Three Applications of Formal Concept Analysis in Biochemistry and Systems Biology

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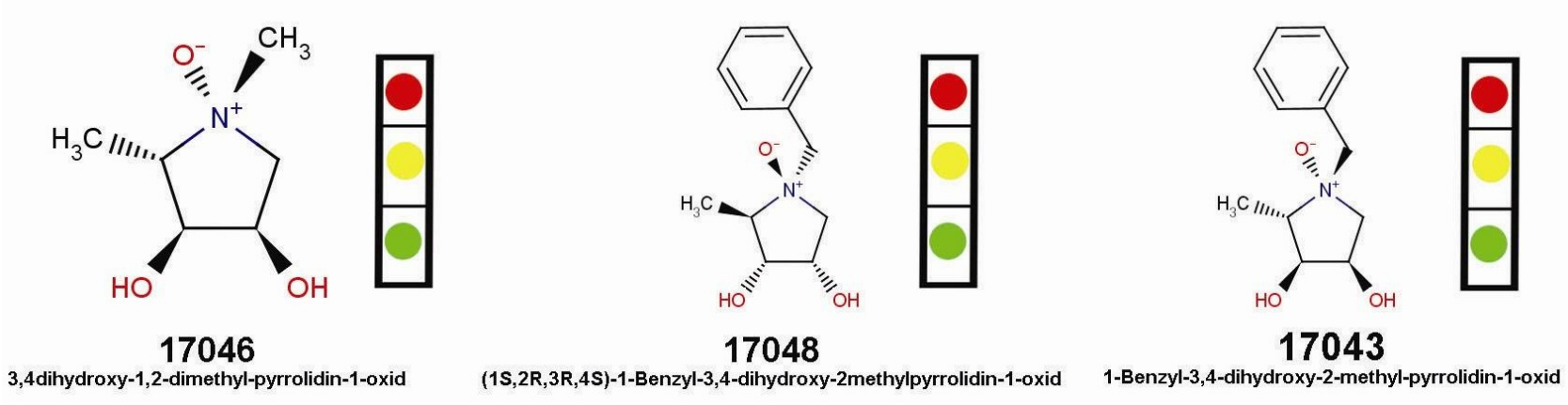
Outline

Example: HKI Natural Products Pool

- Collection of about 9.000 natural products, derivatives and synthetic analogues.
- Analysis of a screening for new drugs against tuberculosis: Substances with specific reaction against the M. tuberculosis complexes pknA:atpD ("hit1") or sigB:Rv2050 ("hit3")
- Ranking within classes according to significantly frequent combinations.
- The aim now: Order all substances by their fragments - may indicate structural similarity.



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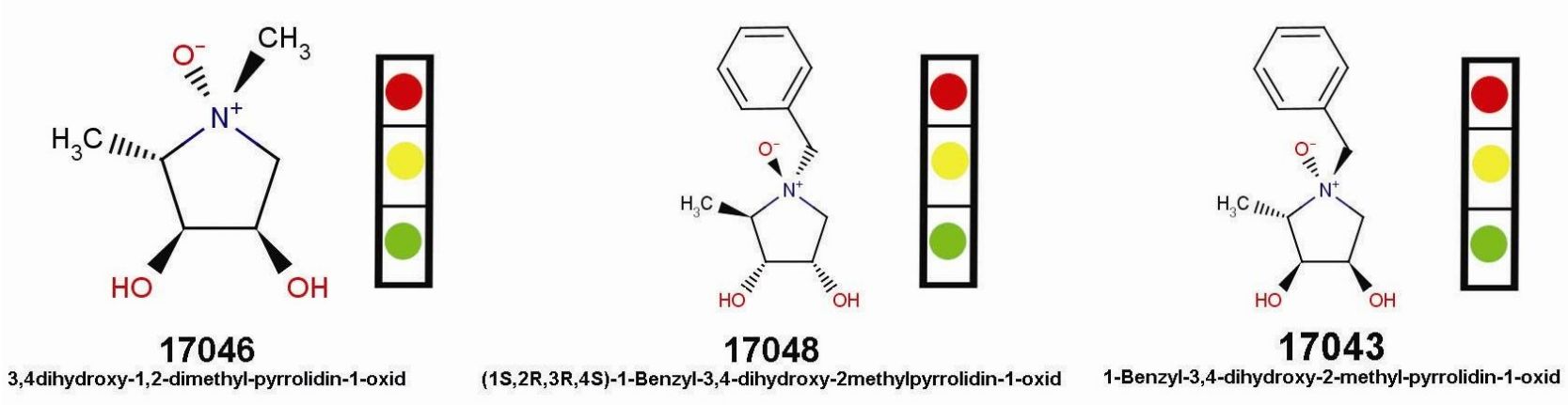

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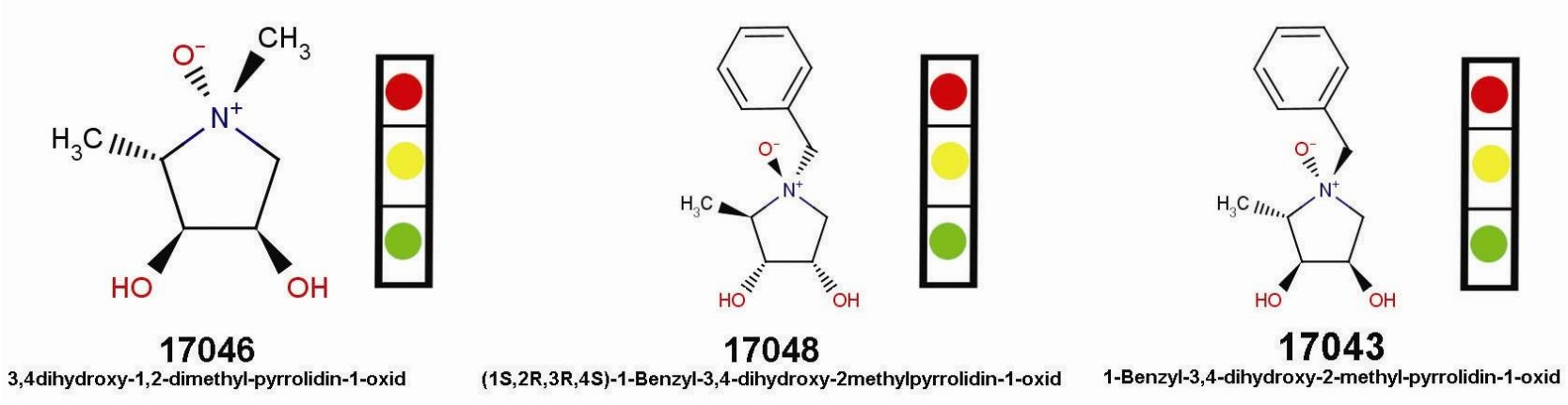

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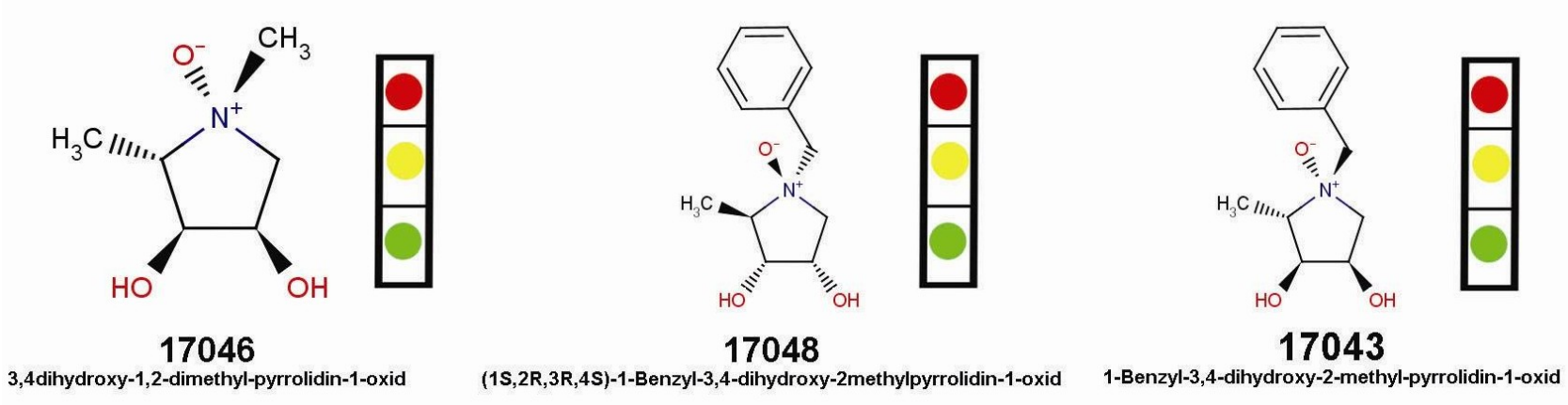
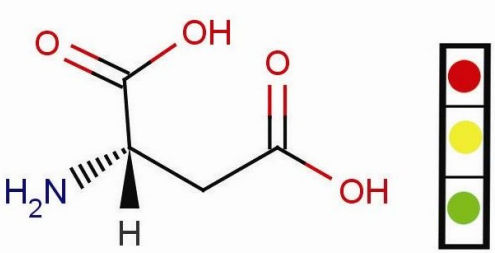
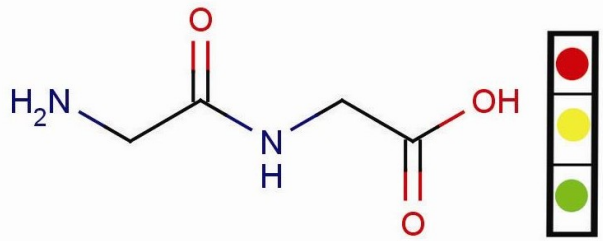


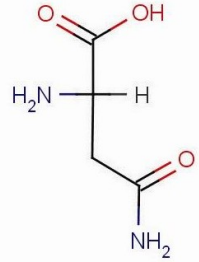
Formal Concepts

fragment	hit1	hit3	2 DOI	3I	5I	8I	9I	6I	7I	4I	6r	7r
substance												
17046	x									x	x	
17043	x									x	x	x
1133		x	x	x	x	x	x					
2892		x	x	x	x	x	x	x				
1055		x	x	x	x	x	x	x	x			

2 fragments common to substances 2892 and 1055:
2DOI C;-O;=O; 3I O;=C;







1133
L-Asparaginsäure

1055
Glycyl-glycin

2892
D/L-Asparagin
(Racemat)

Formal Concepts

fragment	hit1	hit3	2 DOI	3I	5I	8I	9I	6I	7I	4I	6r	7r
substance												
17046	x									x	x	
17043	x									x	x	x
1133		x	x	x	x	x	x					
2892		x	x	x	x	x	x	x				
1055		x	x	x	x	x	x	x	x			

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All fragments common to substances 2892 and 1055: hit3, 2DOI, 3I 0I, 5I, 8I, 9I, 6I

$\Rightarrow$ Formal concept
($\{$2892, 1055$\}$, $\{$hit3, 2DOI, 3I, 5I, 8I, 9I, 6I$\}$)

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Formal Concepts

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2 fragments common to substances 2892 and 1055: 2DOI, 3I

All substances with attributes 2DOI and 3I: 1133, 2892 and 1055

Formal Concepts

fragment	hit1	hit3	2DOI	3l	5l	8l	9l	6l	7l	4l	6r	7r
substance												
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1133		x	x	x	x	x	x					
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All substances with attributes 2DOI and 3l: 1133, 2892 and 1055
All attributes common to substances 1133, 2892 and 1055: hit3, 2DOI, 3l, 5l, 8l, 9l

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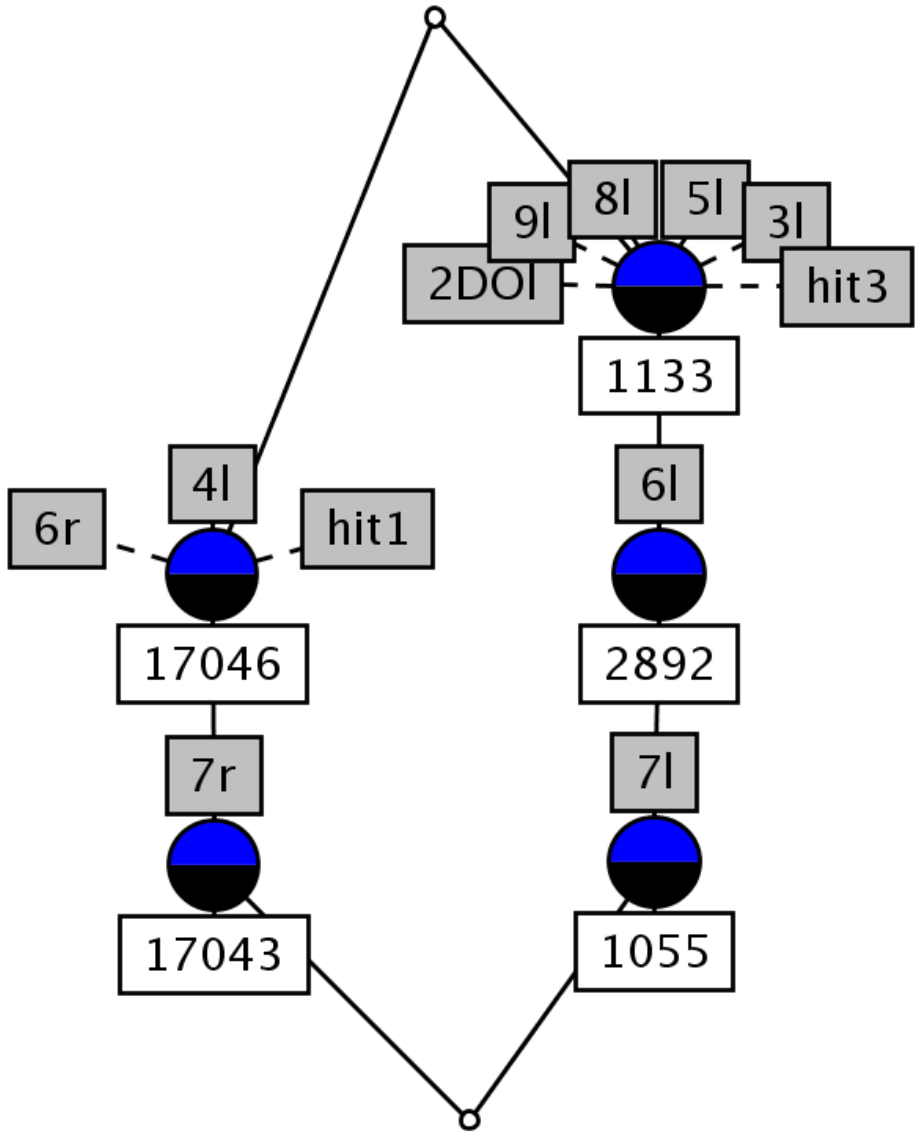
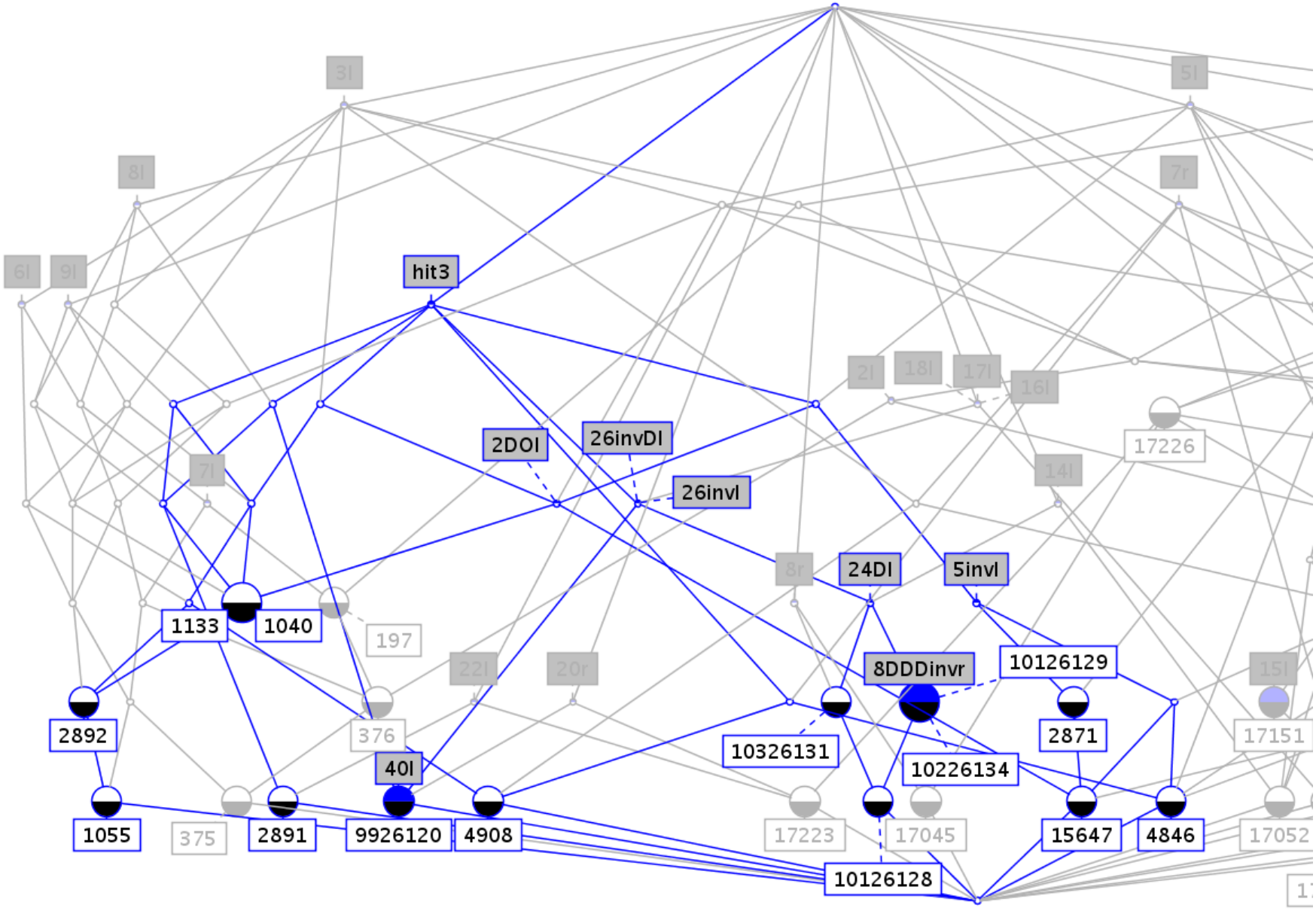
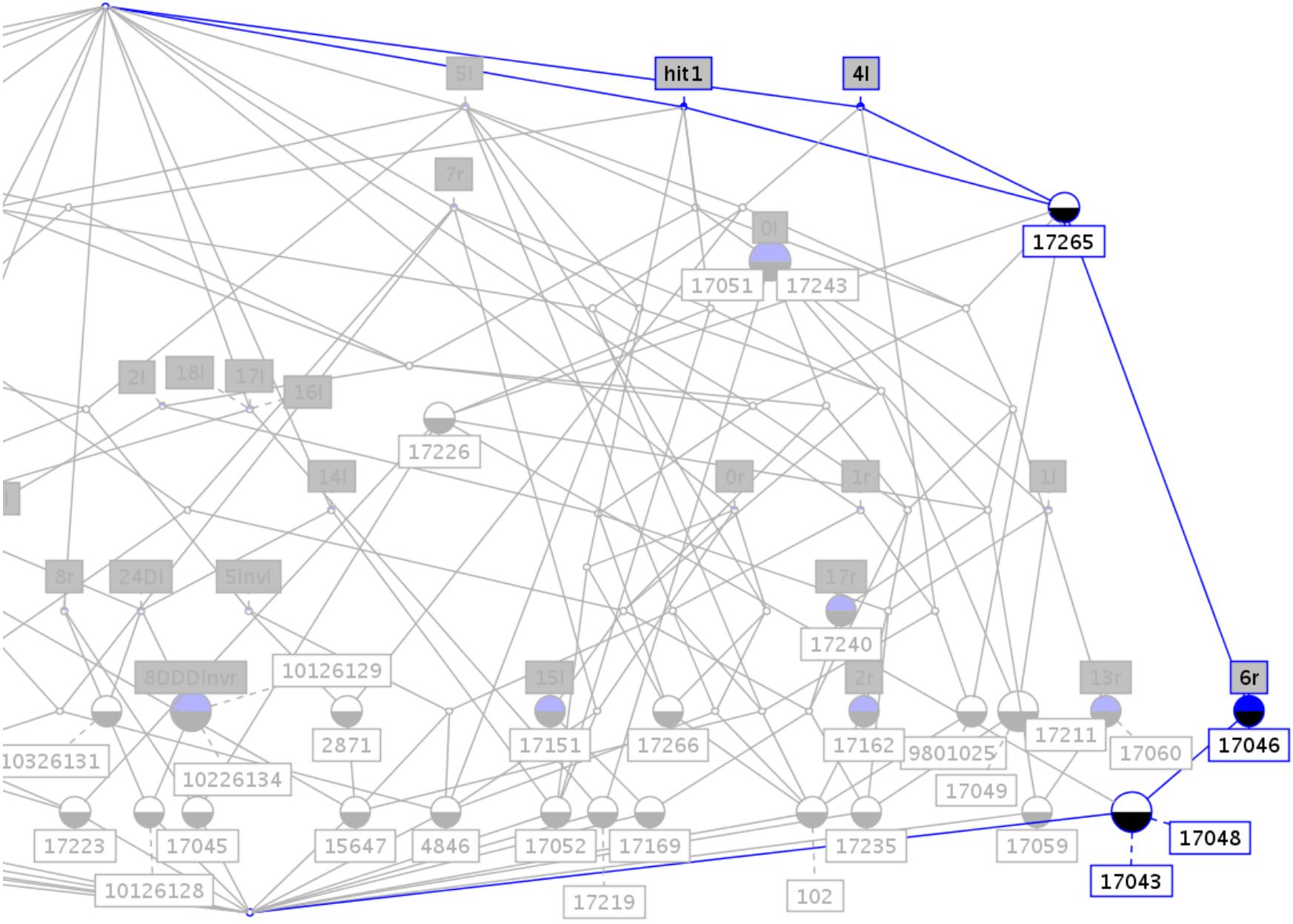
The Conceptual Hierarchy



The Class of Substances Specific Against sigB:Rv2050



A Fragment Specific Against pknA:atpD?



6r $\longrightarrow$ 4l, hit1.

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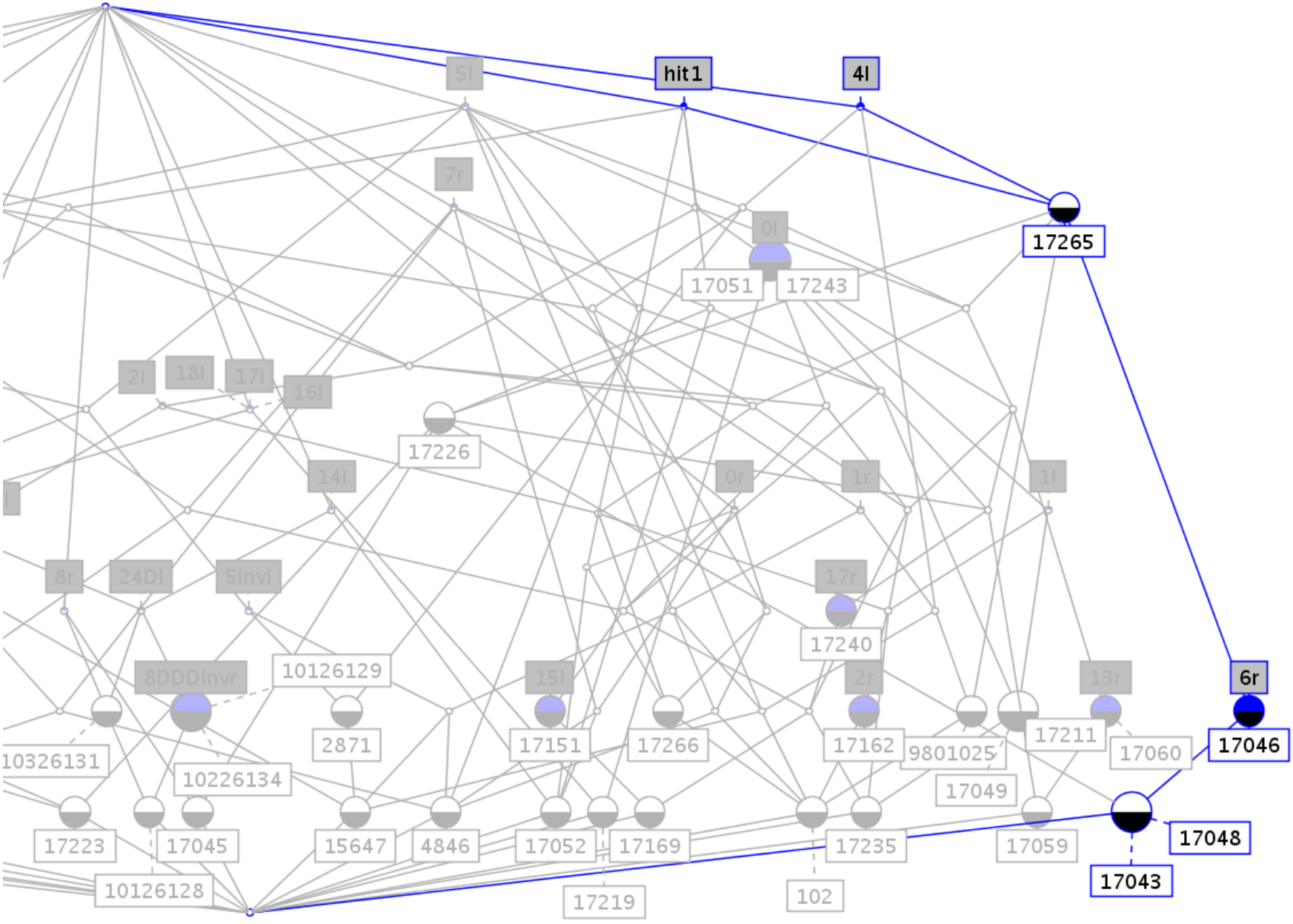

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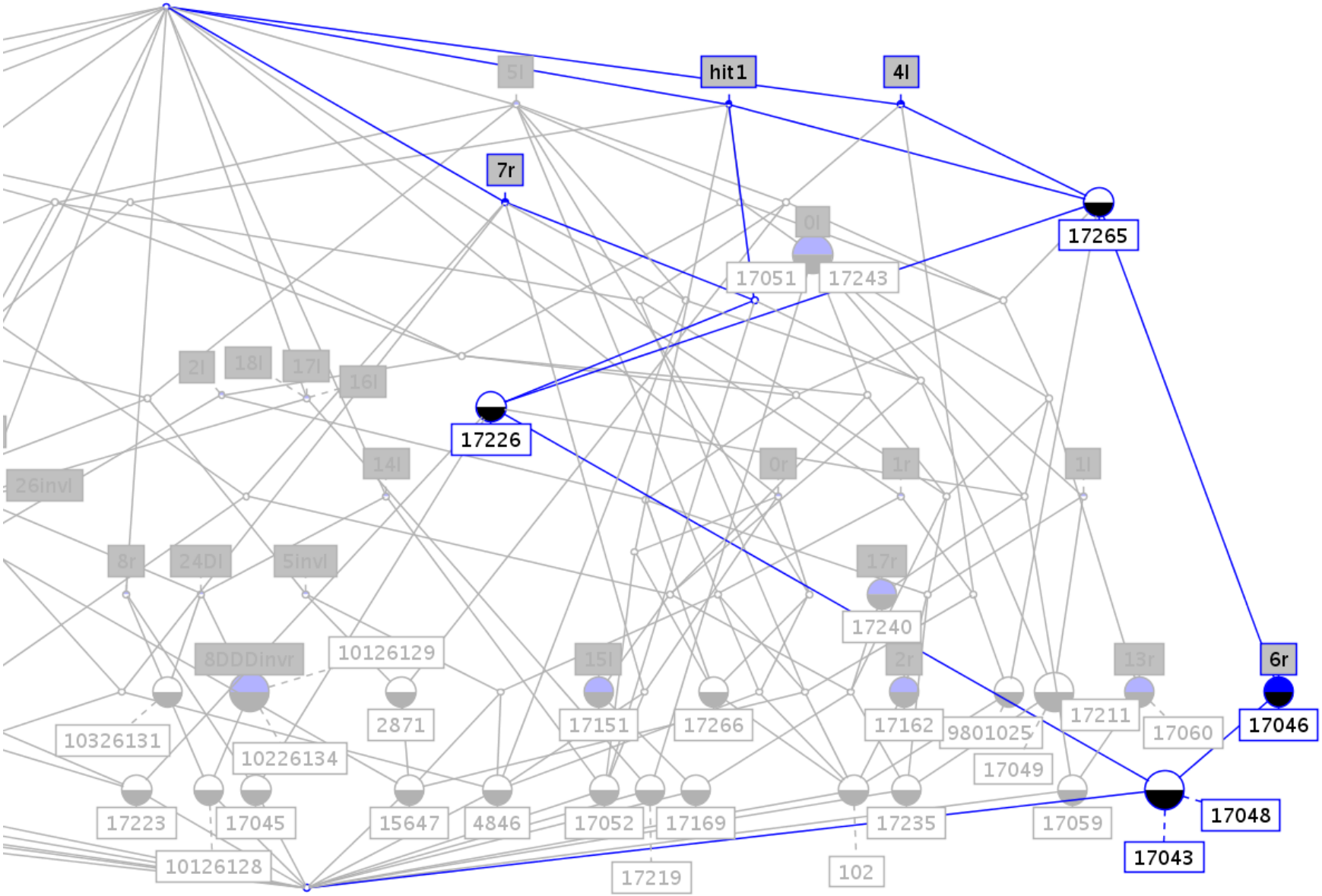

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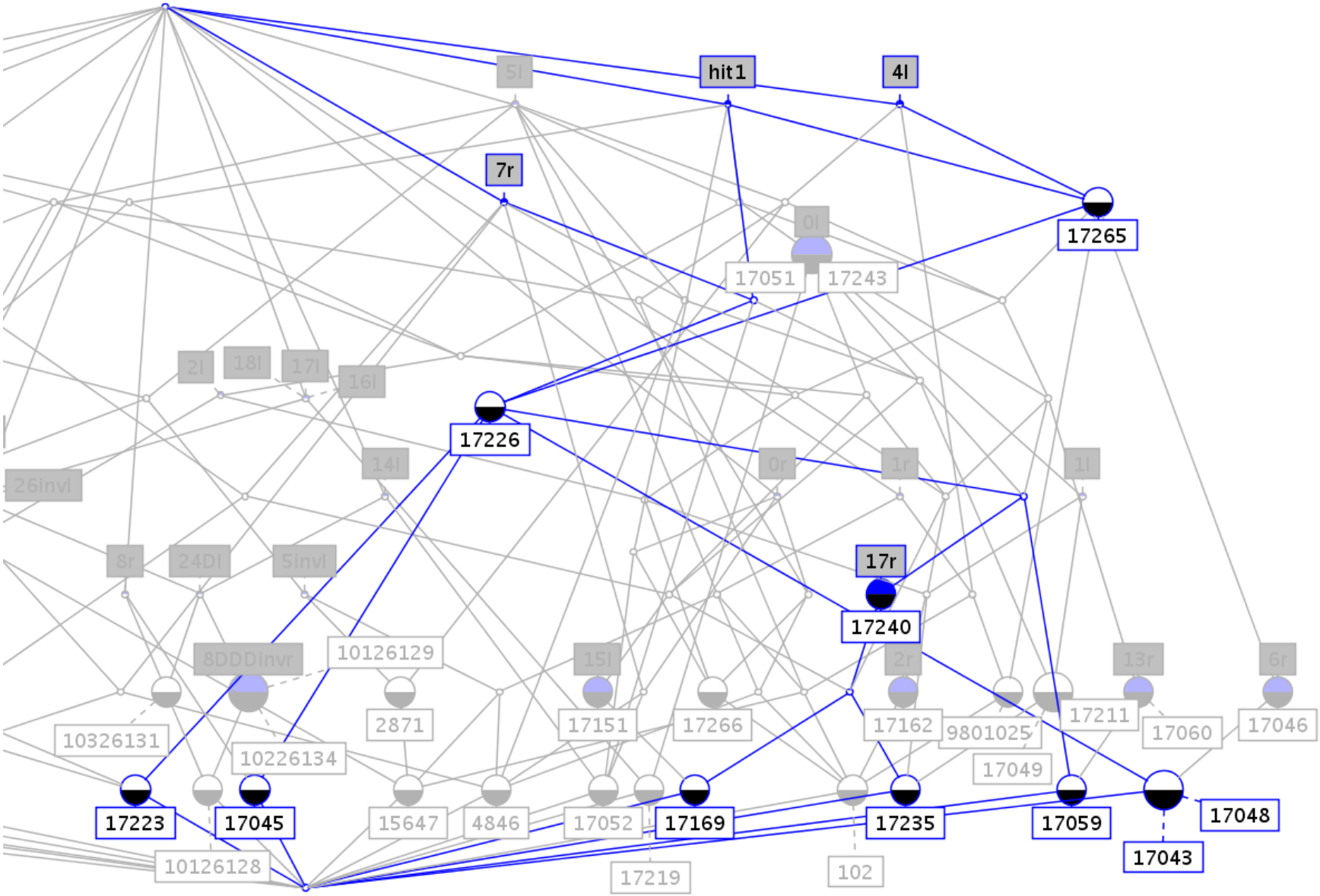
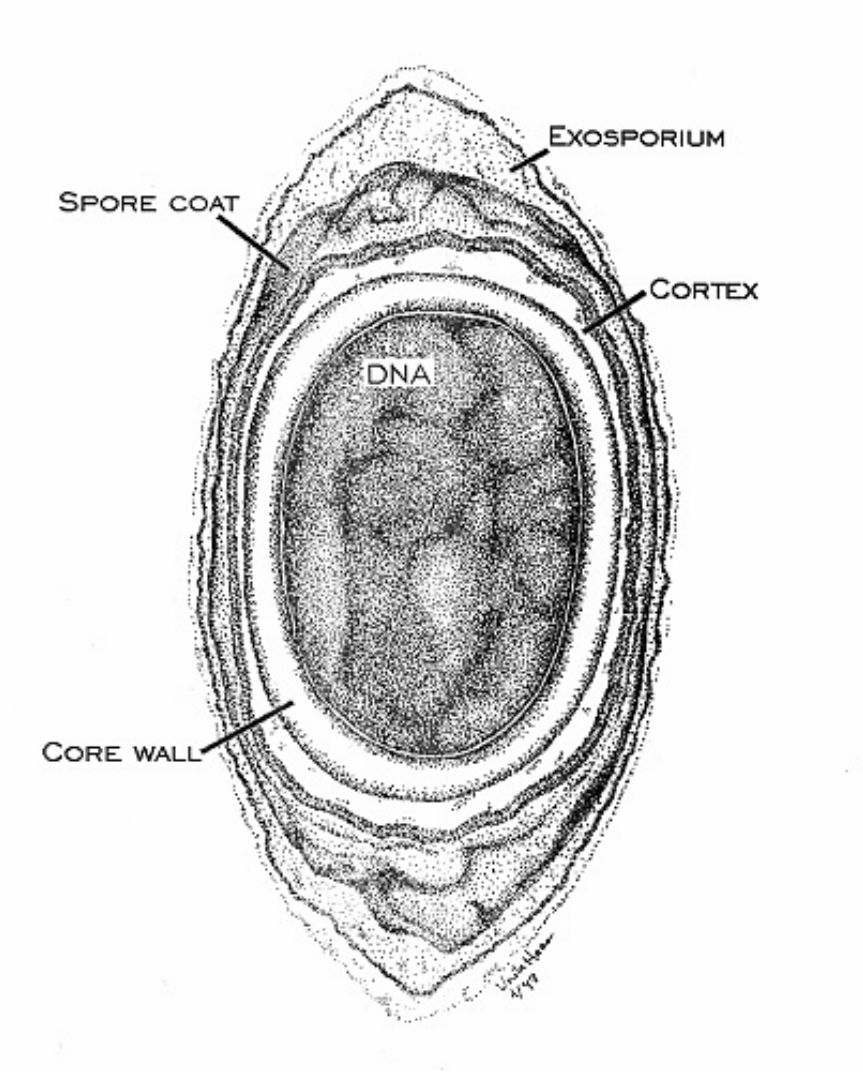


4l, 7r $\longrightarrow$ hit1

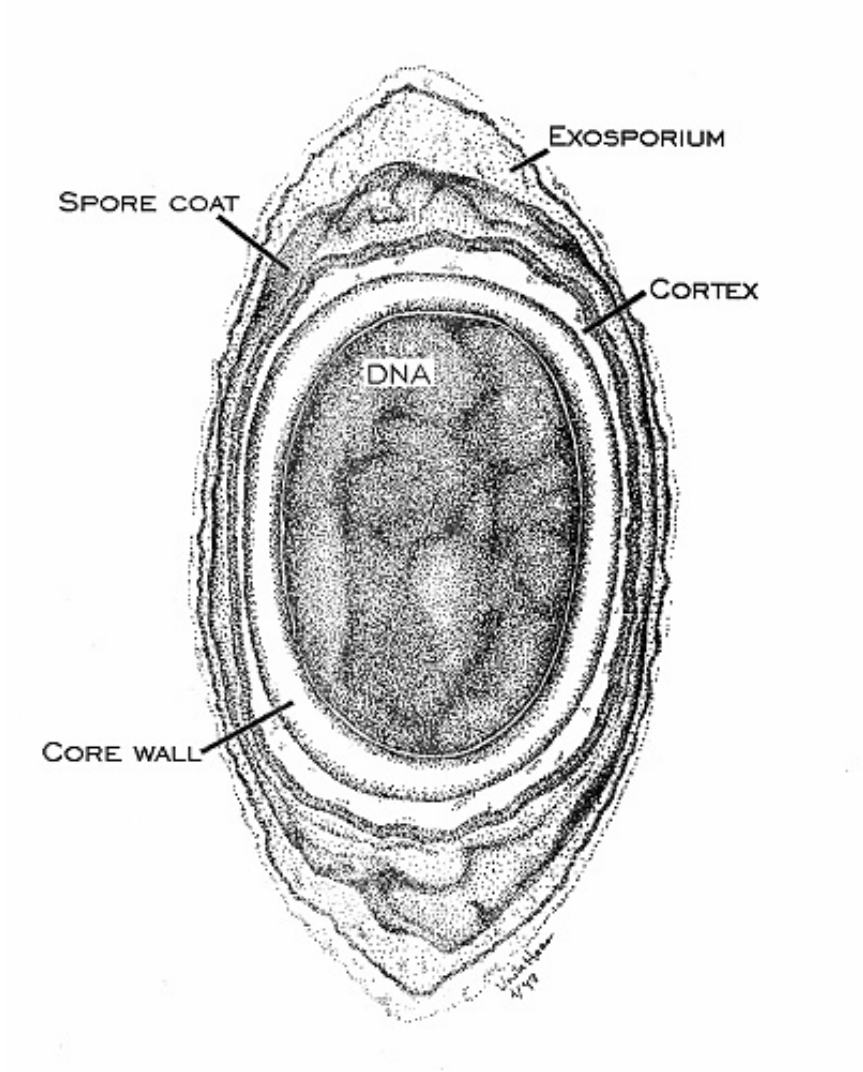
Outline

Bacillus subtilis



- Gram positive soil bacterium.
- Produces single endospores under environmental stress, which can survive ultraviolet or gamma radiation, acid, hours of boiling, or starvation.
- Switch between two completely different genetic programs.
- Model organism.

Bacillus subtilis



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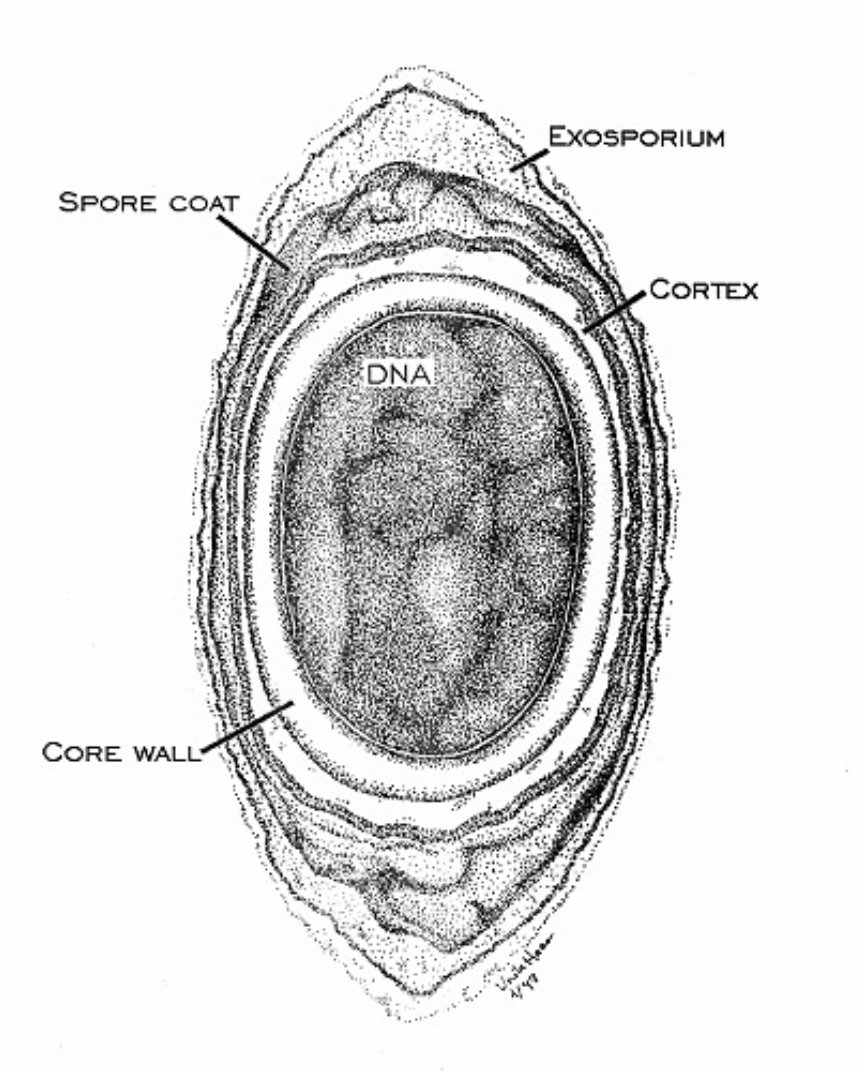

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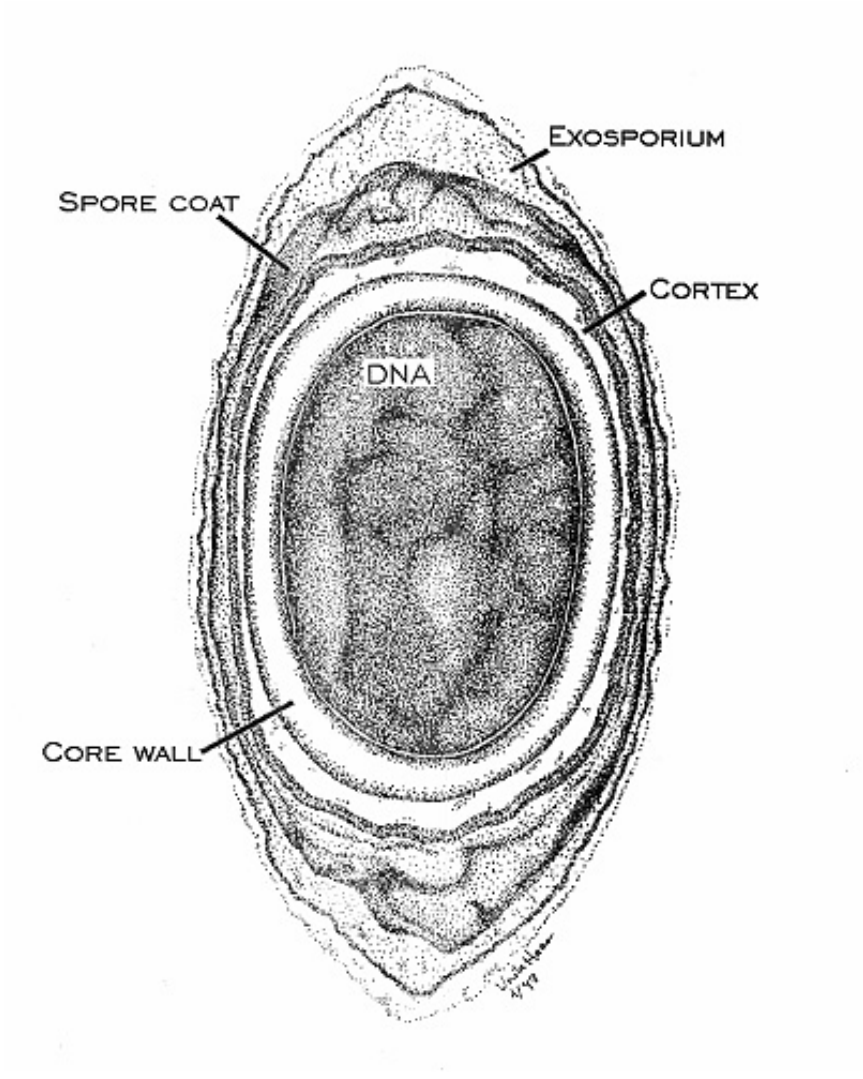

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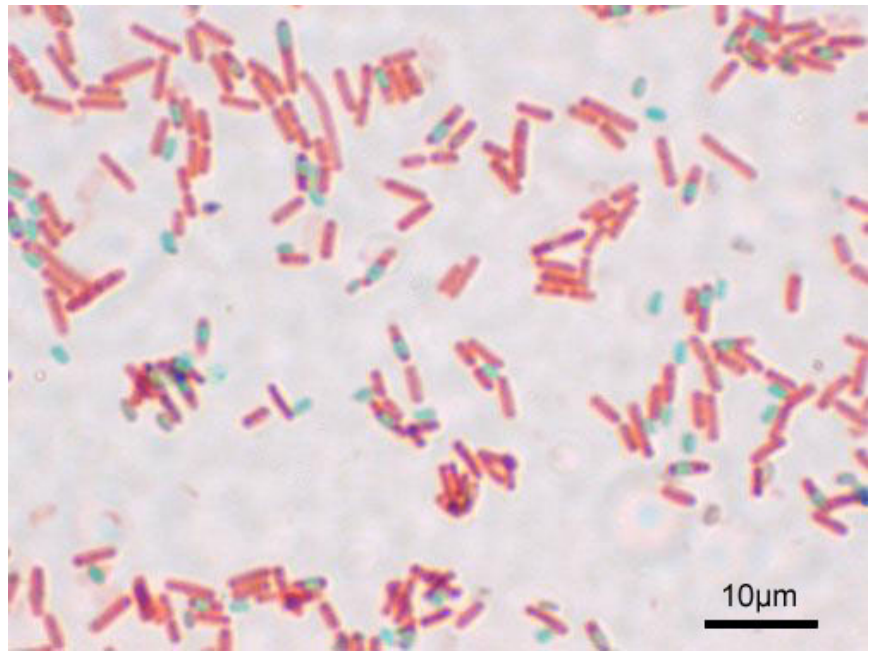
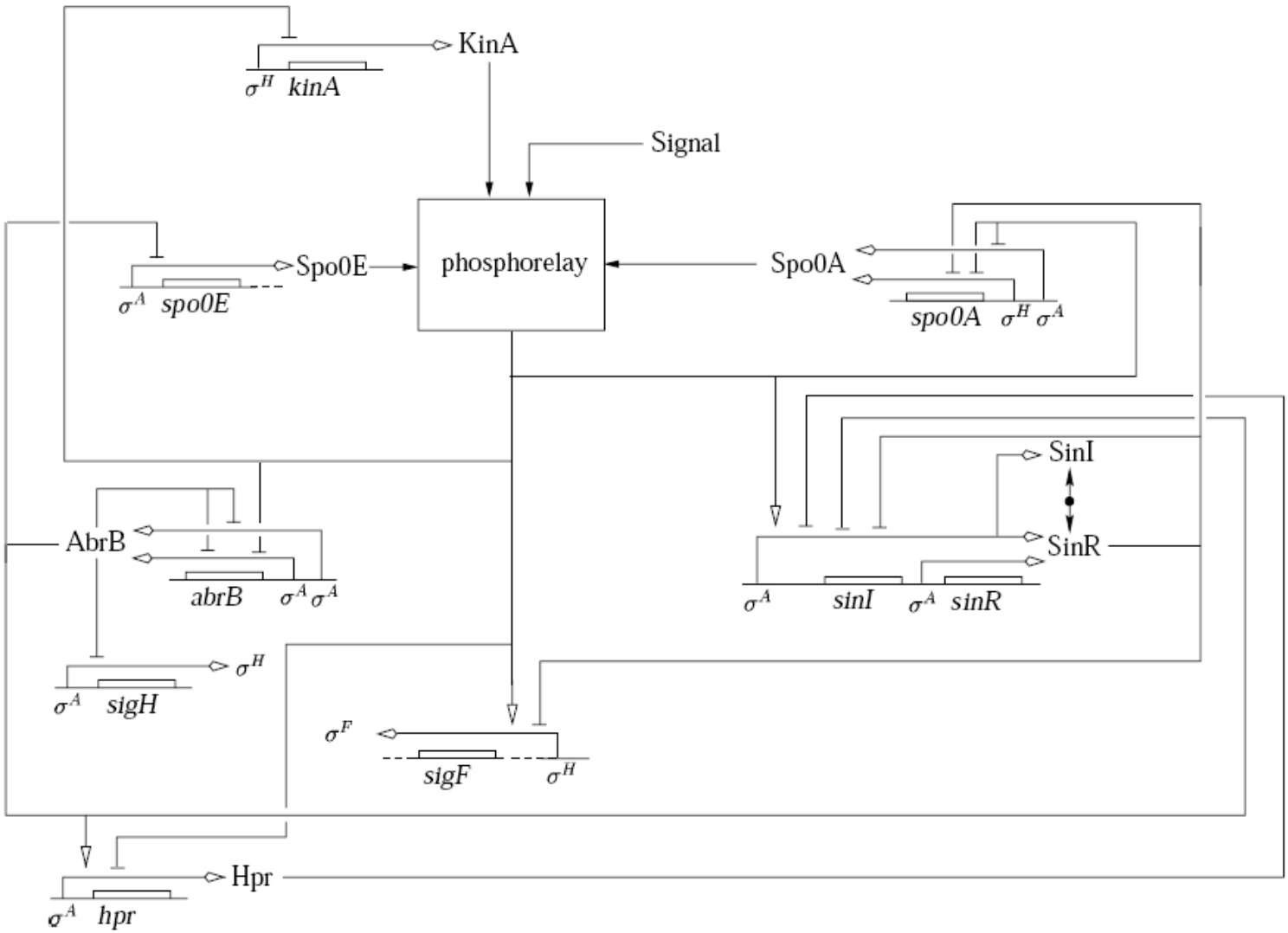
Some Main Regulators

- Signal: nutritional stress.
- Phosphorylation of the transcriptional regulator Spo0A by KinA, Spo0E (phosphatase) and Signal.
- Sigma transcription factors σ^A, σ^F and σ^H.
- Transcription regulators AbrB and Hpr.



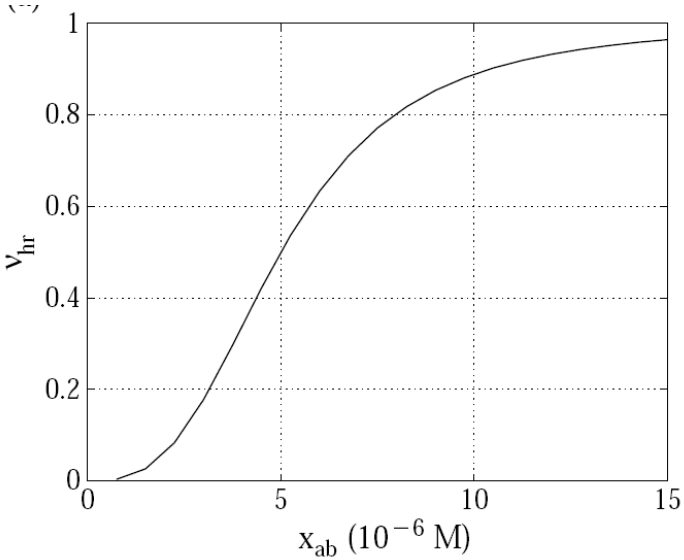
A Gene Regulatory Network

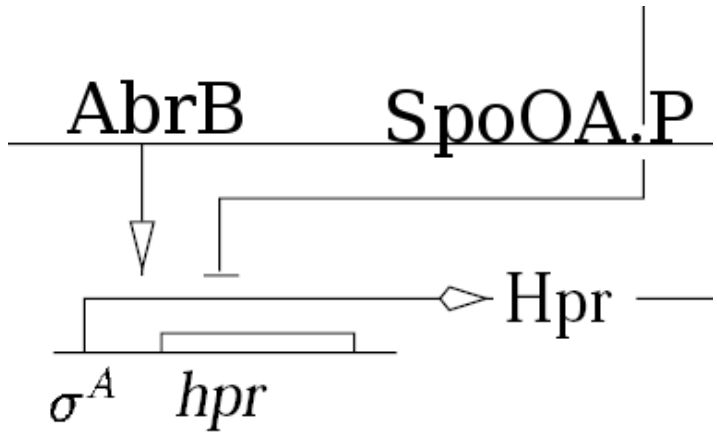


[Hidde de Jong. Qualitative Simulation of the Initiation of Sporulation in Bacillus subtilis. In: *Bulletin of Mathematical Biology* (2004) **66**, 261-299.]

Modeling the Dynamics as a Boolean Network

Thresholds for gene expression $\Rightarrow$ 0/1 levels capture essential properties of the network. Simultaneous update at discrete time points according to Boolean functions [Kau95]:





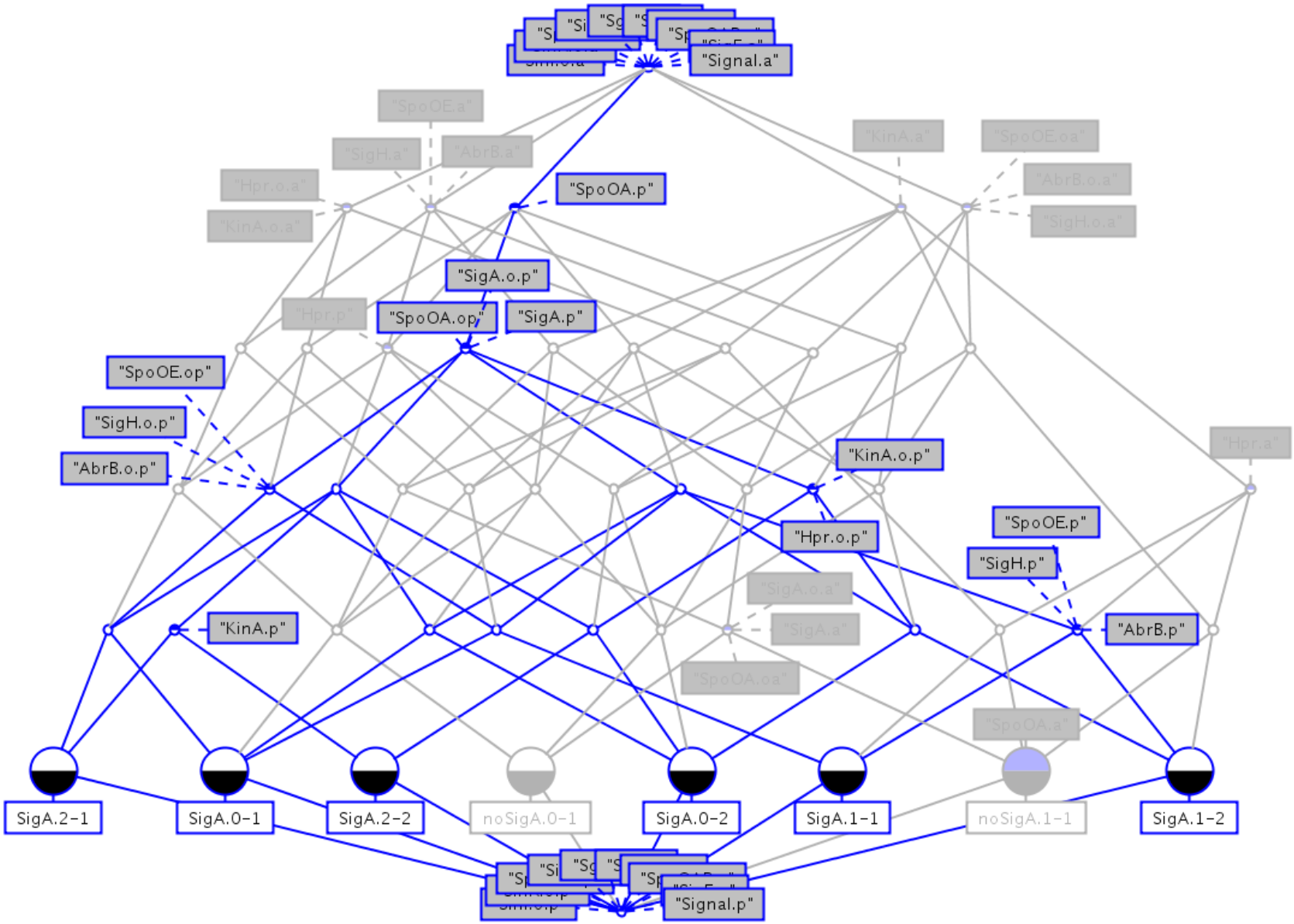
$$\text{Hpr.out} = \text{SigA.in} \wedge \text{AbrB.in} \wedge \overline{\text{SpoOA.P.in}}$$

[L. J. Steggles et al. Qualitatively modelling and analysing genetic regulatory networks: a Petri net approach. In: *Bioinformatics* 23 (3), 2007, 336-343.]

Simulations Starting from an Initial State without Stress

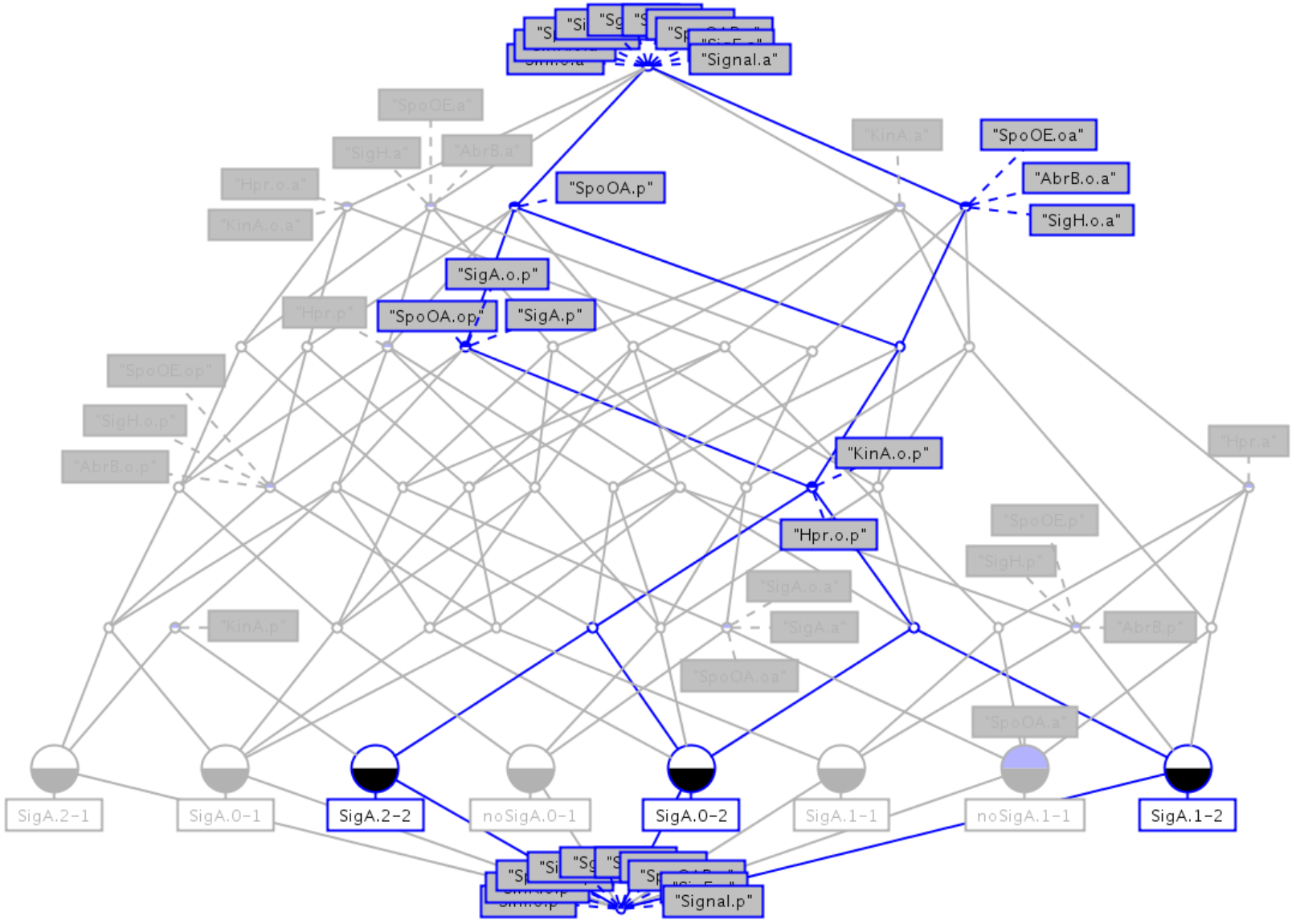
Entity / State	SigA.0	SigA.1	SigA.2	SigA.1	noSigA.0	noSigA.1	noSigA.1
Signal	0	0	0	0	0	0	0
SigA	1	1	1	1	0	0	0
SigF	0	0	0	0	0	0	0
KinA	0	0	1	0	0	0	0
SpoOA	1	1	1	1	1	0	0
SpoOA.P	0	0	0	0	0	0	0
AbrB	0	1	0	1	0	0	0
SpoOE	0	1	0	1	0	0	0
SigH	0	1	0	1	0	0	0
Hpr	1	0	1	0	1	0	0
SinR	0	0	0	0	0	0	0
SinI	0	0	0	0	0	0	0

Transitions with SpoOA.out.pres



$< 6 >$ SpoOA.out.pres $\rightarrow$ SigA.in.pres SpoOA.in.pres SigA.out.pres

Transitions with Hpr.out.pres



$< 3 >$ Hpr.out.pres $\rightarrow$ KinA.out.pres, SpoOA.out.pres, AbrB.out.abs, SpoOE.out.abs, SigH.out.abs

Outline

Attribute Exploration

- Interactive algorithm.
- Generates rules $A \longrightarrow B$ between attribute sets of a given data table.
- An expert or a computer program decides about the general validity of the rule.
- No $\curvearrowright$ counterexample.
- Yes $\curvearrowright$ add $A \longrightarrow B$ to the stem base of the context (sound, complete, non redundant).
- All rules valid in the explored domain are derivable from this knowledge base, e.g. by PROLOG.

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Example: Inspection of all Possible Transitions in the B. subtilis Network

- From all possible $2^{12} = 4096$ initial states, 4224 transitions[1] were generated (quite deterministic rules).
- 524 implications (with support > 0) in the stem base, but $11.023.494 \approx 2^{24}$ concepts.
- Model validation according to [Sea07, 341f.], during attribute exploration or by PROLOG queries to the stem base.

[1] and 11.700 transitive transitions

Verification of Some Implications in the Experimental Literature.

Signal.abs, SigF.abs, SpoOA.P.abs $\longrightarrow$ SigF.out.abs

In the absence of nutritional stress sporulation should never be initiated [de Jong et al., 2004].

SigF.out.pres $\longrightarrow$ KinA.out.abs, SpoOA.out.abs, Hpr.out.abs, AbrB.out.abs

Mutual exclusion: SpoOA.P is reported to activate the production of SigF but also repress its own production. [de Jong et al., 2004]

SigH.out.abs $\longrightarrow$ AbrB.out.abs, SpoOE.out.abs, SinR.out.abs, SinI.out.abs

All these genes are regulated $\overline{gene.out} = \overline{\text{SigA.in}} \wedge \text{AbrB.in} \ (\wedge \ ...)$. Such dependencies can be checked systematically.

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Supplementary Results

The stem base contains the complete implicational logic of the explored temporal transitions. It may be queried for interesting and simple rules:

$< 4500 >$ SpoOA.P.pres, KinA.out.abs $\longrightarrow$ Hpr.out.abs;
$< 4212 >$ SigH.pres. KinA.out.abs $\longrightarrow$ Hpr.out.abs;
$< 3972 >$ AbrB.abs, KinA.out.abs $\longrightarrow$ Hpr.out.abs:

$\overline{\text{Hpr}}$ and $\overline{\text{KinA}}$ are determined by different Boolean functions, but they are coregulated in many cases.

$< 3904 >$ AbrB.out.pres $\longrightarrow$ SigA.pres, SigA.out.pres, SigF.out.abs, SpoOA.out.pres, SpoOE.out.pres, SigH.out.pres, Hpr.out.abs, SinR.out.abs, SinI.out.abs

AbrB is an important "marker" for the regulation of many genes, since its expression is determined by the simultaneous presence / absence of the 3 main genes SigA, $\overline{\text{AbrB}}$ and $\overline{\text{SpoOA.P}}$, which often have an exclusive (OR-) influence.

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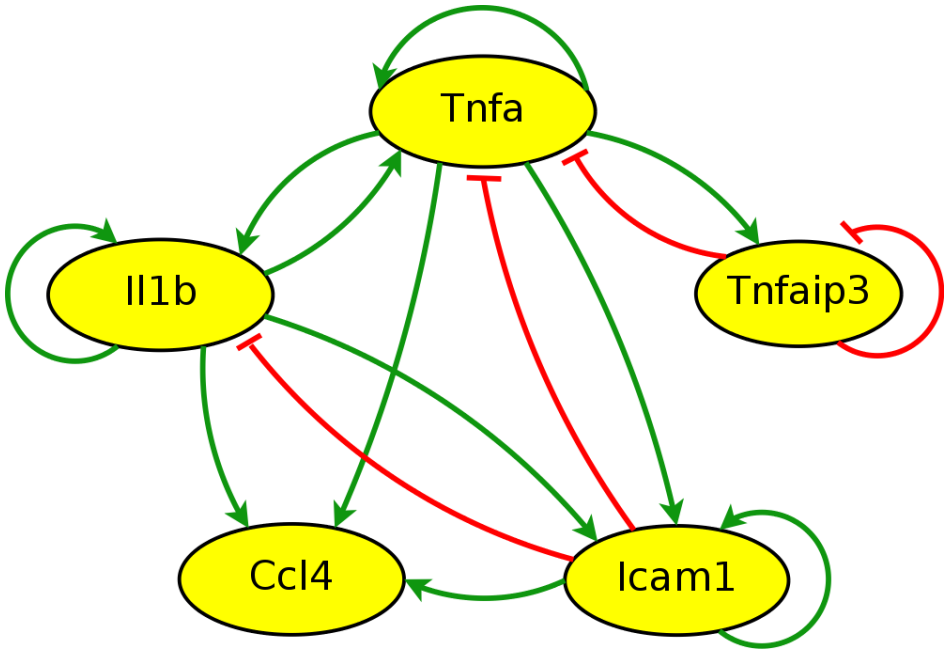
Outline

A Network of 5 Important Genes



- Simulation starting from the initial state of an observed time series (only Tnfa protein was present).
- Non deterministic generalization in the case of inhibition: If Tnfa.in.pres and Tnfaip3.in.pres, generate 2 output states with Tnfaip3.out.abs or Tnfaip3.out.pres.

Exploration Results for the Simulation, Validated Against the Observation

Il1β.pres^{in} $\longrightarrow$ Icam1.pres^{in} Ccl4.pres^{in}
Ccl4.abs^{in} $\longrightarrow$ ... Icam1.abs^{in} Il1β.abs^{in}

Similar regulation of Il1β, Icam1 and Ccl4.

Il1β.abs^{in} Tnfaip3.pres^{out} $\longrightarrow$ Tnfα.pres^{in}
Tnfα.abs^{in} Tnfaip3.pres^{out} $\longrightarrow$ Il1β.pres^{in}

Mirroring the important role of the upregulating genes Il1β and Tnfα.

Tnfα.abs^{in} Il1β.abs^{in} $\longrightarrow$ Tnfα.abs^{out} Tnfaip3.abs^{out} Il1β.abs^{out}

Structural deadlock in Petri net theory.

$\top \longrightarrow$ Icam1.pres^{out}

$\Leftrightarrow \top \longrightarrow$ always(Icam1.pres^{out}) in $\mathbb{K}_s$.

Exploration Results for the Simulation, Validated Against the Observation

$\text{Il1}\beta.\text{pres}^{in} \longrightarrow \text{Icam1.pres}^{in}\ \text{Ccl4.pres}^{in}$
$\text{Ccl4.abs}^{in} \longrightarrow \ldots\ \text{Icam1.abs}^{in}\ \text{Il1}\beta.\text{abs}^{in}$

Similar regulation of Il1β, Icam1 and Ccl4.

$\text{Il1}\beta.\text{abs}^{in}\ \text{Tnfaip3.pres}^{out} \longrightarrow \text{Tnf}\alpha.\text{pres}^{in}$
$\text{Tnf}\alpha.\text{abs}^{in}\ \text{Tnfaip3.pres}^{out} \longrightarrow \text{Il1}\beta.\text{pres}^{in}$

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Outline

Open Problems

- Solve mathematical and logical questions, such that attribute exploration may be applied to larger networks.
- Definition of the expert's role. New transition as counterexample $\longrightarrow$ new transition rule, check affected previous implications?
- Develop a biologically more exact, comprehensive and realistic model (finer steps, cell type...).
- Application to proteins related to the extracellular matrix.

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