State Space Exploration of Spatially Organized Populations of Agents

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MGS : http://mgs.spatial-computing.org

SNAKE : http://pommereau.blogspot.com/

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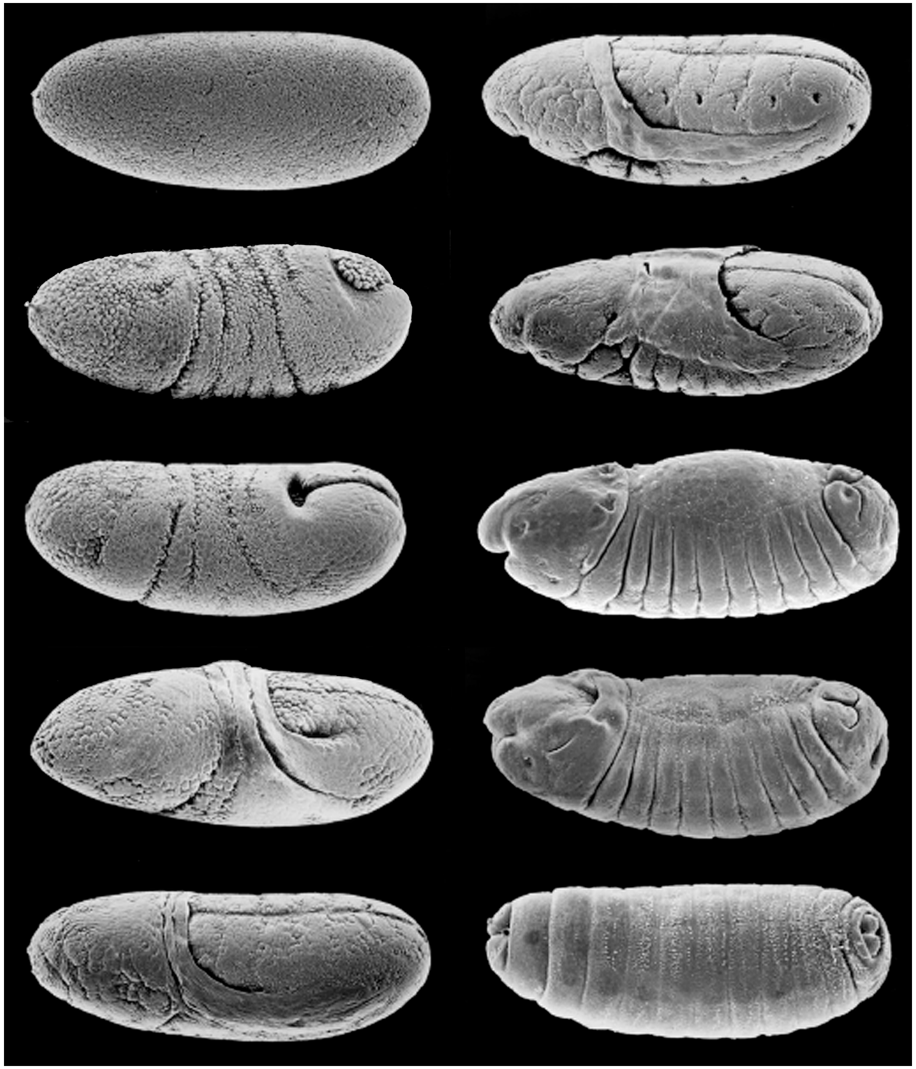
- Context
  - Qualitative modeling
  - Space representations
  - Systematic analysis
- IRN
  - Intuition
  - Syntactical aspects
  - Semantics
- Current prototype
  - SNAKE
  - MGS
- Conclusions

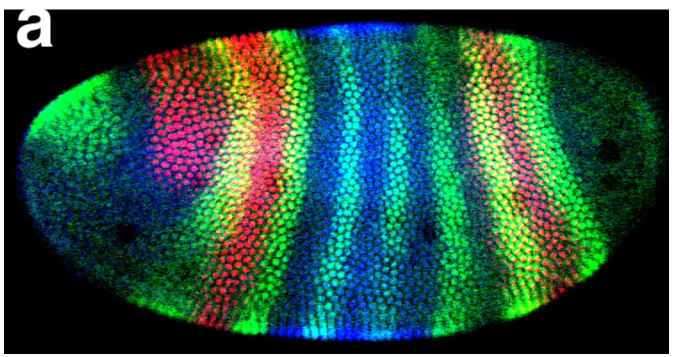
Motivation: qualitative modeling in systems biology

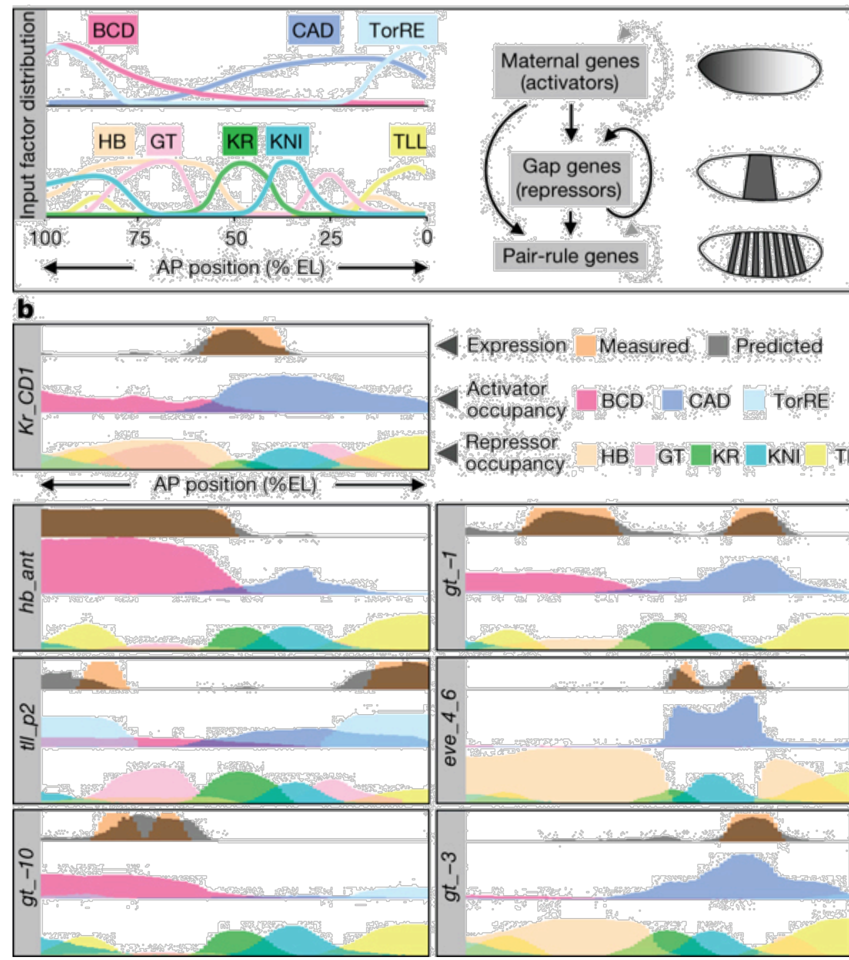
- **Systems Biology**: modelling, simulation and analysis of biological systems



Motivation: qualitative modeling in systems biology

- **Systems Biology**: modelling, simulation and analysis of biological systems
- **Biochemical processes**: regulatory networks, transcription signals, metabolism, diffusion, transport





Motivation: qualitative modeling in systems biology

- **Systems Biology**: modelling, simulation and analysis of biological systems
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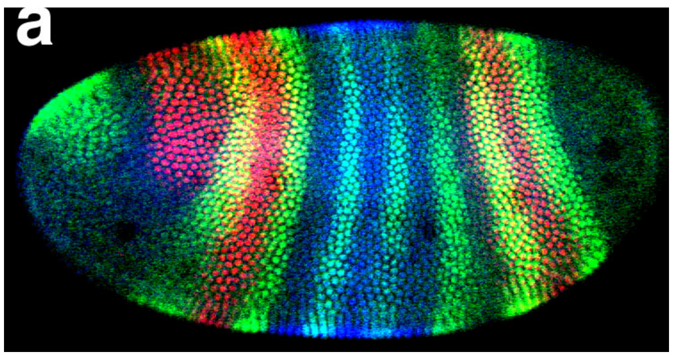
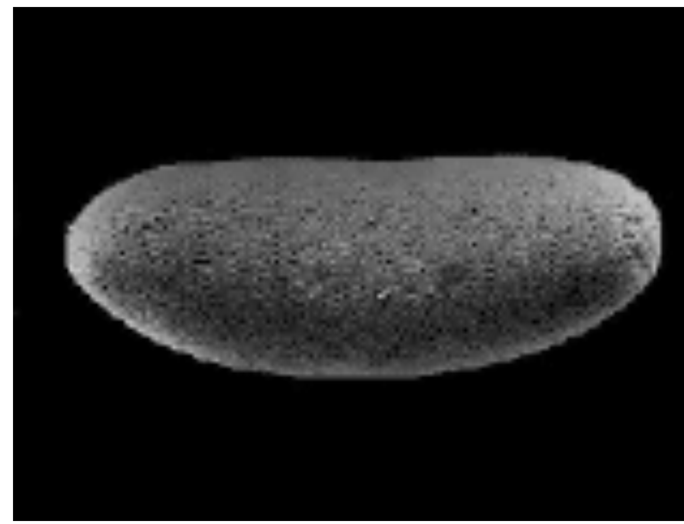
- Taking into account complex & dynamic **spatial relationships**: population, tissue, organ and organism

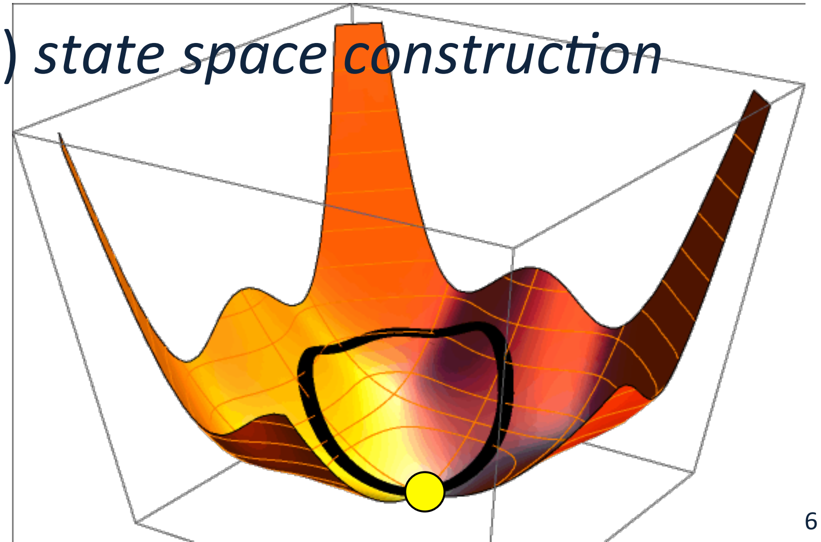




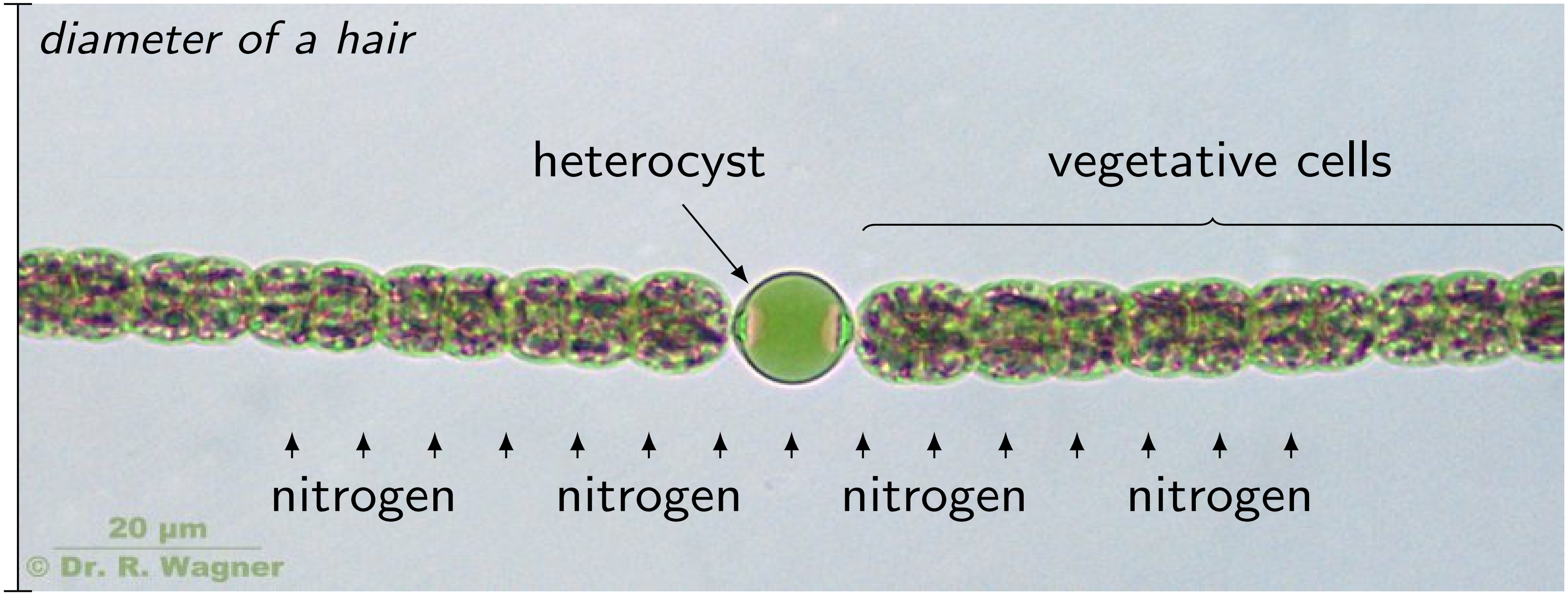
Motivation: qualitative modeling in systems biology

- **Systems Biology**: modelling, simulation and analysis of biological systems
- **Biochemical processes**: regulatory networks, transcription signals, metabolism, diffusion, transport
- Taking into account complex & dynamic **spatial relationships**: population, tissue, organ and organism
- **Applications domain**: developmental biology, tumor growth, tissue engineering (biofilms), etc.

- **Model analysis** through (exhaustive) *state space construction*
  - Stable states
  - Basins of attraction
  - Irreversible action
  - Atteignability and controlability

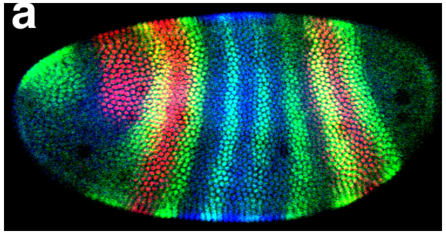


A running example: *Anabaena Catenula*



- small or big cells with polarity
- vegetative cells or heterocysts
  - only big vegetative cells may divide
  - no neighbour heterocysts

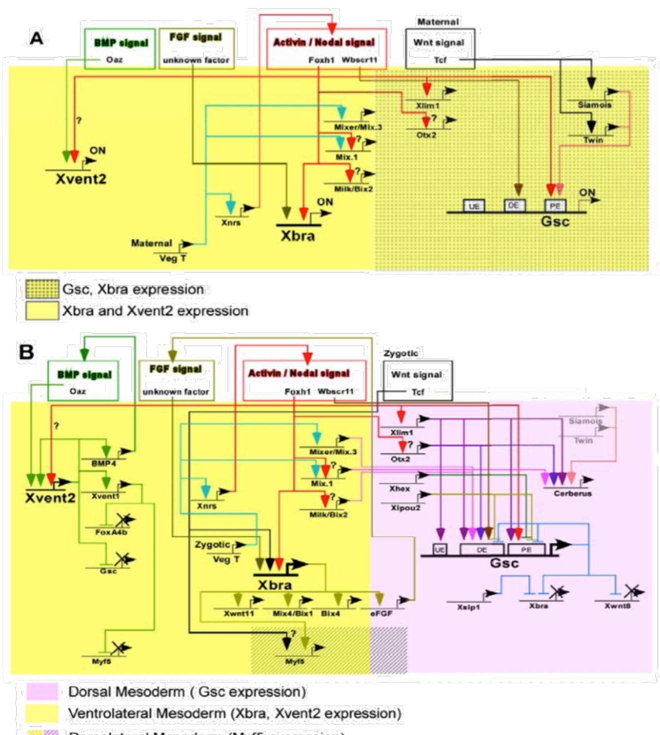
The workflow



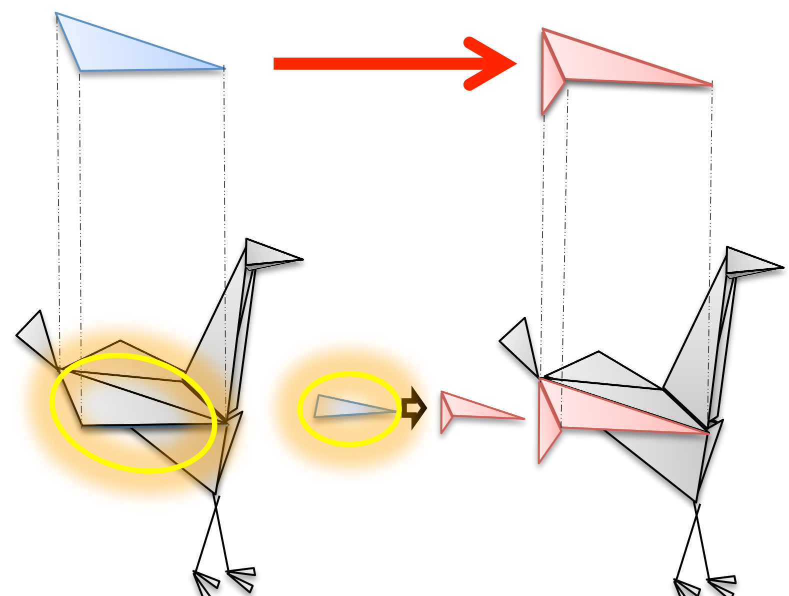
Model
using the IRN language

State
space

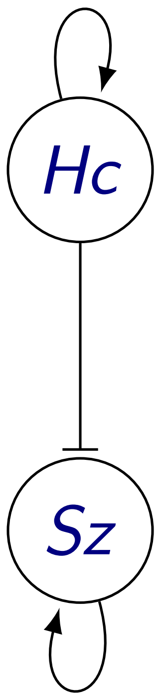
Logical Regulatory Network
à la R. Thomas



Spatial representation
& transformation
à la MGS



Logical Regulatory Network *à la* R. Thomas



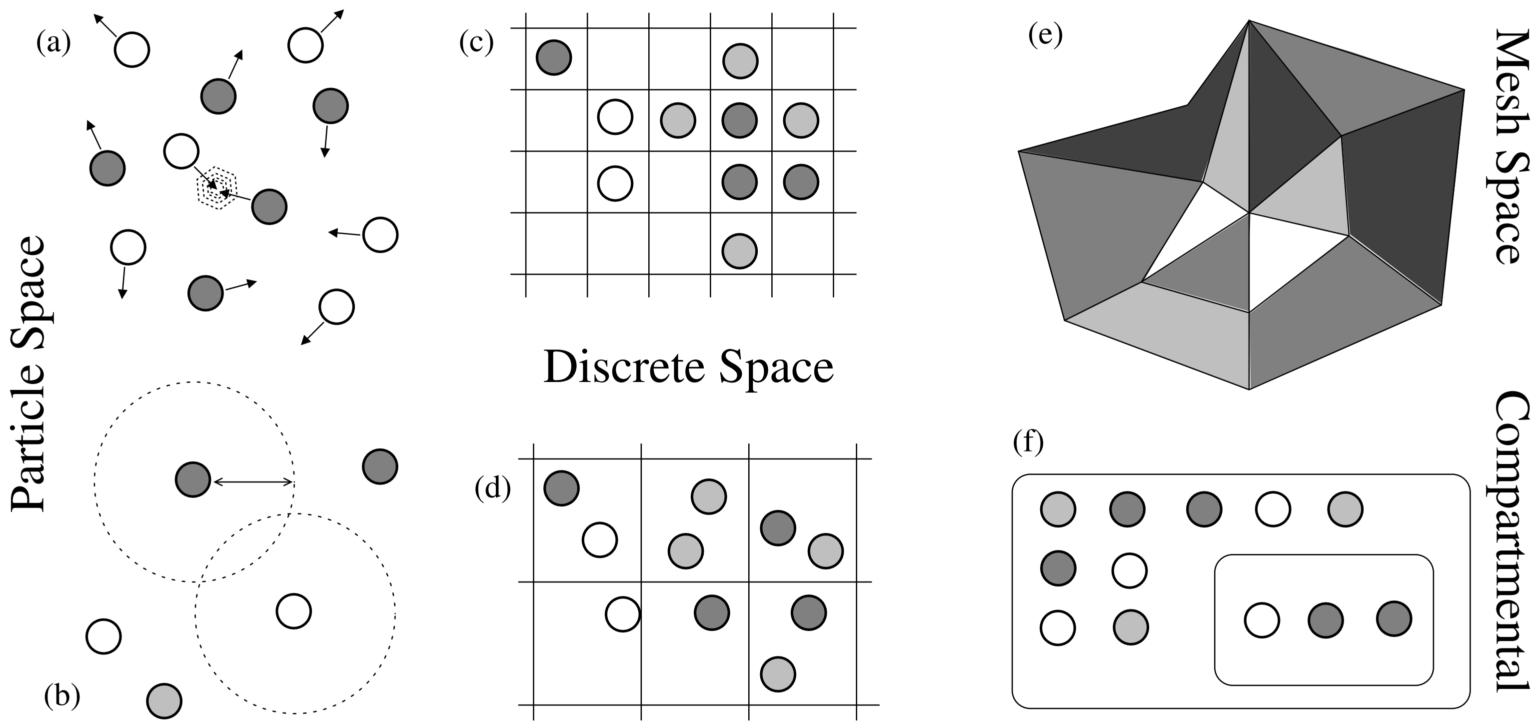
$$\begin{cases} dom(Hc) \stackrel{\text{df}}{=} \{0,1,2\} \\ next_{Hc}(x_{Hc}) \stackrel{\text{df}}{=} \begin{cases} 1 & \text{if } x_{Hc} = 0 \\ 2 & \text{otherwise} \end{cases} \end{cases}$$

$$\begin{cases} dom(Sz) \stackrel{\text{df}}{=} \{0,1\} \\ next_{Sz}(x_{Sz}, x_{Hc}) \stackrel{\text{df}}{=} \begin{cases} x_{Sz} & \text{if } x_{Hc} > 0 \\ 1 & \text{if } x_{Hc} = 0 \end{cases} \end{cases}$$

Extension:

- Arbitrary variable update function
- module (local variable & replication)
- global variable
- local and global measure
- spatial update

Spatial structures



Takahashi, K. and Arjunan, S. N. V. and Tomita, M. Space in systems biology of signaling pathways, towards intracellular molecular crowding in silico. FEBS Letters 579(8), 2005

MGS:

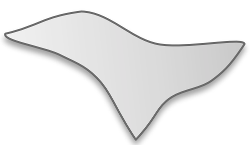
- graph and beyond: topological collection (chain on combinatorial cellular complexes)
- transformation (topological rewriting)

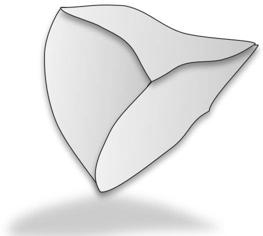
Topological collections

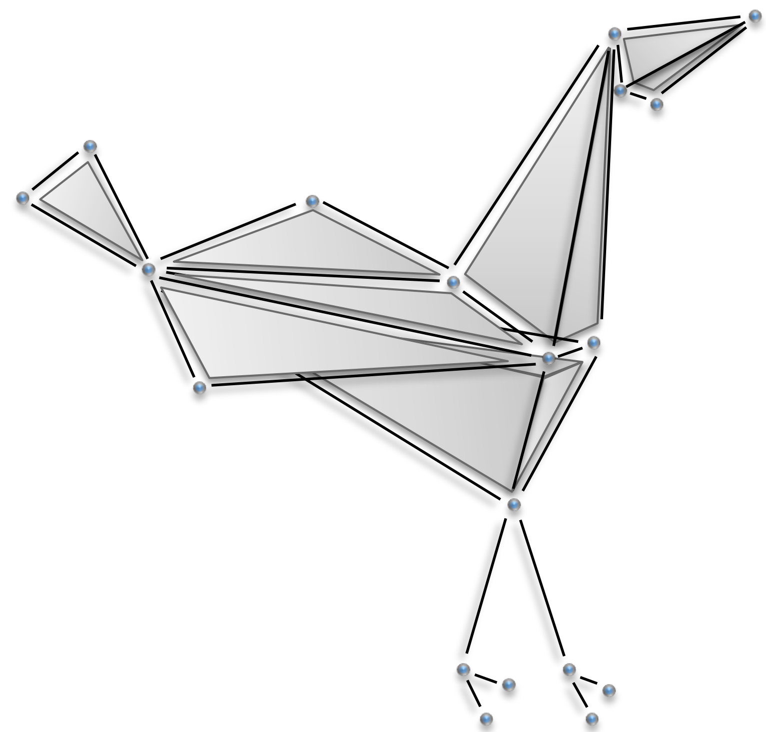
- Structure
  - A collection of topological cells
  - An ***incidence relationship***


vertex


edge

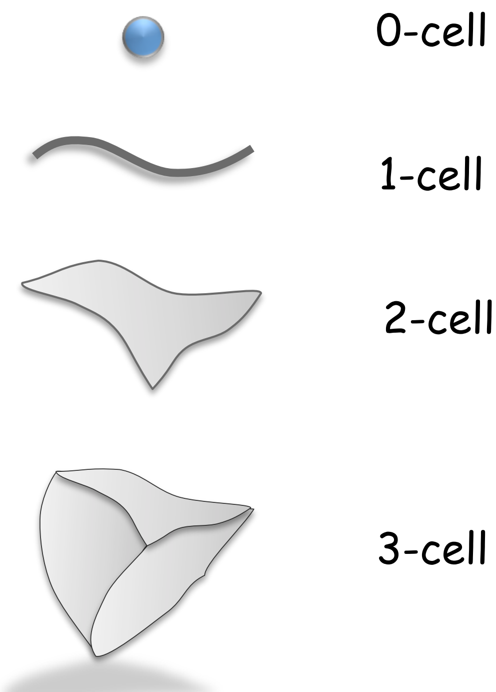

surface

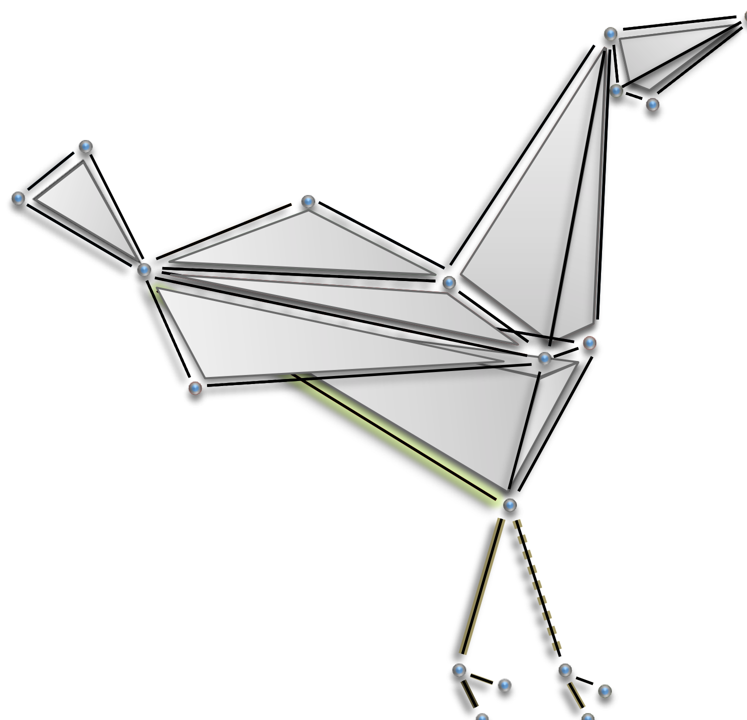

volume



Topological collections

- Structure
  - A collection of topological cells
  - An incidence relationship
  - Data: **association of a value with each cell**



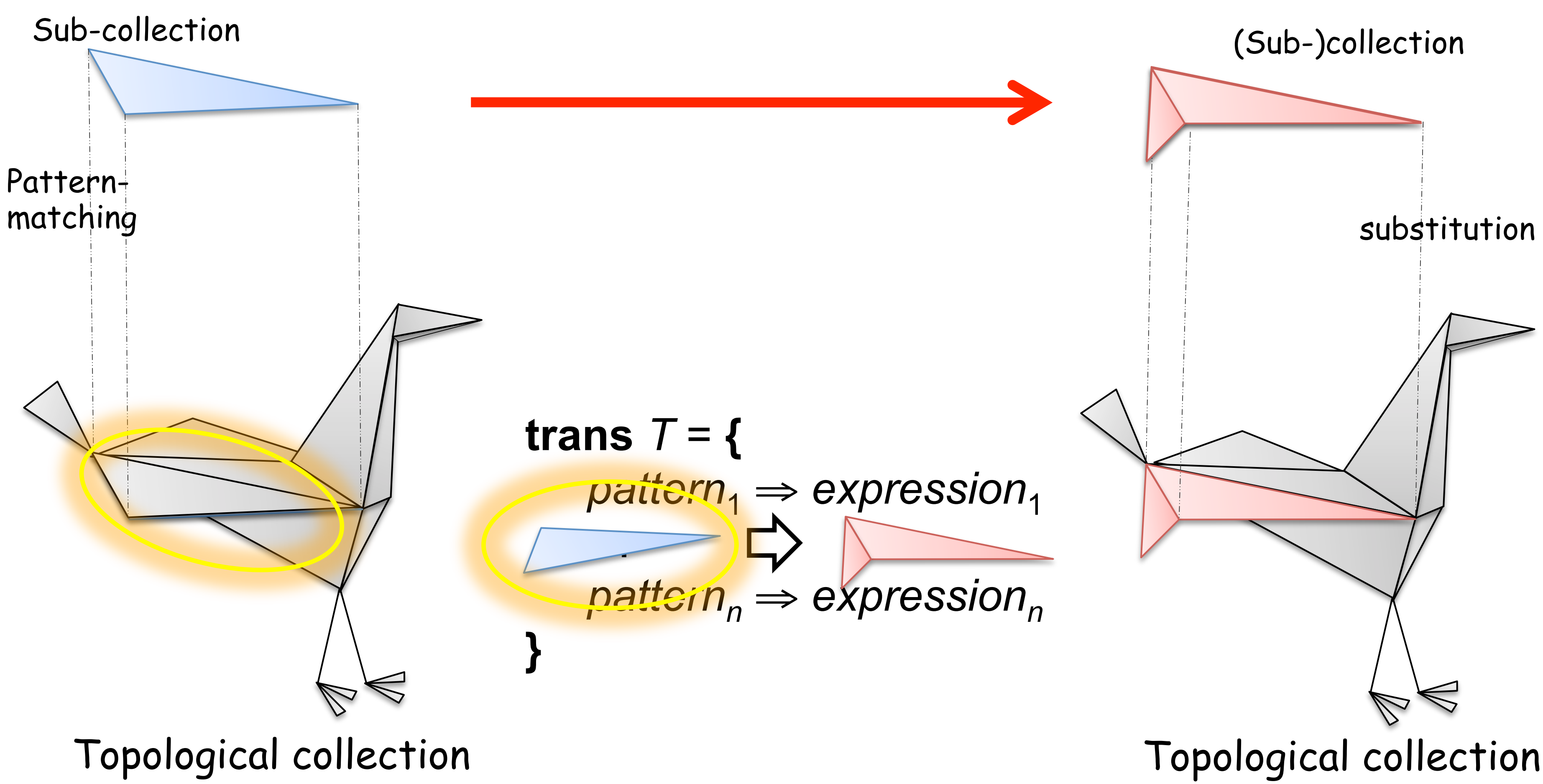


Transformations

- Functions defined by case on collections
  Each case (pattern) matches a sub-collection
- Defining a rewriting relationship: ***topological rewriting***

trans T = **{**
    $pattern_1 \Rightarrow expression_1$
    …
    $pattern_n \Rightarrow expression_n$
}

Transformations



IRN: the big Picture

Labeled graph = state

- Node = modules
- Edges = neighborhood relationships

local variable	*lv*	attached to each module
local measure	*lm*	observation of a module's neighbourhood
global variable	*gv*	attached to the whole system
global measure	*gm*	global observation of the whole system
graph update	*gu*	spatial transformation

IRN: the big Picture

Labeled graph = state
- Node = modules
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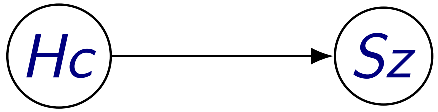
Transition function (*asynchronous evolution*)

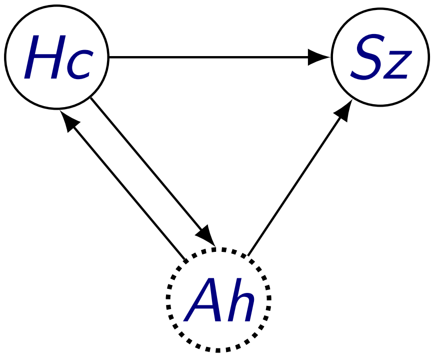
local variable	*lv*	✓	✓	✓	✓	✗
local measure	*lm*	✓	✓	✓	✓	✗
global variable	*gv*	✗	✗	✓	✓	✗
global measure	*gm*	✗	✗	✓	✓	✗
graph update	*gu*	✓	✓	✓	✓	✗

Back to *Anabaena*



$$Hc = \text{cell's kind} \in \{\text{heterocyst}, \text{undetermined}, \text{vegetative}\}$$
$$Sz = \text{cell's size} \in \{\text{small}, \text{big}\}$$

Back to *Anabaena*



$$
\begin{aligned}
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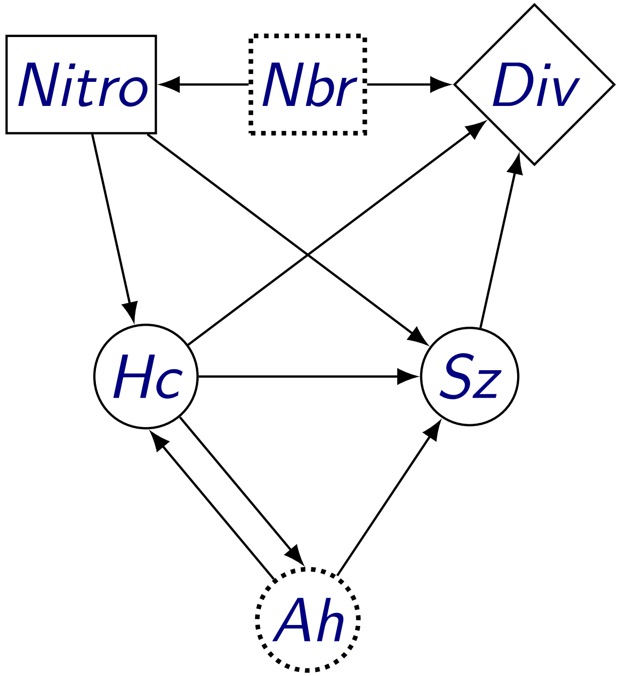
Sz &= \text{cell's size} \in \{\text{small}, \text{big}\} \\
Ah &= \text{any heterocyst around} \in \{\text{false}, \text{true}\}
\end{aligned}
$$

Back to *Anabaena*



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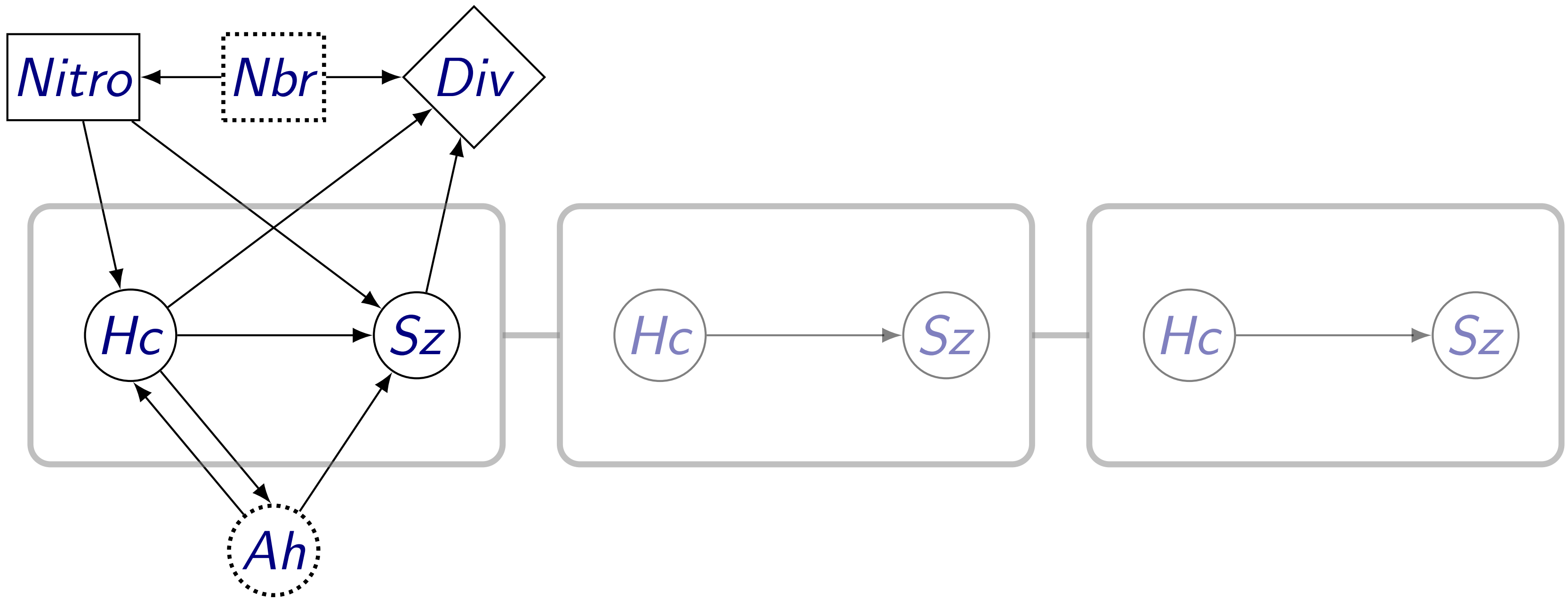
Nitro &= \text{nitrogen level} \leq Nitro_{max} \\
Nbr &= \text{population size} \leq Nbr_N \leq Nbr_{max} \\
Div &= \text{divide (topological transformation)}
\end{aligned}$$

Back to *Anabaena*



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$$

Global Variable *Nitro*

current *Nitro*	*Nbr*	
	$< Nbr_N$	$\geq Nbr_N$
0	0	
any $n > 0$	n	$n - 1$

$$Nitro(x_{Nbr}) = \text{ if } (x_{Nitro} > 0) \wedge (x_{Nbr} \geq Nbr_N) \text{ then } x_{Nitro} - 1 \text{ else } x_{Nitro}$$

Local Variables *Hc* and *Sz*

current *Hc*	*Nitro*		
	0		> 0
	Ah		
	false	true	
vegetative	undetermined	vegetative	undetermined
undetermined	heterocyst	undetermined	
heterocyst	heterocyst	heterocyst	

current *Sz*	*Hc*			
	heterocyst	vegetative or undetermined		
		Nitro		
		0		> 0
		Ah		
		false	true	
small	small	small	big	big
big	big			

Update, measure and transformation

local variable evolution

$$\text{trans } Sz(C, \lambda, i) = c \,/\, (\hat{}c = i)$$
$$\rightarrow c + \{Sz = Sz(c(Sz), \lambda(Nitro), Ah(C, \lambda, i))\}$$

local measure

$$\text{fun } Ah(C, \lambda, i) = NeighborFold(i, (\backslash x, acc.acc \vee (x(Hc) = \text{heterocyst})), \text{false})$$

global measure

$$\text{fun } Nbr(C, \lambda) = size(C)$$

graph update

$$\text{trans } Div(C, \lambda, i) = c_l, \quad (\{\ Sz = \text{big},\ Hc = k\ \} \text{ as } c), \quad c_r$$
$$/\ (\hat{}c = i) \ \wedge\ (Nbr(C, \lambda) < Nbr_{max}) \ \wedge\ (k \neq \text{heterocyst})$$
$$\wedge\ \big(\lambda(Nitro) > 0\ \vee\ c_l(Hc) = \text{heterocyst}\ \vee\ c_r(Hc) = \text{heterocyst}\big)$$
$$\rightarrow\ c_l,\ \text{c}+\{\ Sz{=}\text{small}\ \},\ \text{c}+\{\ Sz{=}\text{small}\ \},\ c_r$$

The prototype

Pilot

States of the system (identifiers)
+
Update functions (identifiers)

Triggers to evaluate
transformation to apply

where to apply

new state

Triggers value
(logical condition)

MGS

States of the system (topology & labels)
+
Update functions (computation)

IRN specification

State space
as
a graph of “labeled graphs”

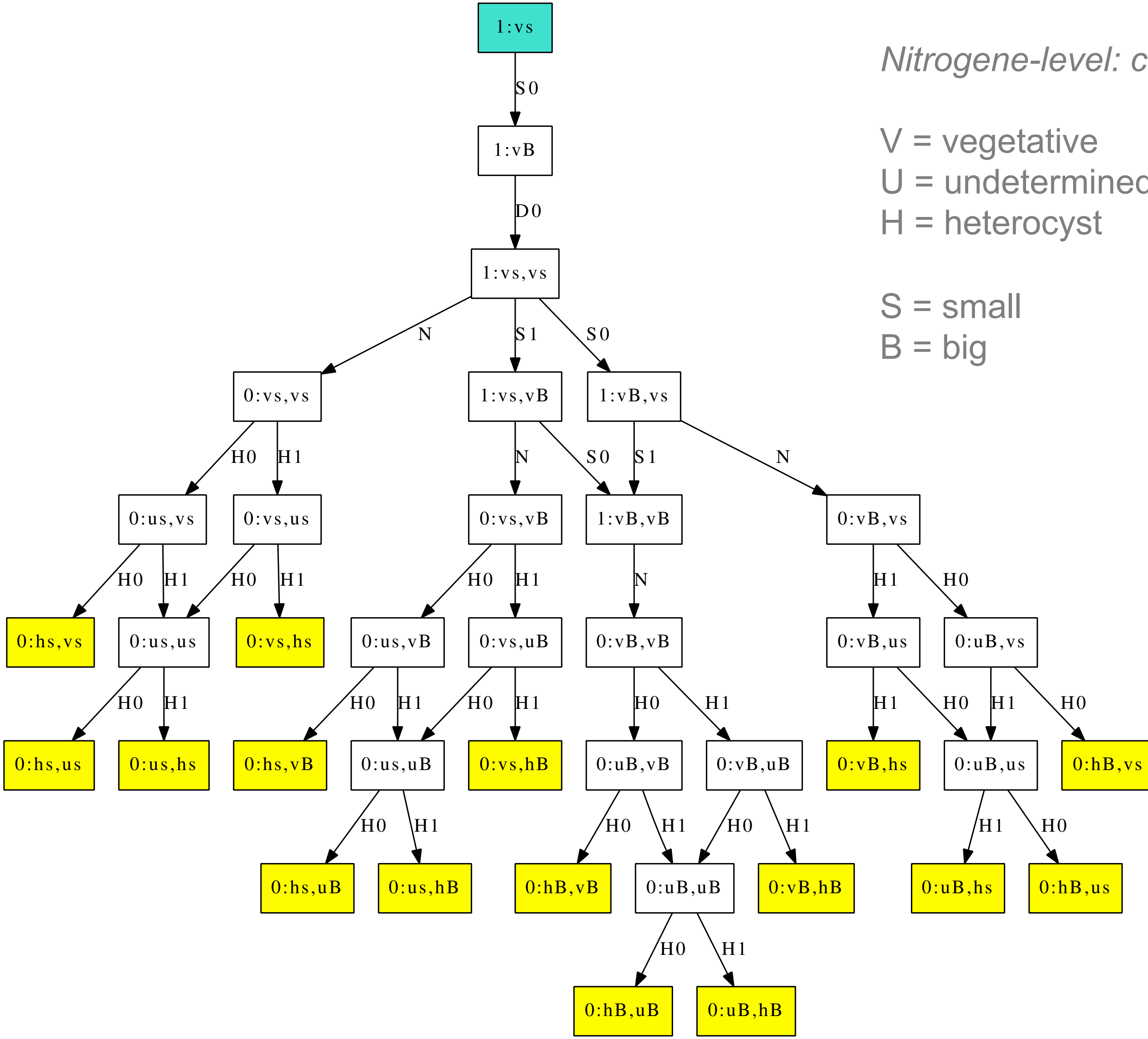
IRN specification

```
local Cell :
    var Hc :
        domain = vegetative, heterocyst
        init = vegetative
        update(Nitro , Ah) =
            trans Hc[i]= {Hc=vegetative} as c
                         / ^c==i && Nitro==0 && ~$Ah
                         => c+{Hc=heterocyst}
    var Sz :
        domain = small, big
        init = small
        update(Hc, Nitro, Ah) =
            trans Sz[i]= {Sz=small, Hc=vegetative} as c
                         / ^c==i && (Nitro>0 || $Ah)
                         => c+{Sz=big}
    measure Ah :
        domain = true , false
        block = ((leftq(c) && left(c).Hc==heterocyst)
                || (rightq(c) && right(c).Hc==heterocyst))
```

IRN specification

```
global :
    var Nitro :
        domain = N
        init = 3
        update(Nbr) =
              fun Nitro() = if ($Nbr<nbrN) || (Nitro==0)
                             then Nitro else Nitro - 1 fi
    const nbrM :
        init = 3
    const nbrN :
          init = 3
    measure Nbr :
        domain = N
        block = size(graph)
    graph_update Div :
        update(Nbr, Hc, Sz, Nitro, Ah) =
            trans Div[i] = {Sz=big, Hc=vegetative} as c
                           / (^c==i) && ($Nbr<nbrM) && (Nitro>0 || $Ah)
                           => c+{Sz=small}, c+{Sz=small}
initial :
    …
```

The Prototype



Nitrogene-level: cell-state, cell-state, …

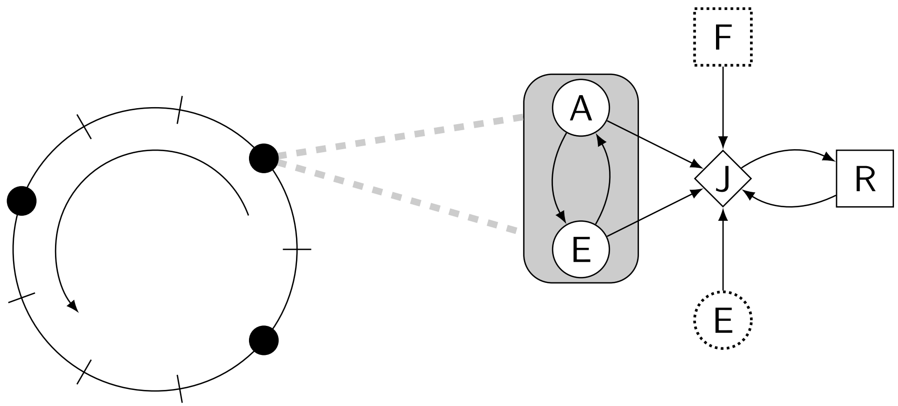
V = vegetative
U = undetermined
H = heterocyst

S = small
B = big

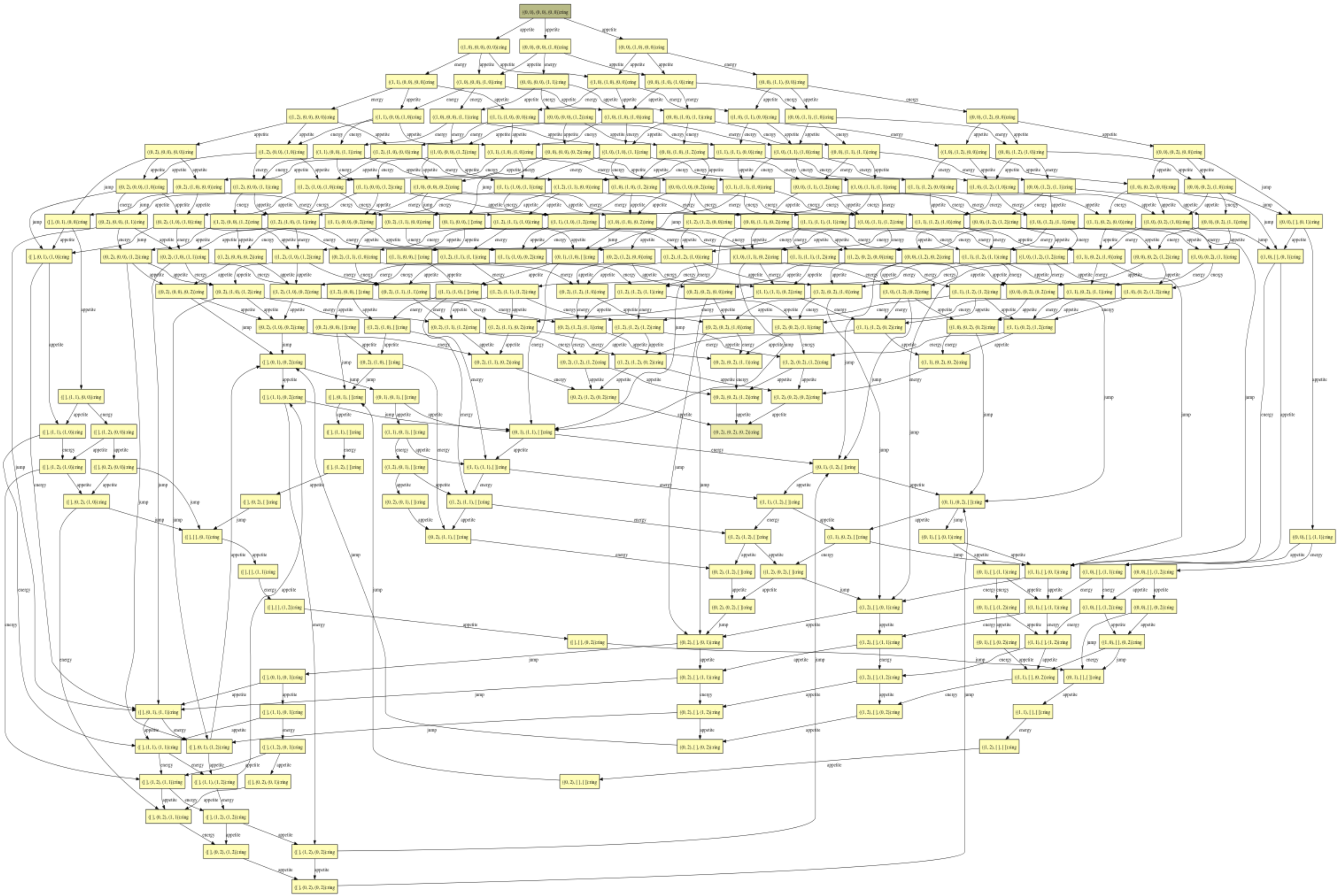
State Space Exploration

Nbr_{max}	Nbr_N	initial state	states	transitions	stable states
2	2	1:vs	39	42	16
2	2	2:vs	43	50	16
2	2	3:vs	47	58	16
3	2	1:vs	223	346	56
3	2	2:vs	235	378	56
3	2	3:vs	247	410	56
3	3	1:vs	191	286	48
3	3	2:vs	199	306	48
3	3	3:vs	207	326	48
5	4	3:vs	5375	12466	896
5	4	3:vs,vs	5373	12464	896
5	4	3:vs,vs,vs,vs	5361	12432	896

The little Horses

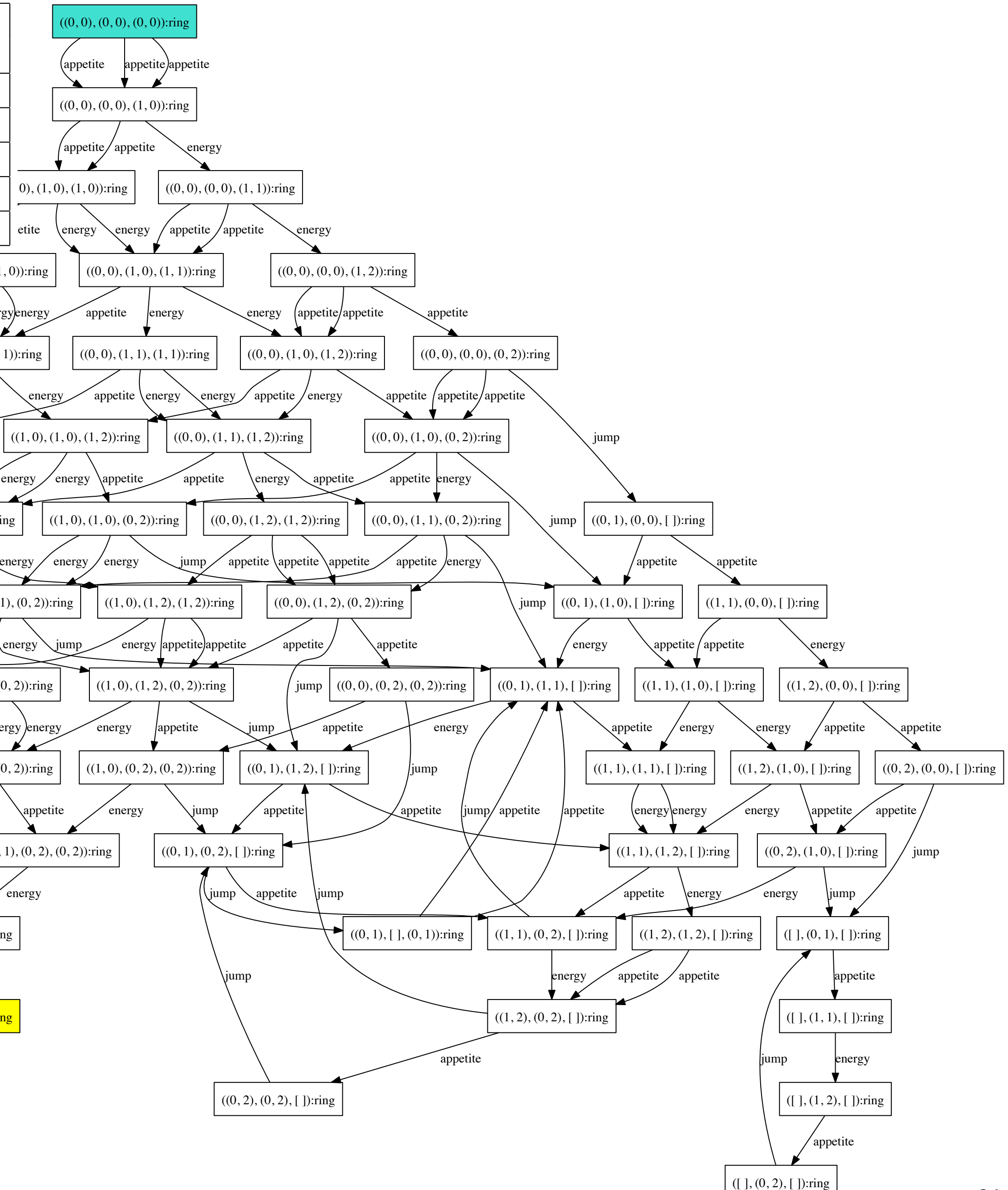


The Little Horses (5 slots): state space explosion



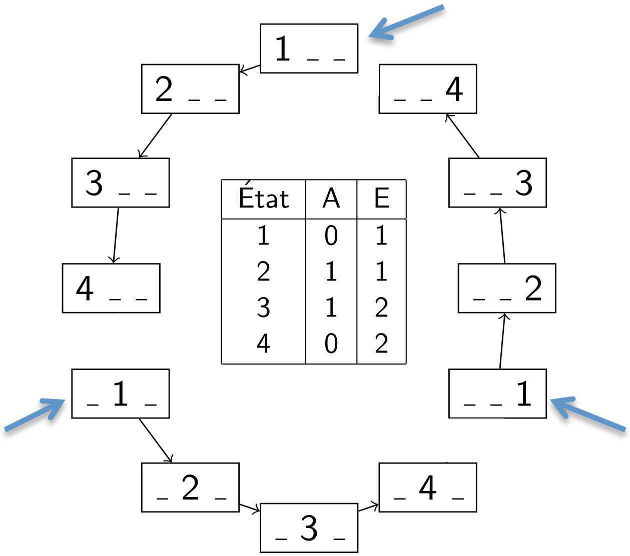
The Little Horses (5 slots) : state space reduction

Modules	États		Transitions		États Stables
	Complet	Réduit	Complet	Réduit	
1	21	5	21	5	0
2	199	28	358	55	0
3	981	214	2446	554	0
4	2828	526	8638	1669	0
5	4345	629	14616	2220	1

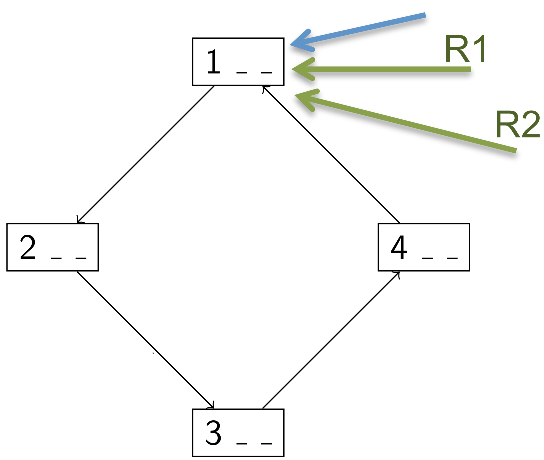


State Space Reduction: Intuition

State Space



Reduced State Space



Two states e1(C1, λ1) and e2(C2, λ2)
are equivalents by symetrie *iff*:

- the global variables are equal: λ1 = λ2
- the labeled graph C1 and C2 are isomorphic
  - expansive to test but can be ok
  - translate labeled graph into graph
  - relies on Nauty

Special case of bisimulation (process algebra)
better approaches exists

- subgraphs
- quotient

The reduced state space is computed on-line

Conclusion and perspective

- Discrete formalism for modelling multi-cellular processes
- Explicit spatial information with transformations
  Hybrid semantics: coloured Petri net + topological collections
- Simulation (SNAKES for Petri nets, MGS for the geometry)
- Model-checking (exhaustive simulation)
- Applications:
  - toy examples
  - segmentation in Drosophilia
  - bladder cancers
  - blood cancers
- model-checking technics for state space reduction
- use spatial information in model-checking
  fluid (blood) and nested structures (membranes/multiscale)