Construction of A Pathway Logic Model of Intracellular Signal Transduction

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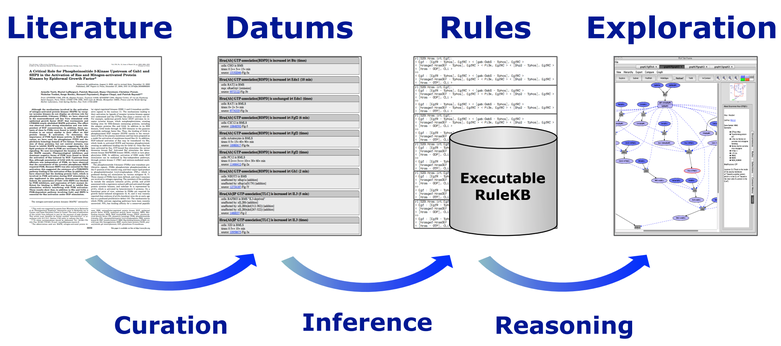
This poster describes how a Pathway Logic (PL) model (called STM7) was made by scientists who study signal transduction in cultured cells for clues about how normal cells differ from cancer cells. It illustrates the formal data structures provided by PL and systematic data collection and modeling processes of PL that are candidates for automation.



Pathway Logic

Pathway Logic is an approach to modeling cellular processes based on rewriting logic, a simple logic designed for modeling and analysis of distributed systems. It allows one to model aspects of the structure and state of interacting components as elements of an abstract data type; to represent individual process steps (reactions) as rewrite rules; and to study possible ways a system might evolve using techniques based on logical inference. Given a network of reactions and a specification of cellular components one can query the network about possible reaction pathways and outcomes. Knockouts that prevent a given outcome can be computed, competing reactions can be found, and pathways can be compared to look for potential cross-talk.

STM7

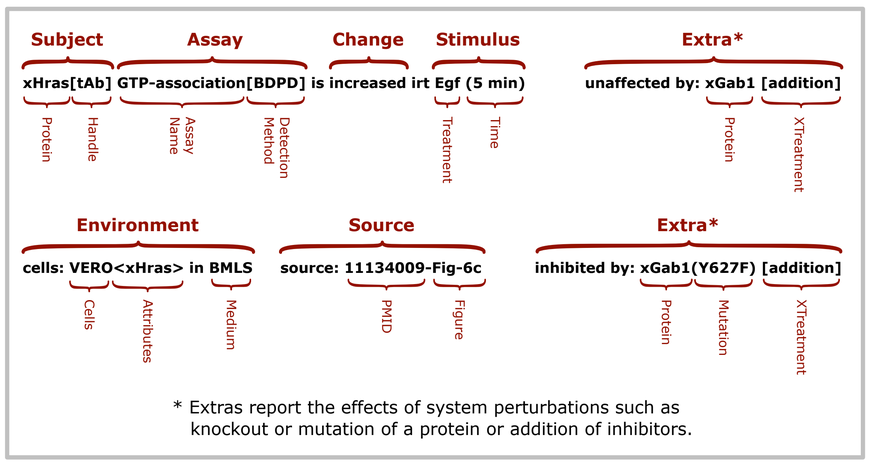
STM7 (Signal Transduction Model v7) uses Pathway Logic to investigate the chain of events that occur after peptides, chemicals, or stresses are added to cultured cells.

The model is based entirely on experimental results and data curated from the published scientific literature. The experimental evidence for each rule is supplied in datum form. Each datum represents a result from a experiment published in a refereed journal.

The rules derived from the datums are collected into a rule knowledge base (RKB). From the RKB, models of response to different stimuli are assembled compoutationally. A base initial state is defined that represents untreated, quiescent cells. For each model the stimuli and associated receptor(s) are added and rules relevant to the treated cell state are computed. The published STM7 knowledge base supports models for combinations of > 30 single stimuli.

Data Collection

A Datum is a manageable chunk of information, sufficient to unambiguously describe an experimental finding, expressed using concepts readily understood by biologists. The required information and the syntax used is illustrated below.



* Extras report the effects of system perturbations such as knockout or mutation of a protein or addition of inhibitors.

Most of the information required by a datum can be found in the figure legend and image but often the curator has to look in the Experimental Procedures or even the Results section to learn what was done to produce the data. The picture below shows the datum produced from Fig-6c in PMID 11134009 color coded with the location in the article where the datum contents were found.

xHras[tAb] GTP-association[BDPD] is increased irt Egf (5 min)
cells: VERO<xHras> in BMLS
unaffected by: xGab1 [addition]
inhibited by: xGab1(Y627F) [addition]
inhibited by: xGab1(Y447F/Y472F/Y589F) [addition]
source: 11134009-Fig-6c

Location: Figure Legend
Figure Image
Experimental Procedures

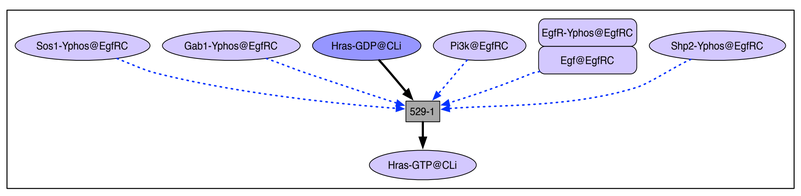
Pathway Logic Rules

In Pathway Logic the rules describe a change in state that occurs when certain conditions are met.

A rule written in Maude looks like this:

```
rl[529.Hras.irt.Egf]:
  {EgfRC | egfrc ([EgfR - Yphos] : Egf) [gab:GabS - Yphos]
                 [hrasgef:HrasGEF - Yphos] Pi3k [Shp2 - Yphos] }
  {CLi   |  cli   [Hras - GDP]                                  }
  =>
  {EgfRC | egfrc ([EgfR - Yphos] : Egf) [gab:GabS - Yphos]
                 [hrasgef:HrasGEF - Yphos] Pi3k [Shp2 - Yphos] }
  {CLi   | cli    [Hras - GTP]                                  } .
```

An instance of the same rule displayed in a Petri net looks like this:



Rule 529 can be paraphrased to say:

If:
- Egf is bound to EgfR in the Egf-receptor-complex and
- Gab1 or Gab2 is phosphorylated on tyrosine in the Egf-receptor-complex and
- a Gef for Hras is phosphorylated on tyrosine in the Egf-receptor-complex and
- Pi3k is in the Egf-receptor-complex and
- Shp2 is phosphorylated on tyrosine in the Egf-receptor-complex and
- Hras is bound to GDP and is attached to the inner side of the cell membrane

Then:
- Hras will become bound to GTP and
- everything else will stay the same.

How is rule 529 derived from datums?

First, all the datums that have Hras as a subject and Egf as a treatment are collected.

A GTP-association assay used in the datums above and below provided evidence for the exchange of GTP for GDP.

What about all the additional components that appear unchanged in the rule? Extras are helpful here. The extras in the datum above are evidence that phosphorylation of Gab1 on Y627 as well as Y447, Y472, or Y589 is required.

Selected Evidence for Rule 529

xHras[tAb] GTP-association[BDPD] is increased irt Egf (10 min)
cells: COS1 in BMLS
inhibited by: xShp2(C459S)"CIA" [addition]
source: 14560030-Fig-3a

Requirement for Shp2 phosphatase activity is demonstrated by addition of a catalytically inactive (CIA) dominant-negative construct.

xHras[tAb] GTP-association[BDPD] is increased irt Egf (5 min)
cells: VERO in BMLS
partially inhibited by: xPik3cb(K805R)"KD" [addition]
source: 11134009-Fig-4b

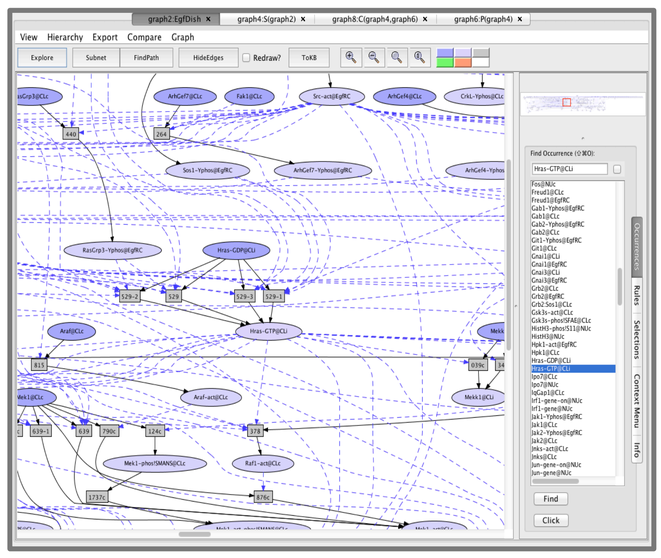
Requirement for Pi3k lipid kinase activity is demonstrated by addition of a kinase-dead (KD) dominant-negative construct.

Find out more about Pathway Logic at: http://pl.csl.sri.com

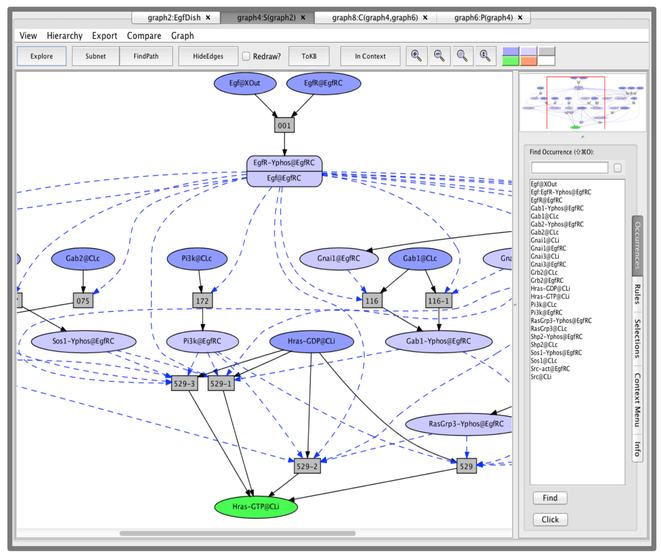
Exploring a Rule KB Network and Models

The Pathway Logic Assistant (PLA) provides tools to assemble models, subnetworks and pathways specified by logical queries. It also provides a way to vizualize the assembled subnets and to navigate and locate features of interest.

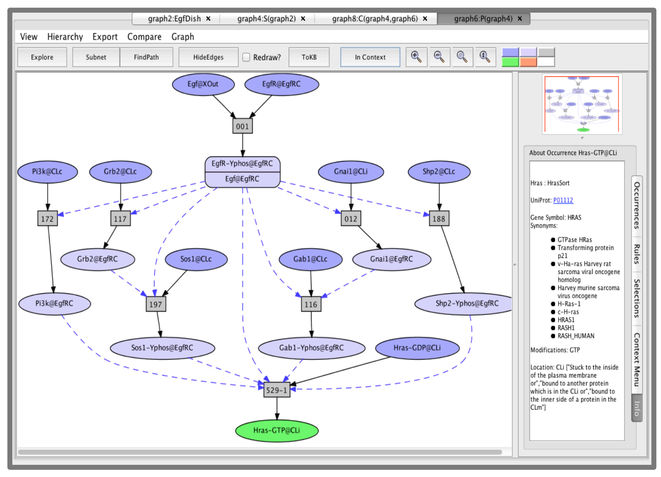
The figure below shows the model of Egf stimulation. Clearly help is needed to navigate and understand what is going on.



What is needed is a way to navigate a route through the networks. You know where you started - for example quiescent cultured cells treated with Egf. If you know where you want to go - for example Hras bound to GTP - you make that a goal and PLA makes a map of all the ways a signal can travel through the rules to reach that goal.



If you want to display just one route to the goal - PLA will do that for you too.



PLA also provides tools to analyze the networks.
Using PLA you can:
- explore the network starting from a chosen rule or occurrence
- compare networks, subnets, and paths
- color nodes from lists of genes, protein, or metabolite produced by "omics" experiments
- perform in silico knockout experiments
- retrieve the evidence used to create a rule
- find out about the protein, modification, and location in each occurrence