Signaling pathways and cell cycle: modeling control mechanisms

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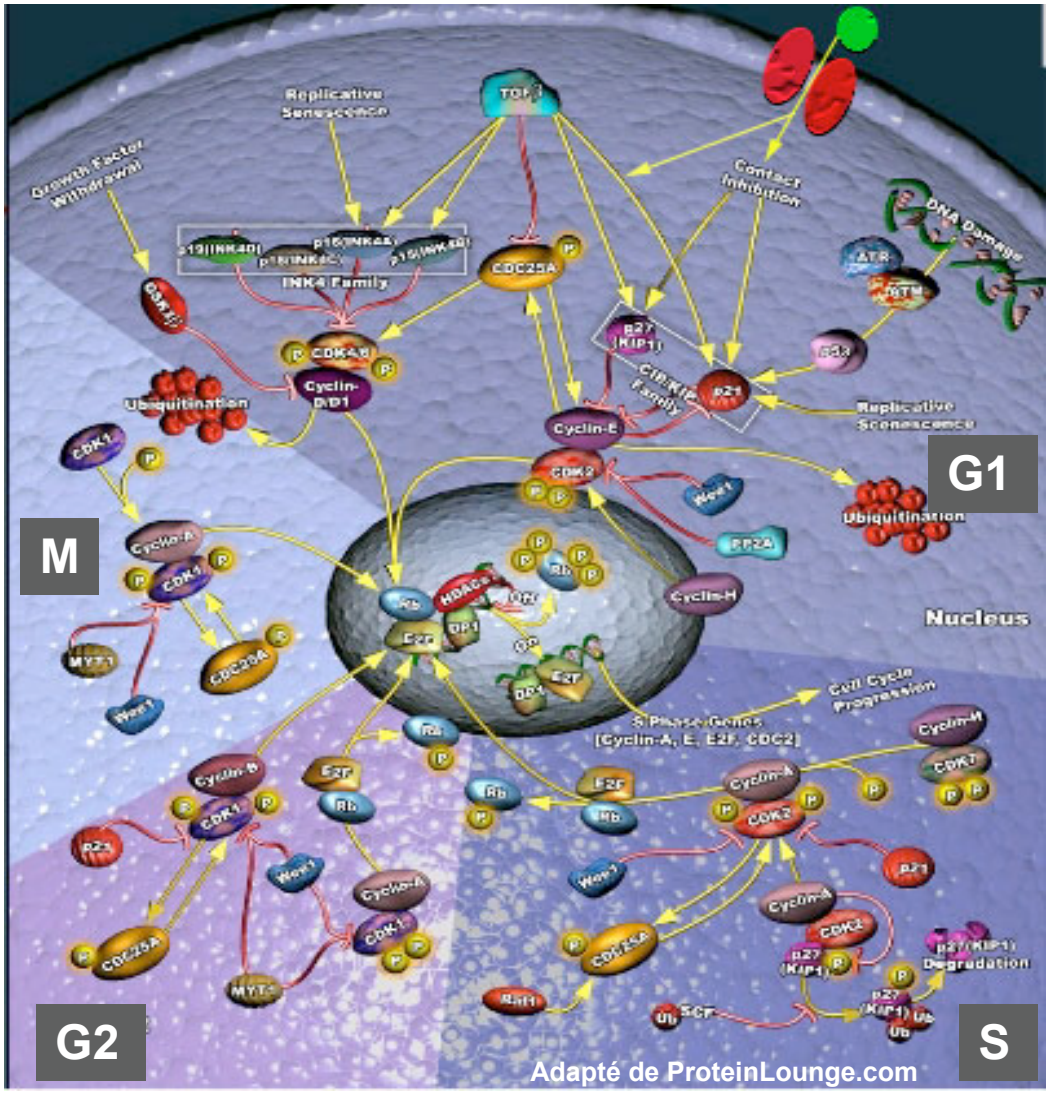
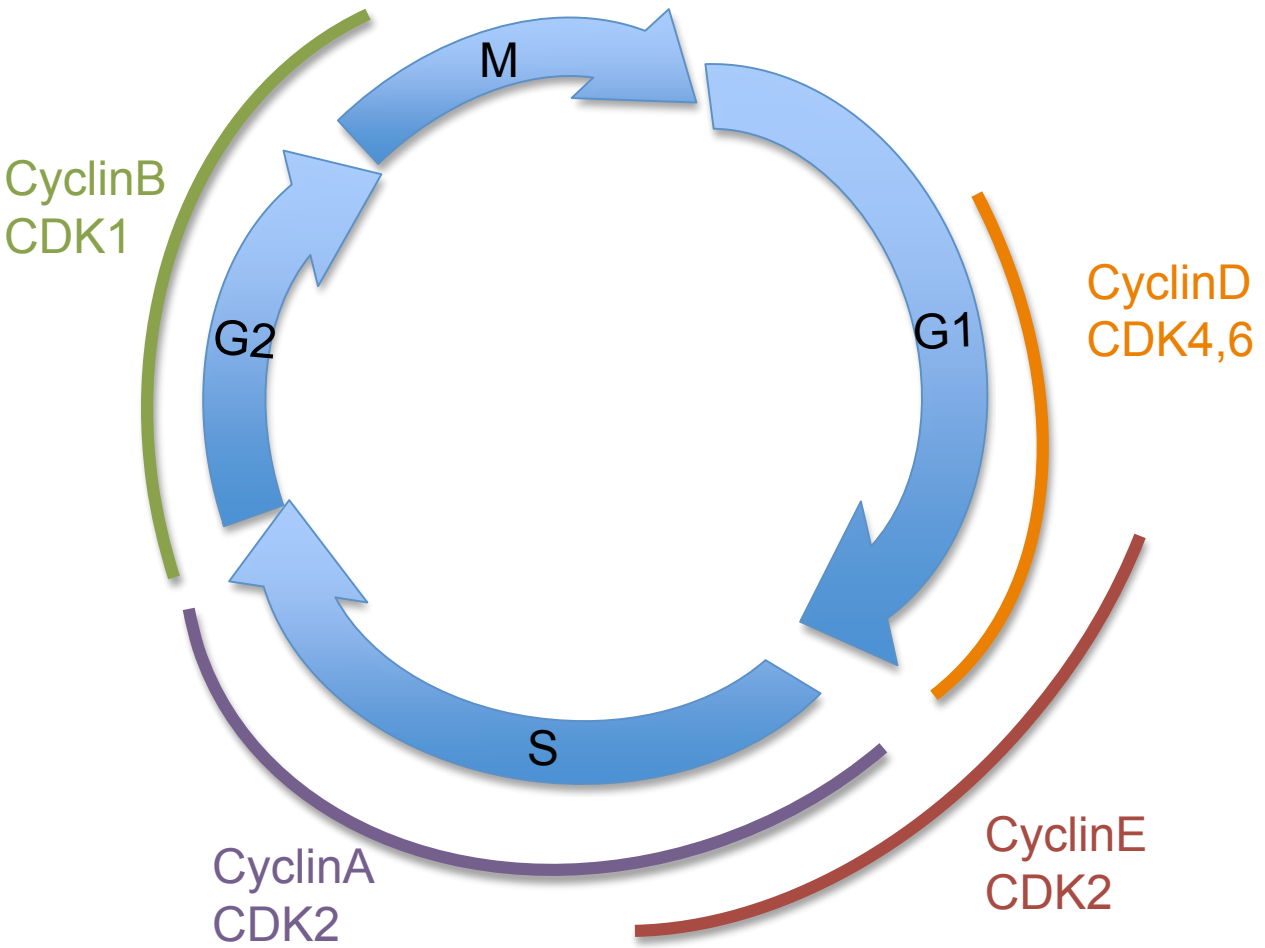
6ème journée de la plate-forme GenOuest

Rennes, 21 October 2008

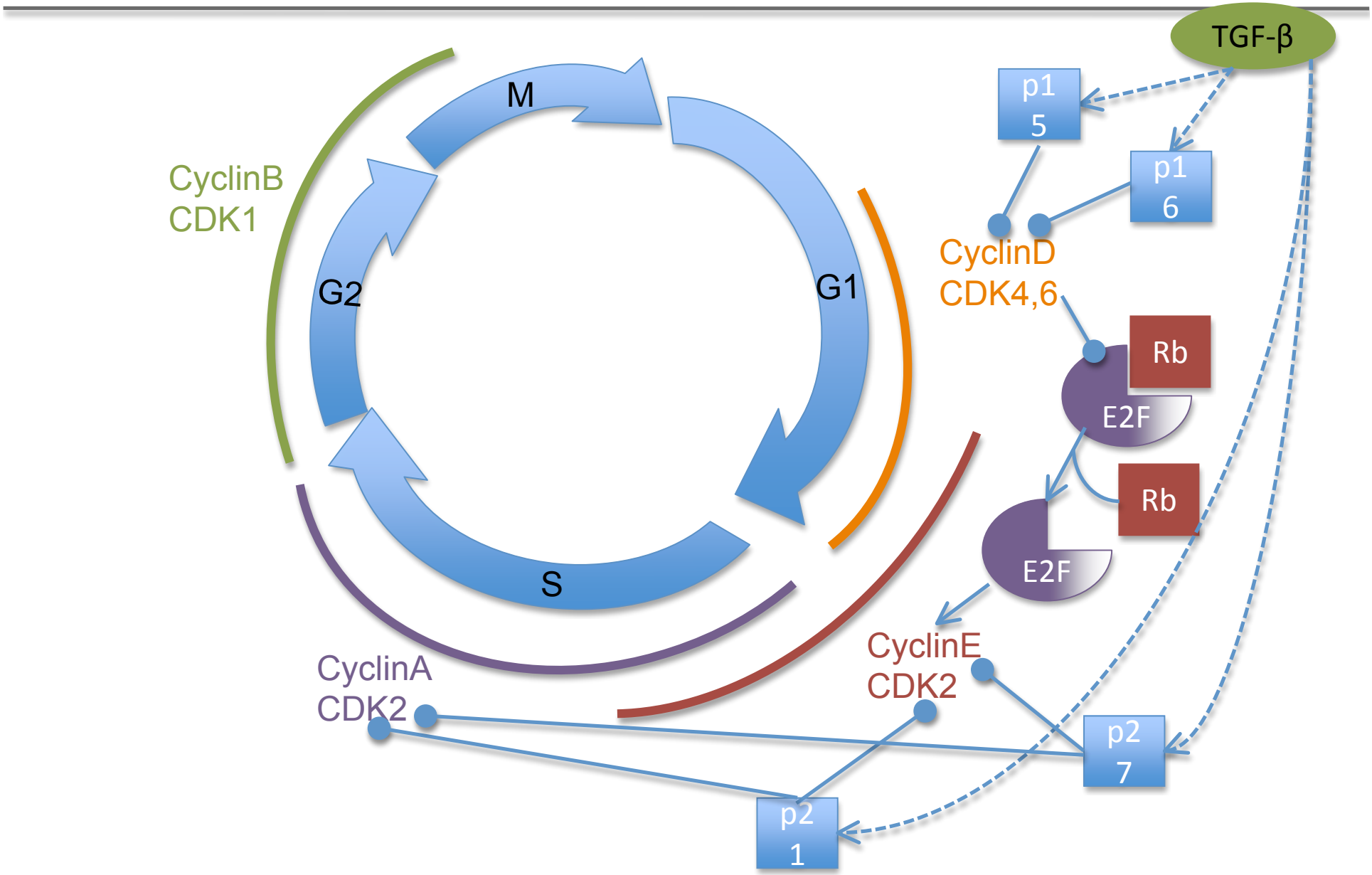
The role of signaling pathways in controling cell cycle



Cell cycle [Basic]



Cell cycle and signaling pathway [Basic]

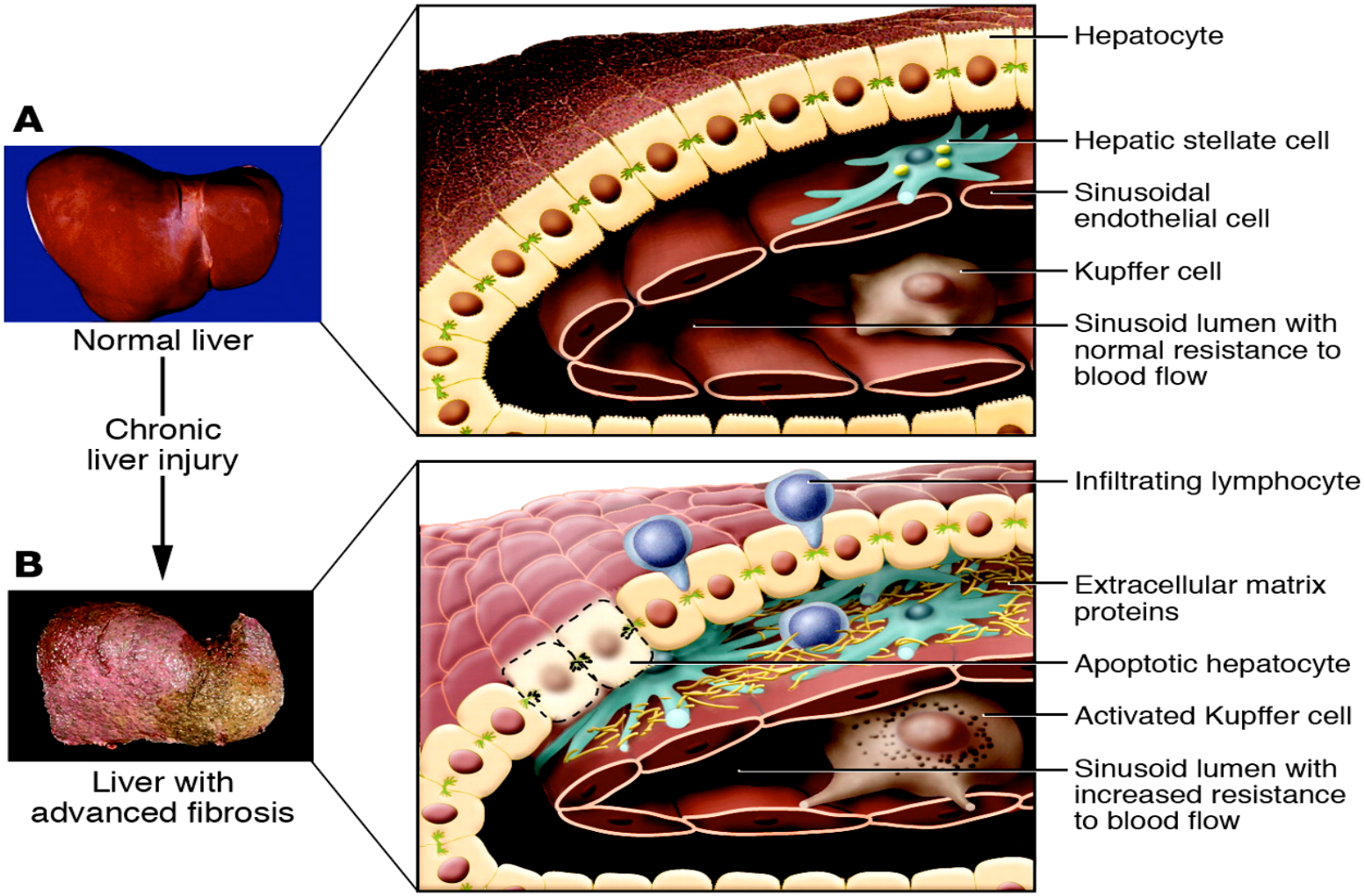


Cell cycle, Signaling and Cancer

Name of gene	Nature of protein function	Type of tumor
RARβ2	nuclear receptor for differentiation	breast, lung
$p57^{Kip2}$	CDK inhibitor	gastric, pancreatic, hepatic; AML
TIMP3	inhibitor of metalloproteinases	diverse tumors
IGFBP	sequesters IGF-1 factor	diverse tumors
$CDKN2A/p16^{INK4A}$	inhibitor of CDK4/6	diverse tumors
$CDKN2B/p15^{INK4B}$	inhibitor of CDK4/6	diverse tumors
$p14^{ARF}$	inhibitor of HDM2/MDM2	colon, lymphoma
APC	inducer of β-catenin degradation	colon carcinomas
p73	aids p53 to trigger apoptosis	diverse tumors
GSTP1	mutagen inactivator	breast, liver, prostate
MGMT	DNA repair enzyme	colorectal
CDH1	cell–cell adhesion receptor	bladder, breast, colon, gastric
DAPK	kinase involved in cell death	bladder
MLH1	DNA mismatch repair enzyme	colon, endometrial, gastric
TGFBR2	TGF-β receptor	colon, gastric, small-cell lung
THBS1	angiogenesis inhibitor	colon, glioblastoma
RB	cell-cycle regulator	retinoblastoma
CASP8	apoptotic caspase	neuroblastoma, SCLC
APAF1	pro-apoptotic cascade	melanoma
CTMP	inhibitor of Akt/PKB	glioblastoma multiforme

Weinberg (2006) The biology of cancer. Garland

From fibrosis to hepatocellular carcinoma



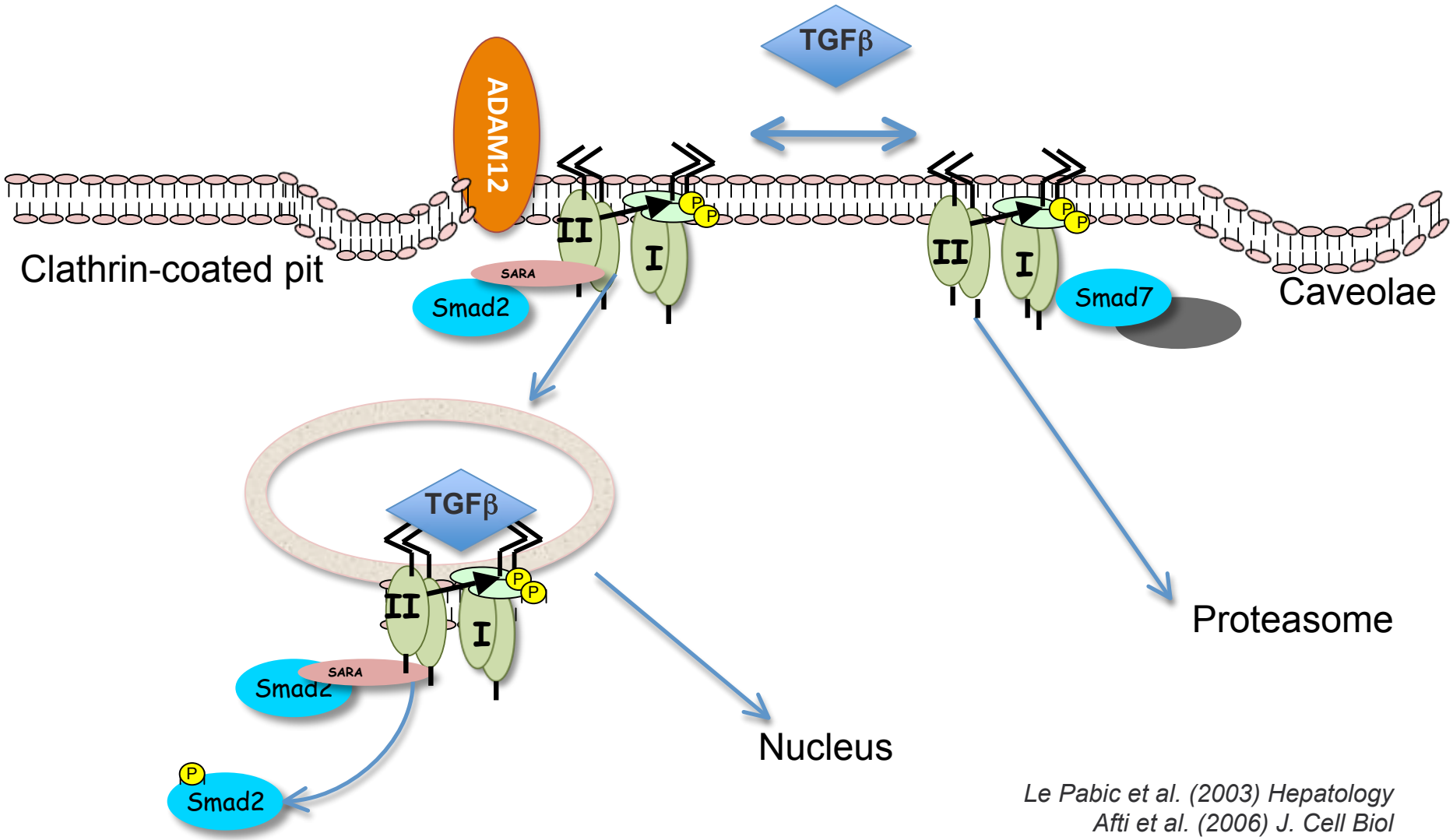
Bataller R. and Brenner D.A (2007). J. Clin. Inv.

TGF-β signaling pathway

- Extracellular matrix production
- Cell proliferation
- Functional differentiation
- Cell motility
- Apoptosis

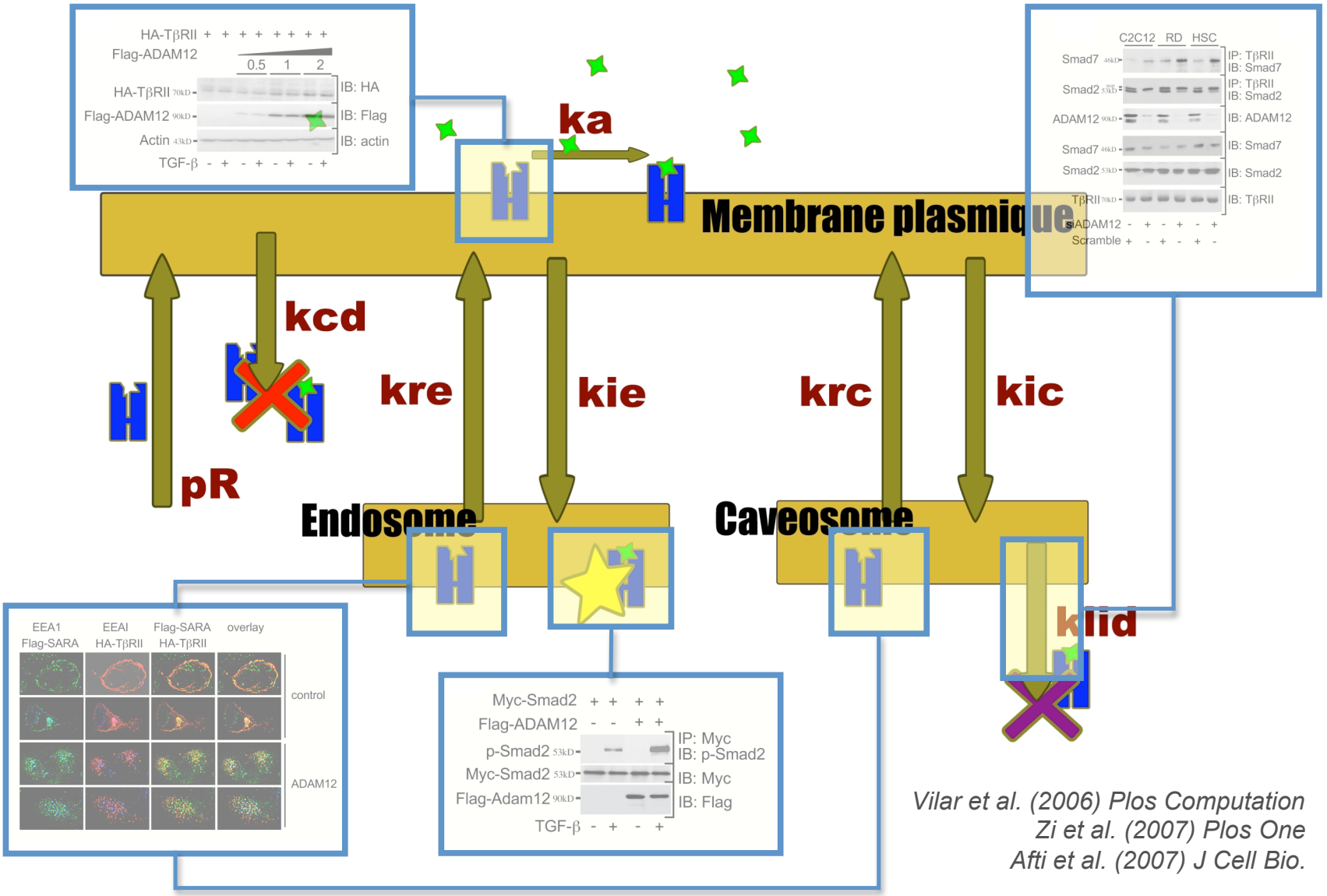
ADAM12 and TGF-β receptors

TGF-β signaling pathways



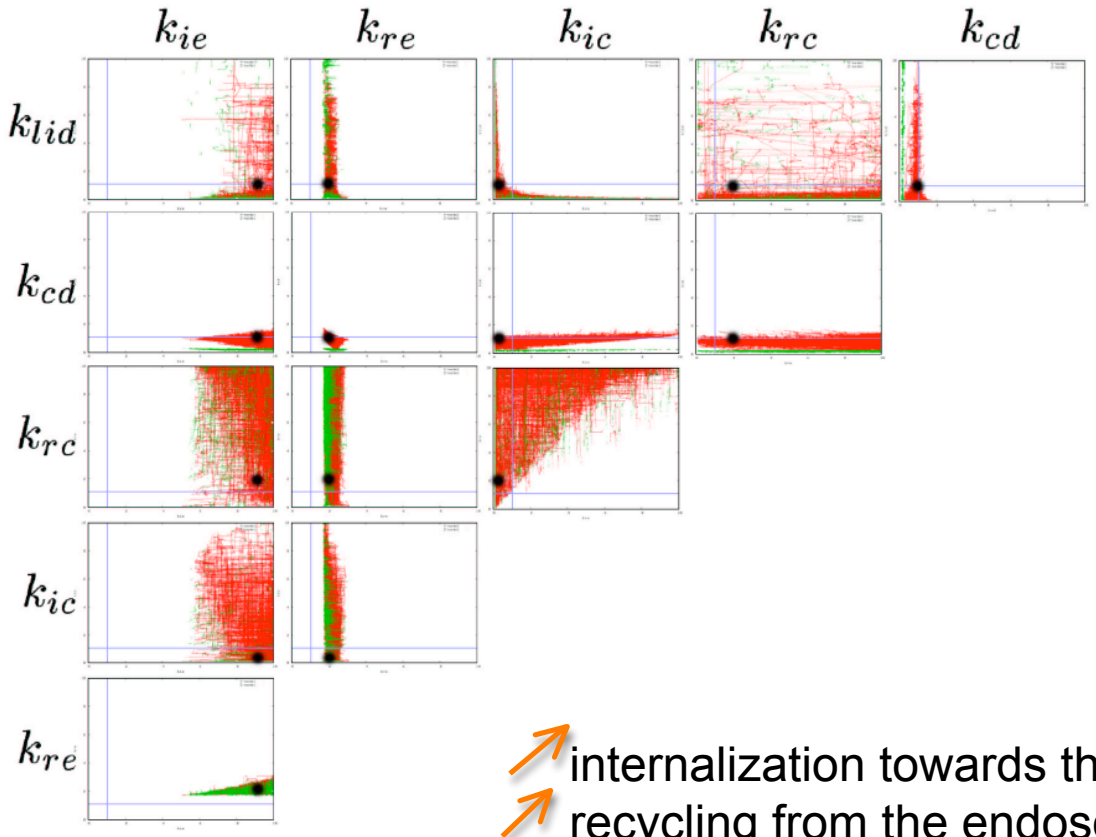
Le Pabic et al. (2003) Hepatology
Afti et al. (2006) J. Cell Biol

ADAM12 in TGF-β receptor trafficking



Vilar et al. (2006) Plos Computation
Zi et al. (2007) Plos One
Afti et al. (2007) J Cell Bio.

ADAM12 and TGF-β signal strength

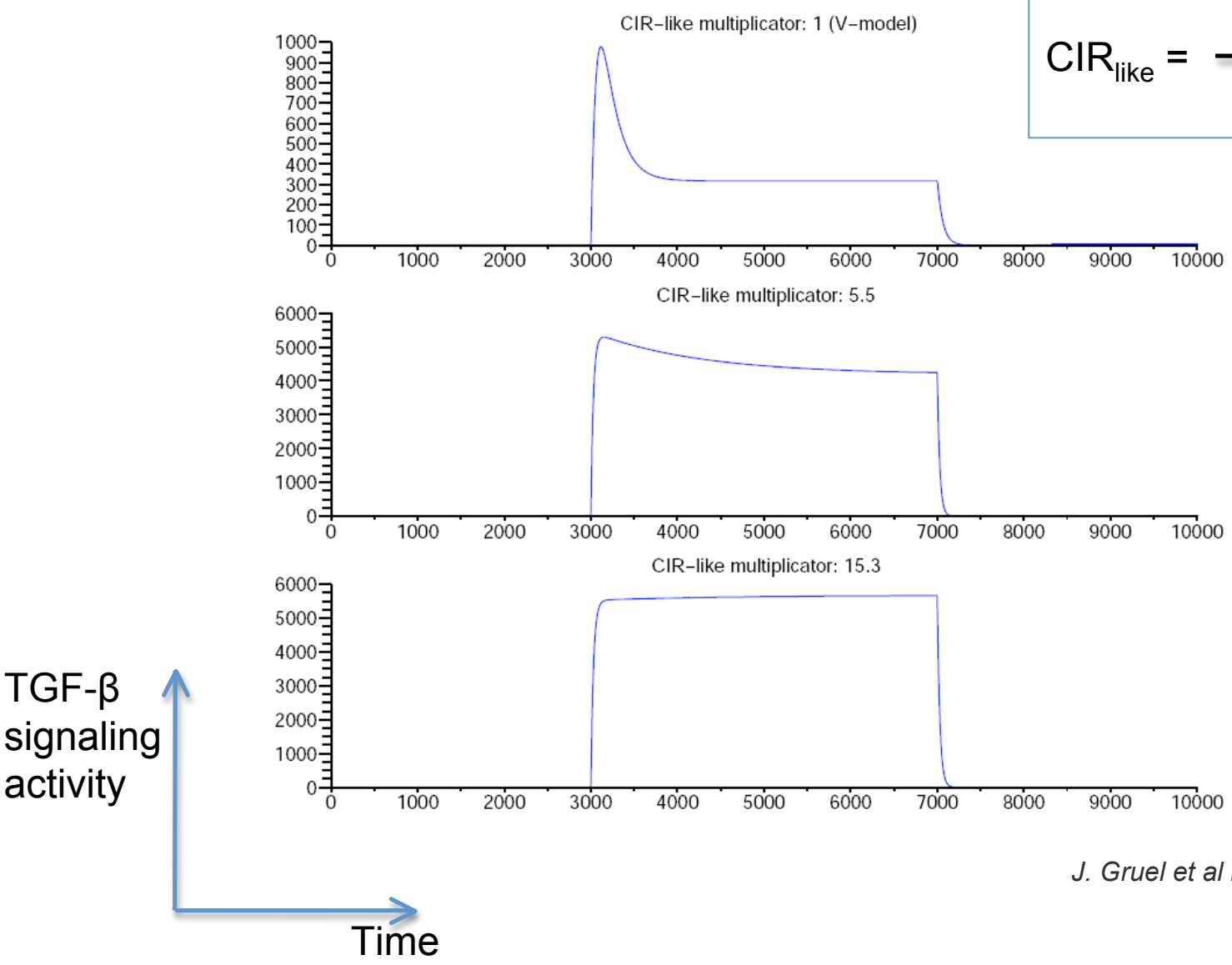


↗ internalization towards the endosome
↗ recycling from the endosome
↘ constitutive degradation

J. Gruel et al. in preparation

ADAM12 and TGF-β signal shape

$$CIR_{like} = \frac{\text{Constitutive}}{\text{Ligand-induced}}$$



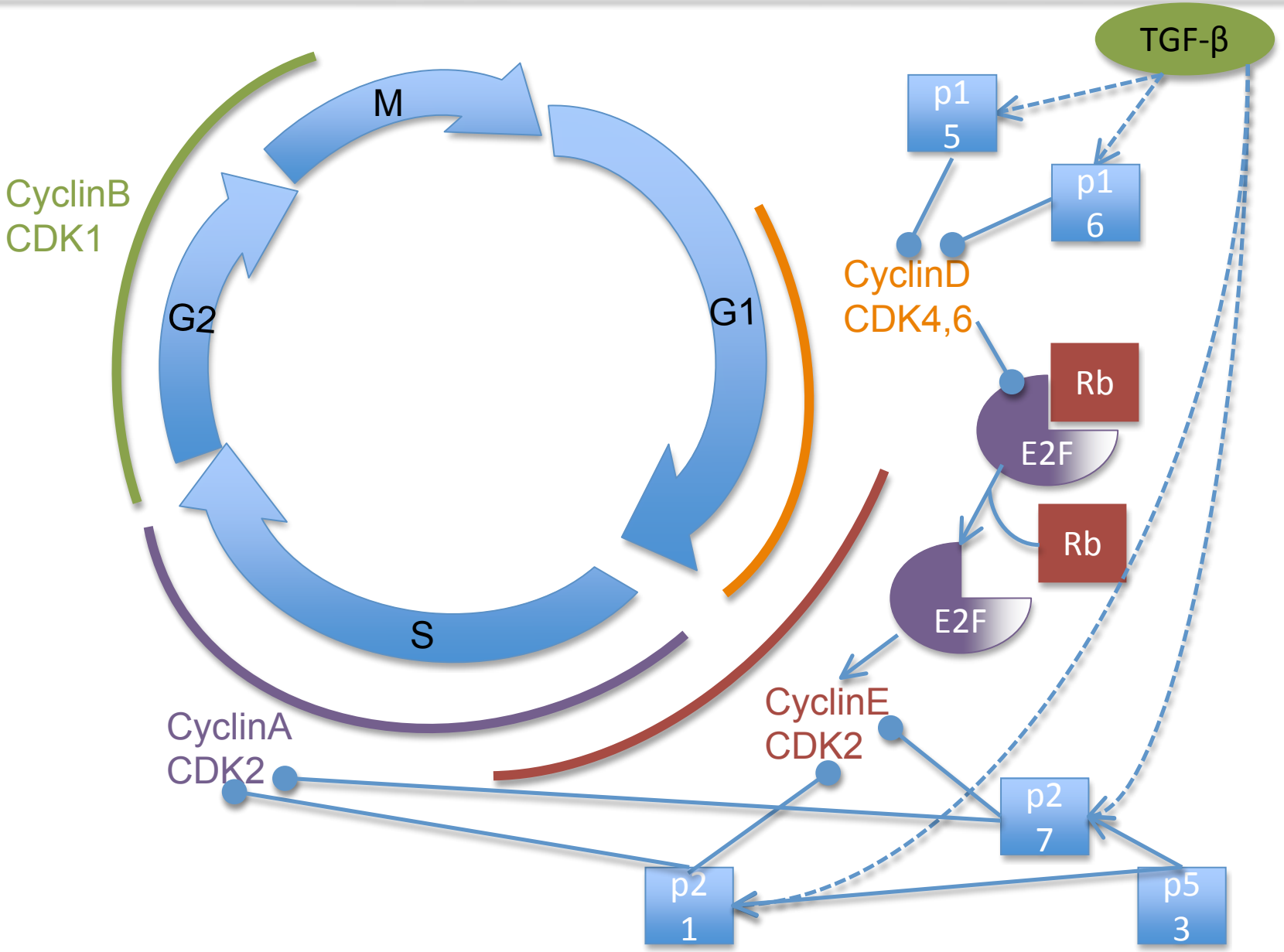
J. Gruel et al in preparation

Fitting algorithm as a exploratory tool

- Mathematical model
  - Differential equation
  - Solution space
- Biological insigths
  - Signal strength
  - Signal shape

Signaling pathways and cell cycle

Cell cycle and signaling pathway [Basic]



Modeling the Cell Cycle

Biophysical Journal Volume 90 June 2006 4361–4379

Analysis of a Generic Model of Eukaryotic Cell-Cycle Regulation

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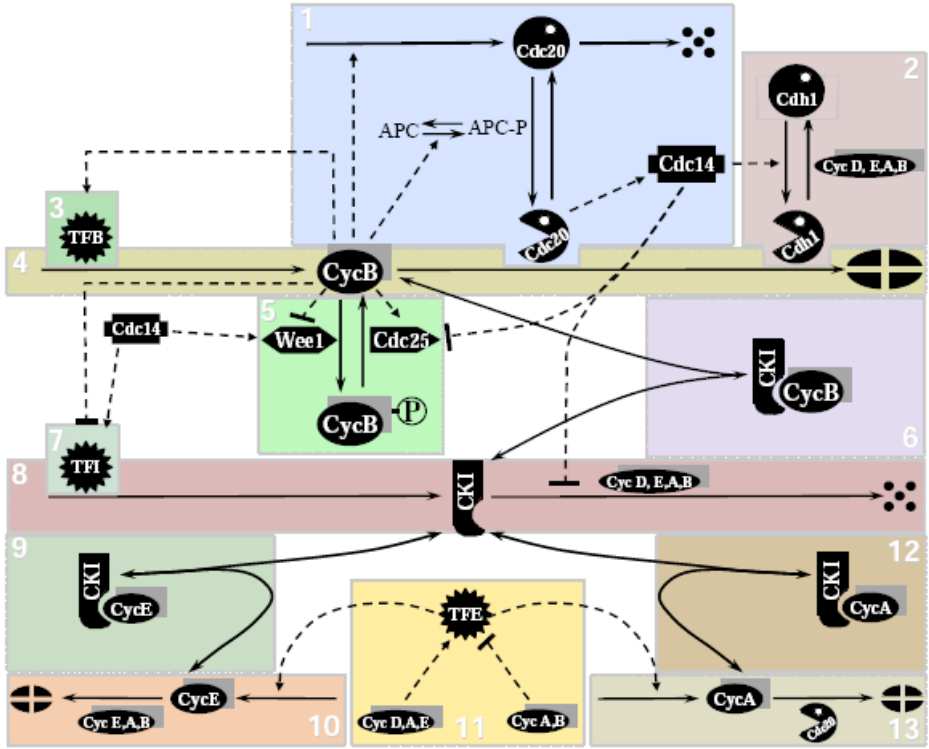
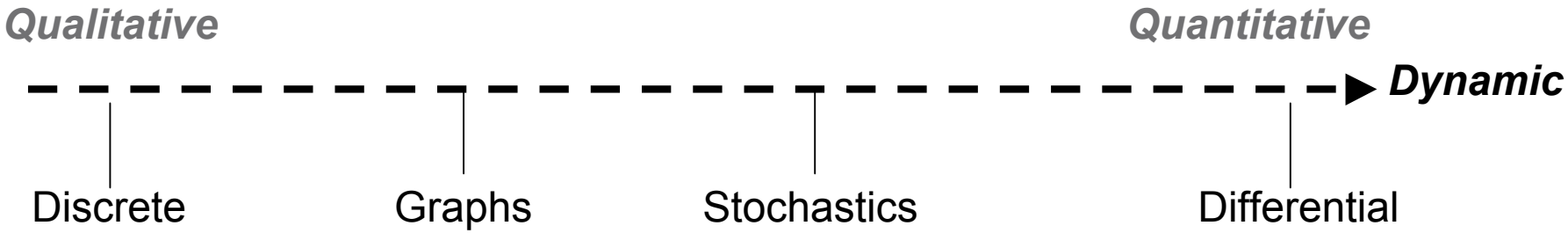
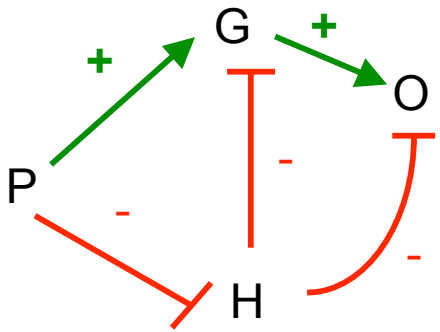
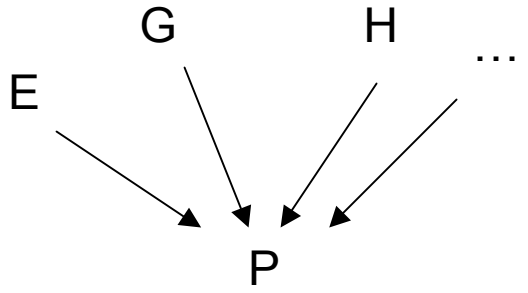


Network Modeling methods







$dP/dt = K_e v(E) + K_g v(G) + \ldots$

Modeling the Cell Cycle

OPEN ACCESS Freely available online

PLoS one

Boolean Network Model Predicts Cell Cycle Sequence of Fission Yeast

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doi:10.1093/bioinformatics/btl210

Dynamical analysis of a generic Boolean model for the control of the mammalian cell cycle

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Regulatory Graph of Cell Cycle

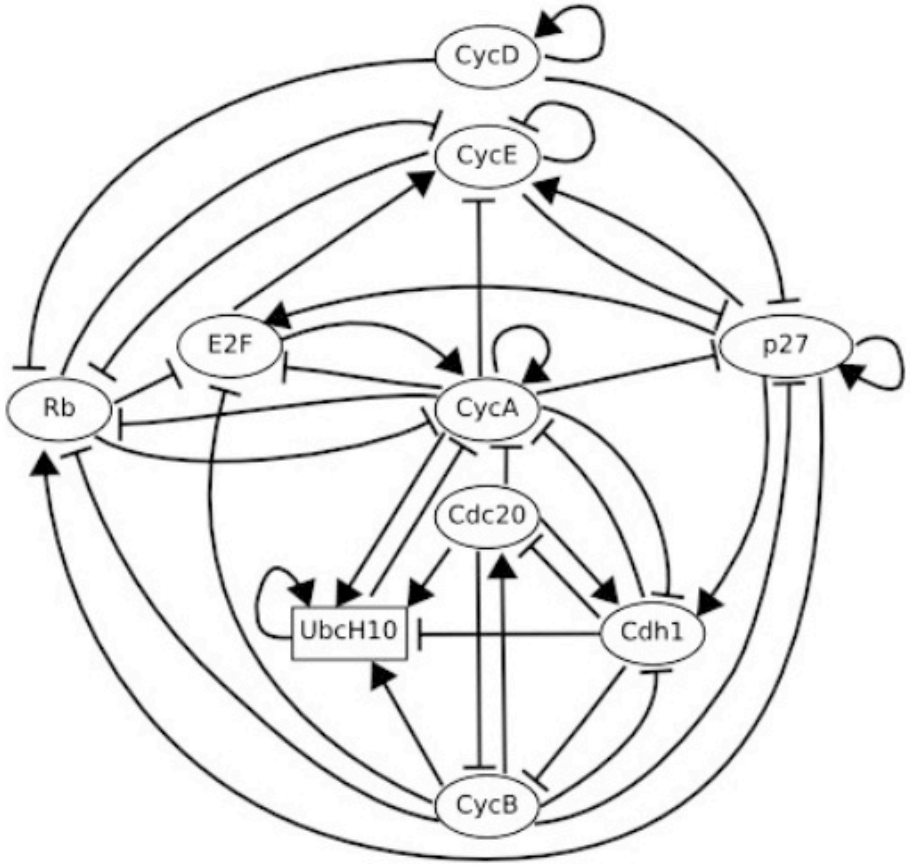


Fig. 1. Logical regulatory graph for the mammalian cell cycle network. Each node represents the activity of a key regulatory element, whereas the edges represent cross-regulations. Blunt arrows stand for inhibitory effects, normal arrows for activations.

Fauré et al. (2006) Bioinformatics

Logical States

Regulatory graph $G = \{g_1, \ldots . g_n\}$

Logical state vector $S = (s_1, \ldots, s_n) \quad s_i \in \{0, \ldots Max_i\}$

CycD	Rb	E2F	CycE	CycA	P27	Cdc20	Chd1	UbcH10	CycB
1	0	1	1	0	0	0	1	0	0

Temporal evolution in the cell cycle

Table 2. Temporal evolution of protein states in the cell cycle network.

Time Step	Start	SK	Cdc2/Cdc13	Ste9	Rum1	Slp1	Cdc2/Cdc13*	Wee1 Mik1	Cdc25	PP	Phase	comments
1	1	0	0	1	1	0	0	1	0	0	START	Cdc2/Cdc13 dimers are inhibited, antagonists are active.
2	0	1	0	1	1	0	0	1	0	0	G1	SK are becoming active
3	0	0	0	0	0	0	0	1	0	0	G1/S	When Cdc2/Cdc13 and SK dimers switch off Rum1 and Ste9/APC, the cell passes 'Start' and DNA replication takes place, Cdc2/Cdc13 starts to accumulate
4	0	0	1	0	0	0	0	1	0	0	G2	Activity of Cdc2/Cdc13 achieves moderate level, which is enough for entering G2 phase but not mitosis, since Wee1/Mik1 inhibits the activity of residue Tyr-15 of Cdc2 (Cdc2/Cdc13* is not active)
5	0	0	1	0	0	0	0	0	1	0	G2	Moderate activity Cdc2/Cdc13 activates Cdc25
6	0	0	1	0	0	0	1	0	1	0	G2/M	Cdc25 reverses phosphorylation, removing the inhibiting phosphate group and activating Cdc2/Cdc13*
7	0	0	1	0	0	1	1	0	1	0	G2/M	Cdc2/Cdc13* reaches high activity level sufficient to activate Slp1/APC mitosis
8	0	0	0	0	0	1	0	0	1	1	M	Slp1 degradates Cdc13, that is inhibits complex Cdc2/Cdc13 and Cdc2/Cdc13*.
9	0	0	0	1	1	0	0	1	0	1	M	Antagonists of Cdc2/Cdc13 are reset.
10	0	0	0	1	1	0	0	1	0	0	G1	Cell reaches G1 stationary state (PP is inactive)

Davidich et al. (2006) Plos One

Synchronous versus Asynchronous

Synchronous = parallel updating
Asynchronous = sequential updating

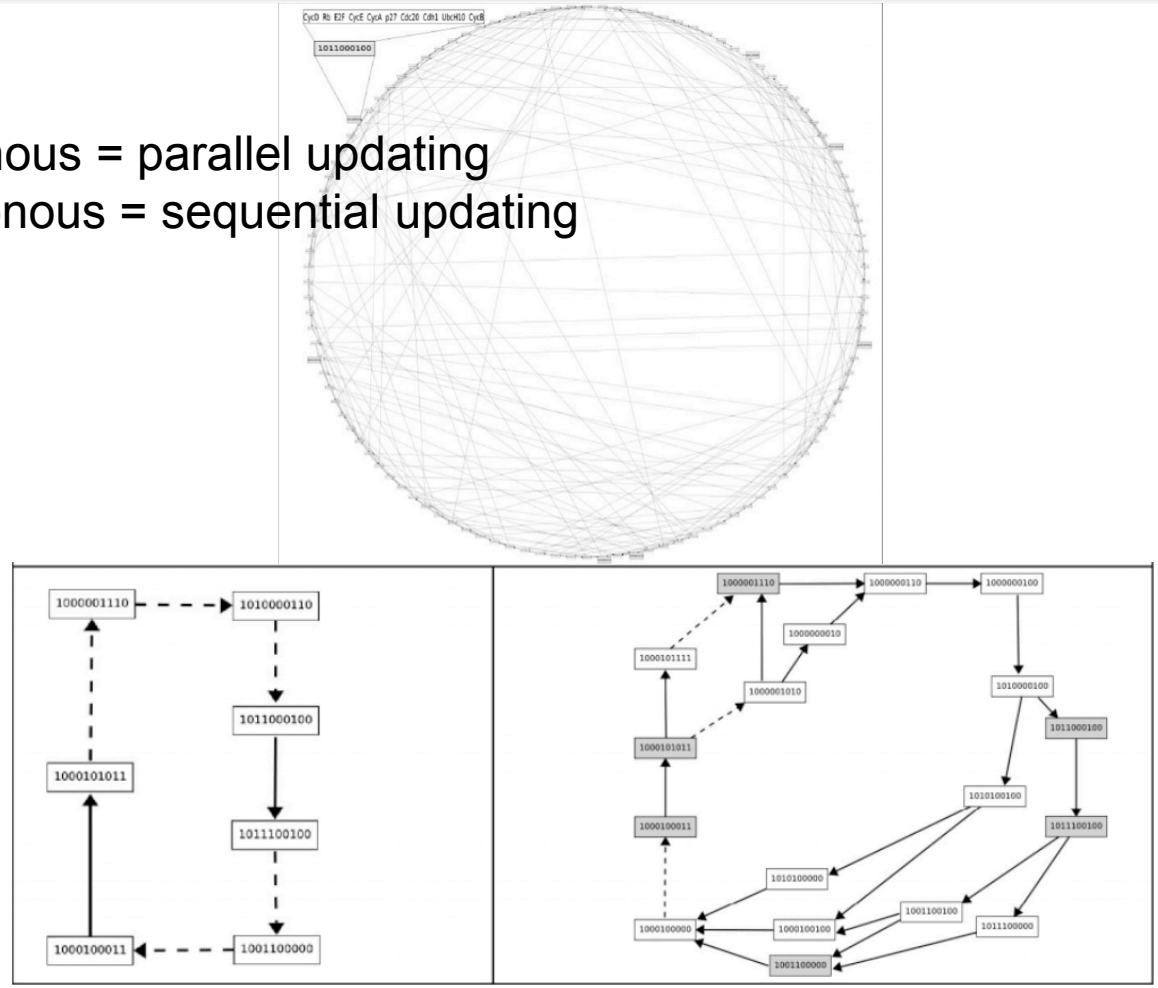


Fig. 2. Simulations of the wild-type cell cycle based on the Boolean model defined in Figure 1 and Table 1. Each vertex (node) represents one state, with the regulatory components ordered as mentioned in the top panel. The three state transition graphs correspond to the comprehensive asynchronous (top), the synchronous (bottom left), and a mixed (bottom right) assumptions. Note the difference of complexity between the asynchronous and synchronous graphs. In the bottom panels, solid arrows stand for single transitions, and dotted arrows for multiple transitions. The seven states involved in the synchronous cycle are grey-shaded in the asynchronous and mixed state transition graphs. For larger resolution pictures, see *GINsim* website.

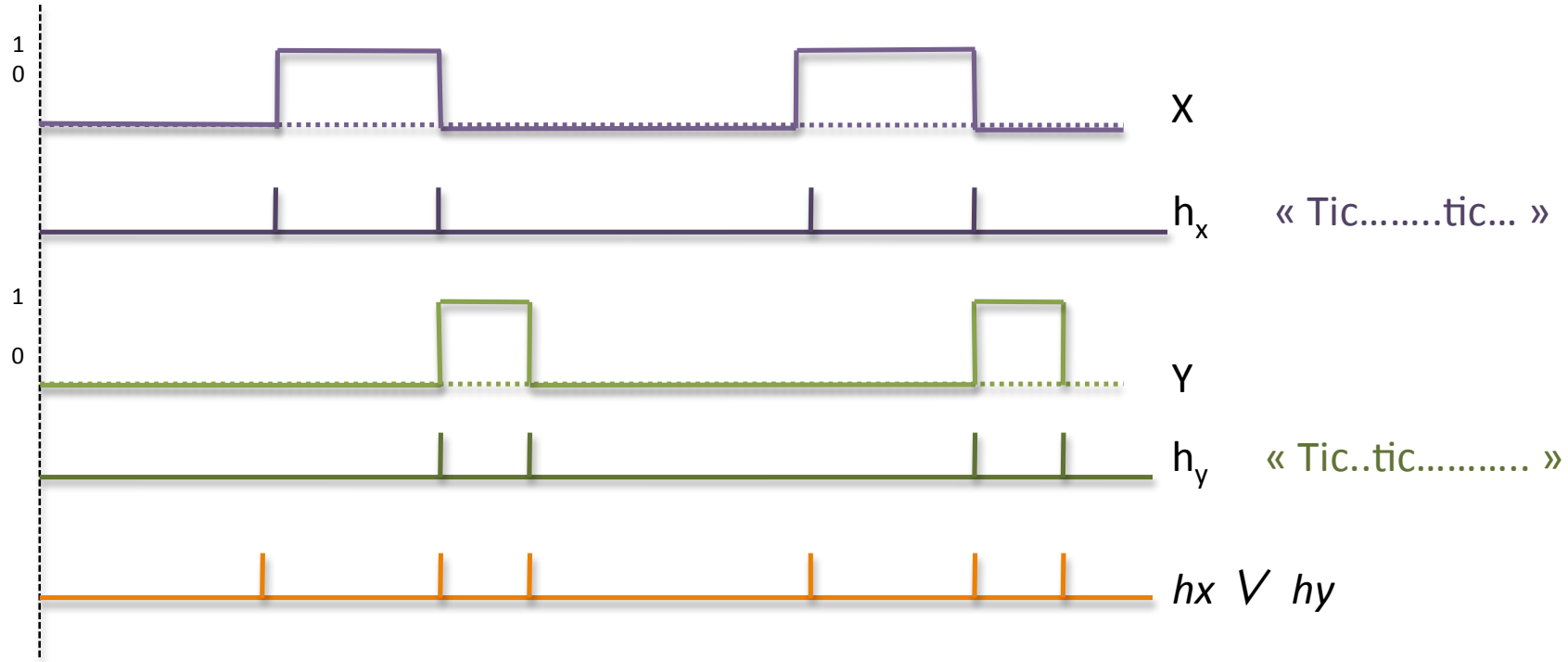
Fauré et al. (2006) Bioinformatics

Discrete dynamic modeling

- Signal updating in the model
  - Synchronous
  - Asynchronous
  - Interlacing
- Answer questions
  - Is molecule A always before molecule B?
  - Are C and E never active at the same time?
  - …

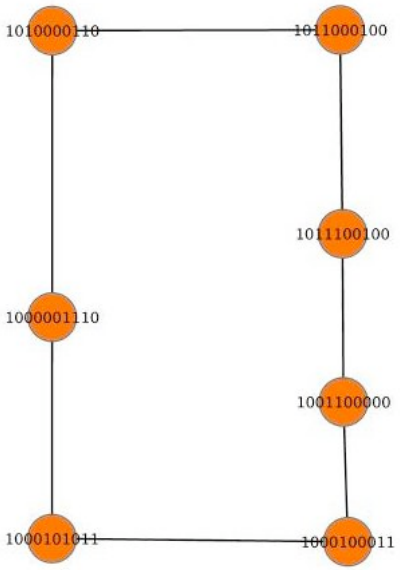
Discrete multi-clock modeling: a new formalism

- Time in the model
- State *X* is modified by a signal *with* a clock h_x

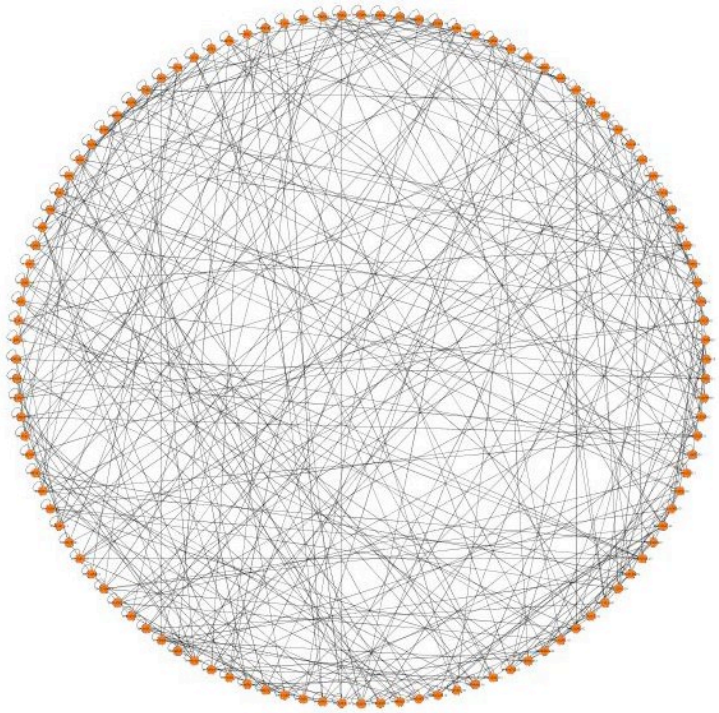


Discrete multi-clock modeling: first results

State: D, f(), D0
Clock: h_D
F()= A and B when h_D



synchronous

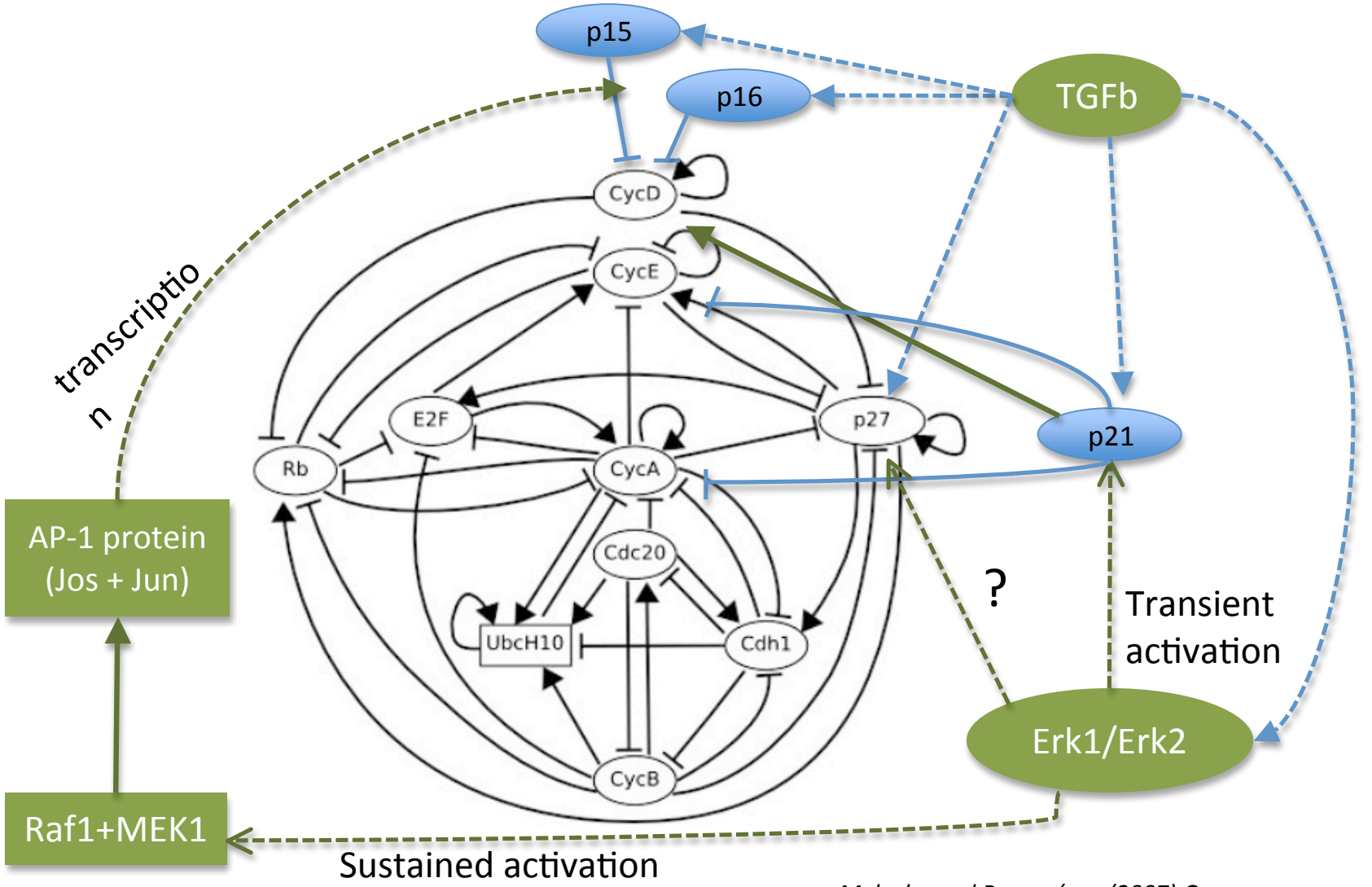


asynchrone

Future work

- Temporal constraints
- Methods and metrics
  - analysis
  - diagnostics
- Validation
  - *In silico*
  - *In vivo*
- Interface biologist/computational model
- Include signaling pathways

Plug-ins: Signaling Pathways



Meloche and Pouysségur (2007) Oncogene

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- O. Radulescu
- J. Nicolas

Kinase and cell cycle

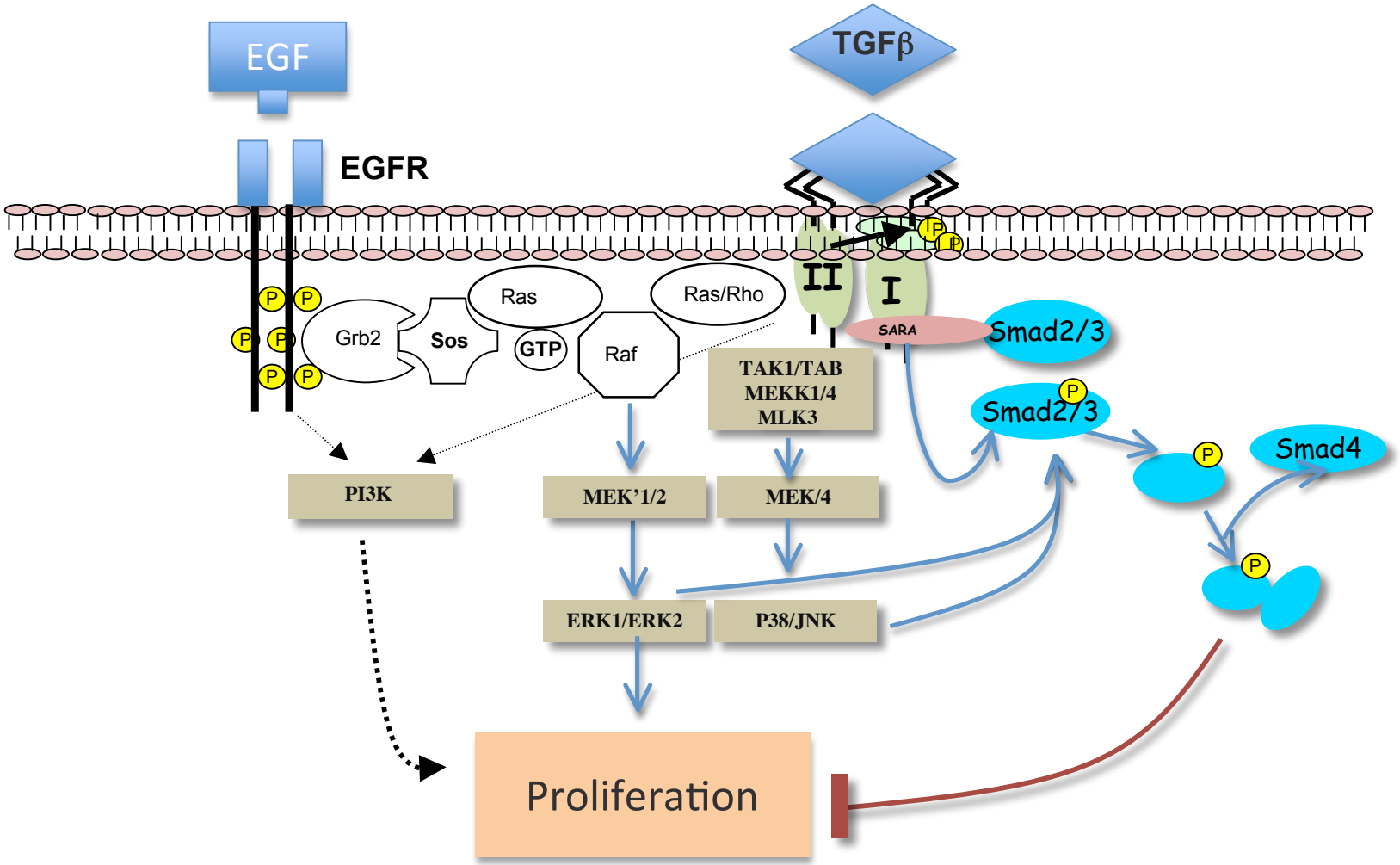
Table 1. Principles of cdk Inhibition

Inhibition of cdk4/6 leads to potent Rb-dependent G_1 arrest; however, compensation by cdk2 is possible
Inhibition of cdk4/6, cdk2, and cdk1 frequently results in arrest at the G_1-S and G_2-M boundaries
More selective inhibition of cdk2 and cdk1 leads to less potent G_1 arrest, S→G_2 effects, and E2F-1–dependent apoptosis
Recruitment to S phase by chemotherapy agents may sensitize cells to cdk inhibition; cdk inhibitor–mediated death may occur by E2F-1–dependent apoptosis, augmentation of DNA damage, or inhibition of DNA repair
Cdk1 inhibition may augment cell death after mitotic checkpoint activation by taxanes or KSP inhibitors
Highly selective cdk2 inhibition does not have antiproliferative effects in many cancer cell types
Inhibition of cdk9 preferentially depletes mRNAs with short half-lives (eg, Mcl-1, cyclin D1, c-myc, p53-induced $p21^{Waf1/Cip1}$, and hypoxia-induced VEGF)

Abbreviations: cdk, cyclin-dependent kinase; Rb, retinoblastoma protein; KSP, hsEg5 or kinesin-5; VEGF, vascular endothelial growth factor.

Shapiro G. (2006) Journal of Clinical Oncology

EGF and TGF-β


EGF
TGFβ
EGFR
II
I
SARA
Smad2/3
Smad2/3
Smad4
Grb2
Sos
Ras
Ras/Rho
GTP
Raf
TAK1/TAB
MEKK1/4
MLK3
PI3K
MEK'1/2
MEK/4
ERK1/ERK2
P38/JNK
Proliferation

The role of signaling pathways in controling cell cycle