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Developing robust Synthetic Biology designs using automatically chosen microfluidic experiments

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April, 2009

Overview

Inductive Logic Programming (ILP)

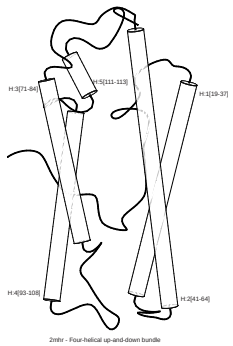
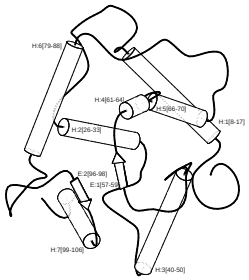
Probabilistic ILP (PILP)

The Robot Scientist project

Synthetic Biology

Microfluidic Robot Scientist

Inducing a logical model for “4-helical up-and-down bundle”

Positive(12)	Negative(12)
	

The protein P has fold class “Four-helical up-and-down bundle” if it contains a long helix H1 at a secondary structure position between 1 and 3, and H1 is followed by a second helix H2.

[JMB, 2001; MLJ, 2001]

Inductive Logic Programming

Background knowledge. Protein sequence, partial grammar, incomplete biological network.

Examples. Molecules, annotated sentences, temporal traces of up/down regulation.

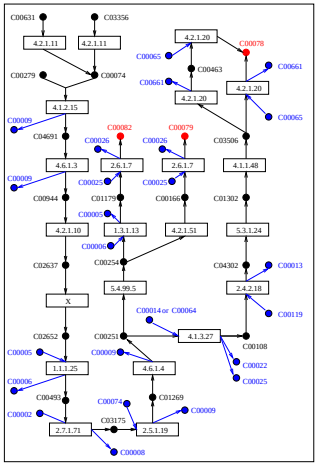
Hypothesis. Explanation of molecular 3-D shape, new clauses in a grammar, extra network annotation.

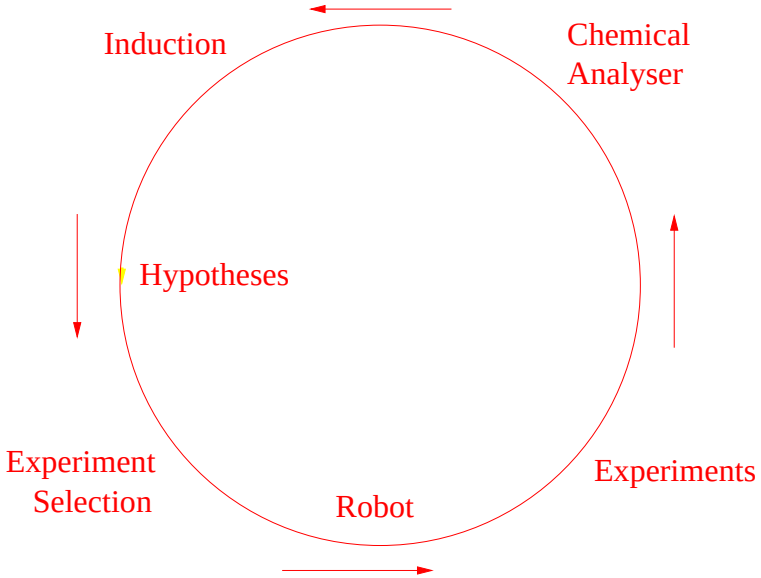
Probabilistic ILP

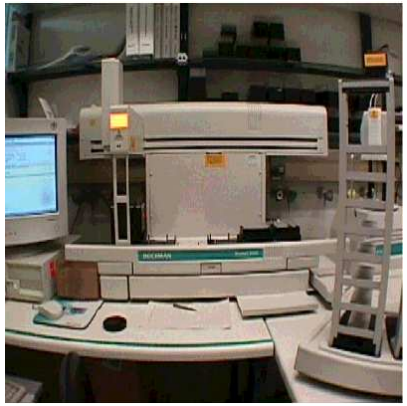
- Active area of research [Getoor and Taskar, 2007; DeRaedt et al 2008]
- SRL/PILP 10 year research challenges [Dietterich et al 2008]
- Experiment design and active learning [King et al, 2004]
- Chemical Turing Machines [Muggleton, 2006]
- Abduction maximising p(H)p(E|H) [Arvanitis+Muggleton, 2006]
- Use of probabilistic examples [Chen, 2008]
- Learnability models for PILP [Watanabe, 2008]

Robot Scientist (Nature, 2004)

Aberystwyth, Manchester, York, Imperial







Active Learning

Optimal Experimentation (Fedorov, 1972)

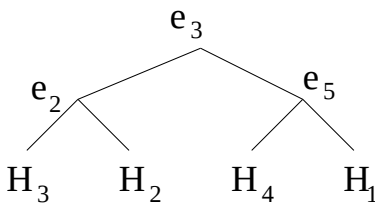
ASE-Progol

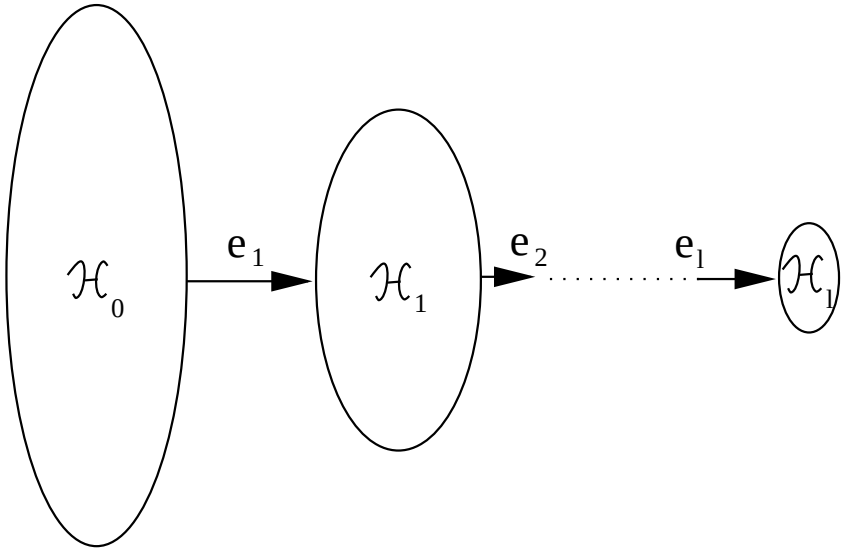
$$X = \{x_1, .., x_m\}, \mathcal{H}_0 = \{H_1, .., H_n\}$$

a)

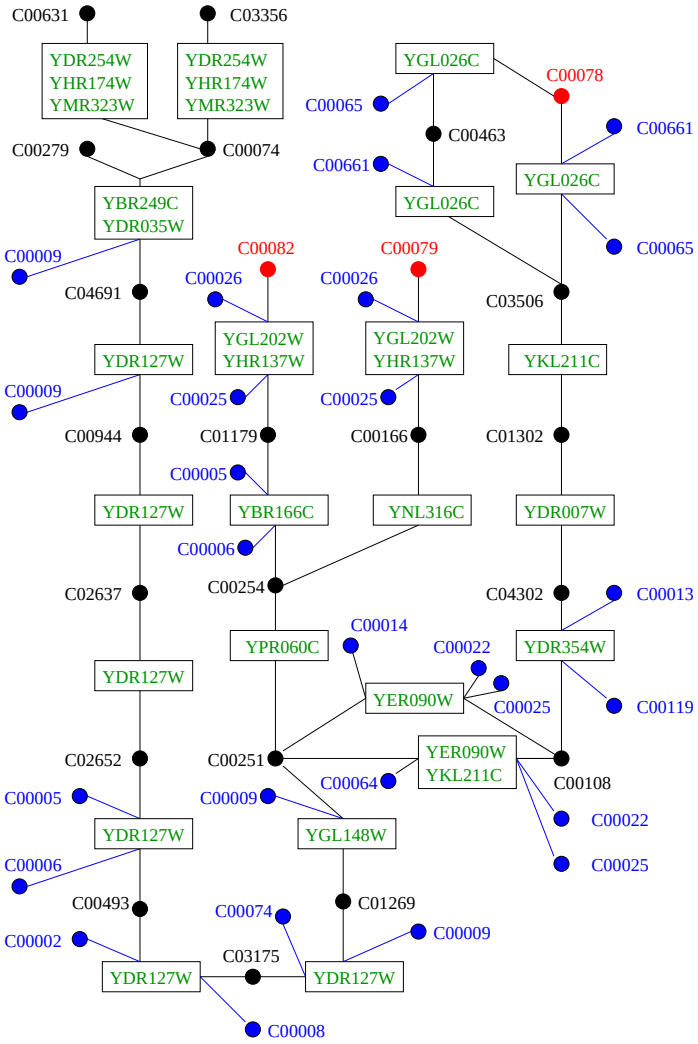
	e_1	...	e_m
H_1			
...			
H_n			

b)

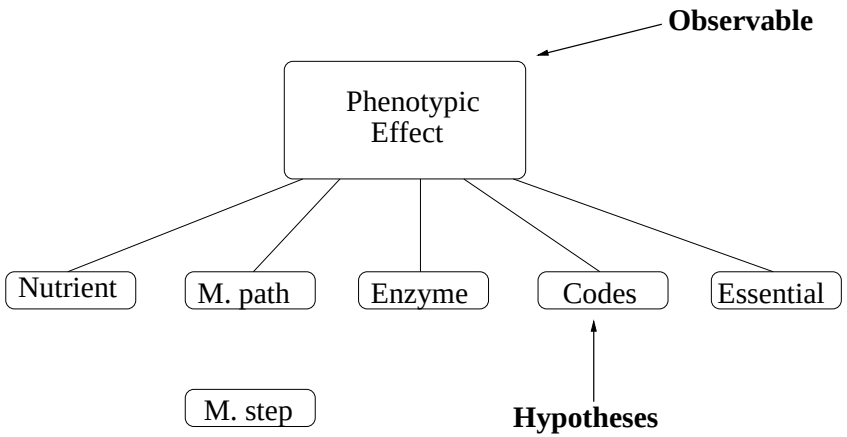




Aromatic amino acid pathways for yeast



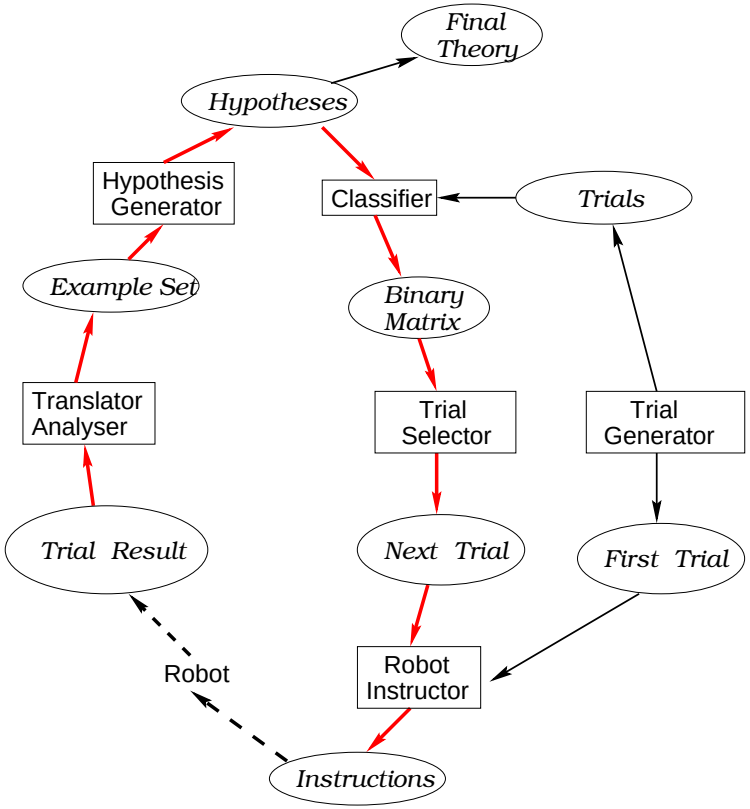
Calling diagram



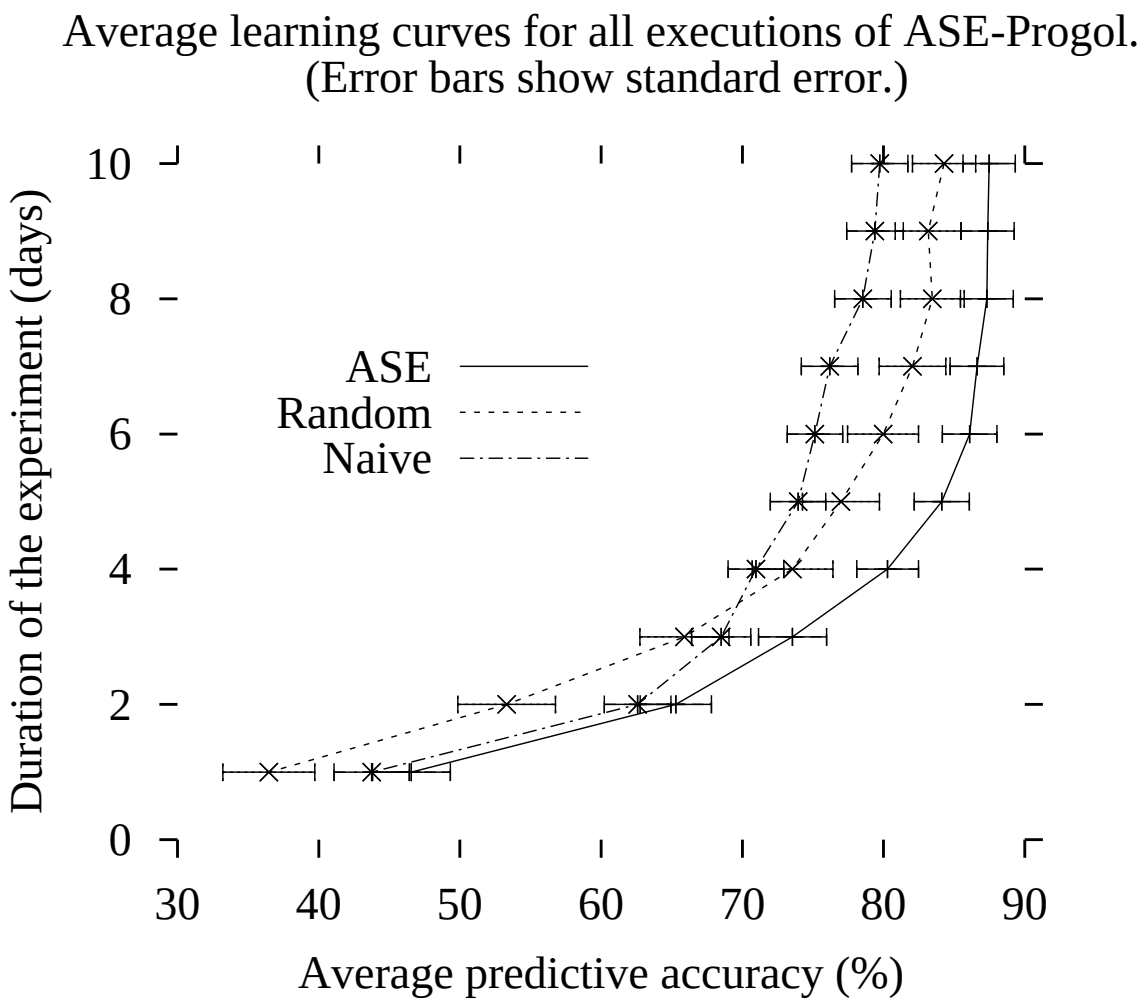
Prolog representation

```
phenotypic_effect(G, Medium):-
          nutrient_in(Nutrient, Medium),
          metabolic_path(Nutrient, Mi),
          enzyme(E, Mi, Mj),
          codes(G,E),
          metabolic_path(Mj, Mn),
          essential_molecule(Mn).
```

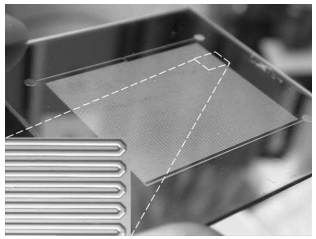
ASE-Progol

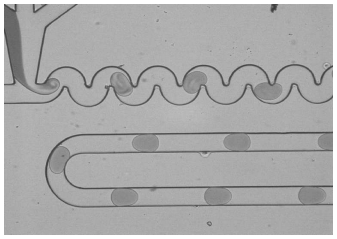

Final Theory
Hypotheses
Hypothesis Generator
Classifier
Trials
Example Set
Binary Matrix
Translator Analyser
Trial Selector
Trial Generator
Trial Result
Next Trial
First Trial
Robot
Robot Instructor
Instructions

Learning curves - time



Microfluidic Chemical Turing Machine [Nature, 2006]



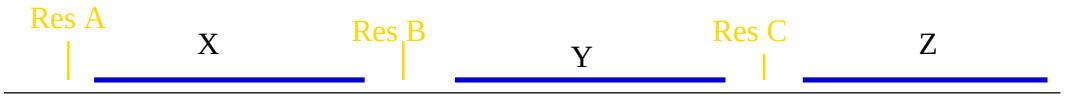


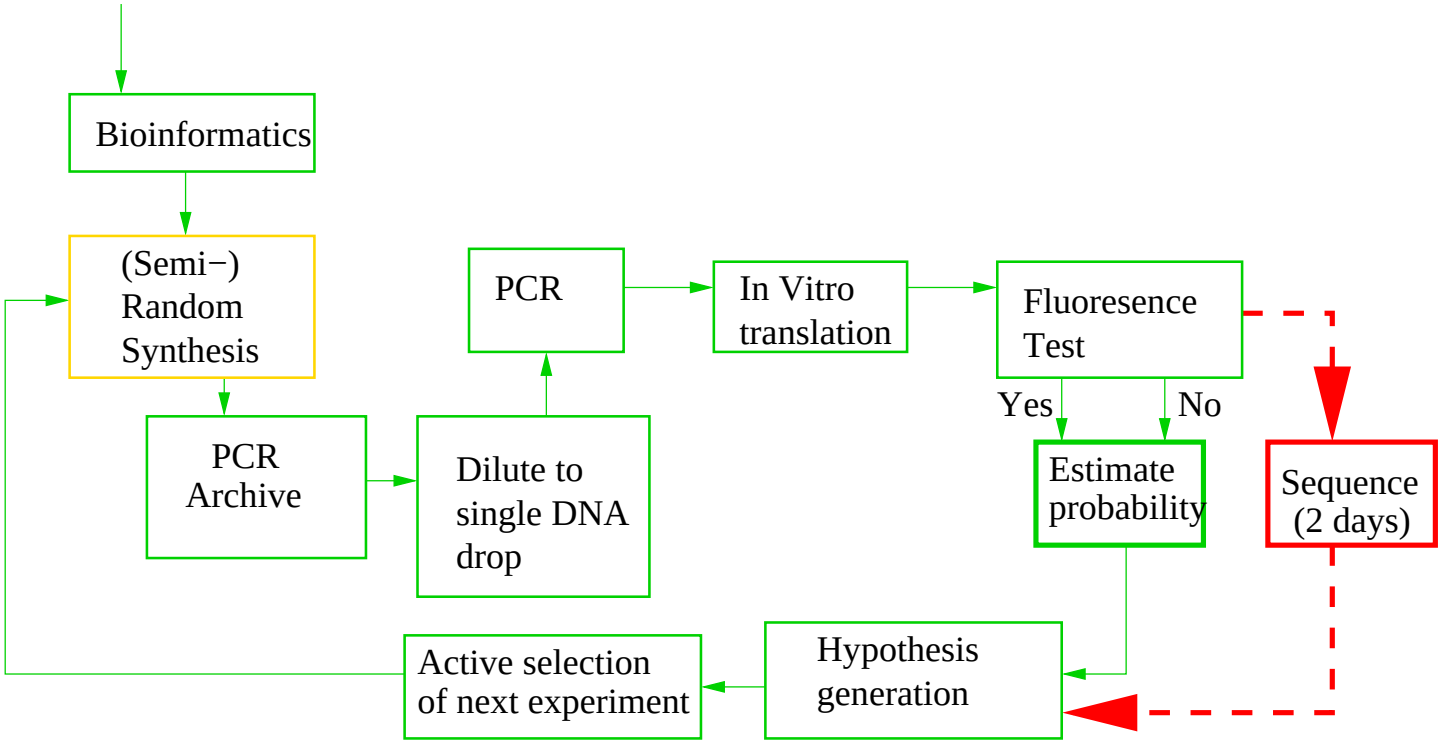
- Existing - custom designed special-purpose machines.
- Etched on silicon and poly-dimethylsiloxane (PDMS).
- Ducts, valves, ionic pumps and fluorescence tests.
- CUTM - addressable storage as micro-droplets($\approx 5\mu m$).
- Computer interface - “robot” replacement.
- Collaboration with Profs de Mello (Chemical Nanosciences), Freemont (Structural Biology), Sternberg (Structural Bioinformatics).

Synthetic Biology application

- MIT BioBrick competition IGem 2007
- Imperial College entry - Kitney+Freemont
- Cell-free biofilm infection detector
- Aim: improve robustness of design
- Microfluidic experiments and reconfiguration

Closed Loop Microfluidic Experiments





Summary and conclusion

- Priolog development
- Microfluidic machine
- Synthetic biology application
- PILP reduces experimental bottlenck
- High-speed cycle
- Comprehensible theories