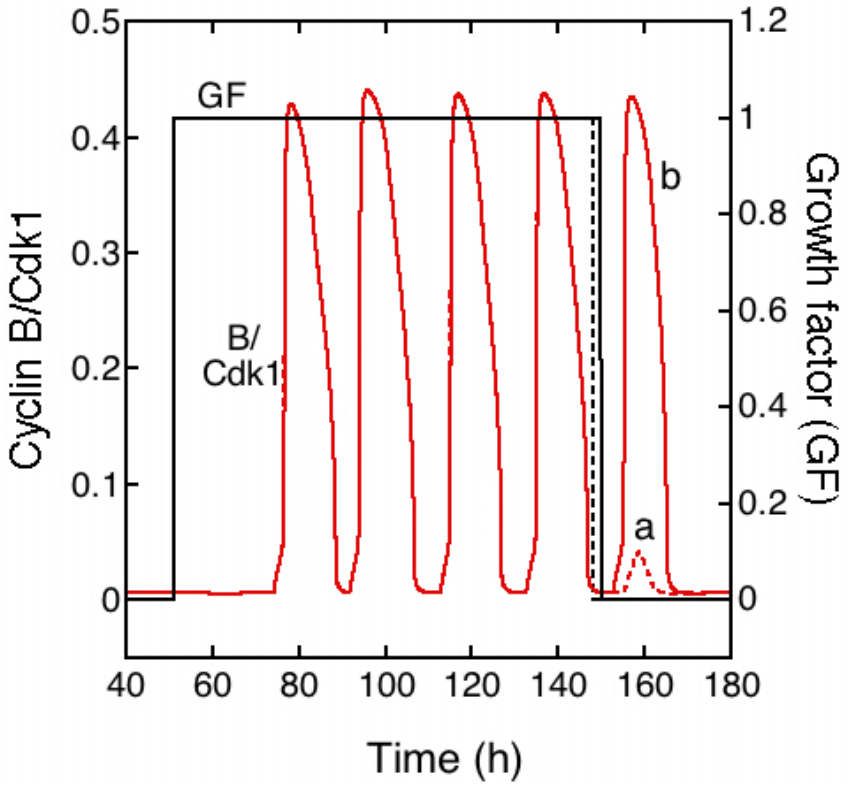


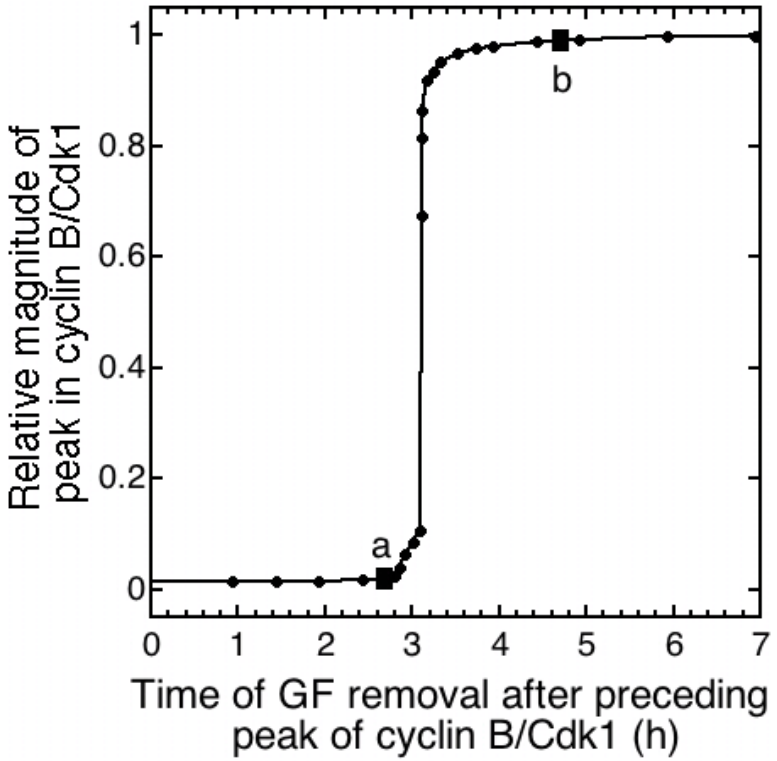




C. Gérard & A. Goldbeter (2009) *PNAS*


Stable
steady
state
Sustained oscillations
independent of GF
Sustained oscillations
dependent on GF
Stable
steady
state
Rate of synthesis of E2F ($V_{se2f}$)
Rate of synthesis of pRB ($V_{spRB}$)
100
10
1
0.1
0.01
0.001
0.0001
0.001
0.01
0.1
1
10

# Existence of a restriction point



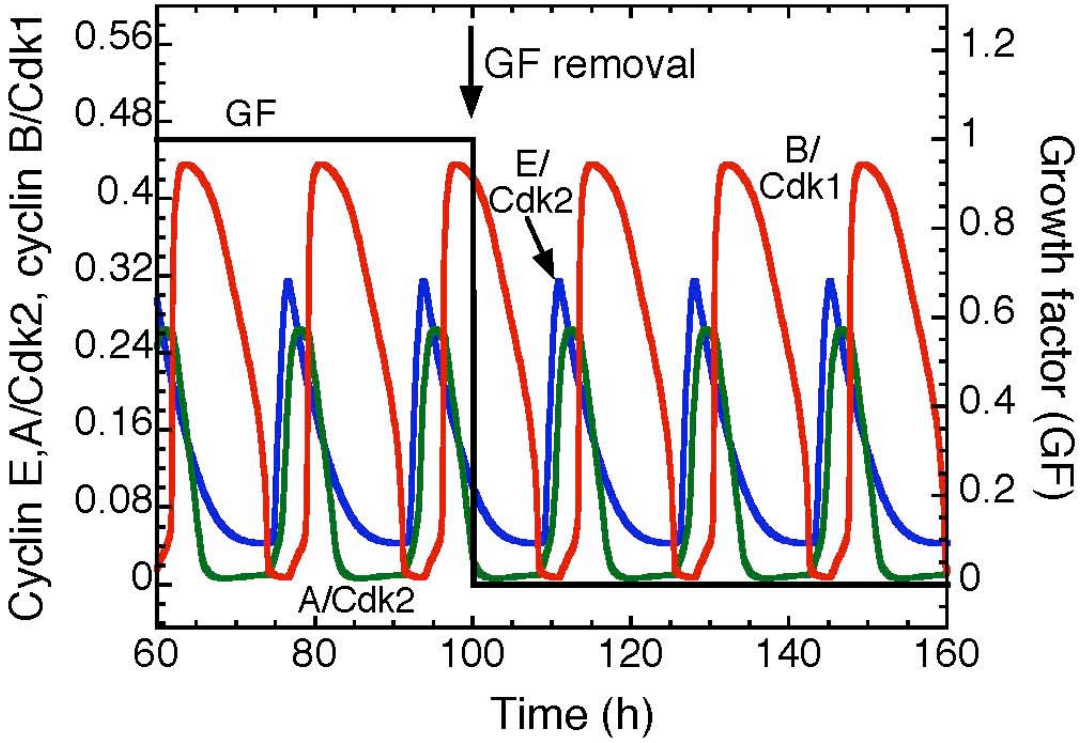




A restriction point is present more or less 3h after the beginning of the cell cycle (during the *G1* phase).

# Cell cycle progression in the absence of pRB

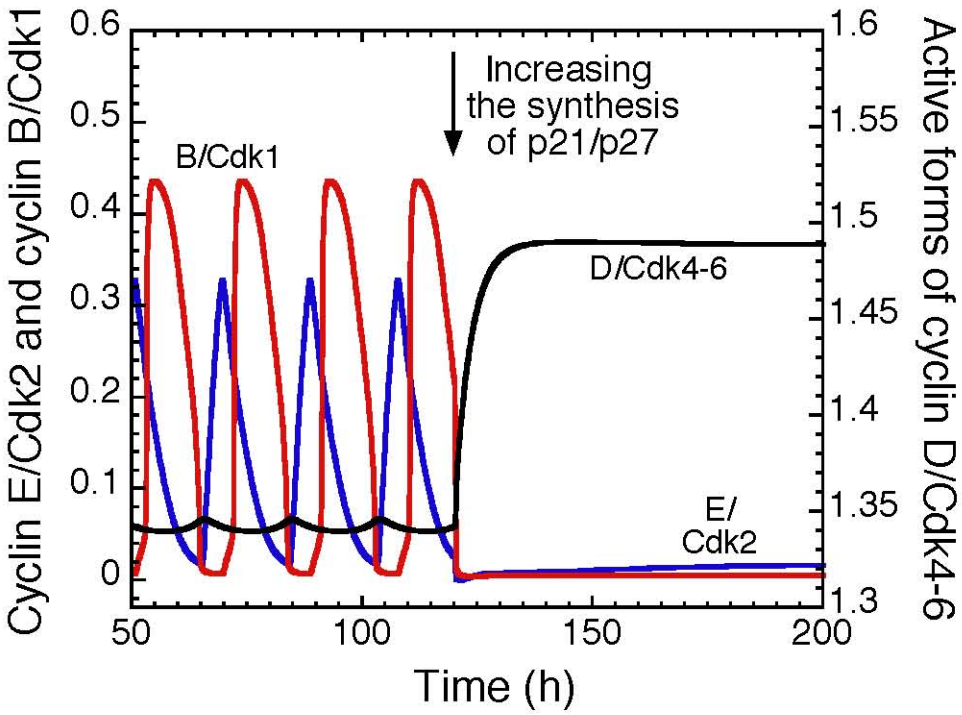
Sage J, et al. (2000) Targeted disruption of the three Rb-related genes leads to loss of G1 control and immortalization. *Genes & Dev* 14:3037-3050.

Dannenberg J-H, van Rossum A, Schuijff L, te Riele H (2000) Ablation of the Retinoblastoma gene family deregulates G1 control causing immortalization and increased cell turnover under growth-restricting conditions. *Genes & Dev* 14:3051-3064.




⇨ In absence of pRB, progression in the cell cycle becomes independent of the growth factor.

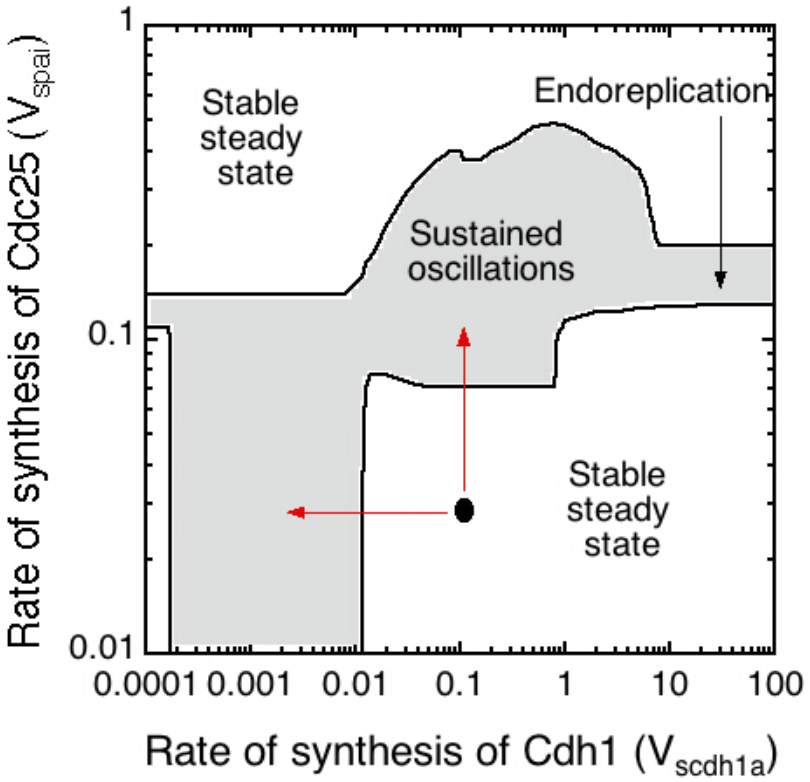
# Effect of increasing the rate of synthesis of p21/p27




Arrest in G1

$V_{s1p27}$ increases from 0.8 to 5 $\mu Mh^{-1}$

# Effect of Cdh1 and Cdc25 on the Cdk network




The phosphatase Cdc25 activates the kinase Cdk by dephosphorylation, which promotes cell cycle progression.

Cdh1 promotes cyclin B degradation and can be viewed as a tumor suppressor.

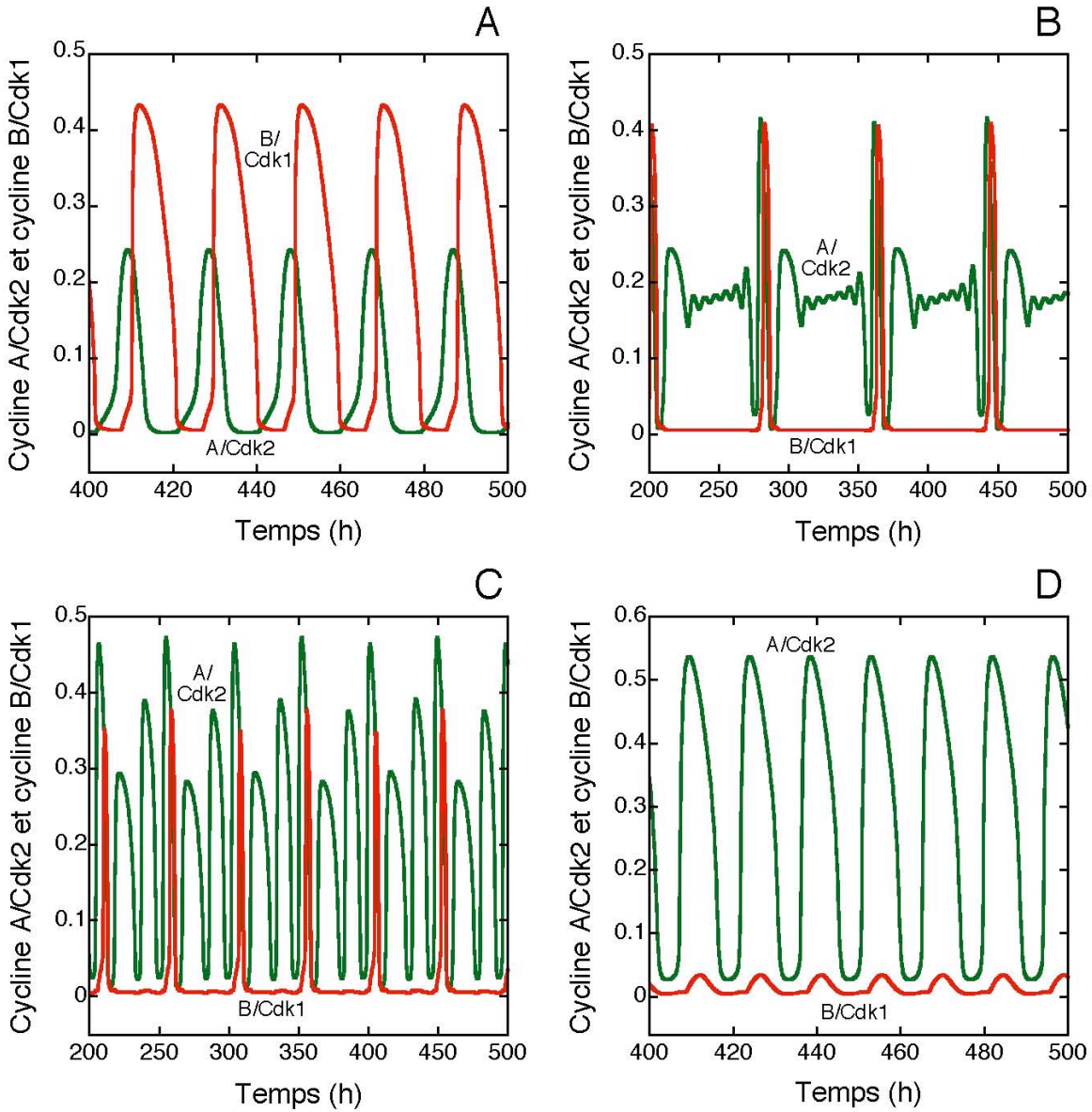
Mutations that increase the activity of the phosphatase Cdc25 or reduce the activity of the tumour suppressor Cdh1 possess tumorigenic effects.


Boutros R, Lobjois V, Ducommun B (2007) CDC25 phosphatases in cancer cells: key players? Good targets? *Nat Rev Cancer* 7:495-507.

Garcia-Higuera I, et al. (2008) Genomic stability and tumour suppression by the APC/C cofactor Cdh1. *Nat Cell Biol* 10:802-811.

Sorensen CS, et al. (2000) Nonperiodic activity of the human anaphase-promoting complex-Cdh1 ubiquitin ligase results in continuous DNA synthesis uncoupled from mitosis. *Mol Cell Biol* 20:7613-7623.

## Endoreplication : effect of the rate of inhibition of Cdh1 on the dynamics of the Cdk network




From A to D the inhibition of Cdh1 decreases.

The Cdk network switches progressively from a mitotic cycle (A) to a cycle of endoreplication (D)

*Nature* 2011

LETTER

doi:10.1038/nature10579

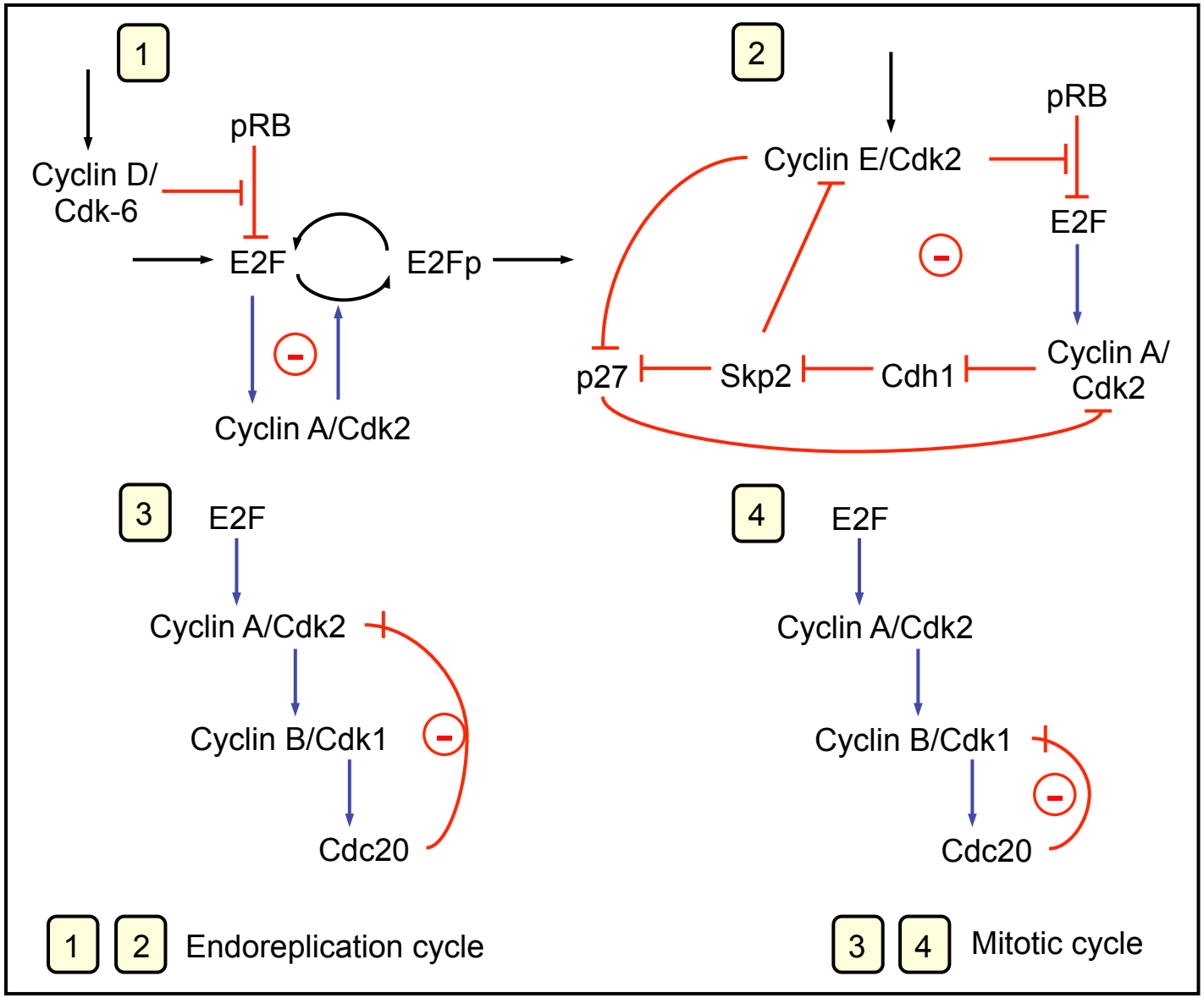
# Control of *Drosophila* endocycles by E2F and CRL4$^{CDT2}$

Norman Zielke[1,2]*, Kerry J. Kim[3]*, Vuong Tran[2]*, Shusaku T. Shibutani[4], Maria-Jose Bravo[2], Sabarish Nagarajan[5,6], Monique van Straaten[1], Brigitte Woods[2], George von Dassow[3], Carmen Rottig[7], Christian F. Lehner[7], Savraj S. Grewal[5,6], Robert J. Duronio[4] & Bruce A. Edgar[1,2]

**Endocycles are variant cell cycles comprised of DNA synthesis (S)- and gap (G)-phases but lacking mitosis[1,2]. Such cycles facilitate post-mitotic growth in many invertebrate and plant cells, and are so ubiquitous that they may account for up to half the world's biomass[3,4]. DNA replication in endocycling *Drosophila* cells is triggered by cyclin E/cyclin dependent kinase 2 (CYCE/CDK2),**

mitotic cell cycles[15], it blocks endocycling (Fig. 2, 3)[5,6]. This is likely due to CYCE/CDK2's ability to suppress APC$^{Fzr/Cdh1}$ and drive geminin accumulation[10,14,16], although CYCE may also inhibit preRC formation directly by phosphorylating preRC components. The importance of CYCE oscillation for endocycling is underscored by the finding that

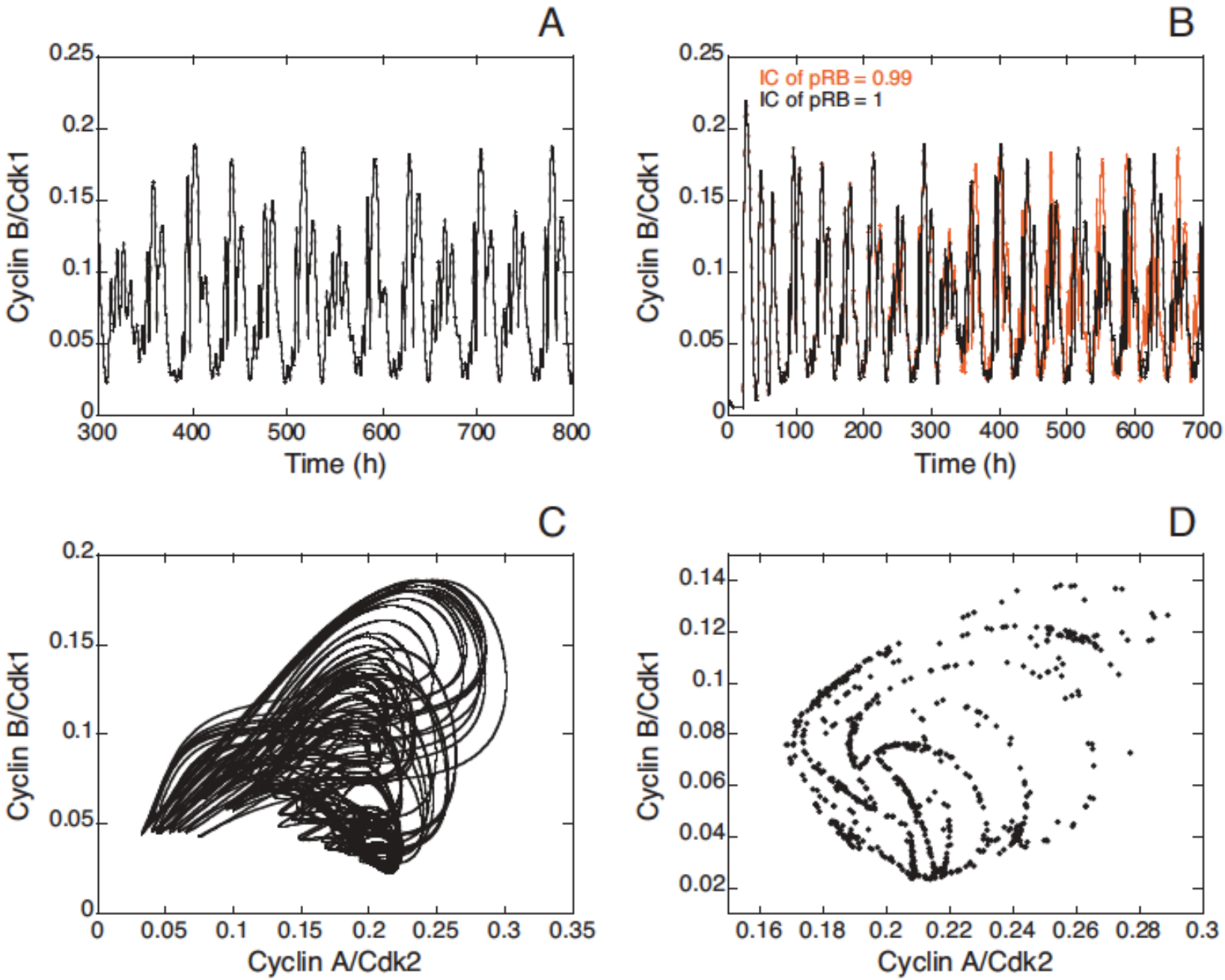
# Multiple oscillatory circuits in the Cdk network



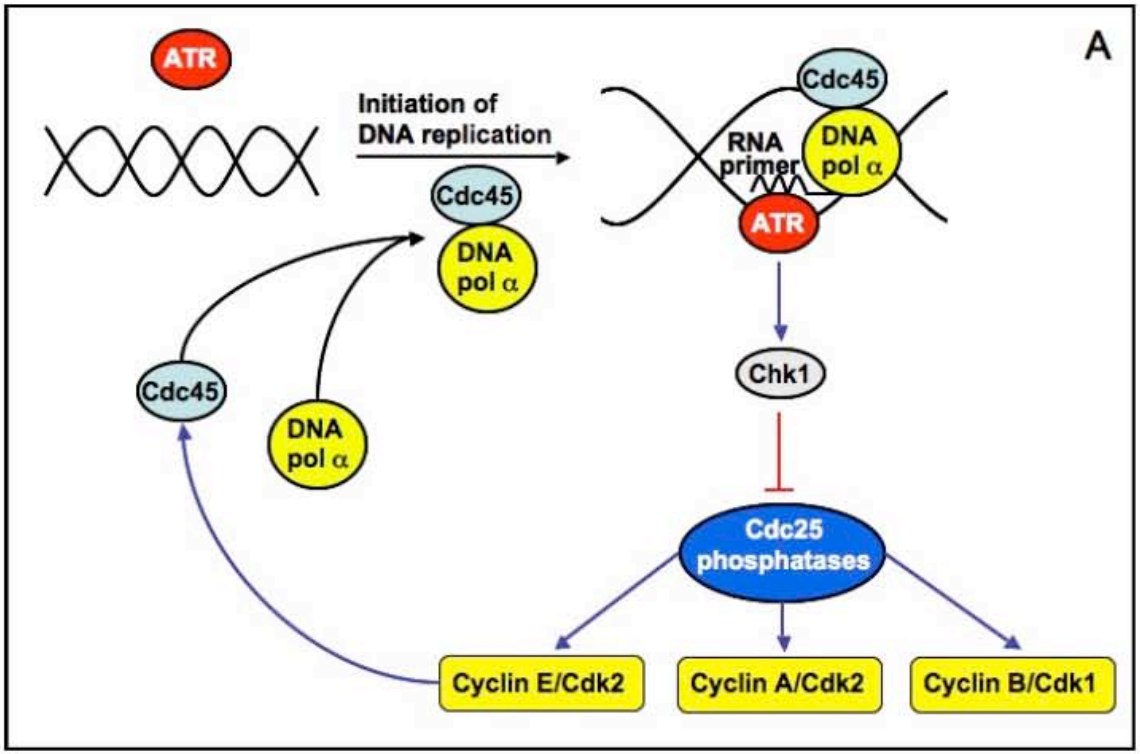
CHAOS **20**, 045109 (2010)

# From simple to complex patterns of oscillatory behavior in a model for the mammalian cell cycle containing multiple oscillatory circuits

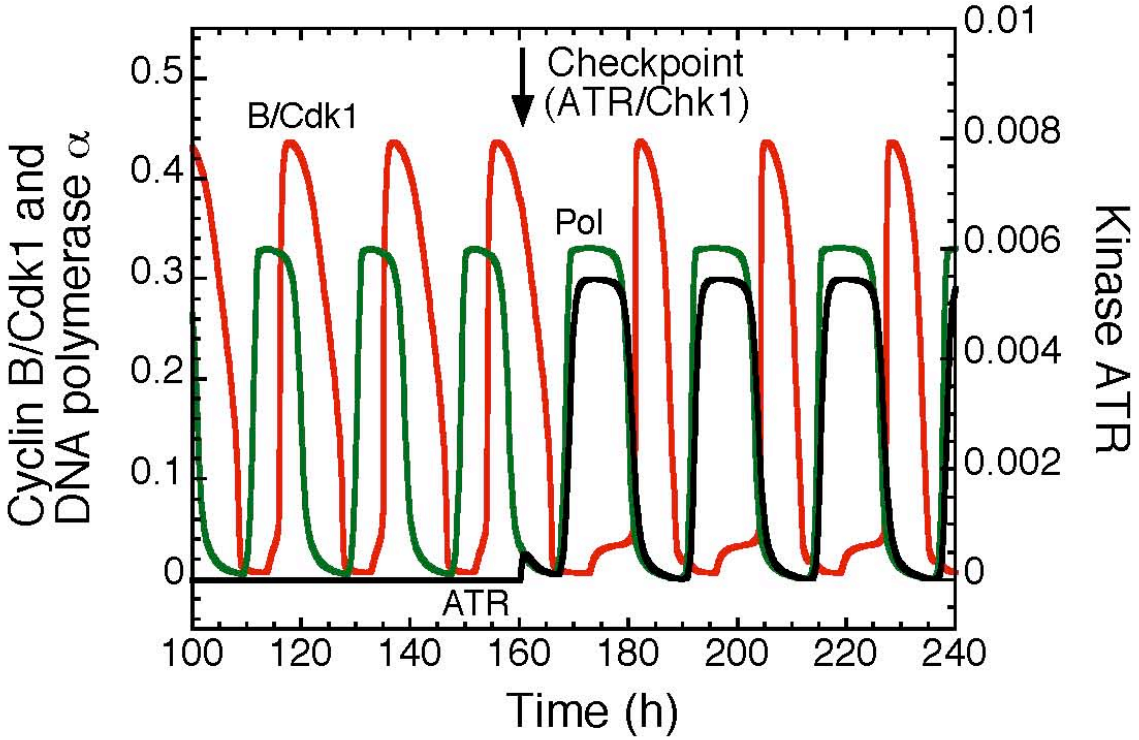
Claude Gérard and Albert Goldbeter[a)]
*Faculté des Sciences, Université Libre de Bruxelles (ULB), Campus Plaine, CP 231, B-1050 Brussels, Belgium*


A
B
C
D
Cyclin B/Cdk1
Time (h)
IC of pRB = 0.99
IC of pRB = 1
Cyclin A/Cdk2

# Incorporation of the ATR/Chk1 DNA replication checkpoint



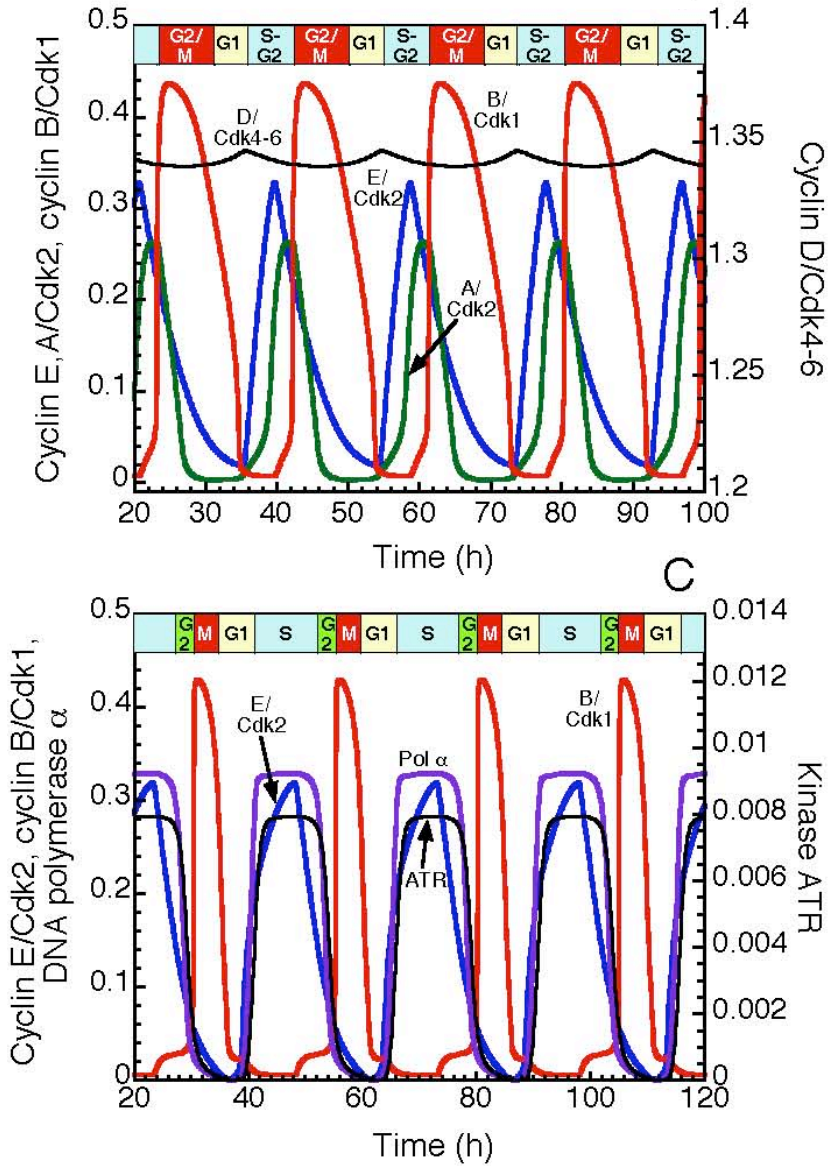
## Incorporation of the ATR/Chk1 DNA replication checkpoint




Gérard & Goldbeter (2009) *PNAS*

Without checkpoint

With checkpoint



# Reducing the complexity of the model for the mammalian cell cycle

Interface Focus

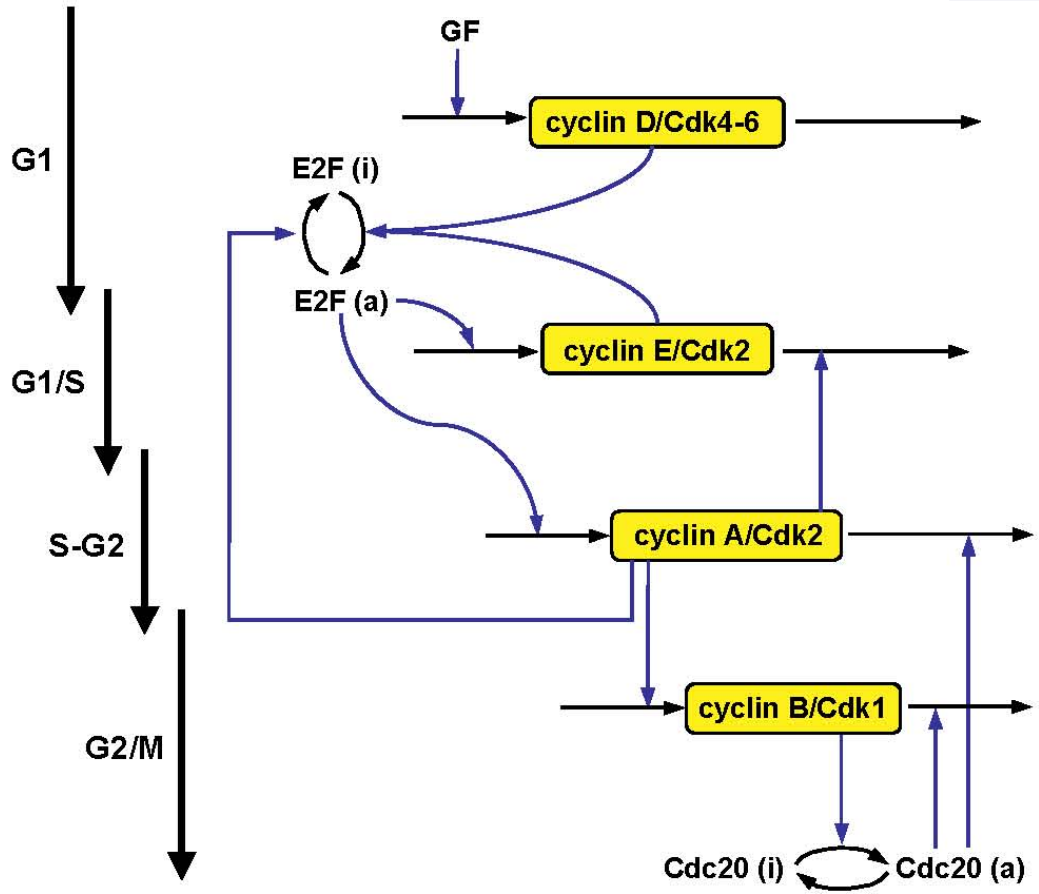
# A skeleton model for the network of cyclin-dependent kinases driving the mammalian cell cycle

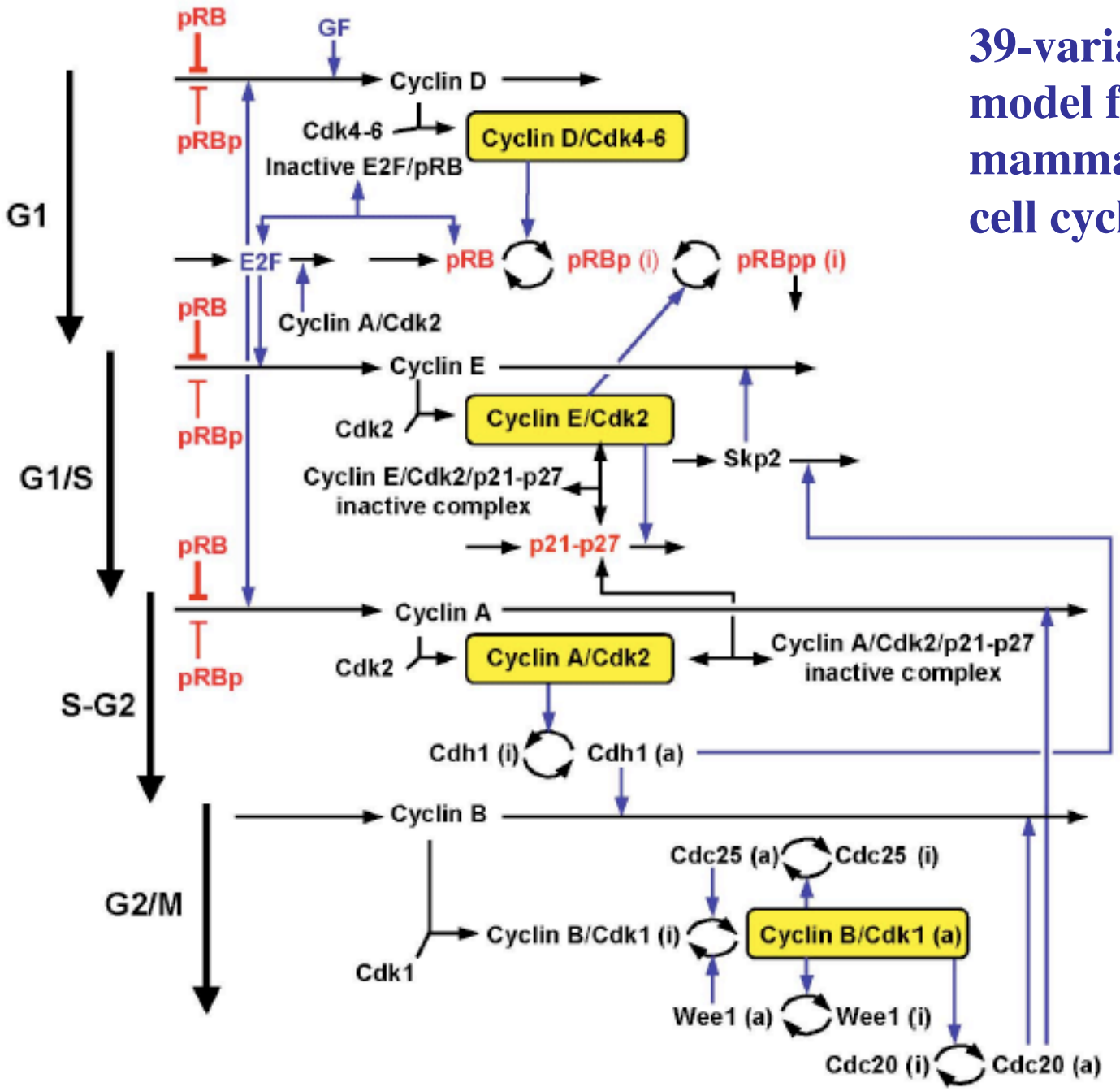
Claude Gérard and Albert Goldbeter

*Interface Focus* 2011 **1**, 24-35 first published online 1 December 2010
doi: 10.1098/rsfs.2010.0008

5 variables

25 parameters






**39-variable model for the mammalian cell cycle**

$$\frac{dMd}{dt} = (v_{sd} \cdot (\frac{GF}{K_{gf} + GF}) - V_{dd} \cdot (\frac{Md}{K_{dd} + Md})) \cdot eps \quad \textbf{[1]}$$

$$\frac{dE2F}{dt} = (V_{1e2f} \cdot (\frac{(E2F_{tot} - E2F)}{K_{1e2f} + (E2F_{tot} - E2F)}) \cdot (Md + Me) - V_{2e2f} \cdot (\frac{E2F}{K_{2e2f} + E2F}) \cdot Ma) \cdot eps \quad \textbf{[2]}$$

$$\frac{dMe}{dt} = (v_{se} \cdot E2F - V_{de} \cdot Ma \cdot (\frac{Me}{K_{de} + Me})) \cdot eps \quad \textbf{[3]}$$

$$\frac{dMa}{dt} = (v_{sa} \cdot E2F - V_{da} \cdot Cdc20 \cdot (\frac{Ma}{K_{da} + Ma})) \cdot eps \quad \textbf{[4]}$$

$$\frac{dMb}{dt} = (v_{sb} \cdot Ma - V_{db} \cdot Cdc20 \cdot (\frac{Mb}{K_{db} + Mb})) \cdot eps \quad \textbf{[5]}$$

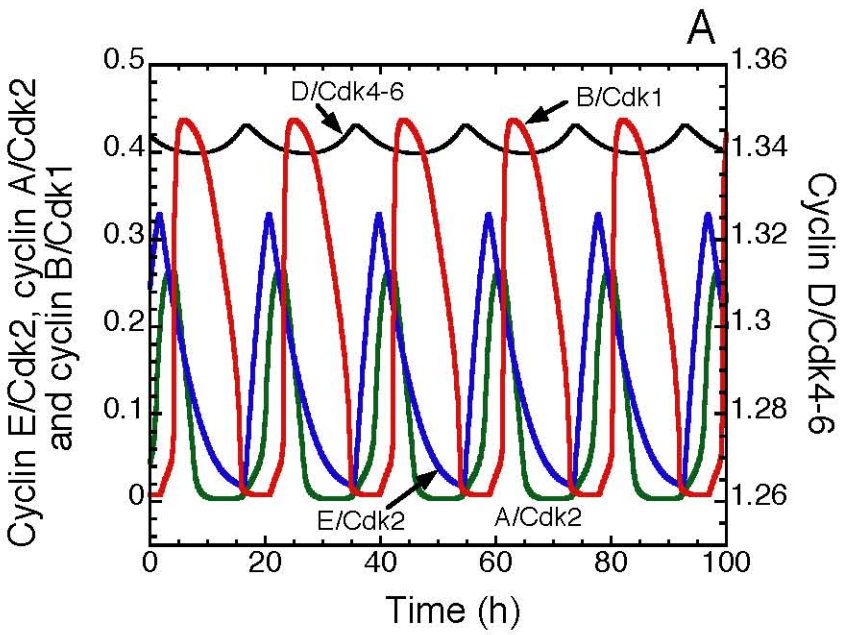
$$\frac{dCdc20}{dt} = (V_{1cdc20} \cdot Mb \cdot (\frac{(Cdc20_{tot} - Cdc20)}{K_{1cdc20} + (Cdc20_{tot} - Cdc20)}) - V_{2cdc20} \cdot (\frac{Cdc20}{K_{2cdc20} + Cdc20})) \cdot eps \quad \textbf{[6]}$$

Md : Cyclin D/Cdk4-6
Mb : Cyclin B/Cdk1
Cdc20 : Protein Cdc20

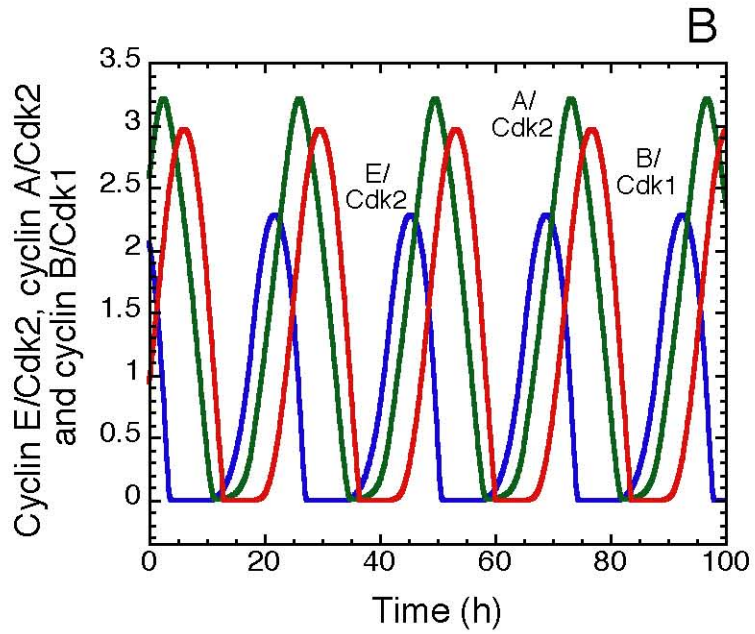
Ma : Cyclin A/Cdk2
Me : Cyclin E/Cdk2
E2F : Transcription factor E2F

# Oscillatory dynamics

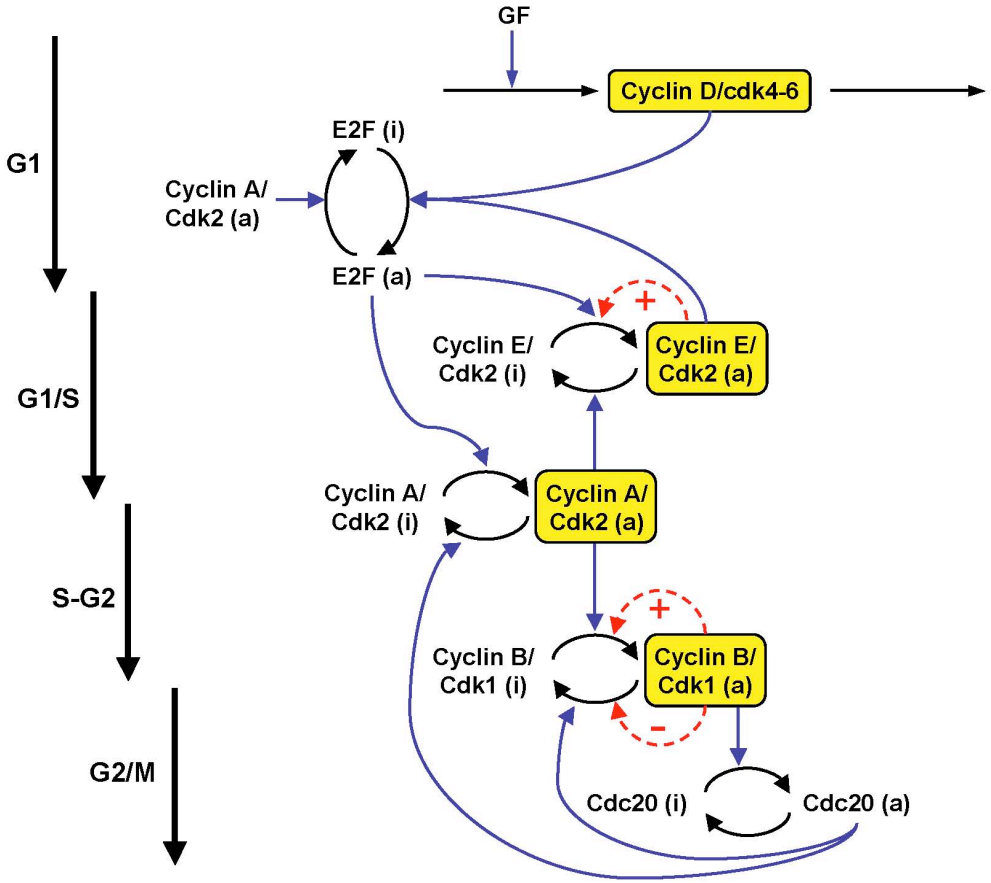
39-variable model




5-variable model



# Extended skeleton model for the cyclin/Cdk network incorporating phosphorylation-dephosphorylation








Gérard, Gonze & Goldbeter (FEBS J, 2012)

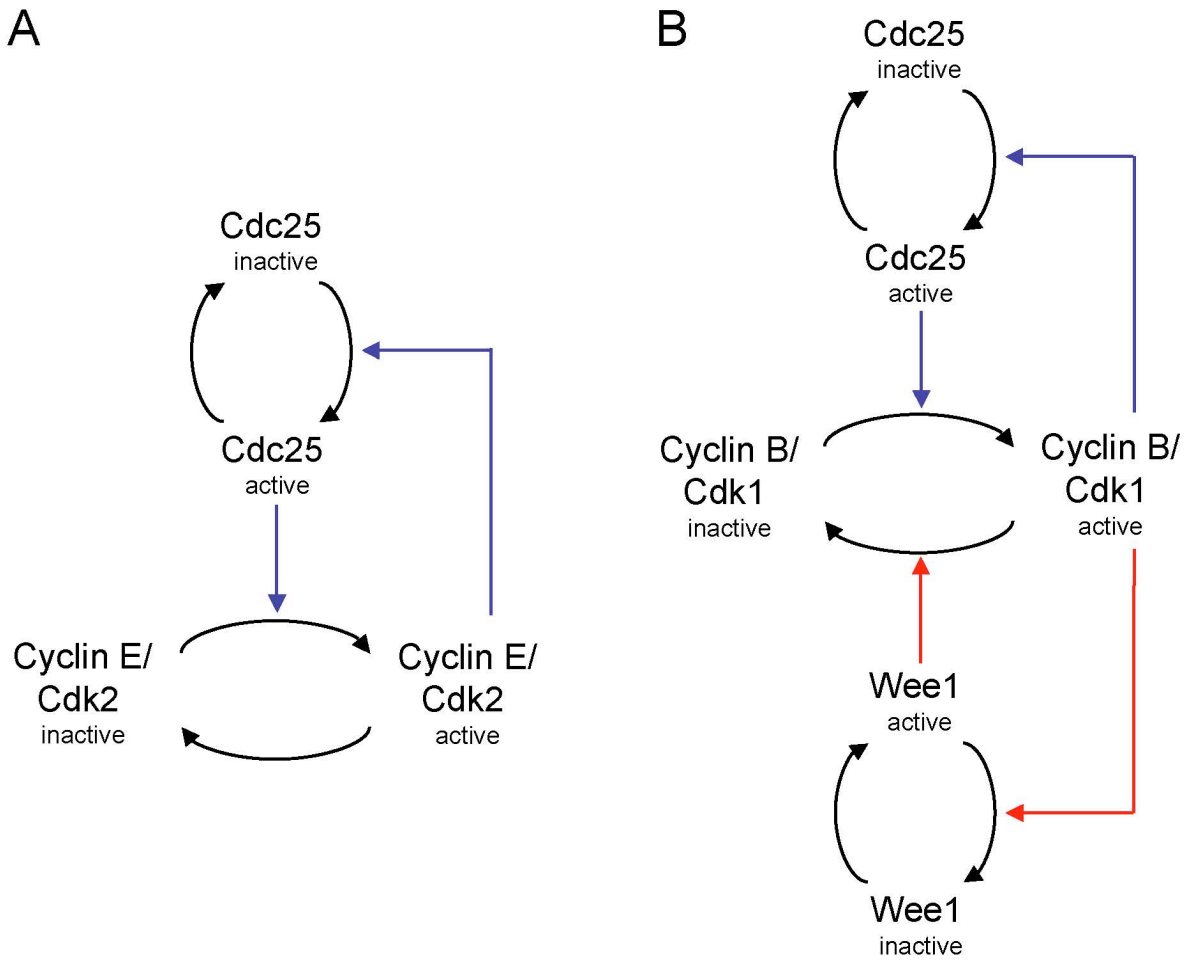
*FEBS J* (2012 )


# Effect of positive feedback loops on the robustness of oscillations in the network of cyclin-dependent kinases driving the mammalian cell cycle

Claude Gérard, Didier Gonze and Albert Goldbeter

Faculté des Sciences, Université Libre de Bruxelles (ULB), Brussels, Belgium

# Role of multiple positive feedback (PF) loops




1 PF in G1/S

2PF in G2/M

| Reaction number | Reaction | Propensity of reaction |
|---|---|---|
| 1 | $\xrightarrow{GF} Md$ | $w_1 = ((v_{sd} \cdot \Omega) \cdot (\frac{(GF \cdot \Omega)}{(K_{gf} \cdot \Omega) + (GF \cdot \Omega)})) \cdot \mu$ |
| 2 | $Md \longrightarrow$ | $w_2 = ((V_{dd} \cdot \Omega) \cdot (\frac{Md}{(K_{dd} \cdot \Omega) + Md})) \cdot \mu$ |
| 3 | $E2F^* \xrightarrow{Md,Me} E2F$ | $w_3 = (V_{1e2f} \cdot (\frac{(E2F_{tot} - E2F)}{(K_{1e2f} \cdot \Omega) + (E2F_{tot} - E2F)}) \cdot (Md + Me)) \cdot \mu$ |
| 4 | $E2F \xrightarrow{Ma} E2F^*$ | $w_4 = (V_{2e2f} \cdot (\frac{E2F}{(K_{2e2f} \cdot \Omega) + E2F}) \cdot Ma) \cdot \mu$ |
| 5 | $Me^* \xrightarrow{E2F,Me} Me$ | $w_5 = ((\frac{V_{1Me}}{\Omega}) \cdot E2F \cdot ((a \cdot \Omega) + b_1 \cdot Me) \cdot (\frac{Me_{tot} - Me}{(K_{1Me} \cdot \Omega) + (Me_{tot} - Me)})) \cdot \mu$ |
| 6 | $Me \xrightarrow{Ma} Me^*$ | $w_6 = (V_{2Me} \cdot Ma \cdot (\frac{Me}{(K_{2Me} \cdot \Omega) + Me})) \cdot \mu$ |
| 7 | $Ma^* \xrightarrow{E2F} Ma$ | $w_7 = (V_{1Ma} \cdot E2F \cdot (\frac{Ma_{tot} - Ma}{(K_{1Ma} \cdot \Omega) + (Ma_{tot} - Ma)})) \cdot \mu$ |
| 8 | $Ma \xrightarrow{Cdc20} Ma^*$ | $w_8 = (V_{2Ma} \cdot Cdc20 \cdot (\frac{Ma}{(K_{2Ma} \cdot \Omega) + Ma})) \cdot \mu$ |
| 9 | $Mb^* \xrightarrow{Ma,Me,(Cdc25)} Mb$ | $w_9 = ((\frac{V_{1Mb}}{\Omega}) \cdot Ma \cdot ((a \cdot \Omega) + b_2 \cdot Mb) \cdot (\frac{(K_{ie} \cdot \Omega)}{(K_{ie} \cdot \Omega) + Me}) \cdot (\frac{Mb_{tot} - Mb}{(K_{1Mb} \cdot \Omega) + (Mb_{tot} - Mb)})) \cdot \mu$ |
| 10 | $Mb \xrightarrow{Cdc20,(Wee1)} Mb^*$ | $w_{10} = (V_{2Mb} \cdot (\frac{(K_{ib} \cdot \Omega)}{(K_{ib} \cdot \Omega) + Mb}) \cdot Cdc20 \cdot (\frac{Mb}{(K_{2Mb} \cdot \Omega) + Mb})) \cdot \mu$ |
| 11 | $Cdc20^* \xrightarrow{Mb} Cdc20$ | $w_{11} = (V_{1cdc20} \cdot Mb \cdot (\frac{(Cdc20_{tot} - Cdc20)}{(K_{1cdc20} \cdot \Omega) + (Cdc20_{tot} - Cdc20)})) \cdot \mu$ |
| 12 | $Cdc20 \longrightarrow Cdc20^*$ | $w_{12} = ((V_{2cdc20} \cdot \Omega) \cdot (\frac{Cdc20}{(K_{2cdc20} \cdot \Omega) + Cdc20})) \cdot \mu$ |

# Stochastic simulations: Gillespie algorithm

A probability $w_i$ is associated to each reaction step. These probabilites are related to the kinetics constants.

Initial number of molecules of each species are specified.

At each time interval,

- the reaction that occurs is chosen randomly according to the probabilities $w_i$
- the number of molecules as well as the probabilities are updated.

$$A \xrightarrow{w_1} B$$

$$B + C \xrightarrow{w_2} D$$

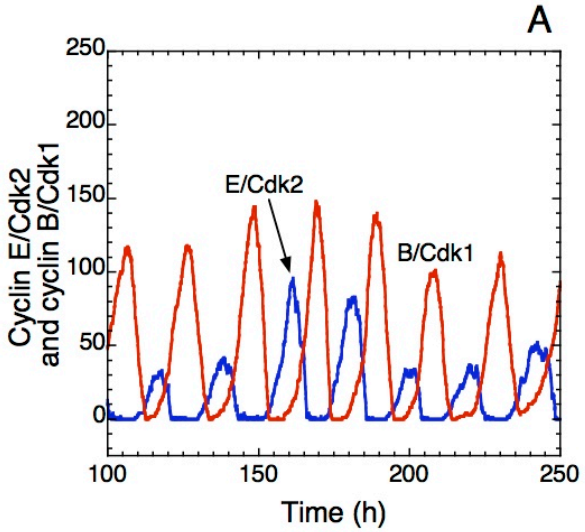
$$D \xrightarrow{w_3} E + F$$

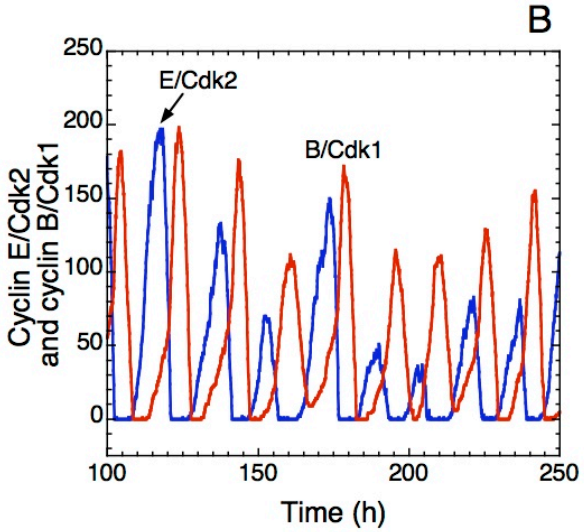
...

***Gillespie D.T. (1977) Exact stochastic simulation of coupled chemical reactions. J. Phys. Chem. 81: 2340-2361.***
***Gillespie D.T., (1976) A General Method for Numerically Simulating the Stochastic Time evolution of coupled chemical reactions. J. Comp. Phys. 22: 403-434.***

# Multiple positive feedback loops increase robustness of Cdk oscillations with respect to molecular noise

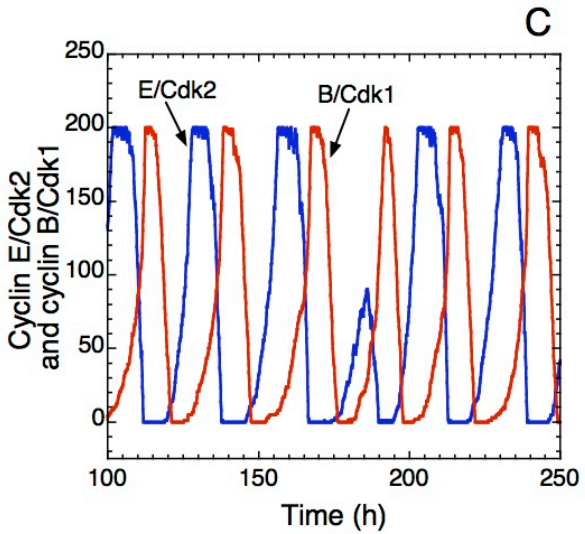
No PF

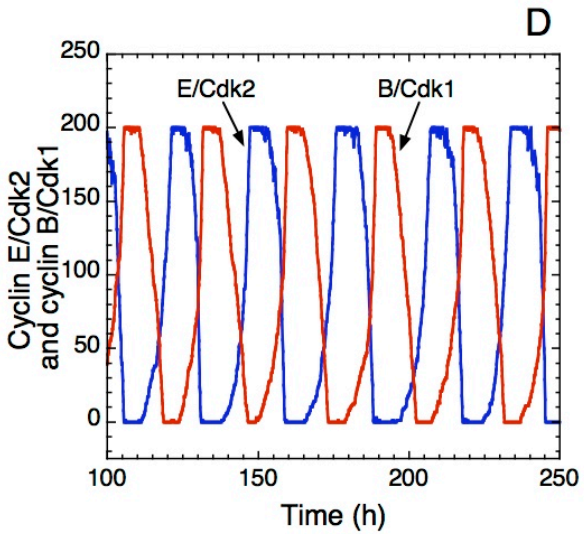



1 PF on G1/S

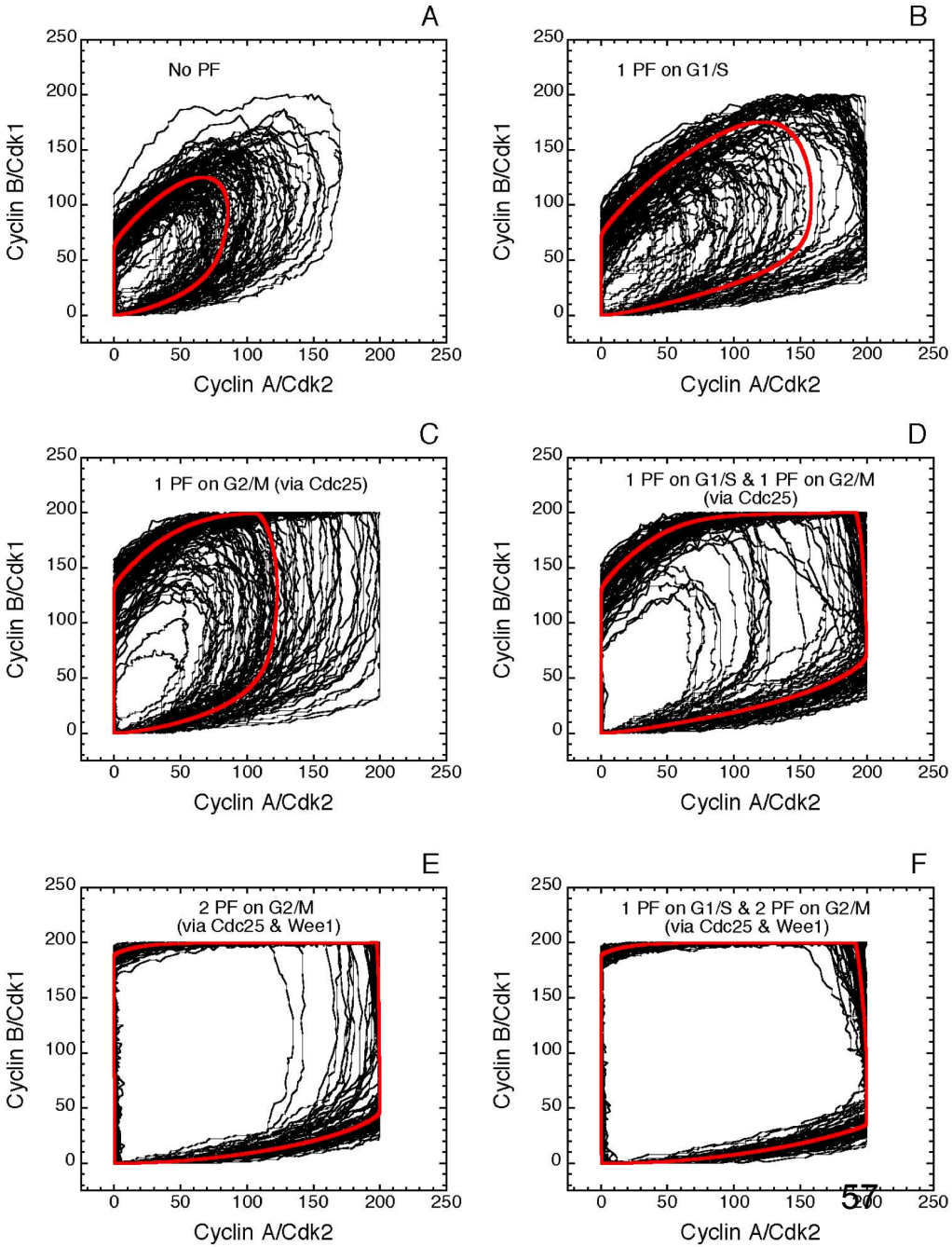
1 PF on G1/S & 1 PF on G2/M



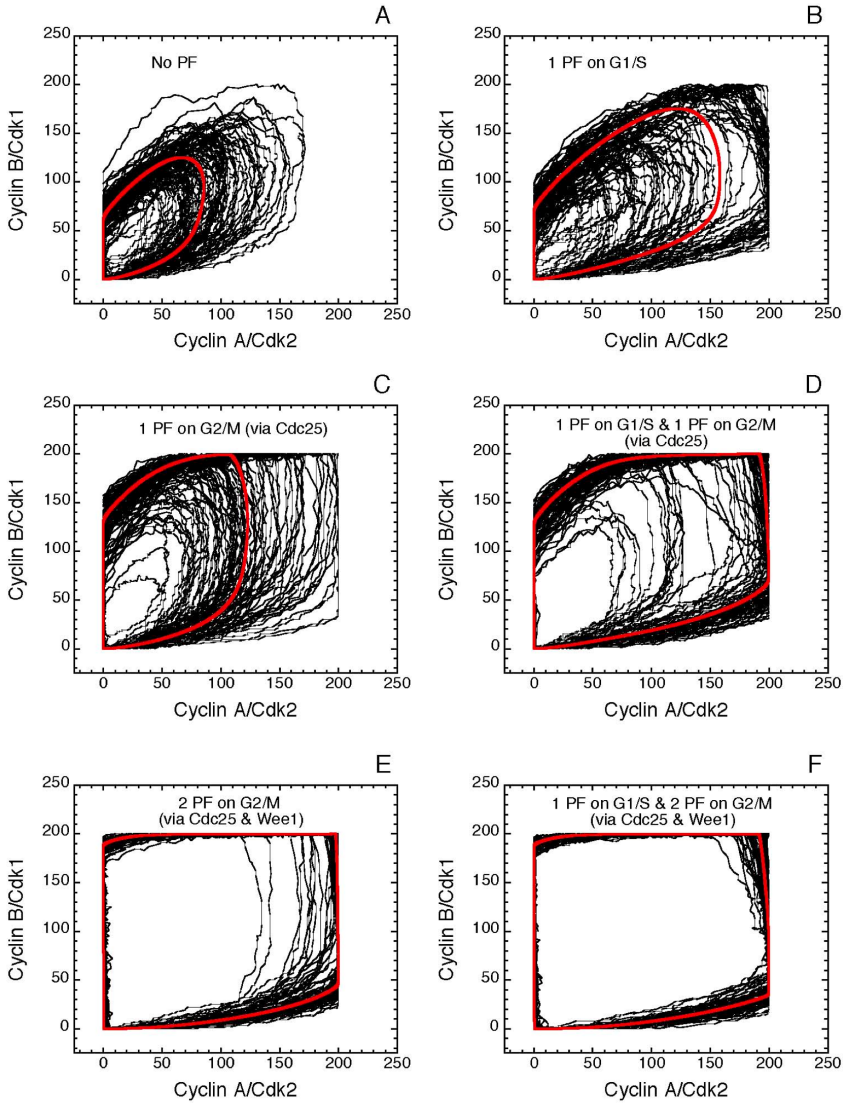




1 PF on G1/S & 2 PF on G2/M

# Stochastic simulations



# Stochastic simulations

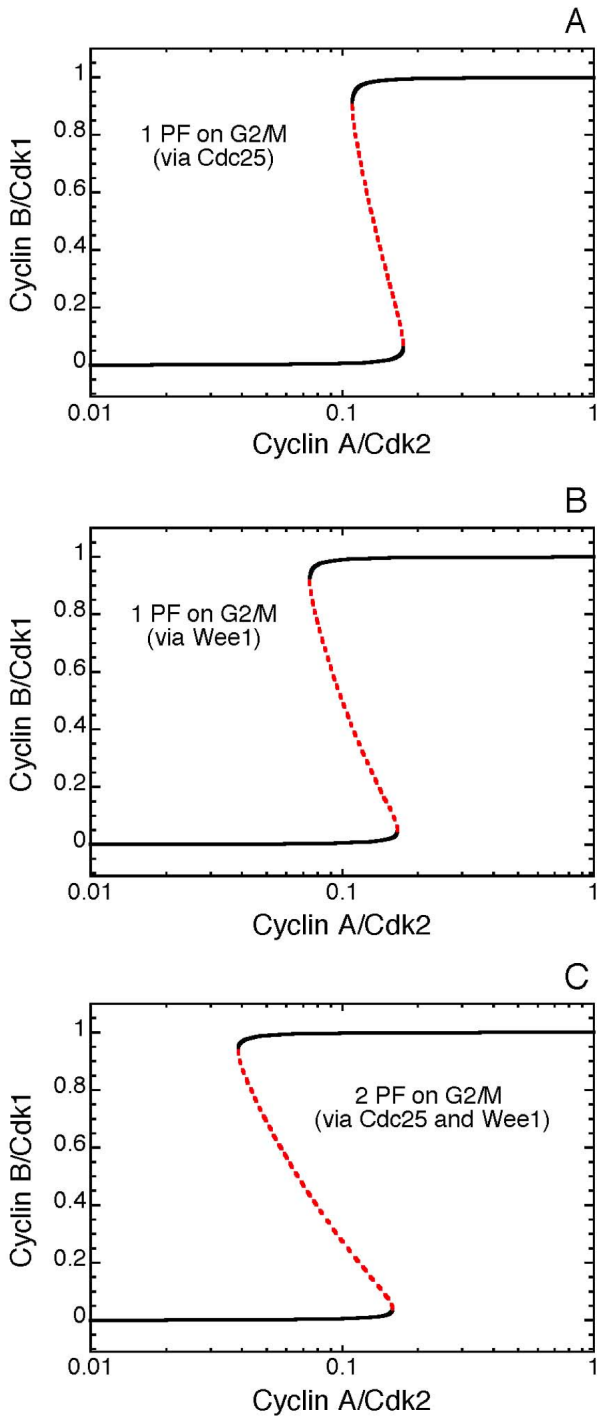



Cell. 2005 Aug 26;122(4):565-78.

**Systems-level dissection of the cell-cycle oscillator: bypassing positive feedback produces damped oscillations.**

Pomerening JR, Kim SY, Ferrell JE Jr.

# Bistability



2014

Interface Focus

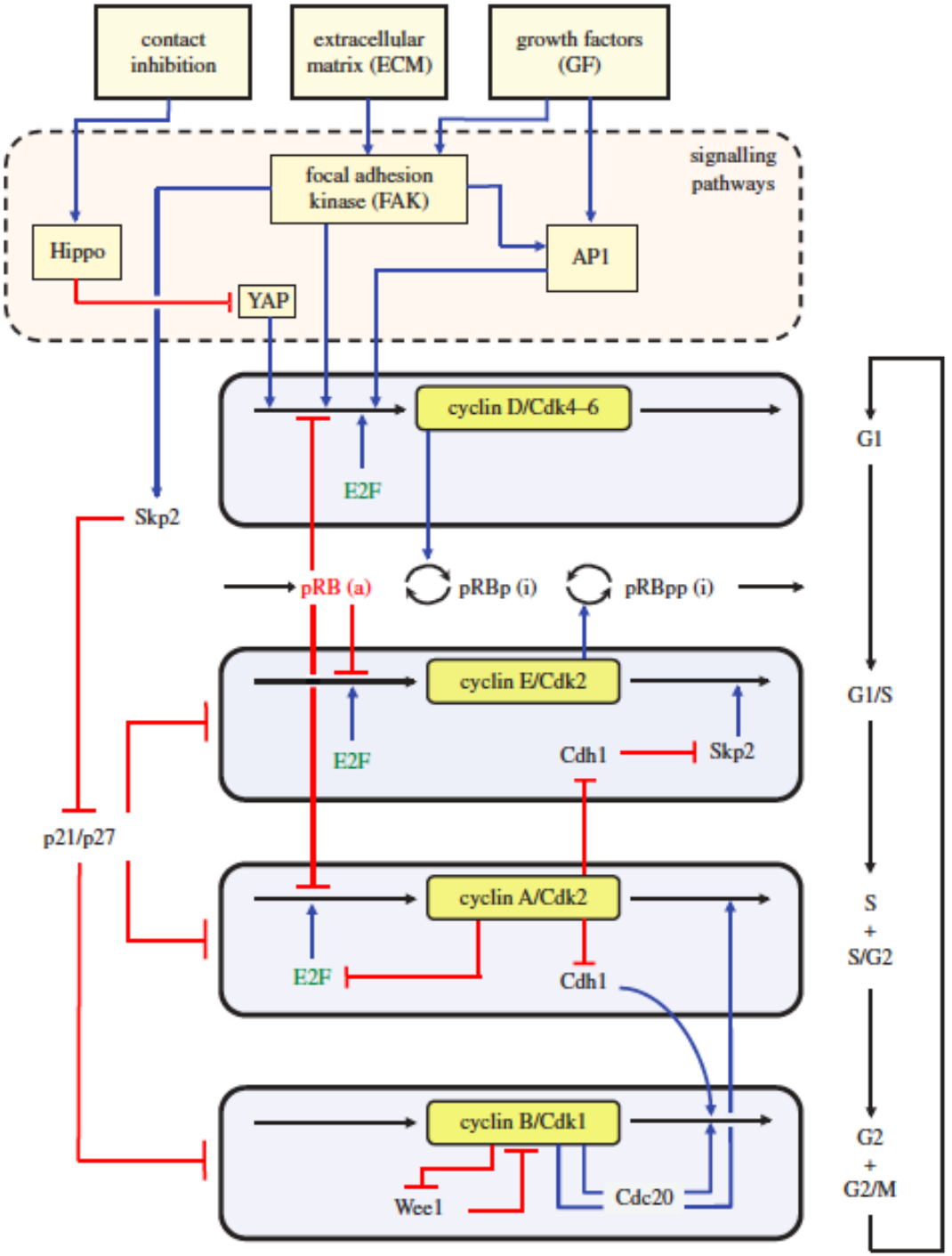
rsfs.royalsocietypublishing.org

# The balance between cell cycle arrest and cell proliferation: control by the extracellular matrix and by contact inhibition

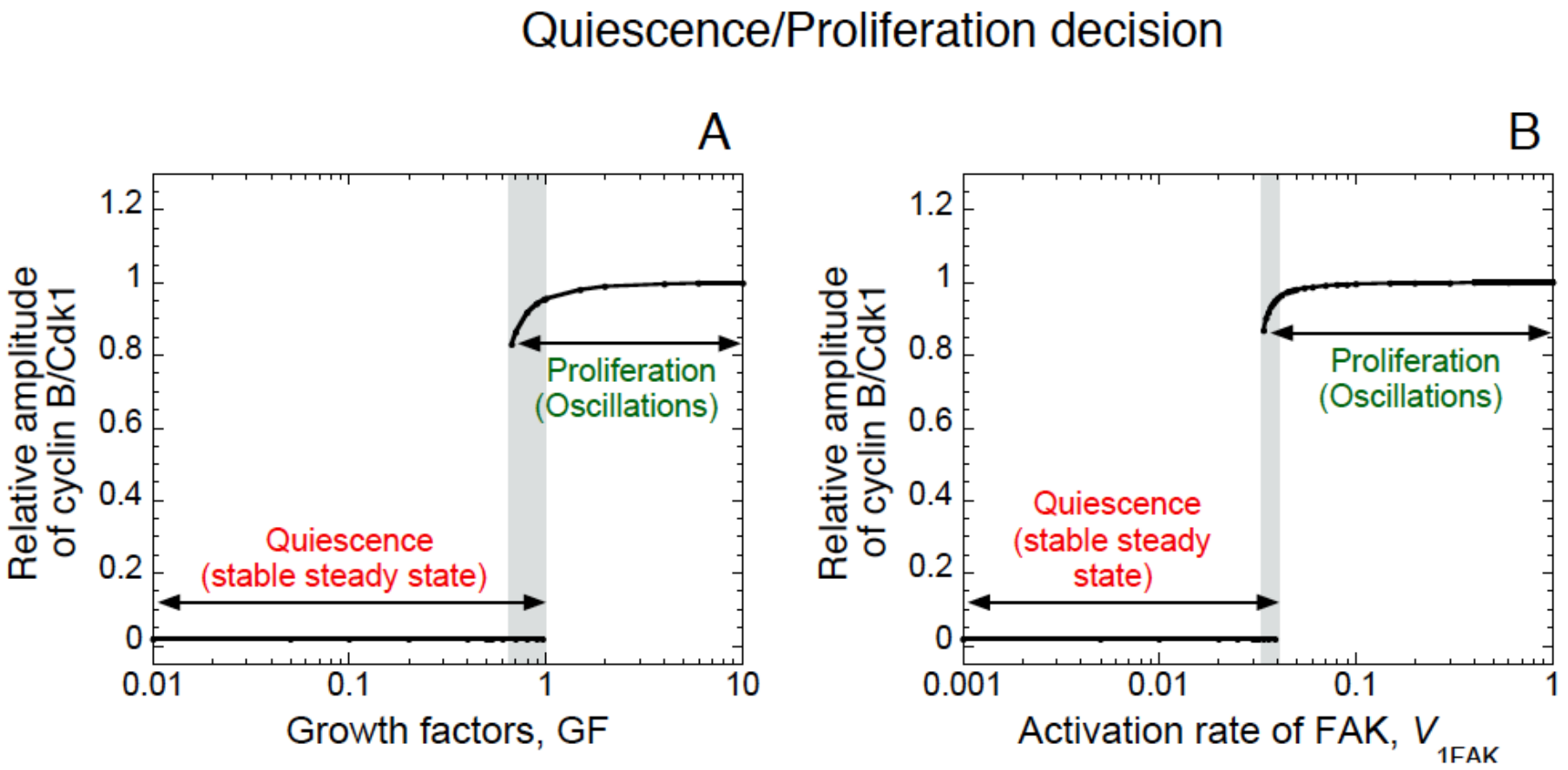
Claude Gérard[1,†] and Albert Goldbeter[1,2]

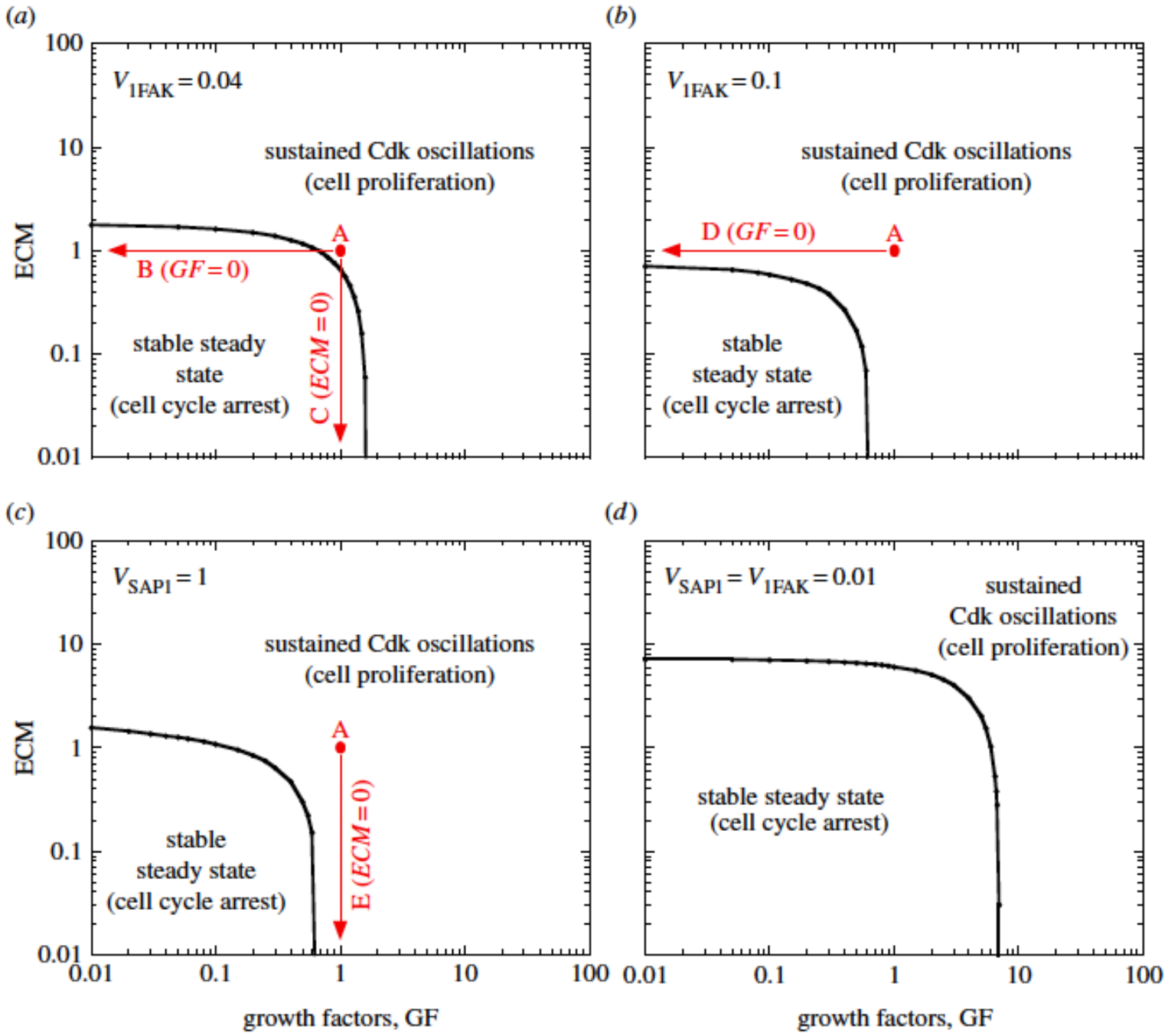
**Stiffness of extracellular matrix:** Integrins → FAK activation

**Cell contact inhibition:** Cadherins → Hippo ⊣ YAP


contact inhibition
extracellular matrix (ECM)
growth factors (GF)
signalling pathways
focal adhesion kinase (FAK)
Hippo
YAP
AP1
cyclin D/Cdk4–6
E2F
Skp2
pRB (a)
pRBp (i)
pRBpp (i)
cyclin E/Cdk2
E2F
Cdh1
Skp2
p21/p27
cyclin A/Cdk2
E2F
Cdh1
cyclin B/Cdk1
Wee1
Cdc20
G1
G1/S
S + S/G2
G2 + G2/M

# Compared effects of GF and FAK




(a)
(b)
(c)
(d)
$V_{1FAK} = 0.04$
$V_{1FAK} = 0.1$
$V_{SAP1} = 1$
$V_{SAP1} = V_{1FAK} = 0.01$
sustained Cdk oscillations
(cell proliferation)
stable steady state
(cell cycle arrest)
stable
steady state
(cell cycle arrest)
sustained
Cdk oscillations
(cell proliferation)
stable steady state
(cell cycle arrest)
A
B (GF = 0)
C (ECM = 0)
D (GF = 0)
E (ECM = 0)
ECM
growth factors, GF
100
10
1
0.1
0.01

Increasing
contact inhibition
in a linear or logistic
manner leads via the
Hippo/YAP pathway to
cell cycle arrest

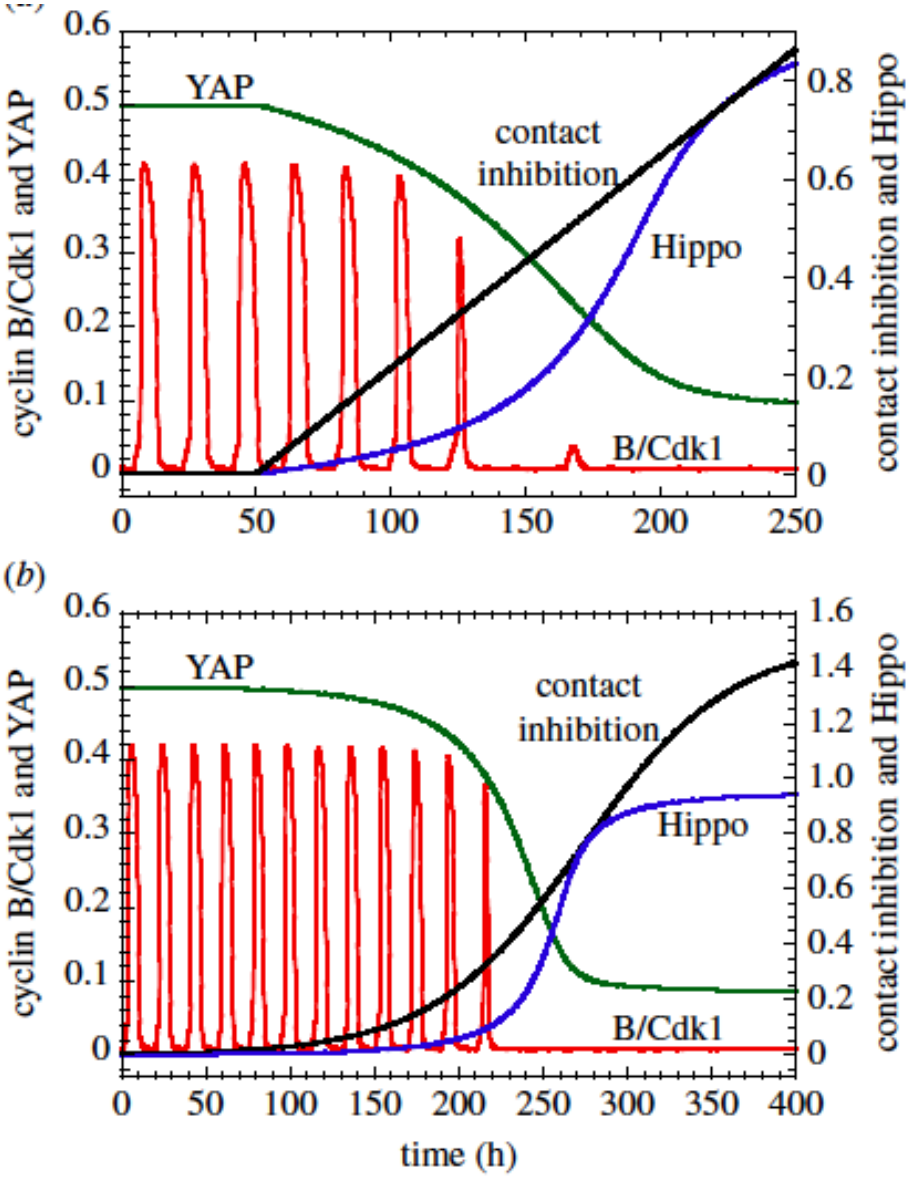
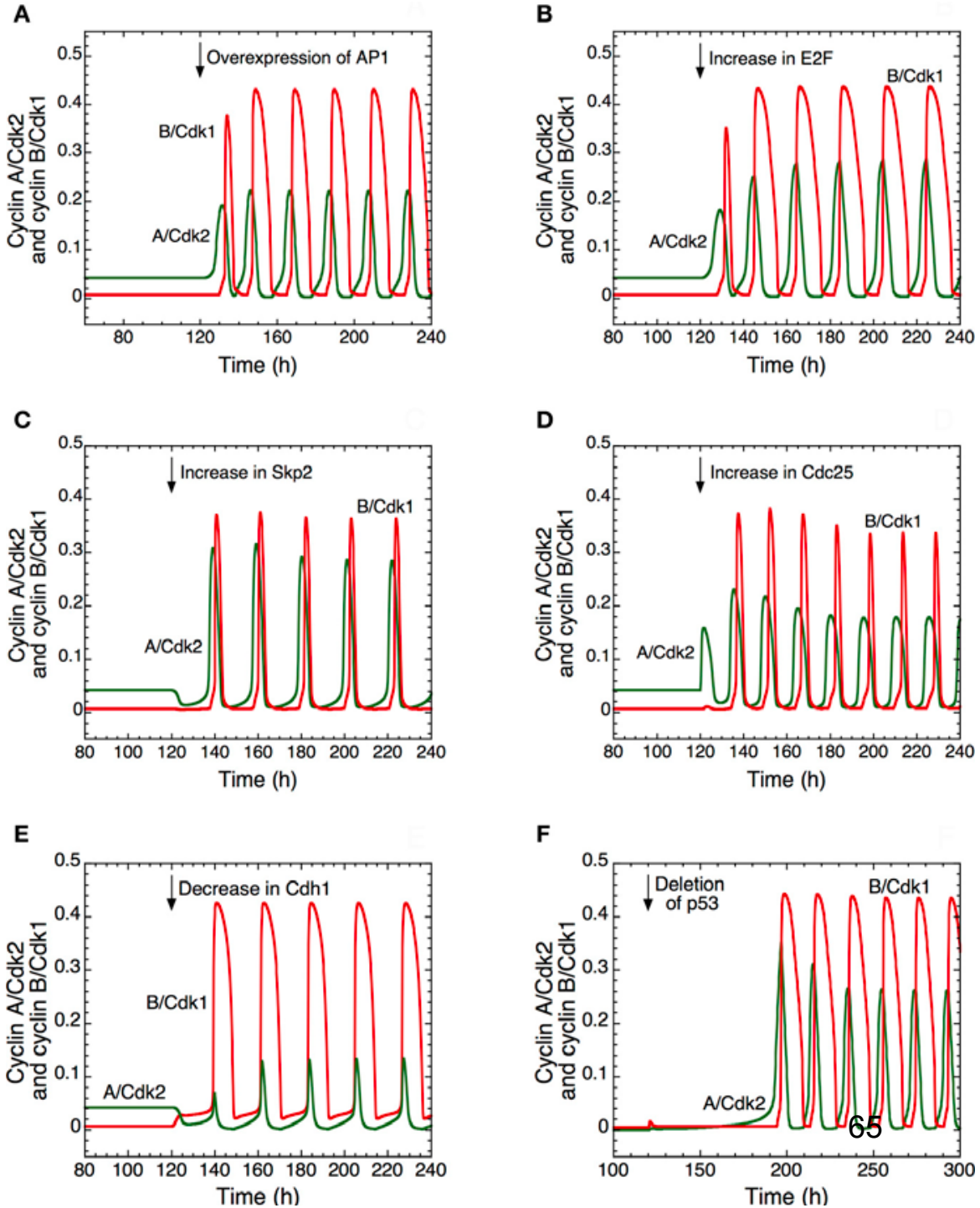
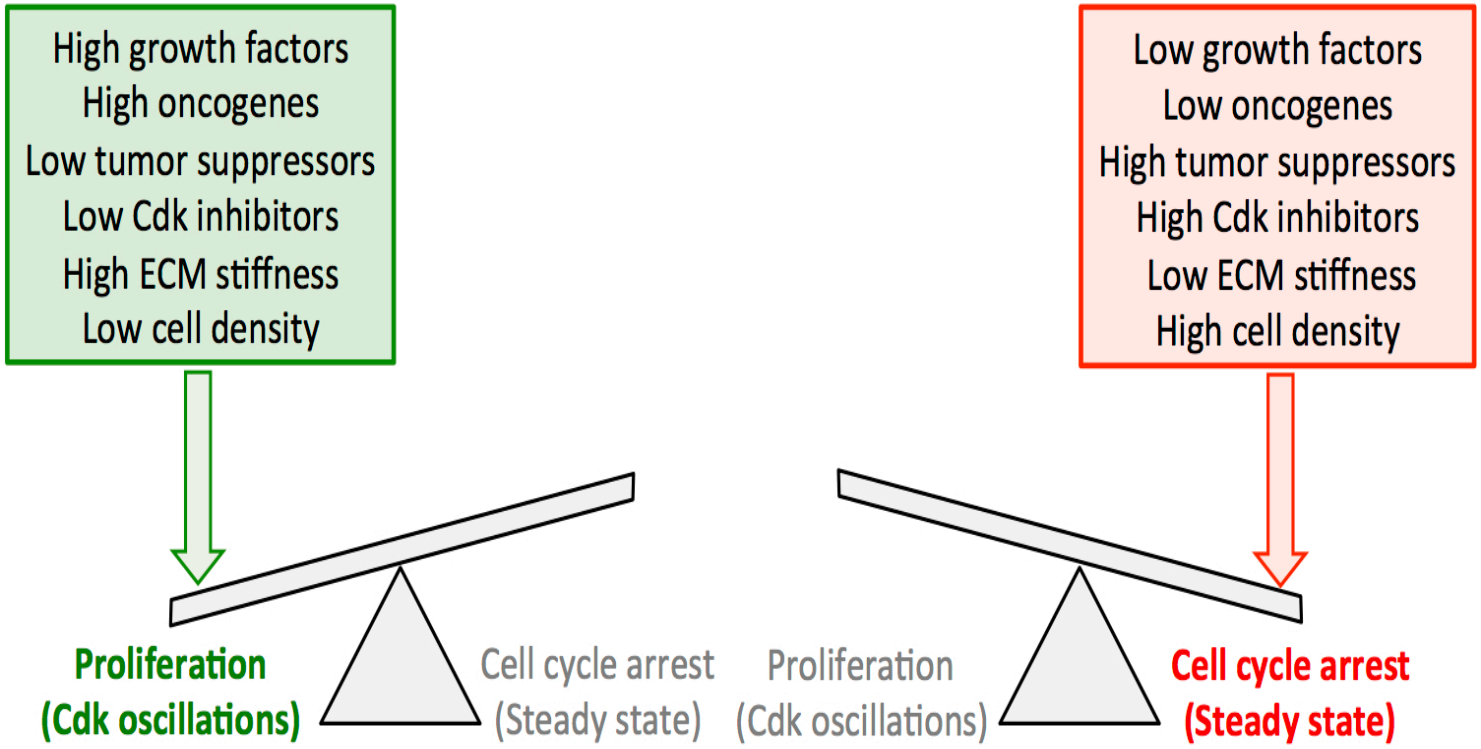



**Figure 8.** Inhibition of cell proliferation by increasing cell density, via the Hippo/YAP pathway. Shown is the time evolution of cyclin B/Cdk1 and of the active forms of Hippo and YAP, when the level of contact inhibition increases (*a*) linearly or (*b*) according to a logistic equation. In both cases, cell proliferation is first slowed down and then arrested at sufficiently high contact inhibition. Between

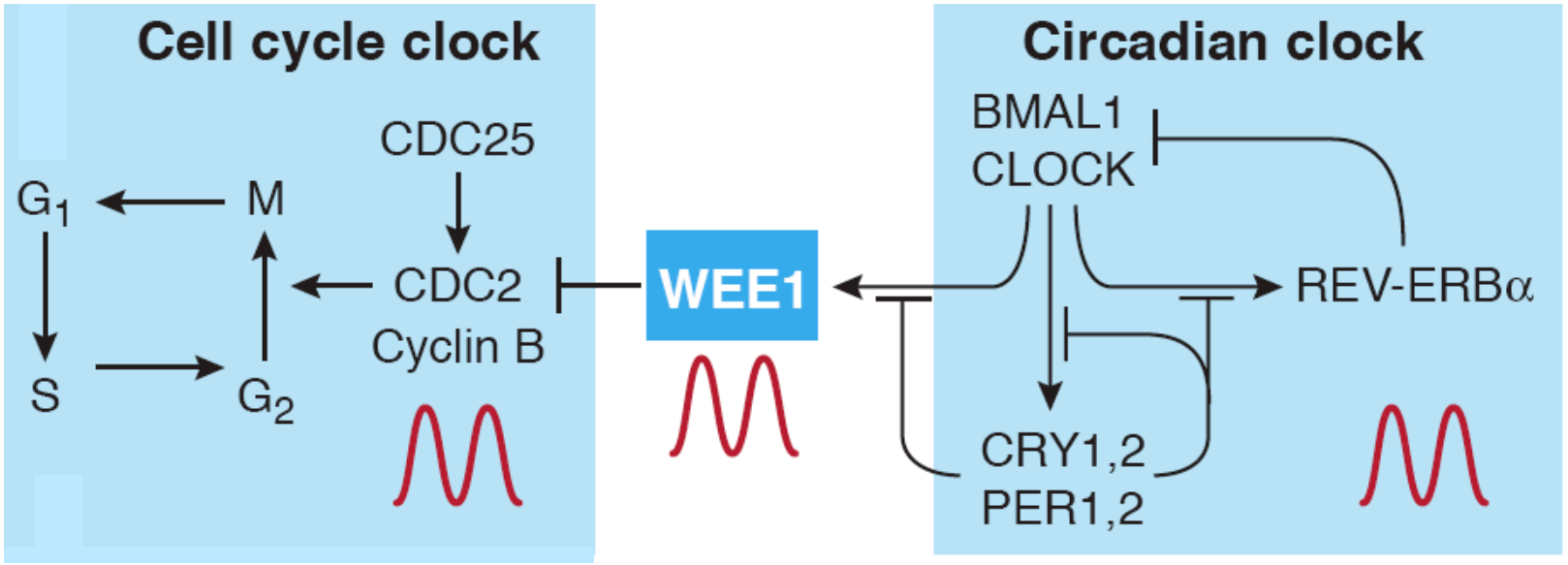
Multiple ways to induce the onset of Cdk oscillations



# The balance between cell cycle arrest and cell proliferation



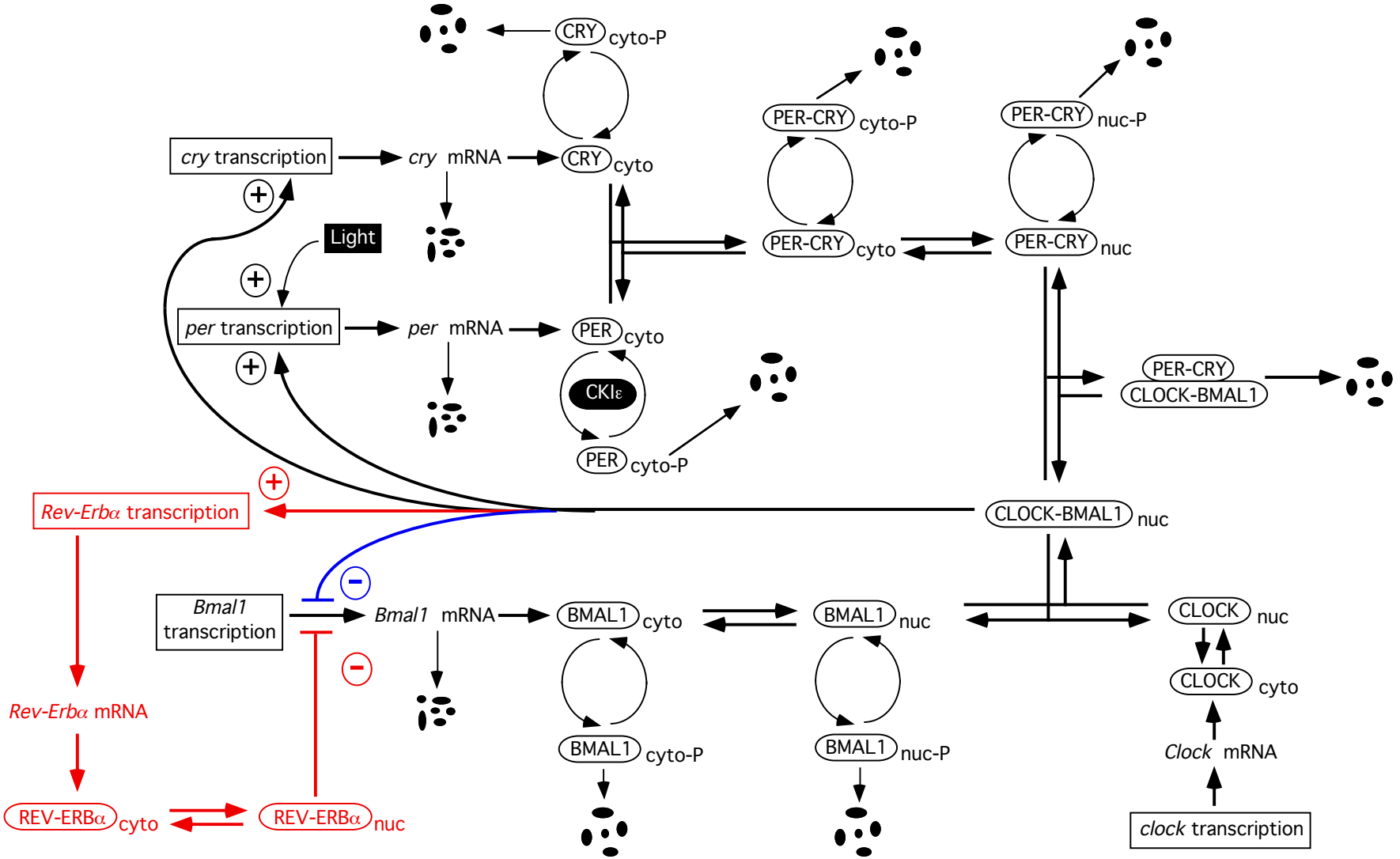
# Link between the circadian clock and the cell cycle




Wee1 : Cell cycle inhibitor
induced by the circadian clock

*Schibler (2003)*
*Matsuo et al (2003)*

# Model for the mammalian circadian clock






J.C. Leloup & A. Goldbeter (2003) *PNAS*

# Entrainment of the cell cycle by the circadian clock

Rate of synthesis of Wee1 driven by the circadian clock :

*Coupling parameter* $k_{sw}$

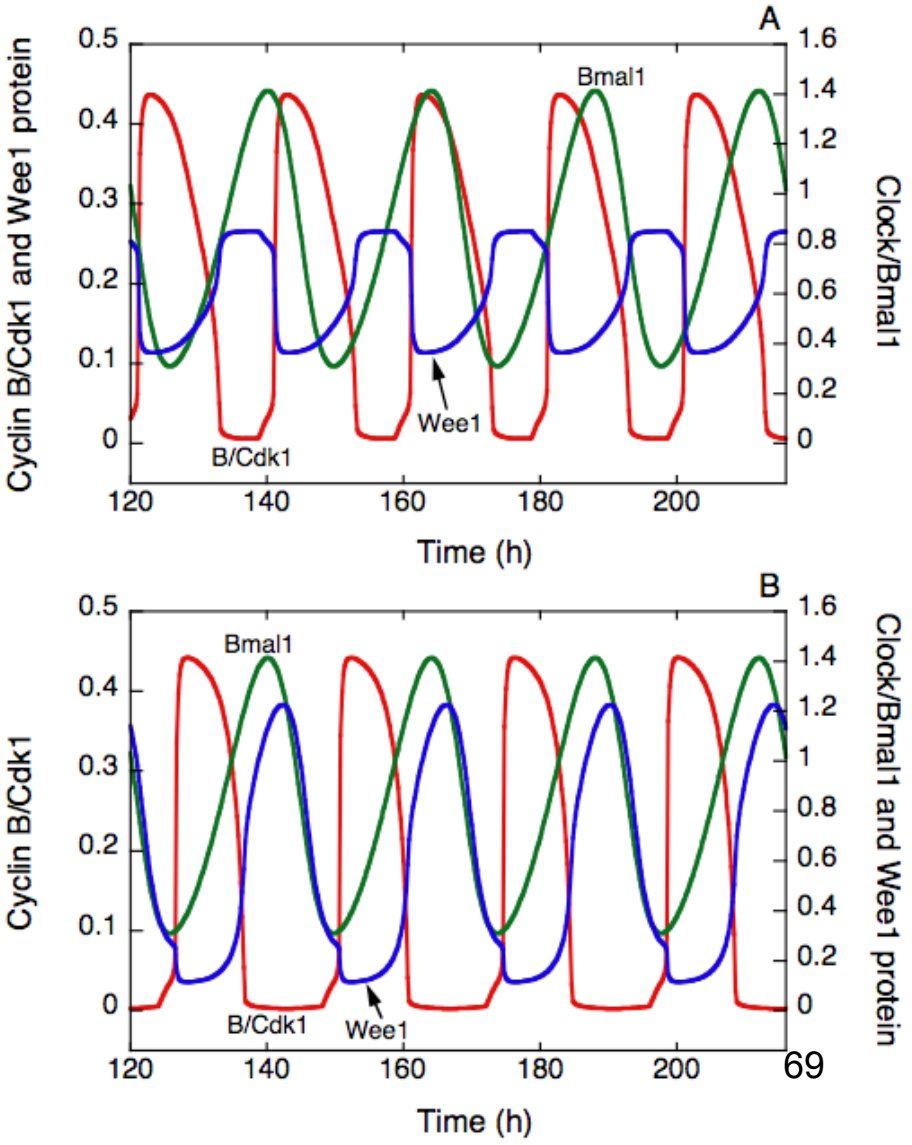
Without coupling ($k_{sw}$ = 0 $h^{-1}$) :

Cell cycle period=20h

With coupling ($k_{sw}$ = 10 $h^{-1}$) :

Entrainment by the circadian clock

Cell cycle period=24 h




A. Goldbeter-ICTS 2018

2012

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PLoS COMPUTATIONAL BIOLOGY

# Entrainment of the Mammalian Cell Cycle by the Circadian Clock: Modeling Two Coupled Cellular Rhythms

**Claude Gérard, Albert Goldbeter***

Faculté des Sciences, Université Libre de Bruxelles (ULB), Campus Plaine, CP 231, Brussels, Belgium

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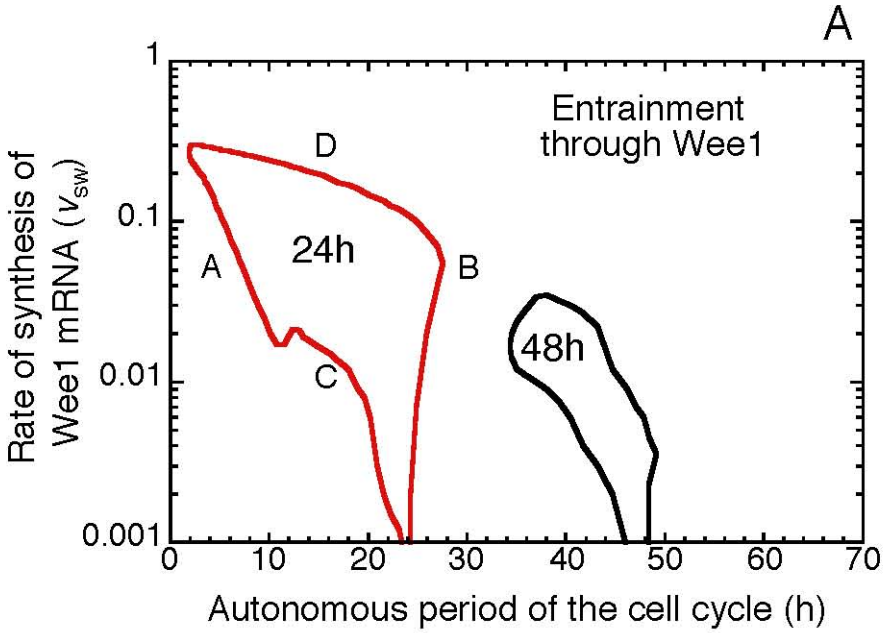
*PNAS 2014*

# Phase locking and multiple oscillating attractors for the coupled mammalian clock and cell cycle

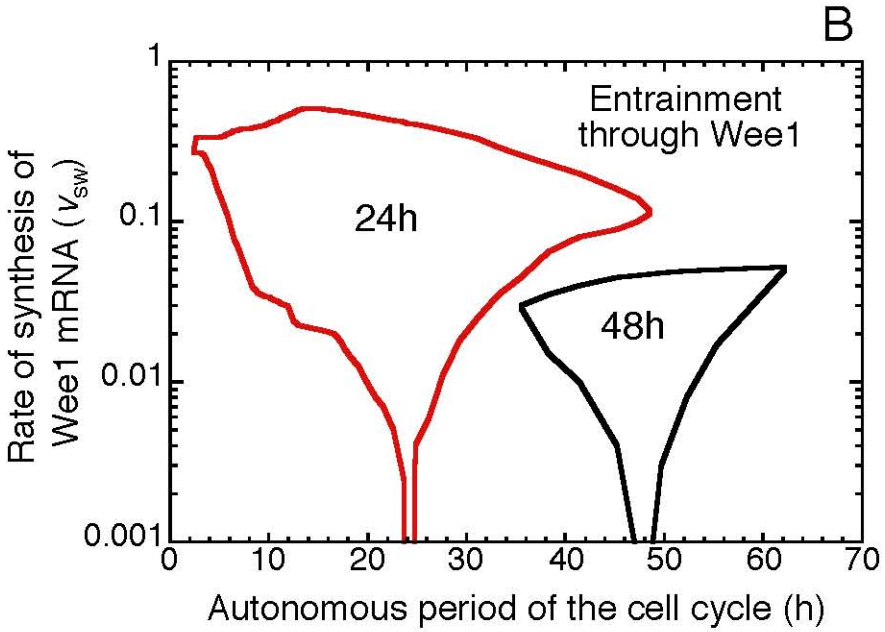
Céline Feillet[a,1], Peter Krusche[b,1], Filippo Tamanini[c,1], Roel C. Janssens[c], Mike J. Downey[b], Patrick Martin[a], Michèle Teboul[a], Shoko Saito[c,2], Francis A. Lévi[b,d], Till Bretschneider[b], Gijsbertus T. J. van der Horst[c,3], Franck Delaunay[a,3], and David A. Rand[b,3]

# Entrainment of the cell cycle by the circadian clock via Wee1

With a basal rate of synthesis of Wee1



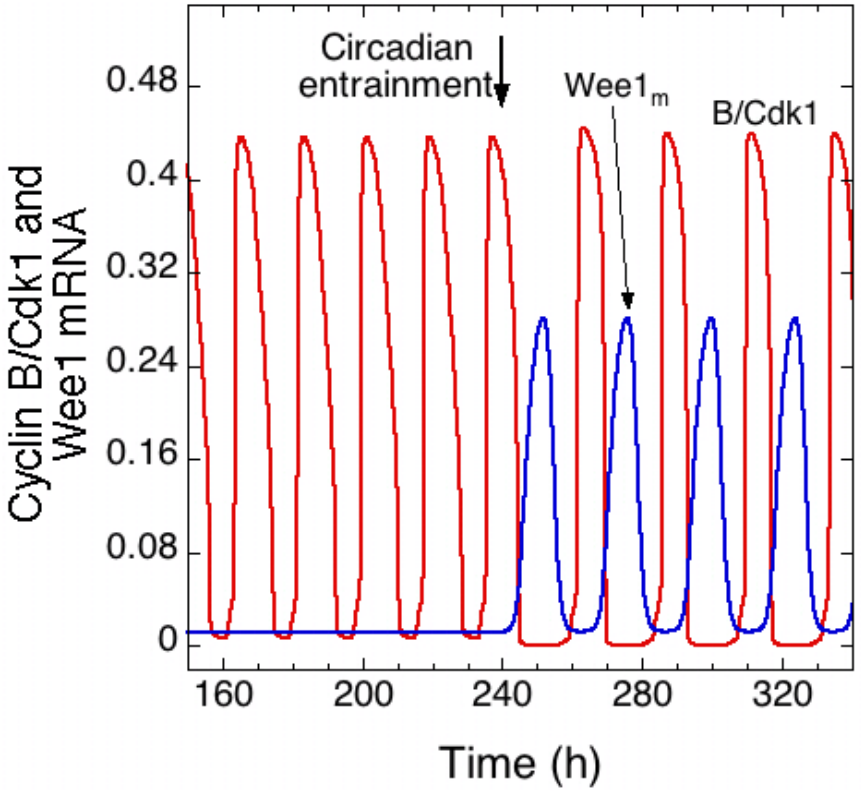

Without a basal rate of synthesis of Wee1



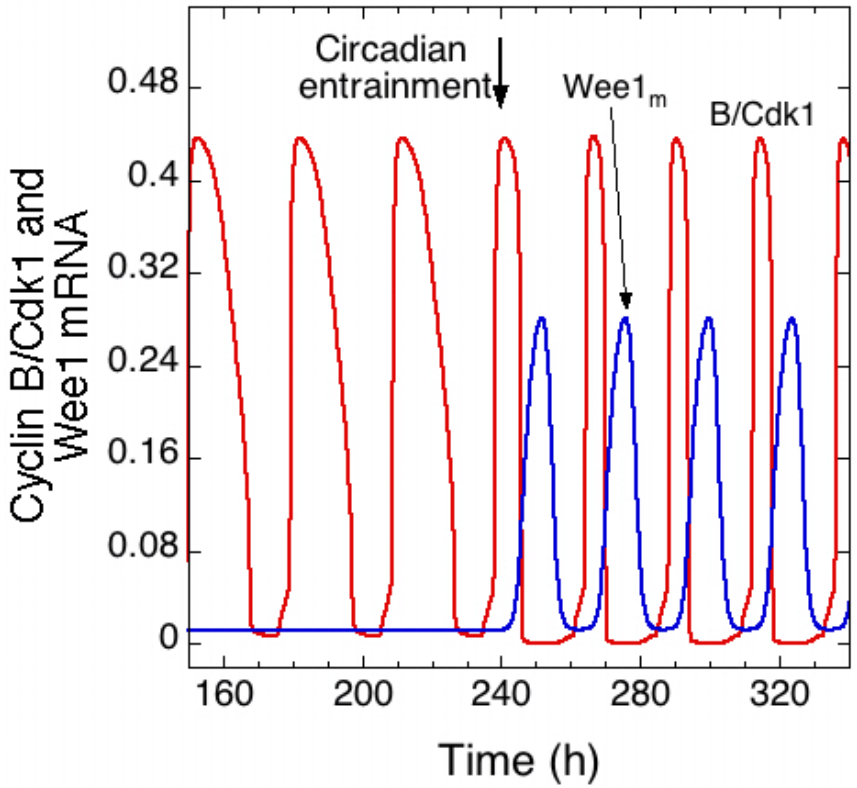

Gérard & Goldbeter (2012) *PLoS Comput. Biol.*

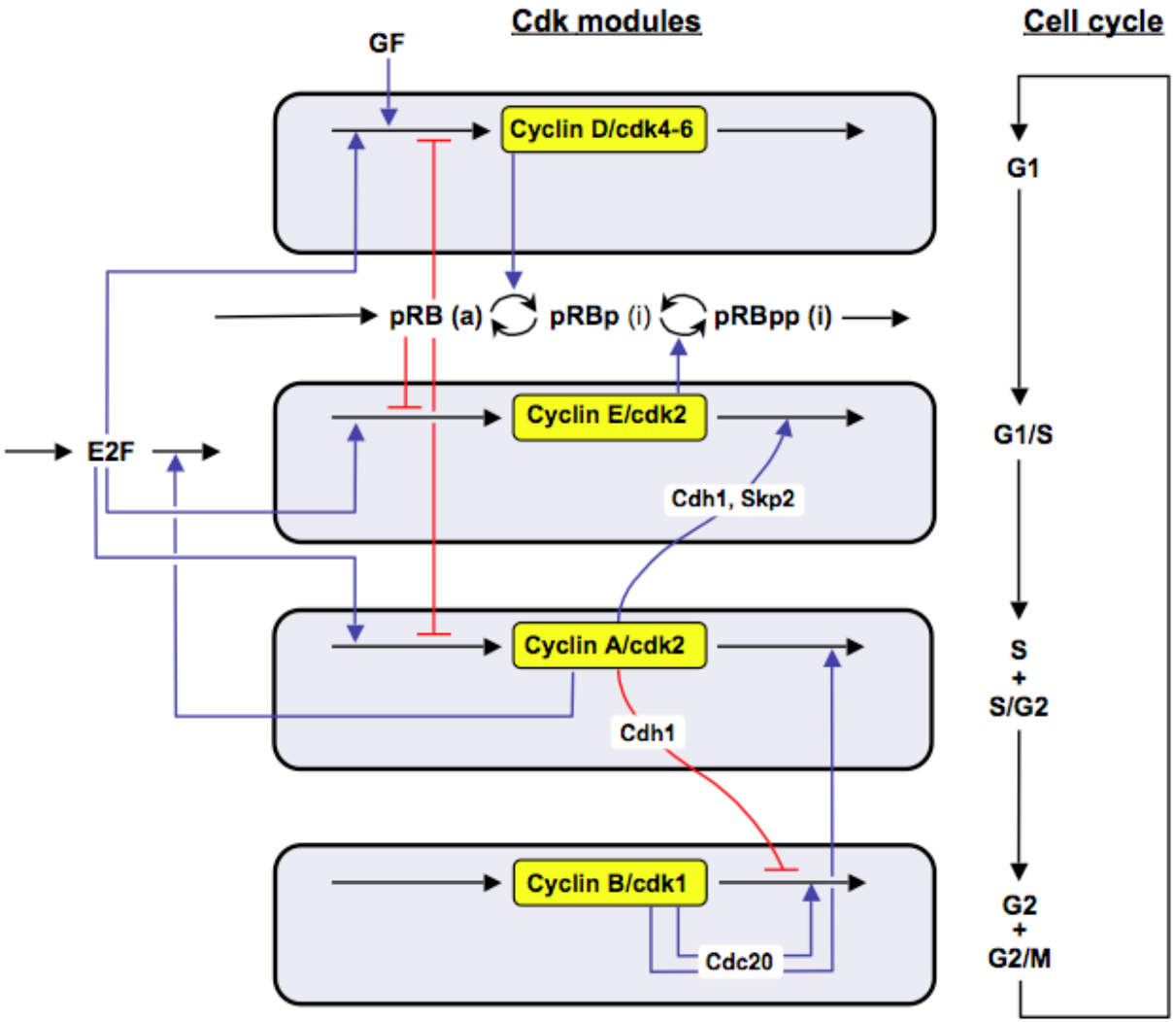
How can the circadian clock entrain via the inhibitor Wee1 cell cycles of period shorter or longer than 24h?

Autonomous period of cell cycle = 18h




Autonomous period of cell cycle = 29.5h






Claude Gérard

# Modeling the cell cycle

# Modeling the cell cycle

- 3-variable model for the embryonic cell cycle

# Modeling the cell cycle

- 3-variable model for the embryonic cell cycle
- 39-variable model for the mammalian cell cycle: oscillatory dynamics of Cdk network

# Extending the model for the mammalian cell cycle

- Checkpoints
- Extracellular matrix
- Cell contact inhibition

*Gérard & Goldbeter, Interface Focus 2014*

# Modeling the cell cycle

- 3-variable model for the embryonic cell cycle
- 39-variable model for the mammalian cell cycle: oscillatory dynamics of Cdk network
- Reduction to 5-variable skeleton model : deterministic *vs* stochastic versions

Cdk oscillations are similar
in extended and skeleton models

⇨ Key role of regulatory wiring of the network