Microarray Experiments
and Abductive Inference of Pathways

A real-life application
of DPS through ALP
Overview

- Biological Pathways & Microarrays
- Abductive Model for Gene Interactions
- Gene Pathways
Biological Pathways

- Data collection in repositories
- Explain signal transduction, gene expression & biological processes triggered
Microarrays

- Monitor gene expression of whole genomes
- Estimate DNA expression levels by measuring fluorescence
- Test a large number of experimental hypotheses
Microarray Experiment

Experiment: gene mutation/environmental stress
increases_expression(Experiment, Gene)
reduces_expression(Experiment, Gene)
Abductive Inference

- Inference from effect to cause
- Theory represented by \( (P, A, IC) \)
  - \( P \) is a logic program
  - \( A \) is a set of abducible predicates
  - \( IC \) Integrity Constraints, logic rules
Gene Interaction Model \(<P, A, IC>\)

- \(P \& IC\): Rules of Gene Interactions

- **Observables:**
  
  \[
  \text{increases\_expression}(\text{Expt}, \text{Gene}) \\
  \text{reduces\_expression}(\text{Expt}, \text{Gene})
  \]

- **Abducibles:**
  
  \[
  \text{induces}(\text{GeneA}, \text{GeneB}) \\
  \text{inhibits}(\text{GeneA}, \text{GeneB})
  \]
The Model in P (of $<P, A, IC>$)

- Concept of gene interaction

\[
\text{increases}\_\text{expression}(\text{Expt, } X) \leftarrow \\
\text{knocks}\_\text{out}(\text{Expt, } G), \\
\text{inhibits}(G, X).
\]
The Model in P: Exceptions

- Top-level: Base case rule

\[
\text{increases_expression}(\text{Expt}, X) \leftarrow \\
\text{knocks_out}(\text{Expt}, G), \\
\text{inhibits}(G,X), \\
\text{not affected_by_other_gene}(\text{Expt}, G, X), \\
\text{not affected_by_EnvFactor}(\text{Expt}, X).
\]
Rules of Gene Interaction cnt

- Top-level recursive rule:

  \[
  \text{increases\_expression(Expt, X) } \leftarrow \nn  \quad \text{knocks\_out(Expt, G)}, 
  \quad \text{intermediary\_gene(Expt,G1,G)}, 
  \quad \text{reduces\_expression(Expt,G1)}, 
  \quad \text{inhibits(G,X)}, 
  \quad \text{not affected\_by\_EnvFactor(Expt, X)}.
  \]

Parameter: intermediary\_gene/3
Rules of Gene Interaction cnt

\[
\text{affected\_by\_other\_gene}(\text{Expt},G,X) \leftarrow \\
\text{increases\_expression}(\text{Expt},Gx), \\
Gx \neq X, Gx \neq G, \\
\text{related\_genes}(Gx,G), \\
\text{induces}(Gx,X).
\]

Parameter: related\_genes/2
Integrity Constraints

- Self-consistency: 
  \textbf{False}: \textit{induces(G1,G2), inhibits(G1,G2)}.

- Consistency with prior knowledge:
  \textbf{False}: \textit{induces(a,G)}.
  \textbf{False}: \textit{induces(G1,X), induces(G2,X), same_operon(G1,G2)}.

- Experimental Consistency:
  \textbf{False}: \textit{intermediary_gene(E,G1,G2),
  \textit{mutates(E,G2), not affects(E,G1)}.}
M. tuberculosis: 1 Observation

- Observation:
  \( \text{increases_expression(hspR, 'Rv0350')} \)

- Hypothesis/Explanations:
  \( \text{Hyp} = [\text{inhibits('Rv0353', 'Rv0350')}] \)
  - ‘Rv0353’ is mutated in hspR
  - ‘Rv0350’ is not affected by Environmental Factor
  - ‘Rv0350’ is not affected by other gene
M. tuberculosis: 2 Hypotheses

- Observation:
  \[\text{reduces\_expression}(\text{sigH}, \text{`Rv2710'})\]

- Hypotheses/Explanations:
  \[\text{Hyp} = [\text{induces}(`\text{Rv3223c}', \text{`Rv2710'})]\]
  \[\text{Hyp} = [\text{induces}(`\text{Rv3223c}', \text{`Rv1221'})],
  \text{induces}(`\text{Rv1221}', \text{`Rv2710'})]\]
Full Experiment

- Data from 5 experiments
- Mutations of transcription regulator genes of \( M\. \)\( \text{tuberculosis} \):

- Single hypothesis/explanation found!
  - (see next slide)
- Confirmed by Biology experts!!

- See ProLogICA file.
M.tuberculosis: Regulators
Yeast

- Data availability, yMGV Database 1544 expts
- Extensive Background Knowledge (Eurofan Project)
- Adaptation of Model, no operons in yeast
- 16 chromosomes, 4,800 genes
- Introduce yeast transcription regulators (source: Yeast Genome Database at MIPS)