The Microsoft Research - University of Trento
Centre for Computational and Systems Biology

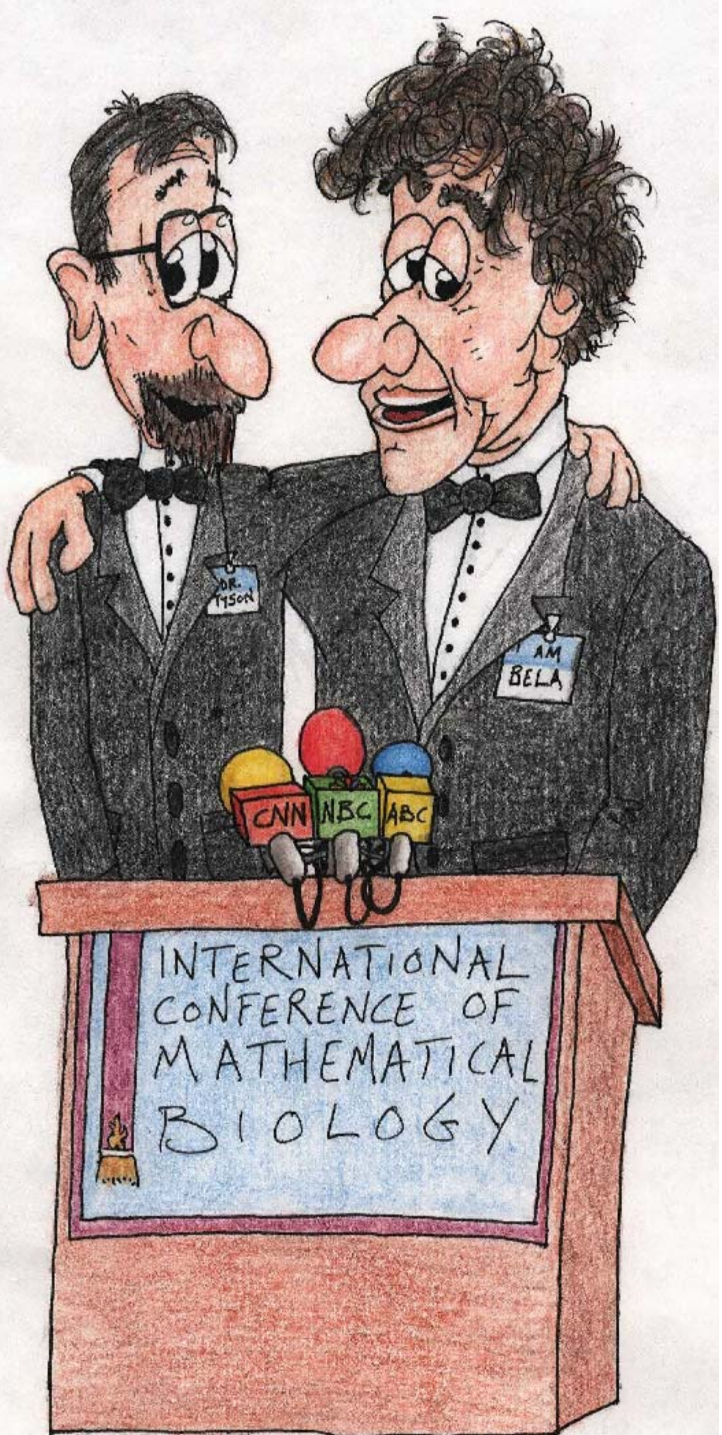
Attila Csikász-Nagy

Models of the fission yeast cell cycle (Switches in time and space)

at

Kavli Institute for Theoretical Physics

VirginiaTech
VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY

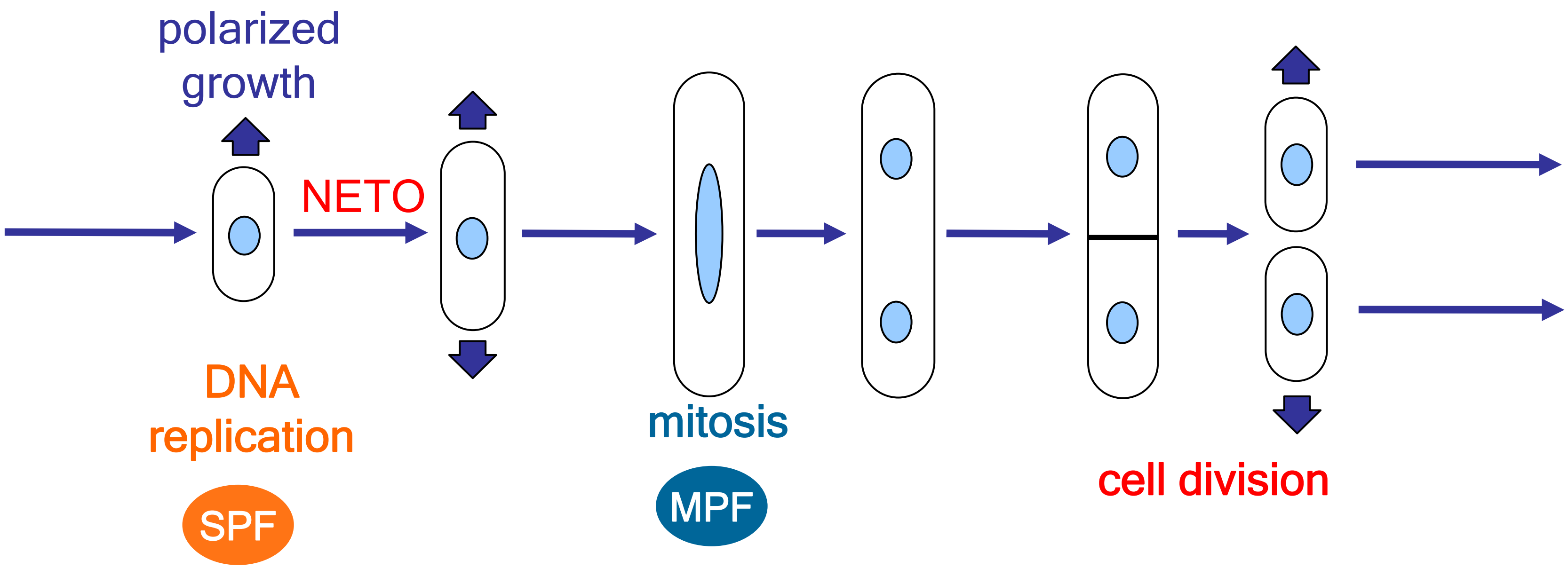


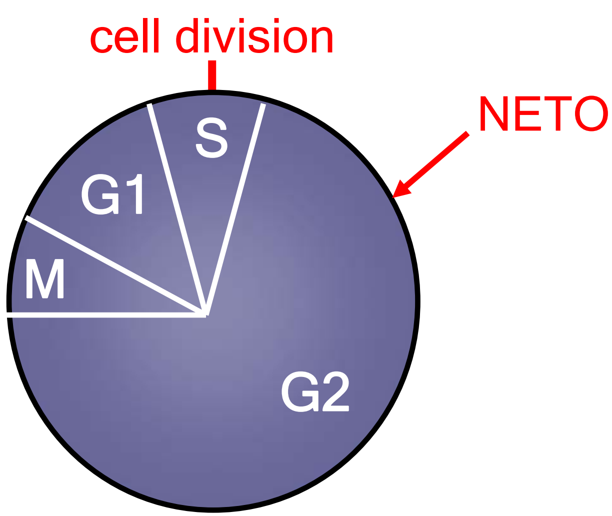
Budapest University of Technology and Economics
Faculty of Chemical Engineering
Department of Agricultural Chemical Technology

John J. Tyson

Béla Novák

Fission yeast - *Schizosaccharomyces pombe*

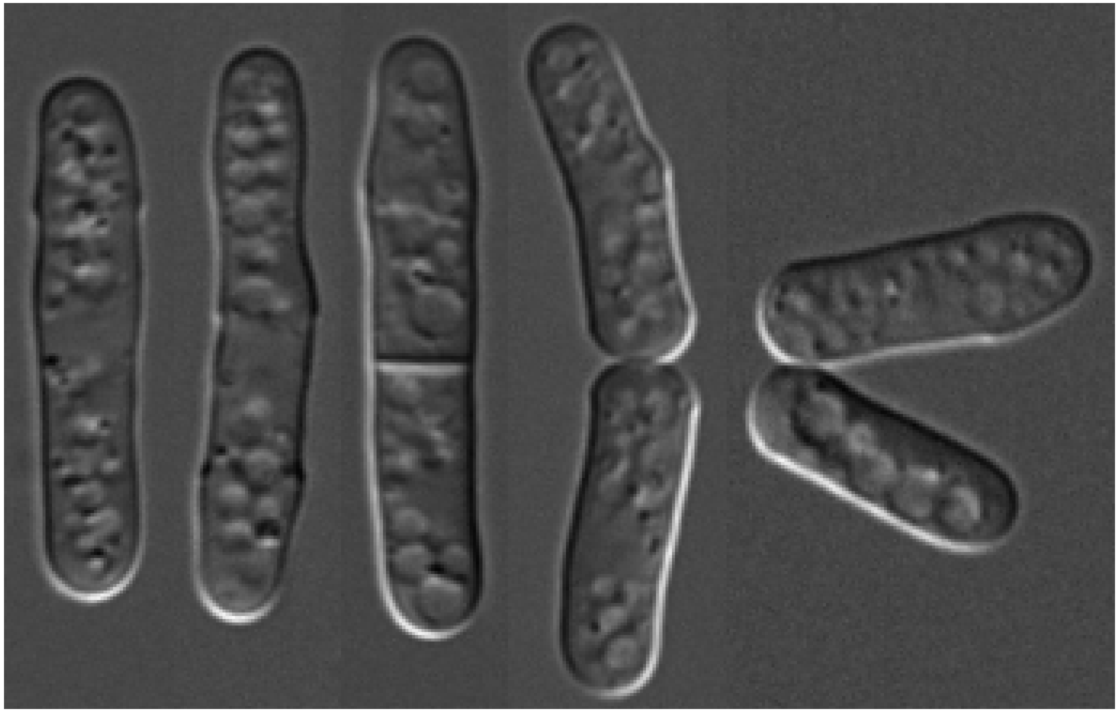




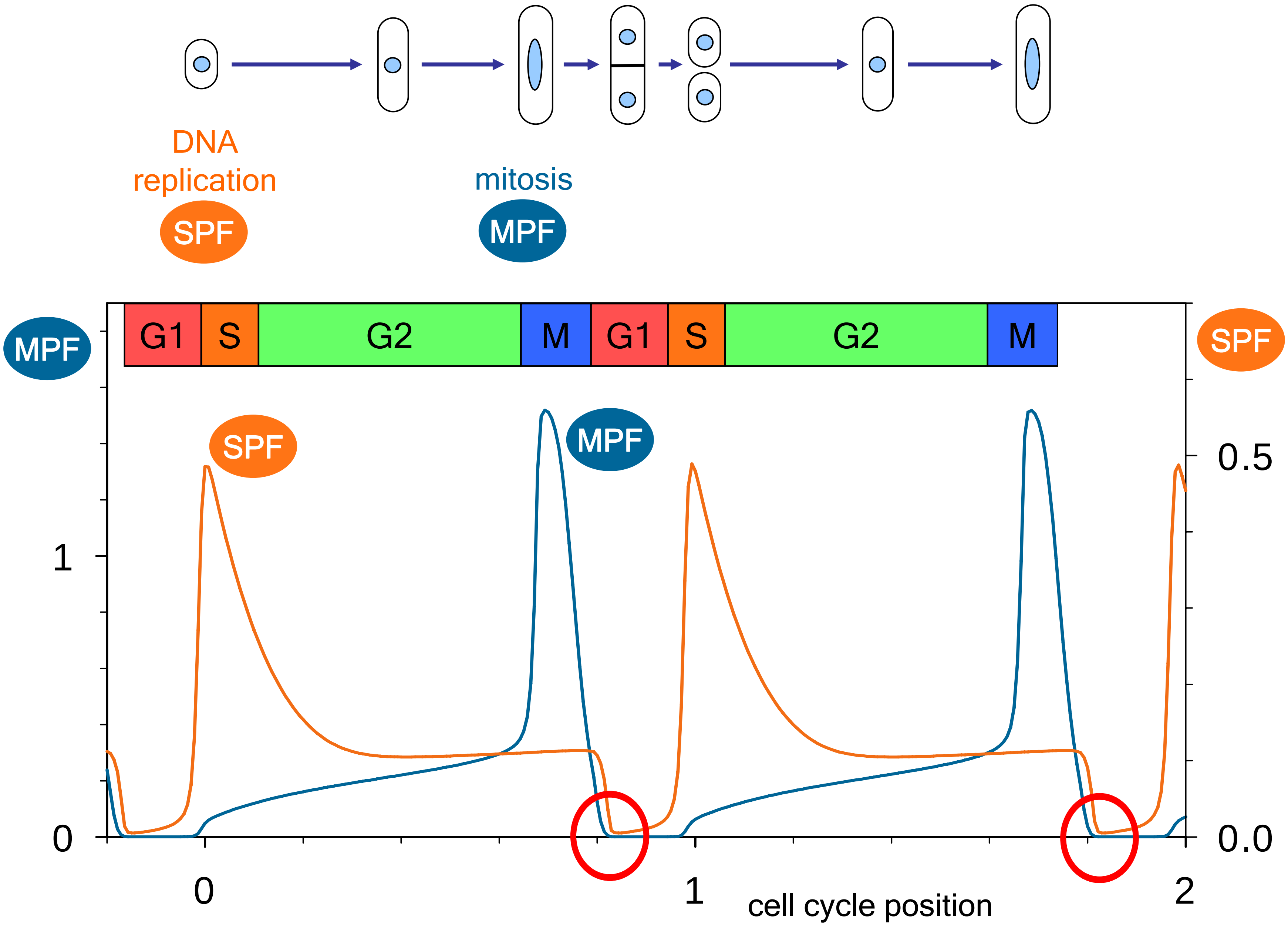
Switches to be described in this talk:

- Initiation of cell division
- Initiation of DNA replication
- NETO

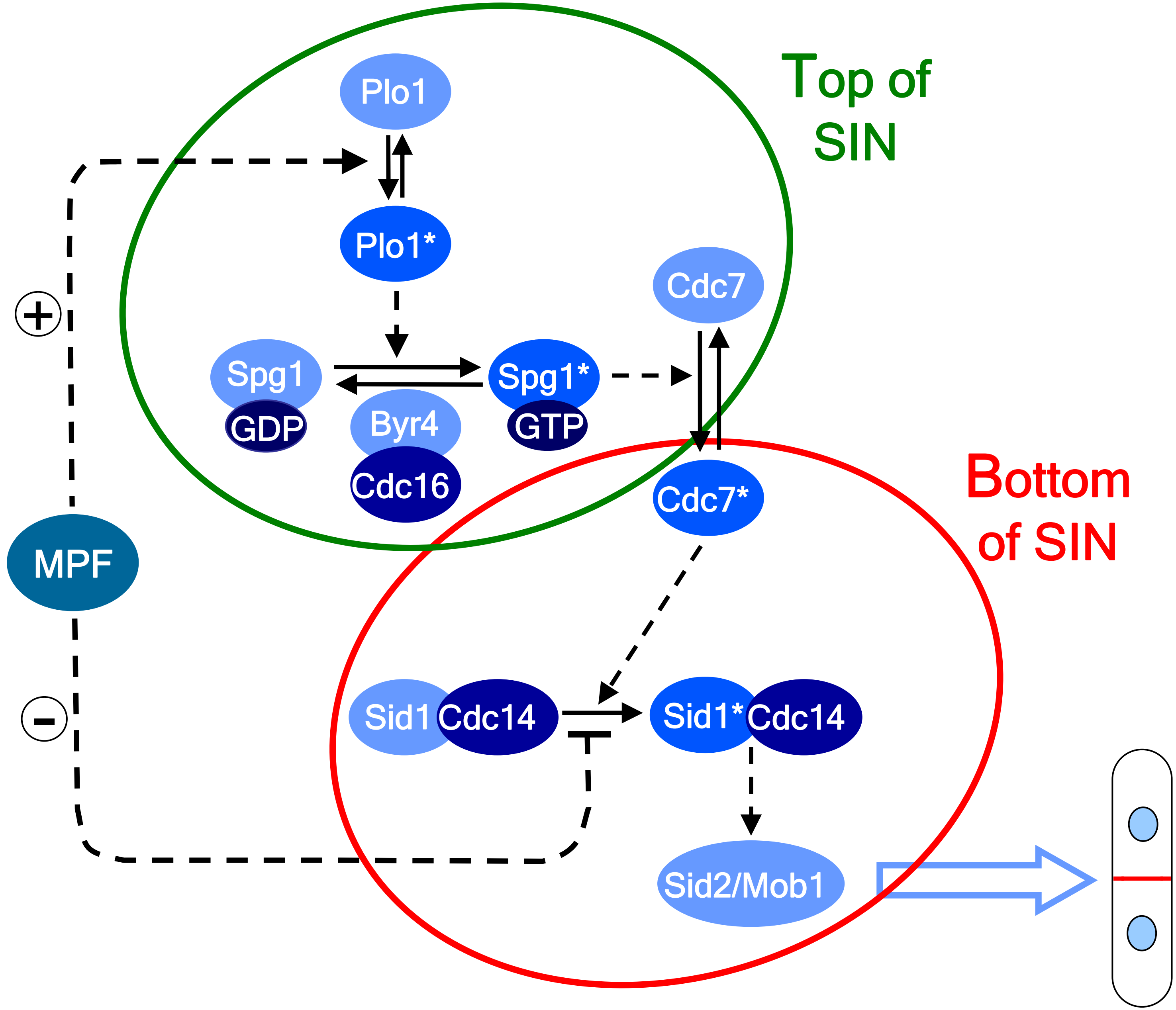
cell divison = fission = septation



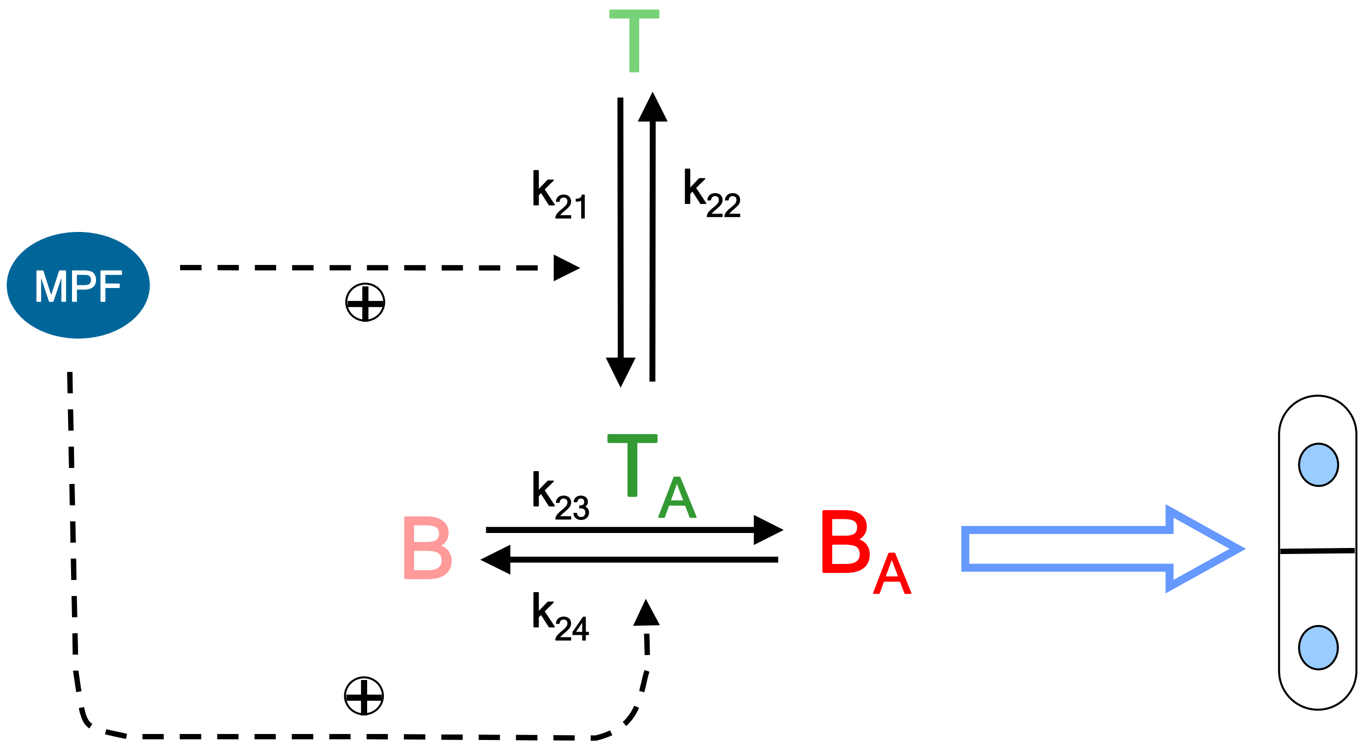
The oscillation of SPF and MPF activity during the cell cycle



SIN = Septation Initiation Network



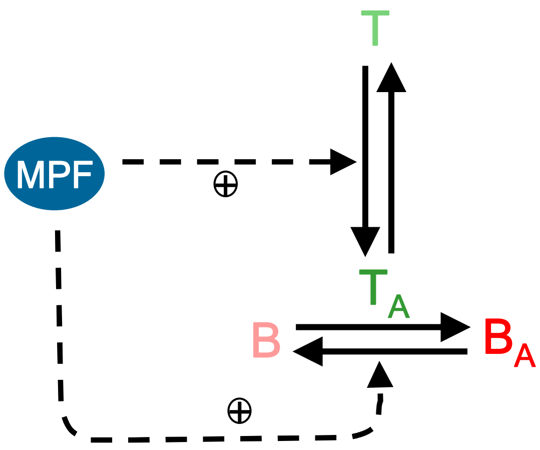
The simple kinetic model of SIN



$$\frac{dT_A}{dt} = k_{21} * MPF * \frac{1-T_A}{J_{21}+1-T_A} - k_{22} * \frac{T_A}{J_{21}+T_A}$$

$$\frac{dB_A}{dt} = k_{23} * T_A * \frac{1-B_A}{J_{23}+1-B_A} - (k_{24}' + k_{24} * MPF) * \frac{B_A}{J_{23}+B_A}$$

Parameter values = ?



SIN can be activated **only** transiently **only** after mitosis and **only** once per cell cycle:

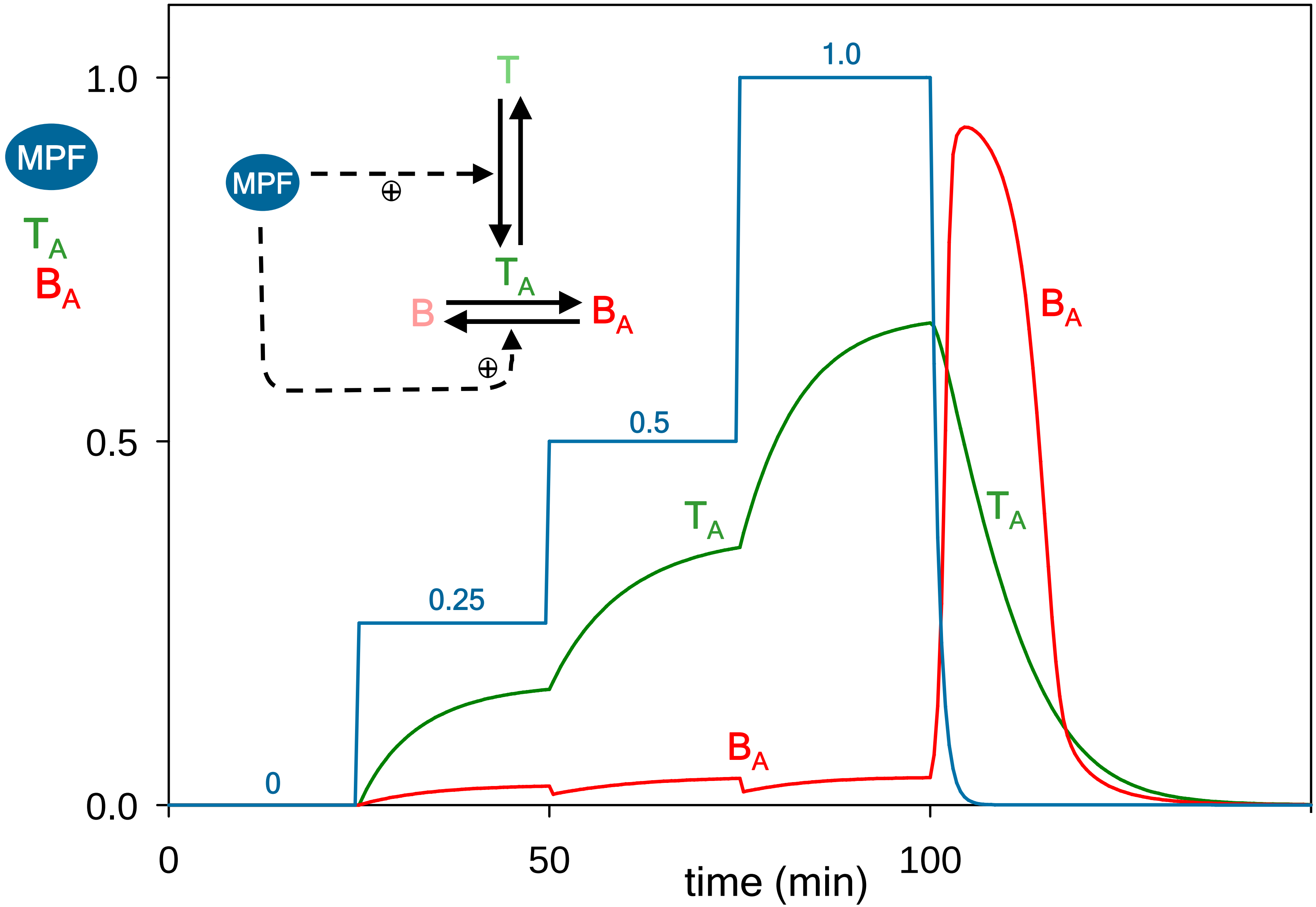
1. SIN should not reside in a stable active state for any values of MPF

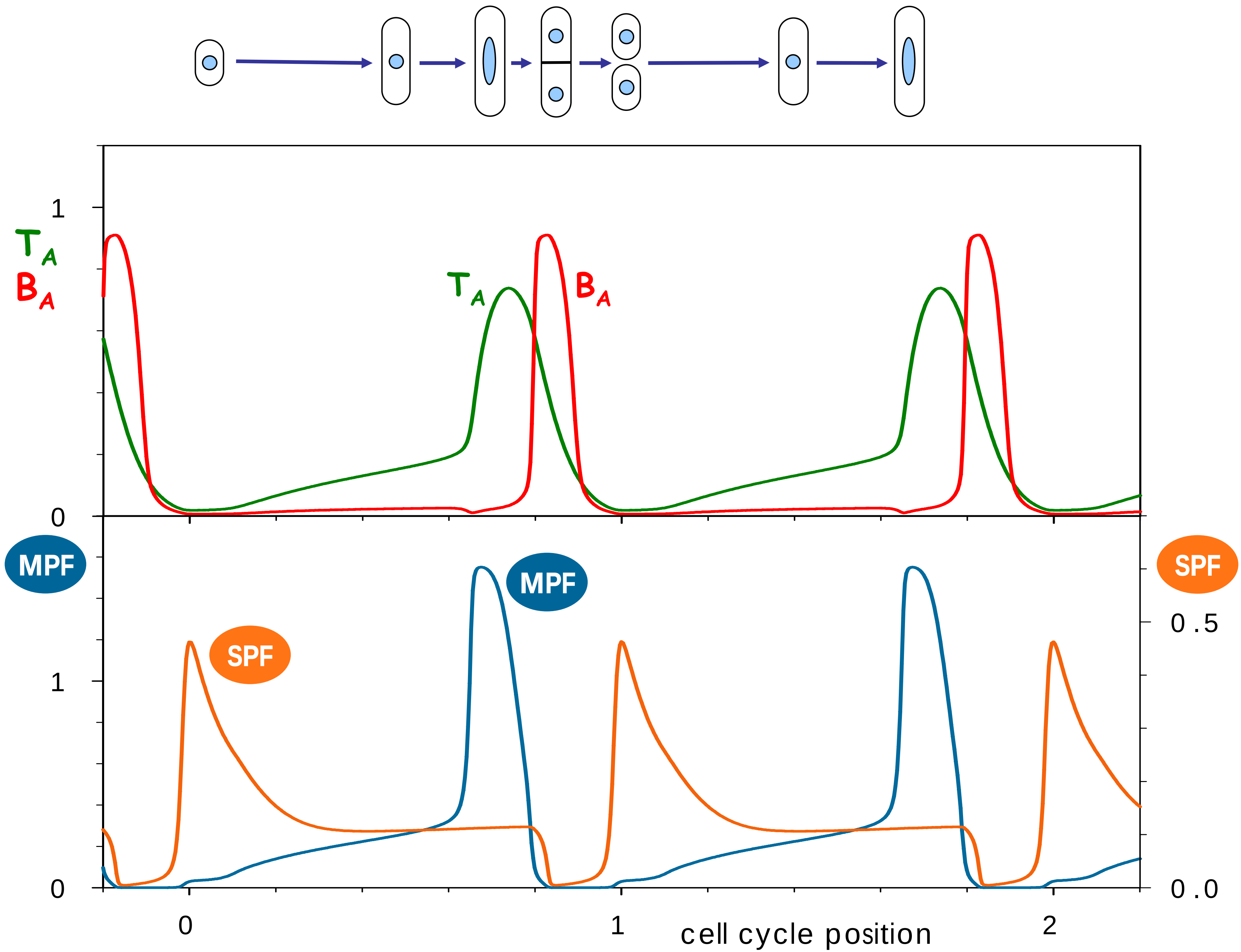
   ⇨ Inhibition by **MPF** has to be stronger than activation

2. SIN should be activated transiently when the MPF activity drops after mitosis

   ⇨ **T**op of SIN changes slower than **B**ottom of SIN

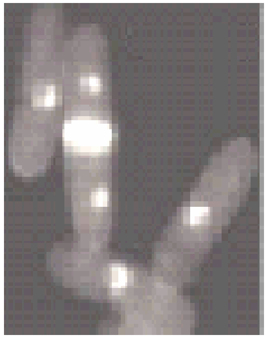
Transient activation of the SIN by MPF

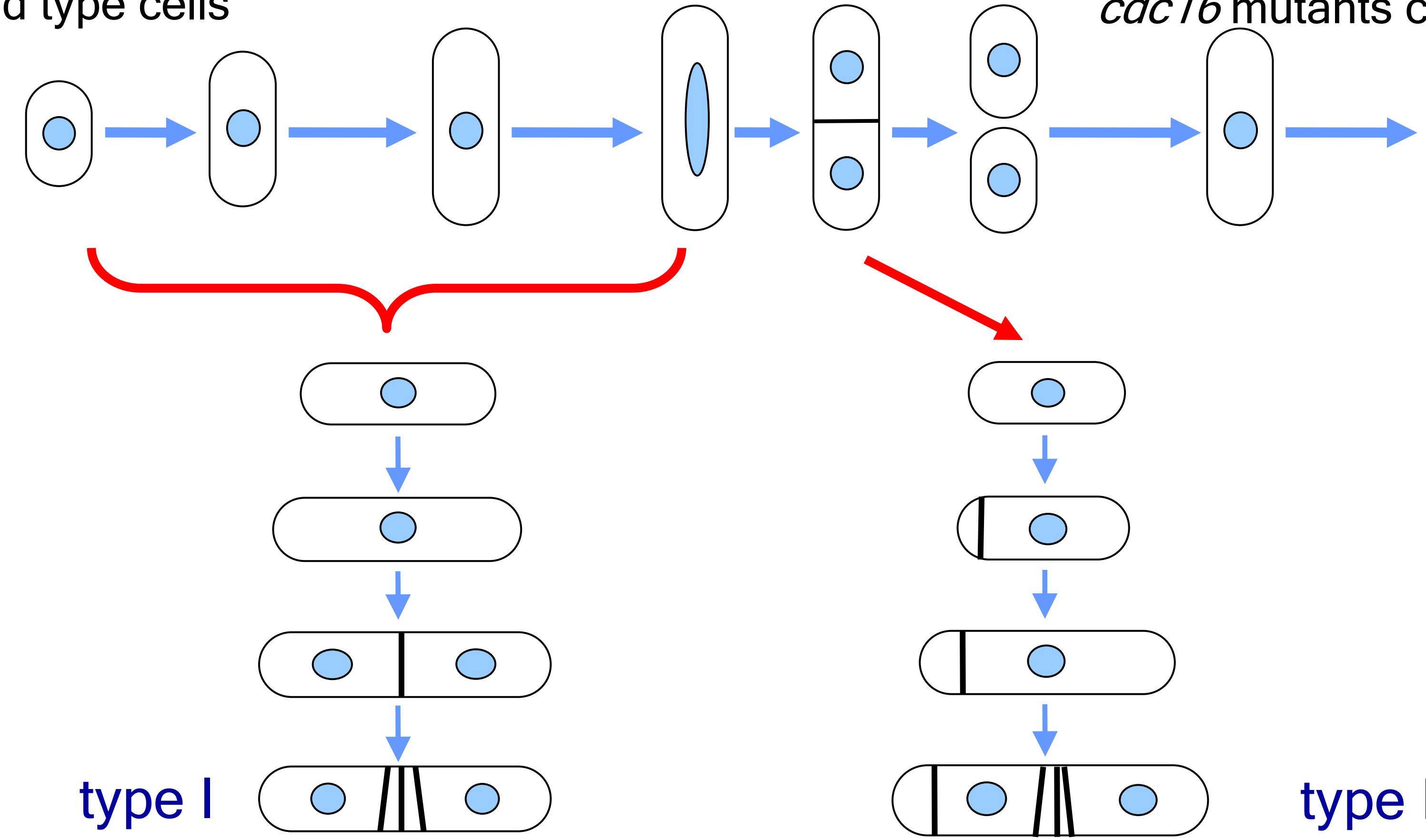




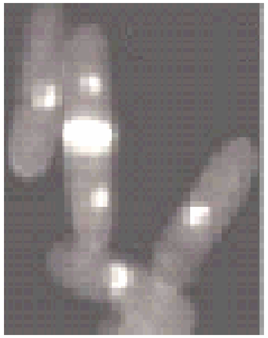
1
0
T_A
B_A
MPF
SPF
0 .5
0 .0
0
1
2
cell cycle position

A *cdc16^ts* mutants can not stop septating



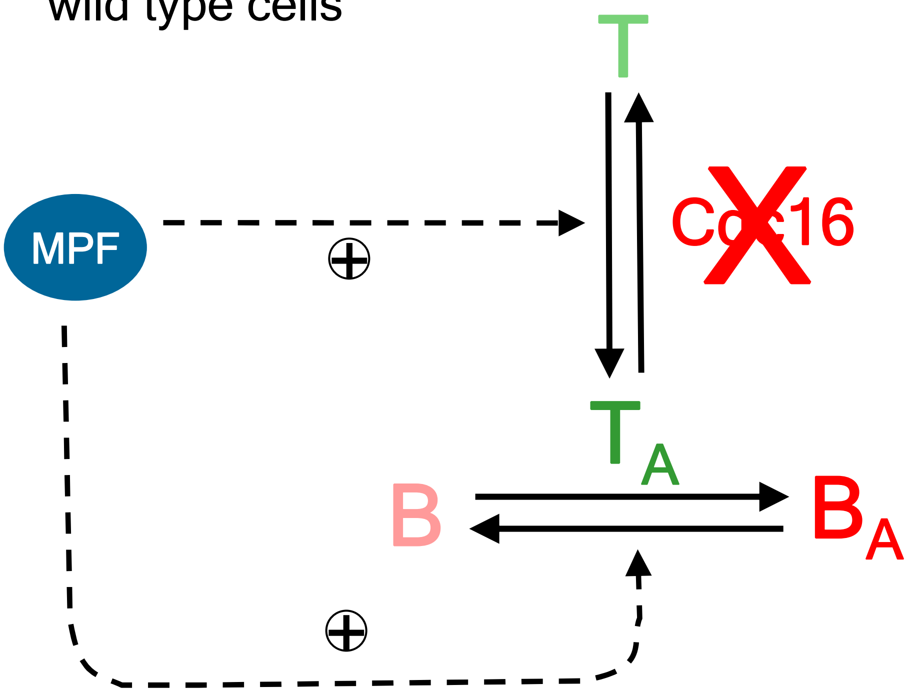


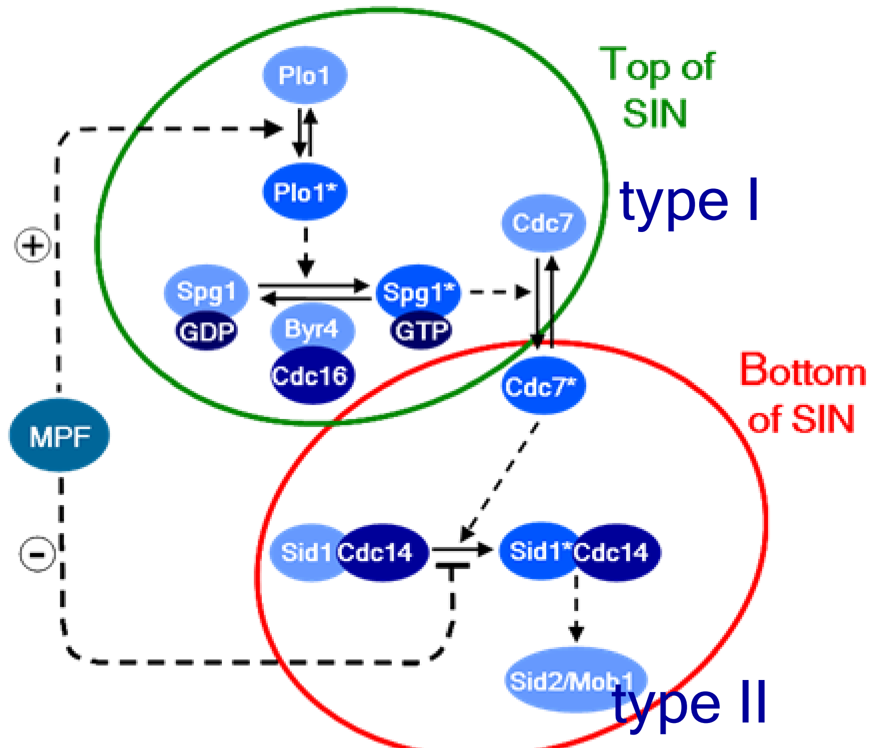
A *cdc16*^{ts} mutants can not stop septating

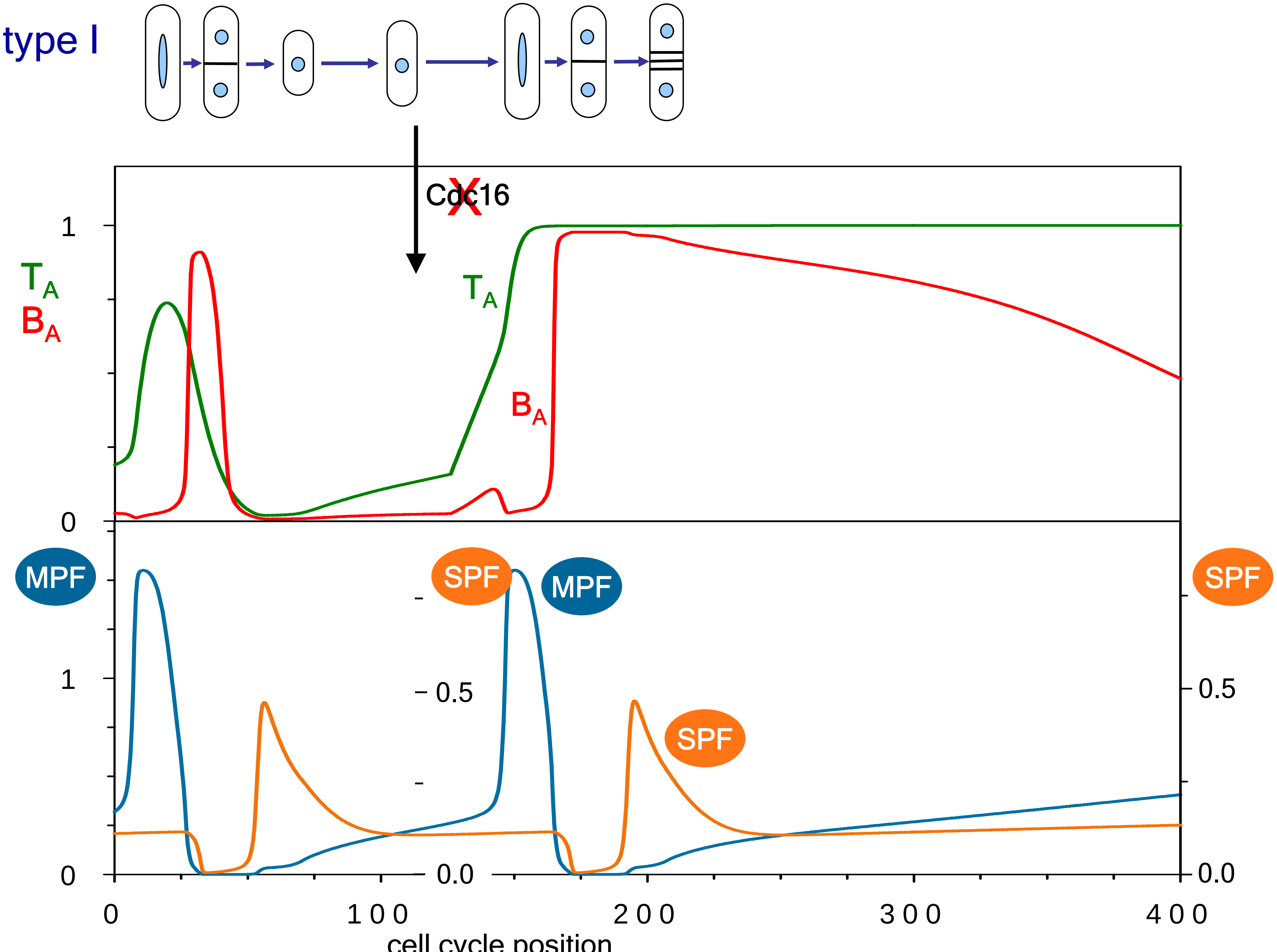


wild type cells

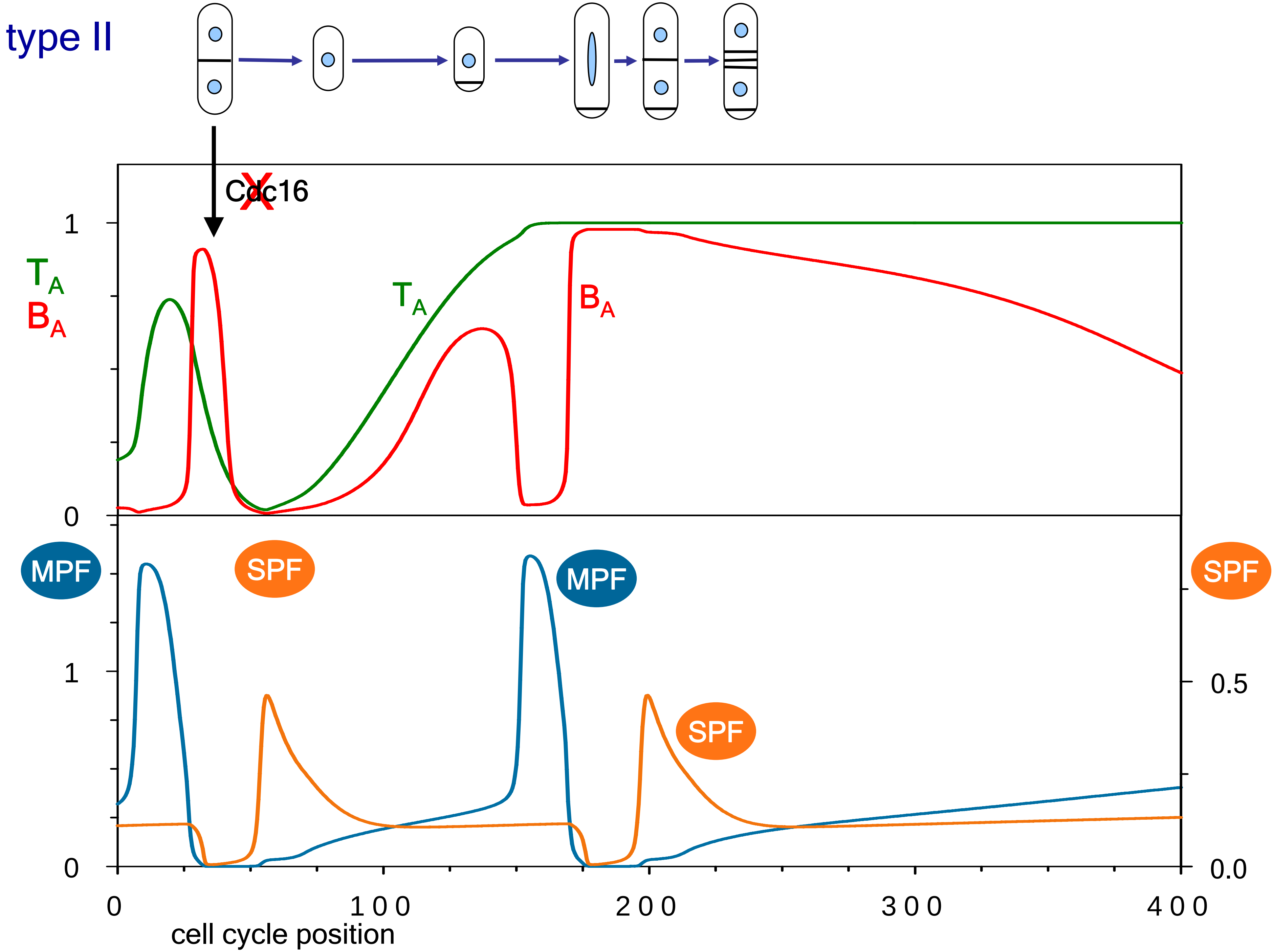
cdc16 mutants cells





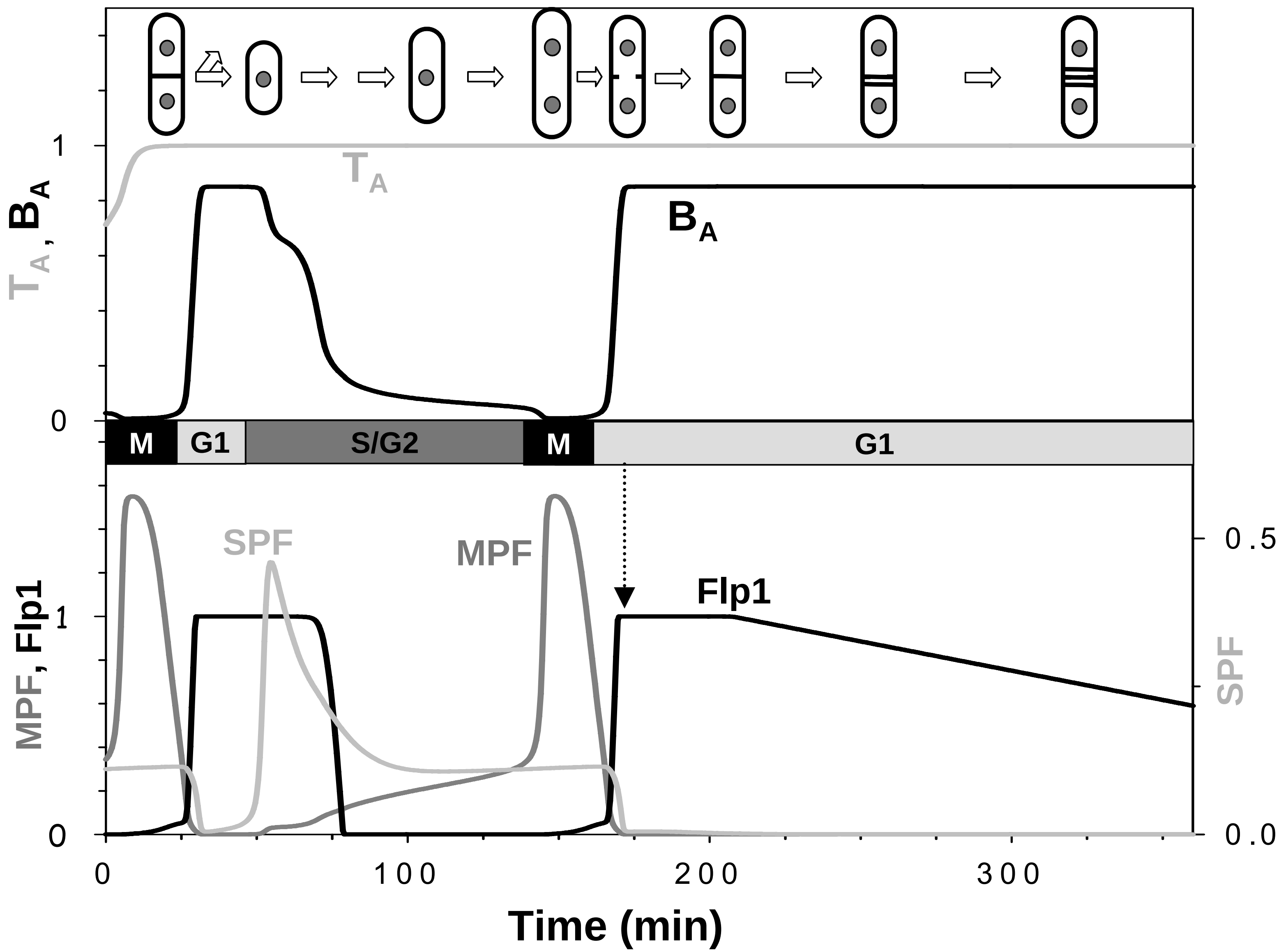


type I
Cdc16
1
0
T_A
B_A
T_A
B_A
MPF
SPF
MPF
SPF
SPF
1
0
0.5
0.0
0.5
0.0
0
100
200
300
400
cell cycle position



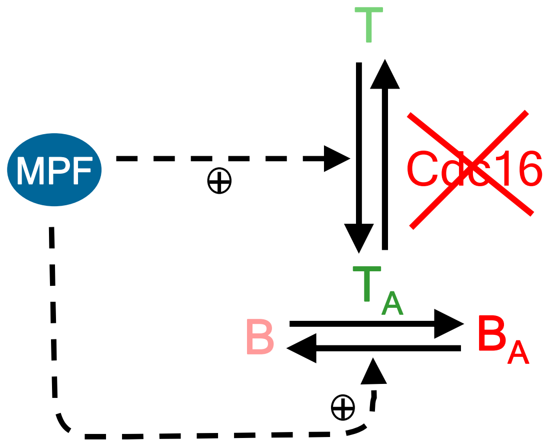
type II
Cdc16
1
0
T_A
B_A
T_A
B_A
MPF
SPF
MPF
SPF
SPF
1
0
0.5
0.0
0
100
200
300
400
cell cycle position

cdc16ts sin- mutant



*cdc16^ts^ sin^-^* mutant

Only MPF inhibits septation in this mutant
In G1 phase MPF is inactive so SIN stays active



Conclusions on this part

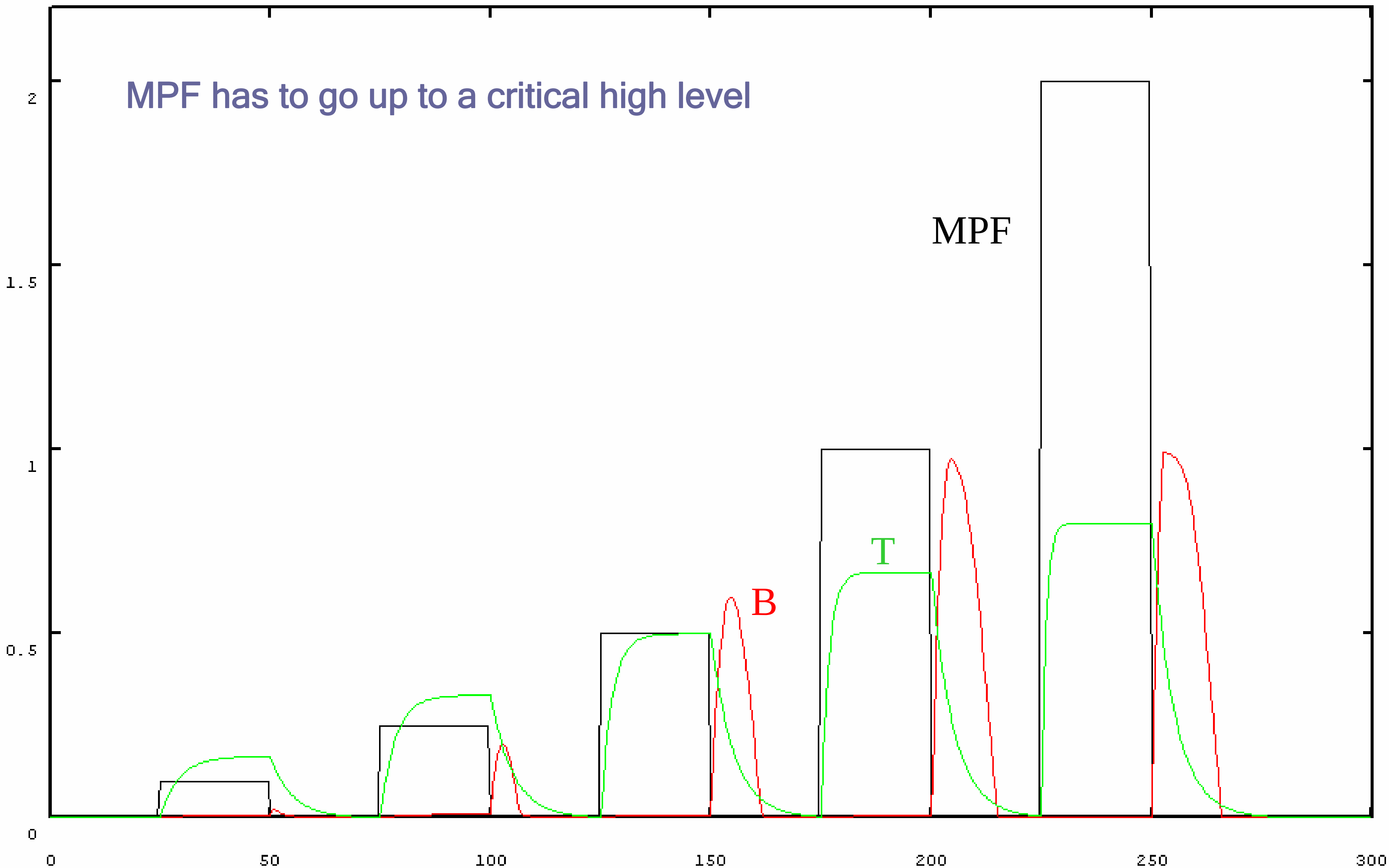
- We have created a simple mathematical model of septation initiation network (SIN) in fission yeast. SIN is regulated by MPF activity.

- SIN should be activated only transiently when MPF activity drops after mitosis, but it should be inactive during the rest of the cell cycle.

- This basic model can explain various mutant phenotypes and predict the behavior of new mutants

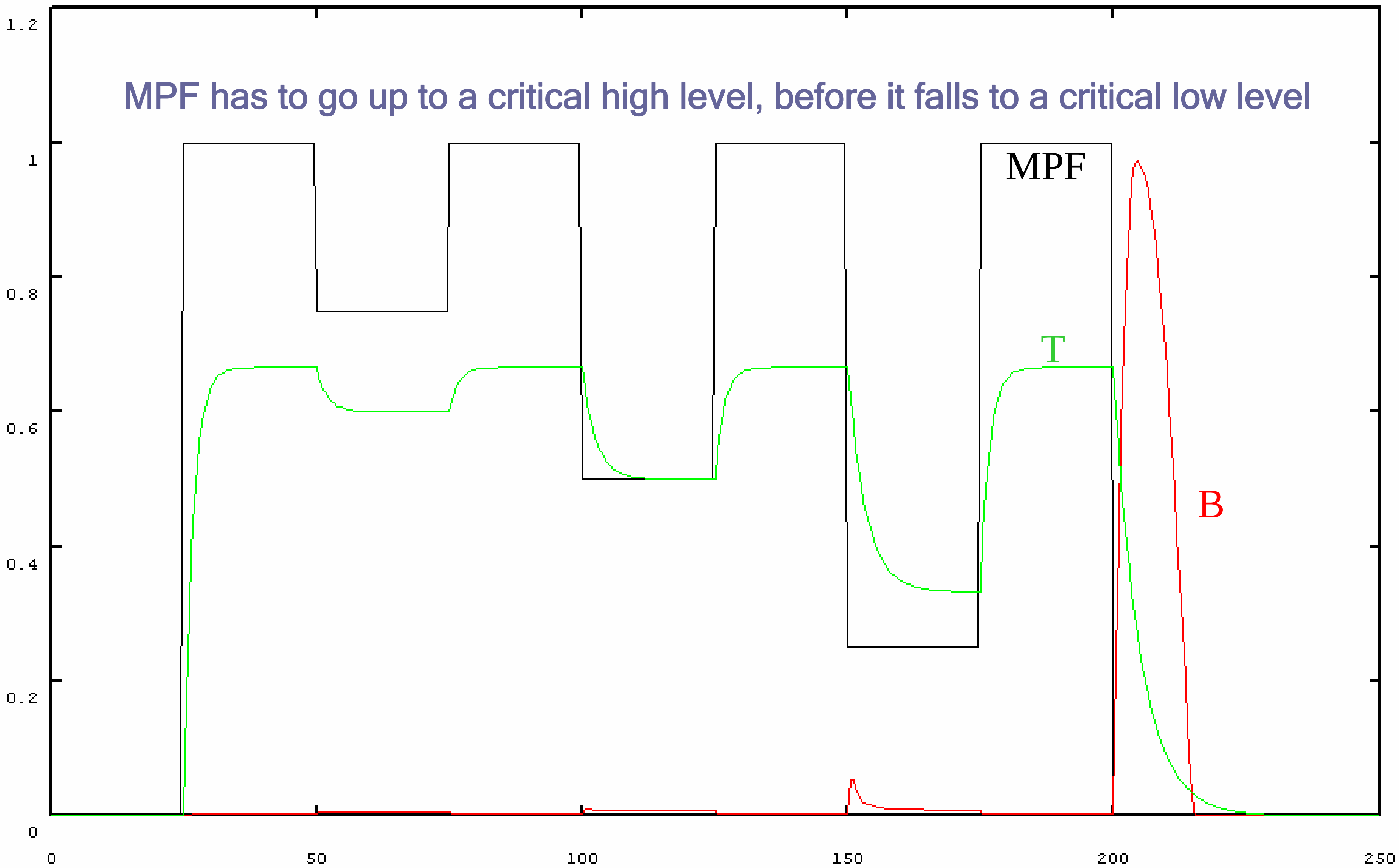
Csikász-Nagy, A., Kapuy, O., Győrffy, B., Tyson, J.J., Novák B. Modeling the septation initiation network (SIN) in fission yeast cells. *Current Genetics* 51(4):245-55 (2007)

Septation



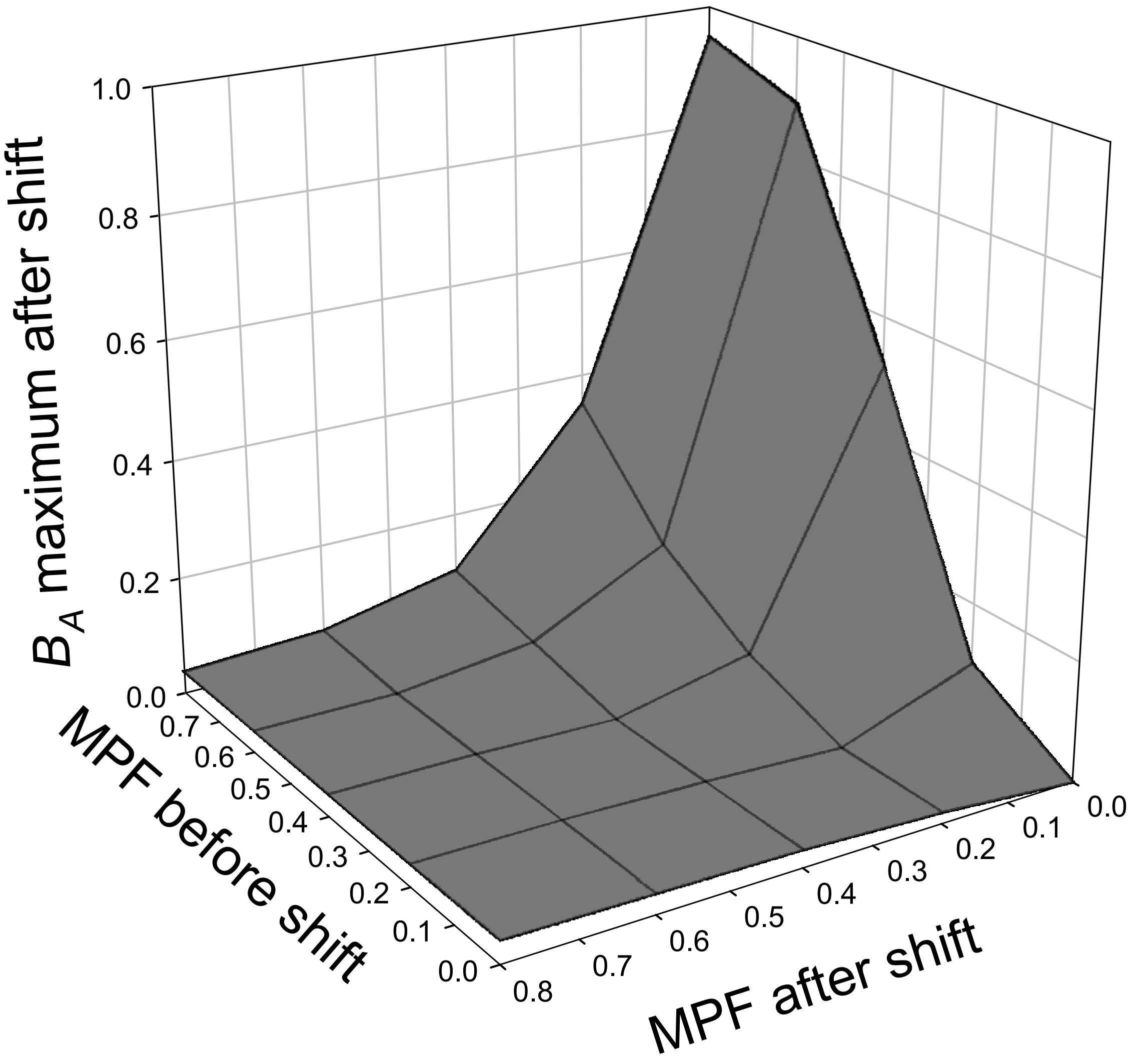
MPF has to go up to a critical high level
MPF
T
B
2
1.5
1
0.5
0
0
50
100
150
200
250
300

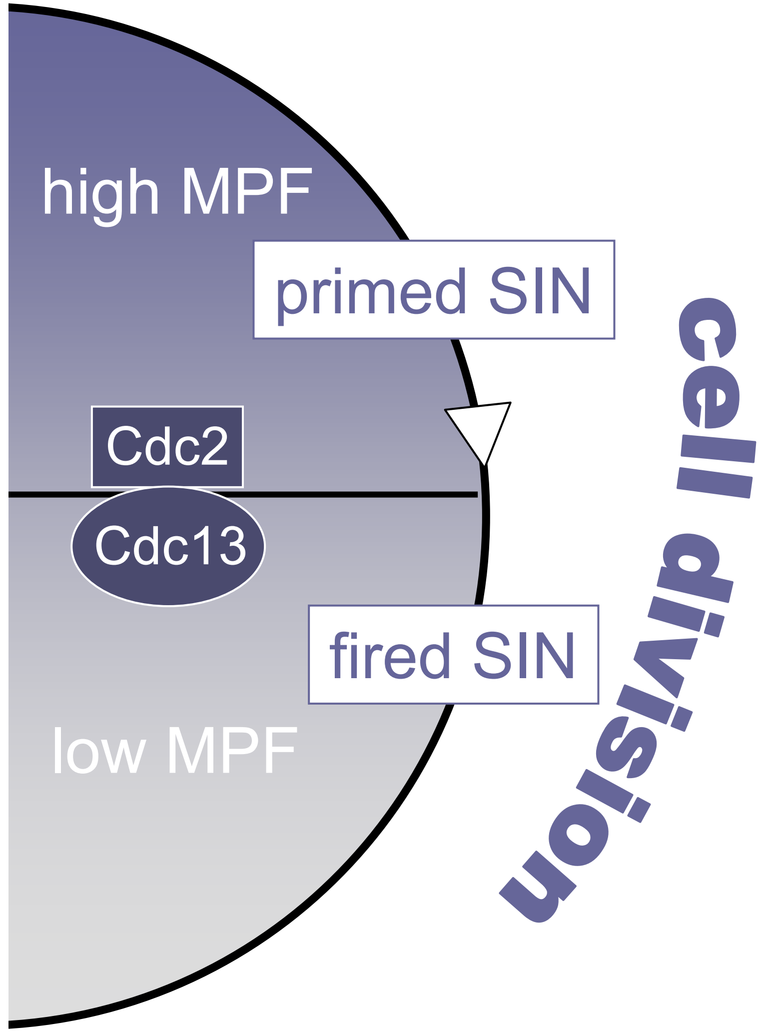
Septation



MPF has to go up to a critical high level, before it falls to a critical low level
MPF
T
B
1.2
1
0.8
0.6
0.4
0.2
0
0
50
100
150
200
250

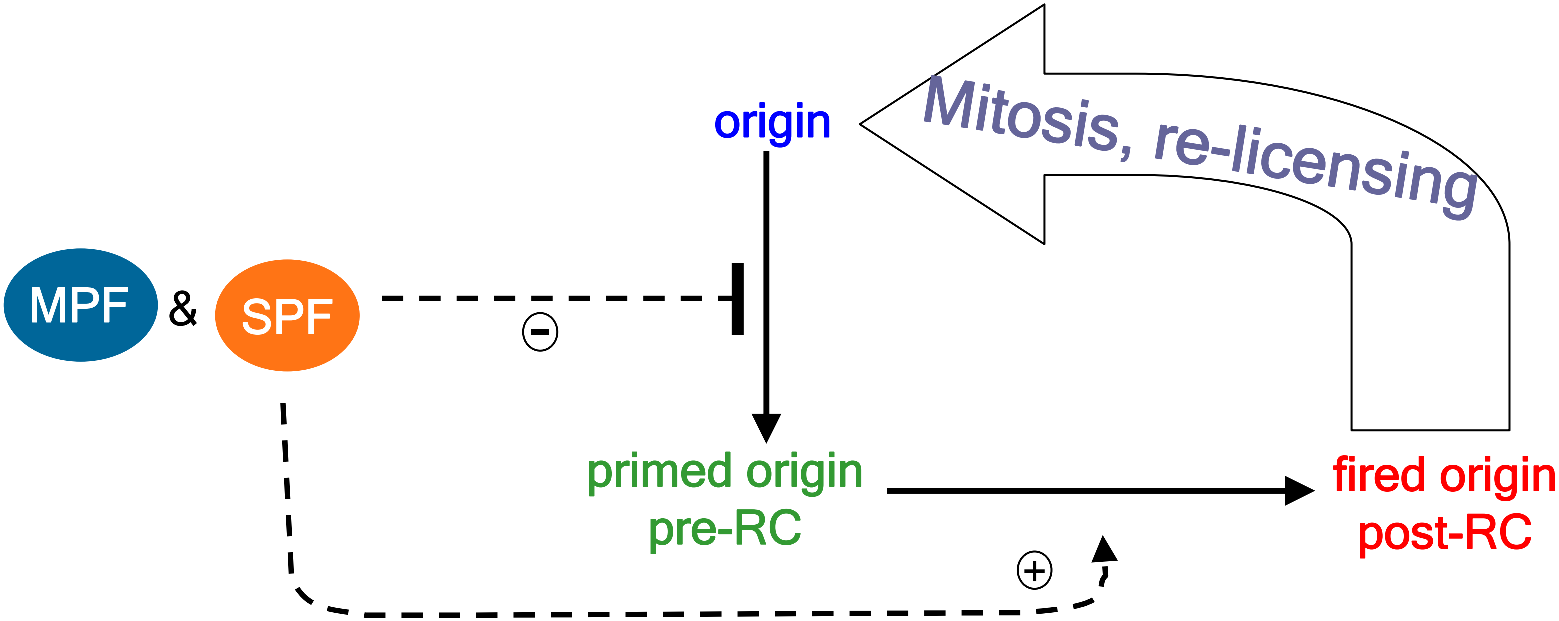
Dependence of **SIN** activity on MPF





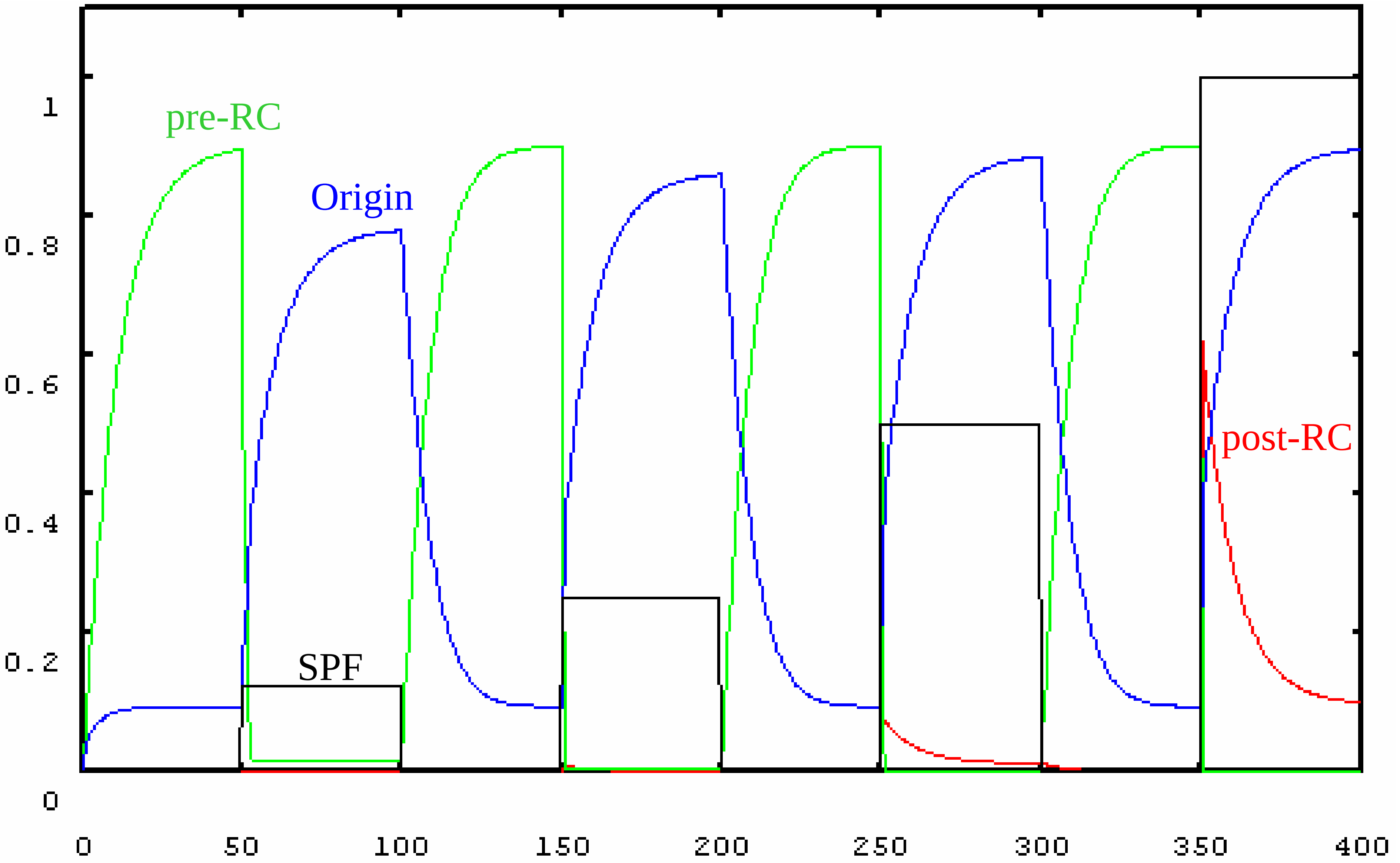
high MPF
primed SIN
Cdc2
Cdc13
fired SIN
low MPF
cell division

DNA replication



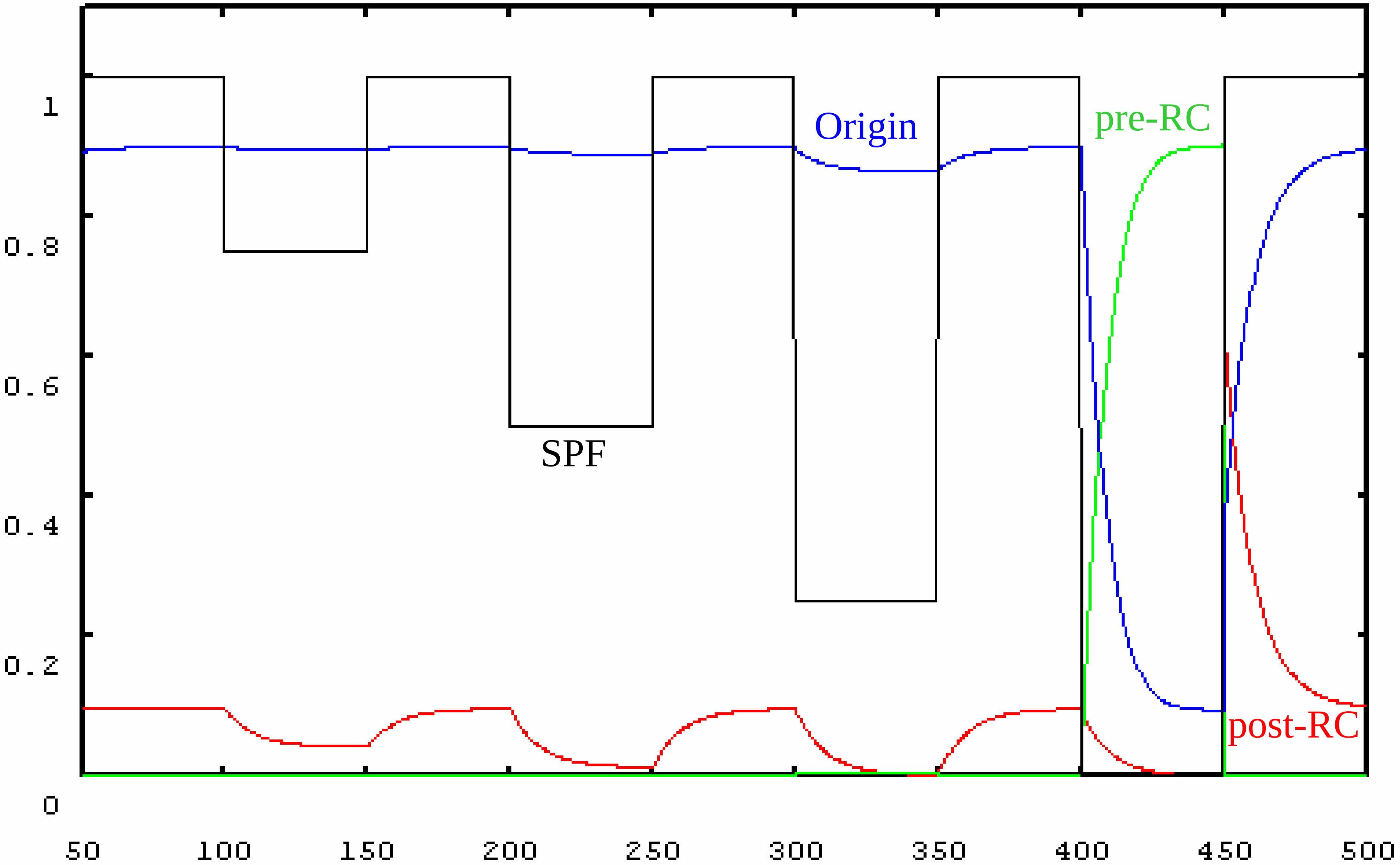
DNA replication

SPF has to go up to a critical level

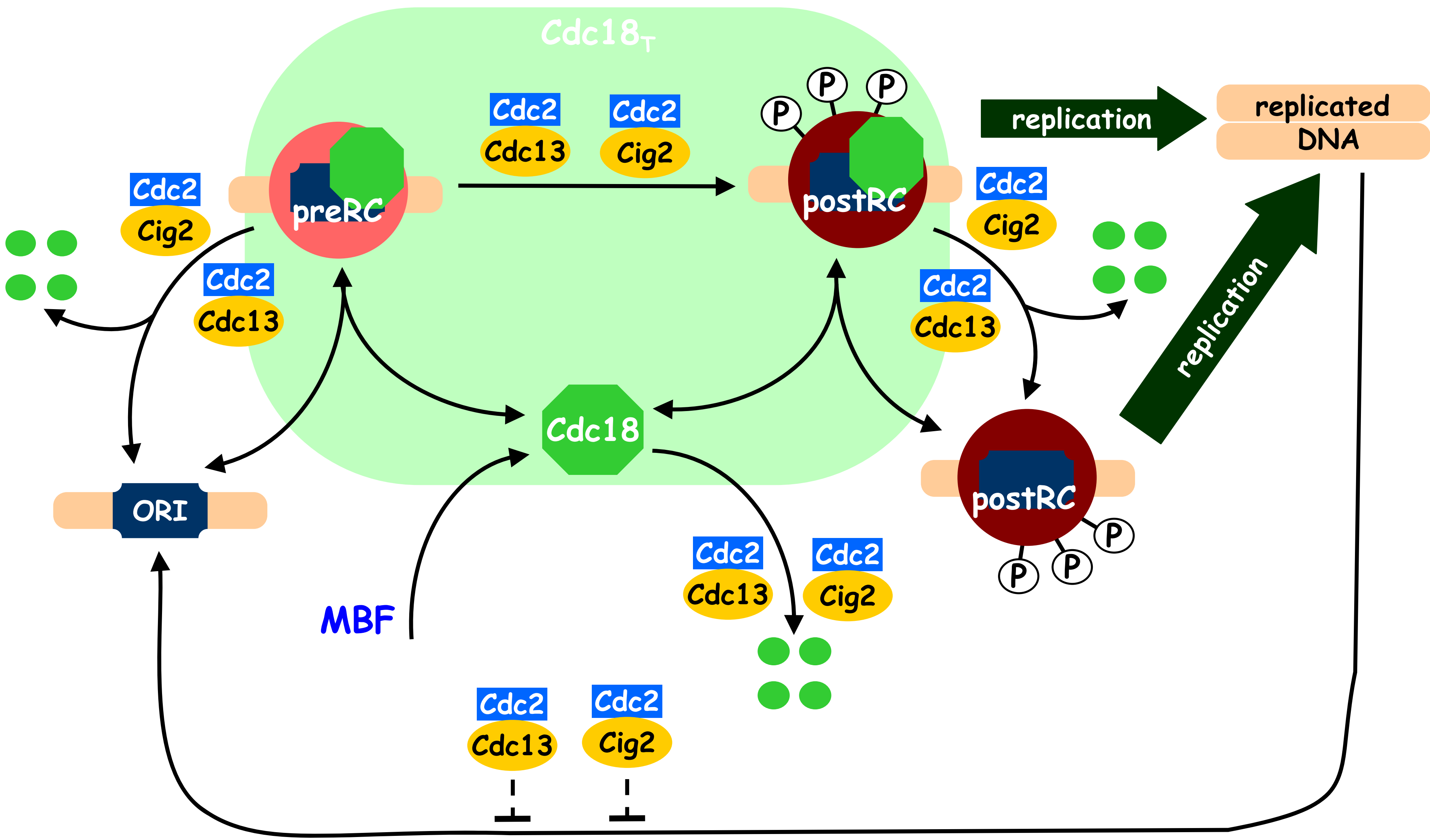


DNA replication

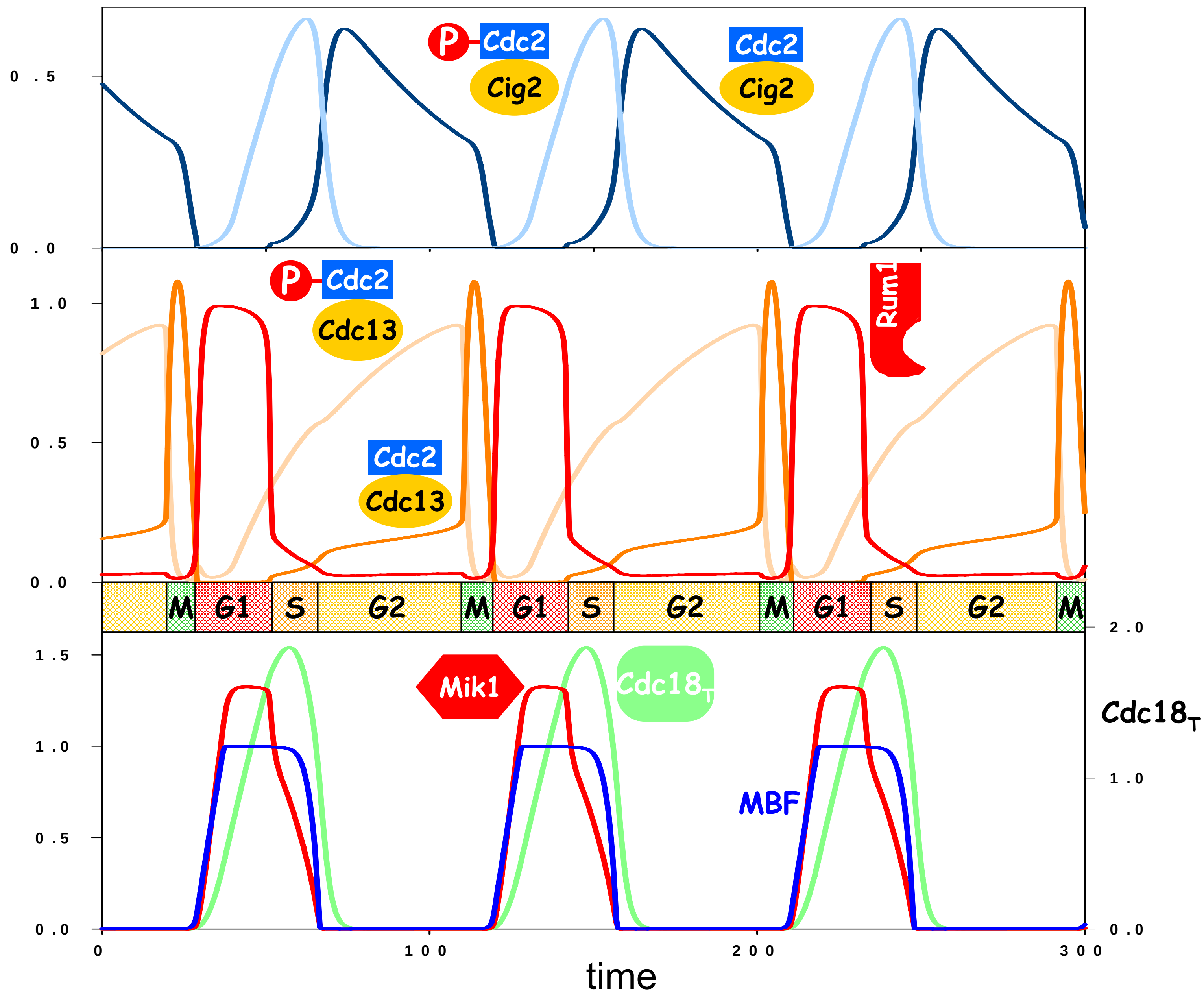
SPF has to go up to a critical level, after it felt to a critical low level

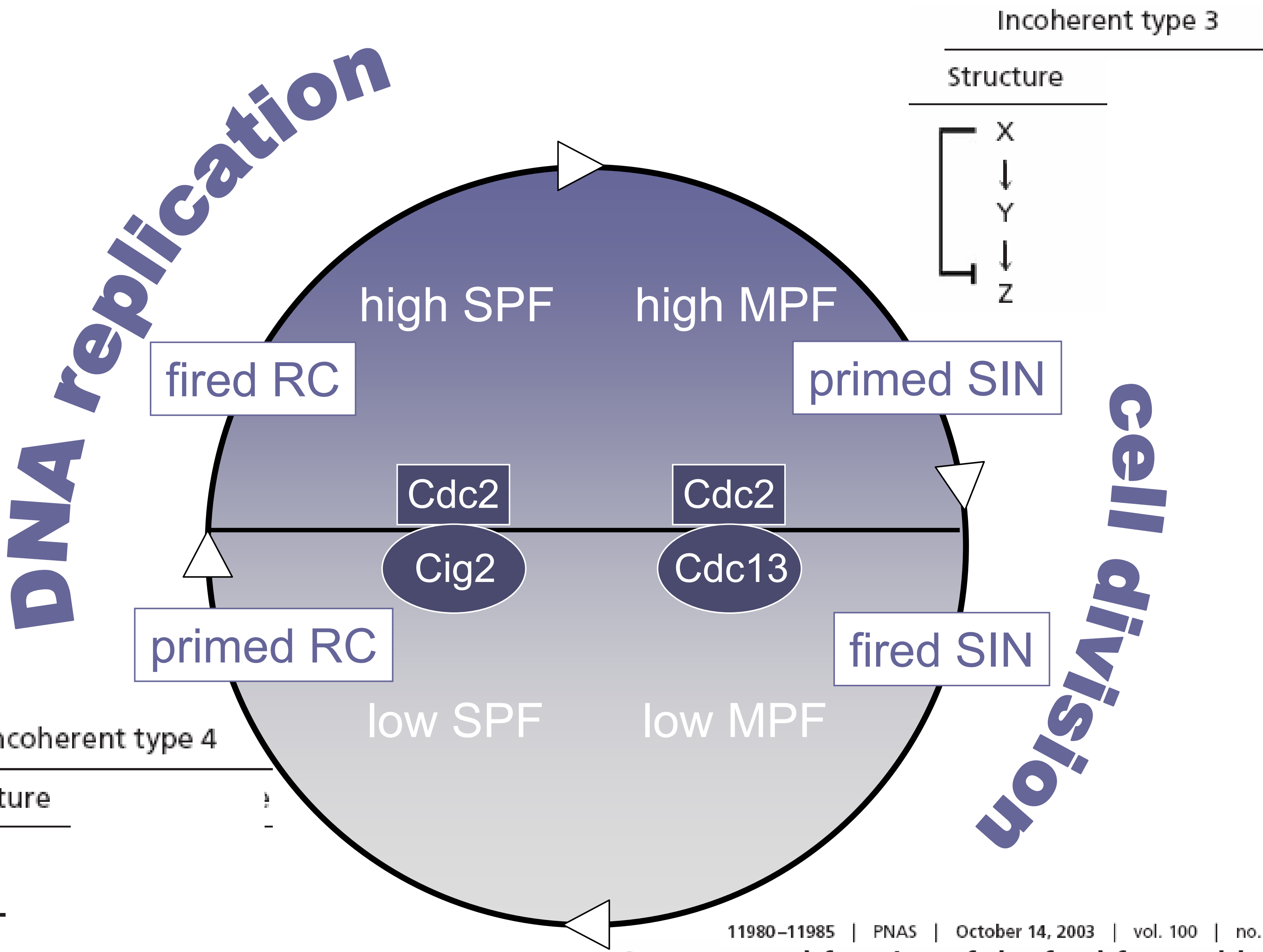


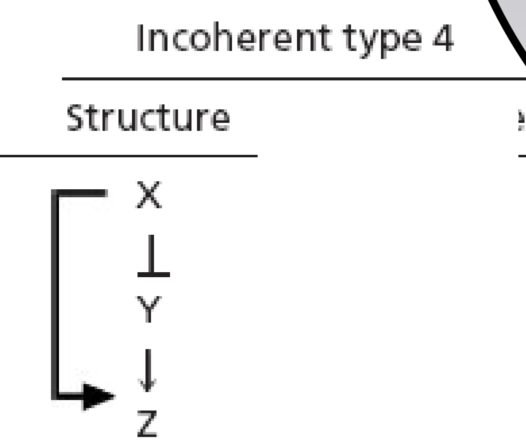
Detailed model of fission yeast DNA replication



Detailed model of fission yeast DNA replication







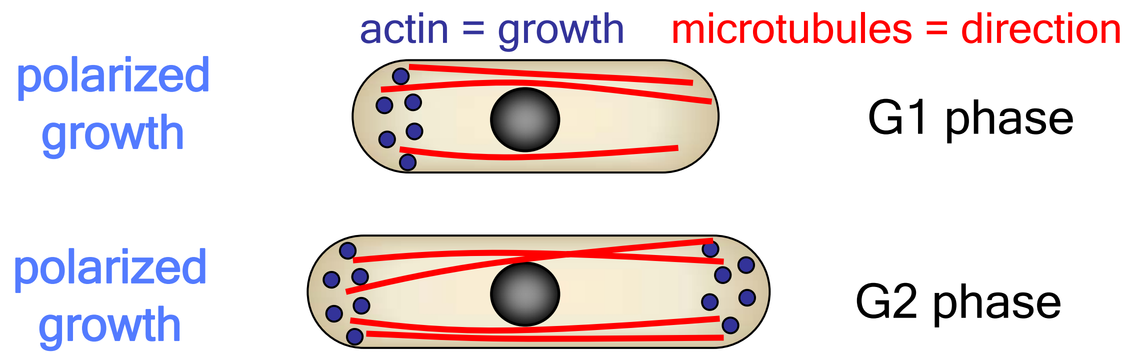
11980–11985 | PNAS | October 14, 2003 | vol. 100 | no. 21

Structure and function of the feed-forward loop network motif

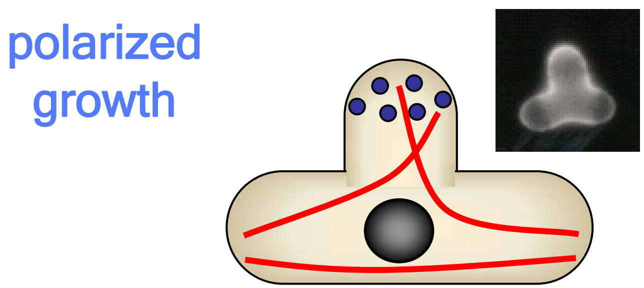
S. Mangan and U. Alon[†]

Modelling fission yeast morphogenesis

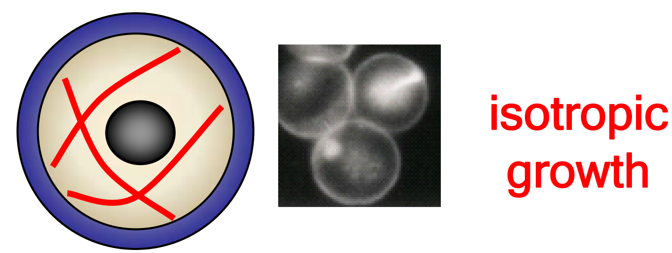
Growth patterns in fission yeasts

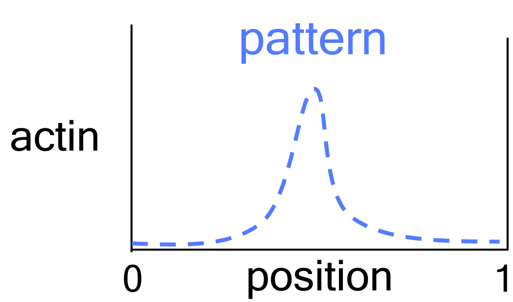


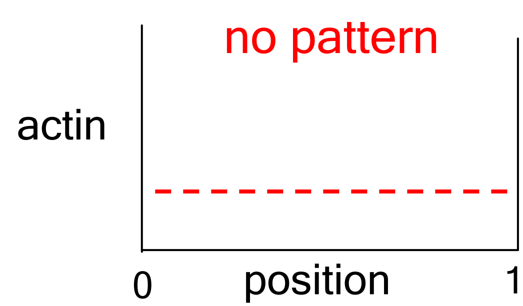
Tea mutants



Orb mutants

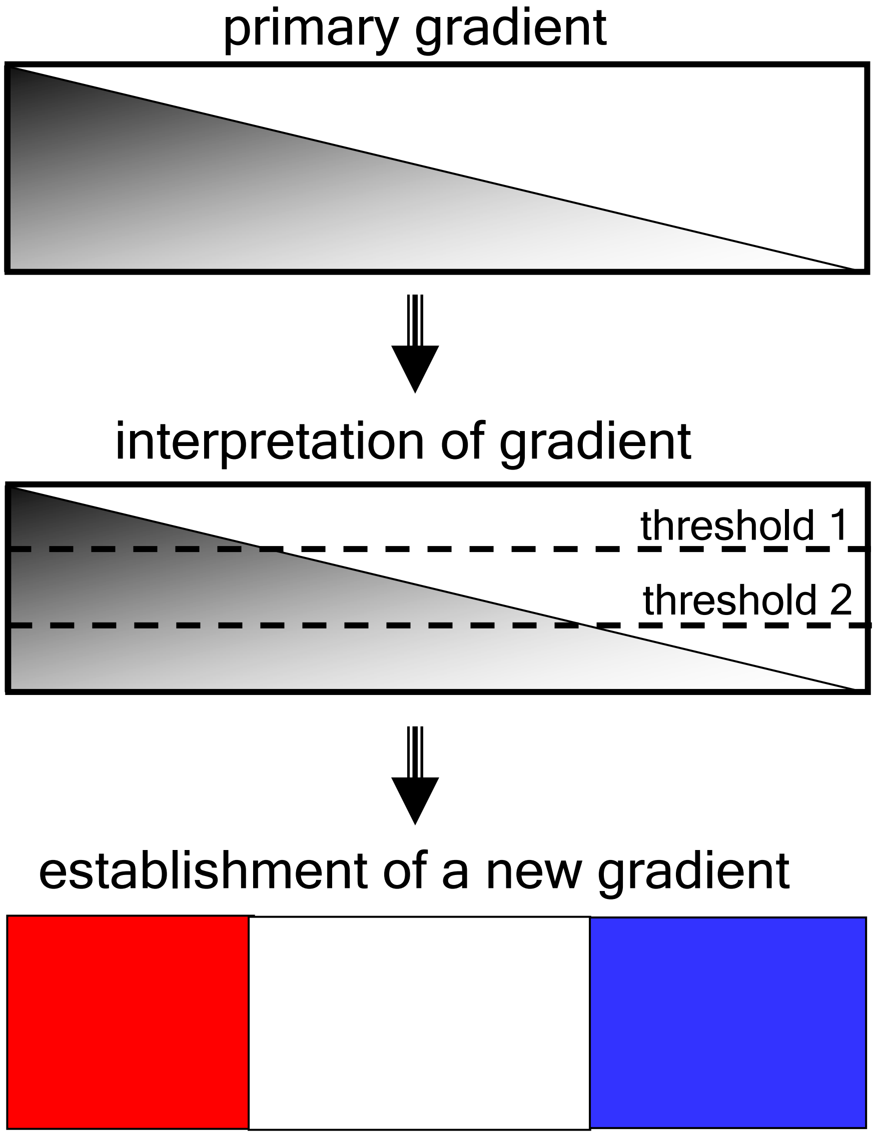






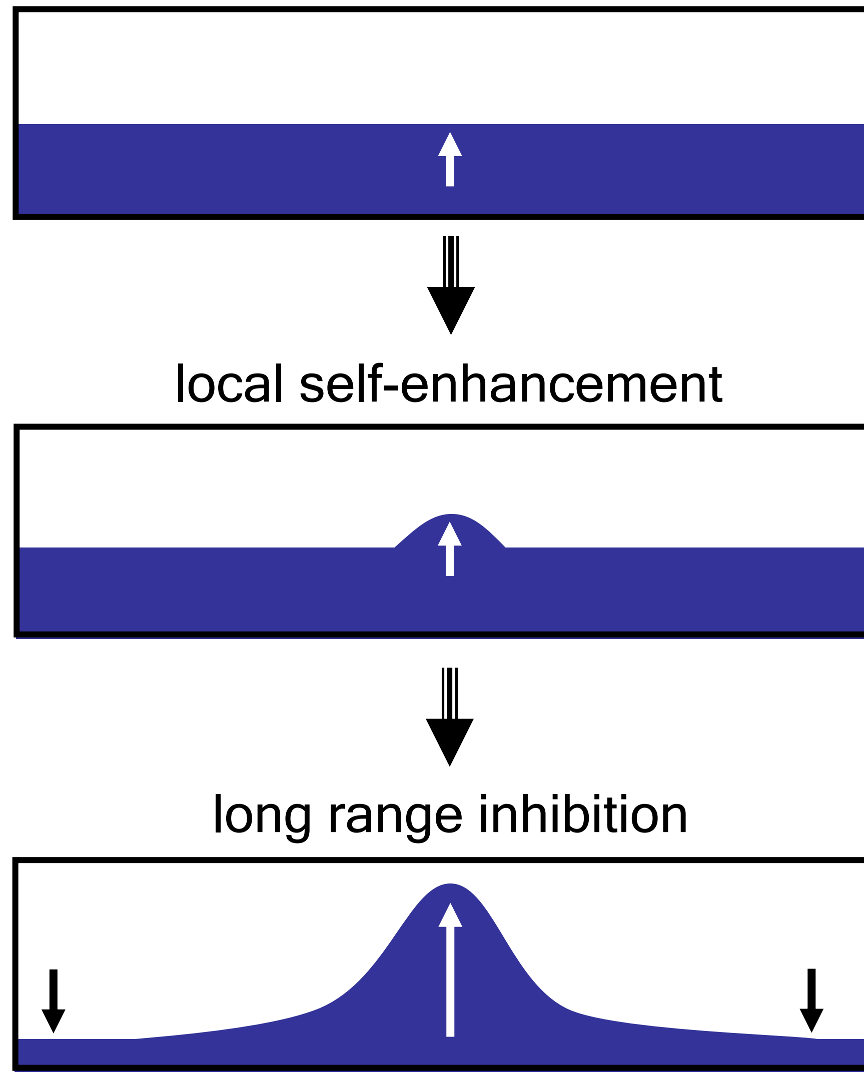
Two different pattern formation mechanisms

positional information



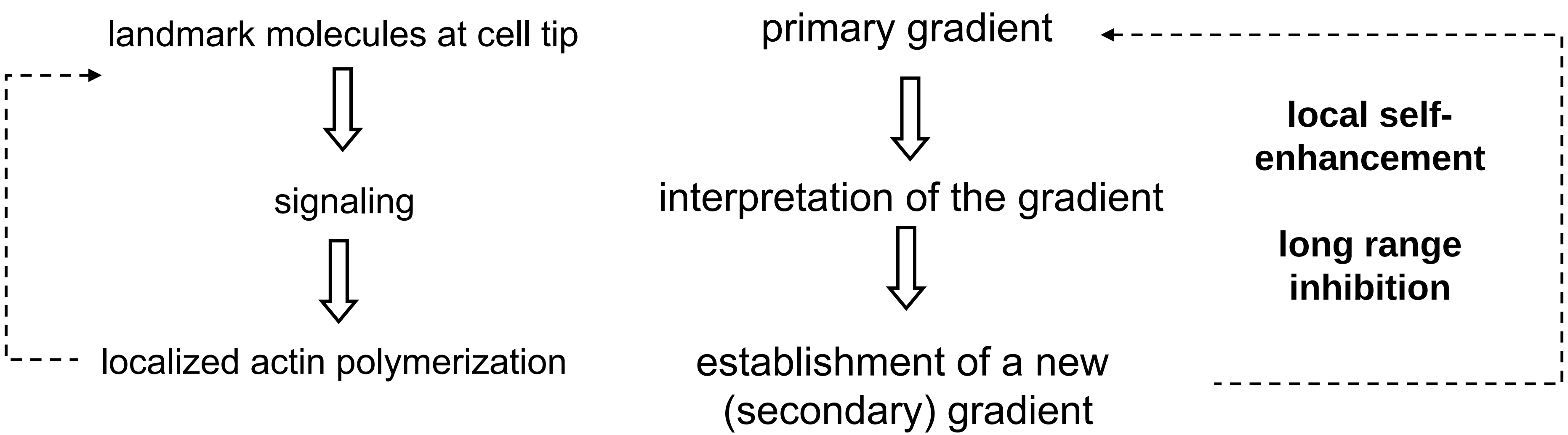
L. Wolpert (1969)

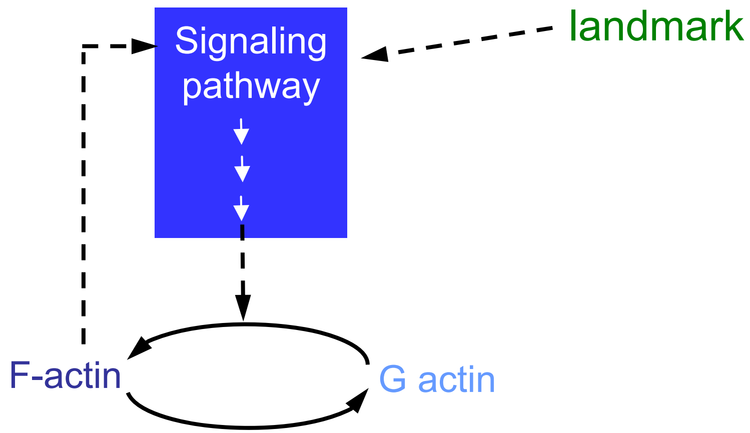
self-organized gradient



A.M. Turing (1952); A. Gierer & H. Meinhardt (1972)

The two mechanisms are not mutually exclusive

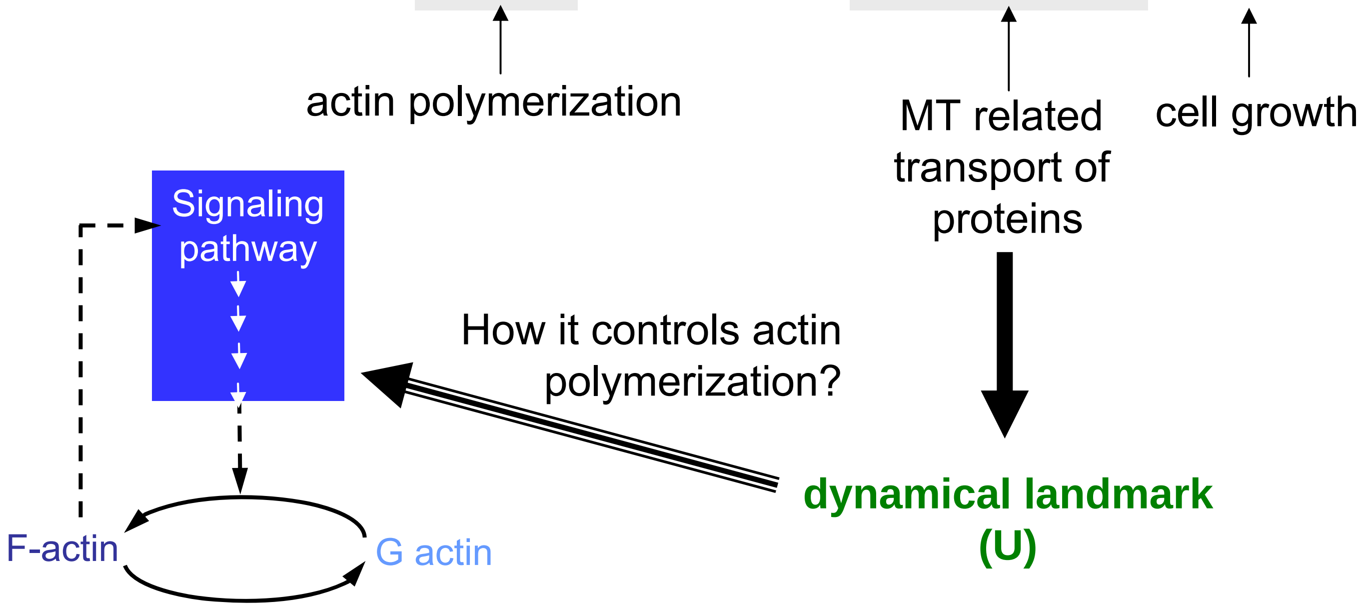




Partial differential equations:

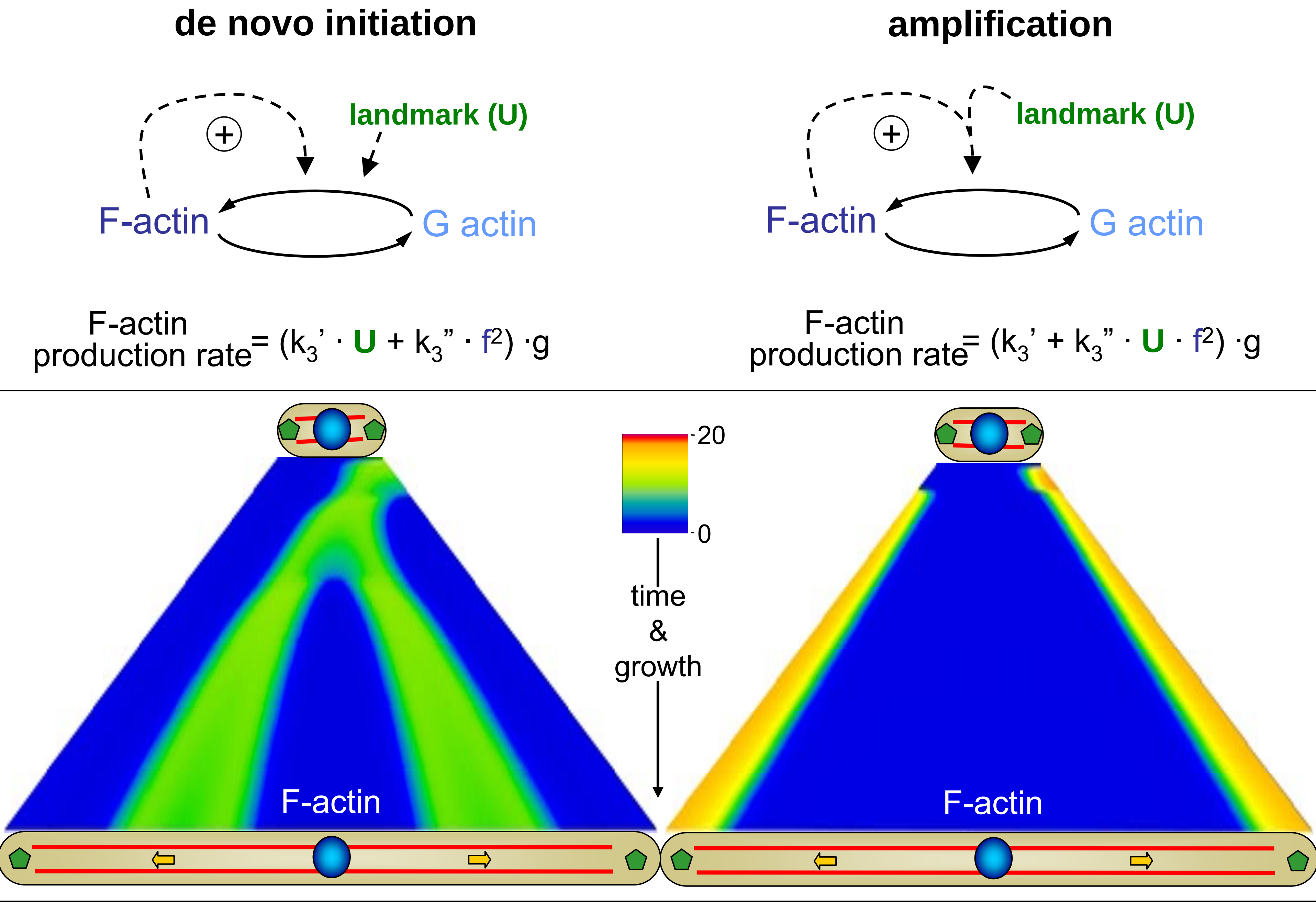
$$\frac{\partial y}{\partial t} = F(y) + D_y \frac{\partial^2 y}{\partial x^2} + v_y \cdot \partial_x (y) - \frac{y}{h} \cdot \frac{\partial h}{\partial t}$$

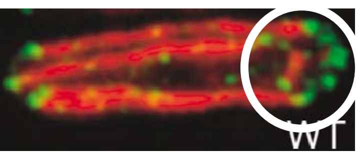
reaction diffusion convection dilution



Three equations :

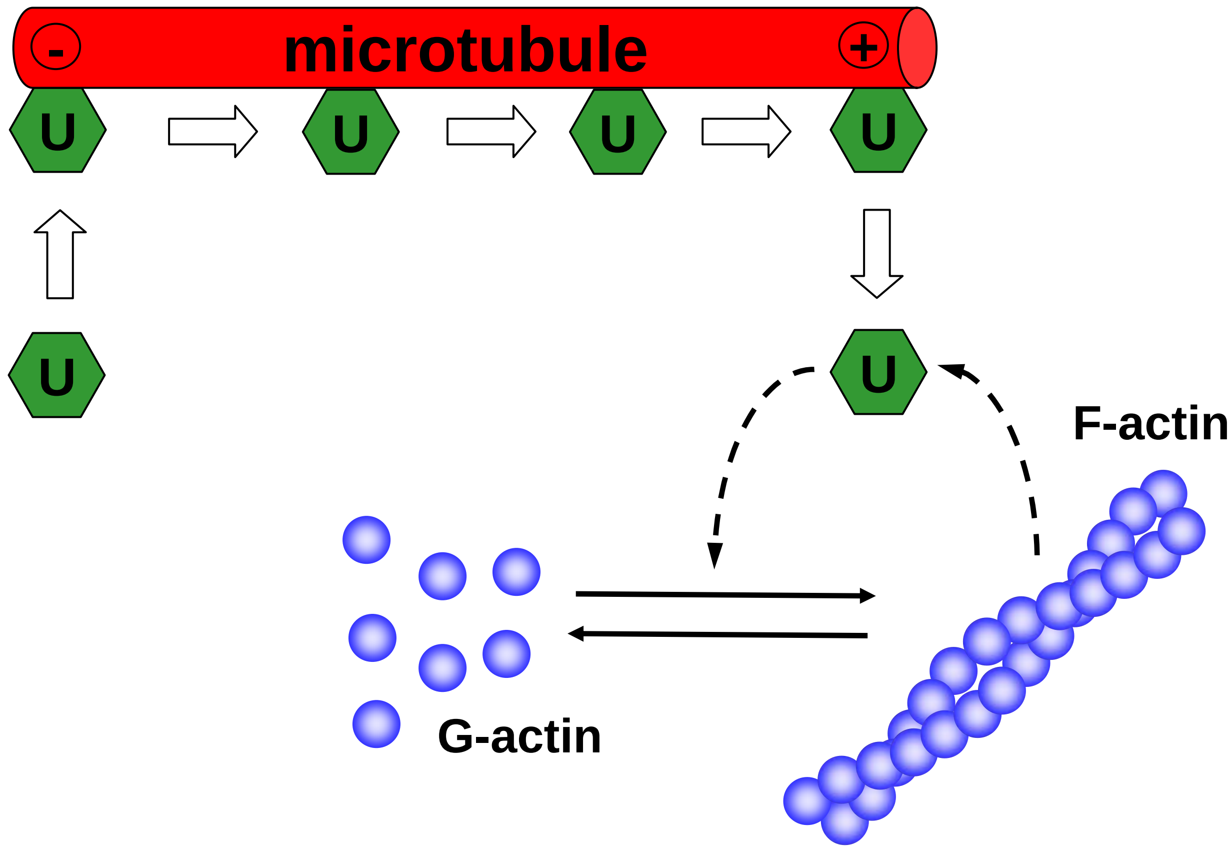
- G-actin
- F-actin
- landmark (U)


de novo initiation
amplification
landmark (U)
F-actin
G actin
landmark (U)
F-actin
G actin
F-actin production rate = (k3' · U + k3" · f2) ·g
F-actin production rate = (k3' + k3" · U · f2) ·g
20
0
time & growth
F-actin
F-actin

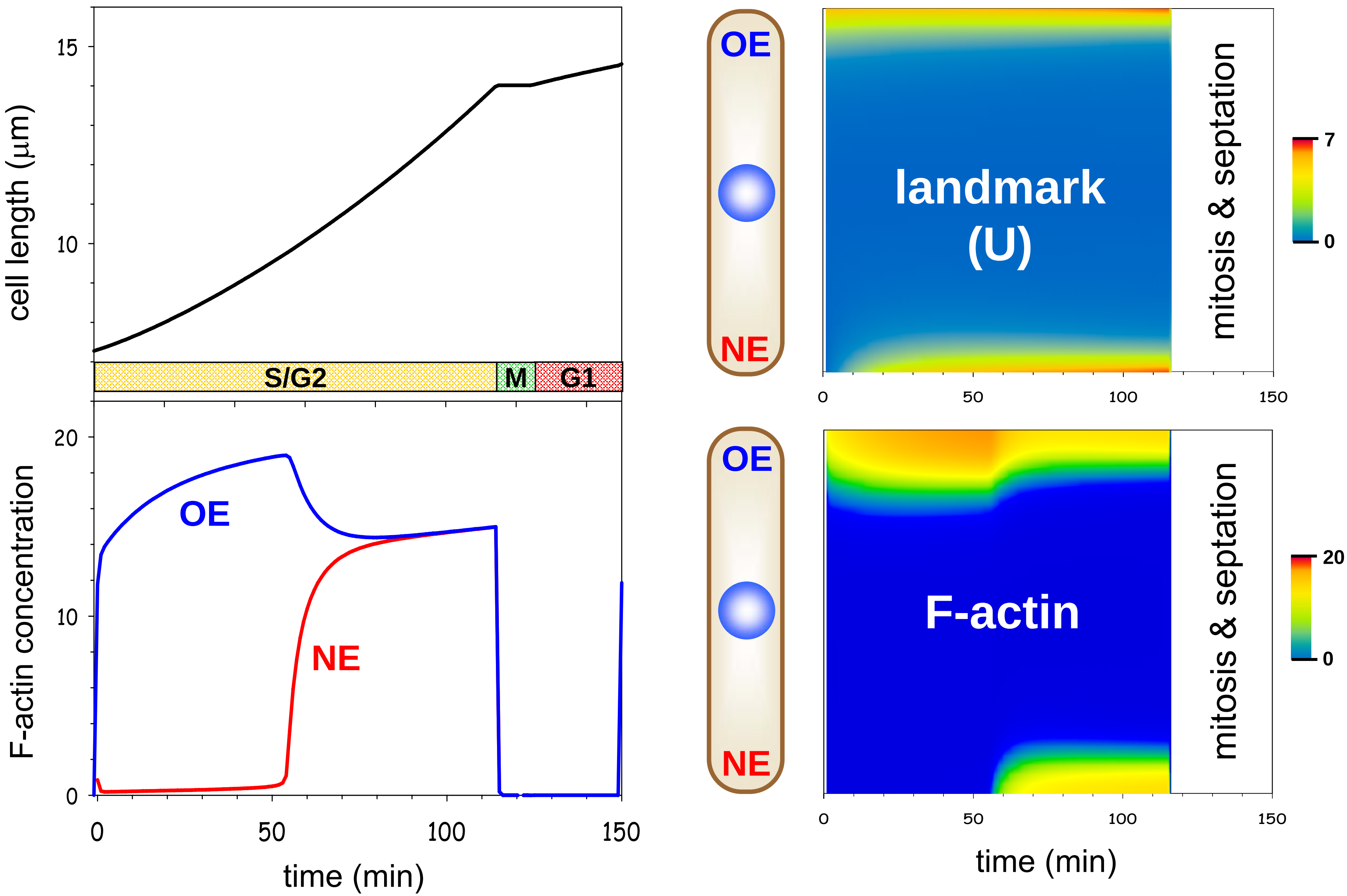


microtubules

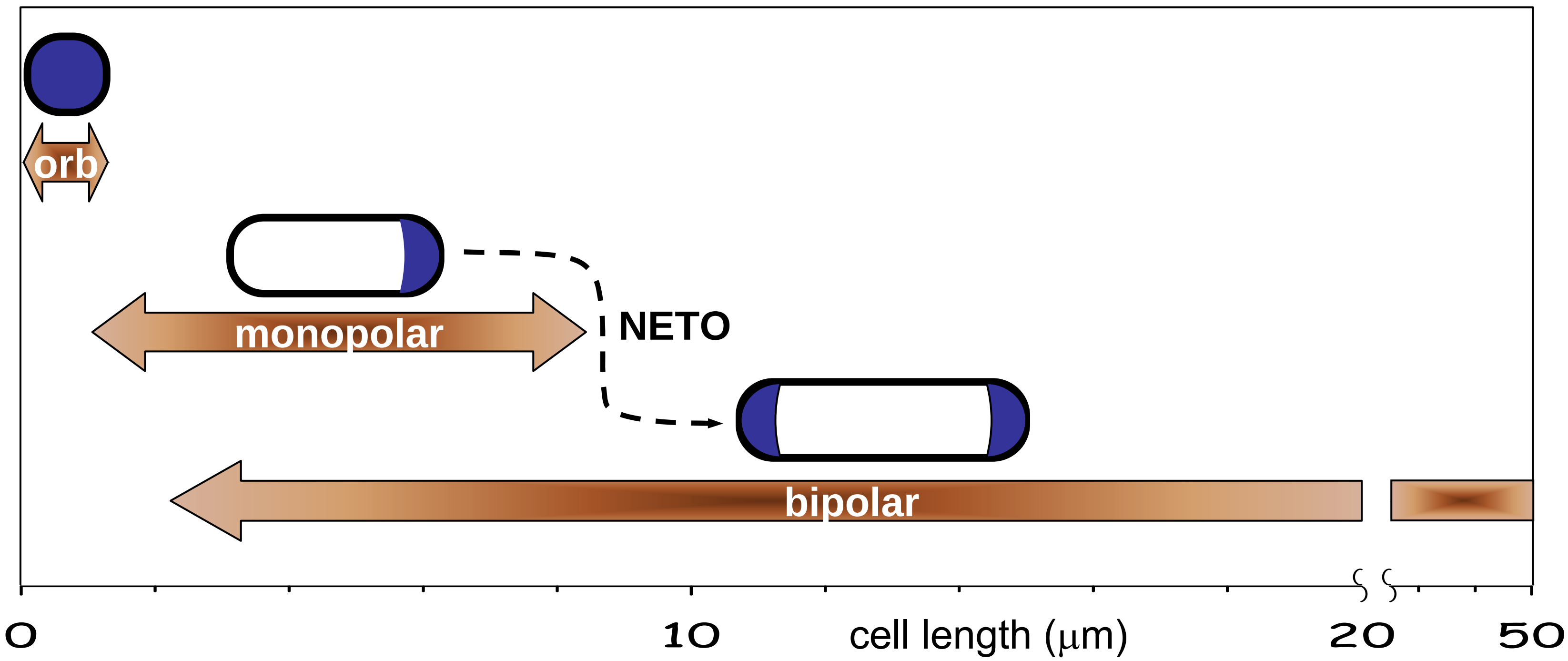
one of the landmarks



Simulation of wild type cells



Predicted possible growth patterns of wild type cells

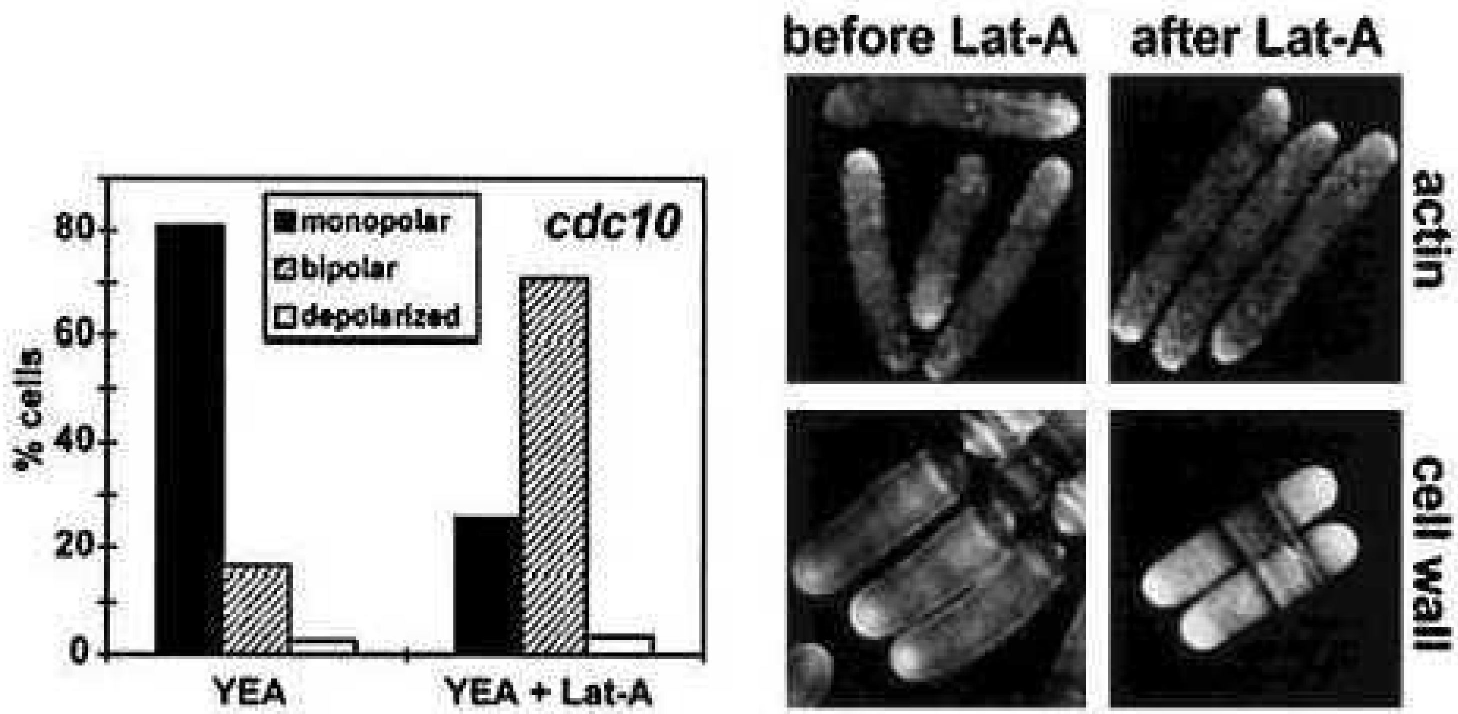


Disruption of the actin system by Latranculin-A

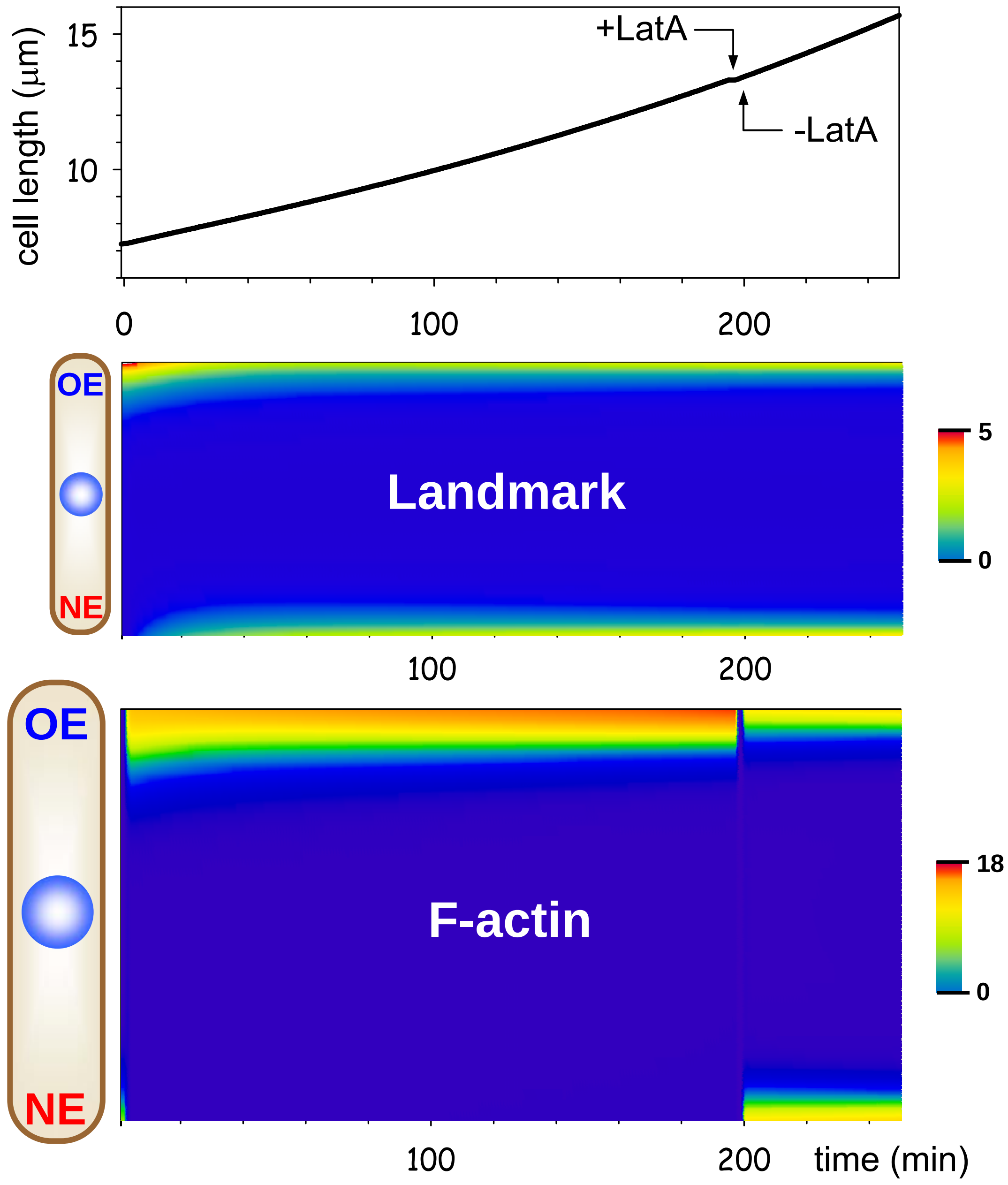
Molecular Biology of the Cell
Vol. 10, 1495–1510, May 1999

Ssp1 Promotes Actin Depolymerization and Is Involved in Stress Response and New End Take-Off Control in Fission Yeast

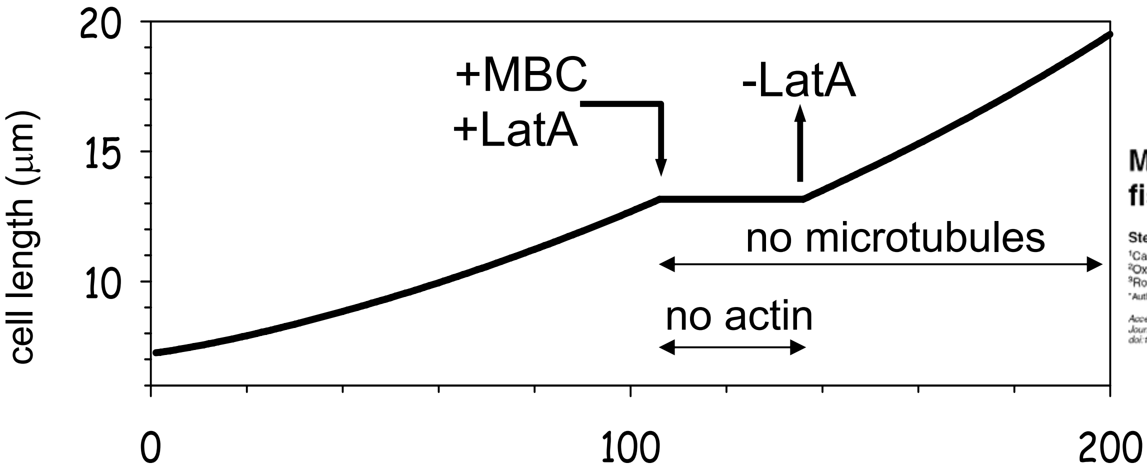
Ivan Rupeš, Zhengping Jia,* and Paul G. Young†



Simulation of the Rupes' experiment



Verification of the underlying pattern forming reaction



Microtubules offset growth site from the cell centre in fission yeast

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[1]Cancer Research UK, Cell Cycle Lab, 44 Lincoln's Inn Fields, London, WC2A 3PX, UK
[2]Oxford Centre for Integrative Systems Biology, University of Oxford, South Parks Road, Oxford, OX1 3QU, UK
[3]Rockefeller University, 1230 York Avenue, New York, NY 10021, USA
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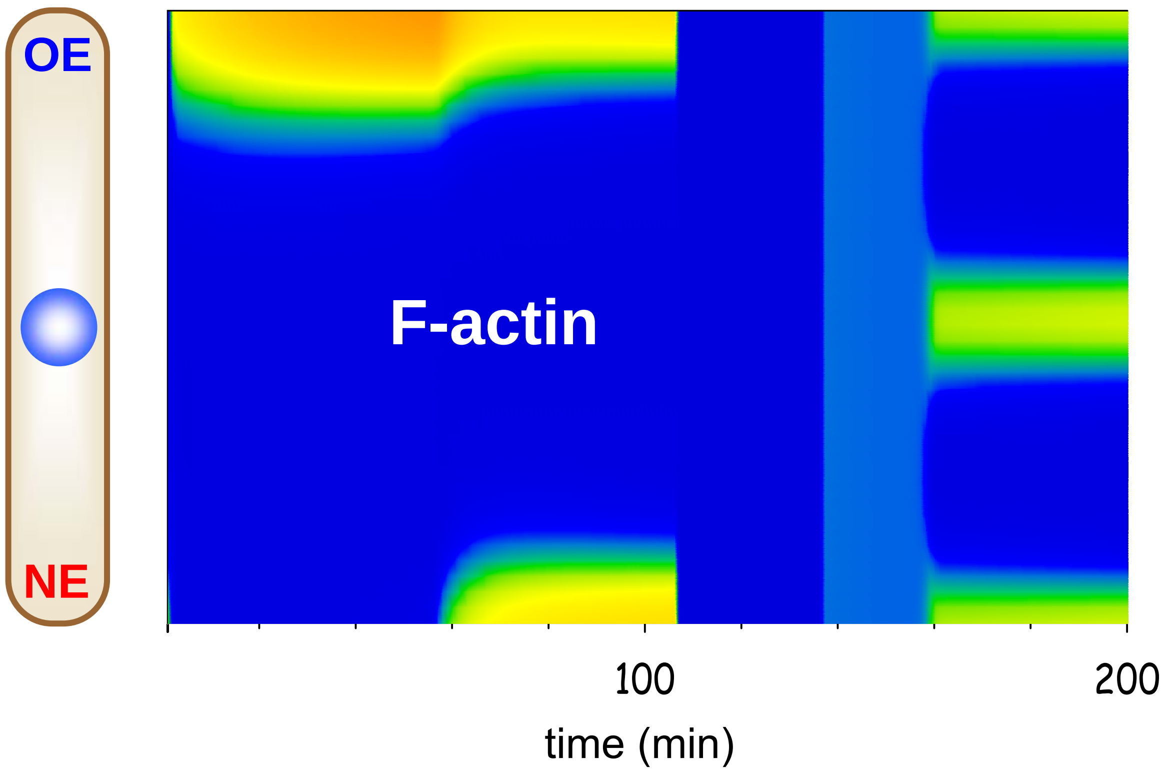
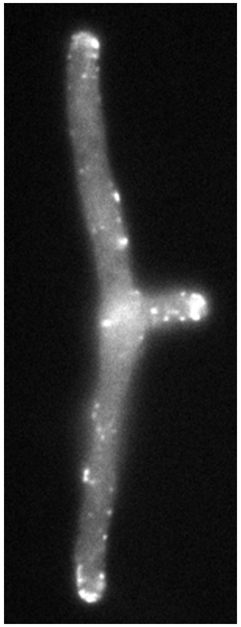
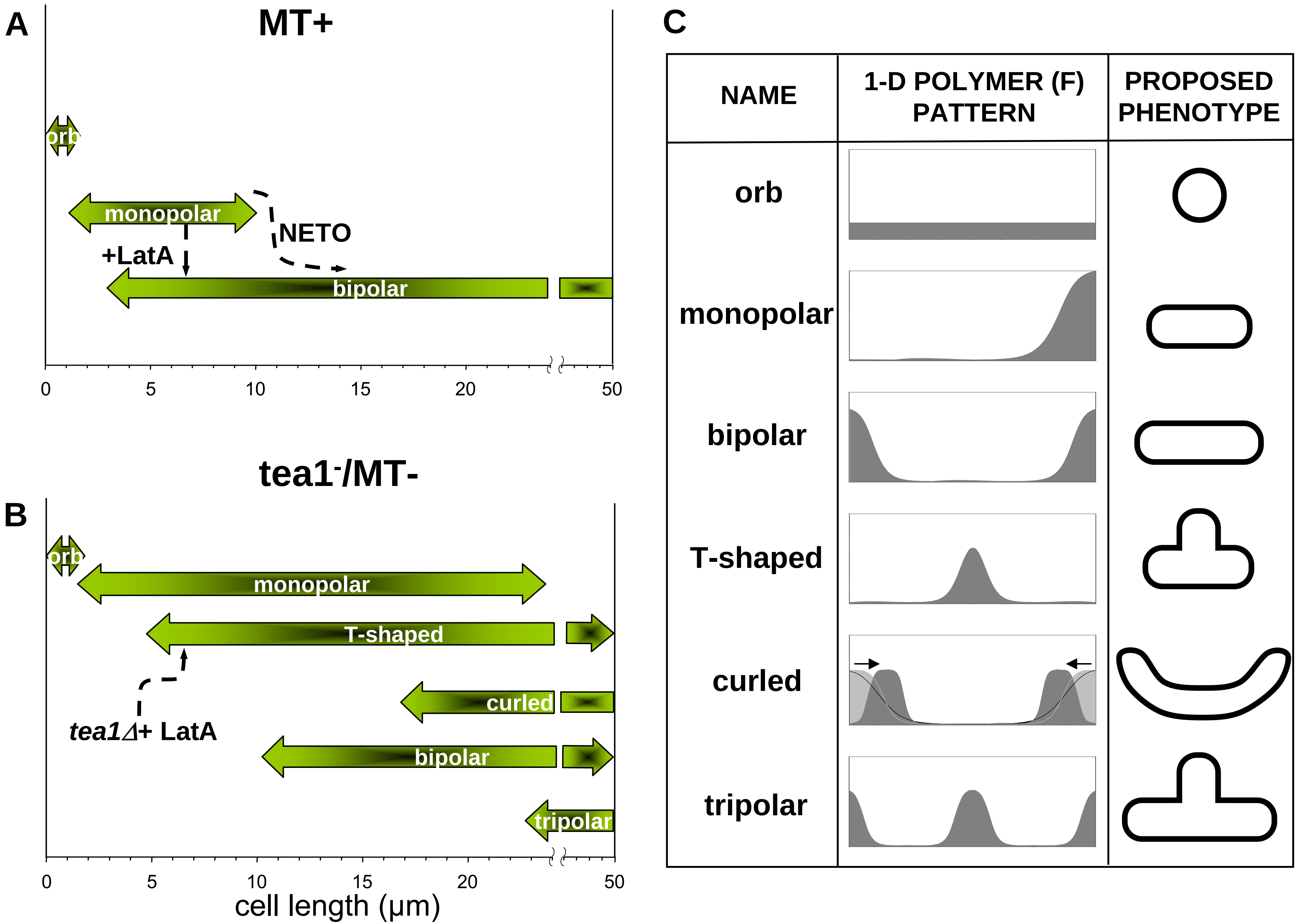
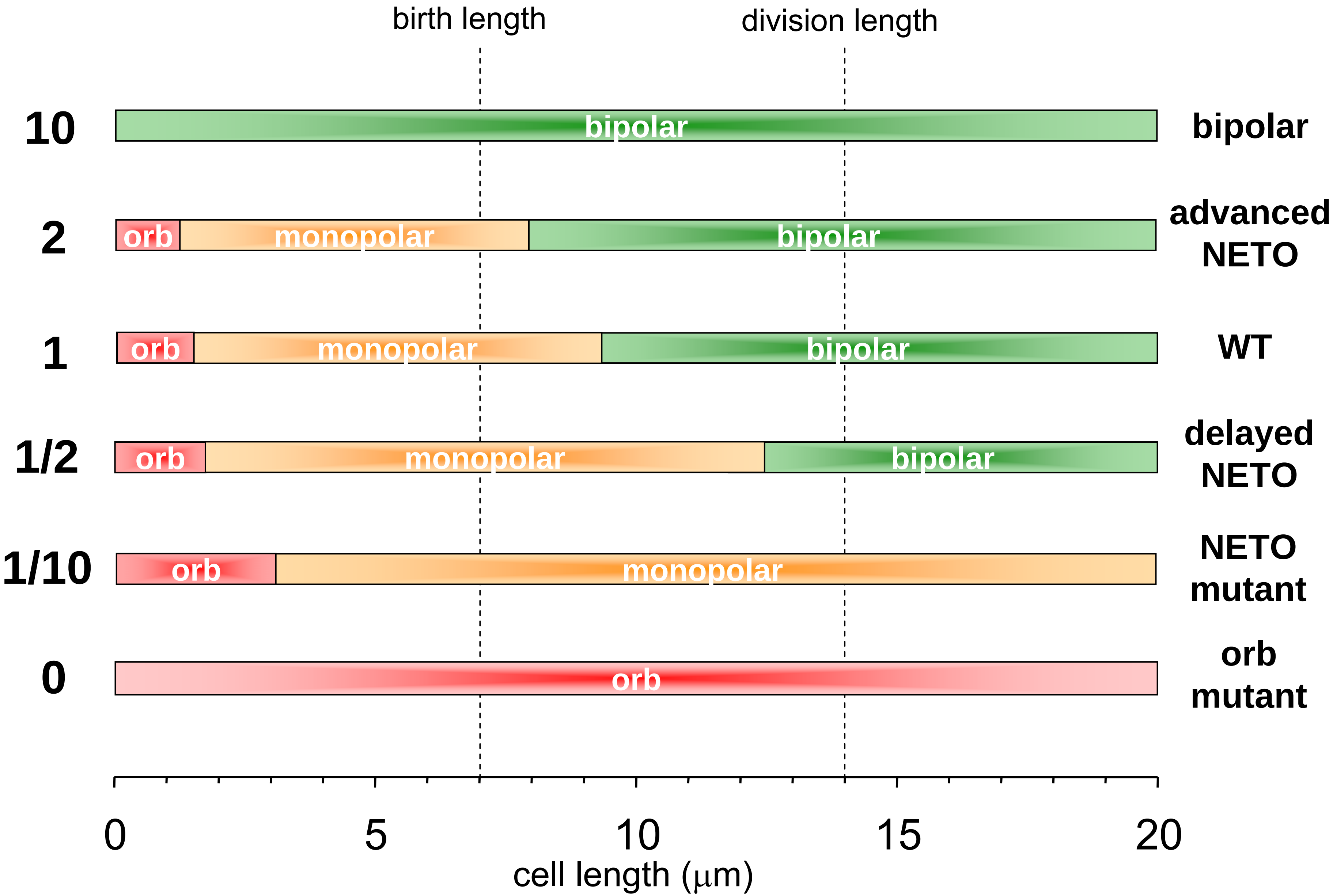





A
MT+
orb
monopolar
NETO
+LatA
bipolar
0
5
10
15
20
50
B
tea1-/MT-
orb
monopolar
T-shaped
curled
tea1Δ+ LatA
bipolar
tripolar
0
5
10
15
20
50
cell length (μm)
C
NAME
1-D POLYMER (F) PATTERN
PROPOSED PHENOTYPE
orb
monopolar
bipolar
T-shaped
curled
tripolar

Morphogenetic mutants & robustness

(positive feedback efficiency)



Conclusions 2:


S. Castagnetti

- Very simple model (3 variables)
- Can produce wild-type and mutant growth patterns → suggests protein function
- Possible biological role for Turing pattern (only in microtubule disrupted case)
- Predicts the role of microtubules in polarized growth regulation

Csikász-Nagy A, Győrffy B, Alt W, Tyson JJ, Novák B. (2007) Modelling fission yeast morphogenesis. *Yeast*, under review

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Orsolya Kapuy

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Ákos Sveiczer

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