Silicell Maker CAD tool for biochemical networks

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Séminaire INRIA - Lifeware

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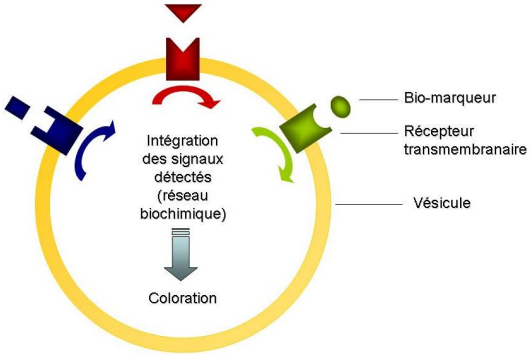
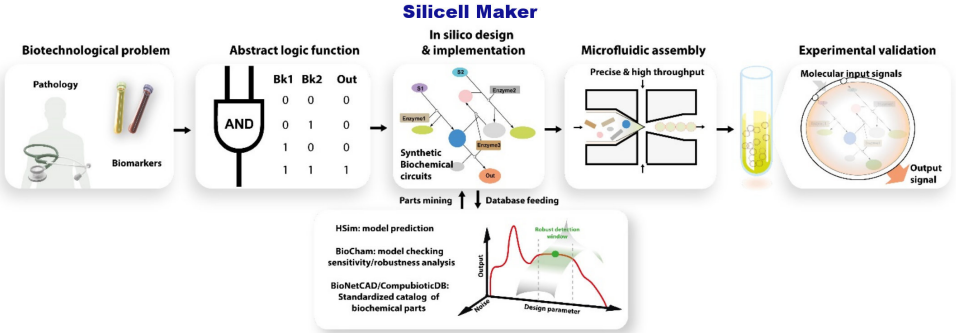
Artificial biochemical nano-system for medical diagnosis

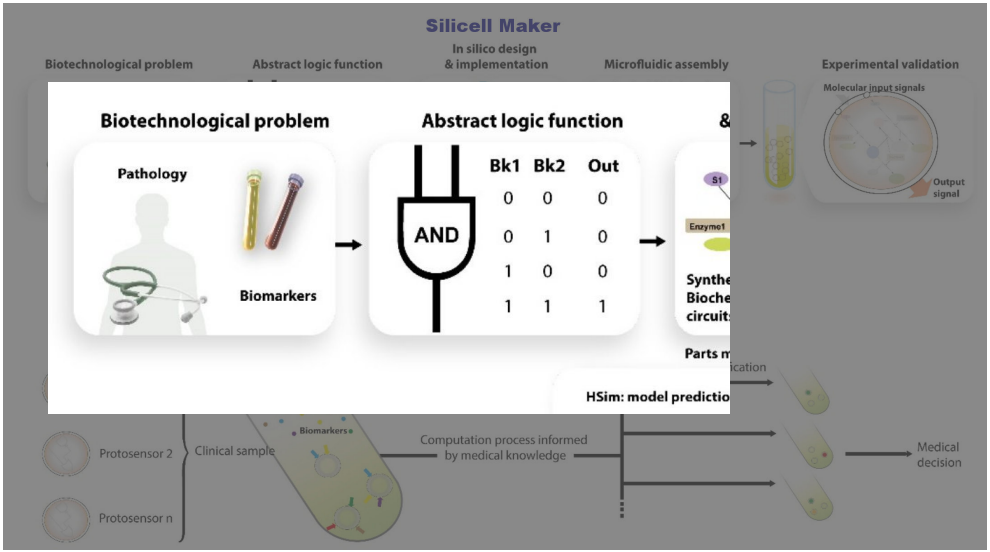


- **stable and robust system** -> no bacterial host, no genetic system
- lipidic vesicle + trans-membrane receptors
- enzymatic network artificially designed
- results easy to get (ex.: color change)

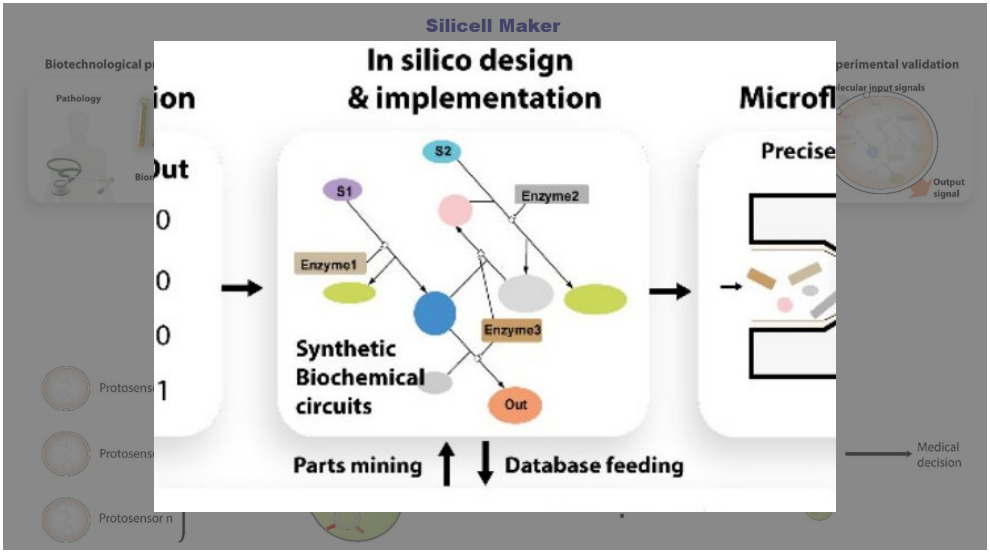
Process overview



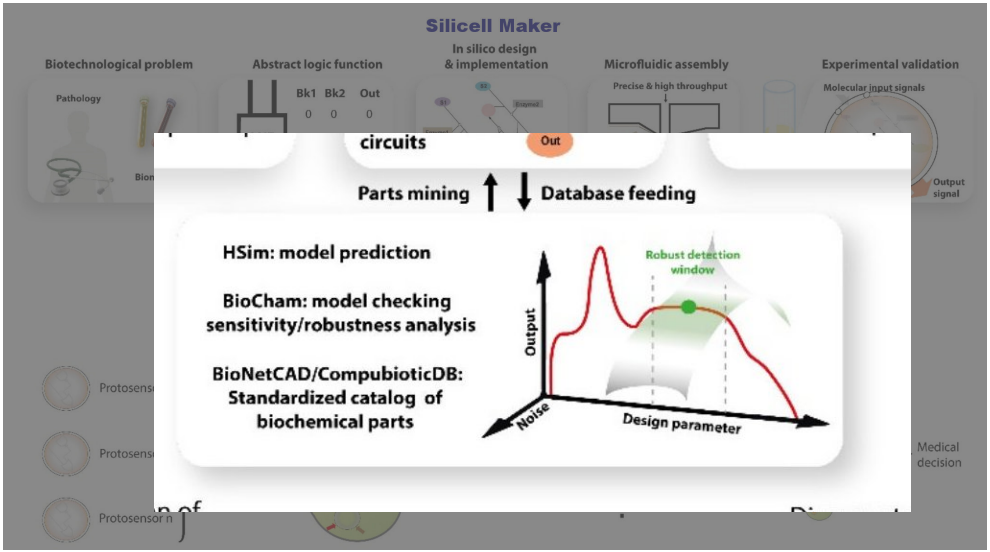
Process overview



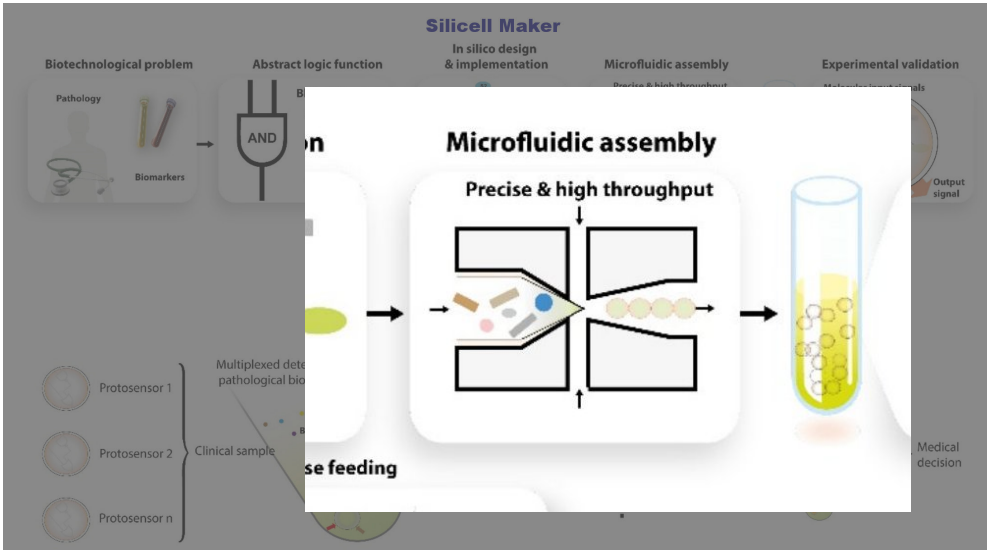
Process overview



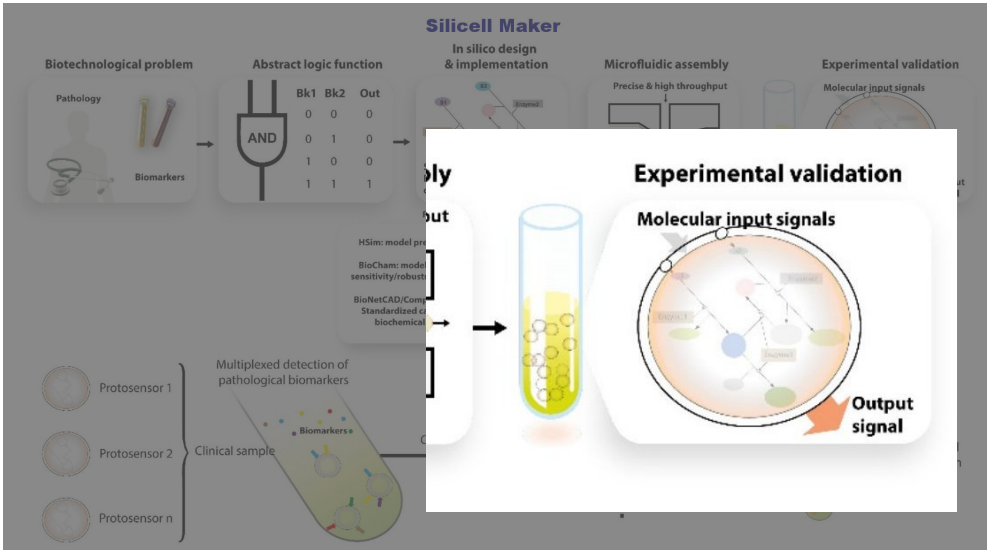
Process overview



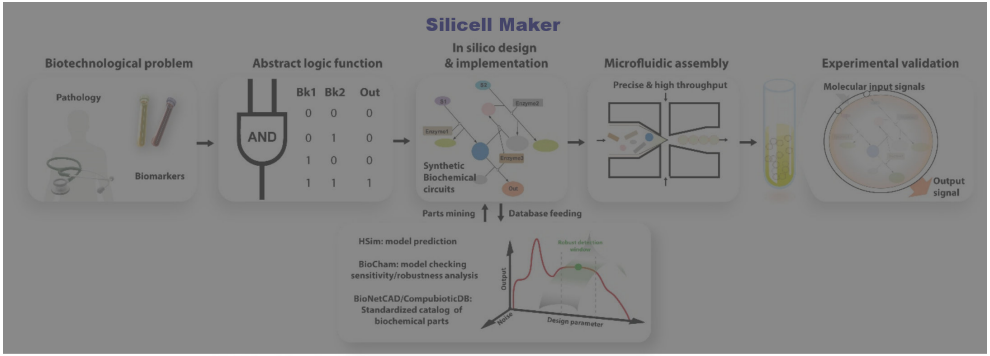
Process overview



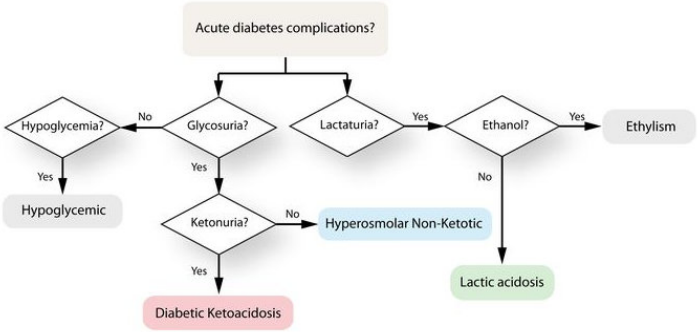
Process overview



Process overview



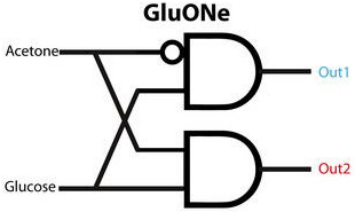
Diagnosis algorithm



Hyperosmolar non-ketonic: output 1

Diabetic Ketoacidosis: output 2

note: the two outputs are never true at the same time

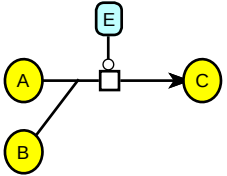


Enzymatic logic gates

Boolean computing with enzymatic reactions

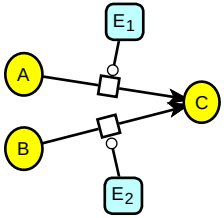
false: $[s] < threshold_l$, true: $[s] > threshold_h$

AND



E: $A + B \rightarrow C$

OR



E_1: $A \rightarrow C$

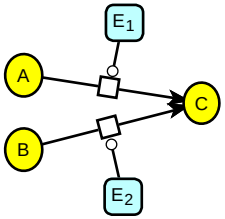
E_2: $B \rightarrow C$

- simple and robust
- constraints and limitations
  - composability and reusability
  - enzyme kinetics

Enzymatic logic gates

Threshold value does matter!

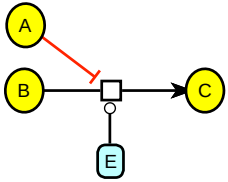
false: $[s] < Th$, true: $[s] \geq Th$



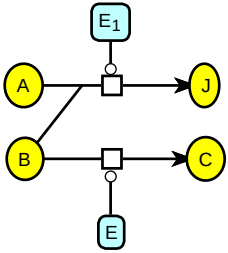
A	B	C	Th = 10	Th = 20
0	0	0	False	False
0	15	15	True	False
15	0	15	True	False
15	15	30	True	True
			OR	**???**

Enzymatic logic gates

Inverters $C = B \wedge \neg A$



Inhibition



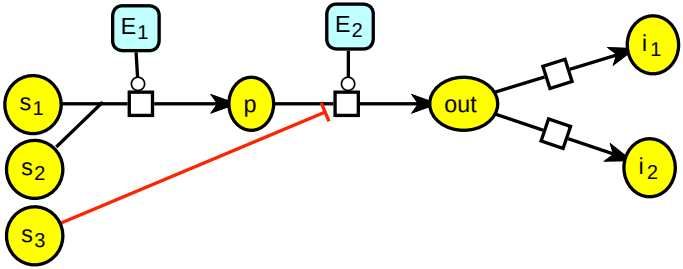
Concurrency

- highly dependent on the enzymes kinetics
- and on the thresholds values...

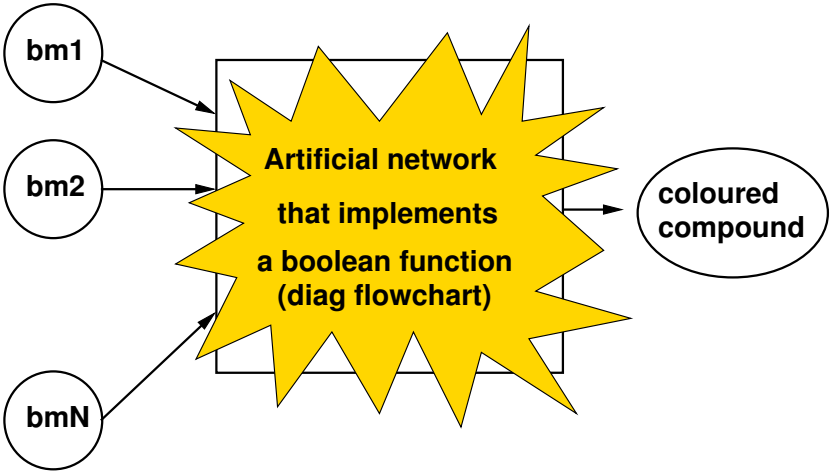
Gates composability

- connection wires: metabolites
  - need to find the ***adequate*** enzymes set...
  - everything is in the same compartment => beware the ***short circuits***!
  - need a large ***variety*** of each type of logic gate
- ***Synchronisation*** constraints (mainly with inverters)
- Signal ***fading*** (fan out)

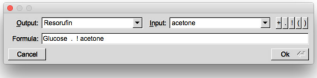
$$out = (s_1 \wedge s_2) \wedge \neg s_3$$

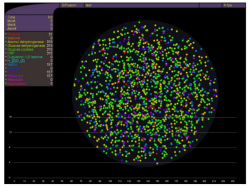


What do we have to do?



Silicell Maker





Entity-centered simulation

Build many implementations of a given Boolean expression (diagnosis algorithm) using the logic gates library

Boolean expression

NetBuild

Enzymatic logic circuits

HSIM

Logic gates library

Metabolic network

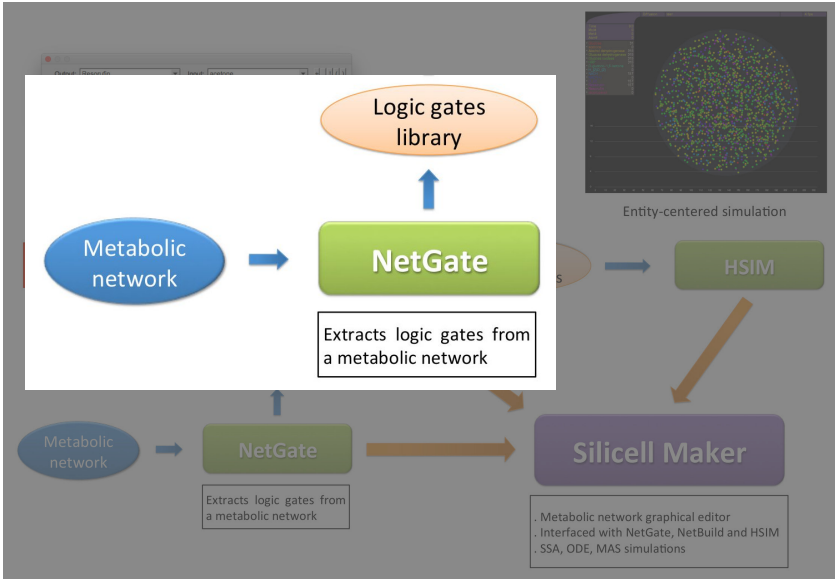
NetGate

Extracts logic gates from a metabolic network

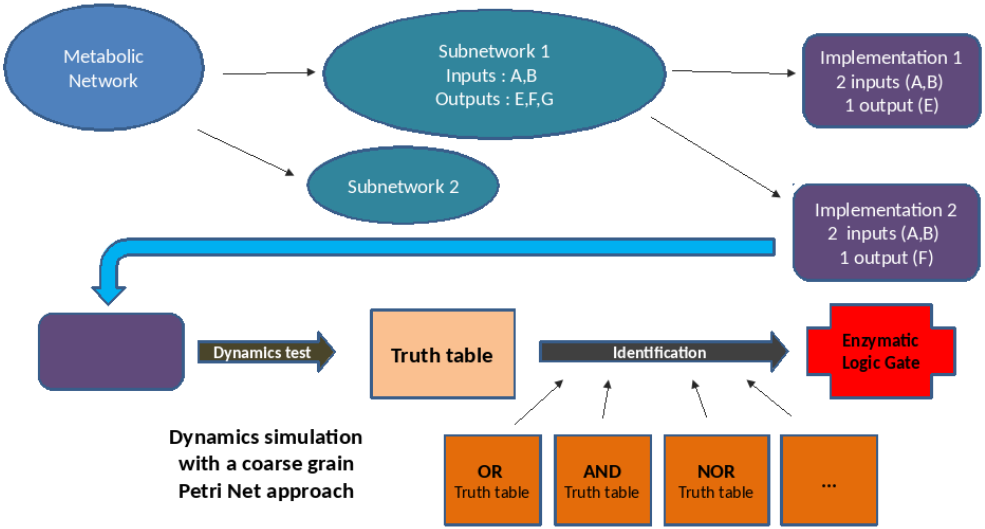
Silicell Maker

. Metabolic network graphical editor
. Interfaced with NetGate, NetBuild and HSIM
. SSA, ODE, MAS simulations

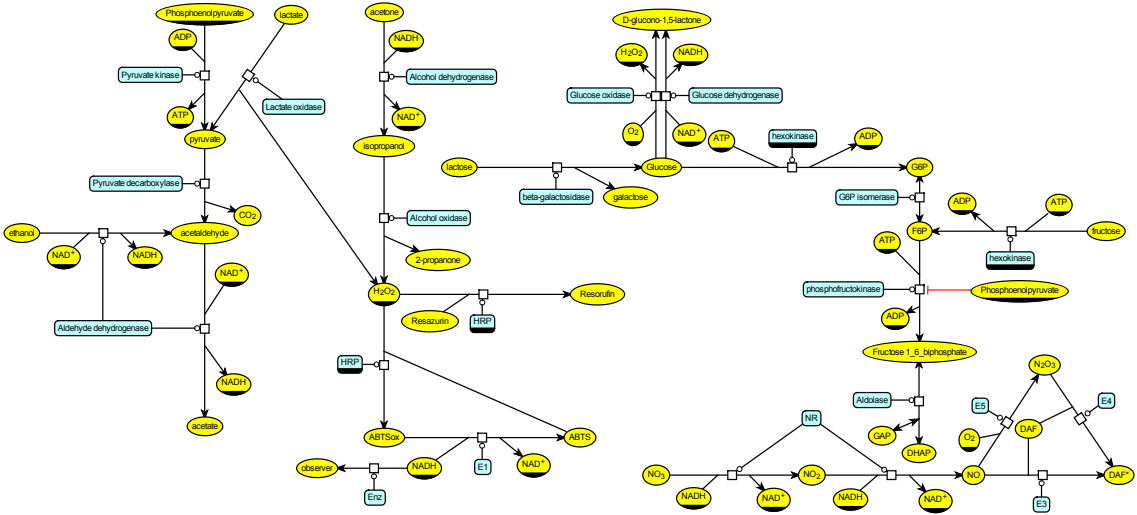
Step 1: build the library



NetGate: overview



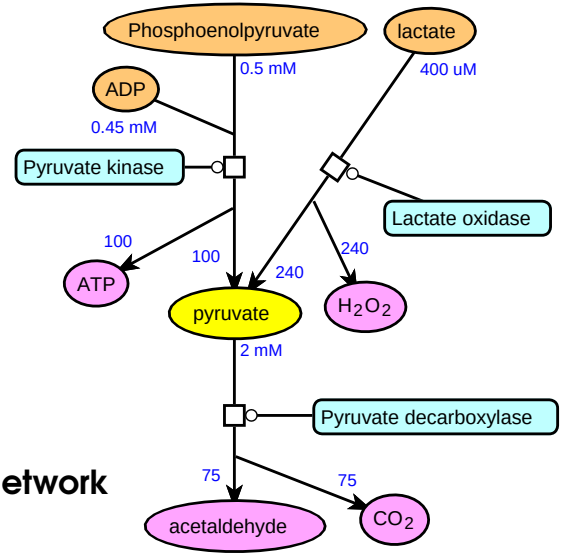
NetGate: base network



NetGate: subnetwork extraction

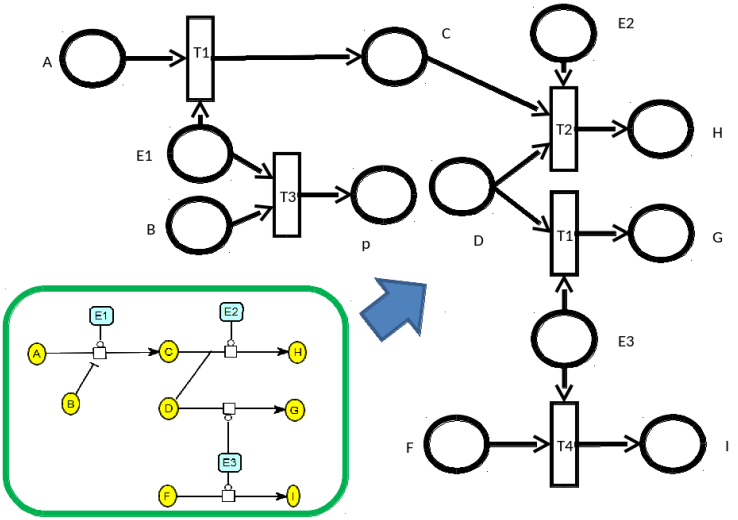
Inputs: orange
outputs: purple
in-out: yellow

3-reactions subnetwork

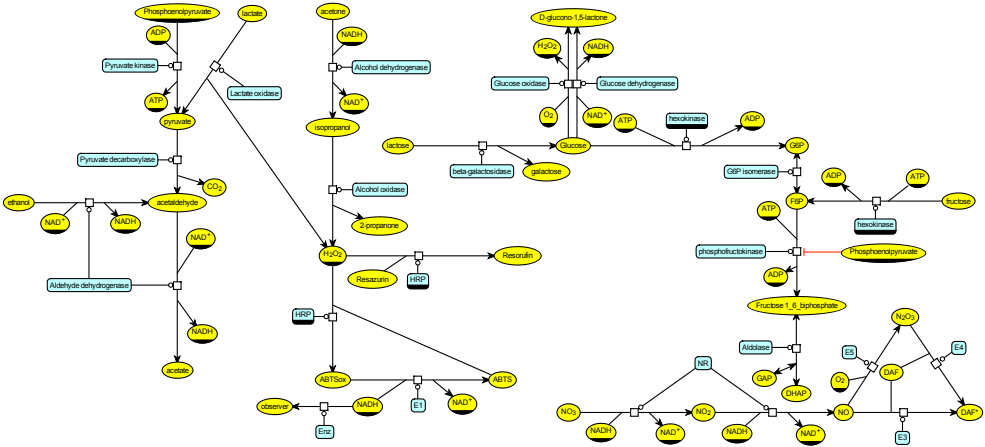


NetGate: subnetwork dynamics

Coarse grain simulation to infer the dynamics



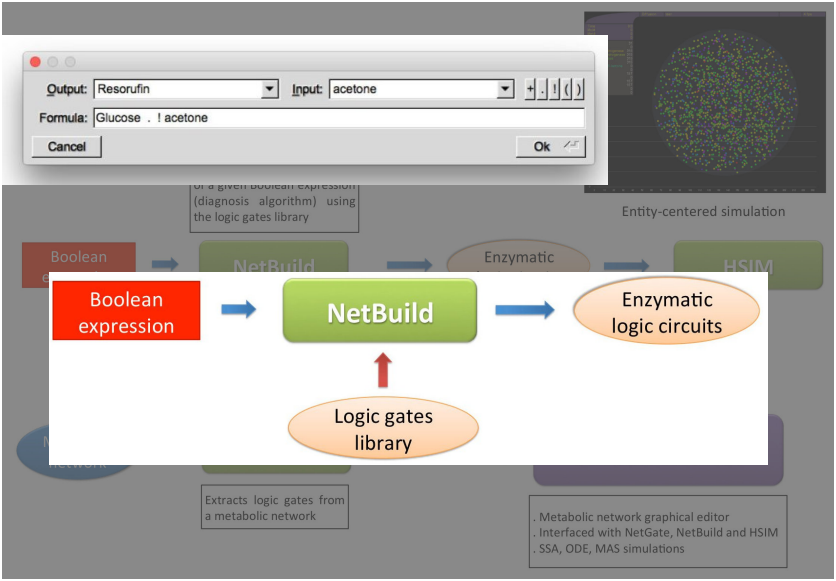
NetGate: results

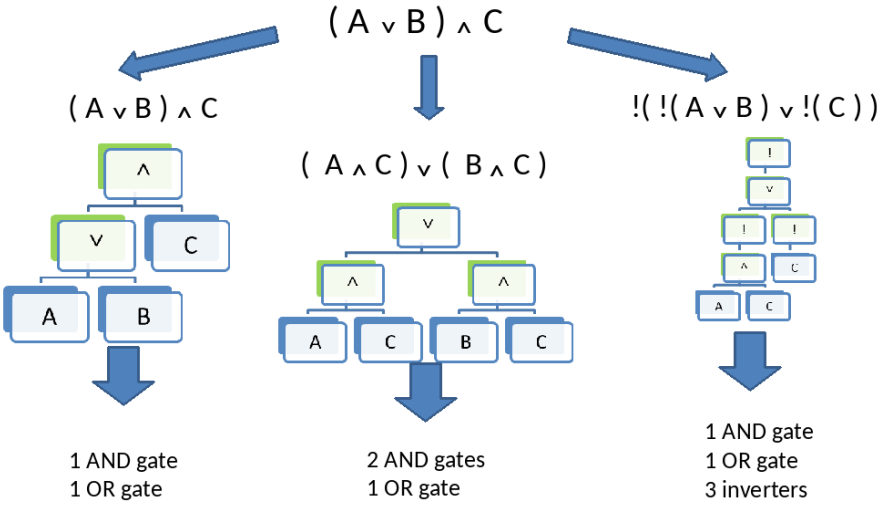


206 AND, **98 OR**, **7 NAND**, **16 NOT-OR**,
29 Inverters, **194 YES**, **203 NOT-AND**

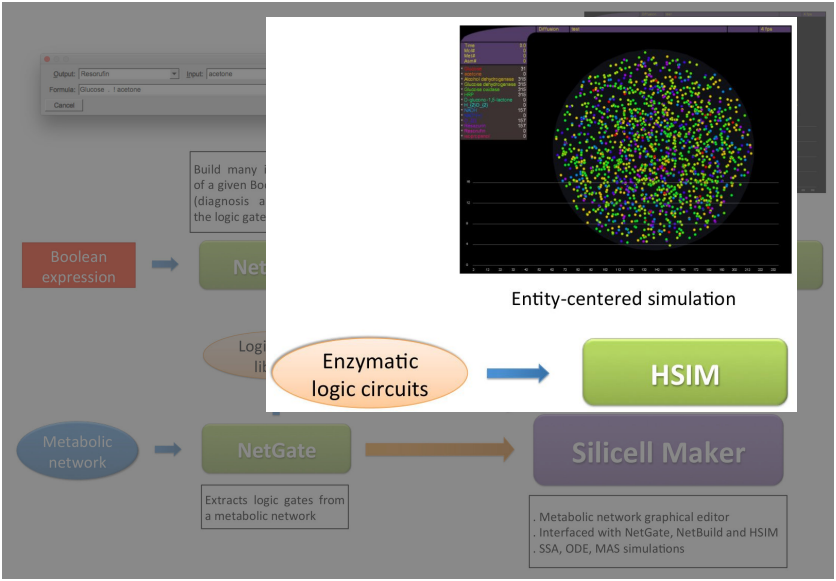
Reactions: **20**
Gates: **753**

Step 2: build implementations

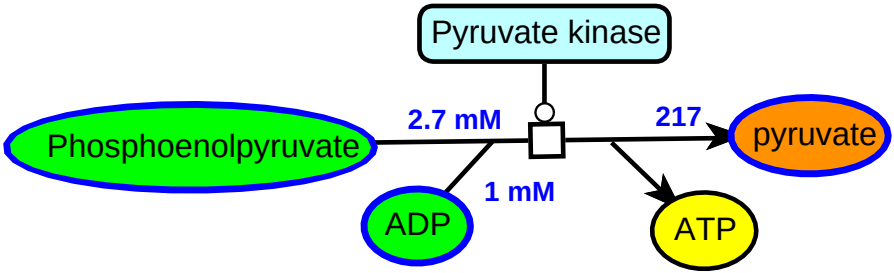



(A ∨ B) ∧ C
(A ∨ B) ∧ C
∧
∨
C
A
B
1 AND gate
1 OR gate
(A ∧ C) ∨ (B ∧ C)
∨
∧
∧
A
C
B
C
2 AND gates
1 OR gate
!(!(A ∨ B) ∨ !(C))
!
∨
!
!
∧
C
A
C
1 AND gate
1 OR gate
3 inverters

Step 3: validation



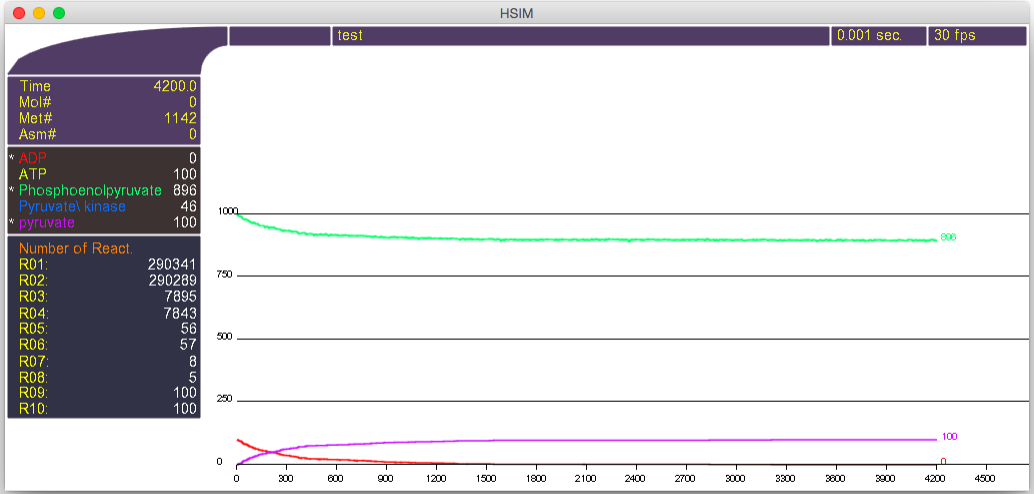
Boolean formula: **pyruvate = PEP ∧ ADP**



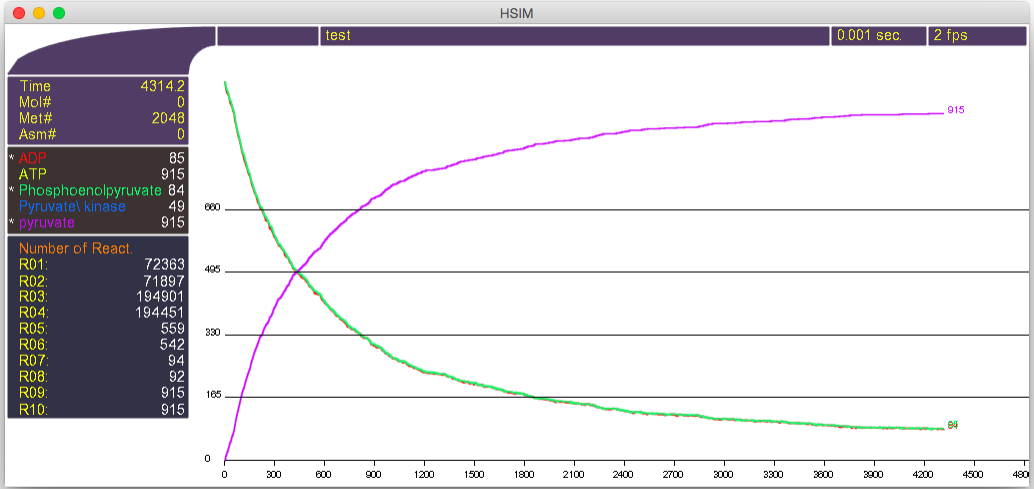
Translation to HSIM model


```
PK    +  PEP  ->  Ea1              [0.0221019]*;
Ea1           ->  PK + PEP         [0.00217]*;
-------------------------------------------------
PK    +  ADP  ->  Eb1              [0.059675]*;
Eb1           ->  PK + ADP         [0.00217]*;
-------------------------------------------------
Ea1   +  ADP  ->  CF1              [0.059675]*;
Eb1   +  PEP  ->  CF1              [0.0221019]*;
-------------------------------------------------
CF1           ->  Ea1 + ADP        [0.00217]*;
CF1           ->  Eb1 + PEP        [0.00217]*;
CF1           ->  CFb1 + pyruvate  [0.0217]*;
-------------------------------------------------
CFb1          ->  PK + ATP         [1];
```

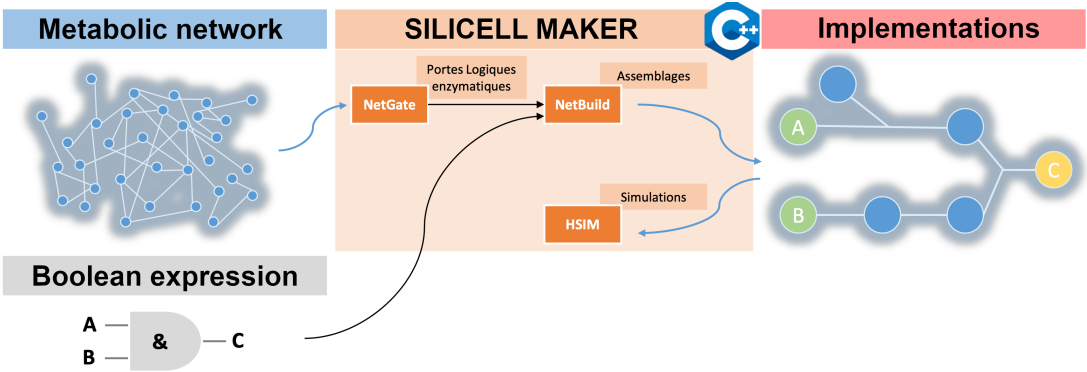
Simulation results



Simulation results



BrendaXplorer: why?



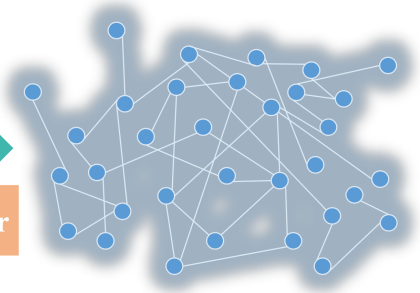
BrendaXplorer: how?

Reactions data base

BrendaReader

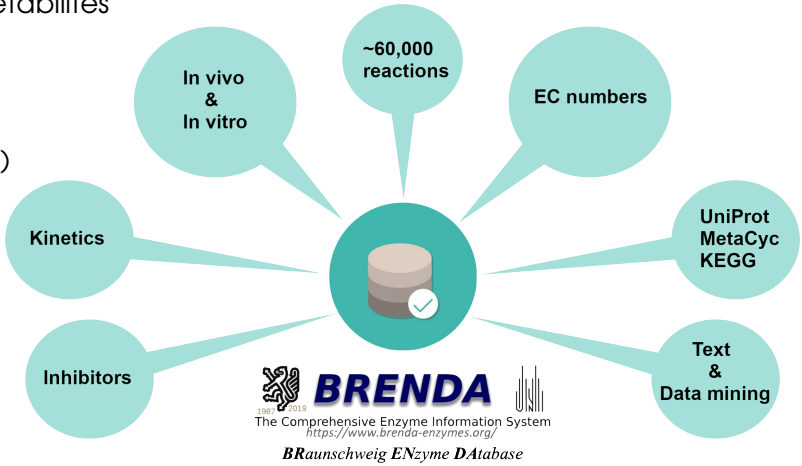
Reactions

BrendaXplorer

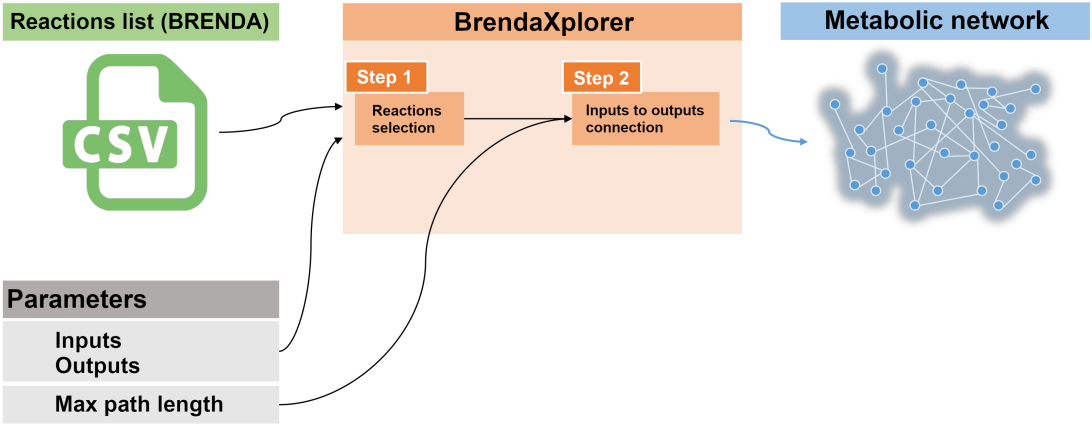


Netgate input network

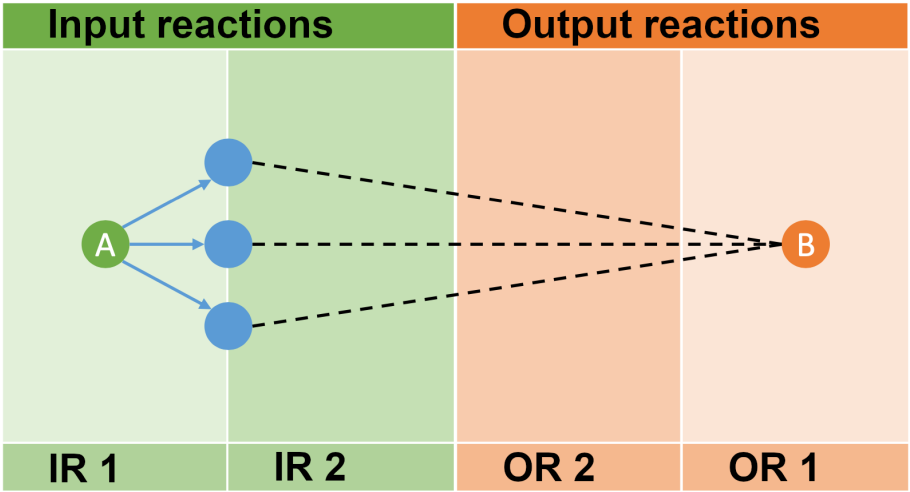
- ≈ 60,000 input metabilites
- ≈ 50,000 output metabilites
- ≈ 6500 enzymes
- 304848 reactions
- ≈ 5 organisms
  (≈ 60,000 reactions)



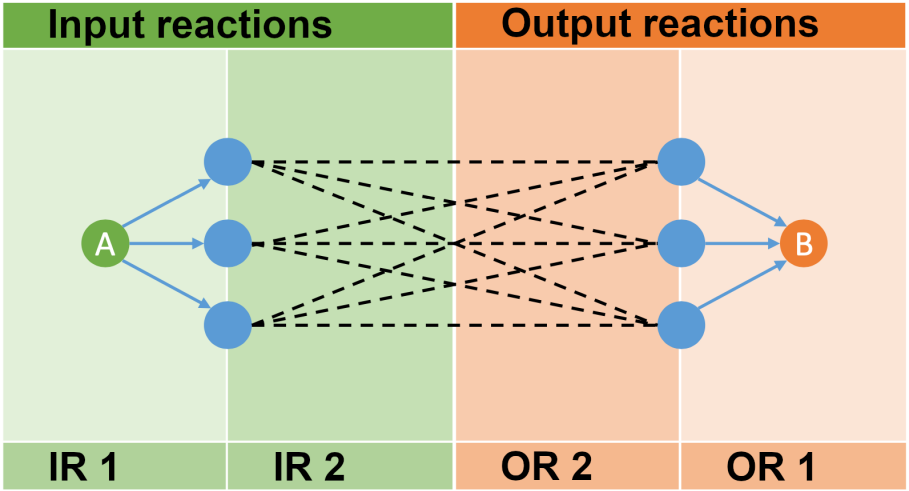
BrendaXplorer: overview



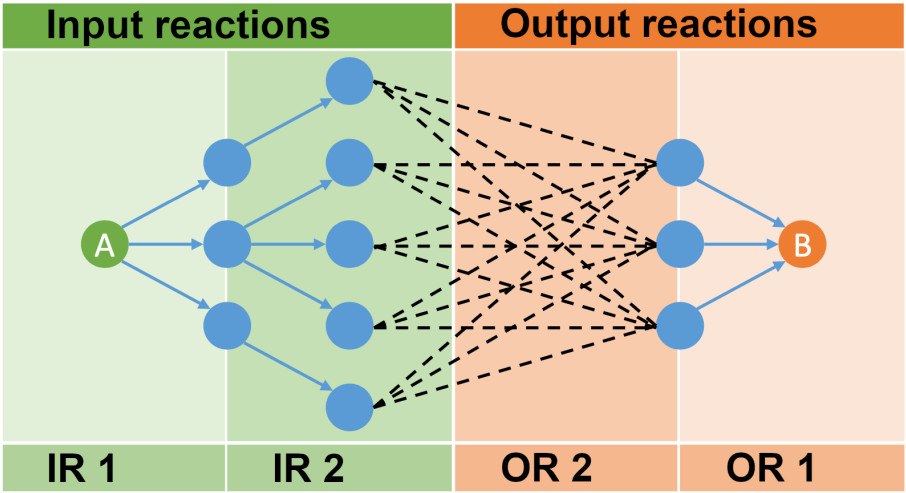
Path length: one reaction



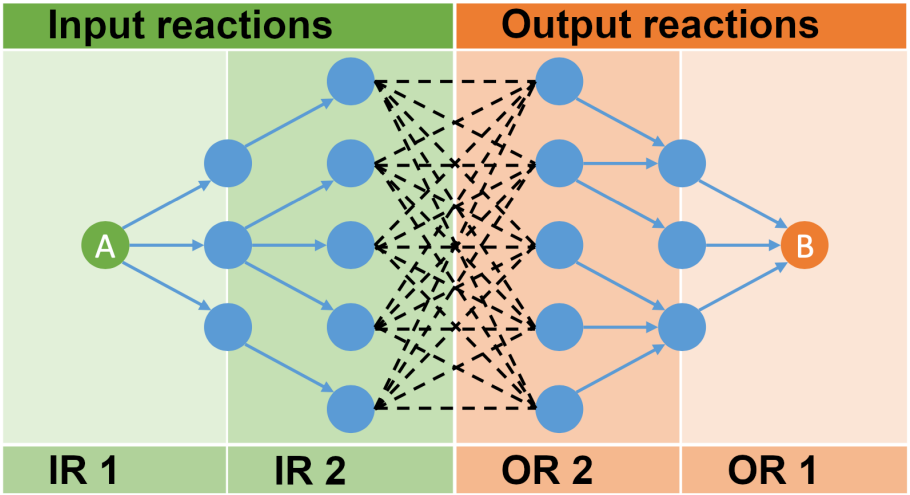
Path length: two reactions



Path length: three reactions

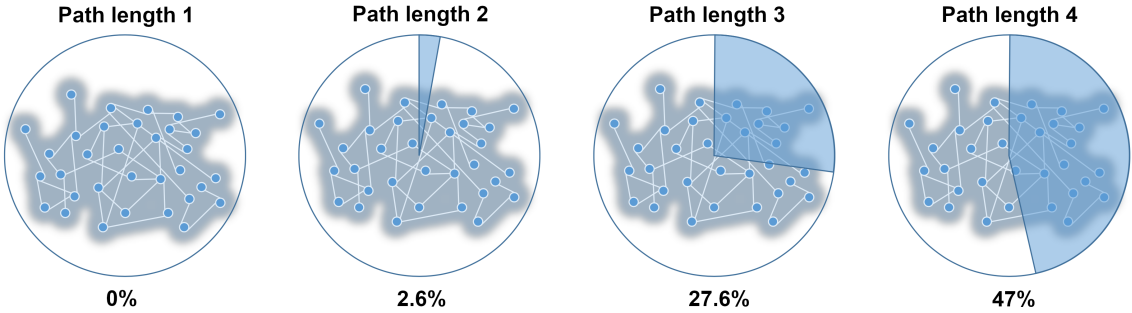


Path length: four reactions



Success ratio

- 500 input-output couples randomly chosen
- success: inputs connected to outputs by at least one path



Merci de votre attention

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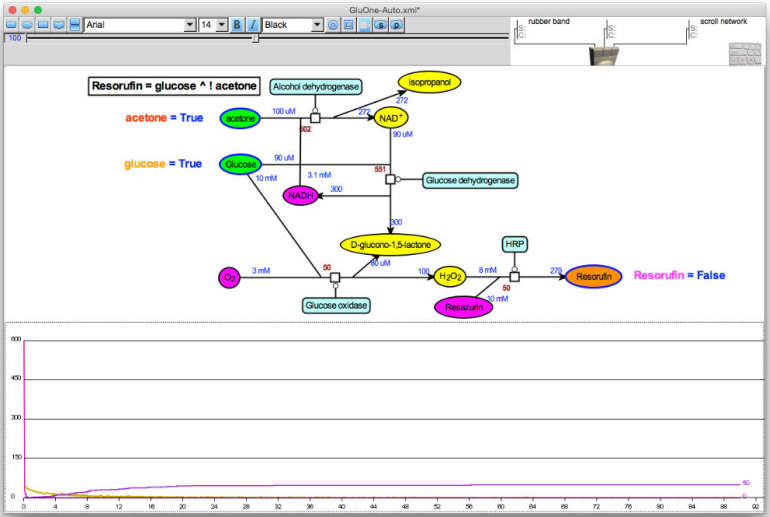
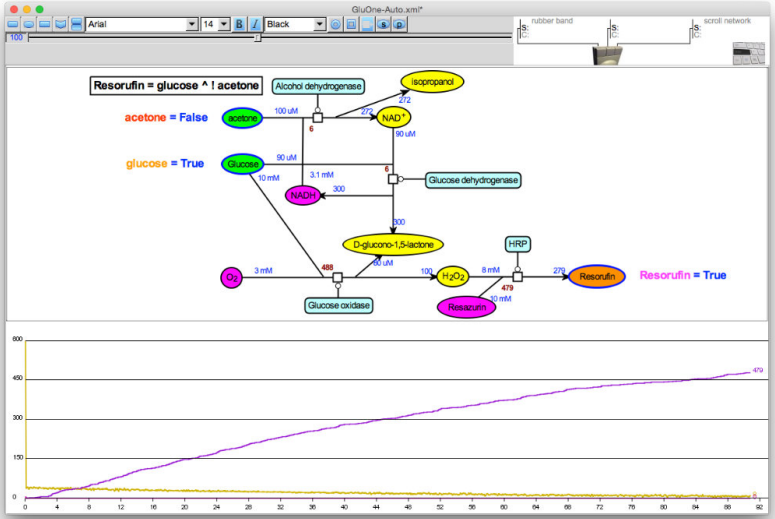
GluOne: implementation



GluOne: implementation



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