Quelques approches formelles pour tester la robustesse de processus de reconstruction de rseaux

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Network inference

Goal Identify the main actors and functions involved in the response of a system.

Methods

- Data-mining. Statistics. Machine Learning...
- Metaheuristics. Search for a local optimal (genetic algorithms...).
- Optimization. Look for best-score solution (ILP).

Most approaches are discriminative:
their output is a ”single” most-probable solution.

Uncertainties appear at different stages of the identification process

- **Confidence** in the resulting predictions?
- Relevance of a **unique** solution?

Explore complete space of solutions?

Large range of inferred properties

- Topological structure. Transcriptional or metabolic network.
- Discrete dynamics. Logical rules
- Continuous dynamics. Parameter estimation.

Fluctuations in data

- Qualitative observations.
- Scoring of errors.

Is it possible to study the set of (sub)-optimal solutions?

→ **Enumeration, sampling ?**
→ **Formal methods?**

Enumeration...

Explore the space of solutions to combinatorial optimization problems which are relevant in system biology

Integer Linear Programming?

- Systems biology. Used in many frameworks (metabolism).
- Diffusion. Few software tools.
- **Expert level required**. Small modifications induce loss of efficiency.

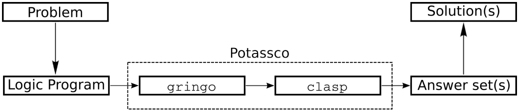
Declarative logics? (Prolog, Inductive Logic Programming...)

- Systems biology. Used mainly for experiment design.
- Diffusion. Appropriate flexibility.
- **Bad for enumeration**. Not scalable !!

→ **Find a compromise between efficiency and flexibility in the problem statement?**

Answer Set Programming: *what?* instead of *how?*

- Declarative logical problem solving paradigm
- Knowledge representation and reasoning problems
- Combinatorial search problems in NP



Potassco: **Potsdam** Answer Set Solving Collection

`http://potassco.sourceforge.net`

Rich modeling language

- Encoding problems as queries on propositional logical programs.
- *Gringo* grounder

Highly efficient inference engines

- Boolean constraint solving technology
- *Clasp* solver
- Competing with the power of SAT algorithms.

Short description

Disjunctive rules

$$\underbrace{k\,\{\,a_1;\ldots;a_n\}\,l}_{\text{head}}\ \text{:-}\ \underbrace{a_{n+1},\ldots,a_r, \mathit{not}\ a_{r+1}, ..., \mathit{not}\ a_s}_{\text{body}}$$

- Atoms. $a_1 \ldots a_n$ can be considered as facts.
- Deduction

Whenever all facts of the body are satisfied, one fact of the left part shall be true.

- Integrity constraint. ”$\leftarrow a$” is always false
- Constraint. ”a.” is always true.

Answer Set

- Set of atoms satisfying all logical rules
- Minimality and stability properties
- Every atom of an answer set appears in the head of at least one rule.

Qui a tué le docteur Lenoir ?

Program

```
3 { nom, arme, pièce } 3
1 { Colonel Moutarde, Mademoiselle Rose } 1 :- nom
1 { chandelier, revolver } 1 :- arme
1 { cuisine, hall, salon, salle à manger } 1 :- pièce
1 { cuisine, hall, salon } 1 :- Colonel Moutarde
Salon :- Colonel Moutarde, not revolver
:- cuisine
Chandelier
```

Answer Sets??

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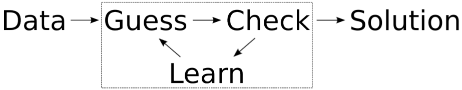
1 { cuisine, hall, salon } 1 :- Colonel Moutarde
Salon :- Colonel Moutarde, not revolver
:- cuisine
Chandelier
```

Answer Sets??

- Colonel Moutarde, salon, chandelier
- Mademoiselle Rose, salle à manger, chandelier
- Mademoiselle Rose, salon, chandelier
- Mademoiselle Rose, hall, chandelier

Guess & Check methodology



Data → Guess → Check → Solution

Learn

- Data: PKN and phospho-proteomics dataset (facts)

```
node(tnfa). node(p38). edge(tnfa,p38,1). exp(1,tnfa,1). obs(1,p38,0).
```

- Guess: Generate candidates models (non-deterministic)

```
{clause(A,N)} :- hyperedge(A,N).
```

- Check: Eliminate invalid models (integrity constraints)

```
:- clause(A,N), clause(B,M), A!=B, redundant(A,B).
```

- Learn: Loop between ”guess” and ”check”
- Optimize: Minimize cost function (weighted sum of atoms)

```
#minimize[mismatch(E,R,W) = W, clause(A,N) : param(P) = N*P].
```

Ongoing issue

ASP technologies are now proved to be mature and very efficient in several computational issues.
→ *constraint satisfaction, diagnosis, repairing, planning...*

Is ASP useful in systems biology?

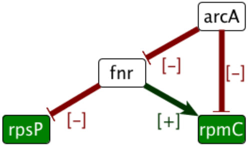
Work in progress...

- Consistency checking of network
- Inference of logical rules for signaling networks
- Inference of robust regulatory nodes
- inference of metabolic network

Validation/Correction of (possibly infered) networks

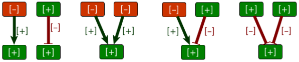
Knowledge-representation

- Regulations. Signed oriented graph.
- Edge colors. Regulatory effects.
- Node colors. Expression data.



Constraint over graph-coloring

- Causal law. Explain the expression of each target gene by the consistent regulation of a source
- Forbidden patterns.



FORBIDDEN COLORED PATTERNS

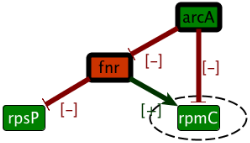
ASP encoding

```
vertex(rpsP). vertex(fnr).
vertex (arcA). vertex(rpmC).
edge(fnr,rpsP). observedE(fnr,rpsP,-).
edge(fnr,rpmC). observedE(fnr,rpmC,+).
edge(arcA,fnr).  observedE(arcA,fnr,-).
edge(arcA,rpmC). observedE(arcA,rpmC,-).
observedV(rpsP,-).  observedV(rpmC,-).
```

```
labelV(I ,+) ; labelV (I ,-) ← vertex(I).
labelV(I ,S) ← observedV(I,S).
labelE(J,I,+) ; labelE (J,I,-) ← edge(J,I).
labelE(J,I,S) ← observedE(J,I,S).
receive(I,+) ← labelE(J,I,S), labelV(J,S).
receive(I,-) ← labelE(J,I,S), labelV(J,T), S≠T.
← labelV (I,S), not receive(I,S).
```

Results *[Guziolowski-BMCGenomics'09, Gebser-KR'10]*

- Prediction. *rpsP* and *fnr* have fixed colors according to allowed patterns.
- Diagnosis. An extra forbidden pattern appears on *rpmC*.
- Correction. Also possible.

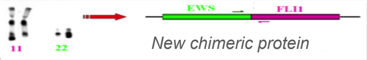


The expression of rpmC cannot be explained.

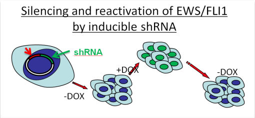
Example of application

Ewing Sarcoma

- Chimeric protein
- Institut Curie. Inactivation of the protein expression.



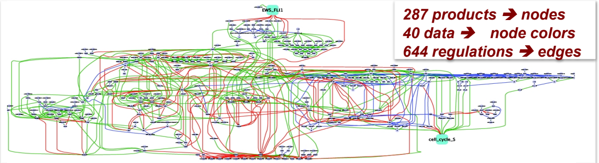
New chimeric protein



Silencing and reactivation of EWS/FLI1 by inducible shRNA

Data *[Institut curie. Barillot & Delattre]*

- Litterature-based regulatory network
- Time-series genes expression after the protein inactivation



287 products → nodes

40 data → node colors

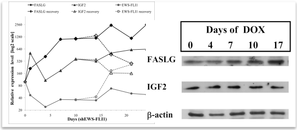
644 regulations → edges

→ What can be surely predicted from this information?

Cancer application

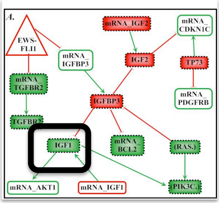
Explain and predict

- Effect of multi-scale competitions.
- Validation of predictions.



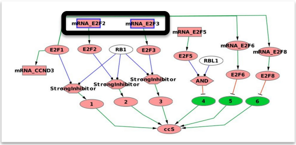
Key pathways *[Baumuratova-BMC syst. bio'10]*

- Missing regulations over IGF1



Design? *[Guziolowski TCBB'11]*

- Two new possible targets for EWI-FLI1
- si-RNA confirmation (unpublished)

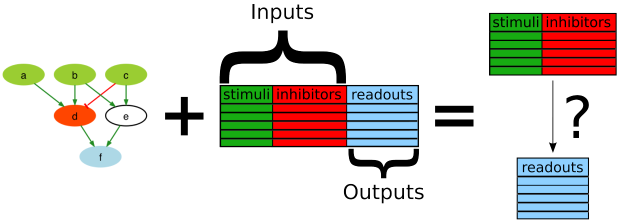


Learning logical static rules

Data

- Signed and directed causal interactions among proteins
- Phosphorylation activity in time *t* after stimulation

Goal Predictive models of immediate-early protein signaling pathways



Prior Knowledge Network

Phospho-proteomics Dataset

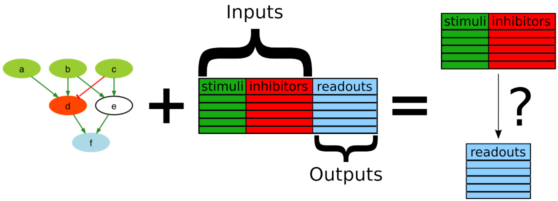
Predictive Model

Underlying assumptions

- Focus on fast reactions
- No time for feedback mechanisms
- Pseudo-steady state assumption

Predictive Signaling Network Challenge *[Prill'11]*.

12 groups with different formalisms (ODEs, machine learning, boolean logic)



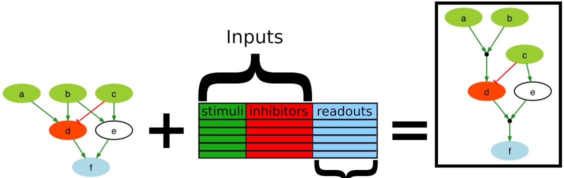
Prior Knowledge Network Phospho-proteomics Dataset Predictive Model

Score **Trade-off between fitness and model size**.

- Biological Property: consistency with experimental data
- Parsimony Principle: minimal/simplest explanation

Discrete approach

Optimization Learning **Logic** Models or **hypergraphs**?



$(a \wedge b) \vee \neg c \iff d$

$c \iff e$

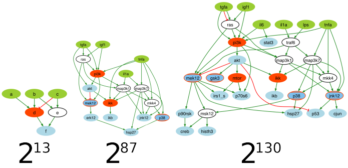
$d \wedge e \iff f$

Prior Knowledge Network

Phospho-proteomics Dataset

Optimal Logic Model (Hypergraph)

Search space. Hypergraphs compatible with the graph ($2^{\#hyperedges}$)

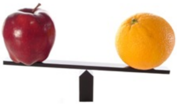


2^{13} 2^{87} 2^{130}

State-of-the-Art CellNOpt *[Saez-Rodriguez’09]*

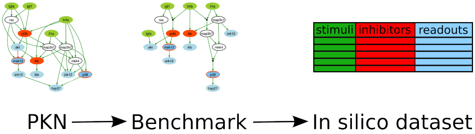
- Genetic algorithm to train logic models
- Weaknesses **Guarantee to find all global optimal models? Scaling?**

Comparing meta-heuristics and declarative logics



Benchmark and comparison sets

- 2 real cases. Middle and large-scale with discretized real dataset.
- 240 in-silico cases. middle-scale, several benchmarks and in-silico datasets.



stimuli	inhibitors	readouts

PKN → Benchmark → In silico dataset

Criteria of comparison

- Success / Completeness
- Time performance

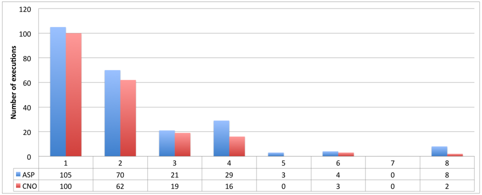
Success / Completeness

Discretized real datasets *[Videla-CMSB'12]*

Optimal models	ASP	CellNOpt
Middle	8	2
Large	2	**0**

- Several optimal models.
- Metaheuristic miss all optimals in the large-scale case.

Generalization: 240 in-silico studies *[Videla-CMSB'12]*



	1	2	3	4	5	6	7	8
🟦 ASP	105	70	21	29	3	4	0	8
🟥 CNO	100	62	19	16	0	3	0	2

- **No single optimal model in more than 60% of studies**.
- Metaheuristics fail in identifying all optimal when they are numerous.

Time performance

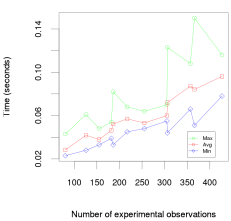
Discretized real datasets

- **Metaheuristics are perturbed by the identification of global optimal models**

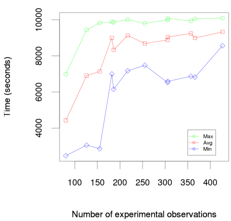
Times	ASP (s)	CellNOpt (h)
Middle	0.09 seconds	9.2 hours
Large	0.5 seconds	27.8 hours

Generalization: 240 in-silico studies

ASP computation time



CellNOpt computation time



- Significant improvement in computation times

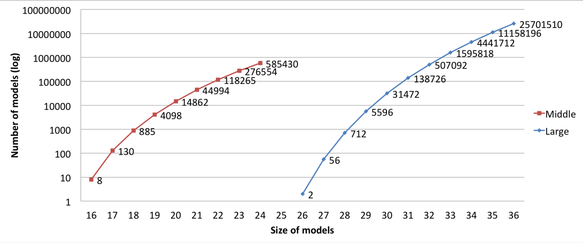
Analysis of incompleteness

Metaheuristics

	Number of saved models	Size	Minimal size
Middle	66	16→24	16
Large	206	27→36	26

- CNO finds suboptimal models “close” to optimal models
  → Are they a good representation of the space of sub-optimal models?

Space of sub-optimal models?



- **ASP allows enumerating** the space of suboptimal models
- Exponential growth with the size
- *No information on the representativity of CNO models*

Impact of real data? Space of sub-optimal models?

Real case *[Videla-Work in progress]*

- Numerical value → 100-value discretizations !
- Loops → new encoding
- Good time performances

(Non)-unicity of solutions

- Still several optimal solutions
- Combinatorics: **mutual exclusive patterns**.

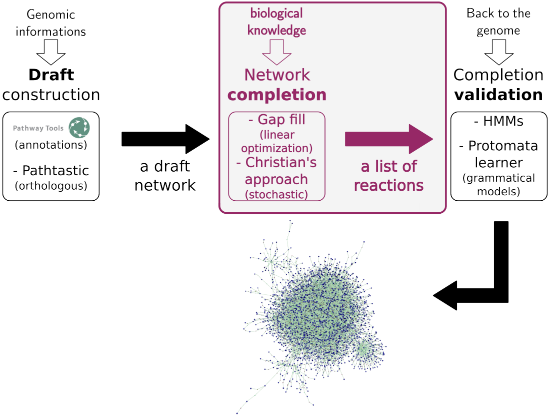
Including noise? *[Guziolowski-Work in progress]*

- A 10% noise over real data is inherent to the technologies.
- **Enumeration: more than 10000 sub-optimal models**

→ **Relevance? Strong need for biological metrics to select models!**

Quite troubling...

Optimization methods → Metabolic network completions



Genomic informations

Draft construction

Pathway Tools (annotations)

- Pathtastic (orthologous)

a draft network

biological knowledge

Network **completion**

- Gap fill (linear optimization)
- Christian's approach (stochastic)

a list of reactions

Back to the genome

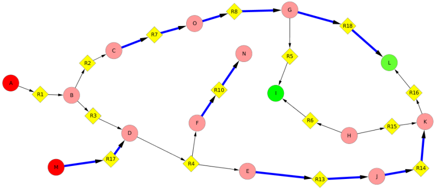
Completion **validation**

- HMMs
- Protomata learner (grammatical models)

Hints on the number of possible completions?

Optimization-based methods

Cardinal minimal completion Add the minimal number of reactions to explain the presence of metabolites.



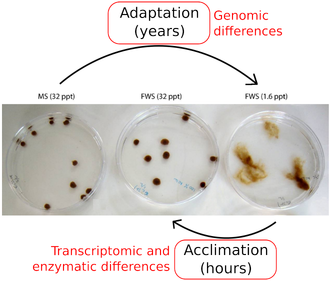
Linear programming: GapFill *[Kumar'07]*

- Single-based completion. *For each compound*, add the minimal number of reactions in the network

ASP *[Thiele'11]*

- Global-based completion. Add the global minimum of reactions in the network required *for all compounds in the same time*

Application to an eukaryot example



Adaptation (years)

Genomic differences

Transcriptomic and enzymatic differences

Acclimation (hours)

Brown algae

- Ectocarpus. Model for brown macro-algae.
- Specifities. Very distant from well-studied green micro-algae.
- Capable of adaptation and acclimation.

Data *[Station Biologique Roscoff]*

- Genome. High-quality annotated genome.
- Metabolism. List of 56 characterized metabolic compounds.

Ectocarpus metabolism reconstruction

Reconstruction *[Prigent. Work in progress]*

- Automatic tools. Bad reconstruction.
- Global cardinal completion. **Adding** 59 **metabolic reactions allows producing 48 compounds over 56**
- Single-based completion. 38 reactions belong to all solutions.

Enumeration *[Prigent&Thiele. Work in progress]*

- ASP. Enumeration is possible.
- Combinatorial explosion. **The full set of possible completions contains 16 millions of solutions**
- Reactions. About 100 reactions occur in at least one solution.
- Performance. High level of RAM. Extreme range of solvers.

Current issues

- New biological metrics to sort information !
- Integration Take advantage of the flexibility of the declarative language to insert new critera of classification.
- Sampling the space of solution? [*Christian'11]*

Conclusion

Novelties brought declarative logic paradigms ??

High-level declarative language

→ Easy ”step-by-step” encoding of data integration and constraints.

- Confrontation of a reconstructed network with additional data.
- Learn the logic quasi-steady state response of signaling networks.
- Completion of metabolic networks.

Enumeration of complete space of solutions

→ Explore the combinatorics responsible of the explosion of the size

- Global correction of transcriptional networks.
- Sub-optimal solutions to middle-case problems (learning the dynamics).
- Global set completion to metabolism reconstruction.

Work in Progress

- Biological criteria to elucidate the structure of the space of solutions.
- Sampling issues.
- ASP: backtrack traces of ”proofs” to classify the importance of initial information.
- Software.

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