Cancer classification based on miRNA profiles using ASP

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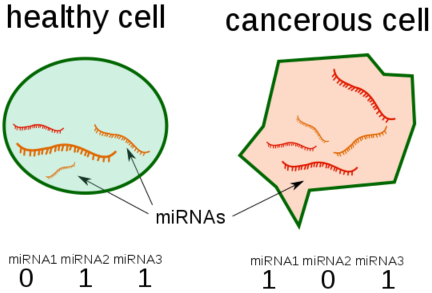
Selective cell targeting

- **Problem:** Discrimination of tumor from healthy tissues



- **Idea:** Cells differ in miRNA profiles

In vitro classification - Biochemical circuits

- synthesized in laboratory

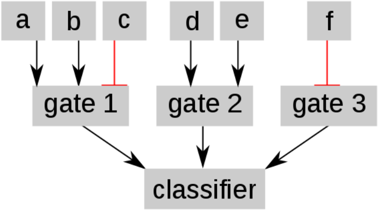
A boolean expression in conjunctive normal form (CNF)

- conjunction (AND) of *gates*
- each gate is a disjunction (OR) of literals
- **example:**

$$(a + b + !c) * (d + e) * (!f)$$

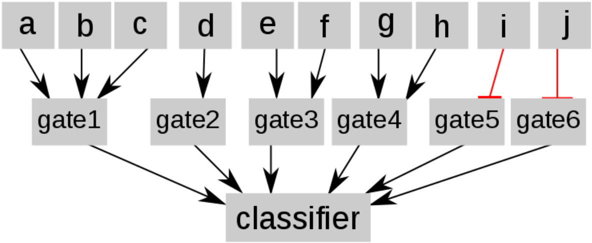
$+$ means disjunction, $*$ means conjunction, ! means negation

- CNF evaluates to 1 (*predicts cancer*) iff every gate evaluates to 1



Constraints from biology

- less than 10 inputs in total
- no more than 6 inputs attached to the AND gate
- no more than 3 inputs atttached to any OR gate
- no NOT gates attached to an OR gate
- no more than 2 OR gates
- no more than 4 NOT gates



Input: Data

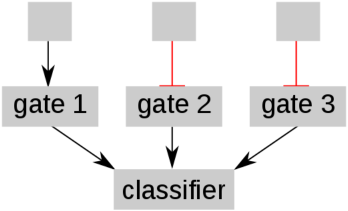
		cancer?	miRNAs		
	ID	Annots	g1	g2	g3
tissues	1	0	1	1	0
	2	0	0	0	1
	3	1	0	1	0

```
tissue(1,healthy). tissue(2,healthy). tissue(3,cancer).

data(1,g1,high). data(1,g2,high). data(1,g3,low).
data(2,g1,low).  data(2,g2,low).  data(2,g3,high).
data(3,g1,low).  data(3,g2,high). data(3,g3,low).

is_mirna(Y) :- data(X,Y,Z).
```

Input: Classifier structure



```
is_gate_type(type1).

upper_bound_pos_inputs(type1, 1).
upper_bound_neg_inputs(type1, 0).
lower_bound_pos_inputs(type1, 0).
lower_bound_neg_inputs(type1, 0).
upper_bound_gate_occurence(type1, 1).

upper_bound_inputs(2).
```

Decision 1: Number of gates

```
1 {number_of_gates(1..2)} 1.

is_integer(1..2).
is_gate_id(GateID) :- number_of_gates(X),is_integer(GateID),
                      GateID<=X.
```

Decision 2: Gate types

```
1 {gate_type(GateID, X) : is_gate_type(X)} 1 :- is_gate_id(GateID).
```

Decision 3: Inputs for each gate

positive inputs:

```
X{gate_input(GateID,positive,MiRNA):is_mirna(MiRNA)}Y
   :-is_gate_id(GateID),gate_type(GateID,GateType),
     lower_bound_pos_inputs(GateType,X),
     upper_bound_pos_inputs(GateType,Y).
```

negative inputs:

```
X{gate_input(GateID,negative,MiRNA):is_mirna(MiRNA)}Y
   :-is_gate_id(GateID),gate_type(GateID,GateType),
     lower_bound_neg_inputs(GateType,X),
     upper_bound_neg_inputs(GateType,Y).
```

Constraints

- conditional count constraints
-

Gates must have inputs

1 {gate_input(GateID, Sign, MiRNA):

```
1 {gate_input(GateID, Sign, MiRNA):
    is_sign(Sign), is_mirna(MiRNA)} :- is_gate_id(GateID).
```

Inputs must be unique

```
{gate_input(GateID,Sign,MiRNA):
  is_sign(Sign), is_gate(GateID)} 1 :- is_mirna(MiRNA).
```

Number of inputs is bounded

```
{gate_input(GateID, Sign, MiRNA):
  is_gate_id(GateID), is_sign(Sign), is_mirna(MiRNA)} X :-
upper_bound_inputs(X).
```

Occurences of gates

```
{gate_type(GateID,GateType):
   is_gate_type(GateType),
   is_gate_id(GateID)} X :-
  upper_bound_gate_occurence(GateType,X).
```

Activity of gates

```
gate_fires(GateID,TissueID) :-
  gate_input(GateID,positive,MiRNA),
  data(TissueID,MiRNA,high).

gate_fires(GateID,TissueID) :-
  gate_input(GateID,negative,MiRNA),
  data(TissueID,MiRNA,low).
```

The classifier

```
classifier(TissueID, healthy) :-
  not gate_fires(GateID, TissueID),
  is_gate_id(GateID), is_tissue_id(TissueID).

classifier(TissueID, cancer) :-
  not classifier(TissueID, healthy),
  is_tissue_id(TissueID).
```

Optimization

- single objective
- with priorities
- weighted sum

Single Objective

```
#minimize{ 1@1,GateID:gate_input(GateID,Sign,MiRNA) }.
#minimize{ 1@2,MiRNA: gate_input(GateID,Sign,MiRNA) }.
```

Priorities

```
#minimize{ 1@1,GateID:gate_input(GateID,Sign,MiRNA) }.
#minimize{ 1@2,MiRNA: gate_input(GateID,Sign,MiRNA) }.
```