Parameter Space Abstraction and Unfolding Semantics of Discrete Regulatory Networks

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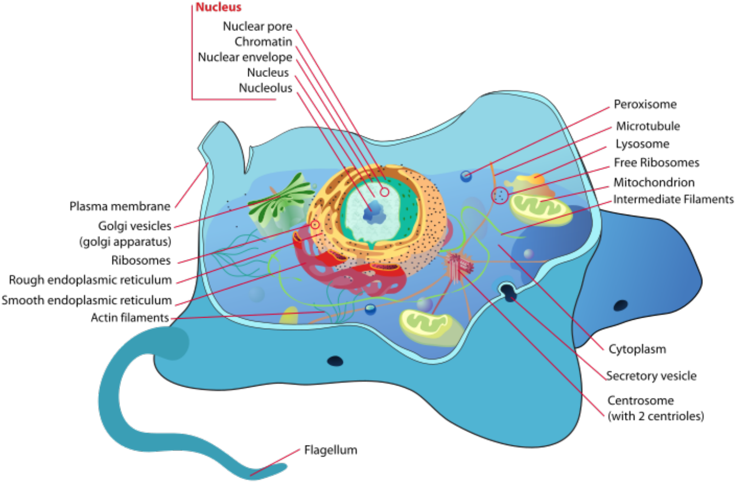
MeFoSyLoMa 29/09/2017

Outline

- Motivation
- Parametric Regulatory Networks
- Abstraction of Parameter Space
- Unfoldings
- Experimental results
- Conclusion

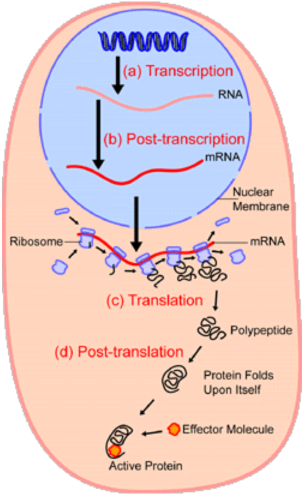
Cell Structure



Source: Wikipedia

Cell Dynamics

Cell Dynamics are facilitated by synthesis of proteins.



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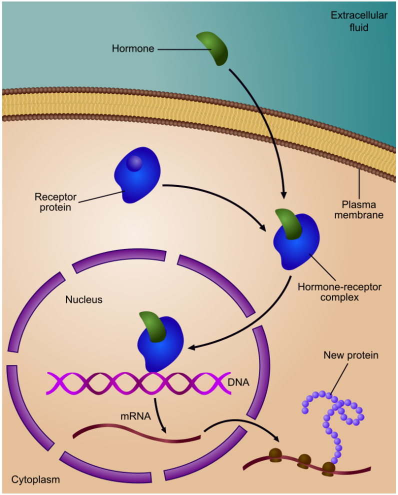
Dynamics Regulation

Gene activation is subject to presence of combination of transcription factors, e.g. proteins or complexes.



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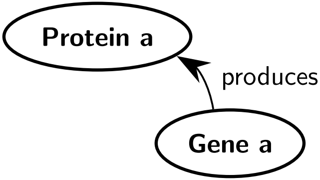

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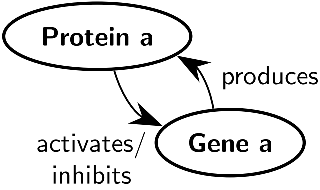

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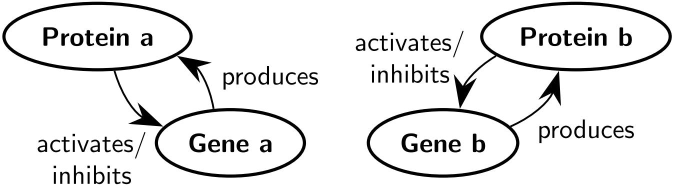

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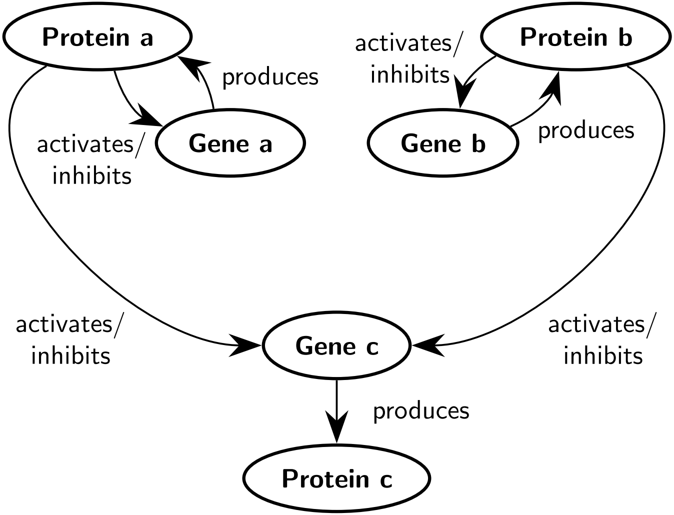

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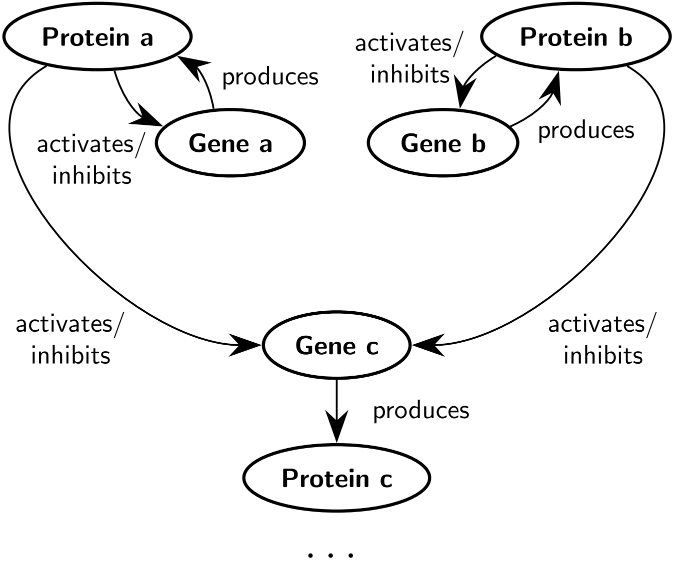

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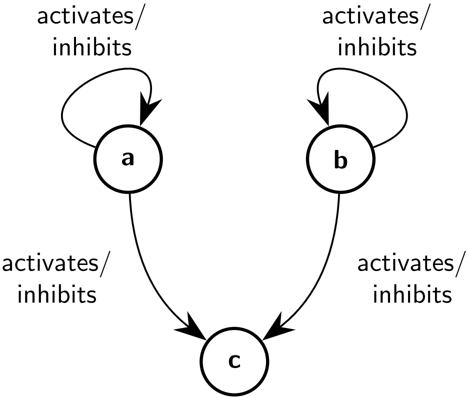

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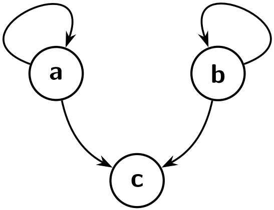
Boolean Networks

Influence graph:



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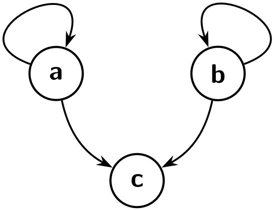

Definition (Boolean Network)

A Boolean network is a set of n Boolean variables $V = \{v_1, \ldots, v_n\}$ and a composite function $F = (f_1, \ldots, f_n) : \{0,1\}^V \to \{0,1\}^V$.

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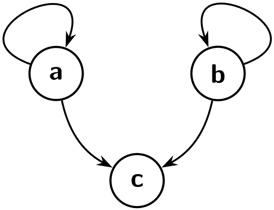

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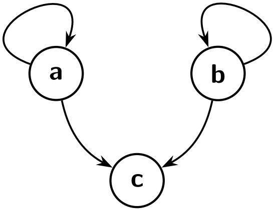

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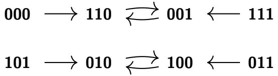

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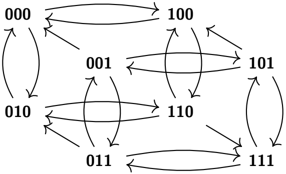

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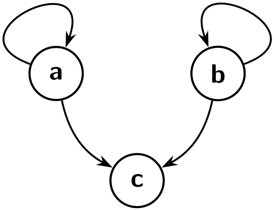

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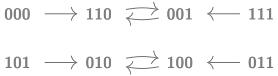

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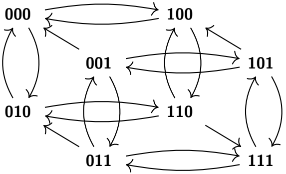

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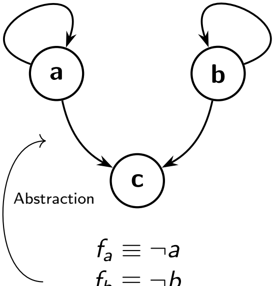

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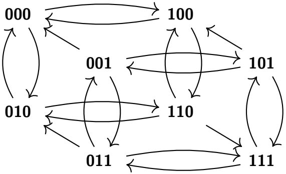

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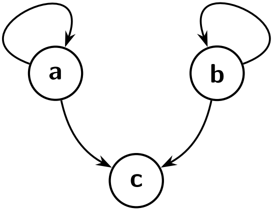

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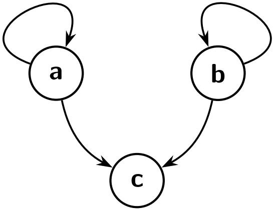

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A parametric regulatory network is an influence graph $G = (V, I)$ where $V = \{v_1, \ldots, v_n\}$ is a set of Boolean variables and $I \subseteq V \times V$.

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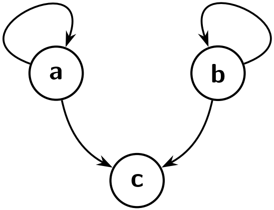

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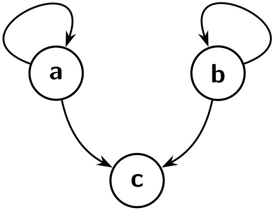

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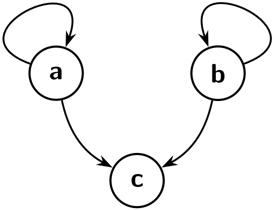

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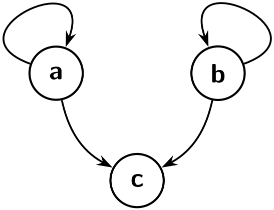

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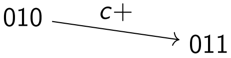

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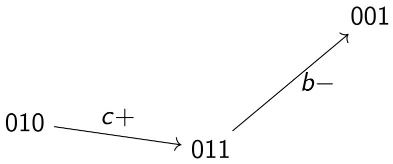

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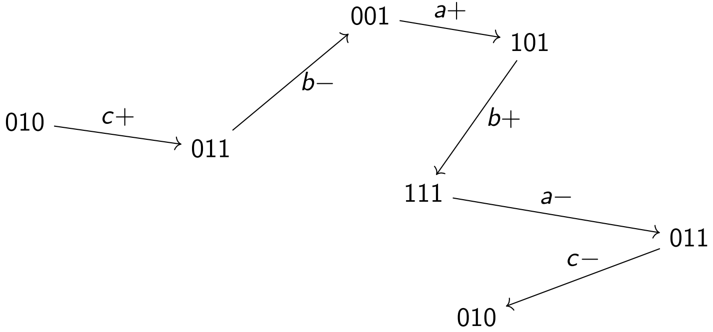

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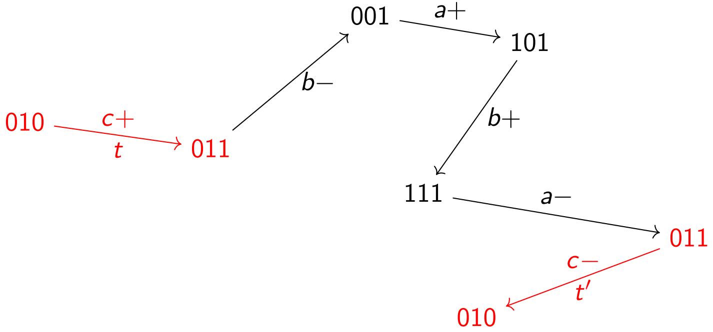

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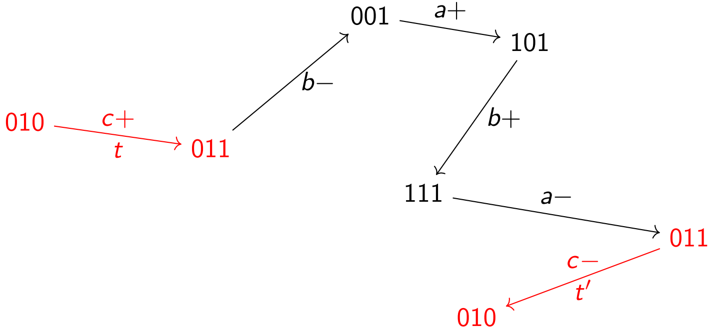

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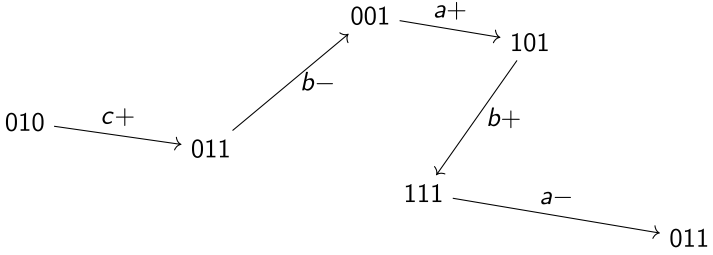

We keep track of a set of viable parametrisations $p(T)$ for a given set of transitions T.
The number of parametrisations is double exponential in the number of regulators.

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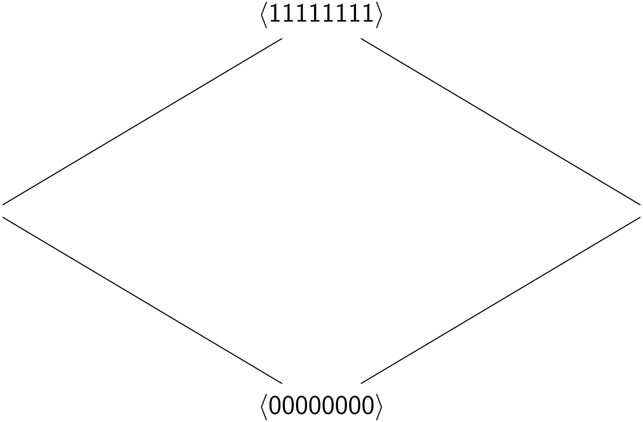
Bounded convex sublattice is given uniquely by its lower and upper bound.
We abstract the parametrisation sets by bounded convex sublattices specified by their infimum and supremum parametrisations (L, U) to obtain the *abstract parametrisation set* $p^{\#}(T)$.

Abstraction of parametrisation sets



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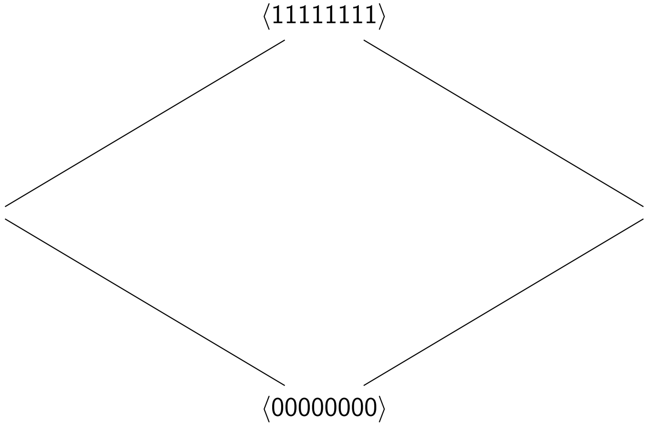

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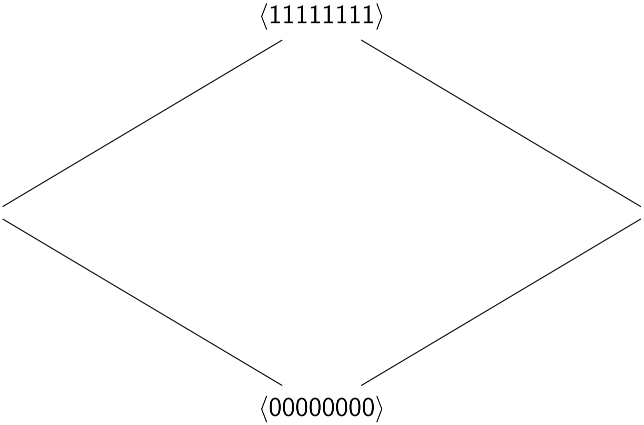

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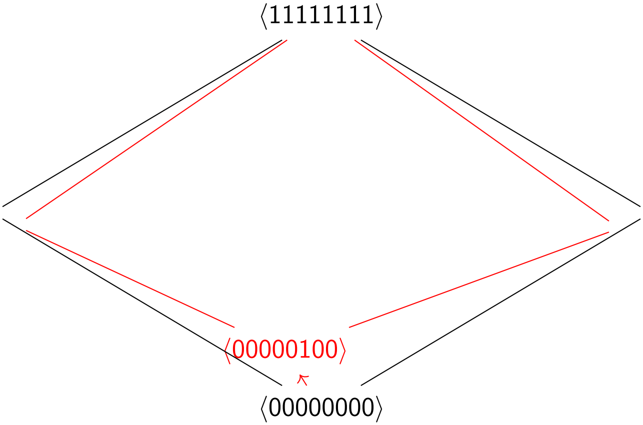

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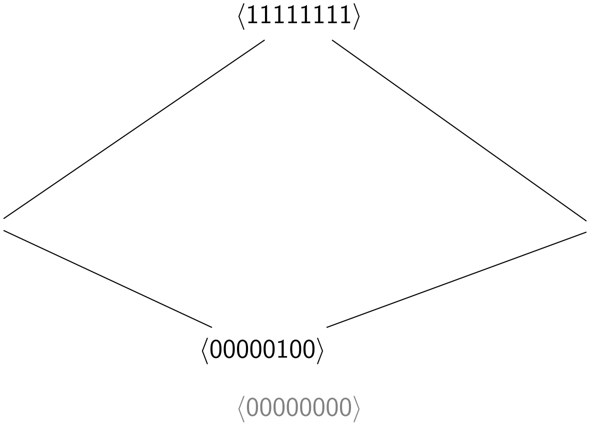

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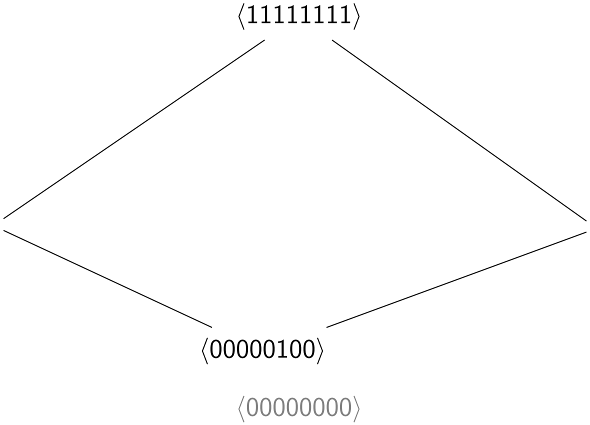

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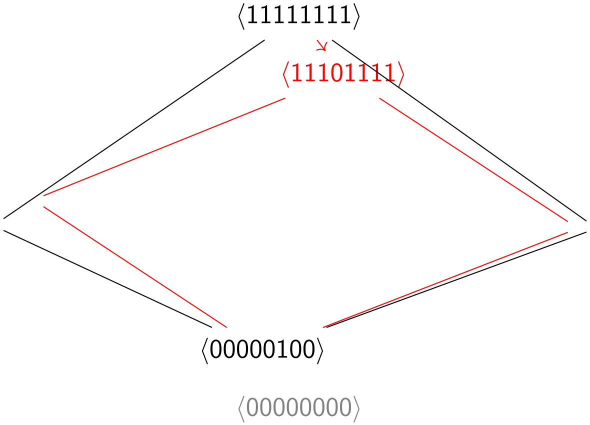

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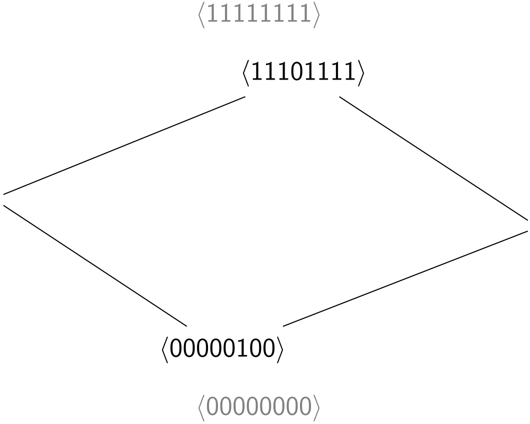

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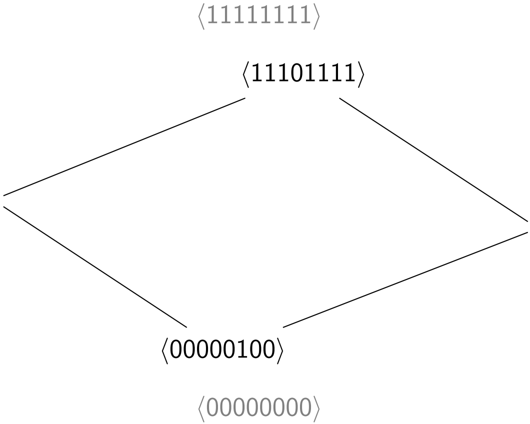

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We compute $p^{\#}(T \cup \{t\})$ from $p^{\#}(T)$ in $\mathcal{O}(1)$.

Properties of Parametrisation Set Abstraction

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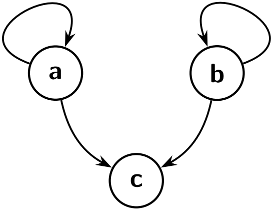
The traces, and in turn, reachable states in the abstract domain are identical to the traces and reachable states in the concrete domain.

Influence Constraints



$a = 0$	$P_{a,0}$
$a = 1$	$P_{a,1}$
$b = 0$	$P_{b,0}$
$b = 1$	$P_{b,1}$
$a = 0, b = 0$	$P_{c,00}$
$a = 0, b = 1$	$P_{c,01}$
$a = 1, b = 0$	$P_{c,10}$
$a = 1, b = 1$	$P_{c,11}$

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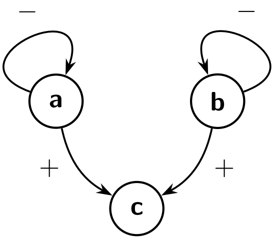

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$b = 0$	$P_{b,0}$
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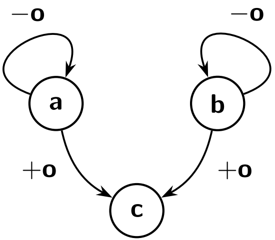
$a = 1, b = 1$	$P_{c,11}$

$(u, v) \in I$ is *positive*-monotonic: $\forall \omega_u < \omega'_u \Rightarrow P_{v,\omega} \leq P_{v,\omega'}$
$(u, v) \in I$ is *negative*-monotonic: $\forall \omega_u < \omega'_u \Rightarrow P_{v,\omega} \geq P_{v,\omega'}$

$(\forall w \in V : w \neq u \Rightarrow \omega_w = \omega'_w)$

Influence Constraints



$a = 0$	$P_{a,0}$
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$b = 0$	$P_{b,0}$
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$(u, v) \in I$ is observable: $\exists \omega_u \neq \omega'_u \Rightarrow P_{v,\omega} \neq P_{v,\omega'}$
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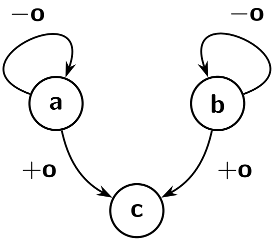

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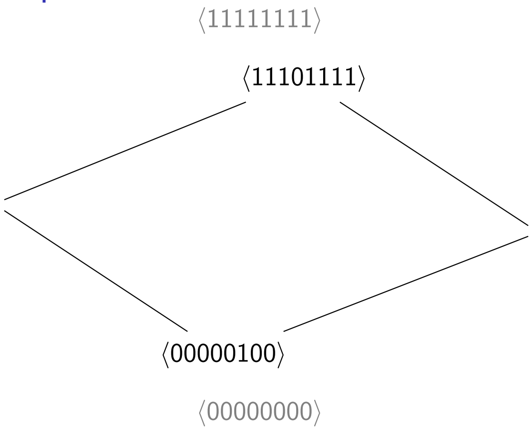
Abstraction of parametrisation sets



$$\langle 010\rangle \xrightarrow{c,+} \langle 011\rangle \xrightarrow{b,-} \langle 001\rangle$$

$$R = \{(a \xrightarrow{+} c), (b \xrightarrow{o} b)\}$$

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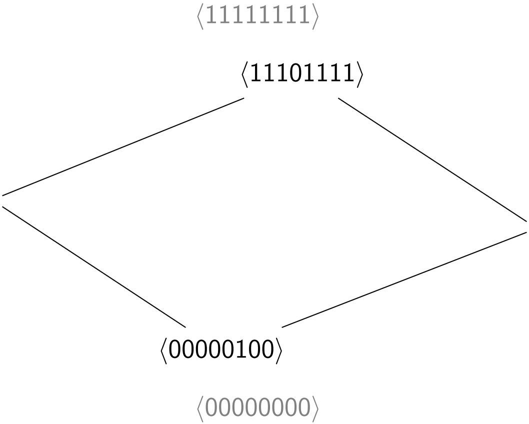

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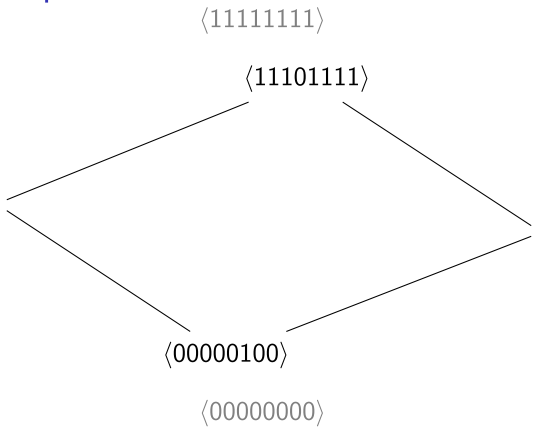

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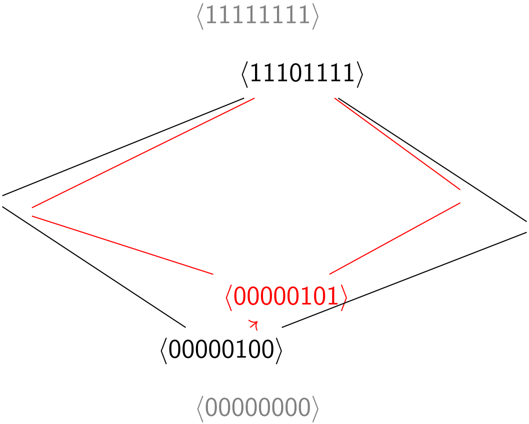

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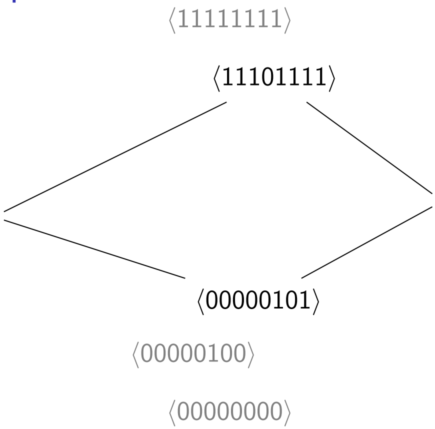

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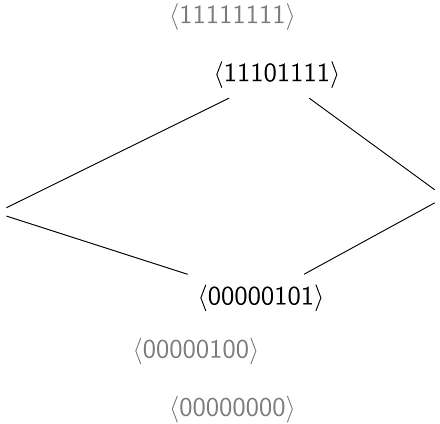

$\langle 010 \rangle \xrightarrow{c,+} \langle 011 \rangle \xrightarrow{b,-} \langle 001 \rangle$

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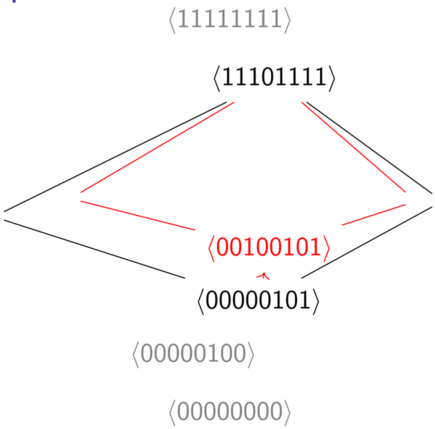
$P_{b,0} \neq P_{b,1}$

Abstraction of parametrisation sets



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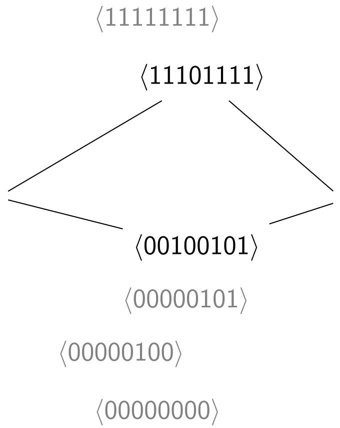

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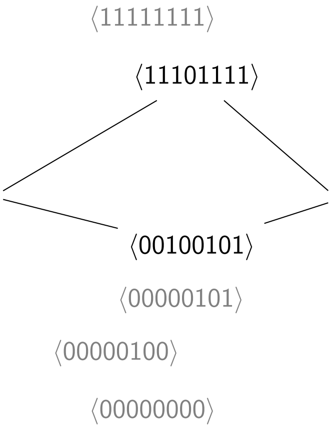

$\langle 010 \rangle \xrightarrow{c,+} \langle 011 \rangle \xrightarrow{b,-} \langle 001 \rangle$
$R = \{(a \xrightarrow{+} c), (b \xrightarrow{o} b)\}$

We compute $p_R^{\#}(T \cup \{t\})$ from $p_R^{\#}(T)$ in $\mathcal{O}(|\Omega_v|)$.

Properties of Parametrisation Set Abstraction

The abstract parametrisation set is equal to the smallest convex sublattice containing concrete parametrisation set,
$p_R^{\#}(T) = [p_R(T)]$.

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$$\Longrightarrow$$

The abstract set is empty exactly when the concrete set is empty, $p_R^{\#}(T) = \emptyset \Leftrightarrow p_R(T) = \emptyset$.

$$\Longrightarrow$$

The traces, and in turn, reachable states in the abstract domain are identical to the traces and reachable states in the concrete domain.

Unfoldings

To combat combinatorial explosion of state space we employ unfolding as understood by Esparza et al., 2002.

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We modify the cut-off criterion to use the subset ordering on parametrisation sets instead of the total adequate order.
This leads to 'backwards' cut-offs.

Results

We compare against the size of the complete symbolic execution tree achieved from the same initial state by methods of Gallet et al., 2014.

Model	Type	# nodes	# events (incl. cut-offs)	Sym. exec. size
CD[1] (Fgf8=0)	BN	5	554 (1,939)	8,312
CD (Fgf8=1)	BN	5	1,054 (3,530)	8,312
EGF-TNFα[2]	BN	13	1,057 (2,658)	534,498
λ-switch[3]	MN	4	170 (575)	68,011
λ-switch (MM)	MN	4	157 (527)	15,139
PSD[4] (MM)	MN	14	19,954 (88,994)	-
DS[5]	MN	15	781 (2,698)	-
DS (MM)	MN	15	731 (2,507)	-

[1] Mammalian Cortical Area Development (Giacomantonio et al. 2010)

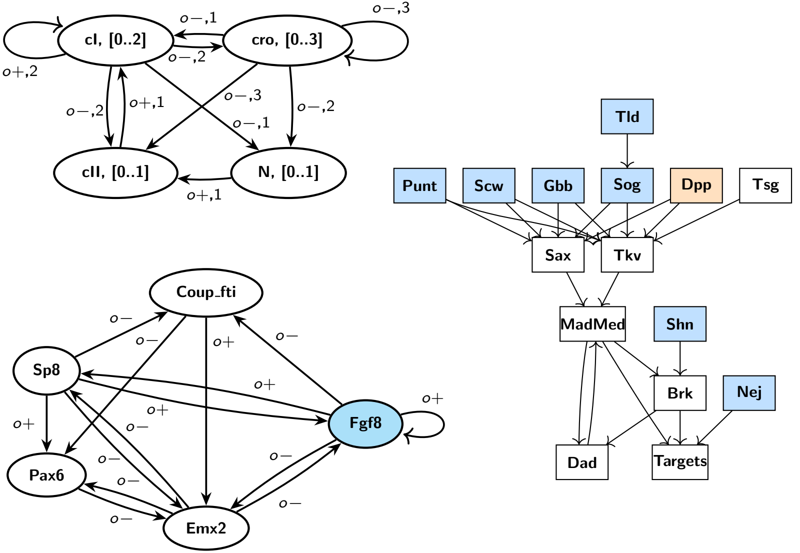
[2] EGF-TNFα Signalling Pathway (MacNamara et al. 2012), (Ostrowski et al. 2016)

[3] Regulatory Network of Bacteriophage λ (Gallet et al. 2014), (Klarner et al. 2012)

[4] Primary Sex Determination of Placental Mammals (Sánchez et al. 2016)

[5] Drosophila Signalling (Mbodj et al. 2013)

Examples of Used Networks



Conclusion

Summary:

- A tight **abstraction of parametrisation sets** using convex sublattices **preserving the reachable state space**.
- **Unfolding** semantics for Parametric Regulatory Networks utilising the parametrisation set abstraction.
- Efficient **reachability analysis** of Parametric Regulatory Networks.

Future Work:

- Attractors of Parametric Regulatory Networks.
- Explore more fine-grained abstractions.
- Exploit concurrency even more (contextual unfolding).