Formalization and Automated Reasoning about a Complex Signalling Network

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A stream-of-consciousness presentation

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...please, PLEASE no questions about carboxypeptidase and the like...

Signalling Networks

In the life of cells, *a signal* corresponds to sensing, by and apt cellular receptor, of external molecules.
Signalling molecules inside the cell interact with each other to *trasduce* such signal in *risposte cellulari* that regulate the introduction of proteins; those proteins control various cellular functions.

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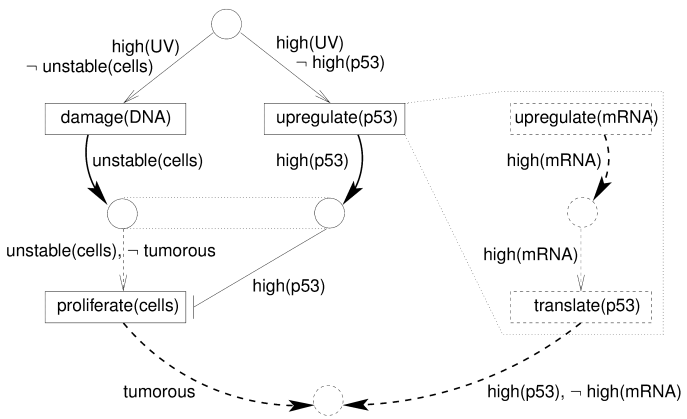
[Tran & Baral, 2009]: *Specific collections of interactions with a common theme in a network are often referred to as signalling pathways or signalling networks (SN) [...] Modeling SNs is thus essential for understanding the cell function and can lead to effective therapeutic strategies that correct/alter abnormal cell behavior.*



Automated Reasoning about Signalling Networks?

Classical sitcalc-like framework:

- fluents (partial descr. of the domain that vary over time)
- actions (events capable of modifying fluents)
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come up with a formalization s. t. we can automate the qualitative (and atemporal) reasoning of, e.g., a student who uses the network as a guide to answer "what if" questions?

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Working hypotheses:

Would real signalling networks become an upper layer to action languages (level 3) and ASP (level 2)?

Action languages: $\mathcal{A}$ e $\mathcal{A}_T^0$

Automated Reasoning

With BioSigNet-RR Baral et al. have extend $\mathcal{A}$ to facilitate the definition of intracellular interactions. Examples of the new syntax:

$binding(br, bki1)$ **causes** $dissociated(bki1)$ **if** $high(bri1)$

$high(br)$ $high(bri1)$ **triggers** $dissociated(bki1)$

$high(bri1)$, $high(bak1)$ **inhibits** $activate(bin2)$

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hypothesis Generation

query with variables that are evaluated by an inferential engine (DLV):
?-F AFTER ACTIVATE(BR)
...
F= [HIGH(BRI1), HIGH(BAK1), LOW(BIN2)]

A successful case study: protein *p53*

p53 inhibits tumouros activation

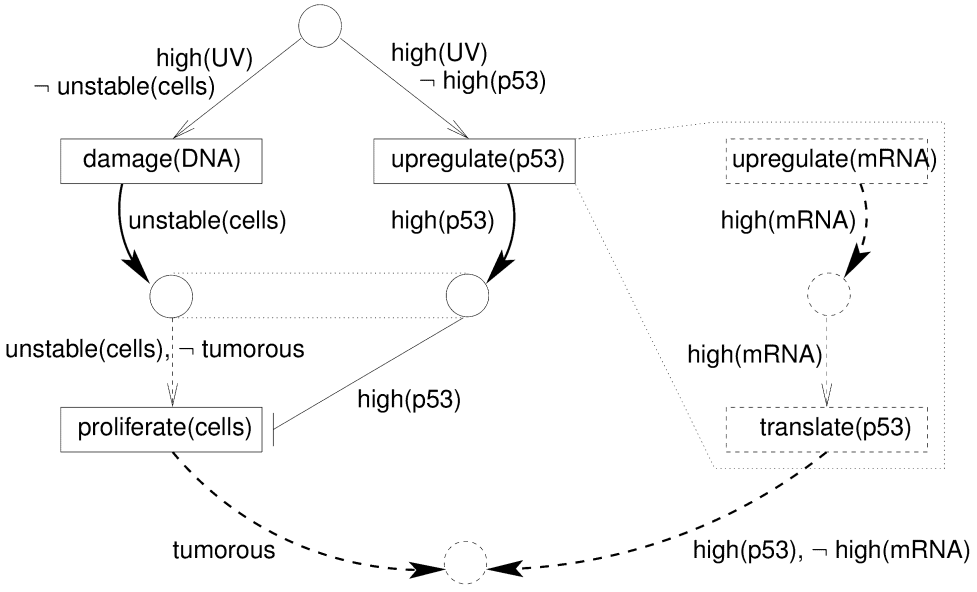

Figure: Signalling Network for protein p53

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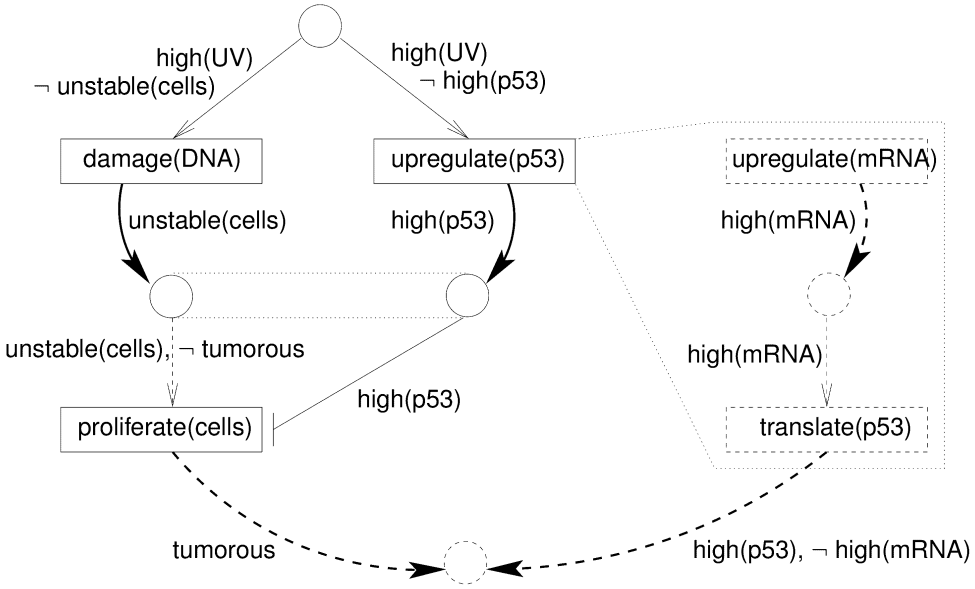

Figure: Signalling Network for protein p53

BioSigNet-RR solution

- a convincing formalization of the pathway for protein *p53*
- the reflexive effect underlying its activation has been successfully modeled
- *direct representation of inhibition is crucial*

Modeling exercise: the SN for Brassinosteroids in thalian Arabidopsis

State of the art

There is research on observed aberrations of some steroids hormones of plant *(poliossidrilates of brassinosteroides (BRS))*.
[Chory et al.] have synthesized what is currently known in a SN

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Observed consequences

plant mutations that create:

- dark green pigmentation;
- dwarf leaves with an epinastic development
- retarded aging
- reduction of fertility

Plants who suffer from...

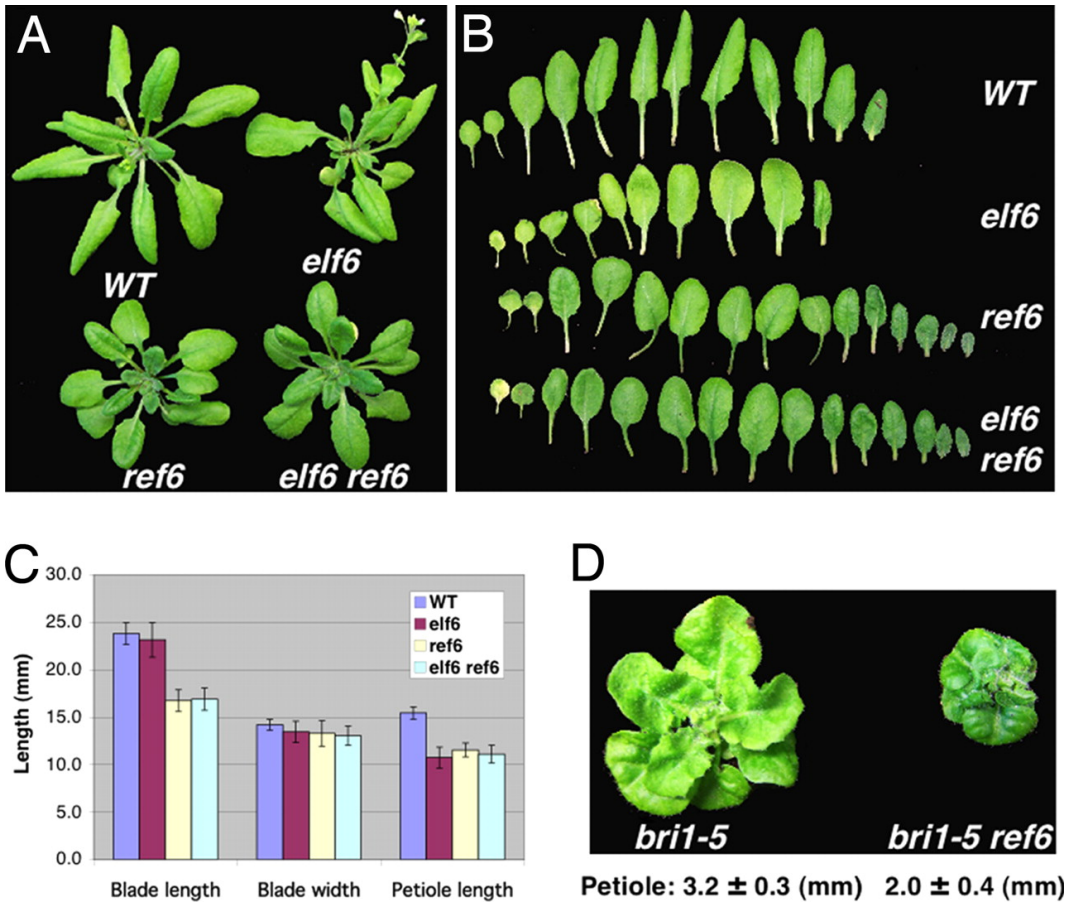

Figure: Examples of mutant plants

Executing the pathway

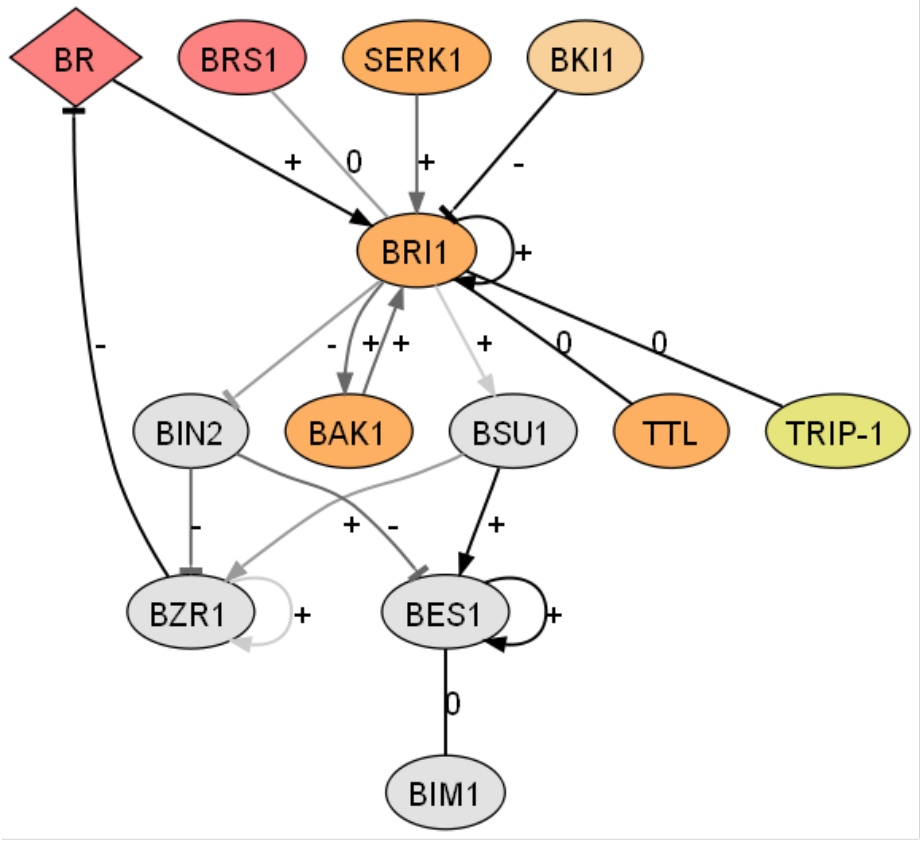

Figure: Signalling network for BR

BRI1 is

- localized on the *plasmatic membrane*
- part of a large class of receptors for plants (LRR-RKS)
- the *key component* of the signal transmission in *BR*.

Signalling pathway

Formalizing the Signalling Network

How to express a query relative to the connections between elements of the cell.

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Face validation of the queries:

- *question*
- *answer*
- *query in* $\mathcal{A}_T^0$
- *illustration on the Signalling Network*

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How to express a query relative to the connections between elements of the cell.

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Temporal aspects:

Time is largely irrelevant and never represented explicitly...

Example Query I

Question

How does *BR* manifests itself to the cell (inside the network)?

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Answer

BR causes the activation of *BRI1* and *BAK1*, who in turn *inactivate* *BIN2*.

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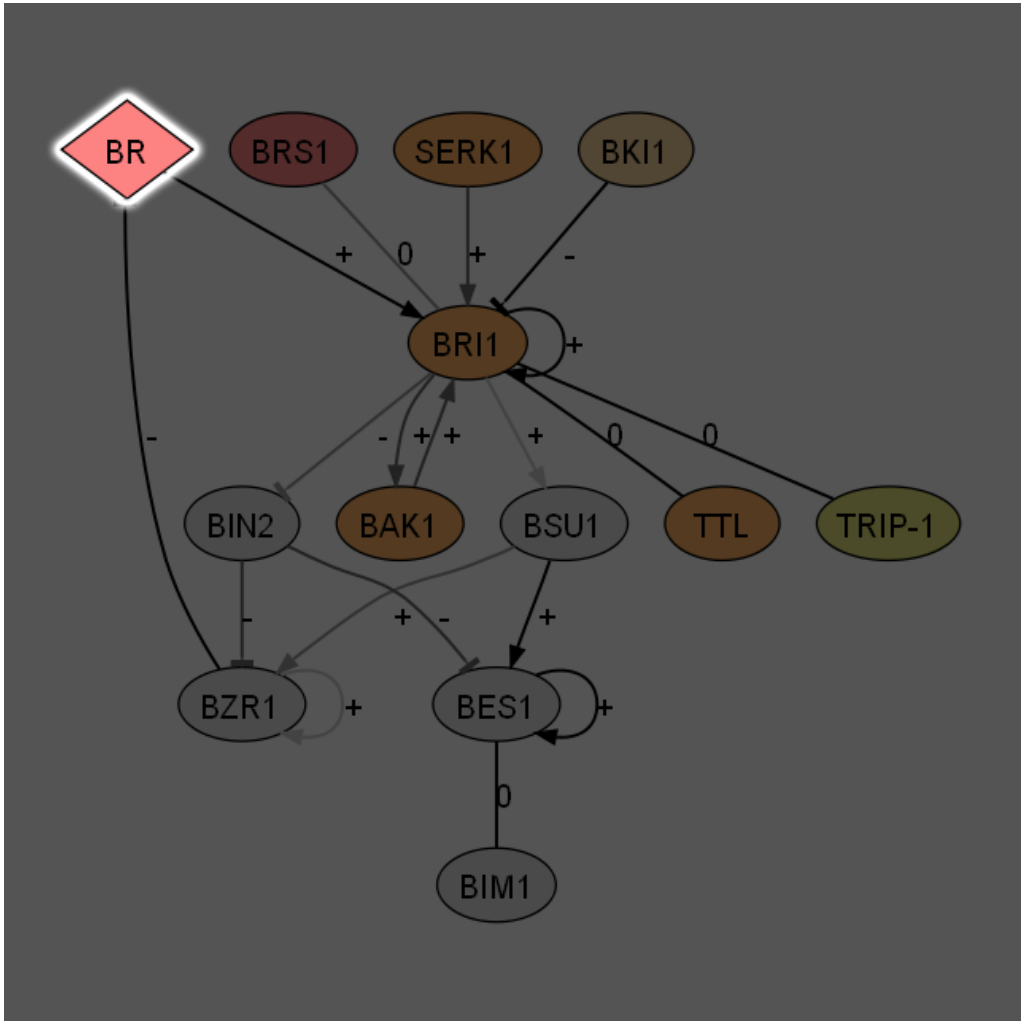
Formula

- ?- high(bri1) **after** activate(br)
- ?- high(bak1) **after** activate(br)
- ?- low(bin2) **after** activate(br)

Example Query II



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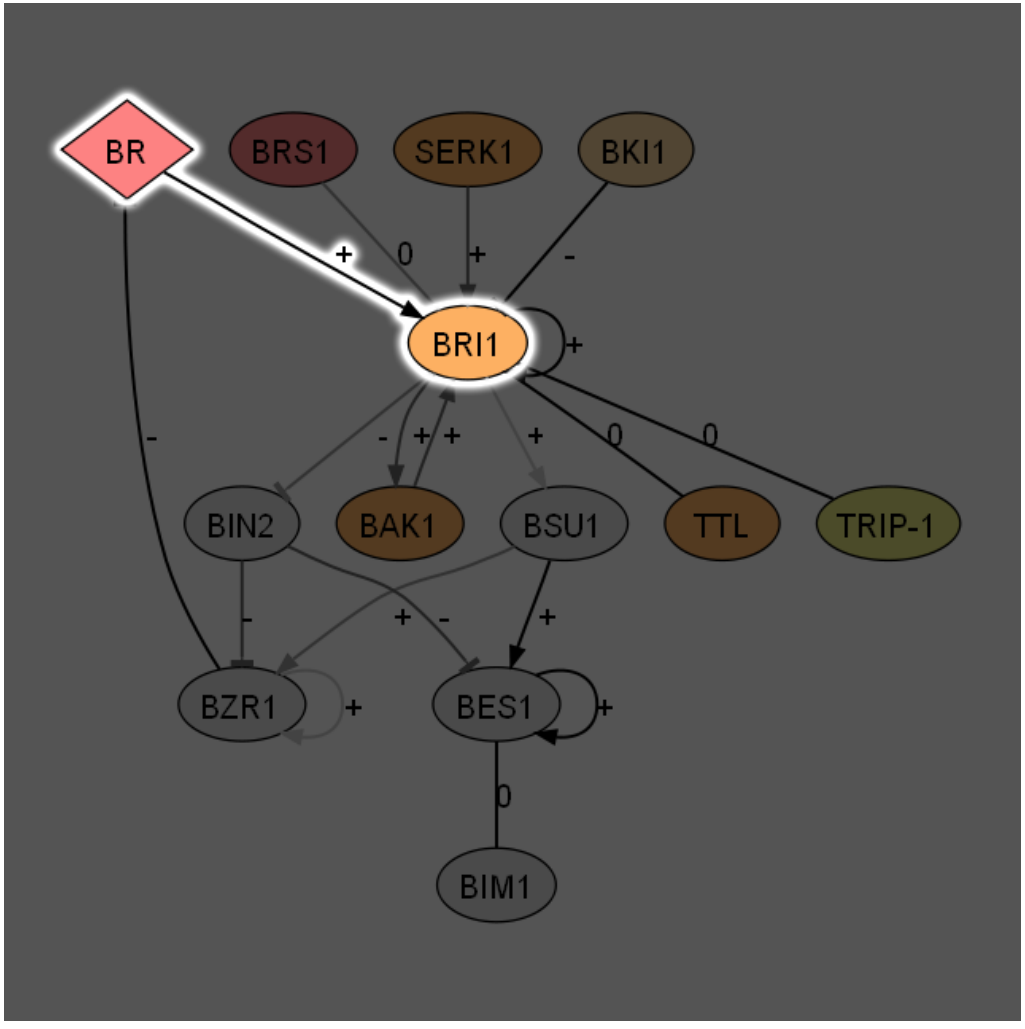

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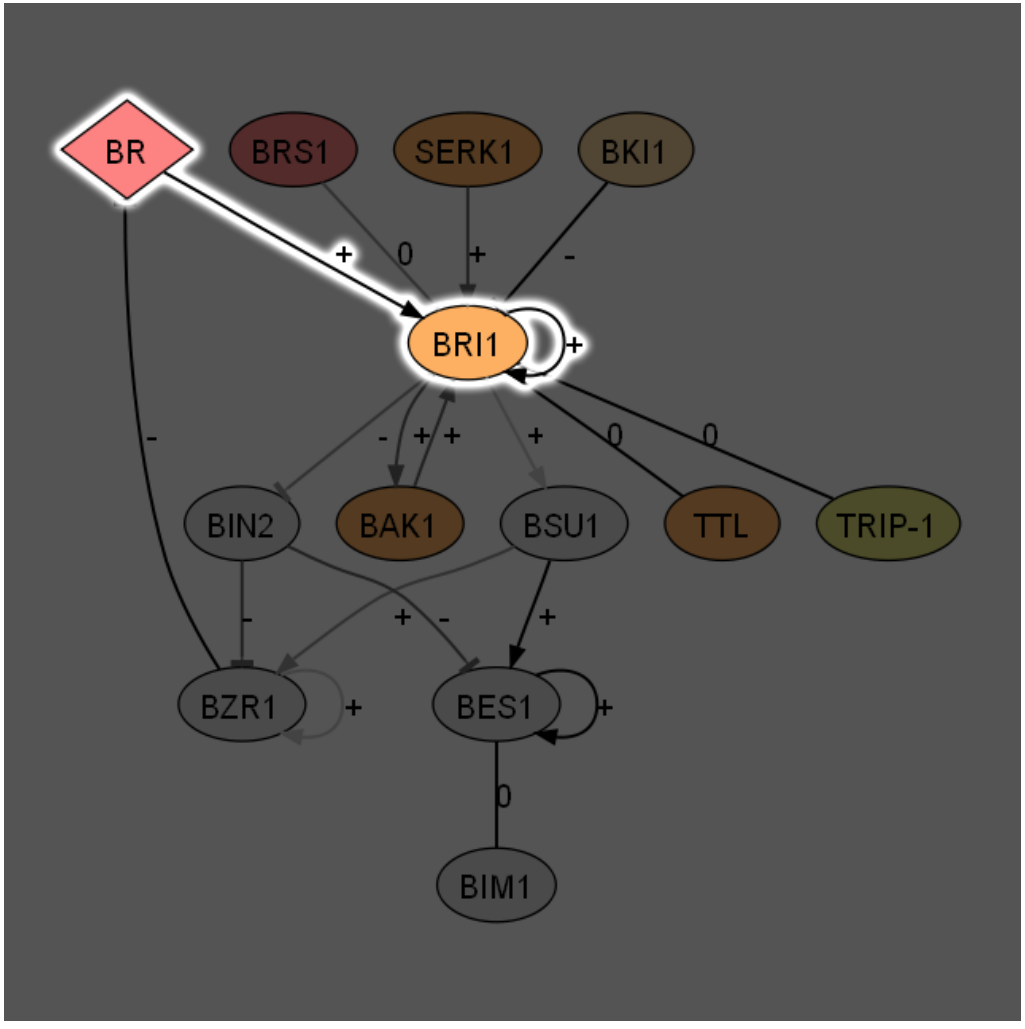

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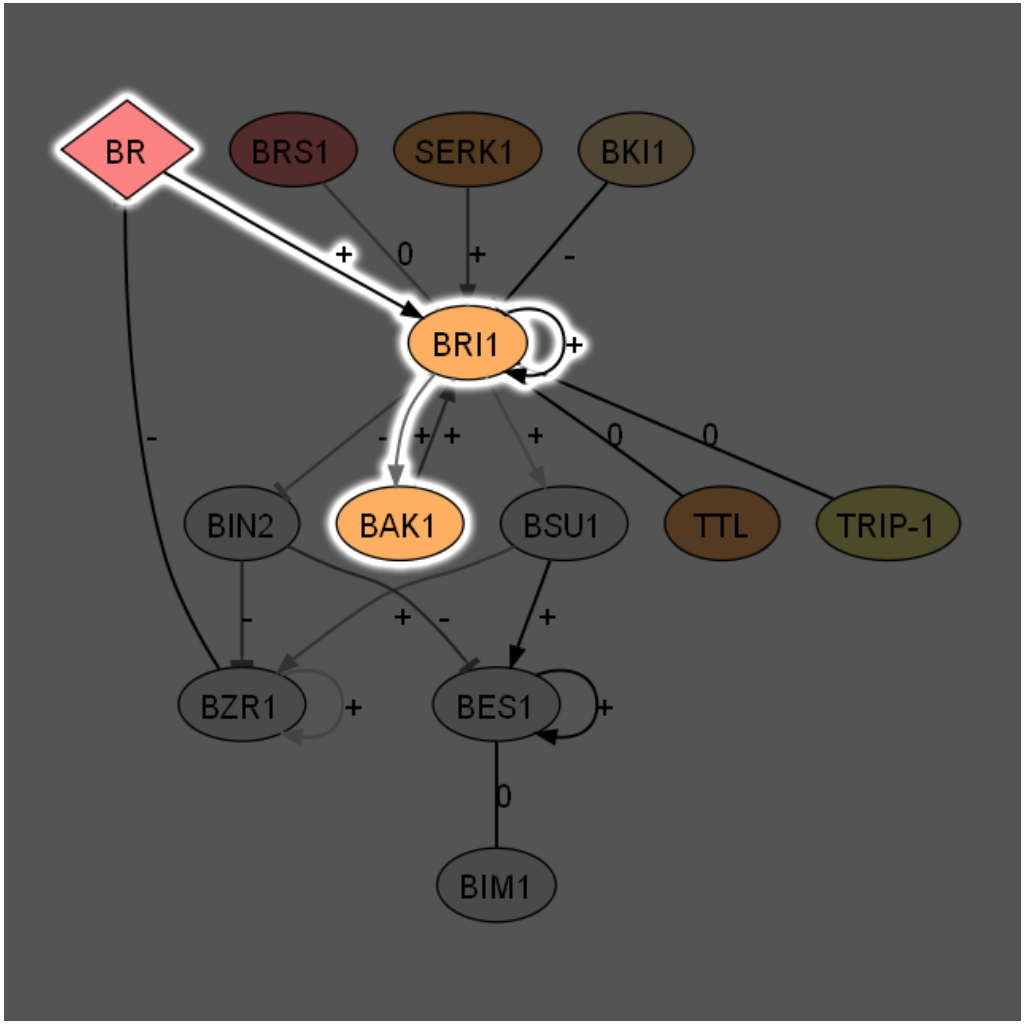

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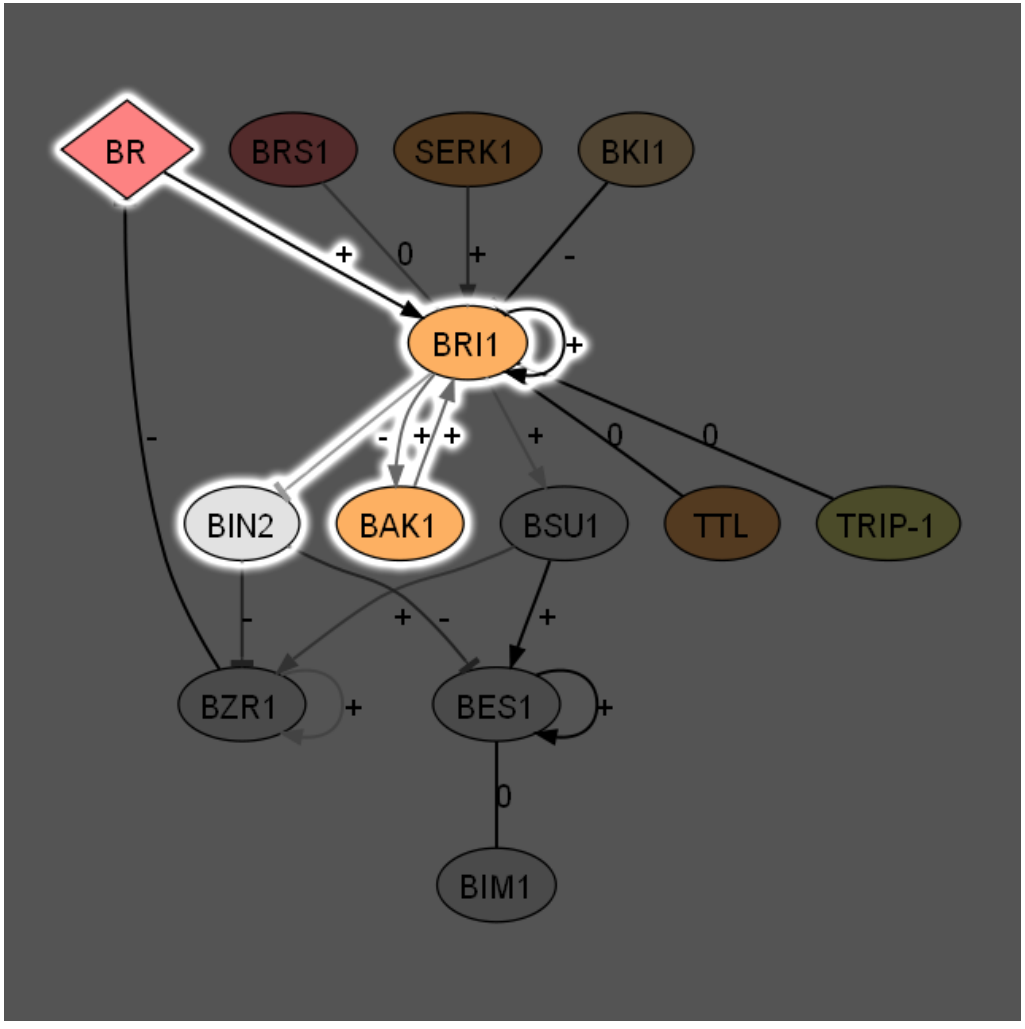

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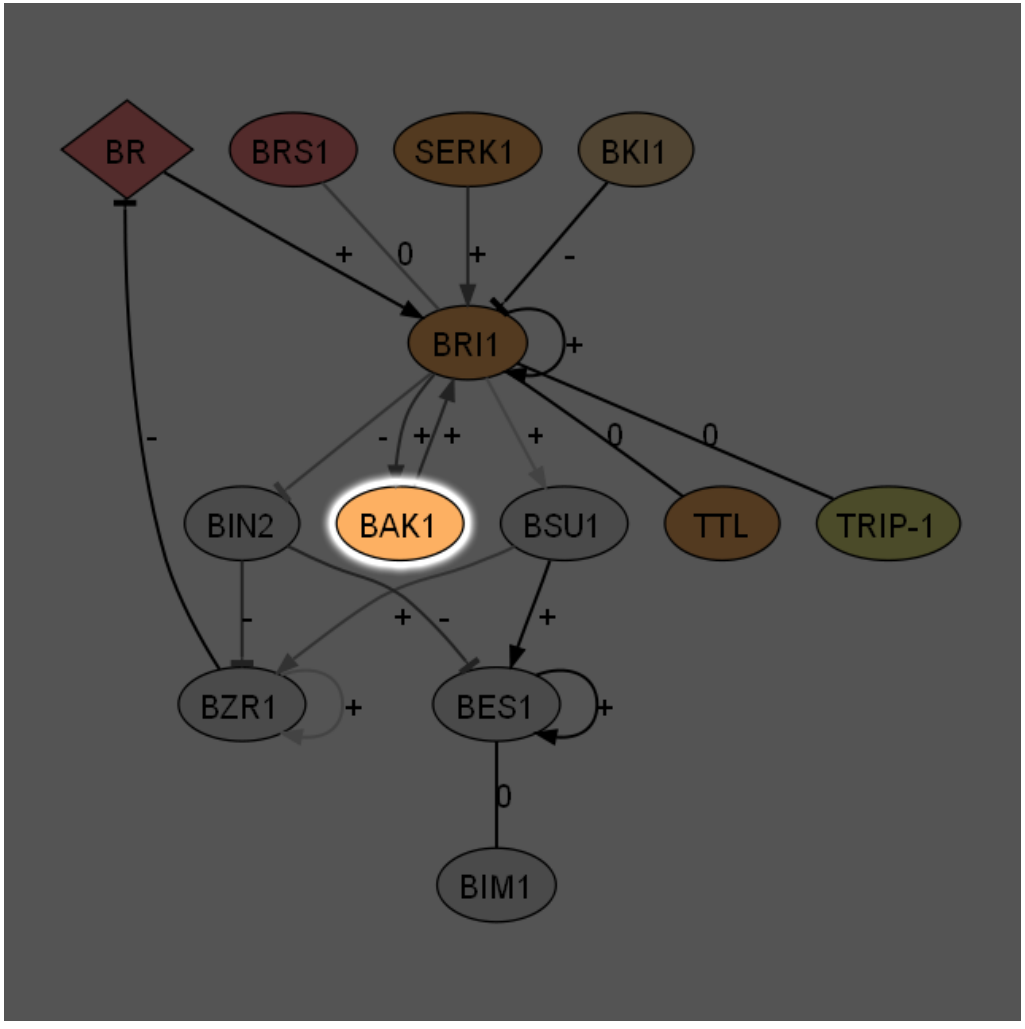

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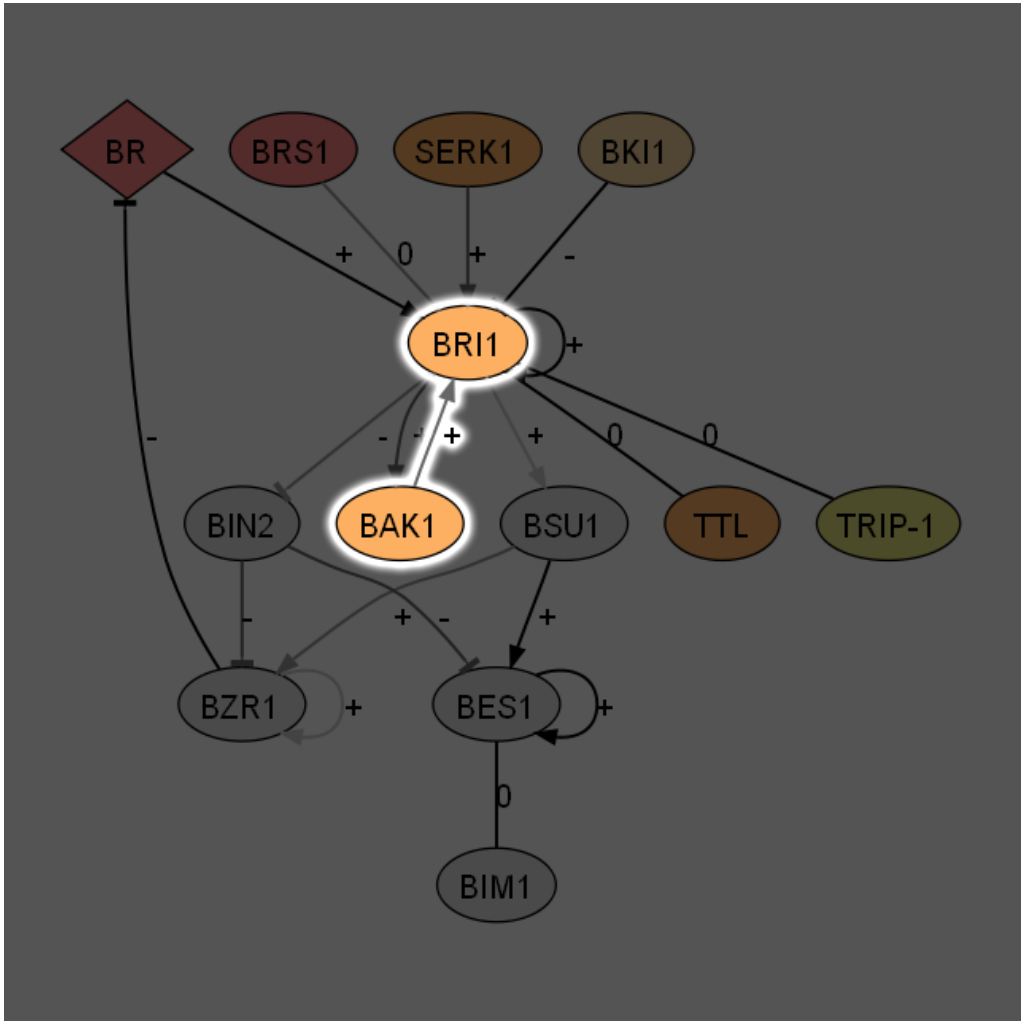

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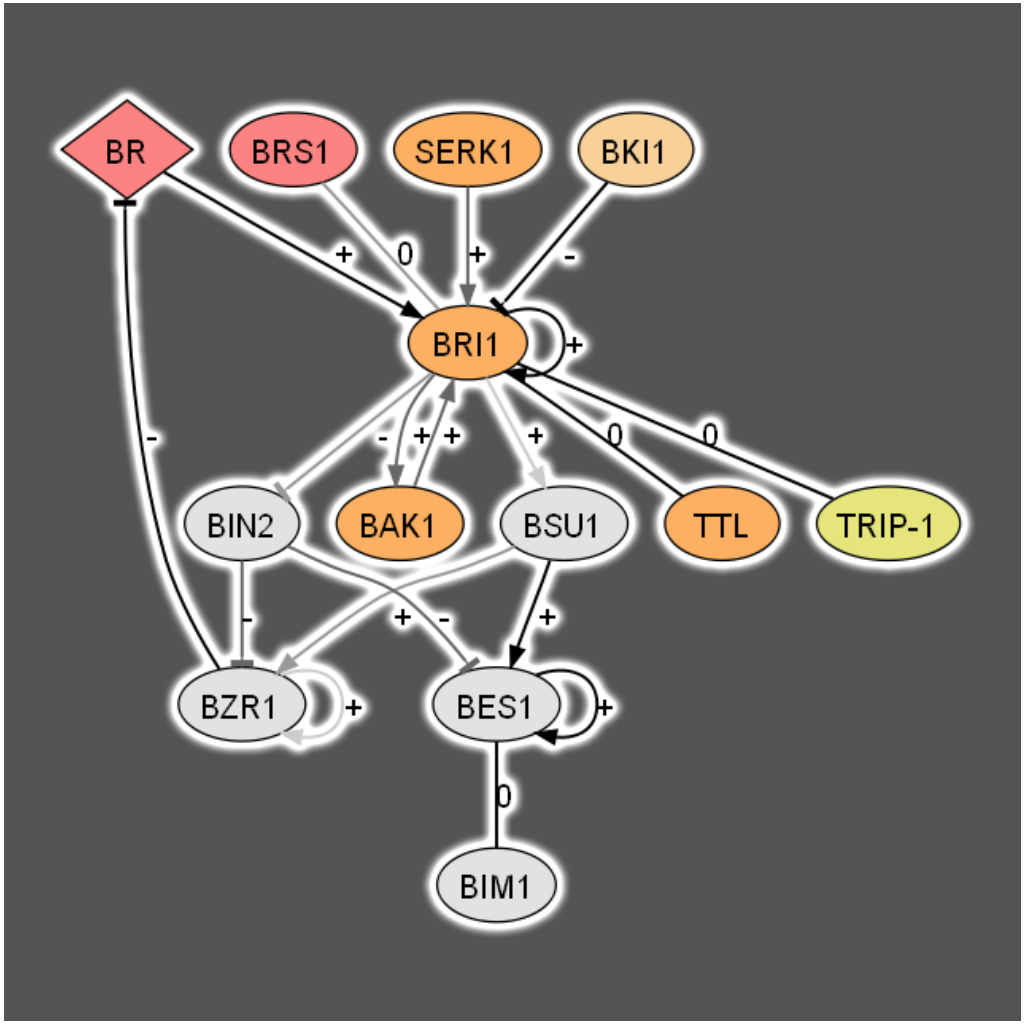

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What are the effects of inactivation of *BIN2*?

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inactivation of *BIN2* will cause the subsequent inhibition of *BZR1* and *BES1*.

Example Query III

Question

What are the effects of inactivation of *BIN2*?

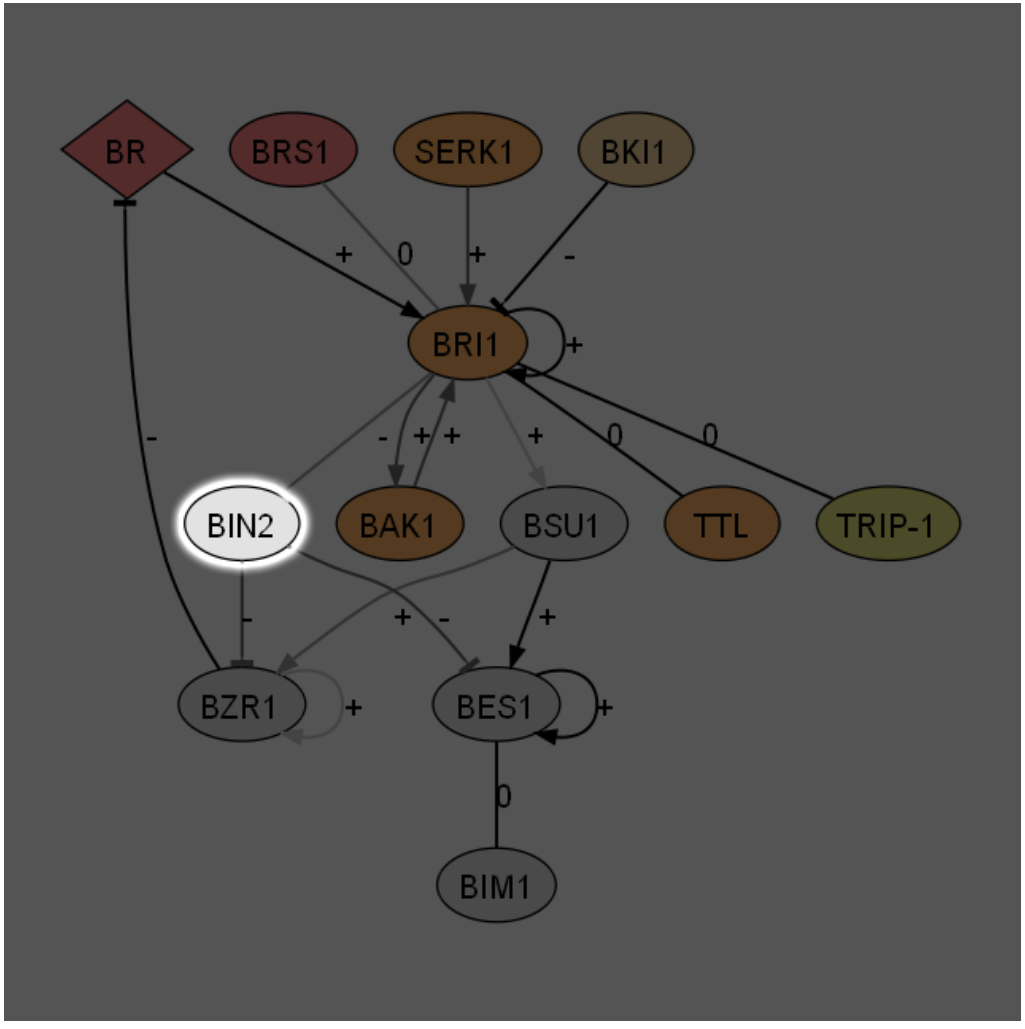
Answer

inactivation of *BIN2* will cause the subsequent inhibition of *BZR1* and *BES1*.

Formula

- ?- low(bzr1) **after** activate(bin2)
- ?- low(bes1) **after** activate(bin2)

Example Query III



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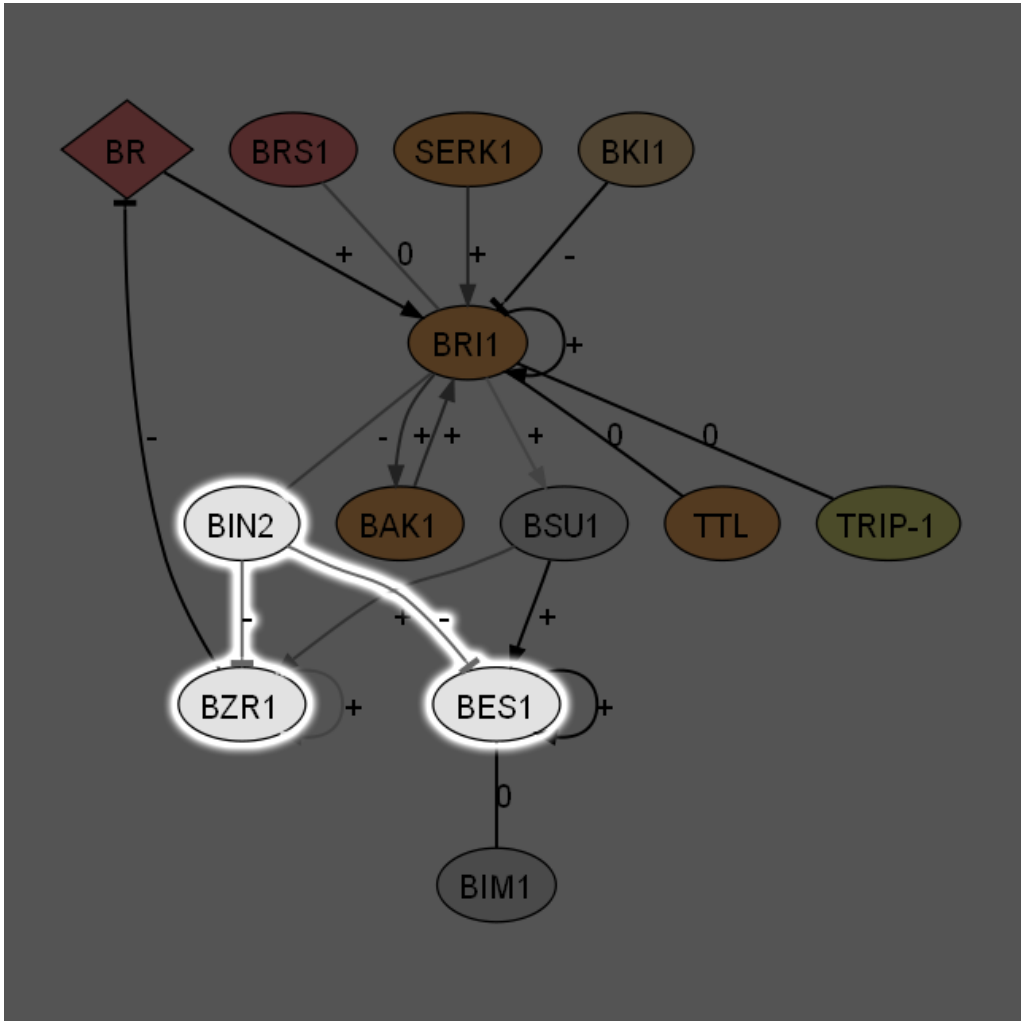

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Better formalization style?

For each fluent we introduce, at translation time, a couple of actions: *high(bri1)* and *low(bri1)* capture observation and -*essentially*- the incomplete nature of our knowledge.

More case studies?

are of course welcome but may require a *strong biological background;*

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