From Reaction Models to Influence Models and Back

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1. Theory of abstract interpretation
2. Syntactical domain of SBML reaction rules
3. Hierarchy of Stochastic to Boolean semantics
4. Activation/inhibition influences abstracted from the syntax of reaction rules
5. Activation/inhibition influences abstracted from the differential semantics of reaction rules
6. Conclusion

1. Abstraction in Systems Biology

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These perspectives can be reconciled by organizing models into hierarchies of abstractions.

"To understand a system is not to know everything about it but to know abstraction levels that are sufficient for answering questions about it"

The Theory of Abstract Interpretation

In this setting [Cousot Cousot 77], a domain is a lattice $\mathcal{D}(\sqsubseteq, \bot, \top, \sqcup, \sqcap)$ where $\sqsubseteq$ is the "information loss" ordering.

Often just a power-set $\mathcal{P}(\mathcal{S})(\subseteq, \emptyset, \mathcal{S}, \cup, \cap)$ ordered by set inclusion.

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A Galois connection $\mathcal{C} \rightarrow_{\alpha} \mathcal{A}$ between two lattices $\mathcal{C}$ and $\mathcal{A}$ is defined by two abstraction and concretization functions $\alpha : \mathcal{C} \rightarrow \mathcal{A}$ and $\gamma : \mathcal{A} \rightarrow \mathcal{C}$ that are monotonic:

- $\forall\ x, y \in \mathcal{C}\ x \sqsubseteq_{\mathcal{C}} y\ \Rightarrow\ \alpha(x) \sqsubseteq_{\mathcal{A}} \alpha(y)$,
- $\forall\ x, y \in \mathcal{A}\ x \sqsubseteq_{\mathcal{A}} y\ \Rightarrow\ \gamma(x) \sqsubseteq_{\mathcal{C}} \gamma(y)$,

and are adjoint:

- $\forall c \in \mathcal{C}, \forall y \in \mathcal{A} : x \sqsubseteq_{\mathcal{C}} \gamma(y) \Leftrightarrow \alpha(x) \sqsubseteq_{\mathcal{A}} y$.

If $\gamma \circ \alpha$ is the identity, the abstraction α loses no information, and $\mathcal{C}$ and $\mathcal{A}$ are isomorphic from the information standpoint (although α may be not onto and γ not one-to-one).

Properties of Galois Connections

1. $\gamma \circ \alpha$ is extensive (i.e. $x \sqsubseteq_{\mathcal{C}} \gamma \circ \alpha(x)$) and represents the information lost by the abstraction;
2. $\alpha \circ \gamma$ is contracting (i.e. $\alpha \circ \gamma(y) \sqsubseteq_{\mathcal{A}} y$);
3. $\gamma \circ \alpha$ is the identity *iff* γ is onto *iff* α is one-to-one.
4. α preserves $\sqcup$, and γ preserves $\sqcap$;
5. $\gamma(a) = max\ \alpha^{-1}(\downarrow a) = \sqcup \alpha^{-1}(\downarrow a)$
6. $\alpha(c) = min\ \gamma^{-1}(\uparrow c) = \sqcap \gamma^{-1}(\uparrow c)$

where $\downarrow a = \{b \mid b \sqsubseteq a\}$ and $\uparrow a = \{b \mid a \sqsubseteq b\}$.

It is equivalent in the definition of Galois connections to replace the condition of adjointness by conditions 1 and 2,

or by condition 5 which also entails the monotonicity of γ.

Systems Biology Markup Language SBML Models

Formally, the concrete domain of reaction models is the powerset of all possible reaction rules ordered by set inclusion :

Def. 1 *Given a finite set $\mathcal{M}$ of molecule names, the universe of reactions is the set of rules*

$$\mathcal{R} = \{e \texttt{ for } S{=}{>}S' \mid \begin{array}{l} e \text{ is a kinetic expression,} \\ \text{and } S \text{ and } S' \text{ are solutions of molecules in } \mathcal{M}\}. \end{array}$$

The domain of SBML reaction models is $\mathcal{C}_{\mathcal{R}} = (\mathcal{P}(\mathcal{R}), \subseteq)$.

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In the SBML exchange format, no semantics are defined.

In BIOCHAM, three semantics are considered:

1. boolean : non-deterministic asynchronous transition system
2. differential : ODE (or hybrid system)
3. stochastic : continuous time Markov chain.

Stochastic Semantics Domain

Def. 3 *Let a discrete state be a vector of integers of dimension* $|\mathcal{M}|$*. The universe* $\mathcal{S}$ *of stochastic transitions is the set of triplets* (S_i, S_j, τ) *where* S_i *and* S_j *are discrete states and* $\tau \in \mathbb{R}^+$ *is a weight for the transition.*

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An element s of the domain precisely defines a Markov chain, where the probability p_{ij} of transition from state S_i to S_j is obtained by normalizing the reaction rate $\tau_{i,j} = \sum_{(S_i,S_j,\tau)\in s} \tau$ in $p_{ij} = \frac{\tau_{ij}}{\sum_{(S_i,S_k,\tau)\in s} \tau}$

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Proposition 6 *Let* $\alpha_{\mathcal{RS}} : \mathcal{C}_\mathcal{R} \to \mathcal{D}_\mathcal{S}$ *be the function associating to a reaction model the state transition graph labelled with the* $\tau_{i,j}$*'s. Let* $\gamma_{\mathcal{RS}}(s) = \cup {\alpha_{\mathcal{RS}}}^{-1}(\downarrow s)$. $\mathcal{C}_\mathcal{R} \underset{\gamma_{\mathcal{RS}}}{\overset{\alpha_{\mathcal{RS}}}{\longleftrightarrow}} \mathcal{D}_\mathcal{S}$ *is a Galois connection.*

Remark that $\alpha_{\mathcal{RS}}$ is not one-to-one nor onto

Discrete Semantics

Def. 7 *The universe $\mathcal{D}$ of discrete transitions is the set of pairs of discrete states. The domain of discrete transitions is $\mathcal{D}_{\mathcal{D}} = (\mathcal{P}(\mathcal{D}), \subseteq)$.*

The discrete semantics is the classical Petri net semantics of reaction models [RML93ismb,SHK06bmcbi,Chaouiya07bioinfo,GHL07cmsb].

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Classical Petri net analysis tools can be used for the analysis of reaction models at this abstraction level. For instance, the elementary mode analysis of metabolic networks [SPM02bioinfo] has been shown in [ZS03insilicobio] to be equivalent to the classical analysis of Petri nets by T-invariants.

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Proposition 10 *Let $\alpha_{\mathcal{SD}} : \mathcal{D}_{\mathcal{S}} \to \mathcal{D}_{\mathcal{D}}$ be the function associating to a set of stochastic transitions the discrete transitions obtained by projection on the two first components, and $\gamma_{\mathcal{SD}}(d) = \cup {\alpha_{\mathcal{SD}}}^{-1}(\downarrow d)$. $\mathcal{D}_{\mathcal{S}} \underset{\gamma_{\mathcal{SD}}}{\overset{\alpha_{\mathcal{SD}}}{\longleftrightarrow}} \mathcal{D}_{\mathcal{D}}$ is a Galois connection.*

Remark that $\alpha_{\mathcal{SD}}$ is onto, but not one-to-one

Boolean Semantics

Def. 11 *Let a boolean state be a vector of booleans of dimension* $|\mathcal{M}|$ *indicating the presence of each molecule in the state. The universe* $\mathcal{B}$ *of boolean transitions is the set of pairs of boolean states.*

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The domain of boolean transitions is $\mathcal{D}_{\mathcal{B}} = (\mathcal{P}(\mathcal{B}), \subseteq)$.

Let $\alpha_{\mathcal{NB}} : \mathbb{N}^{|\mathcal{M}|} \to \mathbb{B}^{|\mathcal{M}|}$ be the zero/non-zero abstraction (or threshold abstraction) from the integers to the booleans, and its pointwise extension from discrete states to boolean states.

Proposition 13 *Let* $\alpha_{\mathcal{DB}} : \mathcal{D}_{\mathcal{D}} \to \mathcal{D}_{\mathcal{B}}$ *be the set extension of* $\alpha_{\mathcal{NB}}$. *Let* $\gamma_{\mathcal{DB}}(b) = \cup {\alpha_{\mathcal{DB}}}^{-1}(\downarrow b)$. $\mathcal{D}_{\mathcal{D}} \underset{\gamma_{\mathcal{DB}}}{\overset{\alpha_{\mathcal{DB}}}{\longleftrightarrow}} \mathcal{D}_{\mathcal{B}}$ *is a Galois connection.*

BIOCHAM boolean semantics S_{BB} with the combinatorics of reactant consumption

Theorem 14 *For any reaction model* R, $\alpha_{\mathcal{DB}}(\alpha_{\mathcal{SD}}(\alpha_{\mathcal{RS}}(R))) \subseteq S_{BB}$.

Differential Semantics ?

The differential semantics of reaction models interprets a set of reaction rules $\{e_i \texttt{ for } S_i => S'_i\}_{i=1,...,n}$ over molecular concentration variables $\{x_1, ..., x_m\}$, by the following system of Ordinary Differential Equations (ODE):

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

where we recall that $r_i(x_k)$ (resp. l_i) is the stoichiometric coefficient of x_k in the right (resp. left) member of rule i.

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- synchronous semantics (evolution of variables in parallel)
- deterministic semantics (average behavior)
- not compatible with the rule set inclusion ordering
- infinite number of molecules
- infinitesimal time steps

Influence Graph Abstraction from the Reaction Rule Syntax

$\mathcal{A}_\mathcal{I} = \mathcal{P}(\{A \text{ activates } B \mid A, B \in \mathcal{M}\} \cup \{A \text{ inhibits } B \mid A, B \in \mathcal{M}\})$.

The influence graph of a reaction model is defined by $\alpha_{\mathcal{RI}} : \mathcal{C}_\mathcal{R} \to \mathcal{A}_\mathcal{I}$

$$\begin{aligned}
\alpha_{\mathcal{RI}}(x) = \quad & \{A \text{ inhibits } B \quad && \mid \exists (e_i \text{ for } S_i \Rightarrow S_i') \in x, \\
& && \quad l_i(A) > 0 \text{ and } r_i(B) - l_i(B) < 0\} \\
& \cup \{A \text{ activates } B && \mid \exists (e_i \text{ for } S_i \Rightarrow S_i') \in x, \\
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\end{aligned}$$

$\alpha_{\mathcal{RI}}(\{\mathtt{A} + \mathtt{B} \Rightarrow \mathtt{C}\}) = \{$ A inhibits B, A inhibits A, B inhibits A, B inhibits B, A activates C, B activates C$\}$

$\alpha_{\mathcal{RI}}(\{\mathtt{A} = [\mathtt{C}] \Rightarrow \mathtt{B}\}) = \{$ C inhibits A, A inhibits A, A activates B, C activates I

$\alpha_{\mathcal{RI}}(\{\mathtt{A} = [\mathtt{B}] \Rightarrow \_\}) = \{$ B inhibits A, A inhibits A$\}$

$\alpha_{\mathcal{RI}}(\{\_ = [\mathtt{B}] \Rightarrow \mathtt{A}\}) = \{$ B activates A$\}$

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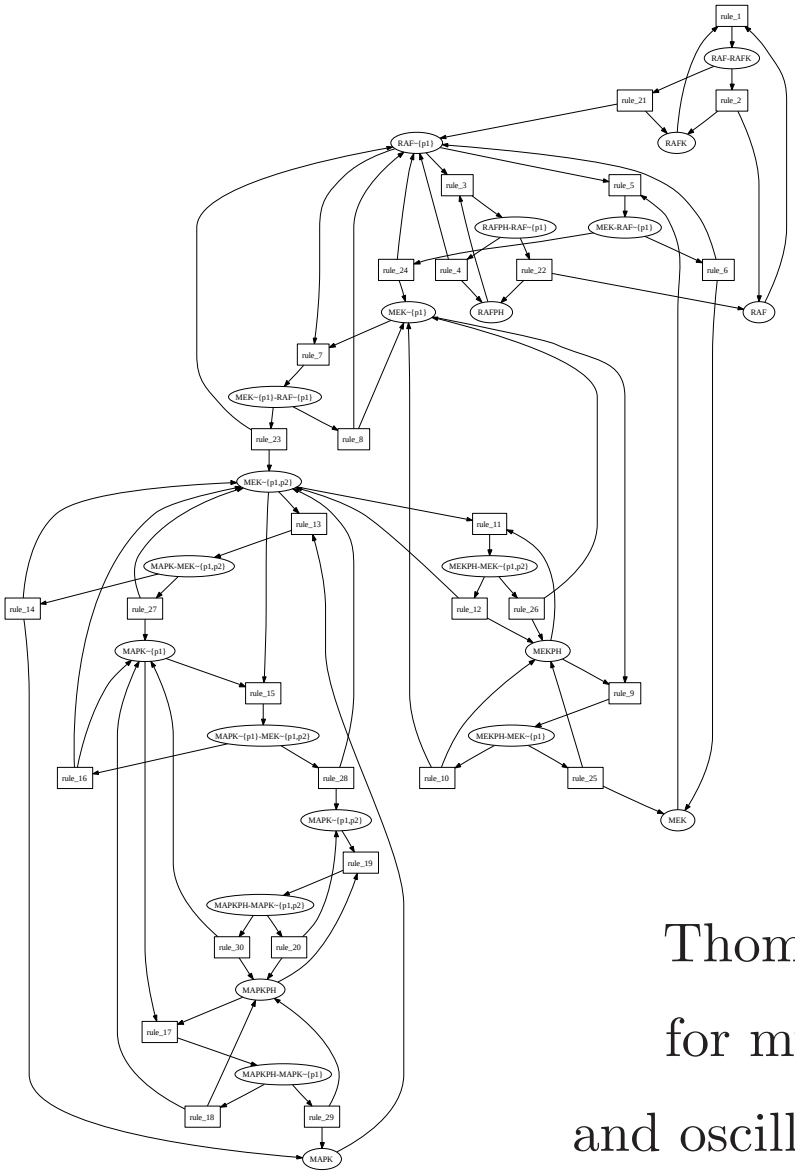
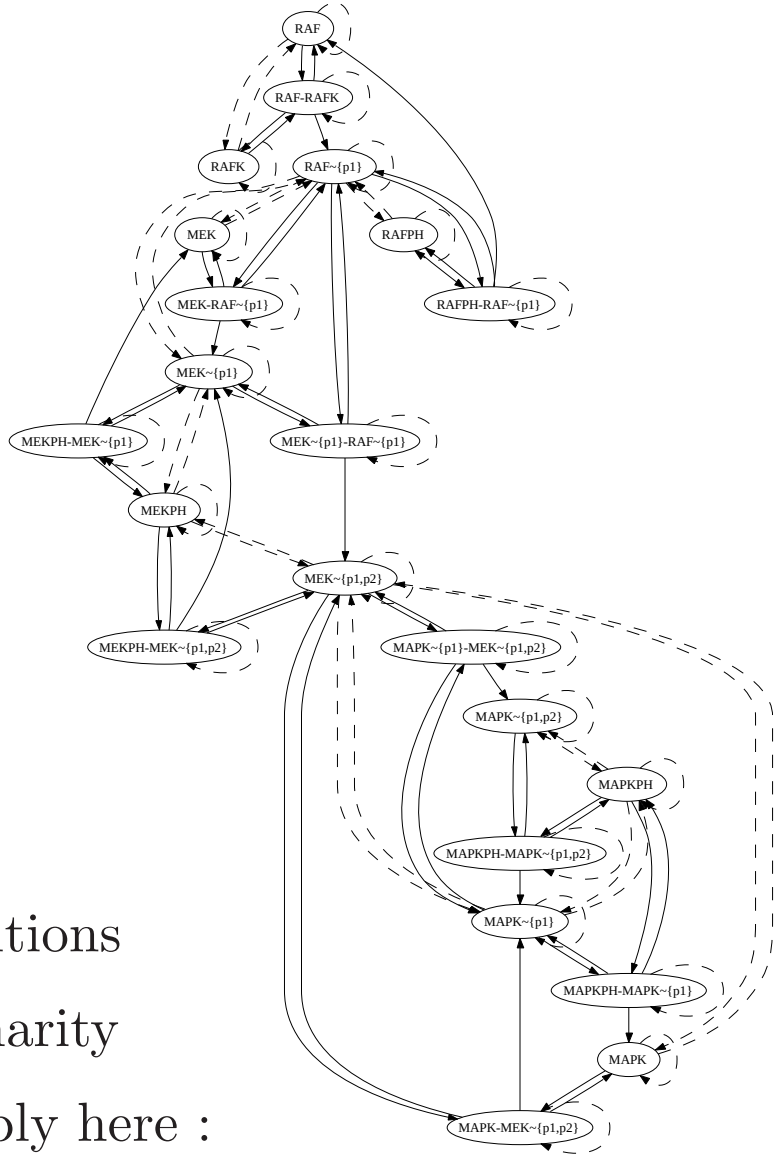
\end{aligned}$$

Proposition 15 *Let* $\gamma_{\mathcal{RI}}(f) = \cup {\alpha_{\mathcal{RI}}}^{-1}(\downarrow f)$, $\mathcal{C}_\mathcal{R} \underset{\gamma_{\mathcal{RI}}}{\overset{\alpha_{\mathcal{RI}}}{\longleftrightarrow}} \mathcal{A}_\mathcal{I}$ *is a Galois connection.*

MAPK model: Reaction Graph $\rightarrow_\alpha$ Influence Graph



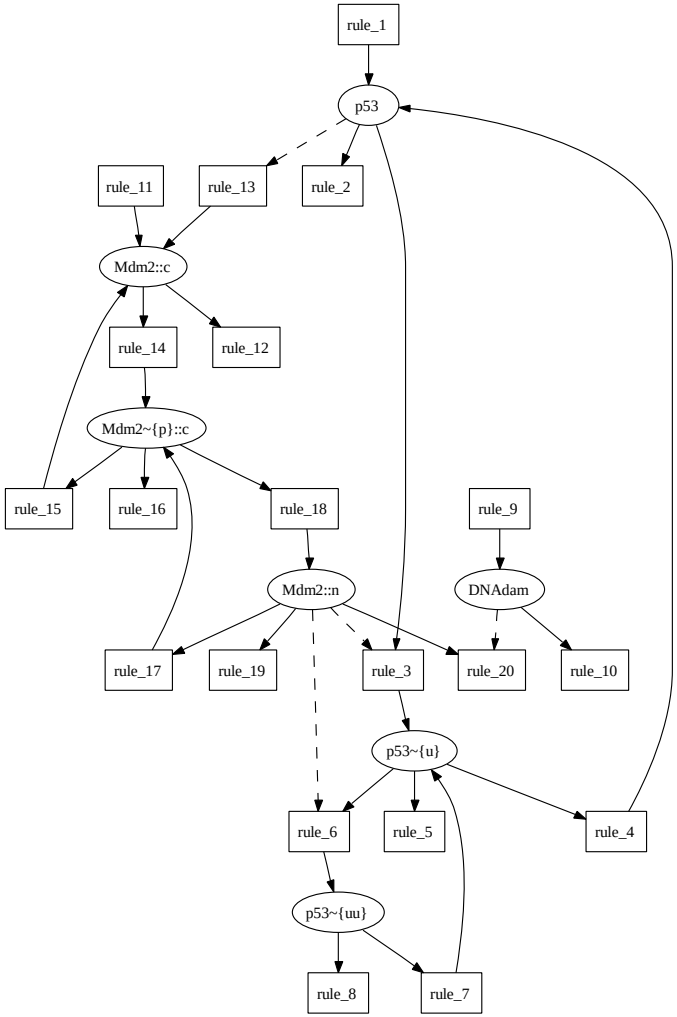


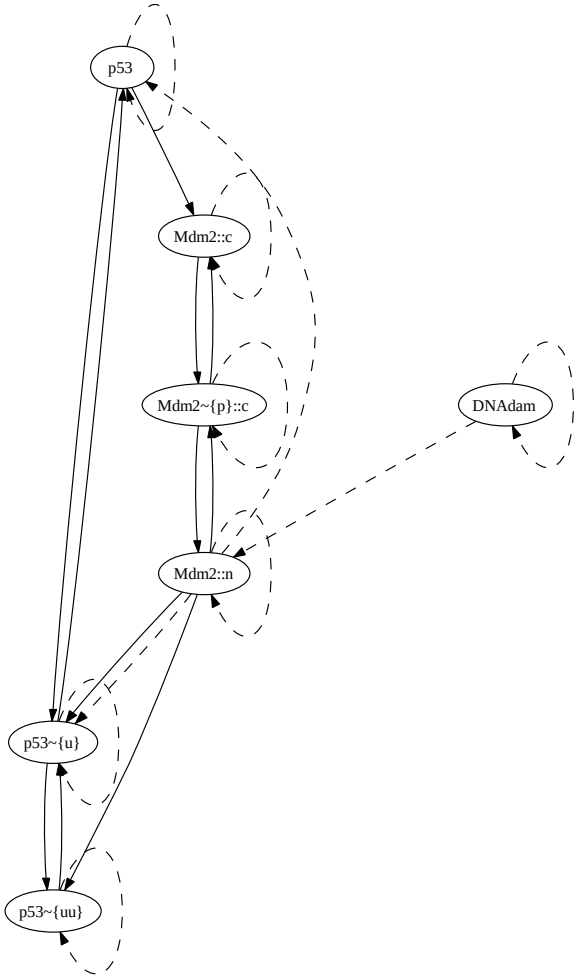
Thomas's conditions

for multistationarity

and oscillations apply here :

P53-Mdm2: Reaction Graph $\rightarrow_\alpha$ Influence Graph





Inhitions hidden in the kinetic expressions are missed

Influence Graph Abstraction from the Differential Semantics

Let us denote by β the mapping from $\mathcal{C}_\mathcal{R}$ to $\mathcal{D}_\mathcal{J}$ that extracts $\dot{x_k}$ and hence the Jacobian from the kinetic expressions in the reaction rules.

Def. 16 *The differential influence abstraction* $\alpha_{\mathcal{JI}} : \mathcal{D}_\mathcal{J} \rightarrow \mathcal{A}_\mathcal{I}$ *is the function*

$$\alpha_{\mathcal{JI}}(x) = \{A \textit{ activates } B \mid \partial \dot{x_B}/\partial x_A > 0 \textit{ in some point of the space}\}$$
$$\cup \{A \textit{ inhibits } B \mid \partial \dot{x_B}/\partial x_A < 0 \textit{ in some point of the space}\}$$

defined purely from the kinetic expressions... compatibility with the rules ?

Monotonic Kinetics

Def. 17 *A kinetic expression e_i is monotonic w.r.t. a reaction model x iff for all molecules x_k we have*

1. *for all points of the space $\partial e_i/\partial x_k \geq 0$*
2. *if there exists a point in the space s.t. $\partial e_i/\partial x_k > 0$ then $l_i(x_k) > 0$*

The mass action law kinetics, $e_i = k * \Pi {x_i}^{l_i}$, are monotonic

Hill's kinetics (and Michaelis-Menten kinetics when $n = 1$)
$e_i = V_m * {x_s}^n/(K_m + {x_s}^n)$ where $V_m = k * (x_e + x_e * x_s/K_m)$ for an enzymatic reaction $x_s = [x_e] => x_p$, are also monotonic.

Theorem 18 *For any reaction model x with monotonic kinetics, $\alpha_{\mathcal{JI}} \circ \beta(x) \subseteq \alpha_{\mathcal{RI}}(x)$.*

Precise Kinetics

Def. 19 *A kinetic expression e_i is precise w.r.t. a reaction model x iff for all molecules x_k we have*

1. *for all points of the space $\partial e_i/\partial x_k \geq 0$*
2. *there exists a point in the space s.t. $\partial e_i/\partial x_k > 0$ iff $l_i(x_k) > 0$*

Note that precise implies monotonic.

Proposition 20 *Mass action law, Michaelis Menten, and Hill kinetics are precise.*

Theorem 21 *If x has precise kinetics and no molecule is at the same time an activator and an inhibitor of the same target molecule, then $\alpha_{\mathcal{RI}}(x) = \alpha_{\mathcal{JI}} \circ \beta(x)$.*

Conclusion

- The algebraic setting of abstract interpretation applies to
  1. the organization of the syntactical, stochastic, discrete, and boolean semantics of reaction models into a hierarchy of semantics
  2. the mathematical definition of activation/inhibition influence graphs either from the syntax of the rules, or from the differential semantics
- the differential semantics does not belong to that hierarchy of semantics (with the rule set inclusion ordering)
- *thm 1* for monotonic kinetics (like all standard kinetics), the syntactical influences over-approximate the differential influences
- *thm 2* for precise kinetics with no both activation and inhibition influences, the syntactical and differential influences are the same
- the (easily computable) syntactical influences reveal hidden negative feedback in purely forward reaction cascades like MAPK [Sepulchre 07]