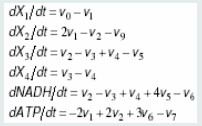

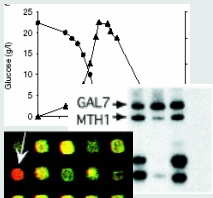

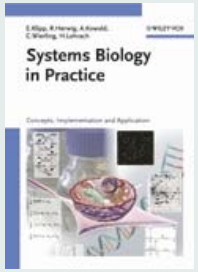

Kinetic Modeling Group

Berlin Center for Genome Based Bioinformatics

GEFÖRDERT VOM
Bundesministerium für Bildung und Forschung

ICSB 2006, Yokohama, Oct 9-13, 2006

Dynamic Modeling of Stress Response of Yeast Cells - Timing of Events

Edda Klipp
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Ihnestr. 73, 14195 Berlin, Germany
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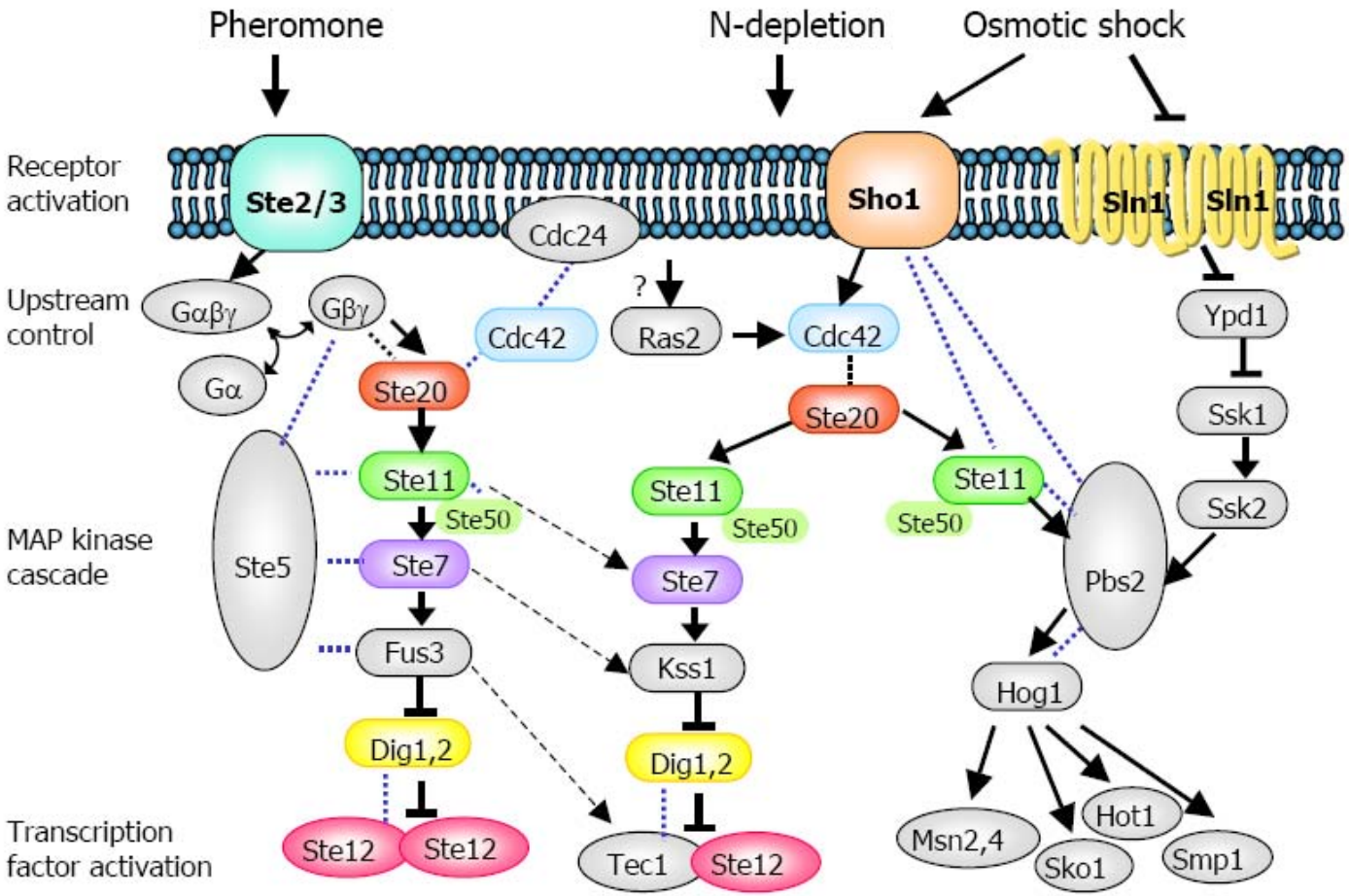
Timing of Stress Response

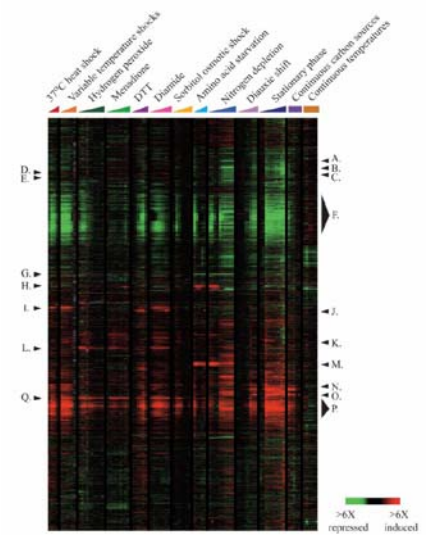
- **Response to Osmotic Stress**
- **Crosstalk of Pheromone Pathway and Filamentous Growth Pathway**
- **Cell Cycle and its Regulation by Signaling Pathways**

Signaling Pathways in Baker's Yeast



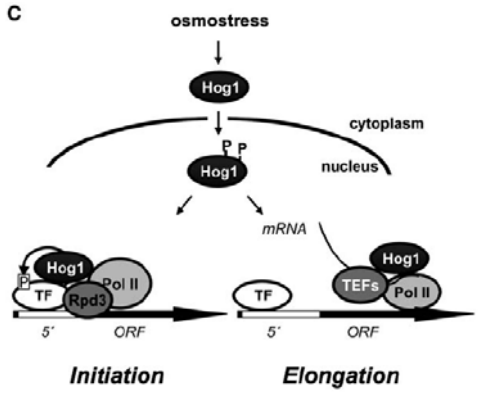
Experiments w.r.t. Stress Response

Stress response on transcriptional level



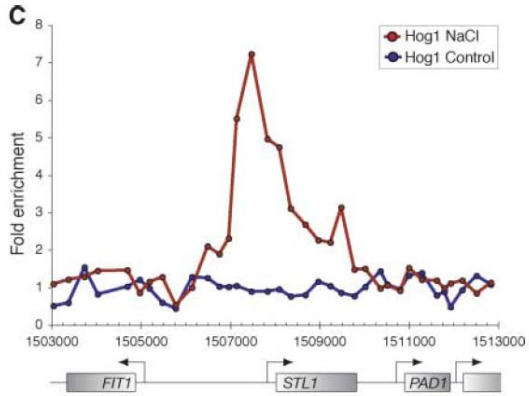
Gasch et al., 2000, Mol Cell Biol

Stress-activated Hog1 – a selective transcription elongation factor for genes responding to osmotic stress



Proft et al., 2006, Molecular Cell

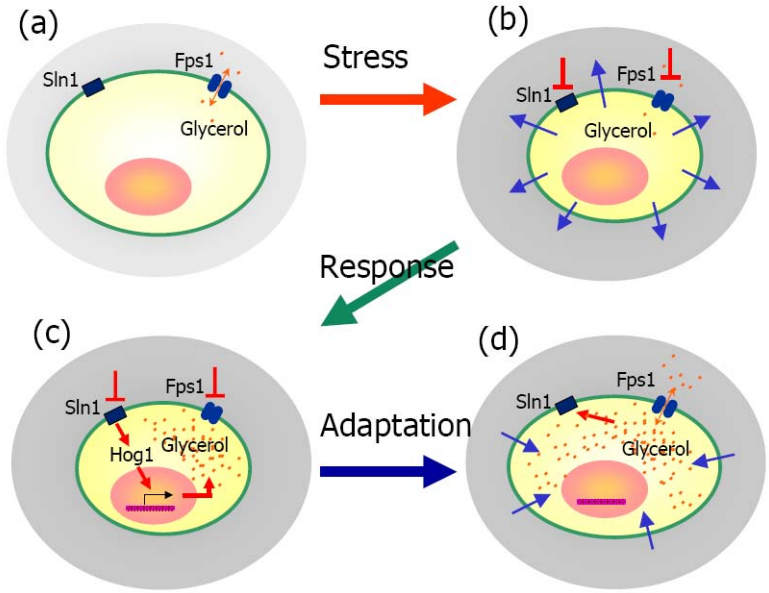
Activated Signal Transduction Kinases Frequently Occupy Target Genes



Pokholok,.., Young, 2006, Science

Yeast: Response to Osmotic Stress

- Active regulation of cellular volume
- Accumulation of glycerol as osmolyte
- Closure of the aquaglyceroporin Fps1 (a glycerol channel)
- „Genome remodeling“ – global change of expression pattern
- Regulation of cell cycle progression



Modeling Pipeline

Construct network from literature data and experts‘ knowledge

Study properties of small modules, e.g. MAPK cascade, G protein cycles, …

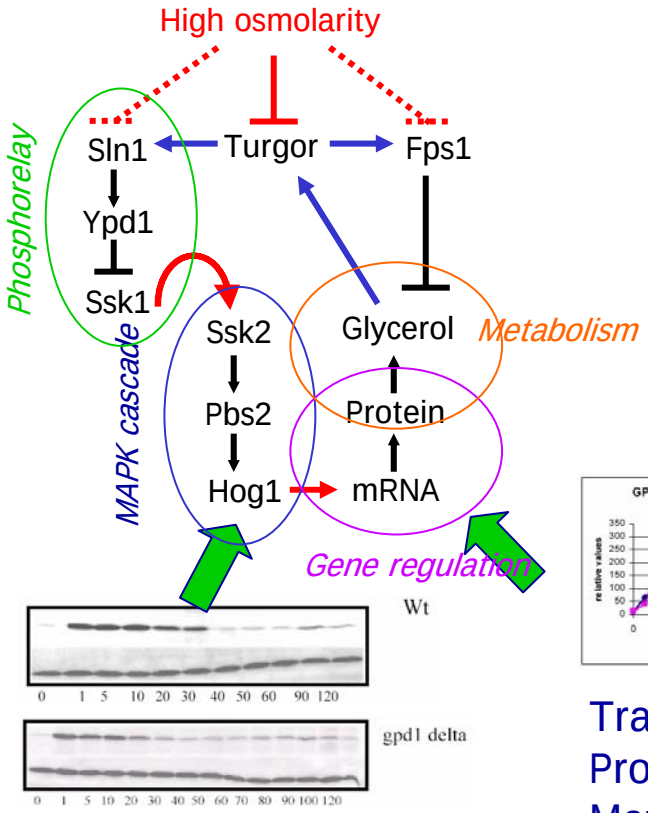
Collect experimental data (time series!!!)

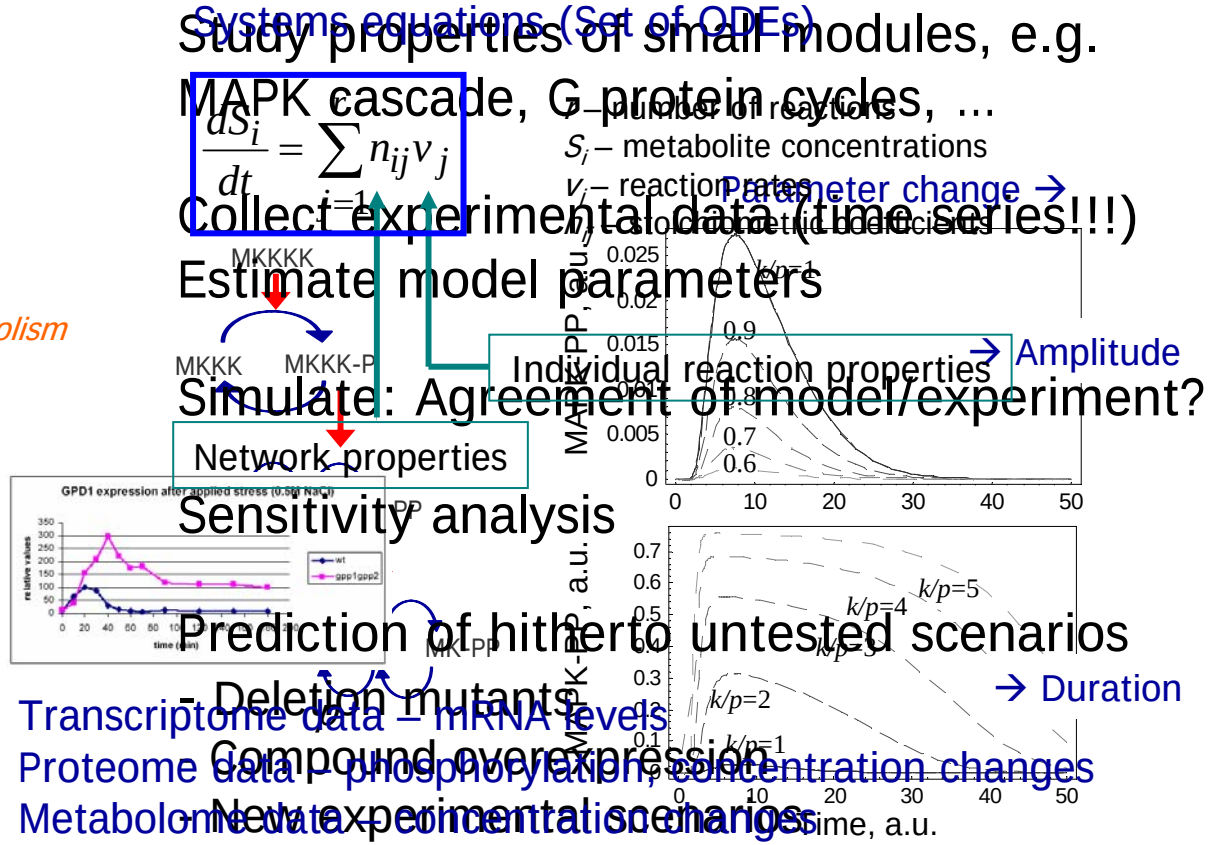
Estimate model parameters

Simulate: Agreement of model/experiment?

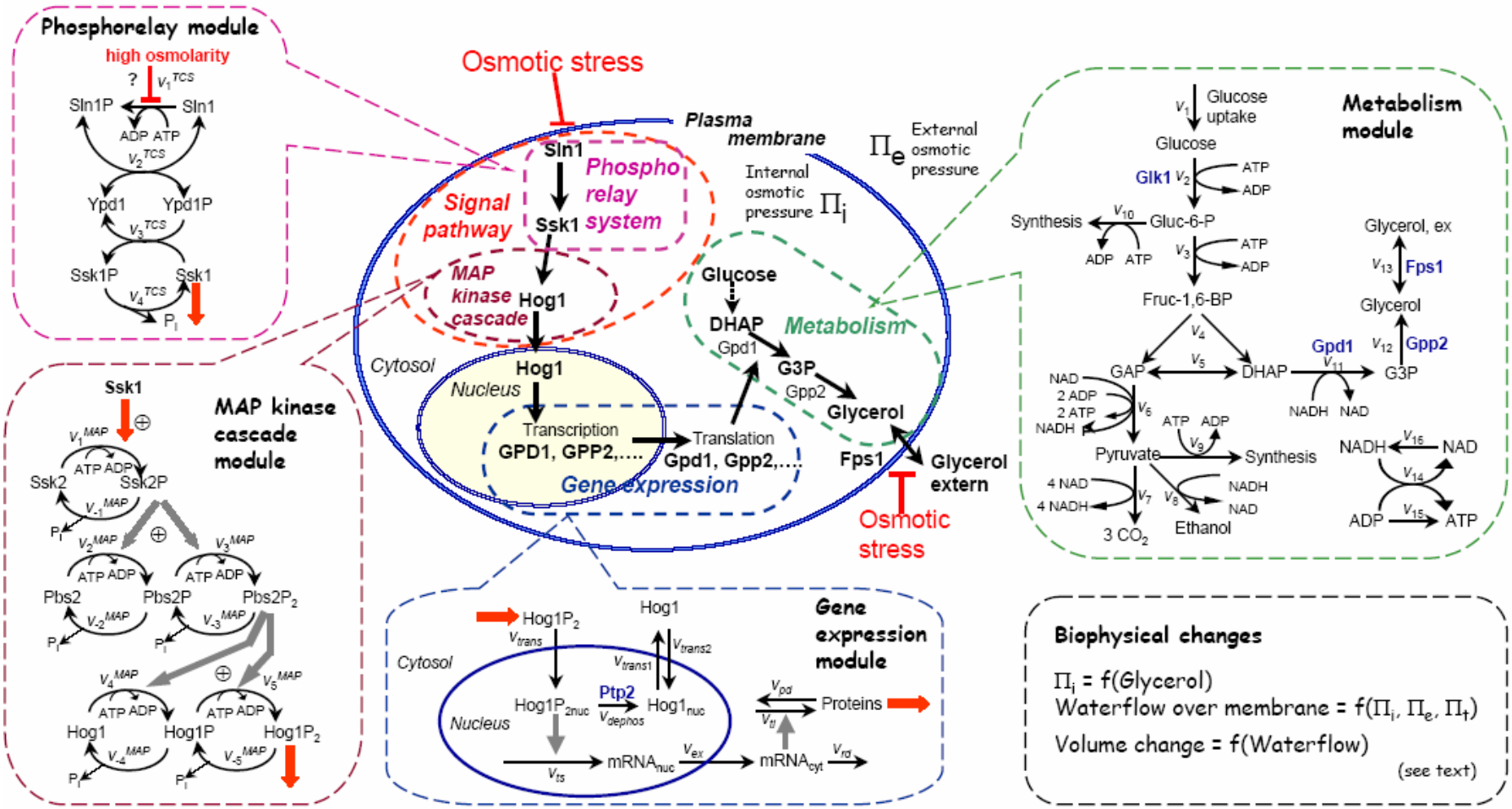
Sensitivity analysis

Prediction of hitherto untested scenarios
- Deletion mutants
- Compound overexpression
- New experimental scenarios





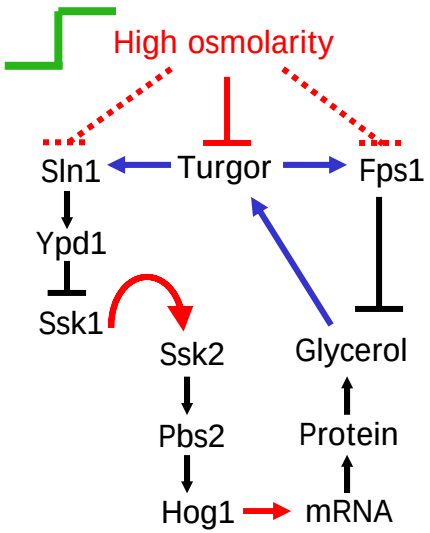
Osmostress Response – Full Model

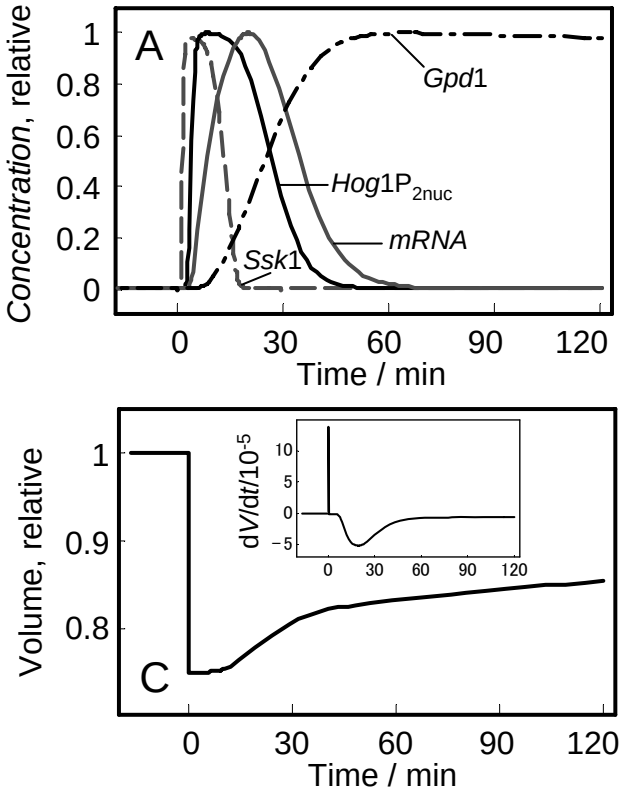


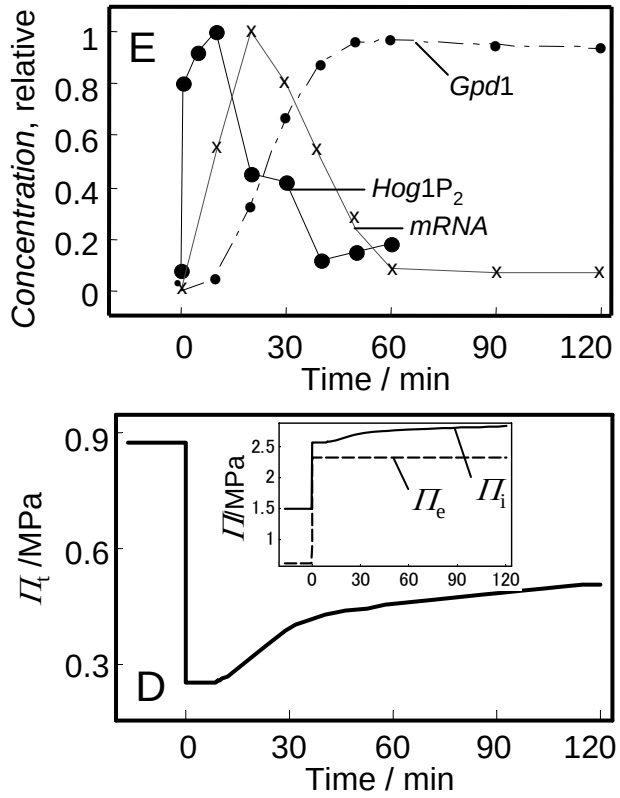
Klipp, Nordlander, Krüger, Gennemark & Hohmann, *Nature Biotechn*, 2005

The Standard Experiment

Wild Type Cells, shock with 0.5 M NaCl

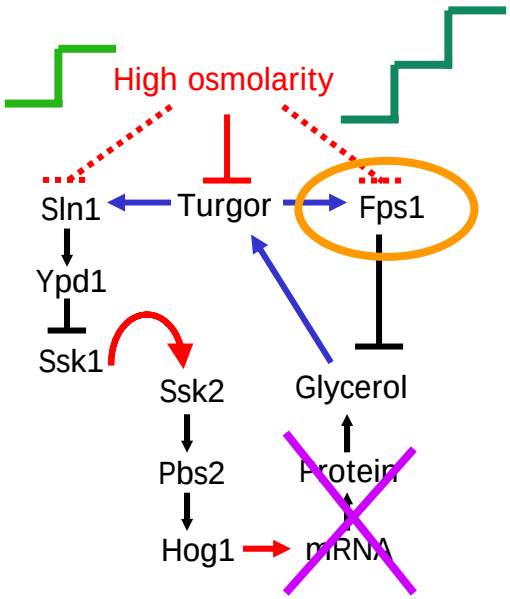






Klipp et al.,*Nature Biotechn*, 2005

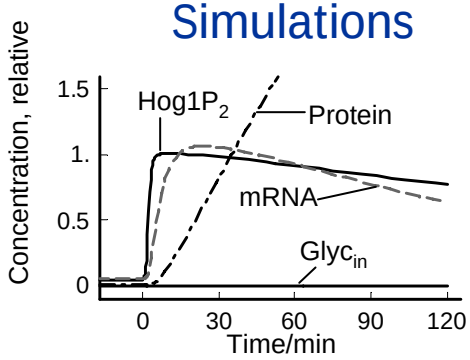
Osmotic stress model: Test cases

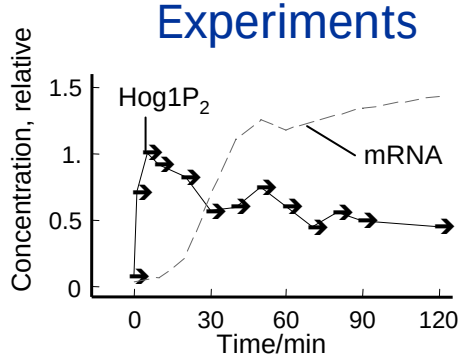


Simulations

Experiments

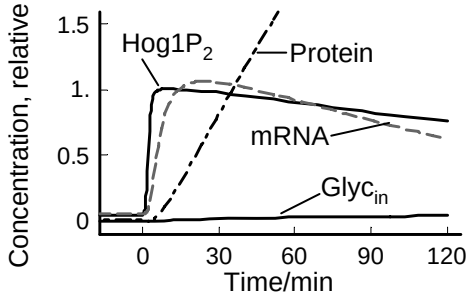
gpd1Δ gpd2Δ mutant

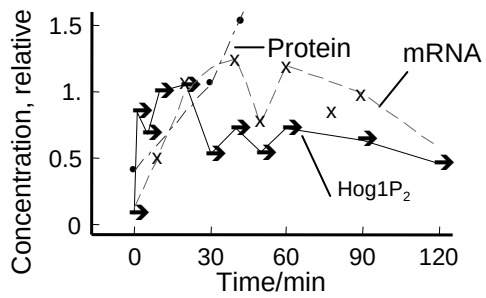




No enzyme production – no glycerol production – no pathway downregulation

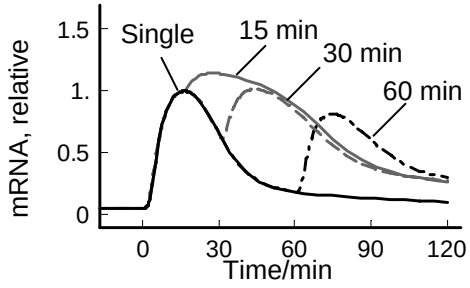
Fps1 open, constitutively

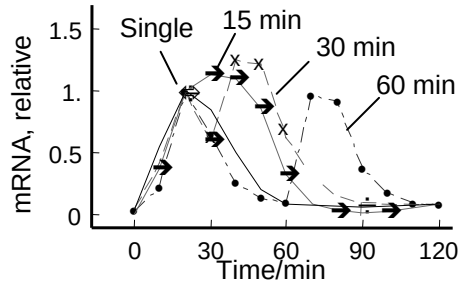




Open Fps1 – reduced glycerol accumulation – reduced pathway downregulation

Repeated osmostress

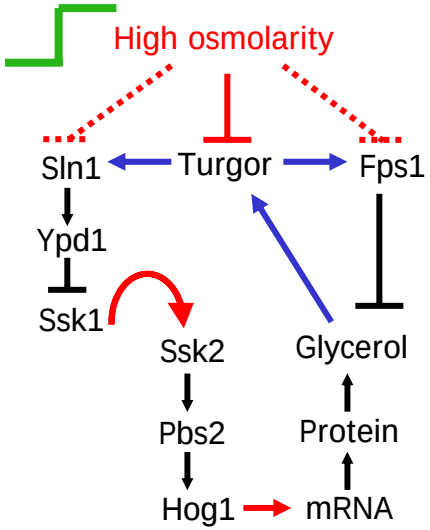




Cells are competent to respond to a second shock.

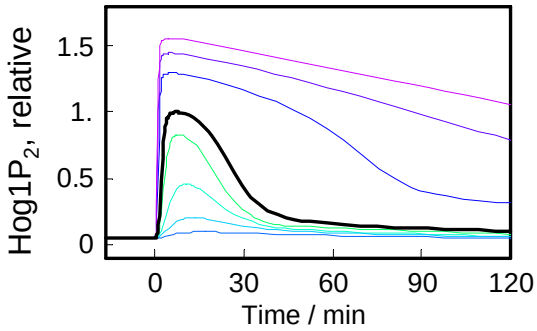
Klipp et al.,*Nature Biotechn*, 2005

Osmotic stress: Different stress levels

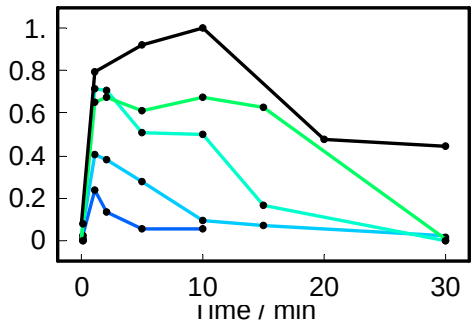


Different activation strengths

Simulations



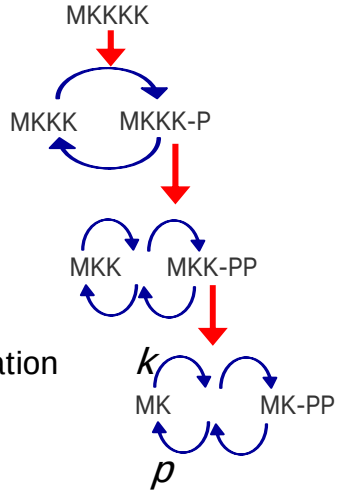
Experiments



NaCl / M 0.1 0.2 0.3 0.4 0.5 0.8 1.0 1.4

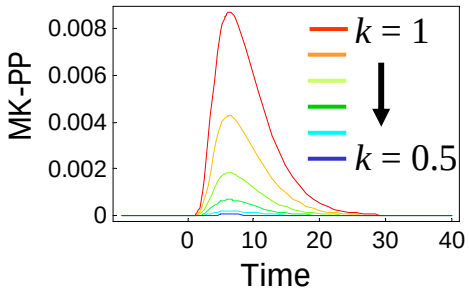
Low activation: increase of amplitude, stronger activation: increase of duration

MAP kinase cascade

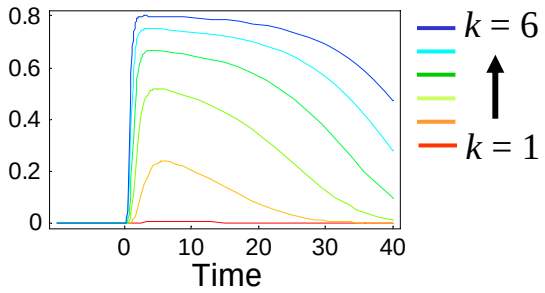


-Hierarchical regulation
-Mass conservation on each level

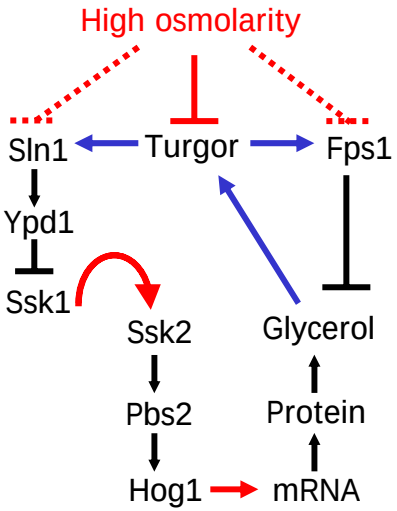
Low activation



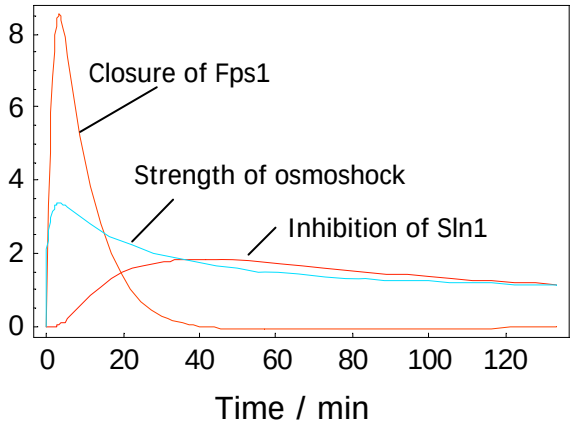
Strong activation

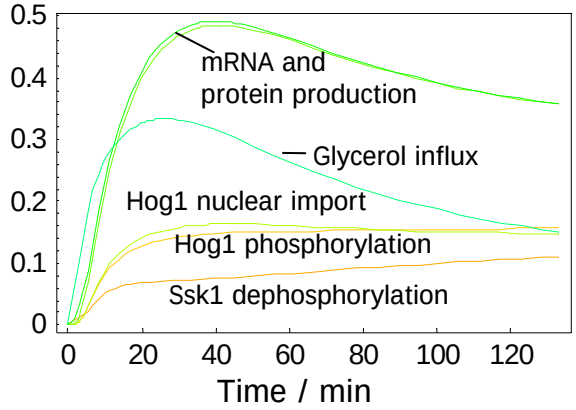


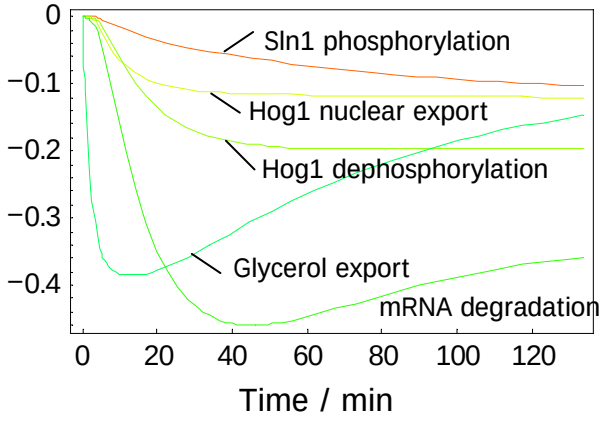
Osmotic stress response: What is the impact of specific components over time ?

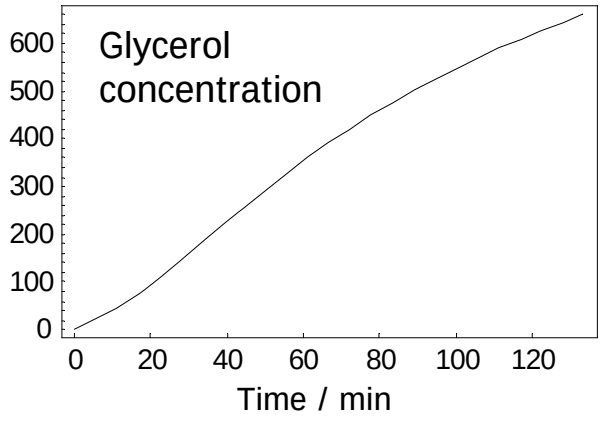


Time-dependent Response Coefficients Related to Glycerol Concentration







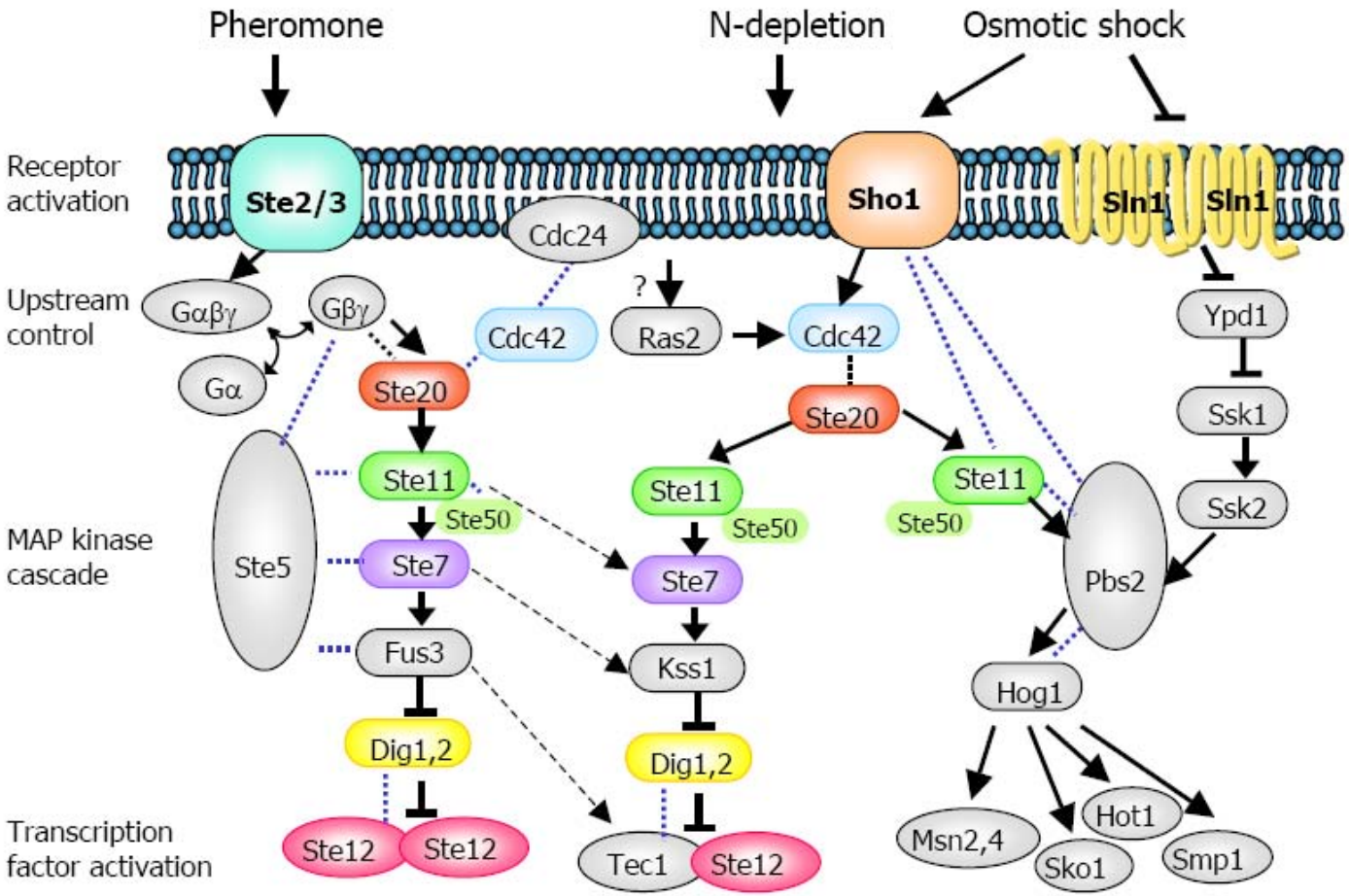


Response coefficients

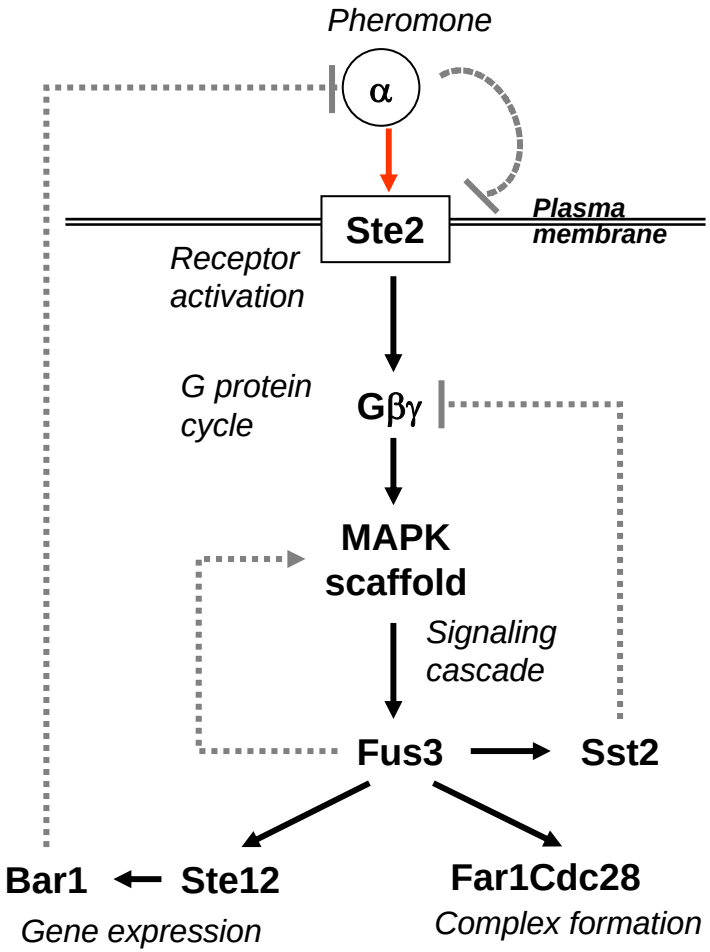
$$R_{p_l}^{S_i} = \frac{p_l}{S_i(t)} \frac{\partial S_i(t)}{\partial p_l}$$

Ingalls & Sauro, JTB, 2003

Signaling Pathways in Baker's Yeast

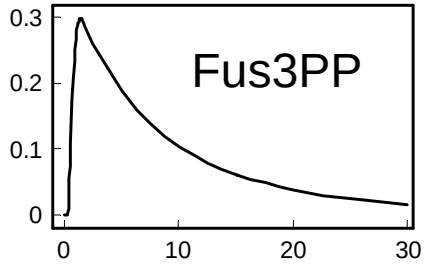


Pheromone Response

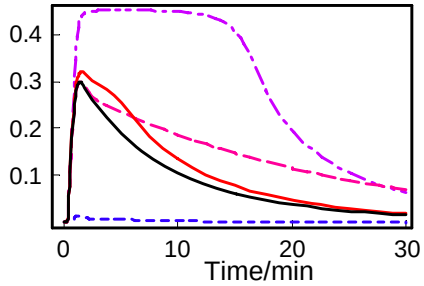


Kofahl & Klipp, Yeast, 2004

Simulation results:

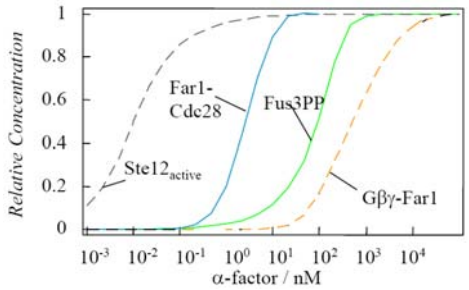


Wild type



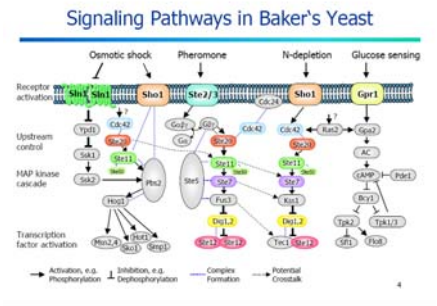
Mutants

- No cleavage of α by Bar1
- No activation of Sst2 by Fus3
- Ste5 reduced binding Ste7
- No receptor degradation

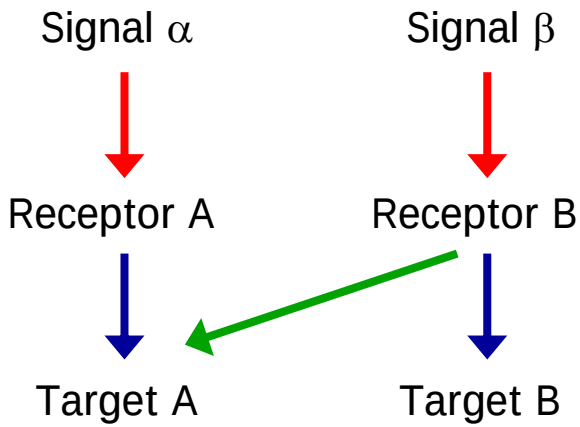


Graded response to dosage of α factor

→ *Transcription*
→ *Cell cycle*
→ *Mating projection*



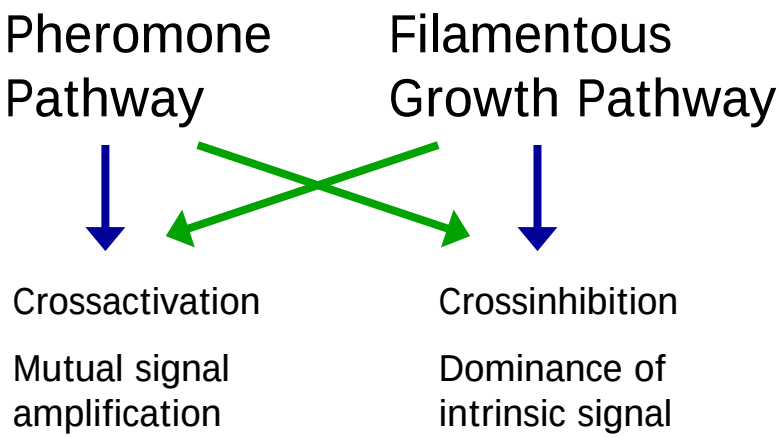
Integration assessment



Measures of crosstalk

$$C = \frac{X(B)}{X(A)} \qquad S_i = \frac{X(A)}{X(A,B)} \qquad S_e = \frac{X(B)}{X(A,B)}$$

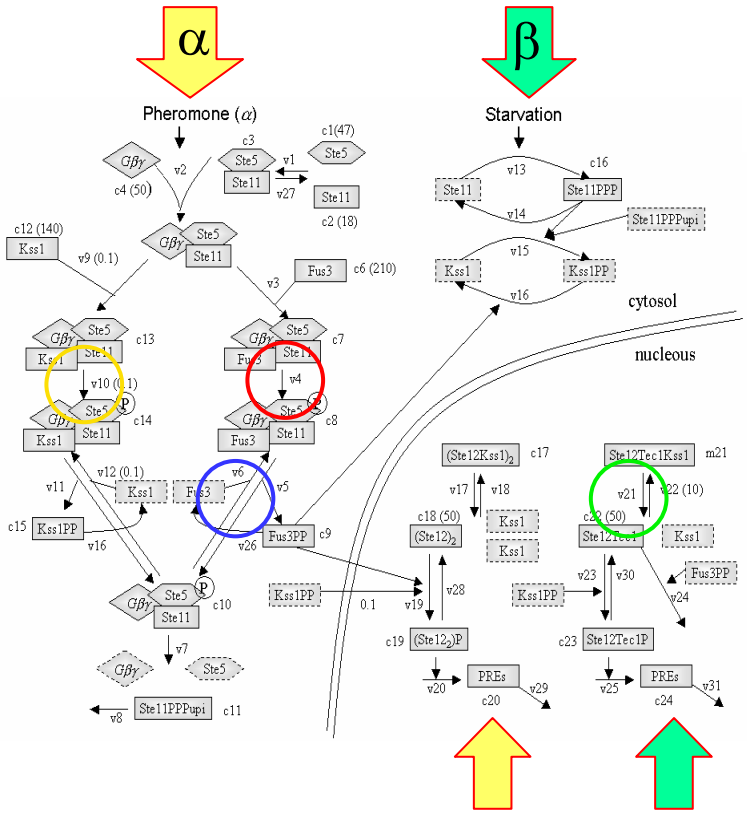
X – function of amplitude, timing or integral of response



	$S_e > 1$	$S_e < 1$
$S_i > 1$	Mutual signal inhibition	Dominance of intrinsic signal
$S_i < 1$	Dominance of extrinsic signal	Mutual signal amplification

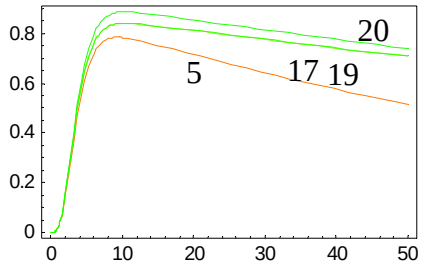
Schaber, Kofahl, Kowald & Klipp, 2006, FEBS J.

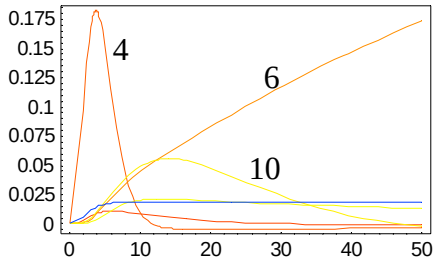
Integration of Signaling Pathways

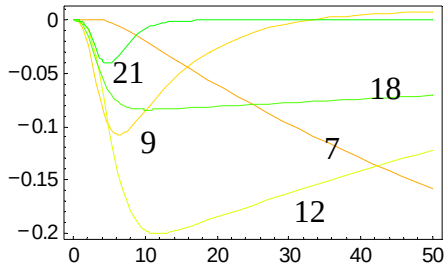


Response coefficients of

PREs

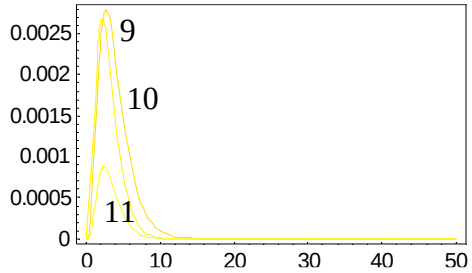


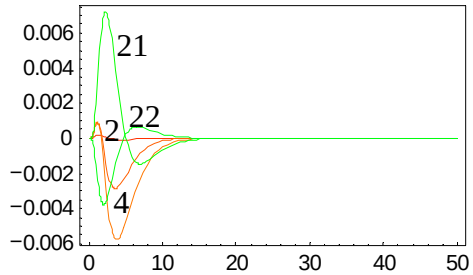


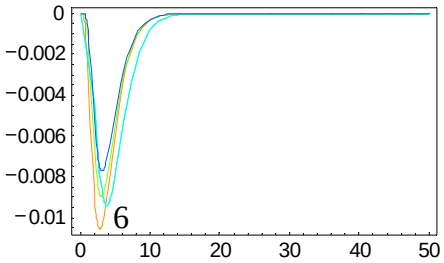


Time/min

FREs



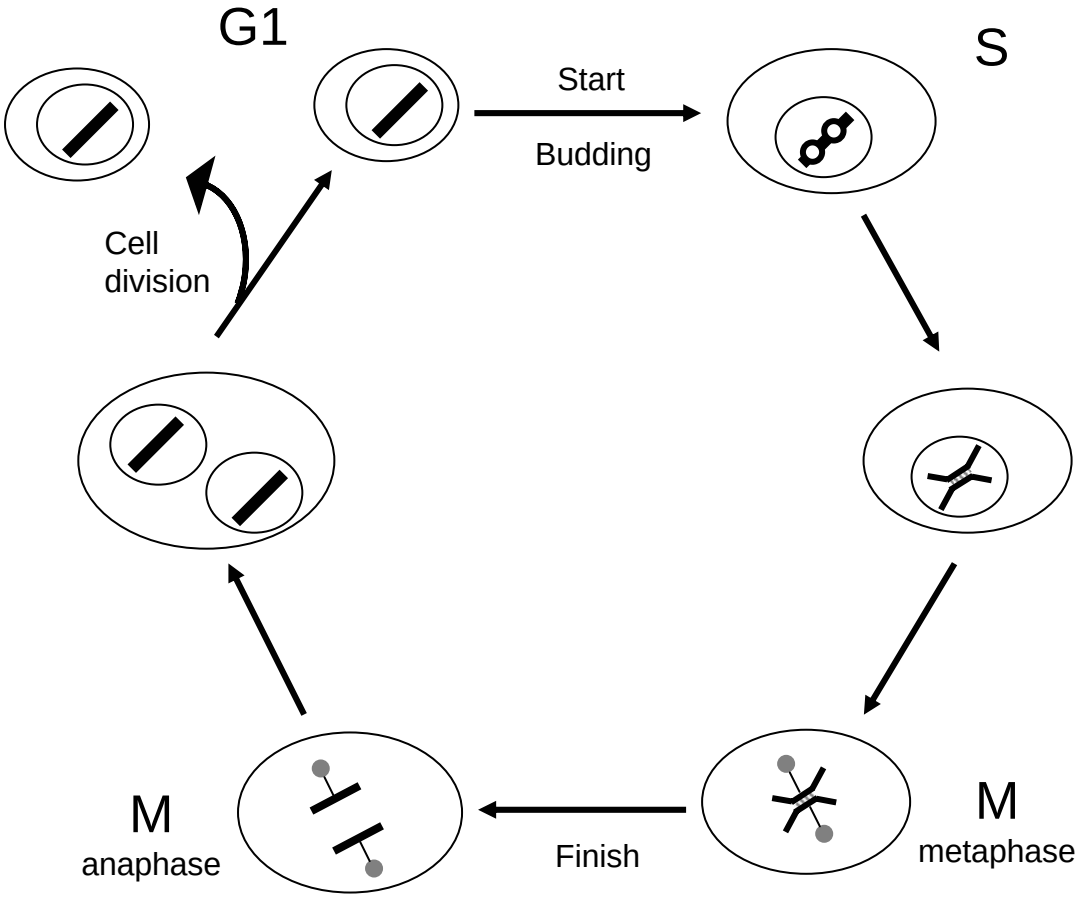




Time/min

4 -Fus3 phosphorylation in MAPKcascade
6 -repeated Fus3 phosphorylation
10-Kss1 phosphorylation in MAPKcascade
21-Kss1 release from Ste12Tec1 complex

Yeast Cell Cycle



Cyclins *active*
Cln1-3, Clb5,6

Cyclin Dependent Kinases (CDK)
Cdk1 (Cdc28)

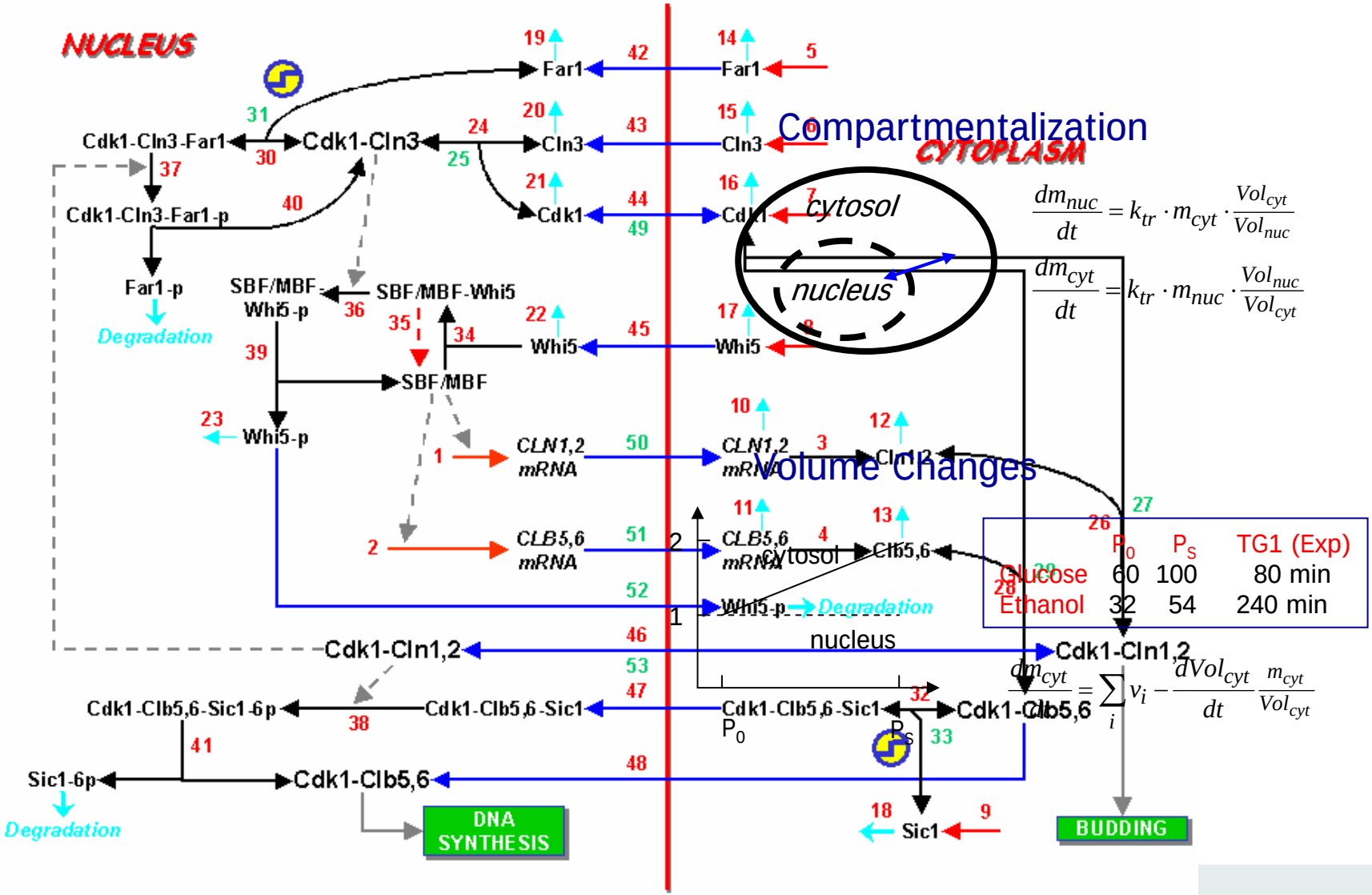
Cyclin Dependent Kinase Inhibitors (CKI)
Far1, Sic1 *inactive*

Transcriptional Activators
SBF (Swi4-Swi6)
MBF (Mbp1-Swi6)

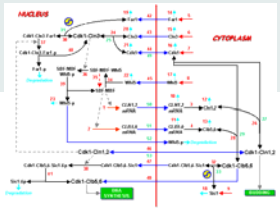
Transcriptional Repressor
Whi5

In collaboration with Alberghina lab, University Milano-Biccoca

Network controlling the G1 to S transition

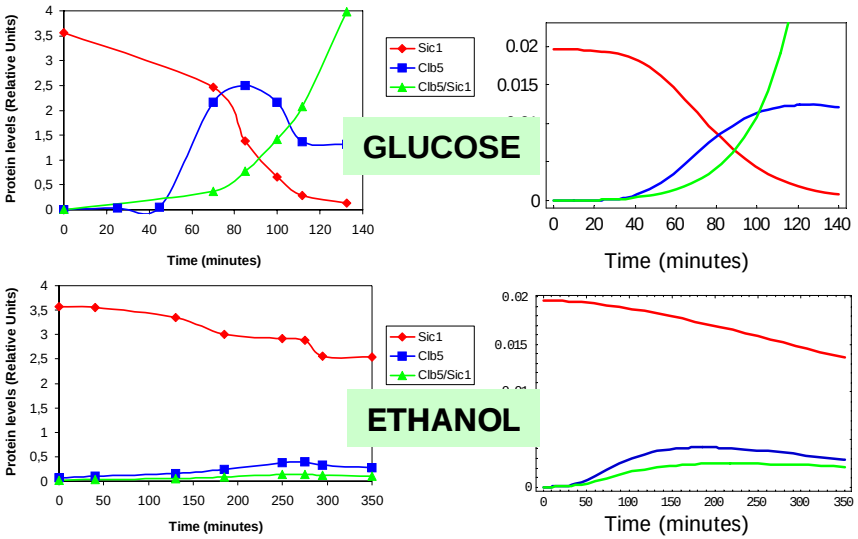


	P_0	P_S	TG1 (Exp)
Glucose	60	100	80 min
Ethanol	32	54	240 min



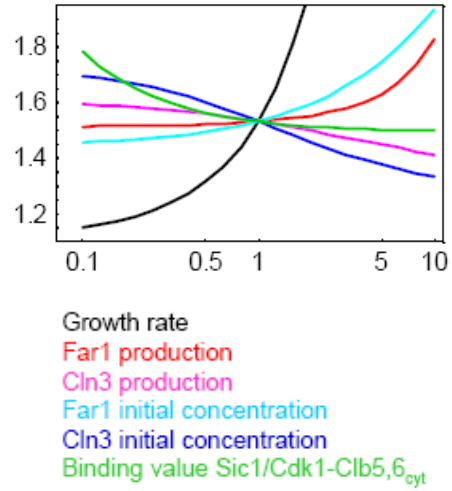
G1 to S transition: Model results

Reproduction of experiments

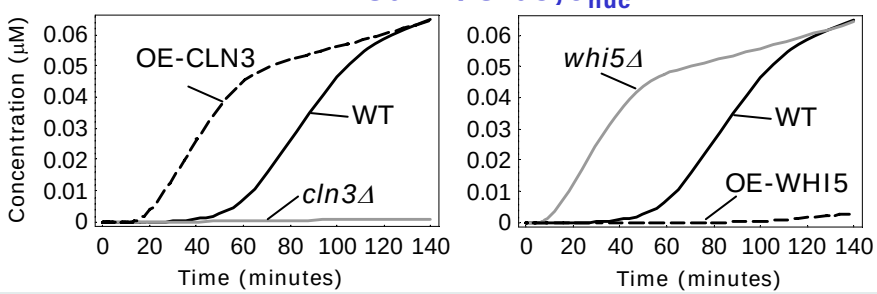


Explanation of critical cell size

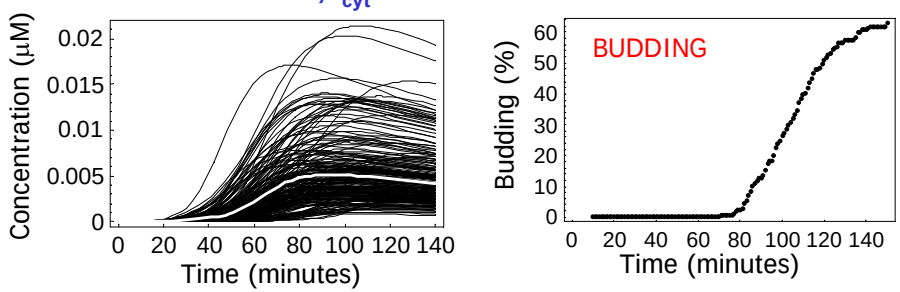
Relevant genotype	Estimated Ps
WT GLUCOSE	1.54
cln3Δ	–
GAL-CLN3	1.26
far1Δ	1.44
GAL-FAR1	–
whi5Δ	1.20
GAL-WHI5	3.31
sic1Δ	6.57
GAL-SIC1	1.50
WT ETHANOL	1.20



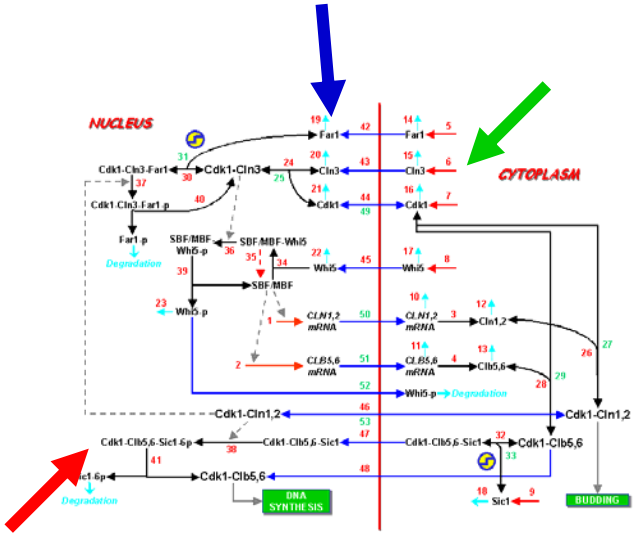
Prediction of mutant phenotypes

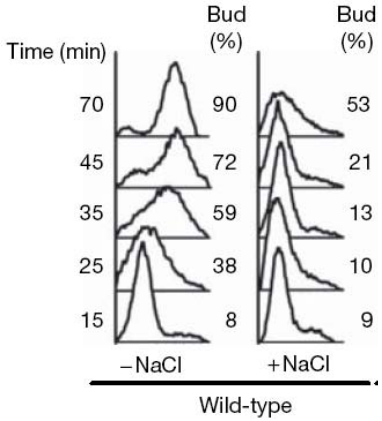


Population effects

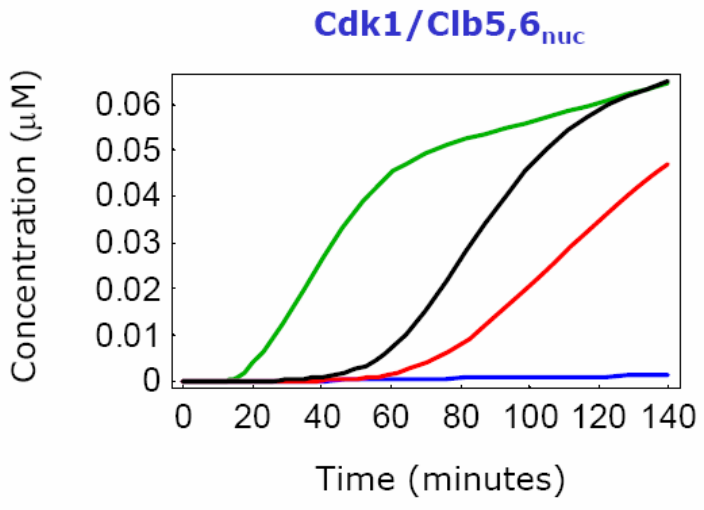


Interplay with signaling pathways





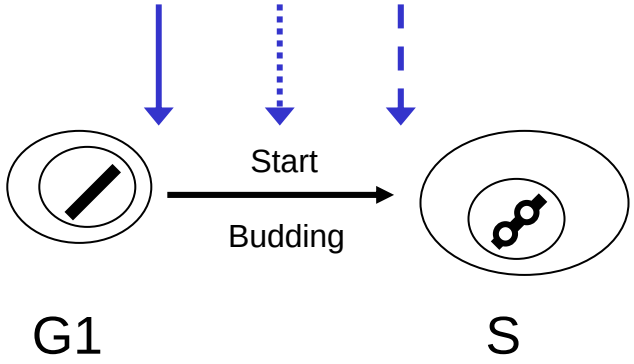
Escoté et al., Nature Cell Biol, 2004

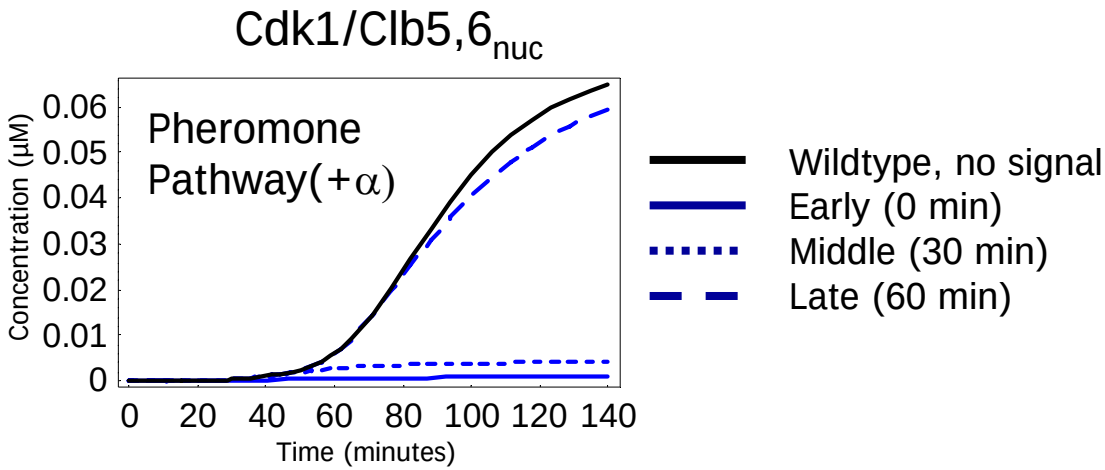


- Wildtype, no stress
- Pheromone pathway
- cAMP/PKA pathway
- HOG pathway/osmotic stress

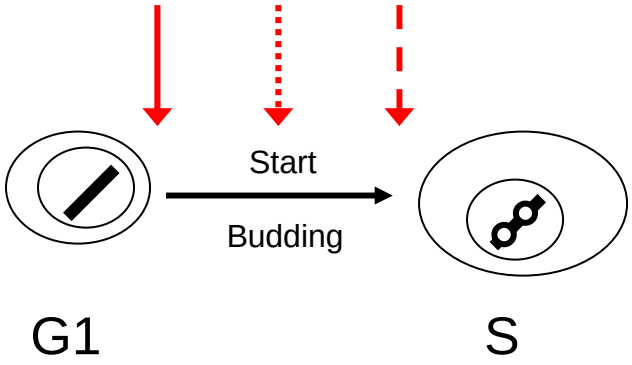
→ Delay or put forward G1/S transition

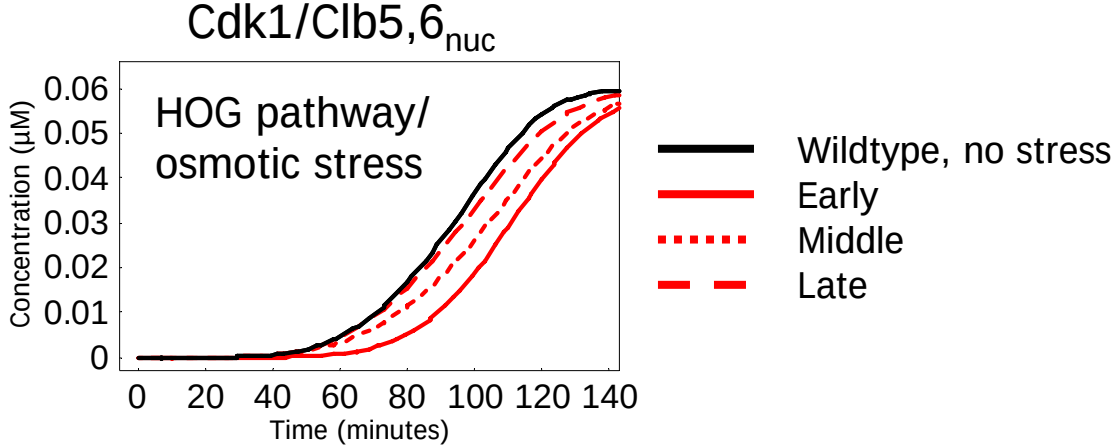
Timing of Signal Activation Determines Effect on Cell Cycle Progression

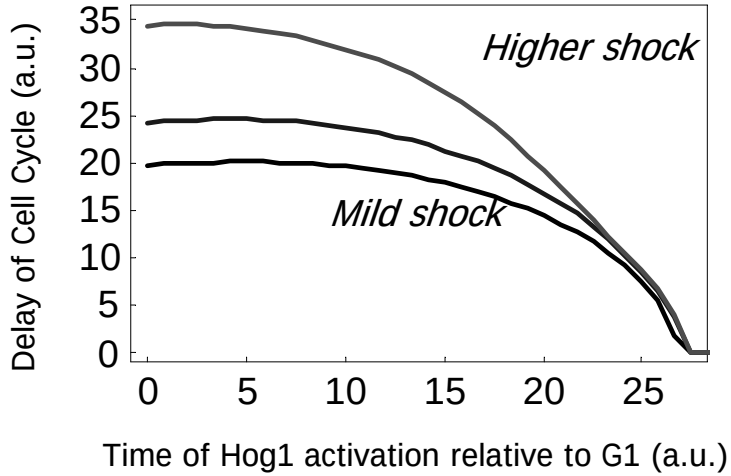




Timing of Signal Activation Determines Effect on Cell Cycle Progression







In collaboration with
Francesc Posas, Barcelona

Tool Development

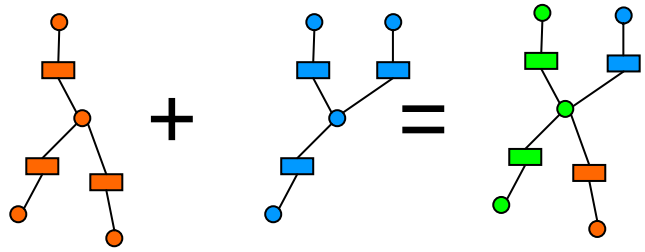
SBMLmerge Tool for model integration based on SBML representation

SBMLannotate → compounds and reactions

SBMLcheck → for consistency and SBML compatibility

SBMLmerge → merges valid models

SBML2dot → graphical output



http://sysbio.molgen.mpg.de/sbmlmerge/

Schulz, Uhlendorf, Liebermeister & Klipp, 2006, Genome Informatics

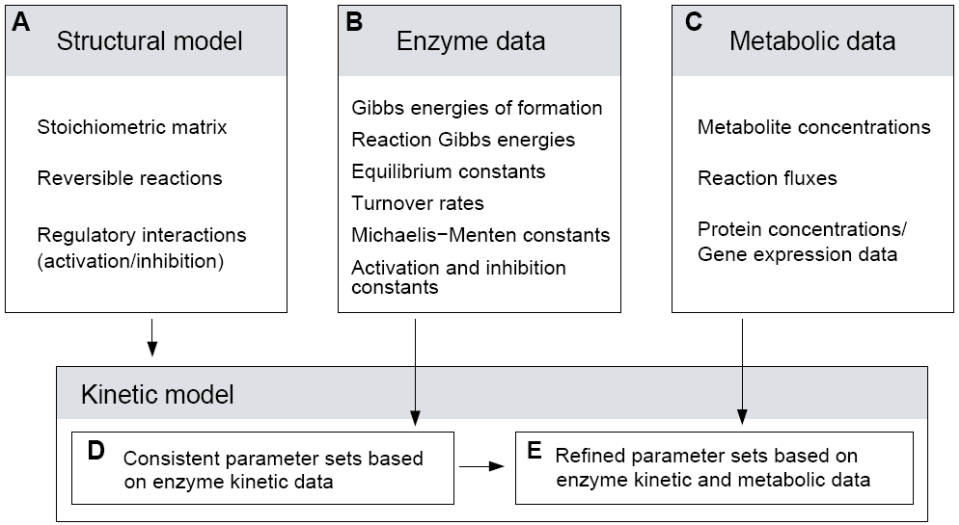
SBML-PET Tool for parameter estimation based on SBML representation

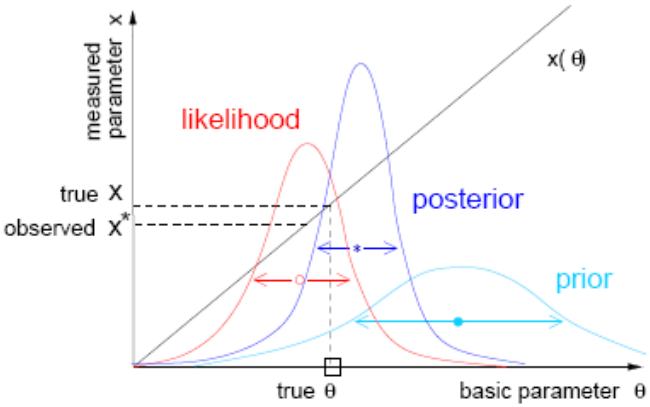
- SBML import and export
- Various types of data
- Various mathematical expressions
- Discontinuous state changes
- Supports Events

http://sysbio.molgen.mpg.de/SBML-PET/

Zi & Klipp, 2006, Bioinformatics

Data Integration





Assignment of Kinetics

Reaction network
+ thermodynamic info
+ kinetic info from DB
+ Convenience kinetics

Bayesian ⇩ *estimation*

1. Parameter distribution

+ metabolomic data
+ genomic data

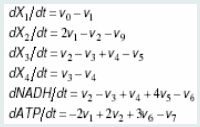
Bayesian ⇩ *estimation*

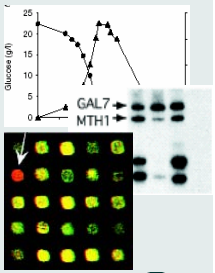
2. Parameter distribution

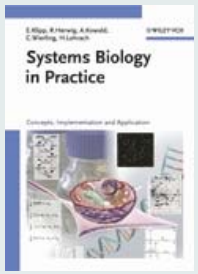
Liebermeister & Klipp, submitted

Conclusions

- Mathematical models of cellular processes allow for a testable representation of experimental knowledge.
- Models allow integration of diverse data and information.
- Modeling reveals regulatory properties of cellular network.
- The temporal organization of cellular events is critical to understand stress response – besides network structure and parameter values.







Kinetic Modeling Group

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U Pompeu Fabra Barcelona

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→ QUASI

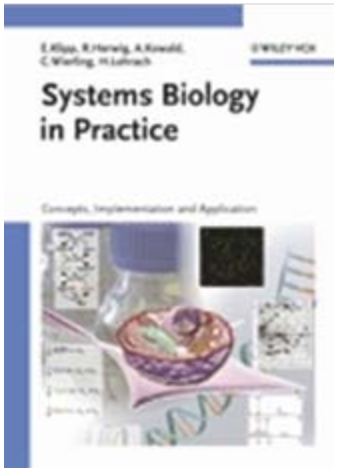
→ EMI-CD

→ Marie Curie Actions
Human Resources and Mobility Activity

Early Stage Training
Systems Biology

→ ENFIN

→ The Yeast Systems Biology Network YSBN

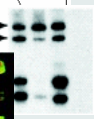


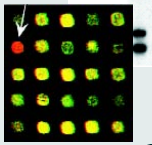
Textbook on Systems Biology

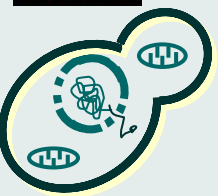
By Klipp E, Herwig R, Kowald A, Wierling C, Lehrach H

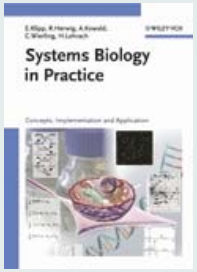
WILEY-VCH, 2005

$dX_1/dt = v_0 - v_1$
$dX_2/dt = 2v_1 - v_2 - v_9$
$dX_3/dt = v_2 - v_3 + v_4 - v_5$
$dX_4/dt = v_3 - v_4$
$dNADH/dt = v_2 - v_3 + v_4 + 4v_5 - v_6$
$dATP/dt = -2v_1 + 2v_2 + 3v_6 - v_7$









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http://www.molgen.mpg.de/~ag_klipp