REGLIS

REGuLarities : Inference and Statistics

From the molecule to the cell: Development, confrontation and integration of formal models and methods of analysis

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A single partner:

HELIX-BAOBAB

now:

BAMBOO-BAOBAB

Main motivation

Arrive, by means of a comparative approach,
to a better understanding of the diversity of
the modes of evolution and functioning of organisms,
both prokaryotes and eukaryotes,
and of the extraordinary combinatorics
of the spatial and temporal interactions among the elements
(genes, metabolites, etc.) composing such organisms

More precisely

Try to provide elements of answers to the following questions:

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- **Are there regularities, structural and functional, in the diversity that is observed, regularities that could provide evidence of a deeper organisation of living organisms?**

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- **Are there regularities, structural and functional, in the diversity that is observed, regularities that could provide evidence of a deeper organisation of living organisms?**

- **Can we identify these regularities in a systematic fashion and thus manage to distinguish an order in the complex network of the observed interactions?**

More precisely

Try to provide elements of answers to the following questions:

- **Are there regularities, structural and functional, in the diversity that is observed, regularities that could provide evidence of a deeper organisation of living organisms?**
- **Can we identify these regularities in a systematic fashion and thus manage to distinguish an order in the complex network of the observed interactions?**
- **How has this network been set up in the course of evolution, to accomplish what functions, and could it have evolved in a different way?**

Or, in other words

Get some clues on a possible answer to this (very general) question:

Is the structure of living organisms

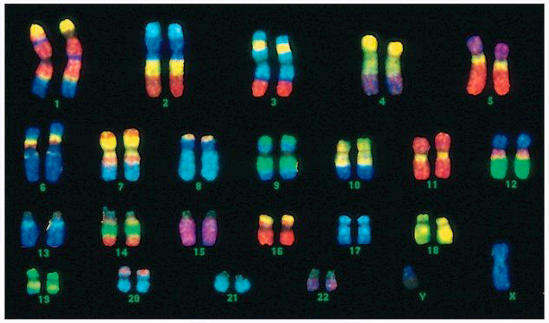
simple or simplifiable into some general principles,

or is life made essentially of exceptions?

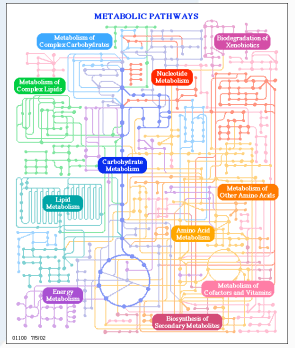
Regularity

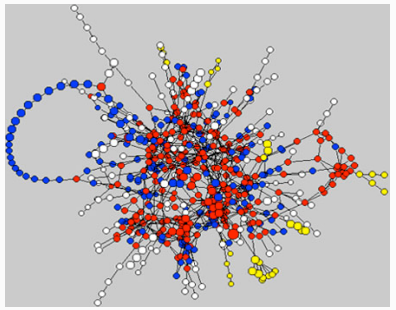
Conservation of some elements

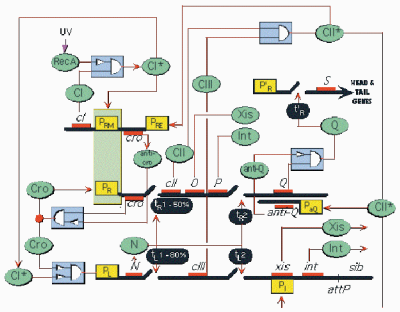
at the level of the genome



at the level of the network of molecular interactions inside a cell







Conclusion

Are there regularities:

YES (this was already partially "known")

Conclusion

Are there regularities:

YES (this was already partially "known")

Is life "simplifiable into some general principles":

THE ANSWER IS STILL NOT IN

What was achieved

Better formalisms and mathematical models
Better algorithms of analysis

- **at the genomic level**
  - **repeats and motifs**
  - **recombination and chromosomal organisation**
  - **ancestral genomes**
  - **synteny blocks and breakpoint regions**
  - **reversal scenarios between genomes**

- **at the network level**
  - **regulatory modules**
  - **motifs**
  - **fluxes**
  - **minimal sets of precursors**

What was achieved

Better formalisms and mathematical models
Better algorithms of analysis

[publications]

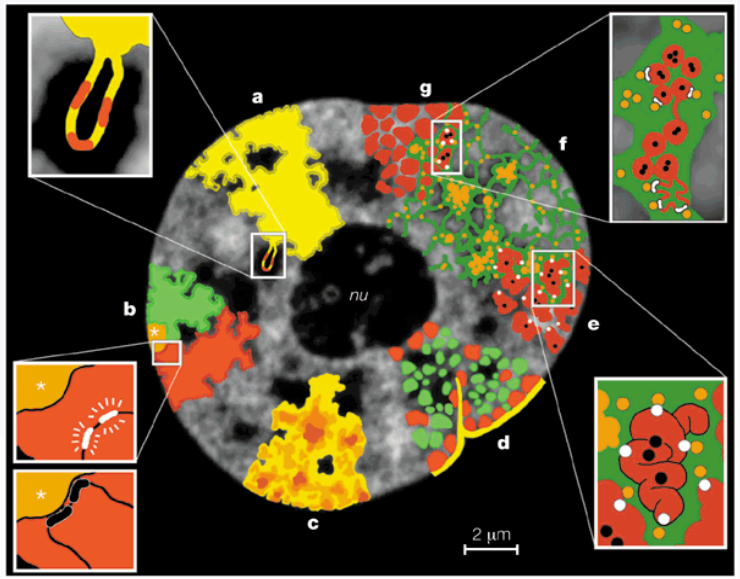
- **at the genomic level** [2][4]
  - **repeats and motifs** [7]
  - **recombination and chromosomal organisation** [1]
  - **ancestral genomes** [3]
  - **synteny blocks and breakpoint regions** [2]
  - **reversal scenarios between genomes** [5]

- **at the network level** [2][6]
  - **regulatory modules** [1]
  - **motifs** [3]
  - **fluxes** [1]
  - **minimal sets of precursors** [2]

[software & databases]

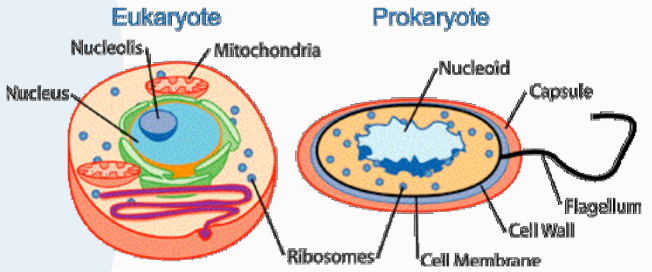
The future (present)

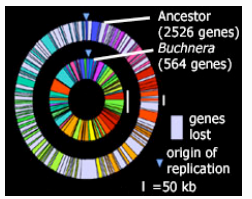
Genomes in space



Nature Reviews | Genetics

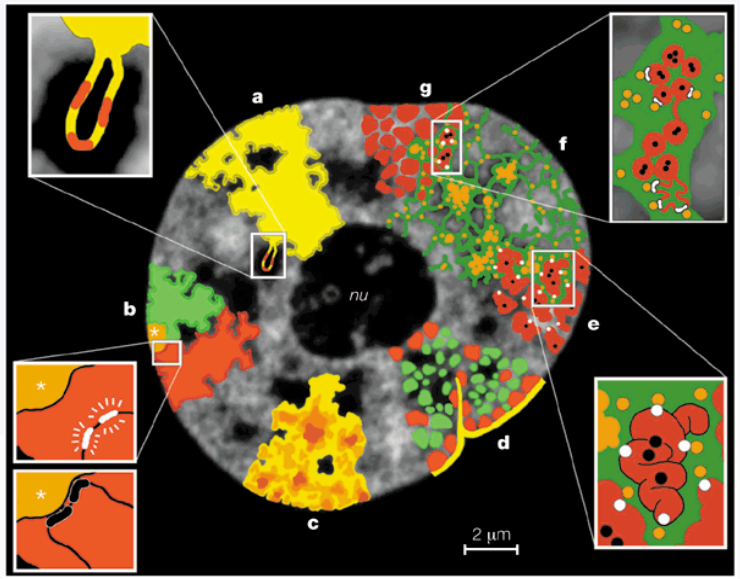
Networks in interaction





The future (present)

Genomes in space



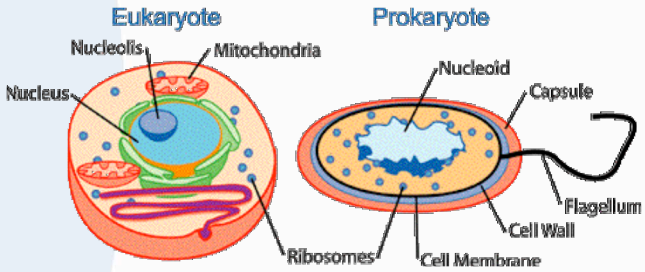
Nature Reviews | Genetics

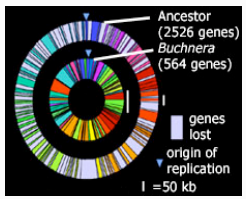
Prototype funded
ARC INRIA 2007-2008
Further funds will be sought

Funded
ANR MIRI
2009-2012

INRIA
Associated Team
Simbiosi

Networks in interaction





Getting back to the past (present)

Better formalisms and mathematical models
Better algorithms of analysis

- **at the genomic level**
  - **repeats and motifs**
  - **recombination and chromosomal organisation**
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- **at the network level**
  - **regulatory modules**
  - **motifs**
  - **fluxes**
  - **minimal sets of precursors**

Foreword: one recurrent characteristic

Little formal (mathematical/algorithmic) definition of what is sought

Formalisation (Modelling)

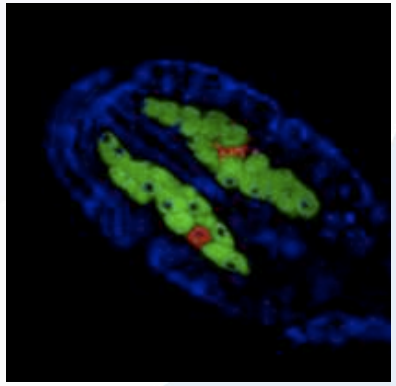
Experiments

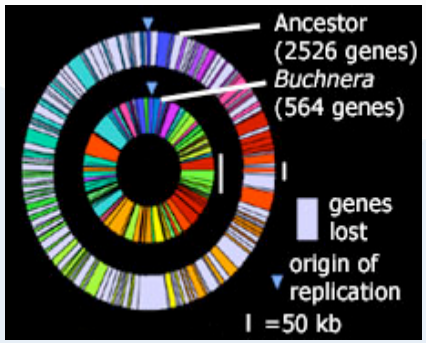
Algorithmic development

Minimal sets of metabolic precursors

Minimal sets of metabolic precursors

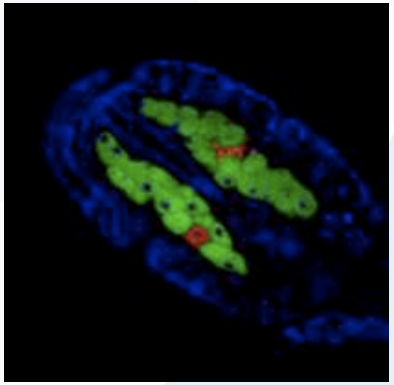
Buchnera
and its host

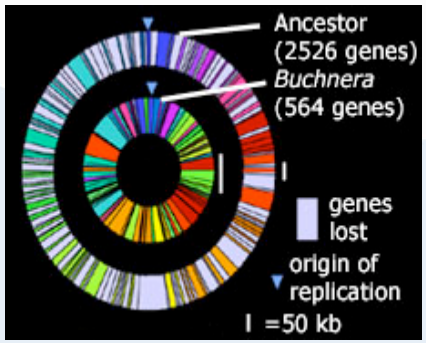




Minimal sets of metabolic precursors

Buchnera **and its host**





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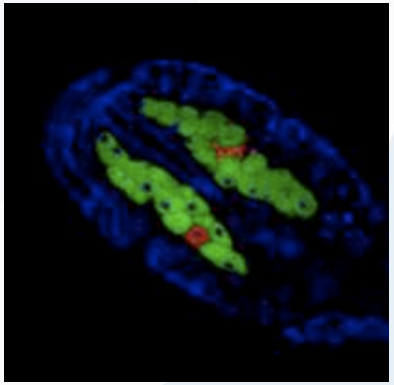
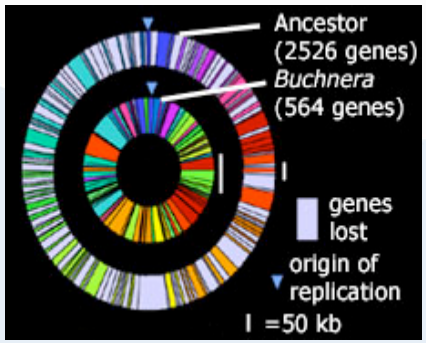


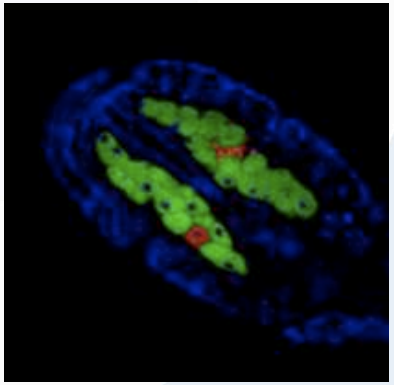


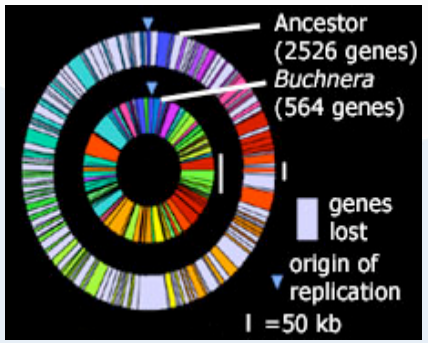
Obligatory endosymbiosis

Live or die together

Minimal sets of metabolic precursors

Buchnera **and its host**





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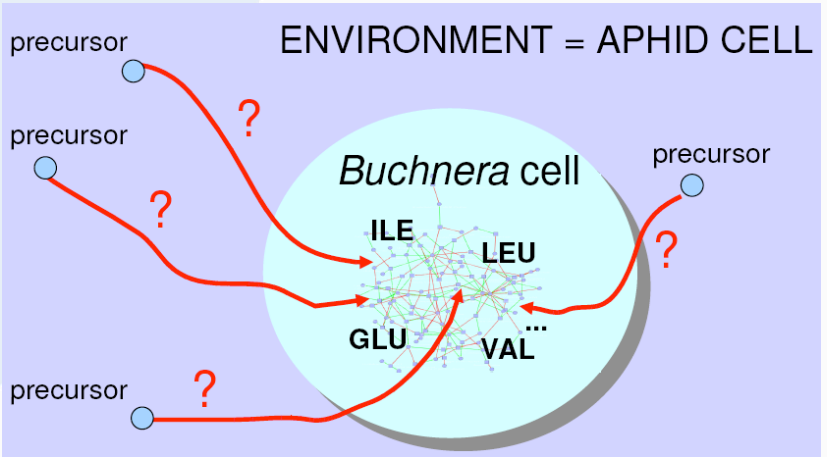
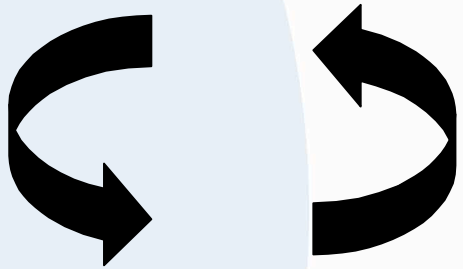


Minimal sets of metabolic precursors

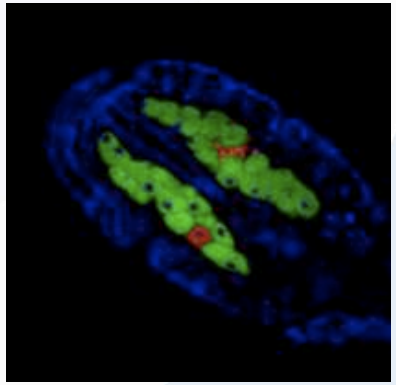
What is transported into *Buchnera*?

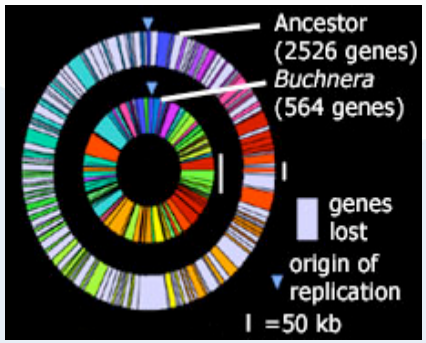


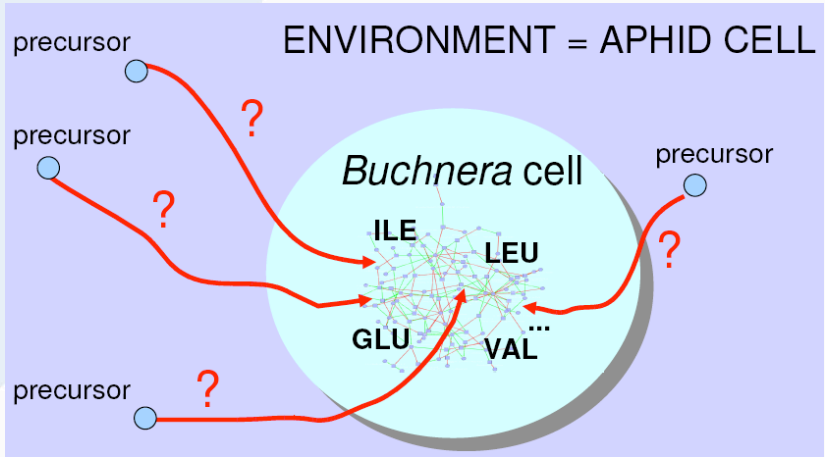
Experiments

Hubert Charles et al. INSA Lyon & INRIA BAMBOO

Buchnera **and its host**





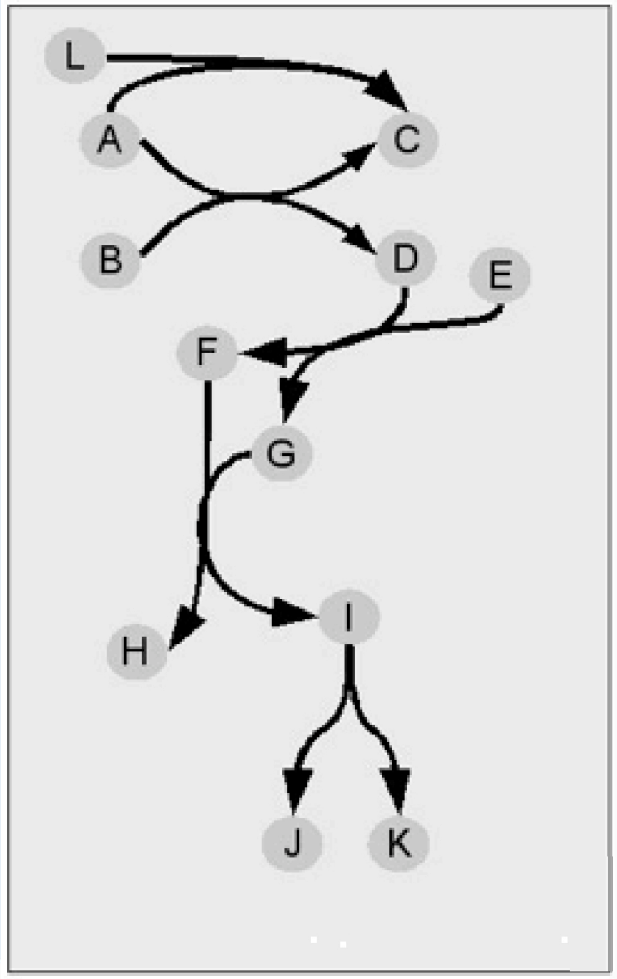


Metabolism and (math) representation

reaction **compound / metabolite**

R1: A + B -> C + D
R2: D + E -> F + G
R3: F + G -> H + I
R4: I -> J + K
R5: A + L -> C

Not traditional definition of hypergraph (but see Ausiello et al.)



Metabolism and (math) representation

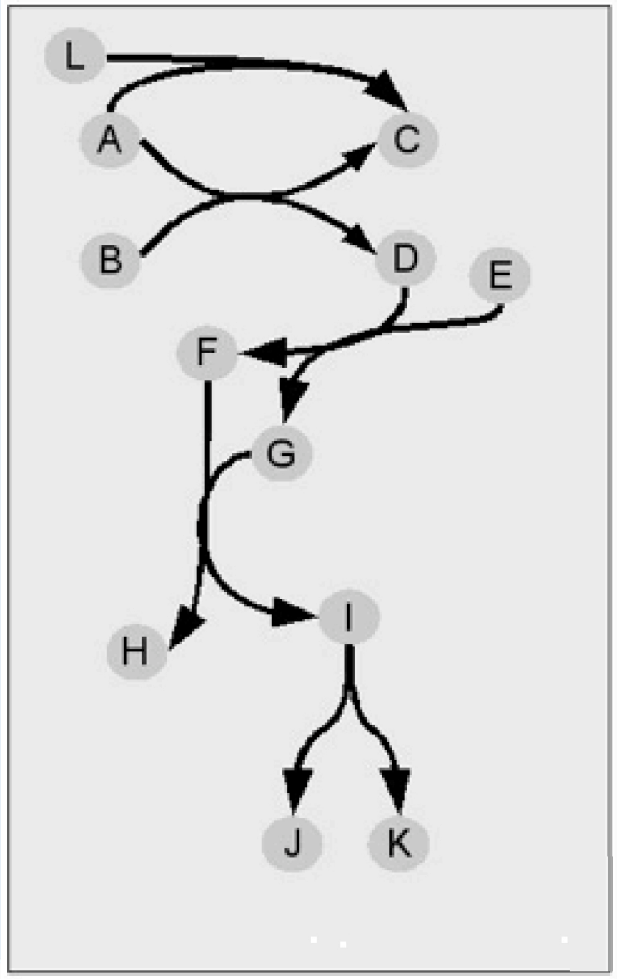
stoichiometry

reaction

compound / metabolite

R1: 1A + 2B -> 2C + 3D
R2: 3D + 1E -> 2F + 2G
R3: 1F + 1G -> 2H + 1I
R4: 3I -> 1J + 2K
R5: 1A + 3L -> 2C

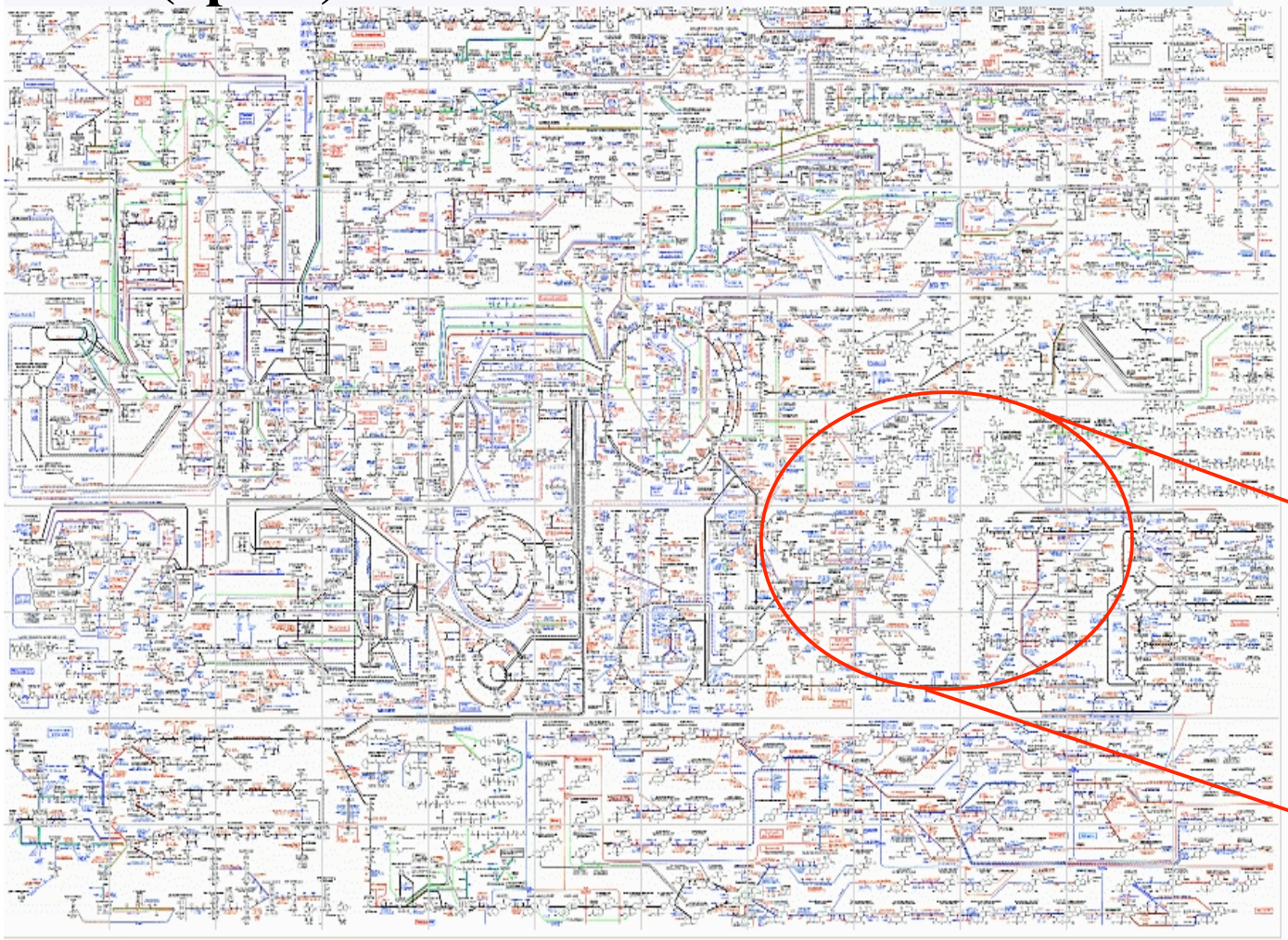
Direction in general not (completely) known

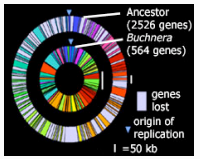


An idea of the different sizes

Host (aphid)

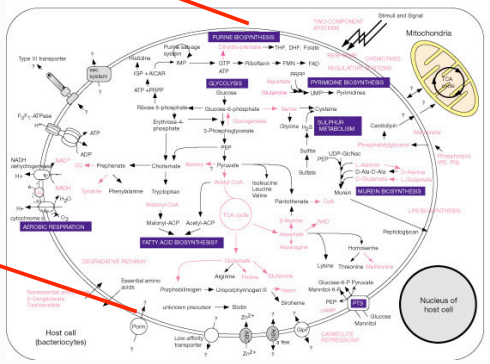
~1000 reactions



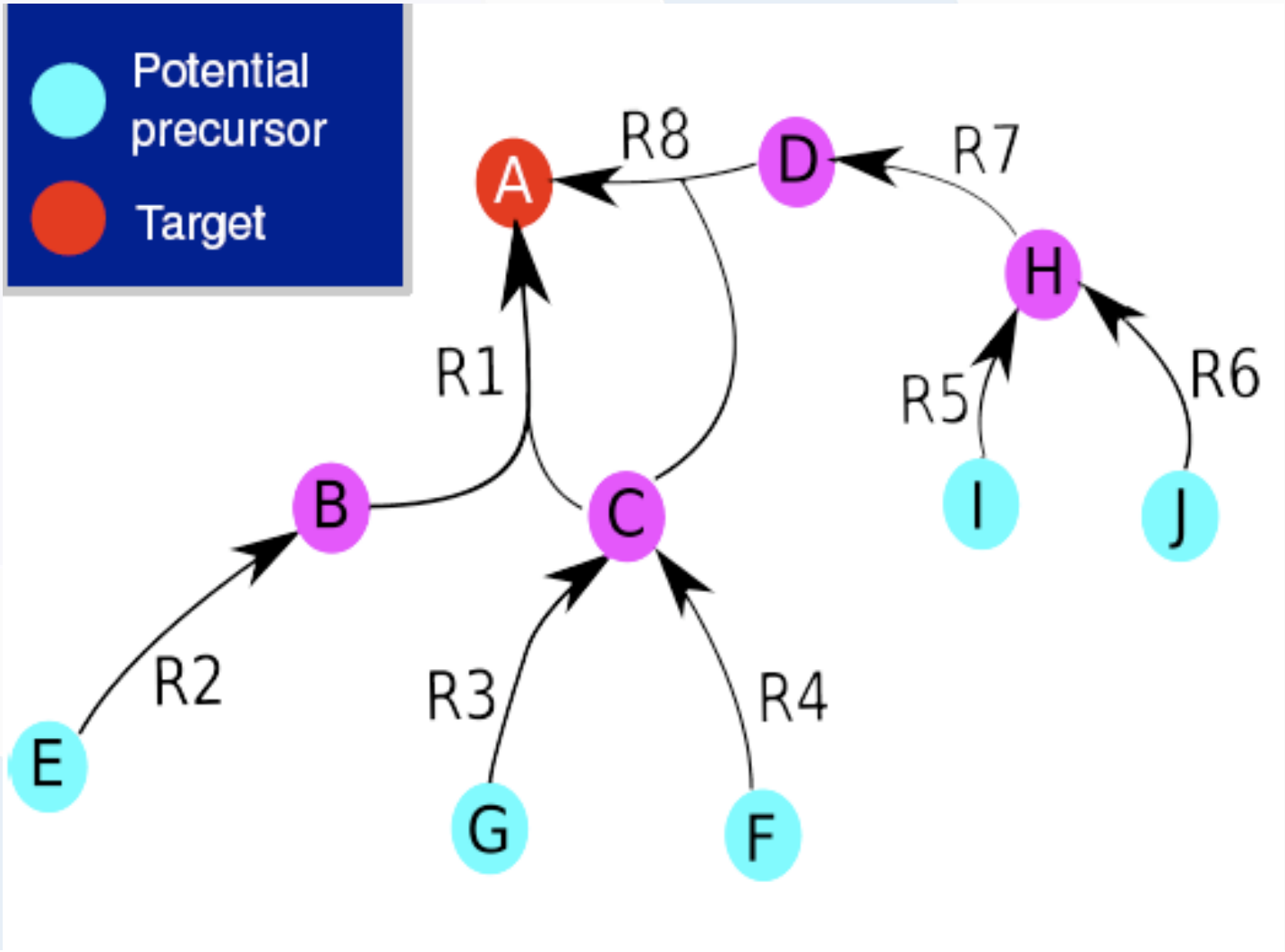


Buchnera

~200 reactions



Set of precursors: An example to start



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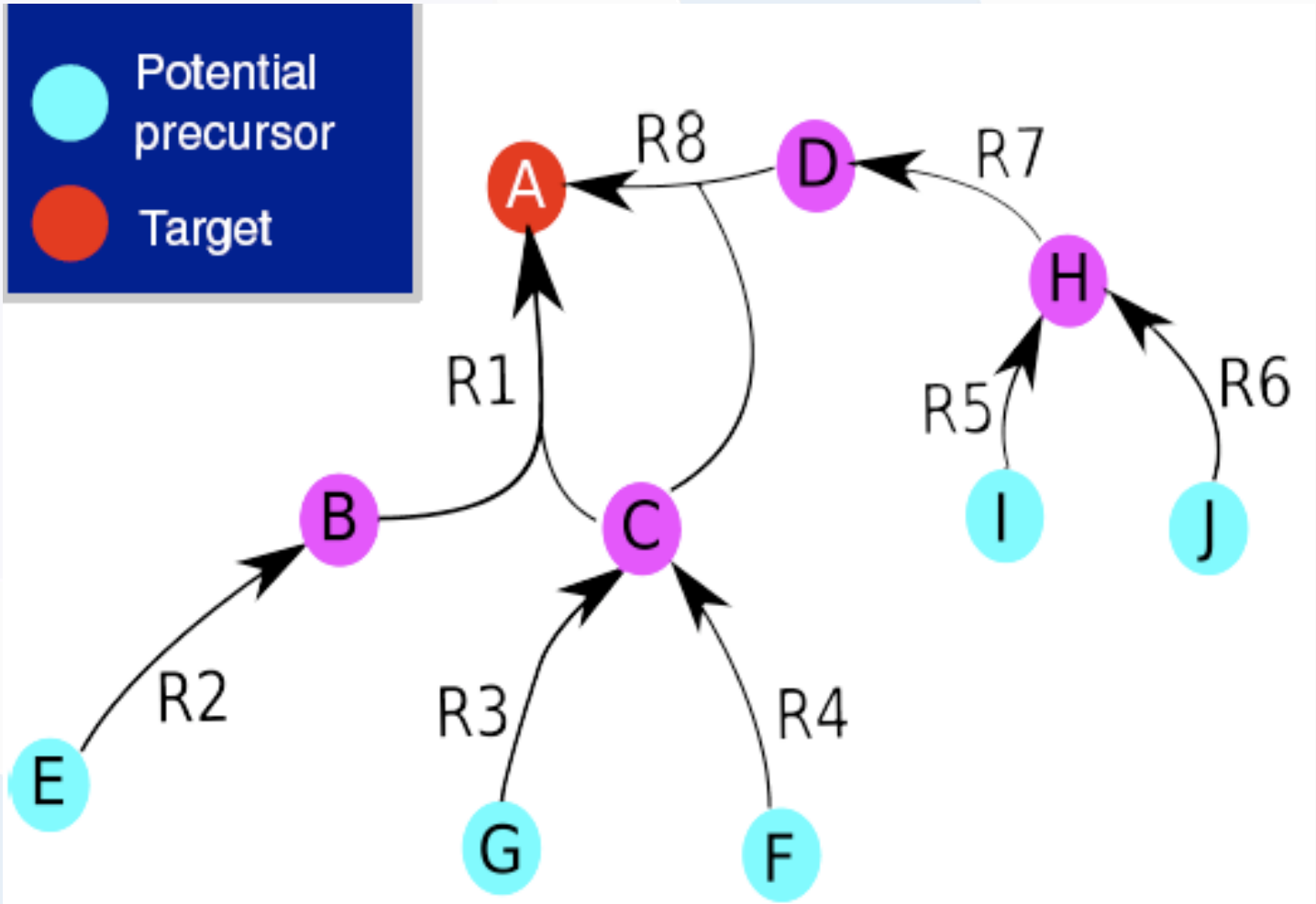
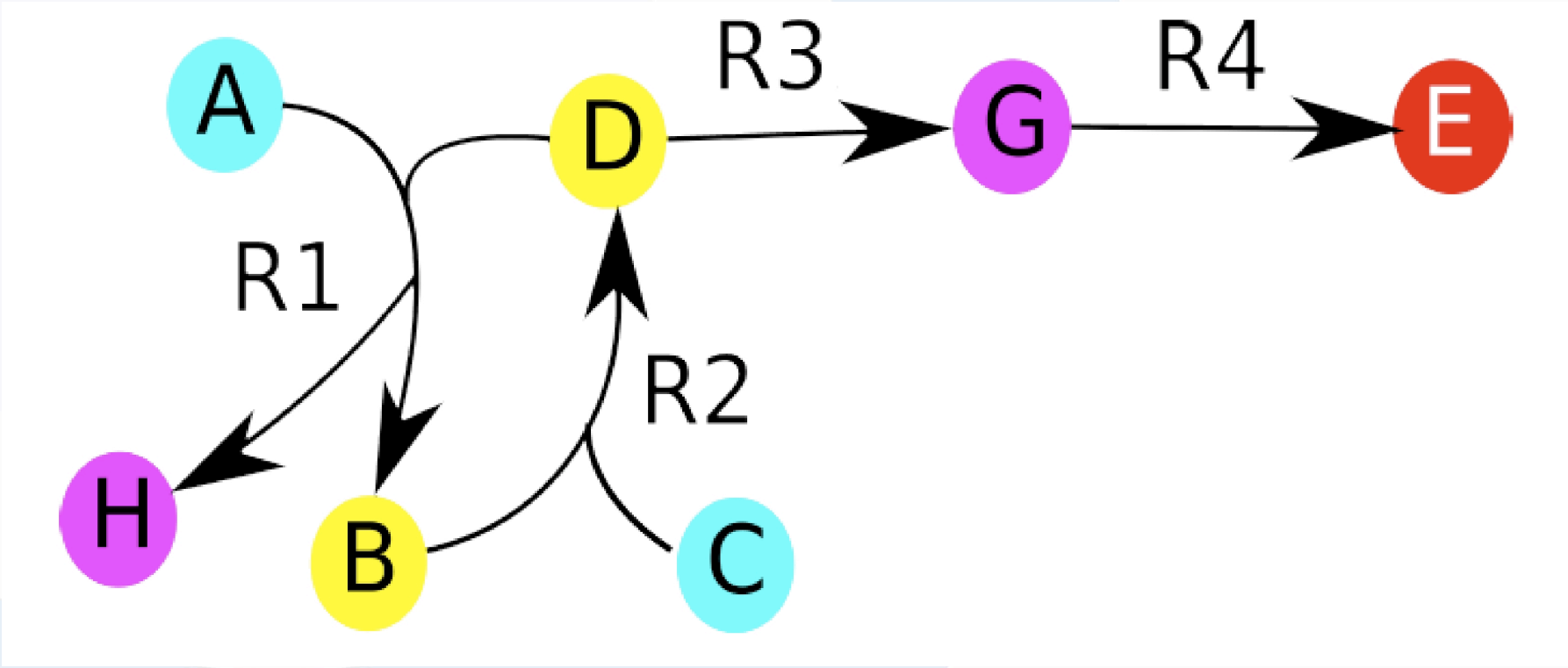


{E,G}
{E,F}
{G,I}
{G,J}
{F,I}
{F,J}

Problem not formally (math.) addressed



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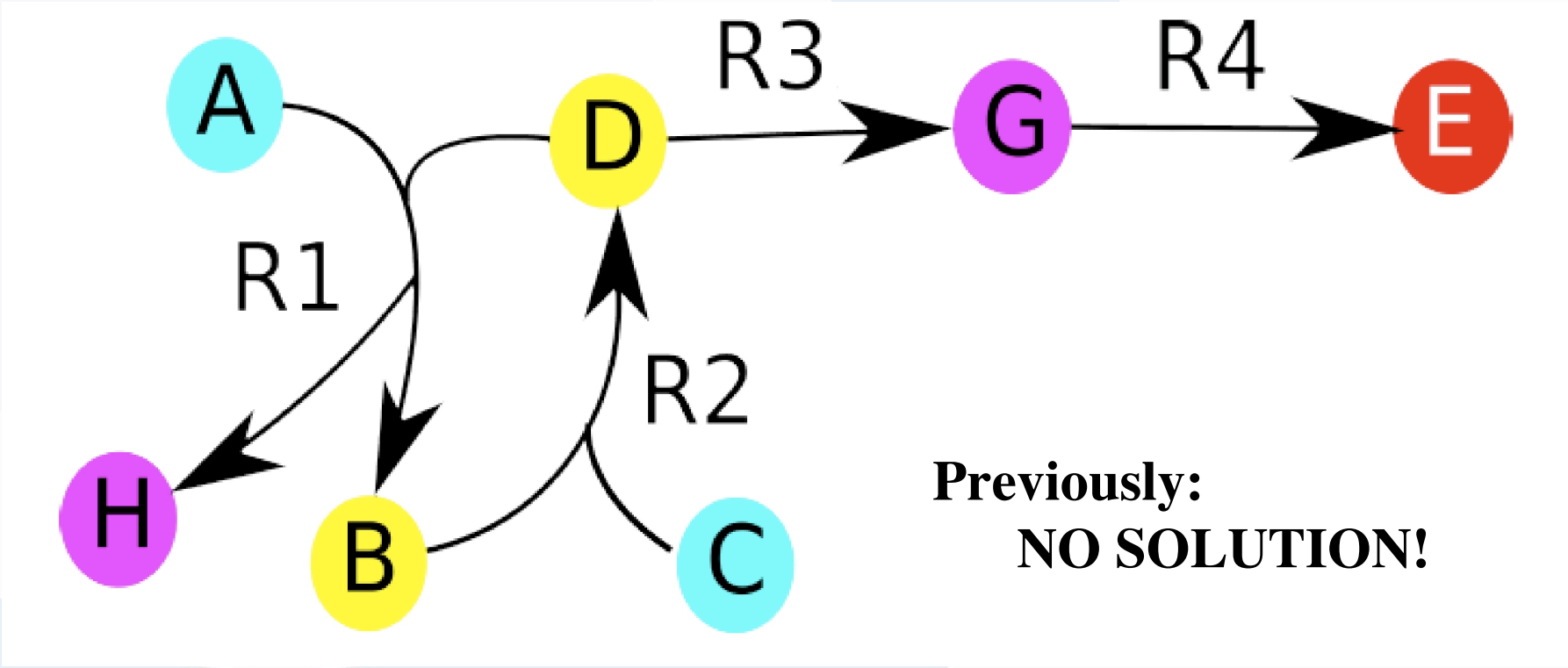
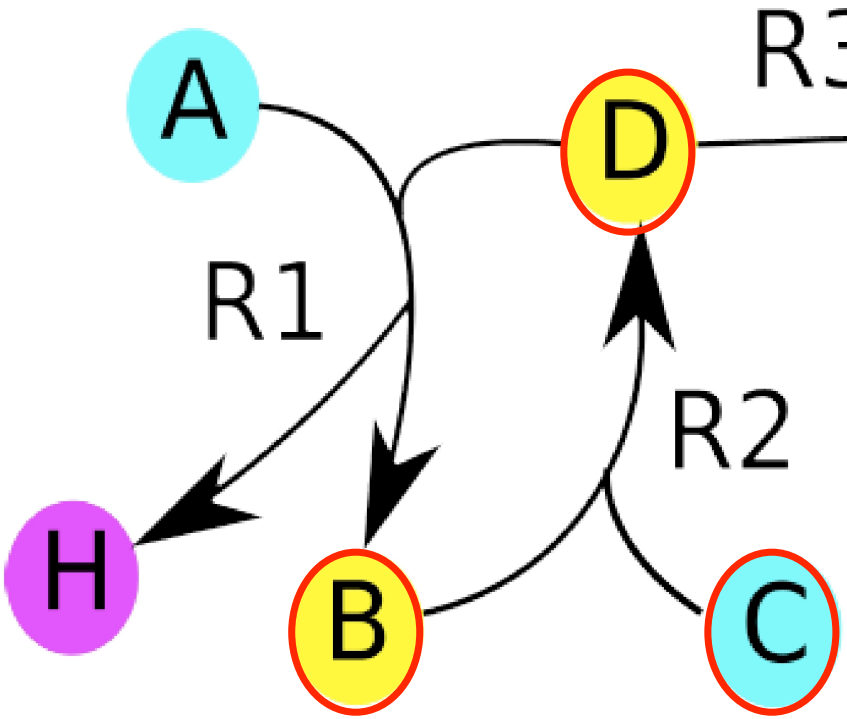


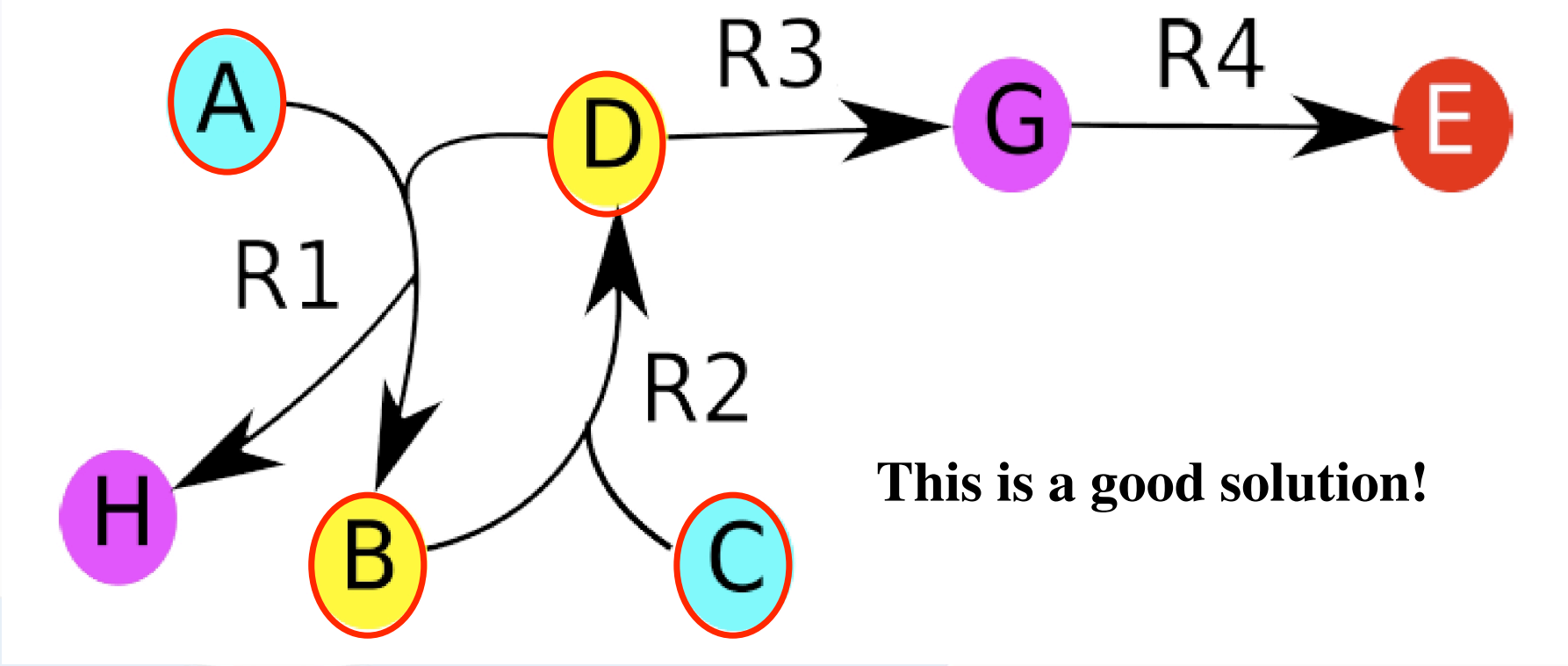
Previously:
NO SOLUTION!

Solution must be biologically "correct"



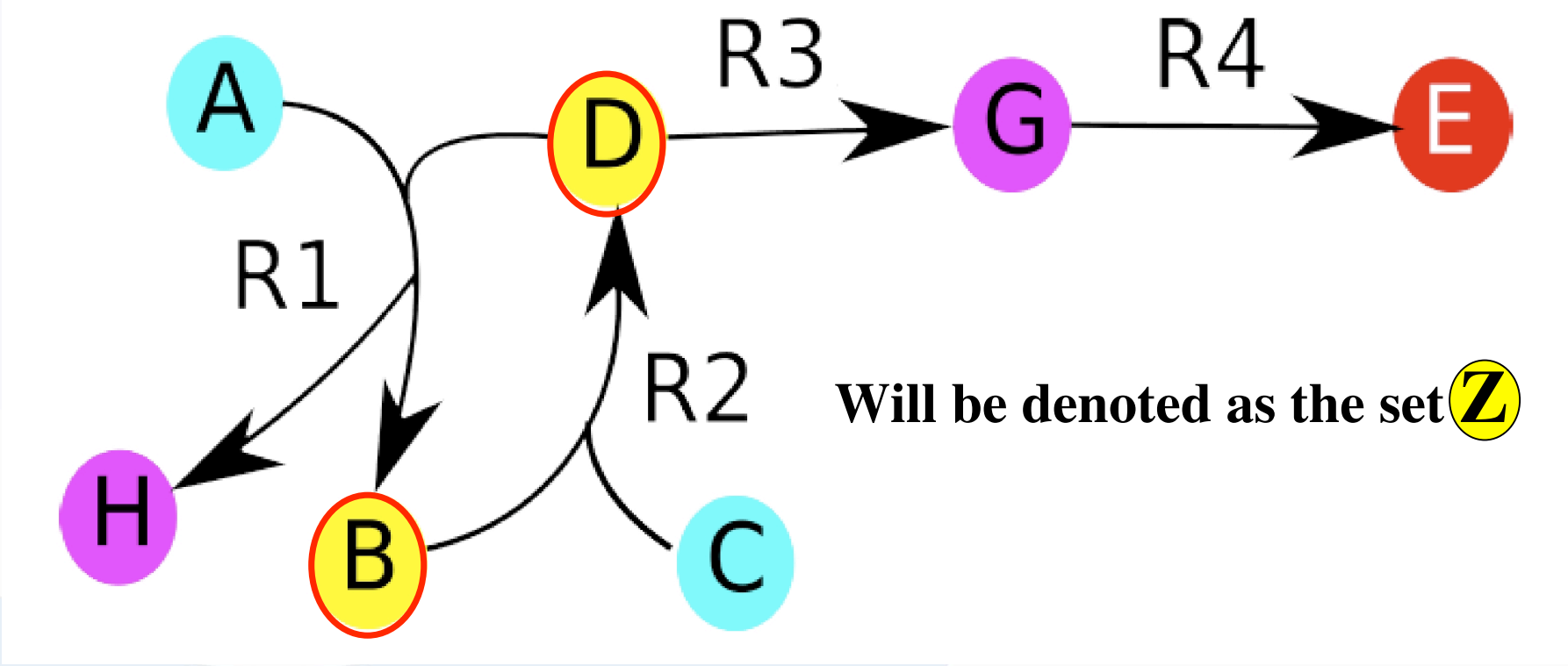
Not all solutions are "good" biological solutions !

Solution must be biologically "correct"

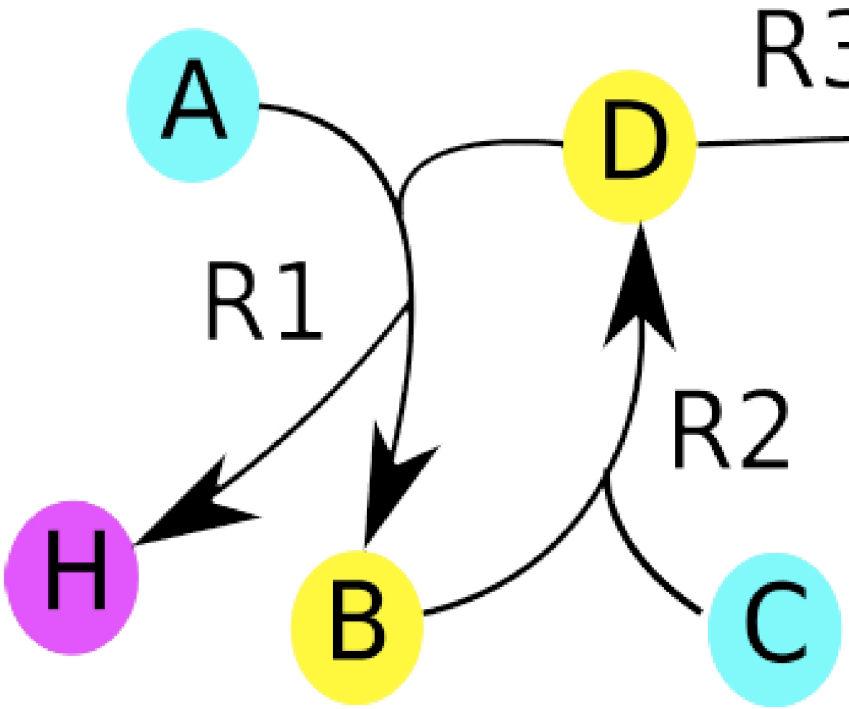


This is a good solution!

Self-regenerating metabolites

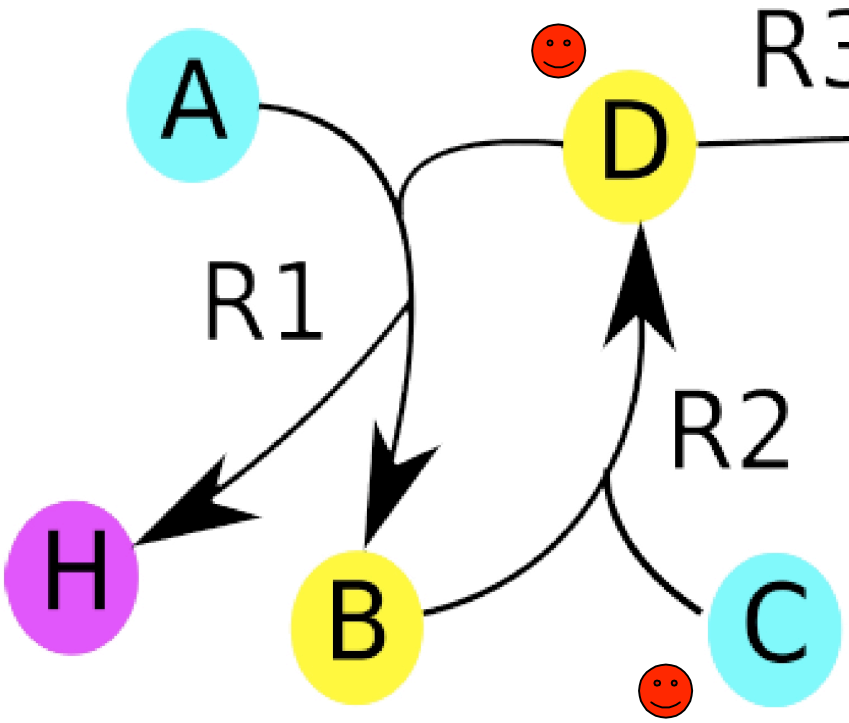


Formal model: Reach and Scope



$\mathbf{Reach_Z(X) =}$
$\mathbf{X \cup products\ (X \cup Z)}$
$\mathbf{Scope_Z(X) =}$
$\mathbf{Reach_Z^*(X)}$

Example 1



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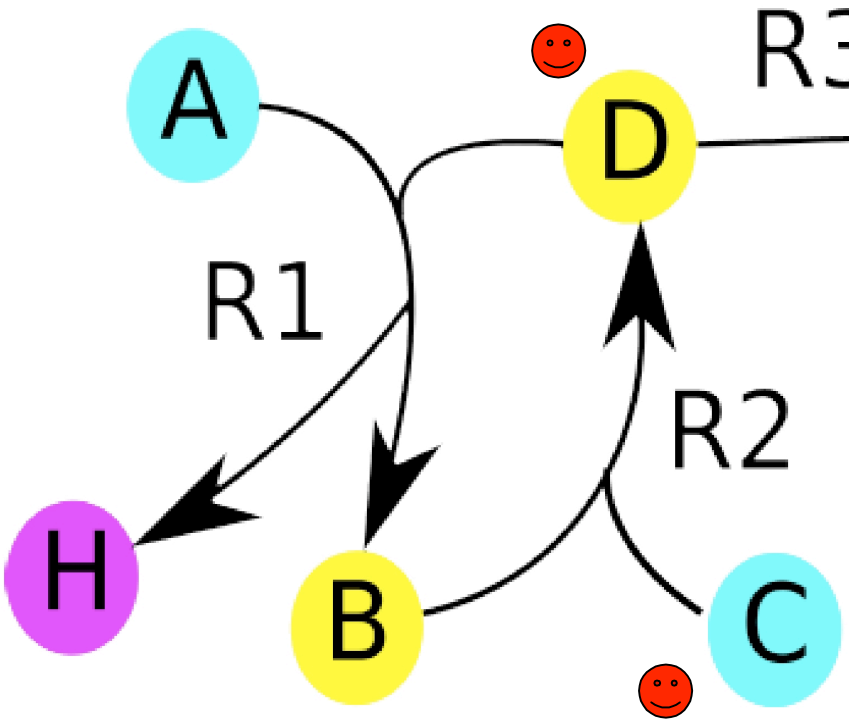
$\mathbf{Scope_B(C) = \{C,D}$

Example 1



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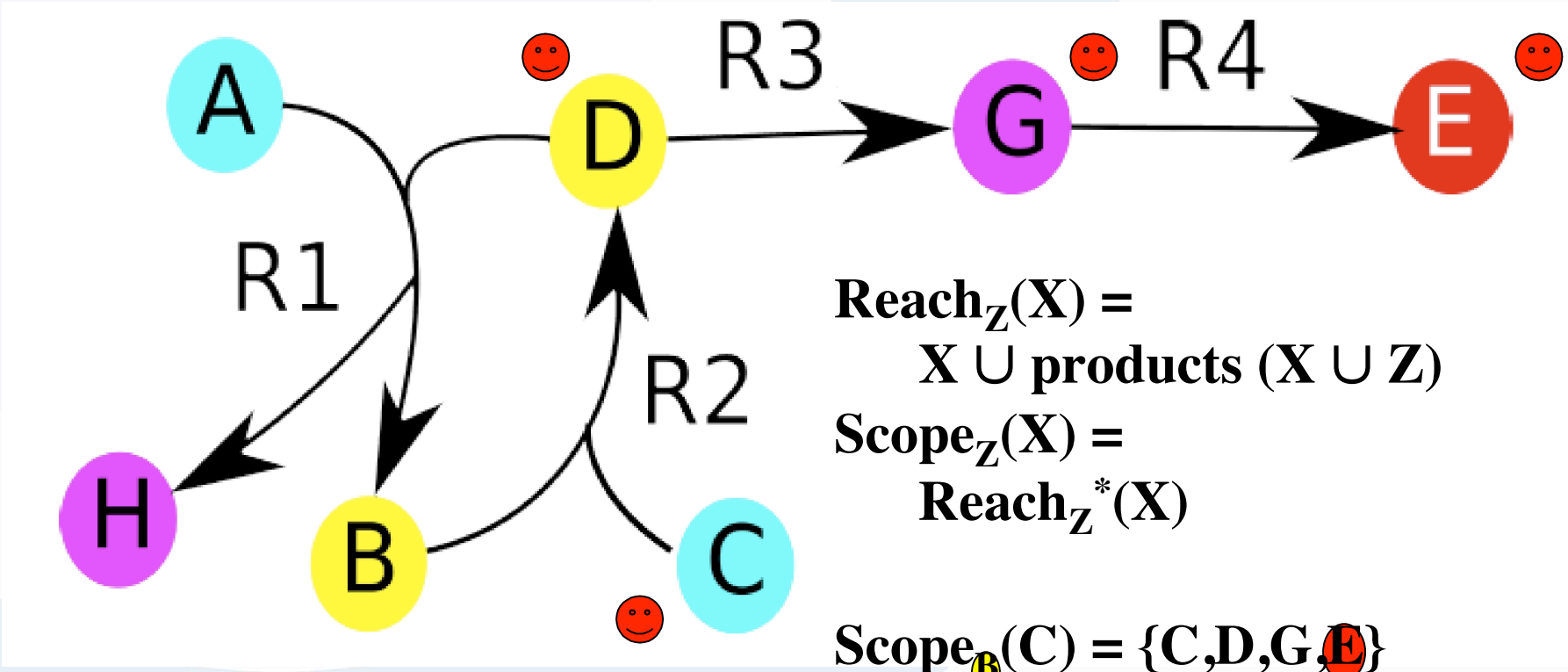
Example 1: Not a solution!



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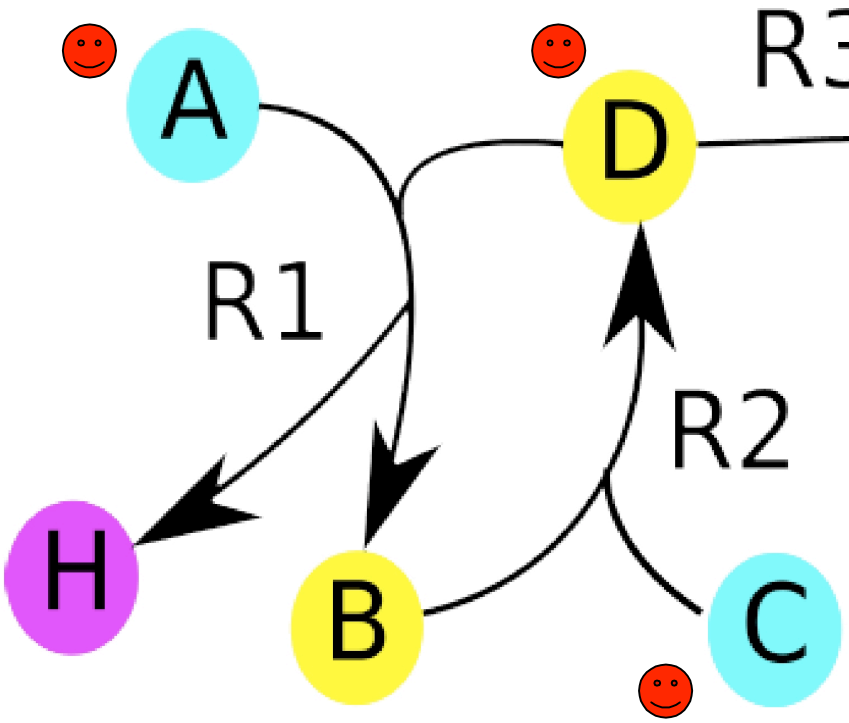
$\mathbf{Scope_B(C) = \{C,D,G,E\}}$

Example 2



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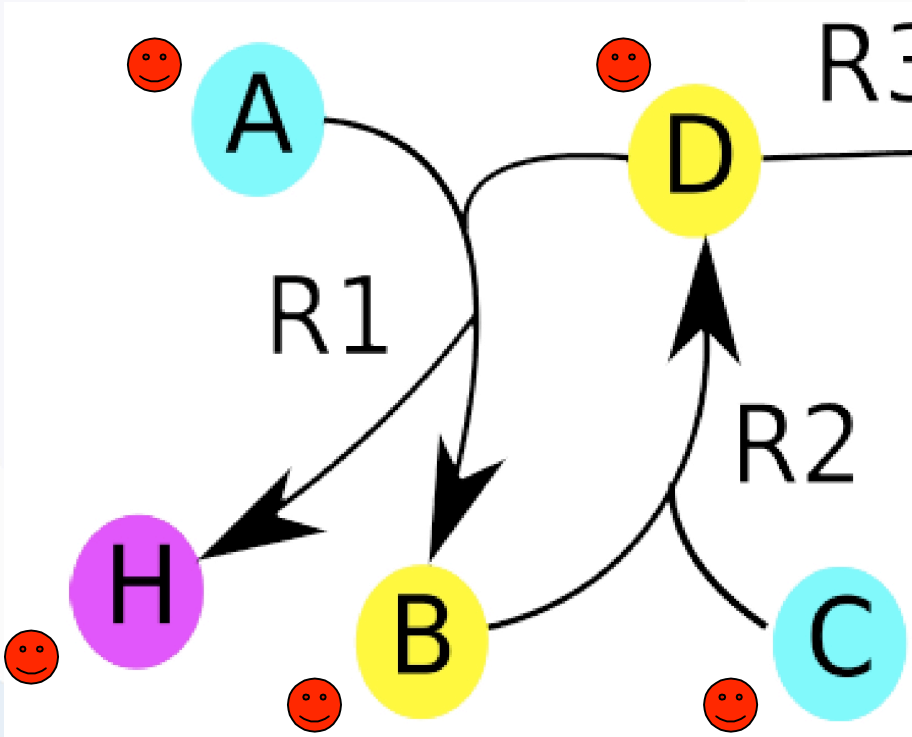
$\mathbf{Scope_B(C) = \{C,D,G,E\}}$

$\mathbf{Scope_B(A,C) = \{A,C,D}$

Example 2



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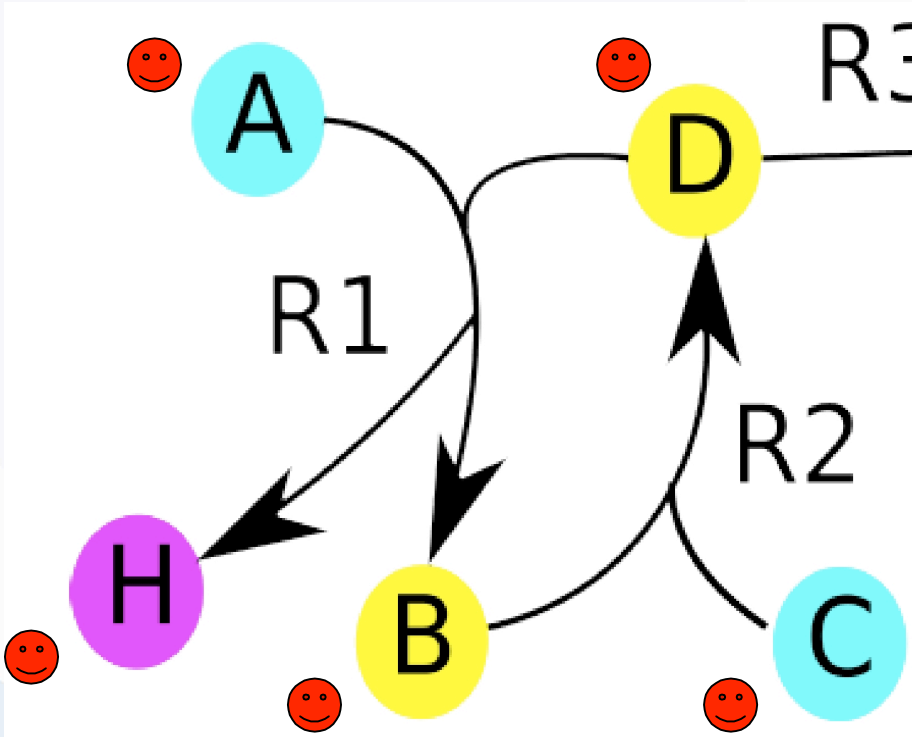
$\mathbf{Scope_B(C) = \{C,D,G,E\}}$

$\mathbf{Scope_B(A,C) = \{A,C,D,H,B}$

Example 2



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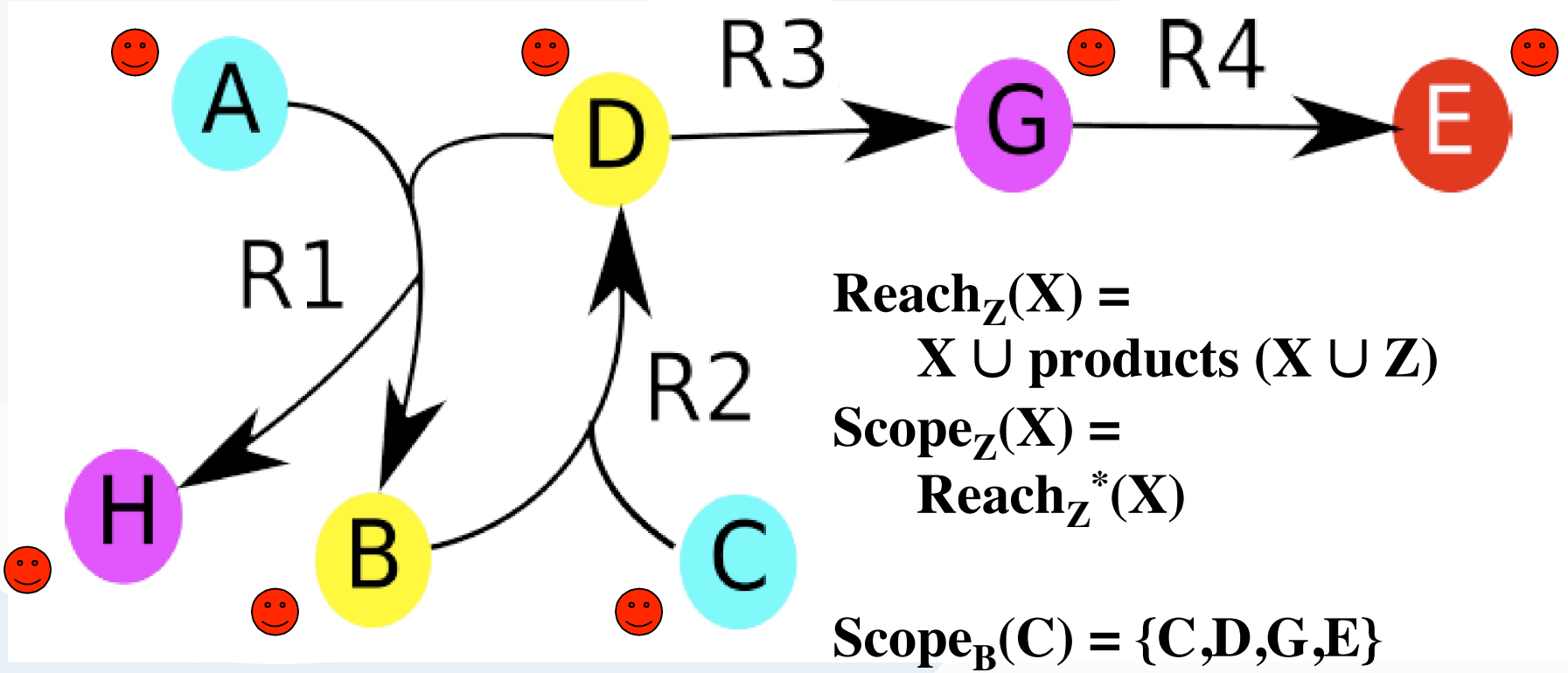
$\mathbf{Reach_Z^*(X)}$

$\mathbf{Scope_B(C) = \{C,D,G,E\}}$

$\mathbf{Scope_B(A,C) = \{A,C,D,H,B,G}$

Example 2: Is a solution!



$\mathbf{Reach_Z(X) =}$
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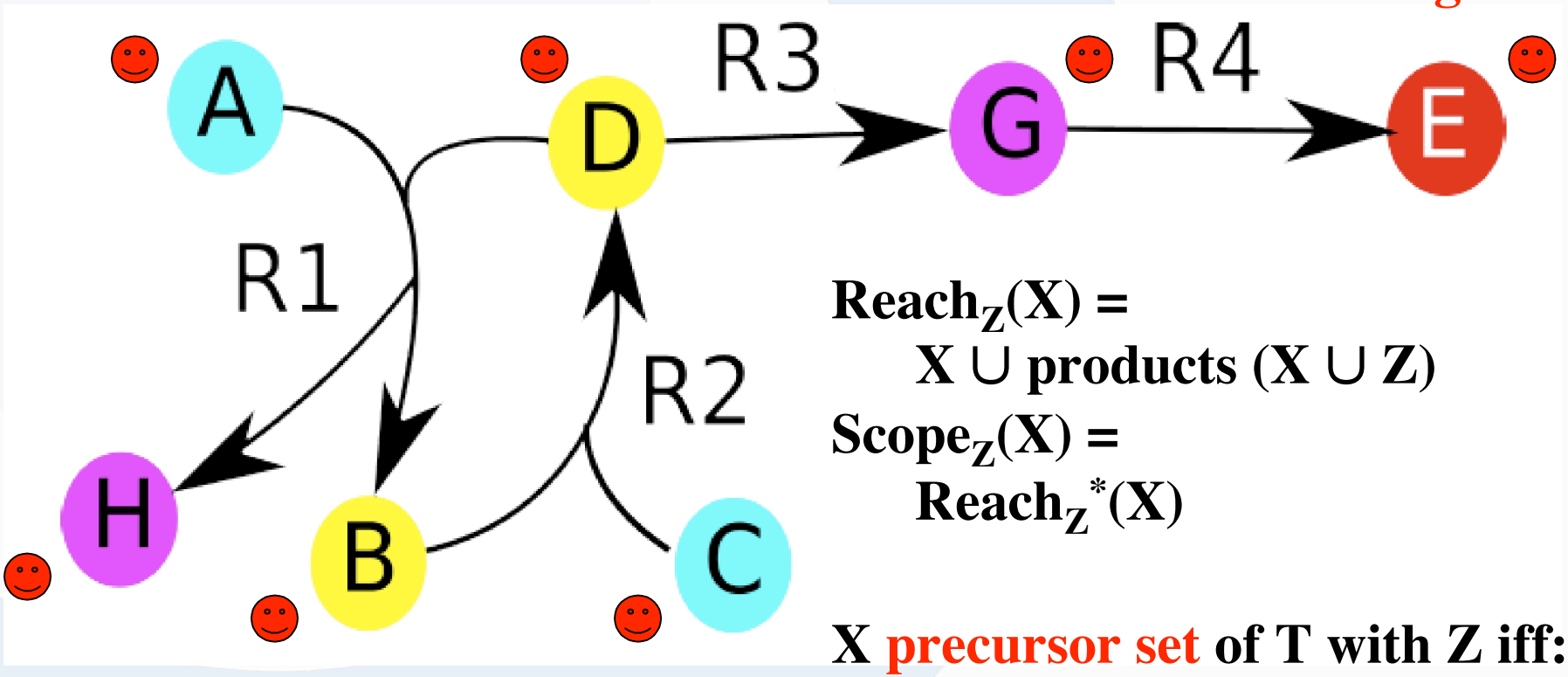
Formal model: Precursor set



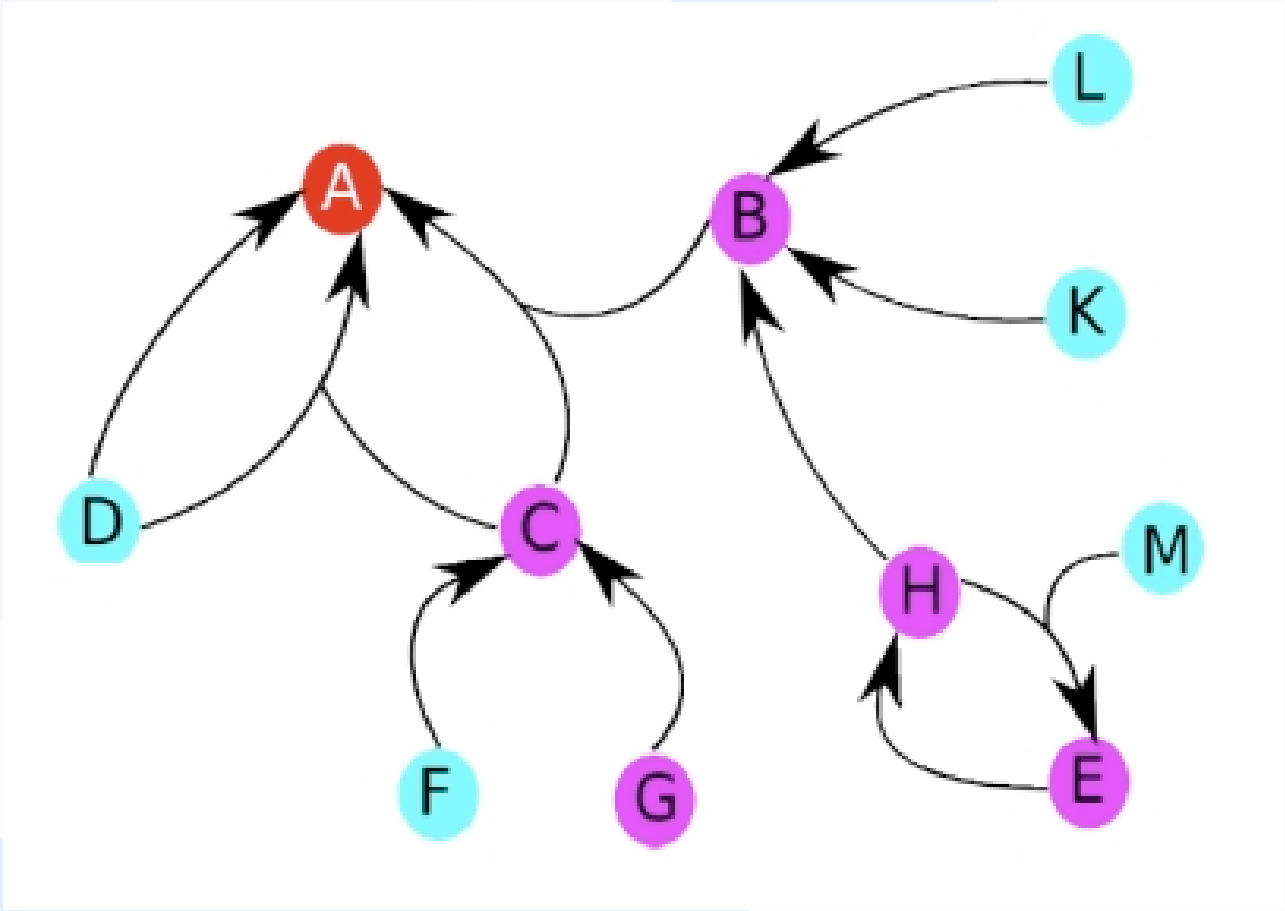
$\mathbf{Reach_Z(X) =}$
$\mathbf{X \cup products\ (X \cup Z)}$

$\mathbf{Scope_Z(X) =}$
$\mathbf{Reach_Z^*(X)}$

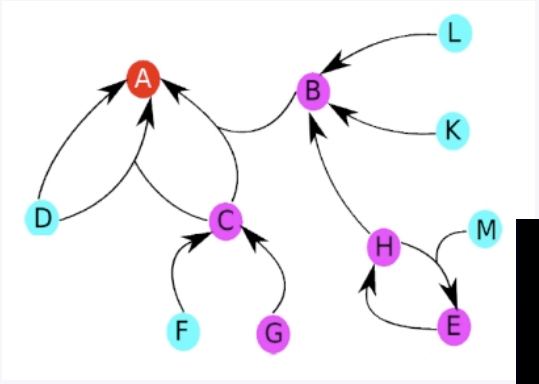
X precursor set of T with Z iff:

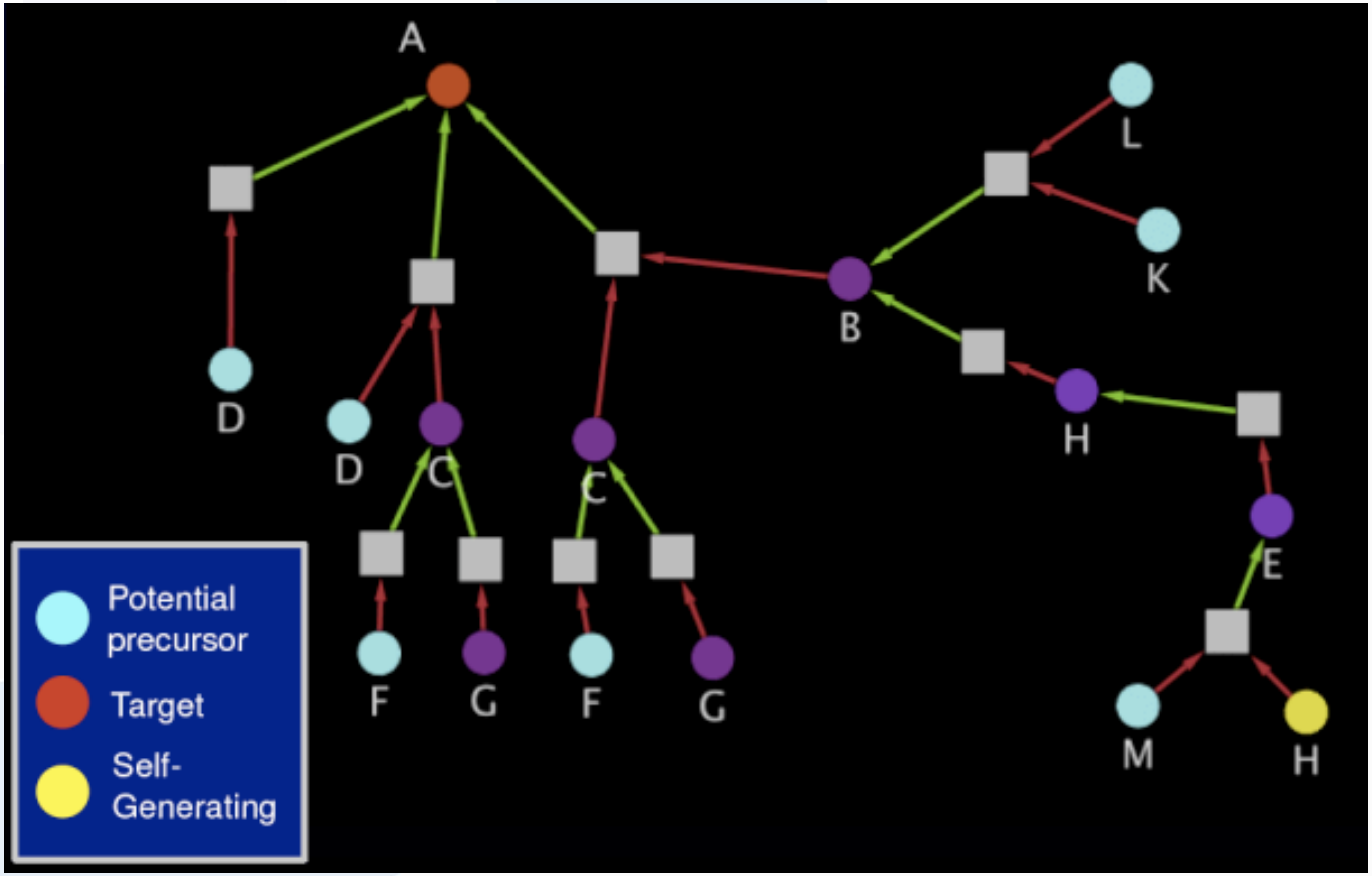
$\mathbf{Scope_Z(X) \supseteq Z \cup T}$

Better algorithm

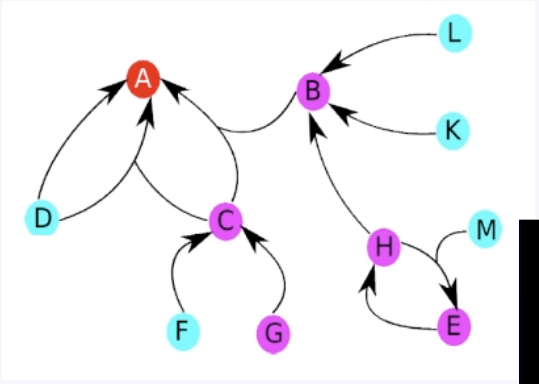


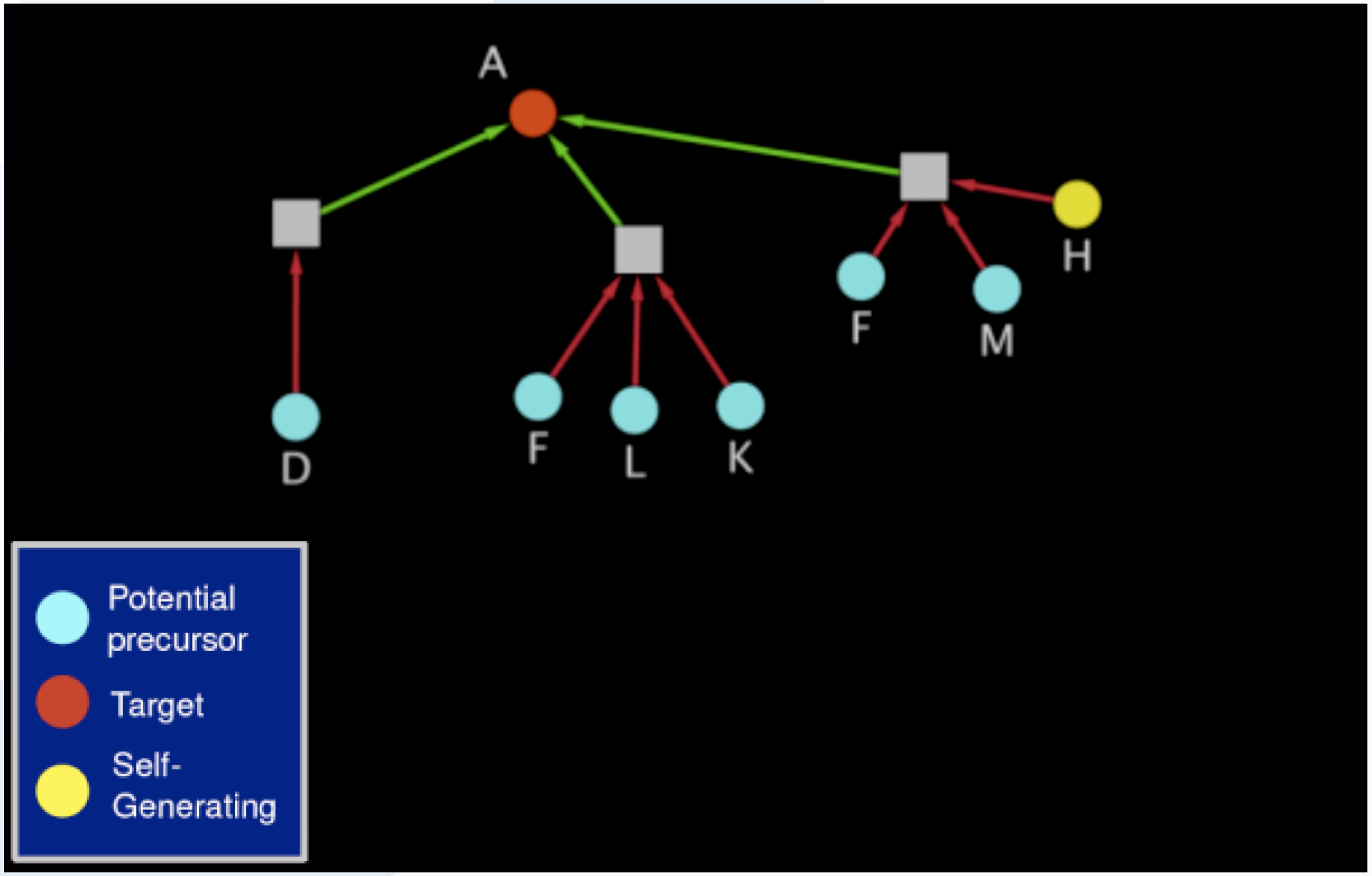
Better algorithm



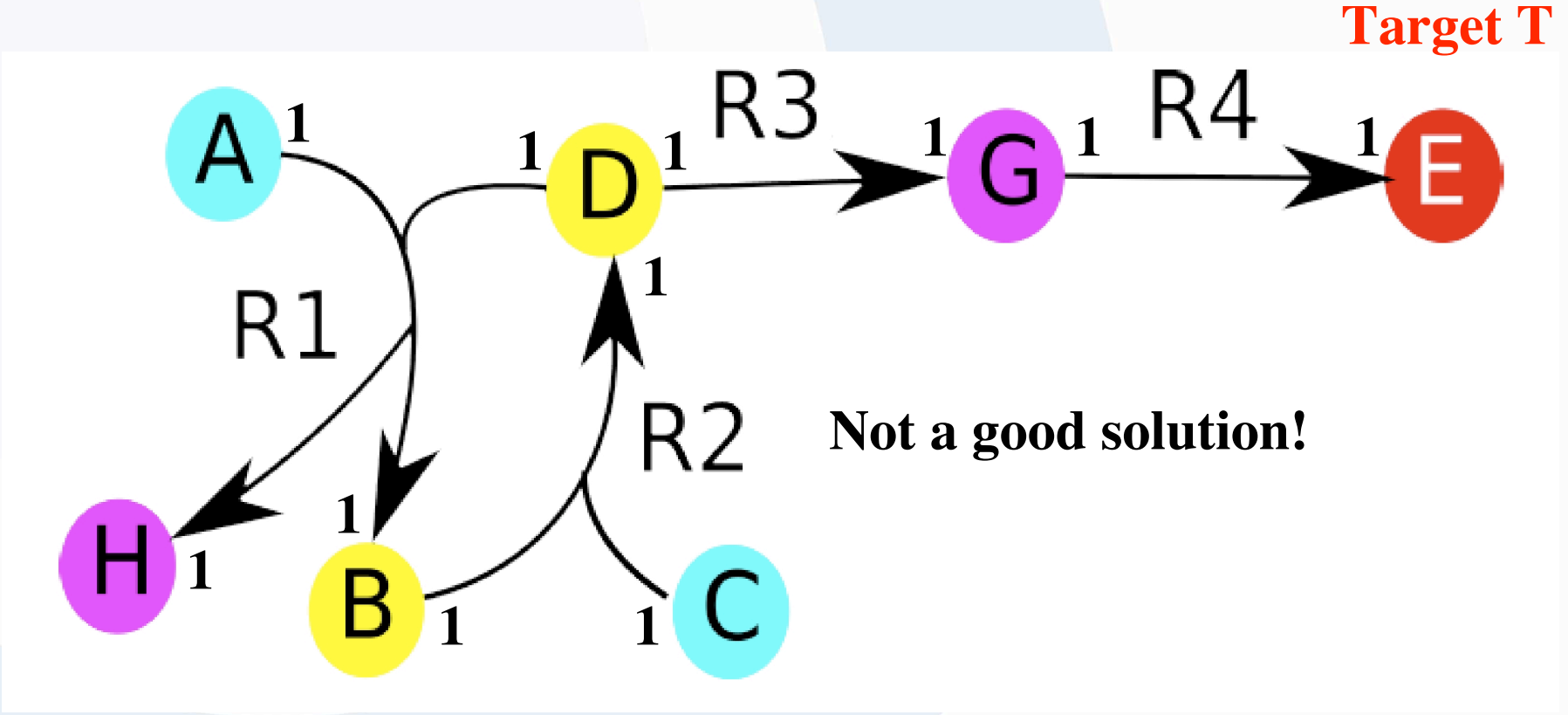


Better algorithm





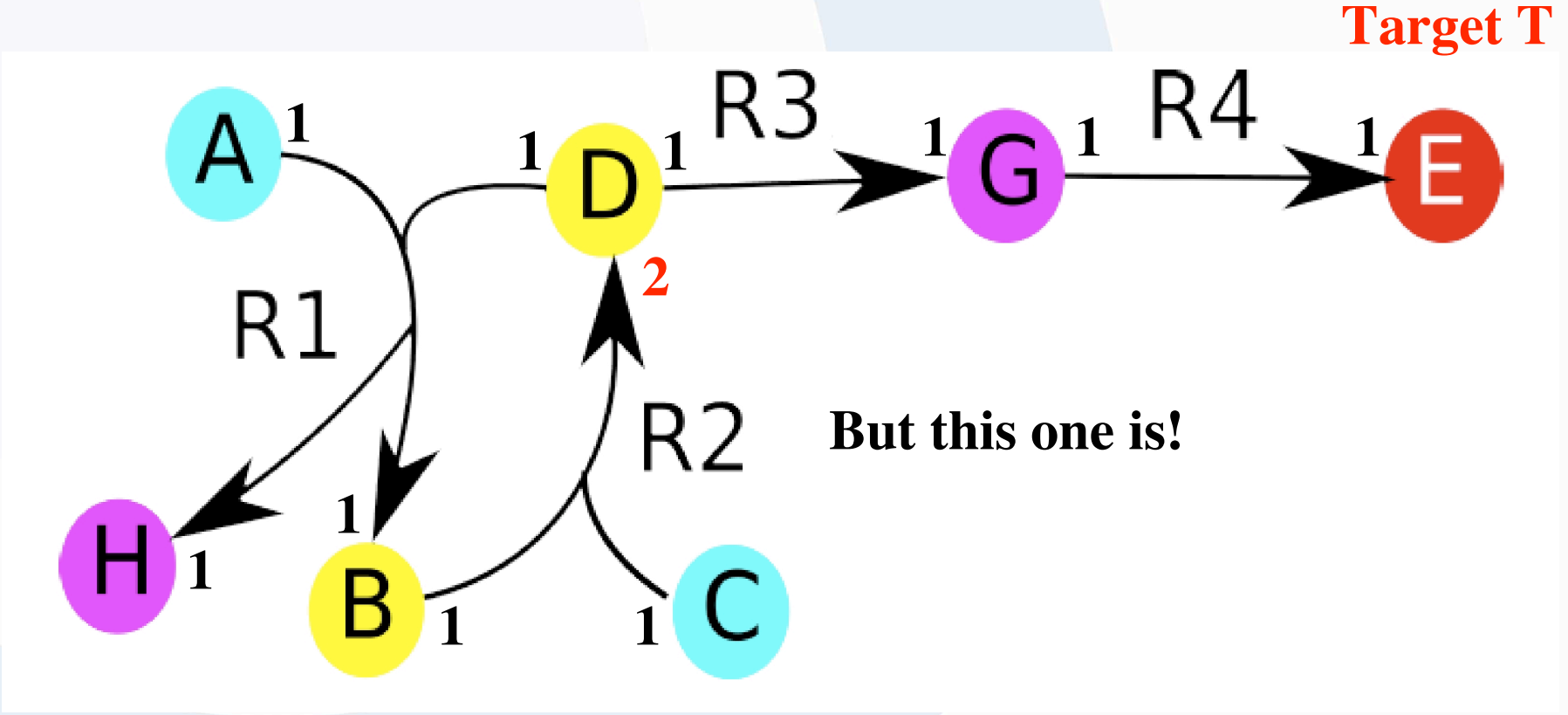
Story not finished



Not a good solution!

~~**$Scope_B(A,C) = \{A,C,D,H,B,G,E\}$**~~

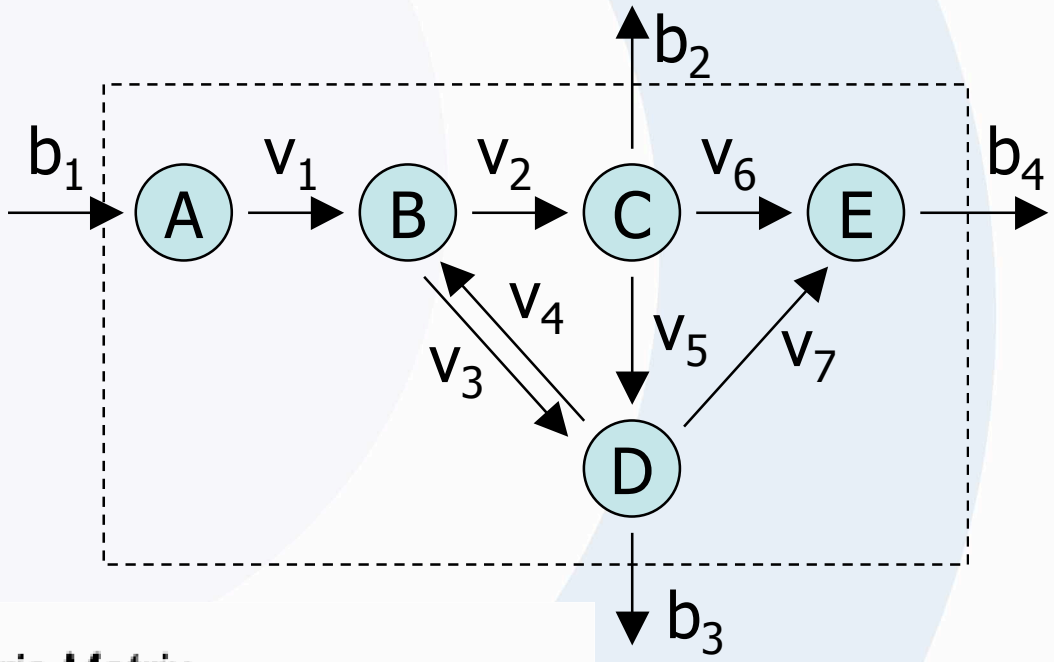
Story not finished



But this one is!

$\mathbf{Scope_B(A,C) = \{A,C,D,H,B,G,E\}}$

Modes and elementary modes



Stoichiometric Matrix

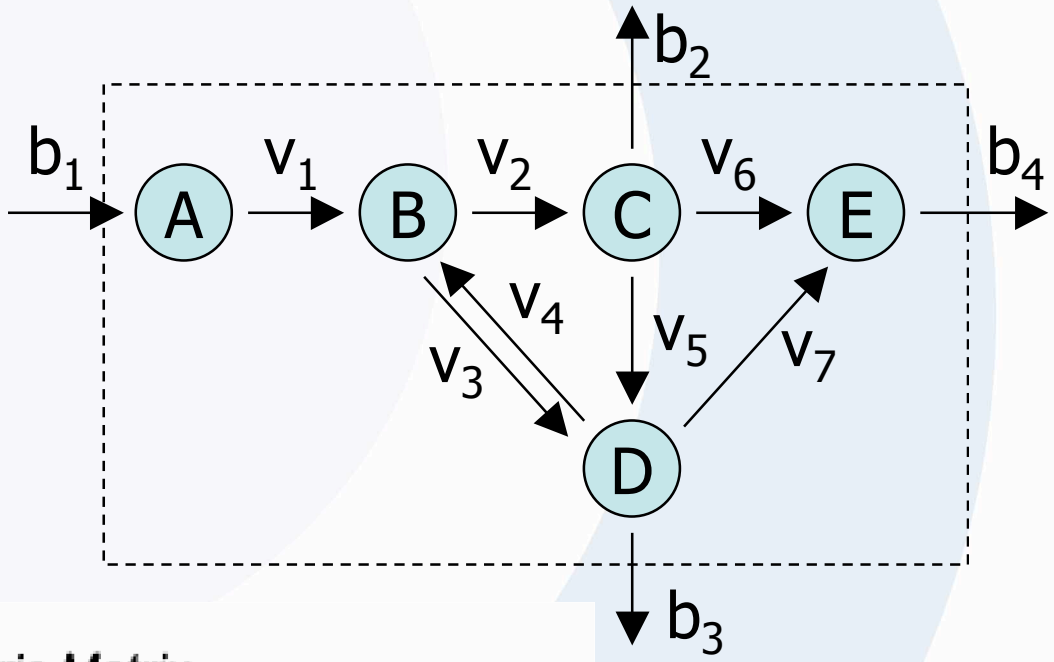
$$\mathbf{S} = \begin{bmatrix} -1 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 \\ 1 & -1 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & -1 & -1 & 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 & 1 & 0 & -1 & 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & -1 \end{bmatrix}$$

Internal Fluxes *Exchange Fluxes*

$$\mathbf{S.v} = 0$$

$$v_i \geq 0 \ \forall \ i \text{ irreversible}$$

Modes and elementary modes



Stoichiometric Matrix

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Internal Fluxes *Exchange Fluxes*

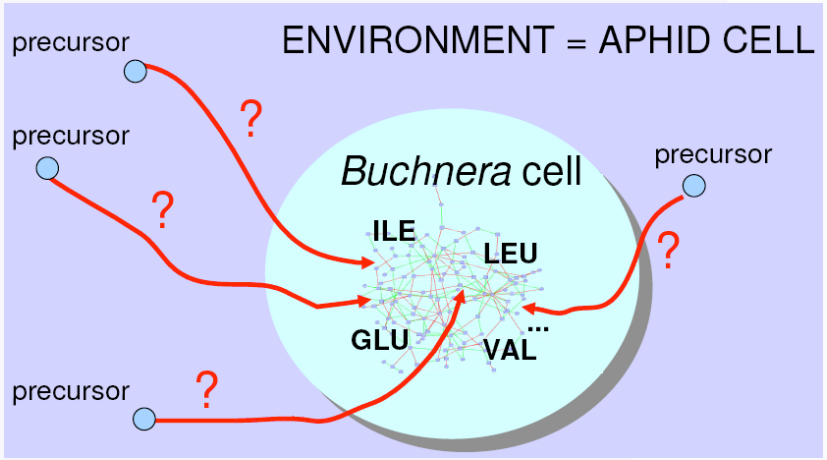
$S.v = 0$

$v_i \geq 0 \ \forall$ i irreversible

no w such that:

support(w) $\subset$ support(v)

Modes and precursor sets

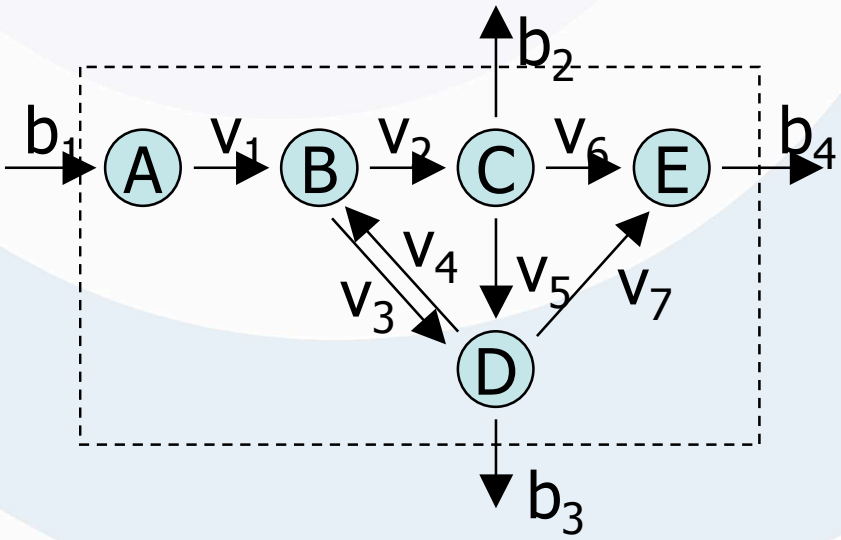


X precursor set of T with Z iff:

$$Scope_Z(X) \supseteq Z \cup T$$

plus stoichiometry

¿LINK?



S.v = 0

$v_i \geq 0$ ∀ i irreversible

no w such that:

support(w) ⊂ support(v)

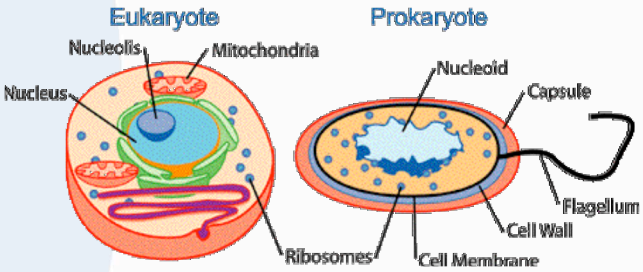
The future (present)

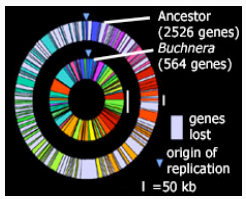
Small part of what will be explored in these projects

Funded
ANR MIRI
2009-2012

INRIA
Associated Team
Simbiosi

Networks in interaction





Experimental part

What is transported into *Buchnera*?

Experiments

Hubert Charles et al. INSA Lyon & INRIA BAMBOO

Buchnera **and its host**