Computational Methods in Systems and Synthetic Biology

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Overview of the Lectures

1. Formal molecules and reaction models in BIOCHAM
2. Kinetics
3. Qualitative properties formalized in temporal logic CTL
4. Quantitative properties formalized in LTL(R) and pLTL(R)
5. Reaction hypergraphs and influence graphs
   - Differential Influence Graph
   - Syntactical Influence Graph
   - Over-approximation and Equivalence theorems
   - Application to models of Cell Cycle control, MAPK signalling and P53/Mdm2
6. Hierarchy of semantics and typing for systems biology by abstract interpretation
7. ...

Related Publications

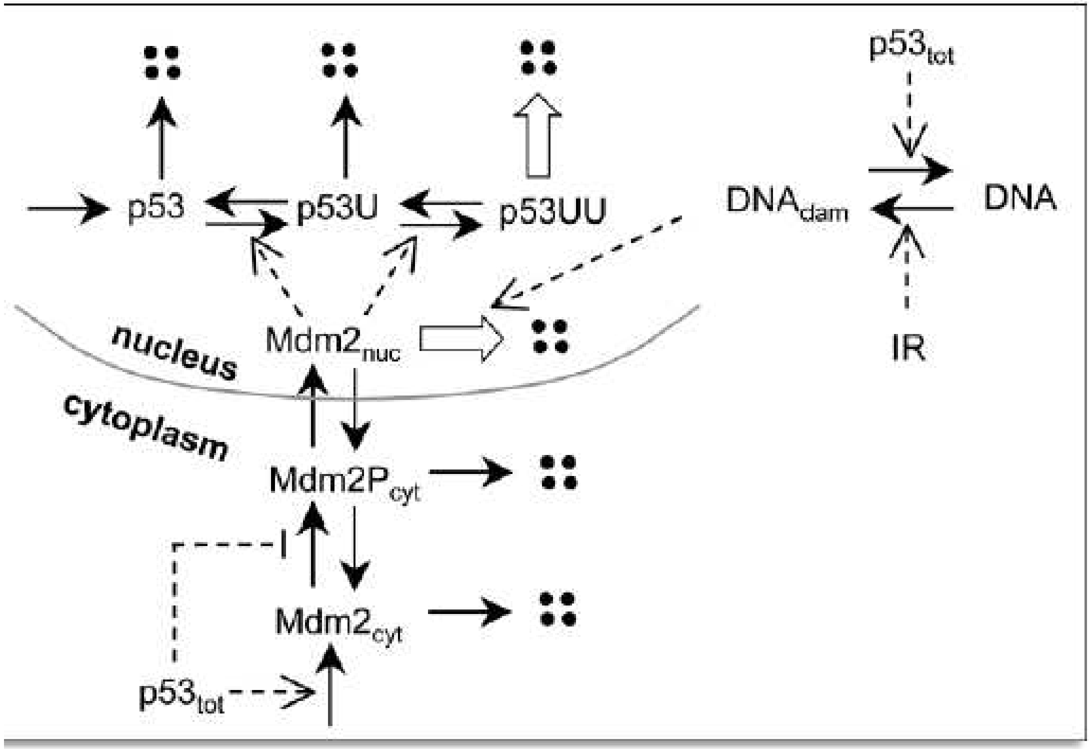
F. Fages and S. Soliman. From reaction models to influence graphs and back: a theorem *Formal Methods in Systems Biology*, Springer-Verlag, Lecture Notes in Bioinformatics, LNBI 5054. June 2008

F. Fages and S. Soliman. Abstract Interpretation and Types for Systems Biology. *Theoretical Computer Science* 403, pp.52-70, 2008

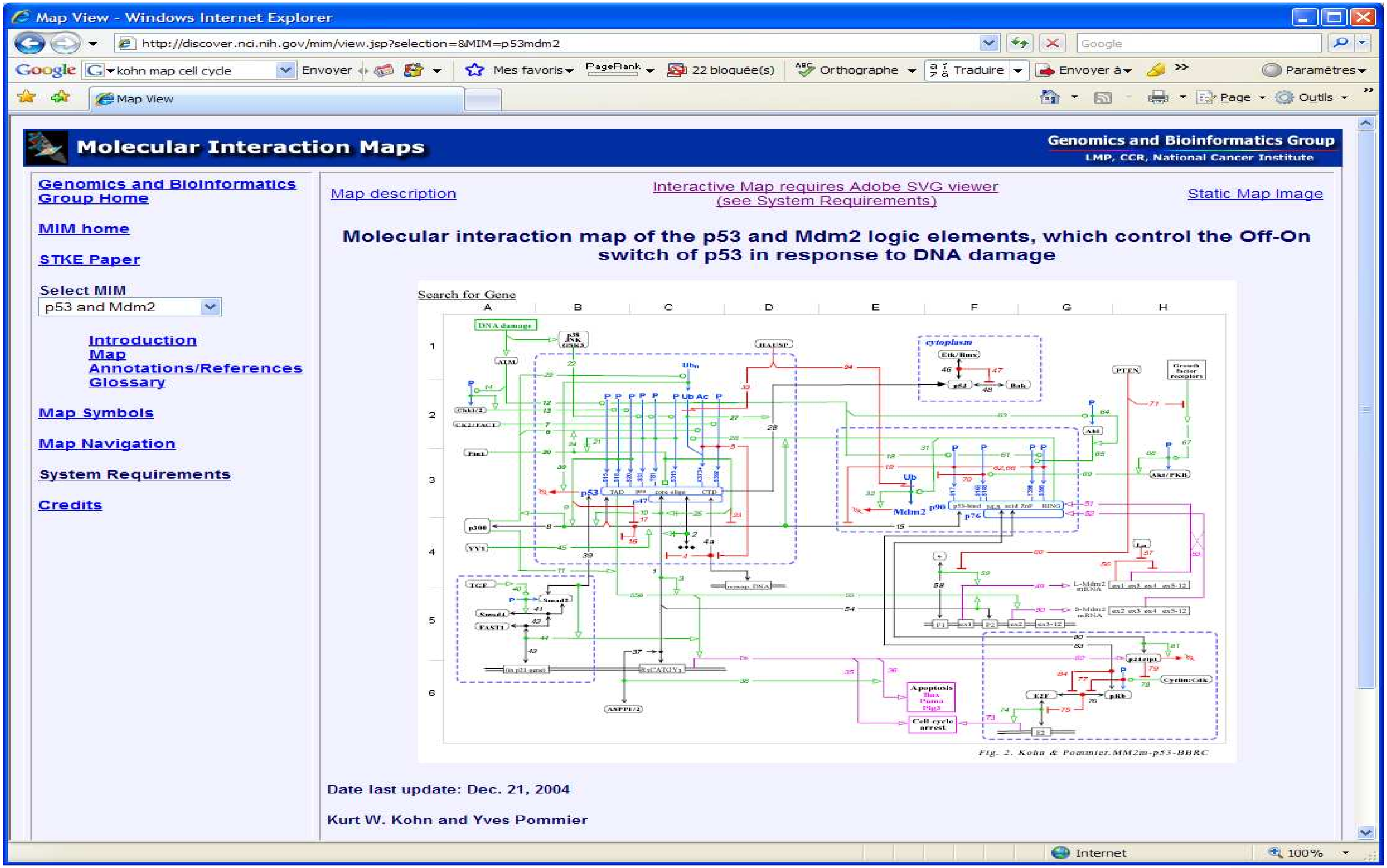
F. Fages and S. Soliman. Type inference in Systems Biology. *Computational Methods in Systems Biology*, CMSB'06 Trento, Springer-Verlag, Lecture Notes in Bioinformatics, LNBI 4210, pp. 48-62, 2006.

Implemented in the Biochemical Abstract Machine modeling environment `http://contraintes.inria.fr/BIOCHAM`

Biologists like Diagrams ...



… also on Computers



Molecular Interaction Maps

Genomics and Bioinformatics Group
LMP, CCR, National Cancer Institute

- Genomics and Bioinformatics Group Home
- MIM home
- STKE Paper

Select MIM
p53 and Mdm2

- Introduction
- Map
- Annotations/References
- Glossary

- Map Symbols
- Map Navigation
- System Requirements
- Credits

Map description | Interactive Map requires Adobe SVG viewer (see System Requirements) | Static Map Image

Molecular interaction map of the p53 and Mdm2 logic elements, which control the Off-On switch of p53 in response to DNA damage

Search for Gene

Fig. 2. Kohn & Pommier.MM2m-p53-BBRC

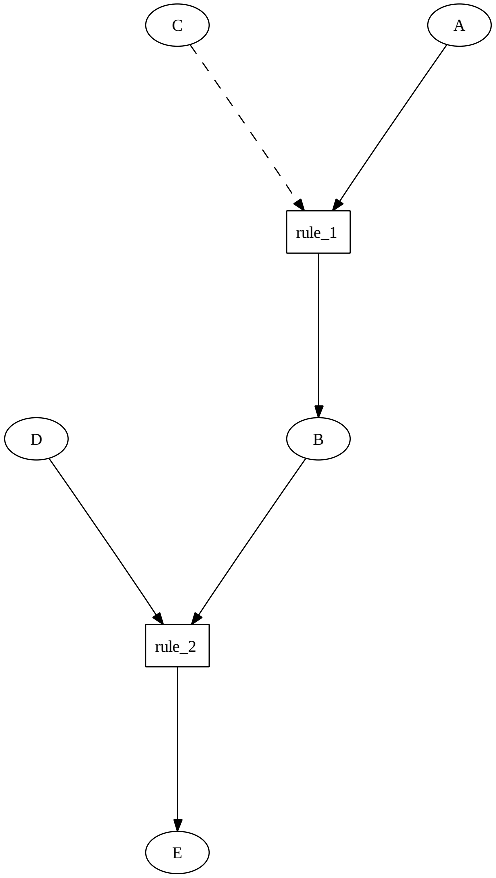
Date last update: Dec. 21, 2004

Kurt W. Kohn and Yves Pommier

Reaction Hypergraphs and Influence Graphs

`k1*[A] for A =[C]=> B.`

`k2*[B]*[D] for B+D => E.`



Reaction Hypergraphs and Influence Graphs

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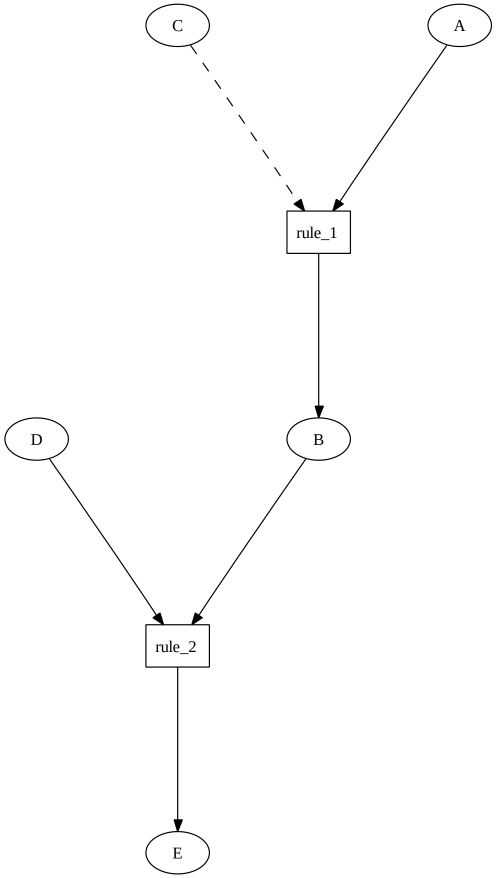
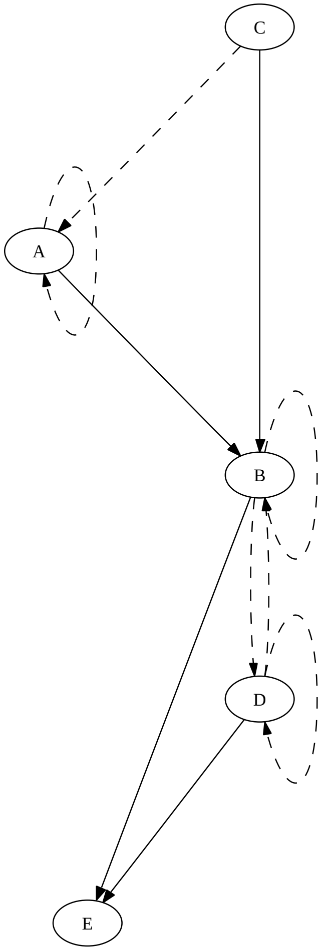
`k2*[B]*[D] for B+D => E.`

$A \xrightarrow{+} B,\ C \xrightarrow{-} A,\ \ldots$





René Thomas's Conditions Apply on Influence Graphs

Originally introduced to reason about gene regulatory networks

[Thomas 73, 81] :

- The existence of positive circuits in the influence graph is a necessary condition for multistationarity (e.g. cell differentiation).

  proved for :

  ODE systems [Soulé 03] ... [Snoussi 89]

  Boolean networks [Rémy Ruet Thieffry 05] ...

  Discrete networks [Richard 06] ...

- The existence of negative circuits is a necessary condition for oscillations (e.g. homeostasis).

  ODE systems [Snoussi 89]

Reaction Rules Models

In SBML (Systems Biology Markup Language) and BIOCHAM,

a reaction model R is a set of reaction rules of the form

$$e \texttt{ for } l => r$$

where l is a multiset of molecule names,

r is the transformed multiset,

and e is a differentiable positive kinetic expression.

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```
k1 for _ => A
k2*[A] for A => _
k3*[A]*[B] for A + B => C
k4*[C] for C => A + B
V5*[A]/(K5+[A]) for A =[B]=> Ap
k6*r*[Acyt] for Acyt => Anuc
```

Differential Semantics of Reaction Models

```
k1 for _ => A
k2*[A] for A => _
k3*[A]*[B] for A + B => C
```

$$\dot{x_A} = k1 - k2 * x_A - k3 * x_A * x_B$$

$$\dot{x_B} = -k3 * x_A * x_B$$

$$\dot{x_C} = k3 * x_A * x_B$$

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$$\dot{x_C} = k3 * x_A * x_B$$

Definition 1 *The differential semantics of a reaction model*

$$R = \{e_i \texttt{ for } l_i \texttt{ => } r_i\}_{i=1,\ldots,n}$$

is the ODE system

$$dx_k/dt = \dot{x_k} = \sum_{i=1}^{n} (r_i(x_k) - l_i(x_k)) * e_i$$

where $r_i(x_k)$ *(resp.* l_i*) is the stoichiometric coefficient of* x_k *in the right (resp. left) hand side of rule* i*.*

Differential Influence Graph (DIG)

Consider a reaction model R and its differential semantics.

The Jacobian matrix J is formed of the partial derivatives

$$J_{ij} = \partial \dot{x_i} / \partial x_j$$

Definition 2 *The differential influence graph (DIG) of a reaction model R is the graph of molecules with two kinds of edges:*

$$DIG(R) = \{A \xrightarrow{+} B \mid \partial \dot{x_B} / \partial x_A > 0 \textit{ in some point of the phase space}\}$$
$$\cup \{A \xrightarrow{-} B \mid \partial \dot{x_B} / \partial x_A < 0 \textit{ in some point of the phase space}\}$$

Not necessarily immediate to compute.

Example of DIG

```
k1 for _ => A
k2*[A] for A => _
k3*[A]*[B] for A + B => C
```

$$\dot{x_A} = k1 - k2 * x_A - k3 * x_A * x_B$$

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$$\dot{x_C} = k3 * x_A * x_B$$

DIG = ?

Example of DIG

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k2*[A] for A => _
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$$\dot{x_B} = -k3 * x_A * x_B$$

$$\dot{x_C} = k3 * x_A * x_B$$

$$\text{DIG} = \{A \xrightarrow{-} A,\ B \xrightarrow{-} A,\ A \xrightarrow{-} B,\ B \xrightarrow{-} B,\ A \xrightarrow{+} C,\ B \xrightarrow{+} C\}$$

Stoichiometric Influence Graph (SIG)

Definition 3 *The* stoichiometric influence graph *(SIG) of a reaction model R is defined by*

$$\begin{aligned} SIG(R) = \quad & \{A \xrightarrow{+} B \quad & \mid \exists (e_i \; for \; l_i \Rightarrow r_i) \in R, \\ & & l_i(A) > 0 \; and \; r_i(B) - l_i(B) > 0\} \\ & \cup \{A \xrightarrow{-} B & \mid \exists (e_i \; for \; l_i \Rightarrow r_i) \in R, \\ & & l_i(A) > 0 \; and \; r_i(B) - l_i(B) < 0\} \end{aligned}$$

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\end{aligned}
$$

$$SIG(\{\texttt{_ =[B]=> A}\}) = \{\mathrm{B} \xrightarrow{+} \mathrm{A}\}$$

$$SIG(\{\texttt{A =[B]=> _}\}) = \{\mathrm{B} \xrightarrow{-} \mathrm{A},\ \mathrm{A} \xrightarrow{-} \mathrm{A}\}$$

$$SIG(\{\texttt{A =[C]=> B }\}) = \{\mathrm{C} \xrightarrow{-} \mathrm{A},\ \mathrm{A} \xrightarrow{-} \mathrm{A},\ \mathrm{A} \xrightarrow{+} \mathrm{B},\ \mathrm{C} \xrightarrow{+} \mathrm{B}\}$$

$$
\begin{aligned}
SIG(\{\texttt{A + B => C}\}) = \{ & \mathrm{A} \xrightarrow{+} \mathrm{C},\ \mathrm{B} \xrightarrow{+} \mathrm{C},\ \mathrm{A} \xrightarrow{-} \mathrm{B}, \\
& \mathrm{B} \xrightarrow{-} \mathrm{A},\ \mathrm{A} \xrightarrow{-} \mathrm{A},\ \mathrm{B} \xrightarrow{-} \mathrm{B},\ \}
\end{aligned}
$$

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$SIG(\{\_ \; \texttt{=[B]=> A}\}) = \{\mathrm{B} \xrightarrow{+} \mathrm{A}\}$

$SIG(\{\texttt{A =[B]=> } \_\}) = \{\mathrm{B} \xrightarrow{-} \mathrm{A},\ \mathrm{A} \xrightarrow{-} \mathrm{A}\}$

$SIG(\{\texttt{A =[C]=> B }\}) = \{\mathrm{C} \xrightarrow{-} \mathrm{A},\ \mathrm{A} \xrightarrow{-} \mathrm{A},\ \mathrm{A} \xrightarrow{+} \mathrm{B},\ \mathrm{C} \xrightarrow{+} \mathrm{B}\}$

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$$\mathrm{B} \xrightarrow{-} \mathrm{A},\ \mathrm{A} \xrightarrow{-} \mathrm{A},\ \mathrm{B} \xrightarrow{-} \mathrm{B},\ \}$$

Proposition 4 *The SIG of n reaction rules is computable in $O(n)$ time*

The SIG of Kohn’s Map of the Mammalian Cell Cycle

Reaction model:

500 variables

800 reaction rules

Stoic. Influence Graph:

computed in *0.2 sec.*

1231 activation edges

1089 inhibition edges

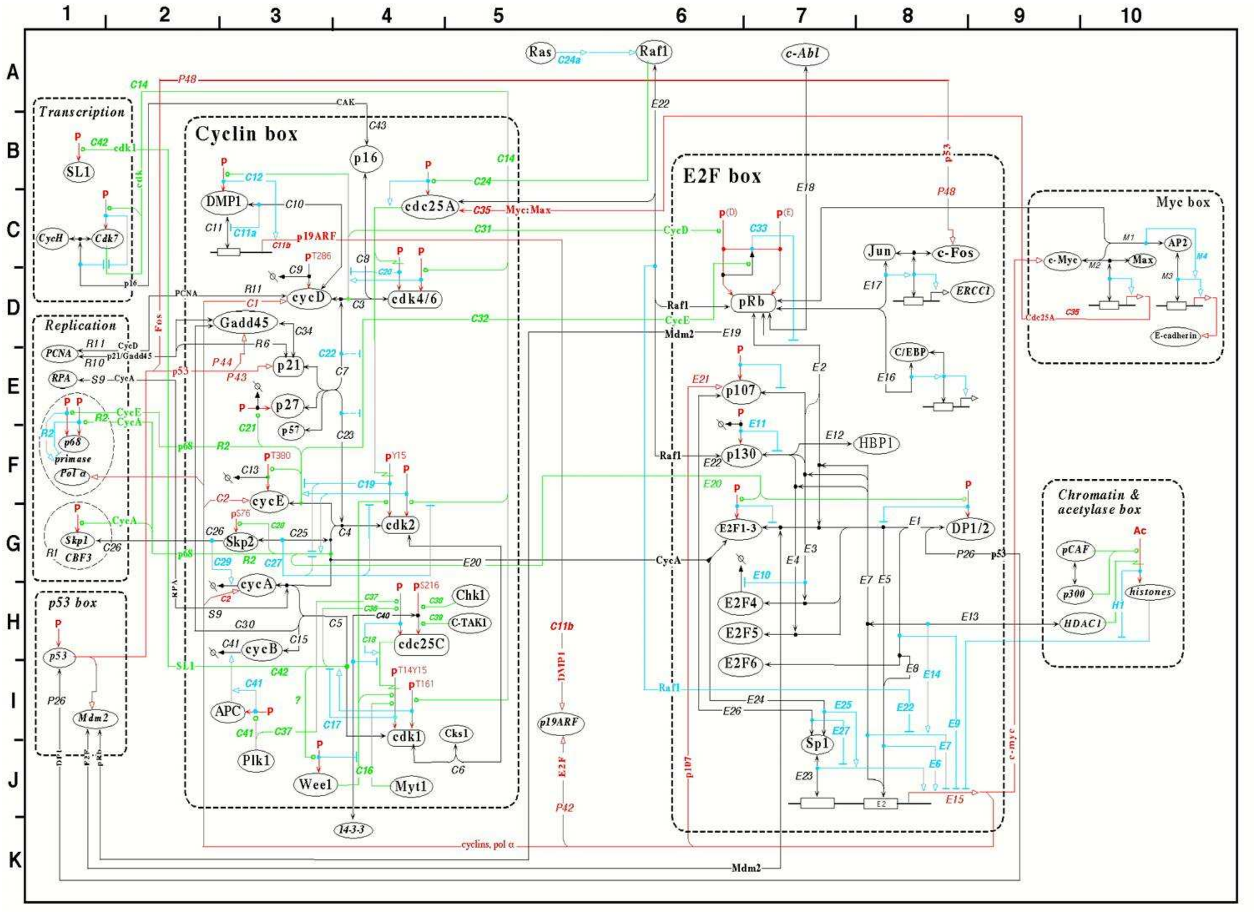
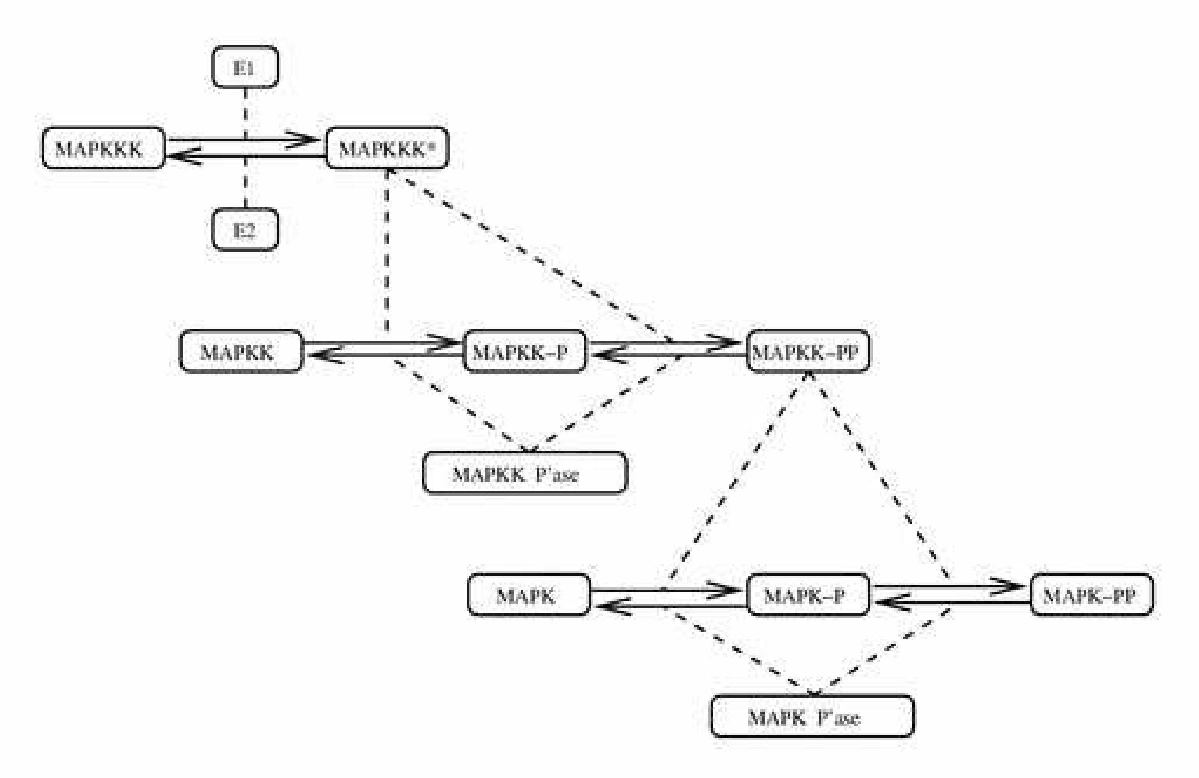


Figure 6A: The Cyclin - E2F cell cycle control system (version 3a - June 8, 1999)

MIM C&E 2k

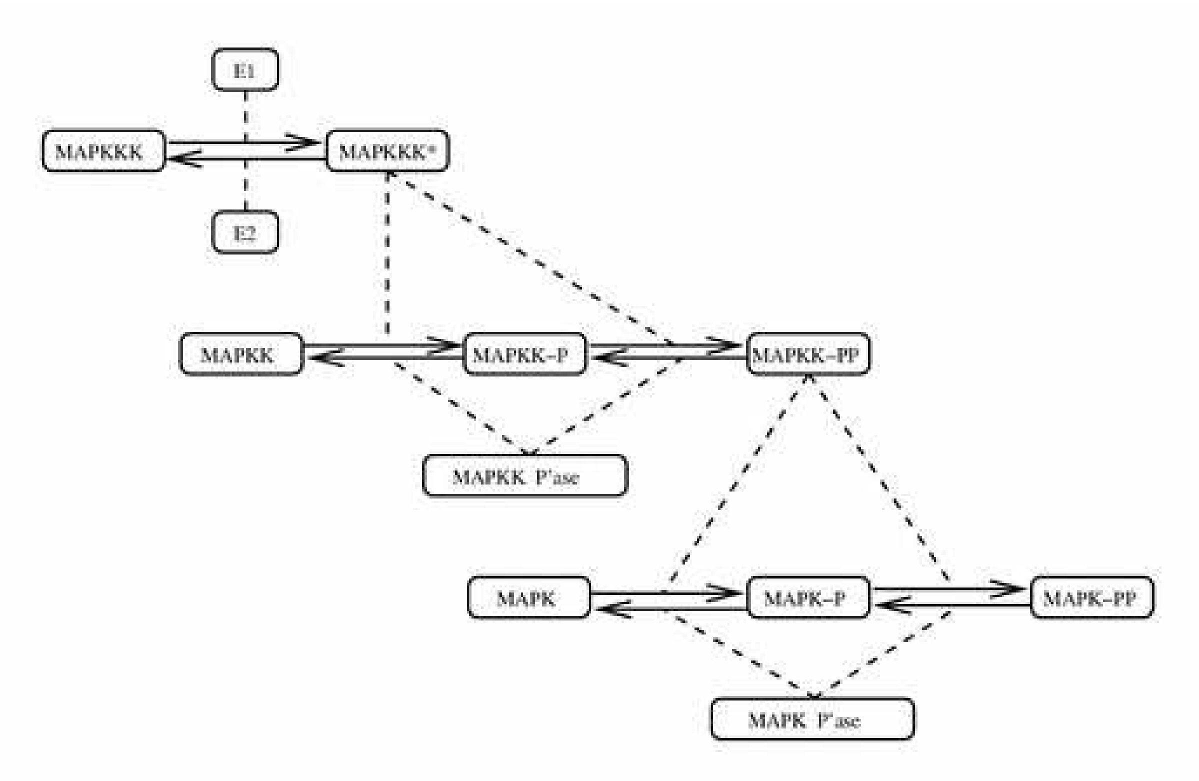
no molecule is at the same time an activator and an inhibitor of a same target molecule

MAPK Signalling Cascade



Purely directional “cascade” of reactions: no negative feedback

MAPK Signalling Cascade



Purely directional "cascade" of reactions: no negative feedback

sustained oscillations observed [Qiao et al. 07]

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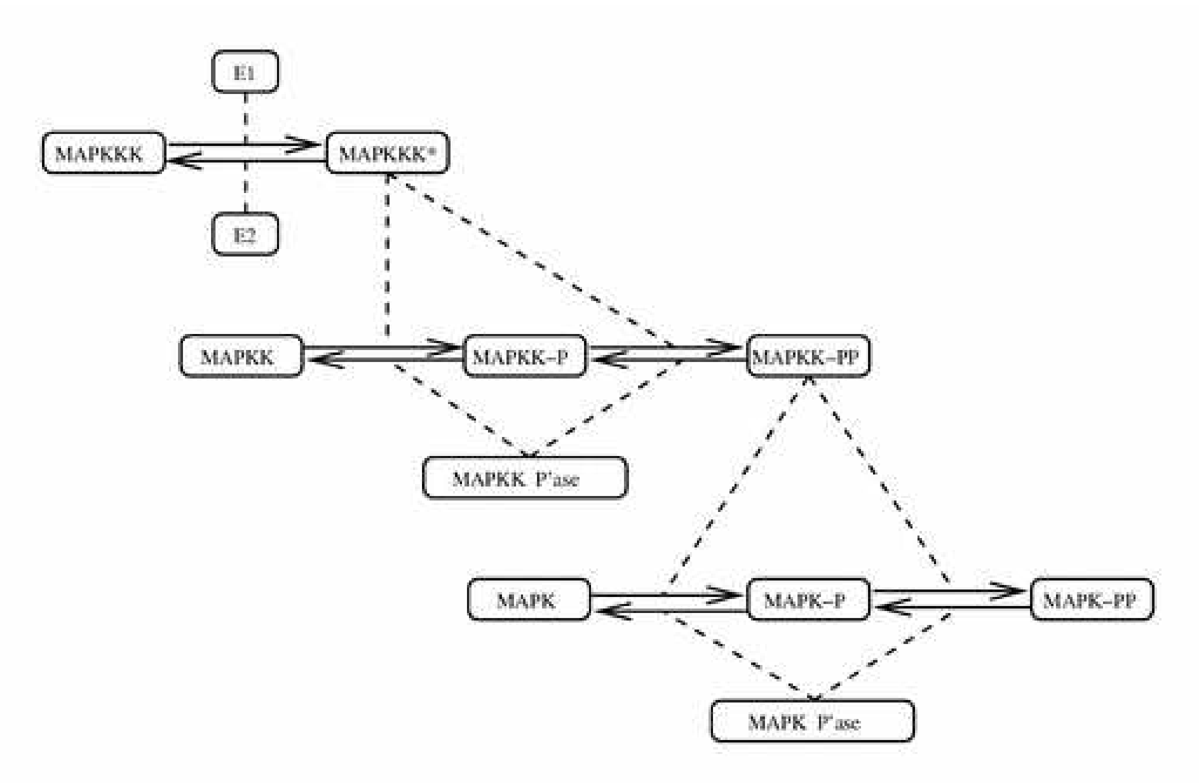

Purely directional "cascade" of reactions: no negative feedback

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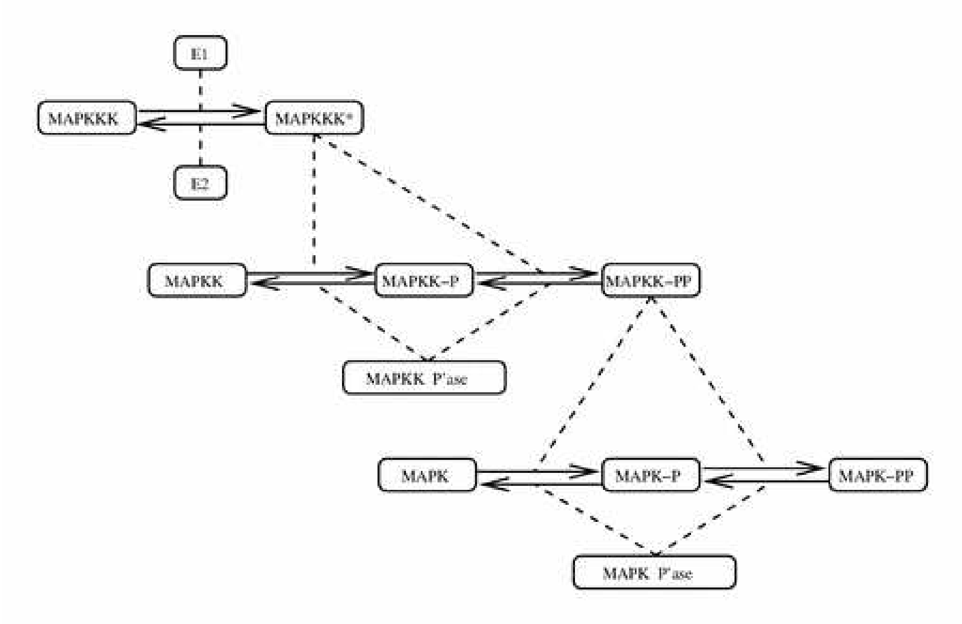
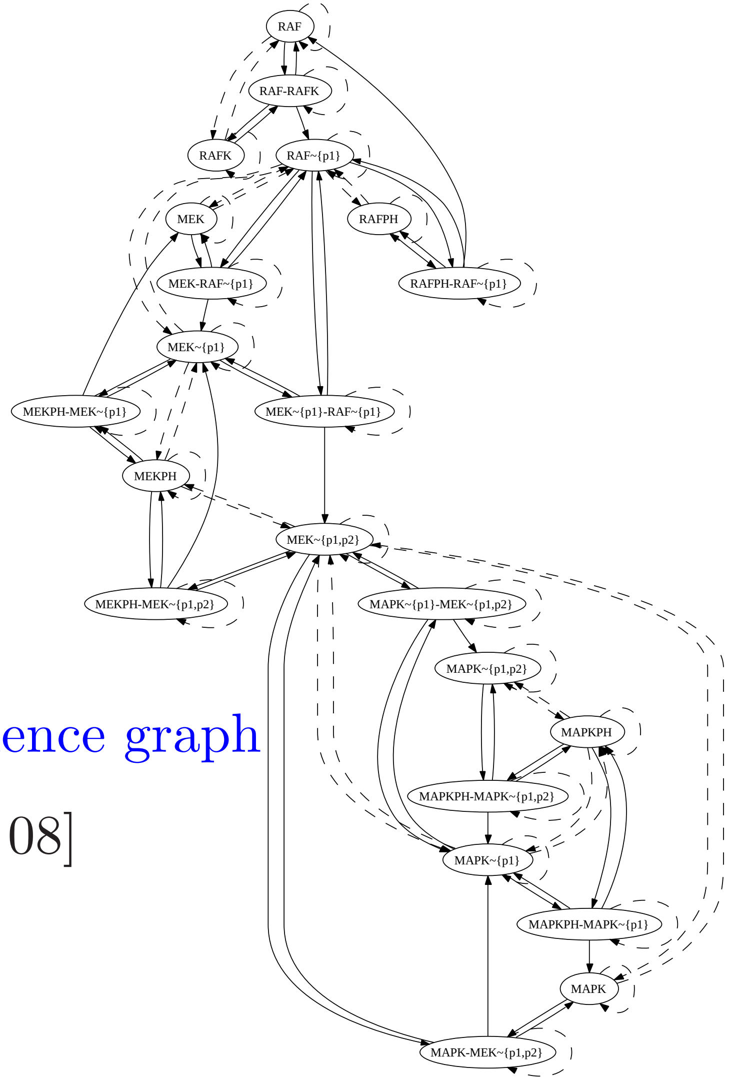
multistability observed [Kholodenko et al. 06]

MAPK Reaction and Influence Graphs

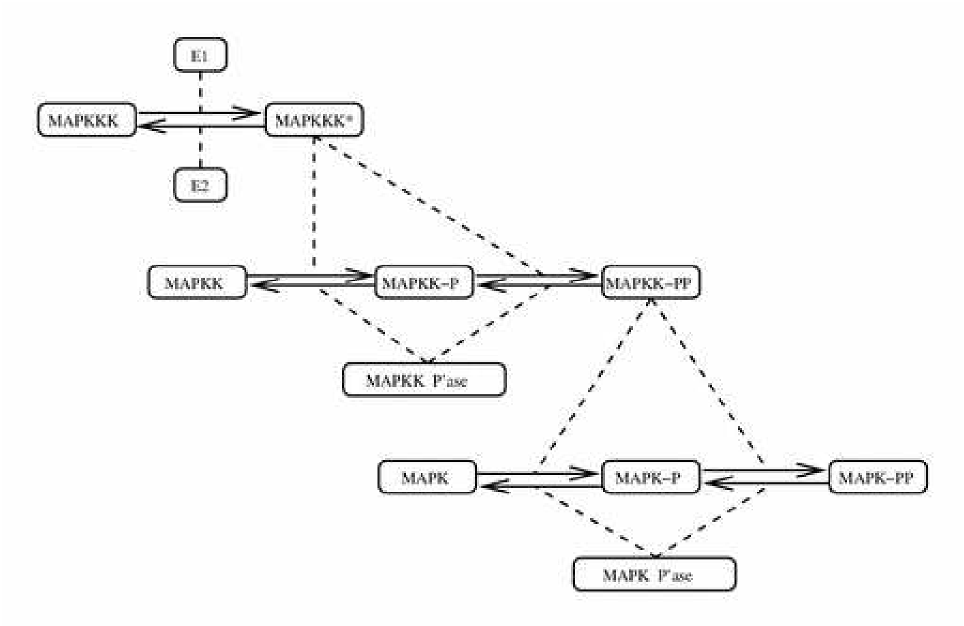


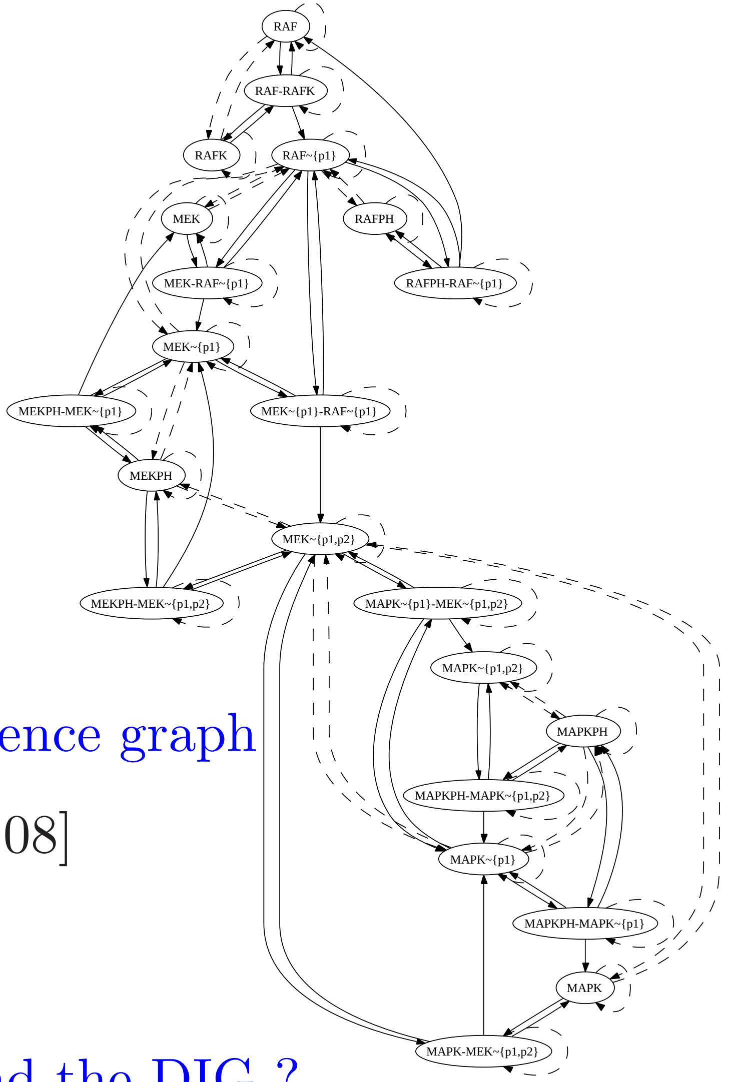


Negative feedback in the stoichiometric influence graph

Inhibition by sequestration [Sepulchre et al. 08]

MAPK Reaction and Influence Graphs





Negative feedback in the stoichiometric influence graph

Inhibition by sequestration [Sepulchre et al. 08]

What is the relationship between the SIG and the DIG ?

Increasing Kinetics

Definition 5 *In a reaction model* $R = \{e_i$ `for` l_i`=>`$r_i \mid i \in I\}$, *we say that a kinetic expression* e_i *is increasing iff for all molecules* x_k *we have*

1. $\partial e_i / \partial x_k \geq 0$ *in all points of the phase space,*
2. $l_i(x_k) > 0$ *whenever* $\partial e_i / \partial x_k > 0$ *in some point of the phase space.*

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Proposition 6 *The mass action law kinetics,* $e = k * \Pi {x_i}^{l_i}$*, Michaelis-Menten and Hill's kinetics* $e = V_m * {x_s}^n / ({K_m}^n + {x_s}^n)$ *are increasing.*

Negative Hill kinetics $e_i = V_m / ({K_m}^n + {x_s}^n)$ are not increasing

(used for inhibitions).

Over-approximation Theorem

Theorem 7 *For any reaction model* R *with increasing kinetics, the DIG is a subgraph of the SIG:* $DIG(R) \subseteq SIG(R)$.

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PROOF: If $(A \xrightarrow{+} B) \in DIG(R)$ then $\partial \dot{x}_B / \partial x_A > 0$ in some point of the phase space.

□

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PROOF: If $(A \xrightarrow{+} B) \in DIG(R)$ then $\partial \dot{x}_B / \partial x_A > 0$ in some point of the phase space. Hence there exists a term in the differential semantics, of the form $(r_i(B) - l_i(B)) * e_i$ with $\partial e_i / \partial x_A$ of the same sign as $r_i(B) - l_i(B)$.

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Let us suppose that $r_i(B) - l_i(B) > 0$, then $\partial e_i / \partial x_A > 0$ and,

□

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Proof: If $(A \xrightarrow{+} B) \in DIG(R)$ then $\partial \dot{x_B} / \partial x_A > 0$ in some point of the phase space. Hence there exists a term in the differential semantics, of the form $(r_i(B) - l_i(B)) * e_i$ with $\partial e_i / \partial x_A$ of the same sign as $r_i(B) - l_i(B)$.

Let us suppose that $r_i(B) - l_i(B) > 0$, then $\partial e_i / \partial x_A > 0$ and, since e_i is increasing, we get that $l_i(A) > 0$ and thus that $(A \xrightarrow{+} B) \in SIG(R)$.

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If on the contrary $r_i(B) - l_i(B) < 0$, then $\partial e_i / \partial x_A < 0$, which is not possible for an increasing kinetics.

The proof is symmetrical for $(A \xrightarrow{-} B)$. □

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DIG(R)$\neq$ SIG(R) for $R = \{k_1 * A \ \texttt{for} \ A => \_ \quad k_2 * A \ \texttt{for} \ \_ = [A] => A\}$

as $\dot{x}_A = (k_2 - k_1) * x_A$ can be made always positive, null or negative.

Strongly Increasing Kinetics

Definition 8 *In a reaction model* $R = \{e_i$ `for` l_i`=>`$r_i \mid i \in I\}$, *a kinetic expression* e_i *is strongly increasing iff for all molecules* x_k *we have*

1. $\partial e_i / \partial x_k \geq 0$ *in all points of the phase space,*
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Proposition 9 *Mass action law, Michaelis Menten, and Hill kinetics are strongly increasing.*

Strongly Increasing Kinetics

Lemma 10 *Let R be a reaction model with strongly increasing kinetics.*

If $(A \xrightarrow{+} B) \in SIG(R)$ *and* $(A \xrightarrow{-} B) \notin SIG(R)$ *then* $(A \xrightarrow{+} B) \in DIG(R)$.

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PROOF: Since $\partial \dot{B}/\partial A = \sum_{i=1}^{n}(r_i(B) - l_i(B)) * \partial e_i/\partial A$ and all e_i are increasing we get that $\partial \dot{B}/\partial A = \sum_{\{i \leq n | l_i(A)>0\}}(r_i(B) - l_i(B)) * \partial e_i/\partial A$.

... □

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Now if $A \overset{+}{\rightarrow} B \in$SIG, but not $(A \overset{-}{\rightarrow} B)$, then all rules such that $l_i(A) > 0$ verify $r_i(B) - l_i(B) \geq 0$ and there is at least one rule for which the inequality is strict.

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Now if $A \xrightarrow{+} B \in$SIG, but not $(A \xrightarrow{-} B)$, then all rules such that $l_i(A) > 0$ verify $r_i(B) - l_i(B) \geq 0$ and there is at least one rule for which the inequality is strict. We thus get that $\partial \dot{B}/\partial A$ is a sum of positive numbers, amongst which one is such that $r_i(B) - l_i(B) > 0$ and $l_i(A) > 0$ which, since M is strongly increasing, implies that there exists a point in the space for which $\partial e_i/\partial A > 0$. Hence $\partial \dot{B}/\partial A > 0$ at that point, and $A \xrightarrow{+} B \in$DIG.

... □

Strongly Increasing Kinetics

Lemma 10 *Let R be a reaction model with strongly increasing kinetics.*

If $(A \overset{+}{\rightarrow} B) \in SIG(R)$ *and* $(A \overset{-}{\rightarrow} B) \notin SIG(R)$ *then* $(A \overset{+}{\rightarrow} B) \in DIG(R)$.

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PROOF: Since $\partial\dot{B}/\partial A = \sum_{i=1}^{n}(r_i(B) - l_i(B)) * \partial e_i/\partial A$ and all e_i are increasing we get that $\partial\dot{B}/\partial A = \sum_{\{i \leq n | l_i(A) > 0\}}(r_i(B) - l_i(B)) * \partial e_i/\partial A$.

Now if $A \overset{+}{\rightarrow} B$ ∈SIG, but not $(A \overset{-}{\rightarrow} B)$, then all rules such that $l_i(A) > 0$ verify $r_i(B) - l_i(B) \geq 0$ and there is at least one rule for which the inequality is strict. We thus get that $\partial\dot{B}/\partial A$ is a sum of positive numbers, amongst which one is such that $r_i(B) - l_i(B) > 0$ and $l_i(A) > 0$ which, since M is strongly increasing, implies that there exists a point in the space for which $\partial e_i/\partial A > 0$. Hence $\partial\dot{B}/\partial A > 0$ at that point, and $A \overset{+}{\rightarrow} B$ ∈DIG.

Same reasoning for inhibitions with opposite sign for $r_i(B) - l_i(B)$. □

Equivalence Theorem

Main Theorem 11 *Let* R *be a reaction model with strongly increasing kinetics and where no molecule is at the same time an activator and an inhibitor of the same target molecule, then* $SIG(R) = DIG(R)$.

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Corollary 12 *The DIG of a reaction model is independent of the kinetic expressions as long as they are strongly increasing, if there is no activation+inhibition pair in the SIG.*

Corollary 13 *The DIG of a reaction model of n rules with strongly increasing kinetics is computable in time $O(n)$ if there is no activation+inhibition pair in the SIG.*

Cell Cycle Control Models

The SIG of Kohn's map contains no activation+inhibition pair hence the DIGs of Kohn's map are the same for any strongly increasing kinetics and any strictly positive parameter values.

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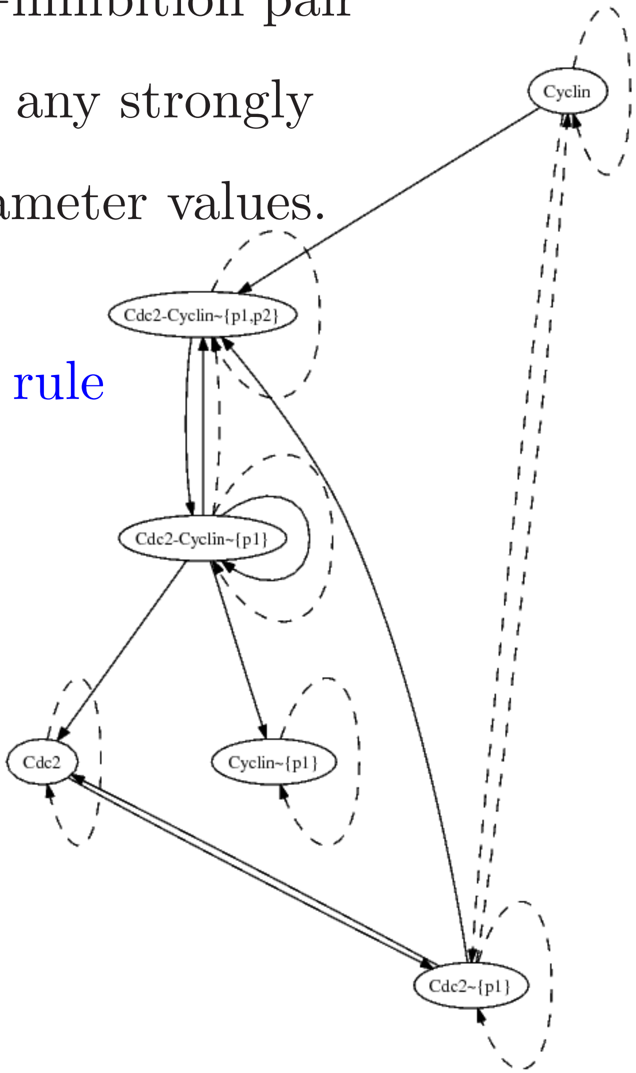

In smaller models [Tyson 91] the autoactivation rule

`pMPF =[MPF]=> MPF` with `MPF => pMPF`

creates a pair

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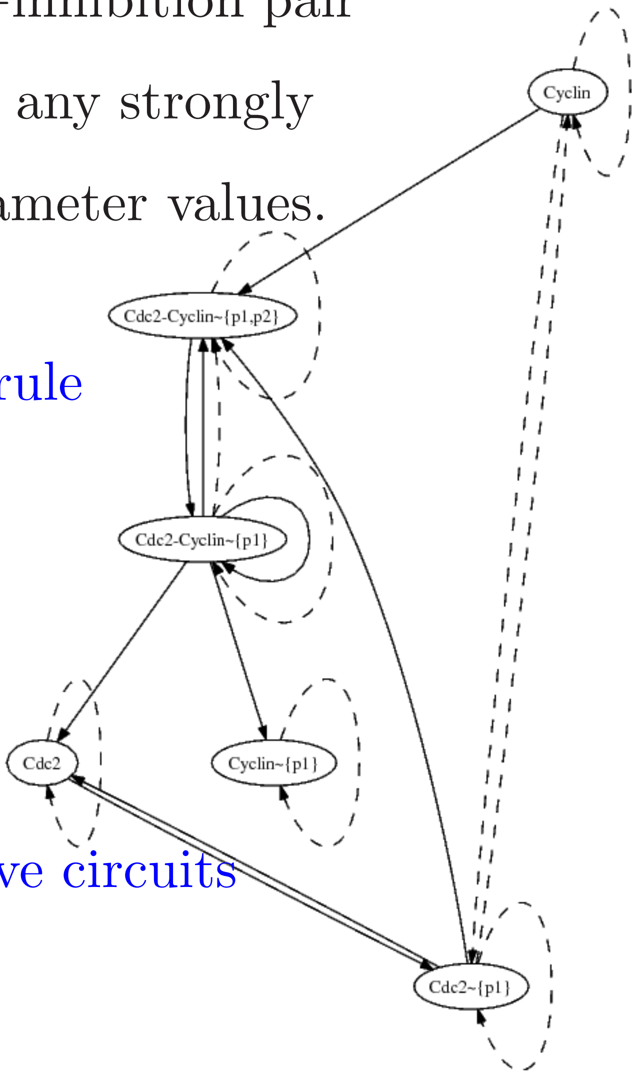

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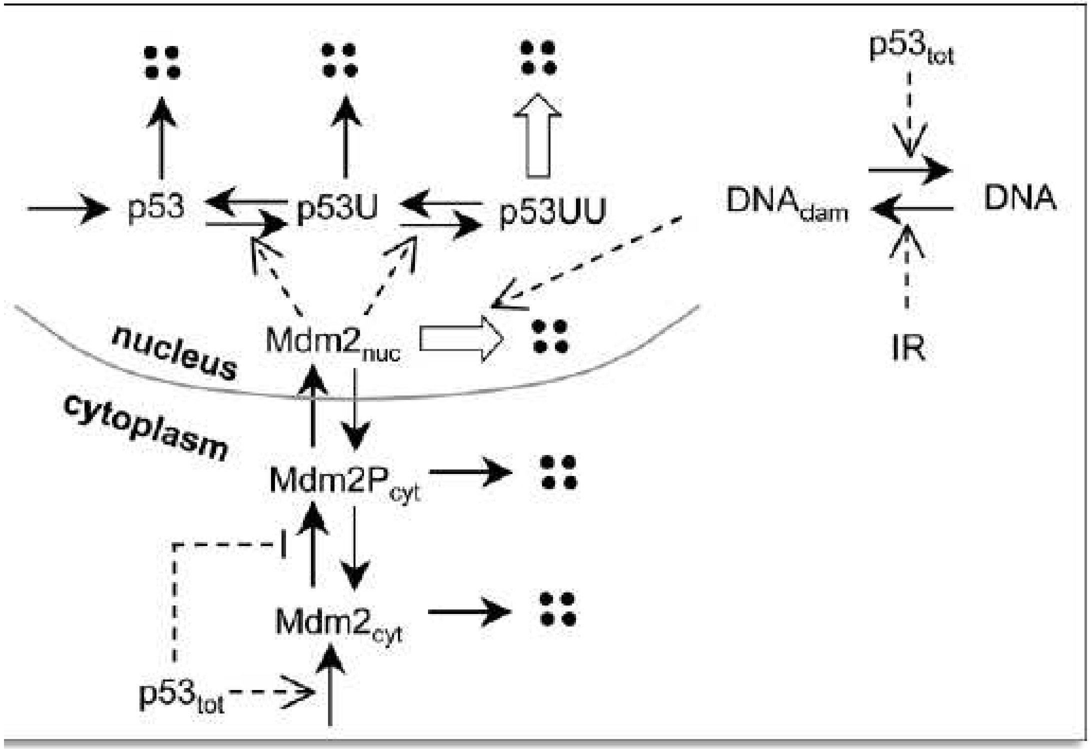
In kohn's map, this is decomposed in two positive circuits

- one mutual inhibition `Wee1 |-| MPF`,
- one mutual activation `Cdc25 <-> MPF`.

Reaction Inhibitors

In Ciliberto et al.'s Model of P53/Mdm2 [CNT05cc]



P53 $\overset{-}{\rightarrow}$the phosphorylation of `Mdm2`

```
k1*Mdm2/(k2+P53) for Mdm2 => Mdm2p
```

the kinetic expression is not increasing

Reaction Rules with Antagonists

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\end{aligned}$$

SIG(`A=[/I]=>B`})=$\{A \xrightarrow{+} B,\ I \xrightarrow{-} B,\ I \xrightarrow{+} A,\ A \xrightarrow{-} A\}$

Compatible Kinetics with Antagonists

Definition 15 *In a generalized reaction rule e* `for` *l* `=[/a]=>` *r, a kinetic expression e is compatible (resp. strongly compatible) iff for all molecules x_k we have*

1. $l(x_k) > 0$ *if (resp. iff) there exists a point in the phase space such that* $\partial e/\partial x_k > 0$,
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Negative Hill kinetics are strongly compatible.

For instance, the kinetics `k1*Mdm2/(k2+P53) for Mdm2 =[/P53]=> Mdm2p` for the inhibition by `P53` of `Mdm2` phosphorylation is strongly compatible.

Equivalence Theorem with Antagonists

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Theorem 17 *For any generalized reaction model R with a strongly compatible kinetics, and a GSIG containing no activation+inhibition pair, DIG(R)=GSIG(R).*

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- ODE's systems derived from reaction rules enjoy remarkable properties

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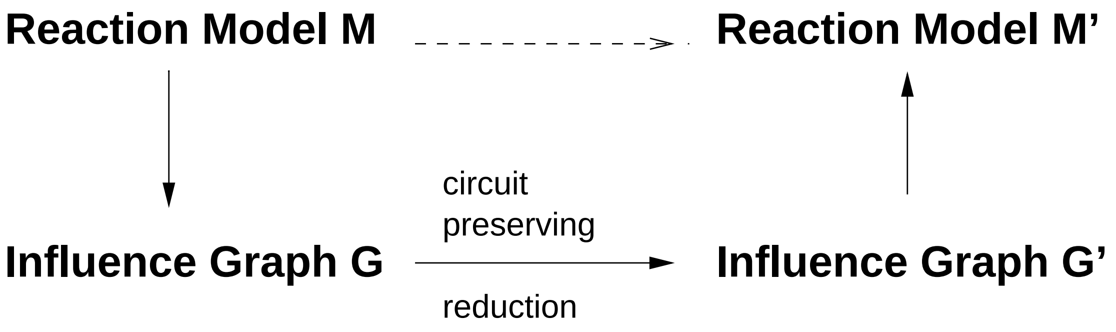
- Extend the syntax of (SBML) reaction rules with a notation for antagonists

On-Going Work

→ Model reduction strategies based on circuits preserving reductions of the SIG.



Reaction Model M

Reaction Model M’

Influence Graph G

circuit preserving reduction

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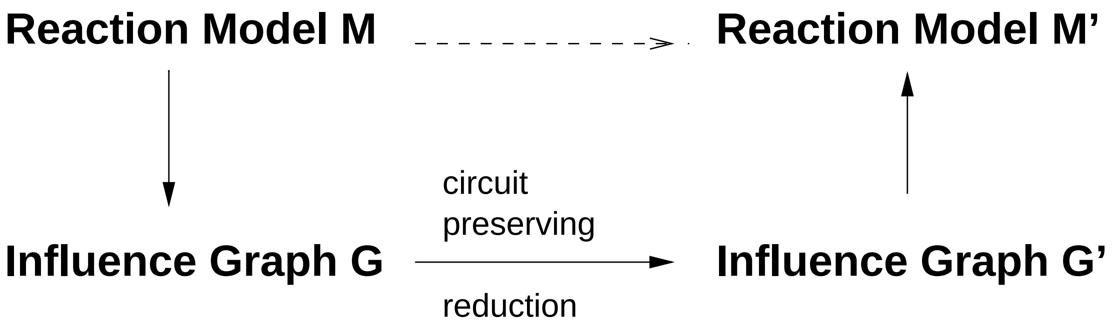

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- Sufficient conditions for multistability ? for oscillations?

→ *“Structural” dynamical properties independent from the kinetics*

→ *Property peserved by model reduction*