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Soft to Wet: Morphogenetic Engineering in Synthetic Biology

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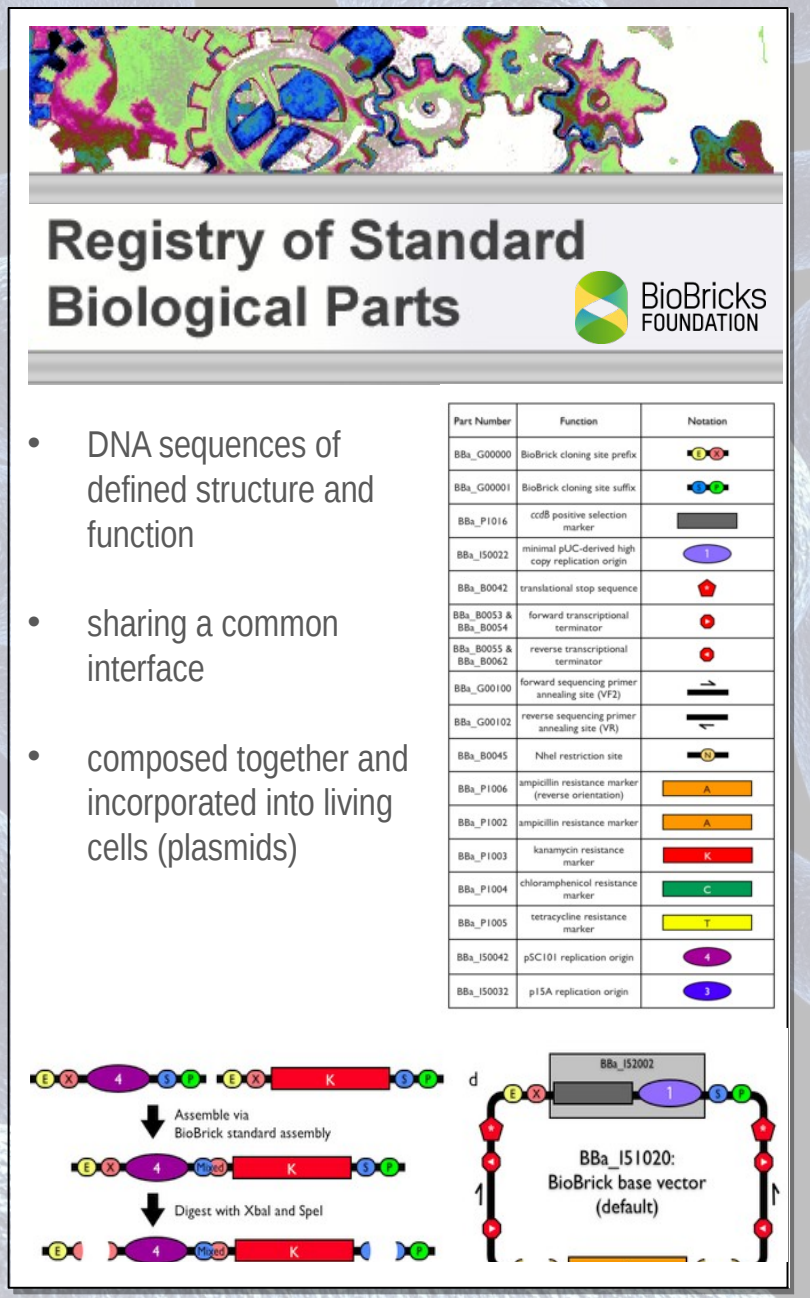
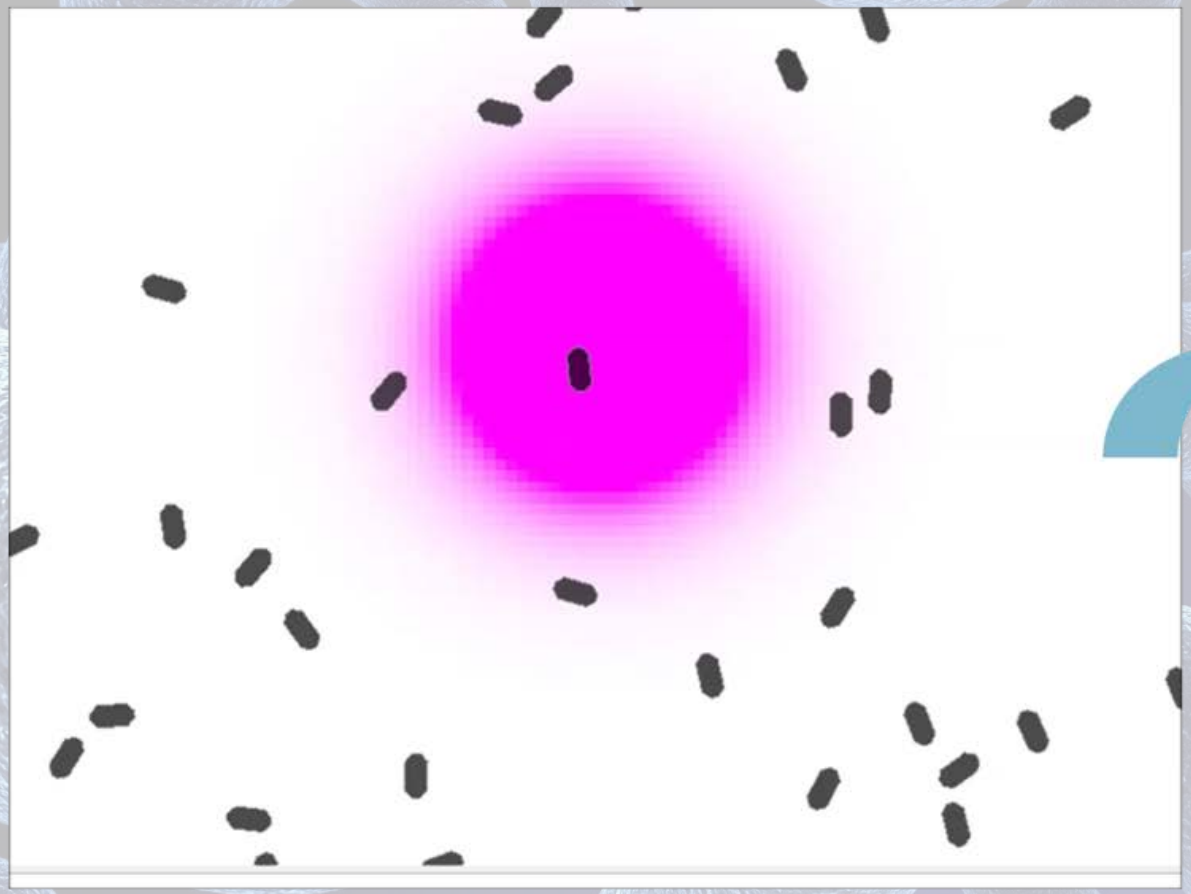
Introduction

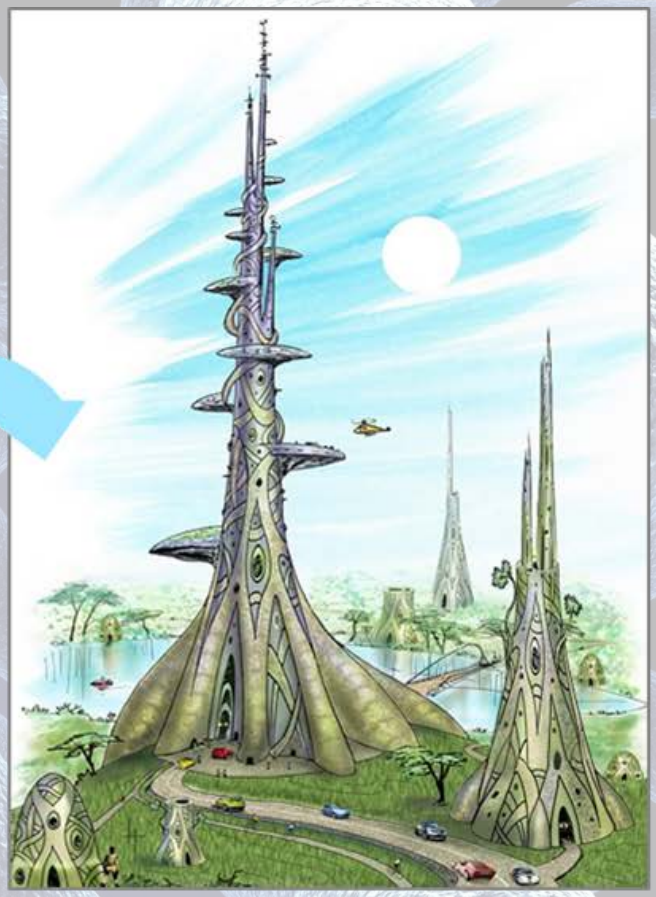
Synthetic biology's ambitions

- ✓ **construct new biological functions and systems not found in nature**
- ✓ **(re-)build cells to make them**
  - transform chemicals
  - create new materials
  - produce energy and food
  - improve human health and environment
  - process information, compute
  - create spatial structures (organs, buildings)
- ✓ **introduce the engineering principles of abstraction & standardization into biology**
- ✓ **design and manufacture reusable biological components**



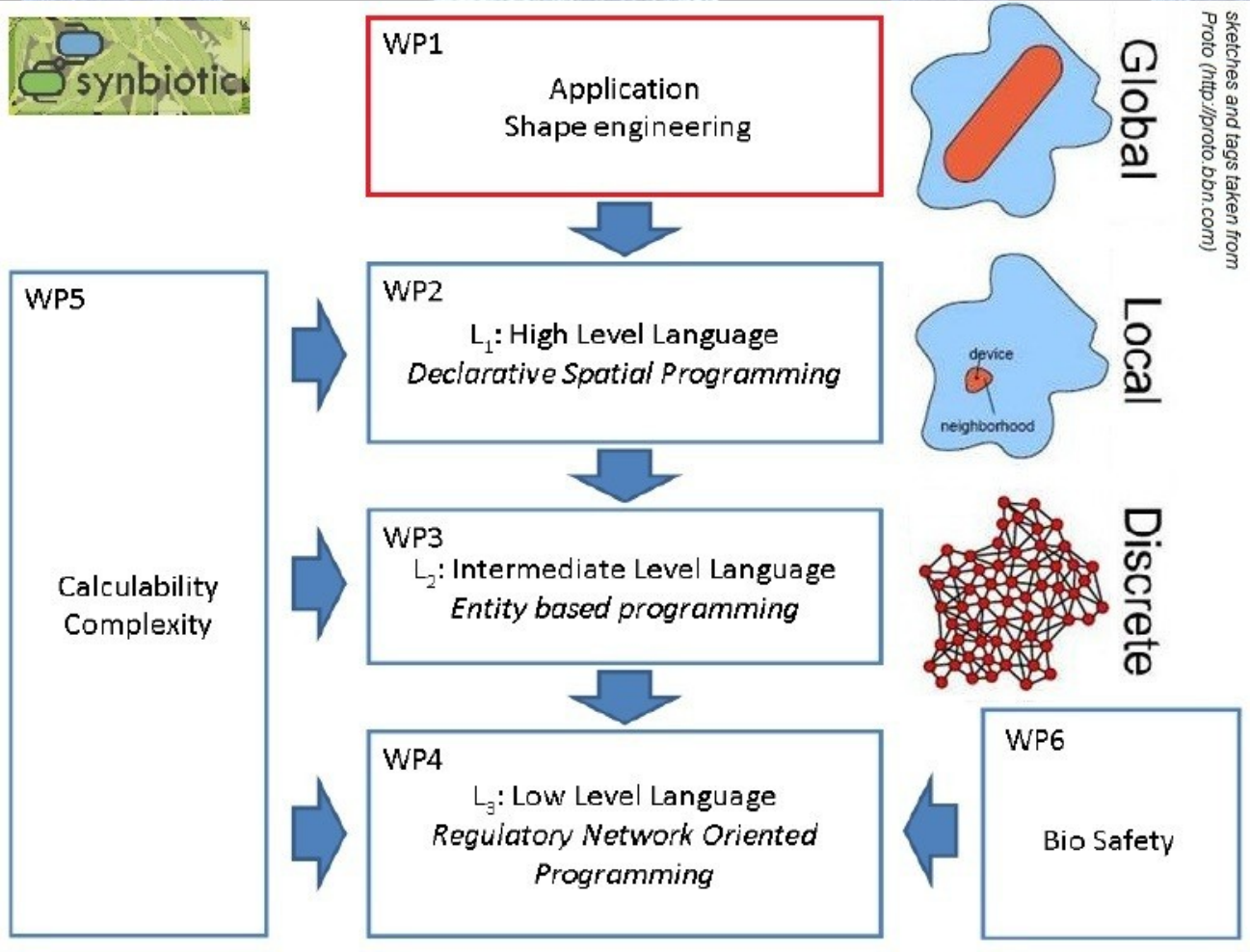


Jang, Oishi, Egbert, Klavins, "Specification and simulation of multicelled behaviours", ACS Synthetic Biology, 2012.



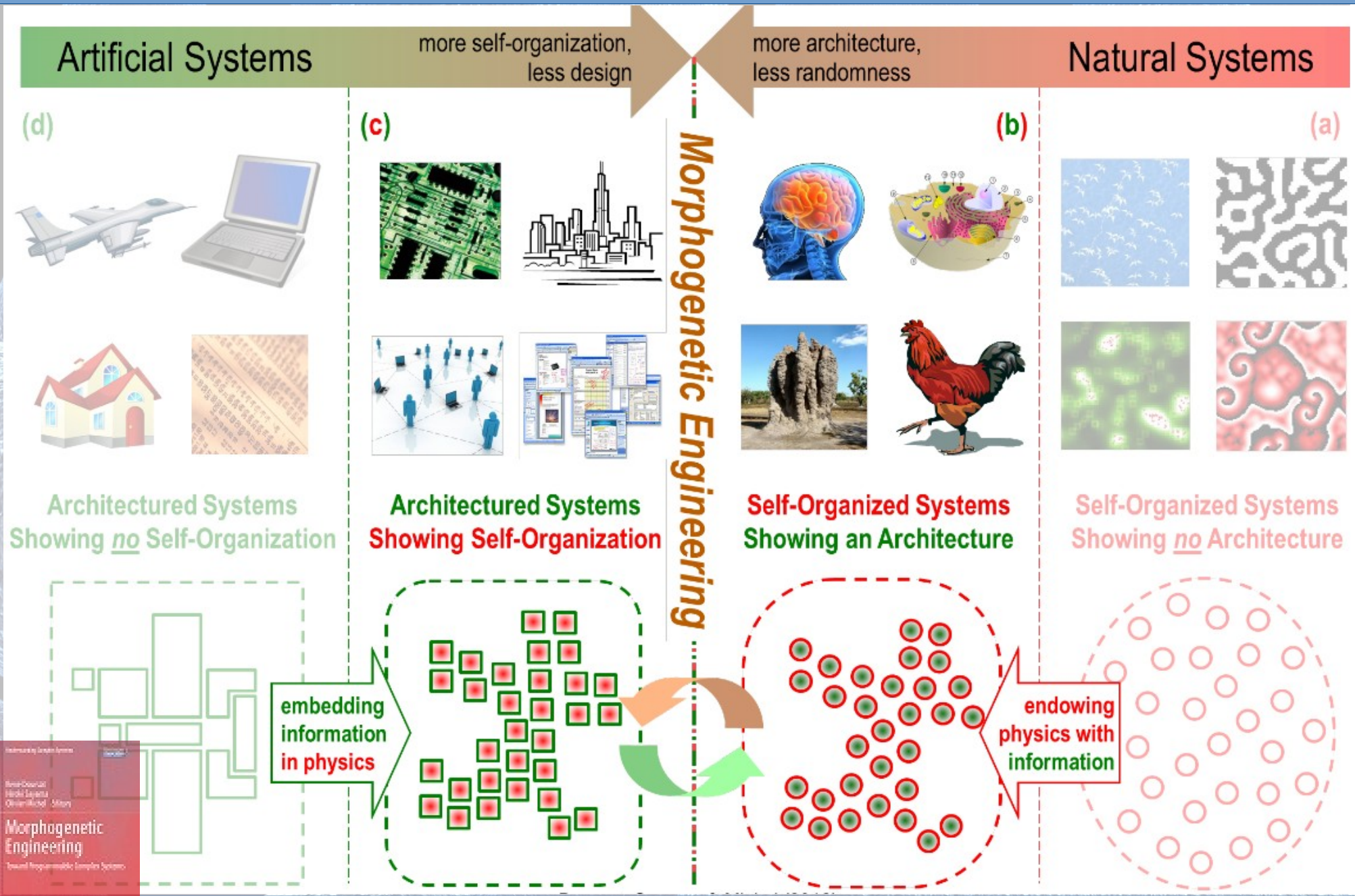
Susan Stepney et al. (2012) GroCyPhy Project: Gardening cyber-physical systems.

- The **SynBioTIC** project envisions a top-down tower of languages from global shape descriptions to local component rules, expressable by bacteria



- **goals: high-level morphogenetic engineering / spatial computing applications**
  - ✓ design, develop, implement various examples of pattern and shape formation
  - ✓ abstract the principles of pattern formation, collective motion and morphogenesis

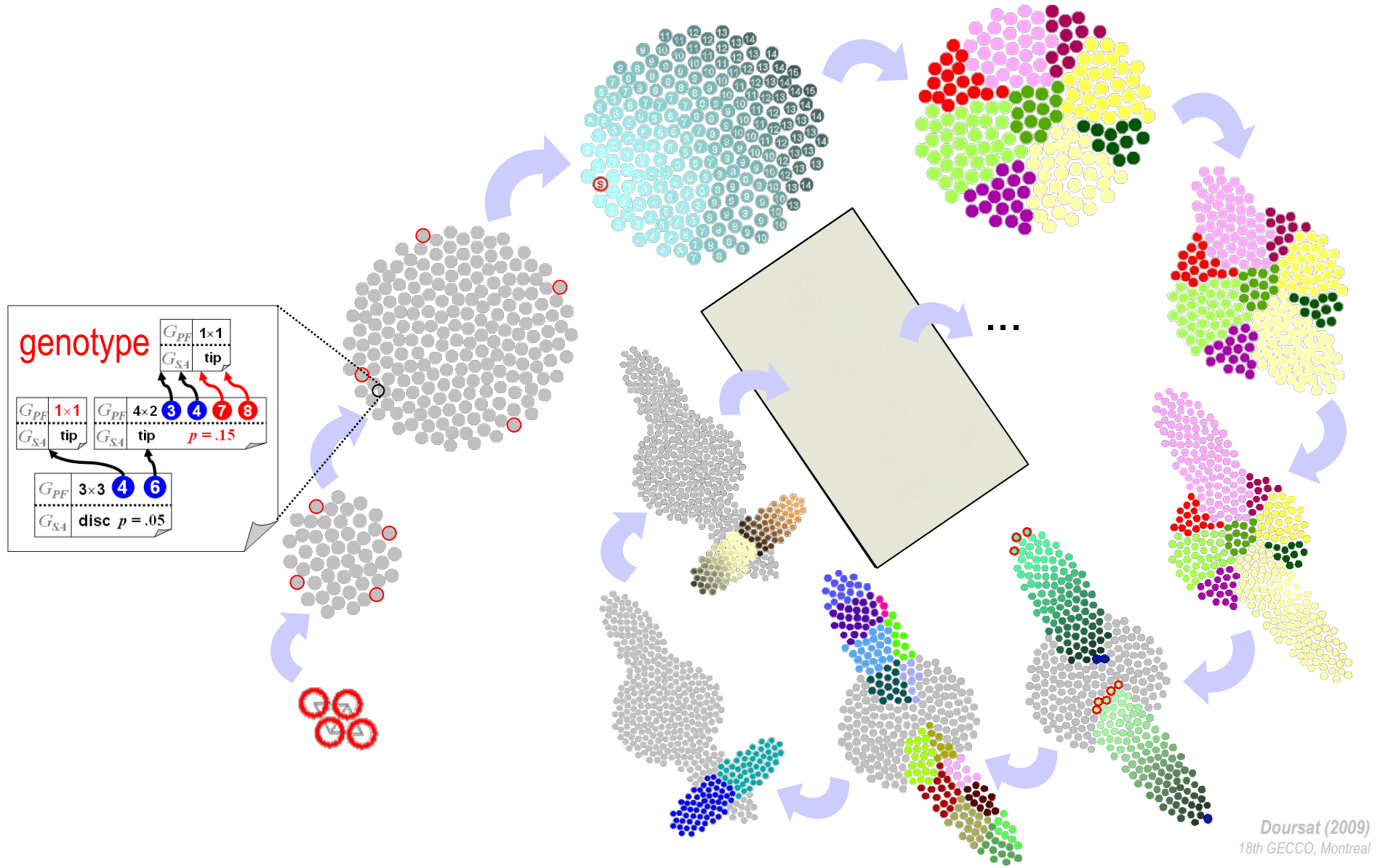
Morphogenetic Engineering



Gro Programming Language

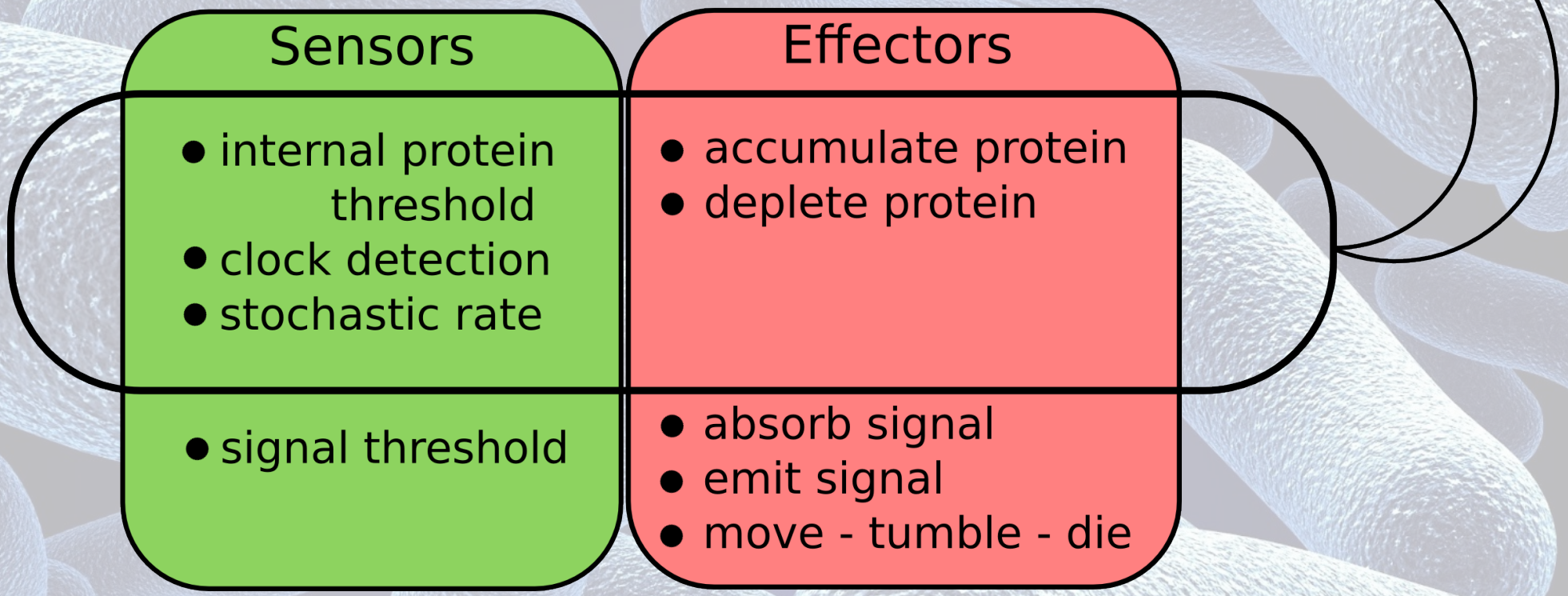
- The **Gro** language (E. Klavins) includes pre-programmed capabilities such as bacterial physics, cell behaviors, and diffusive chemical signals
- Capable of simulating experiments involving the growth and self-organization of *E. Coli* colonies on agar dishes


```
...
p.type = EMITER & get_signal(A) > .5 :
{
    emit_signal(B,6) ;
}

p.type = DEPLETER & get_signal(B) > 6.5 :
{
    absorb_signal(B,17) ;
}
...
```


genotype
G_{PF} 1×1
G_{SA} tip
G_{PF} 4×2 3 4 7 8
G_{SA} tip $p = .15$
G_{PF} 3×3 4 6
G_{SA} disc $p = .05$
...
Doursat (2009)
18th GECCO, Montreal

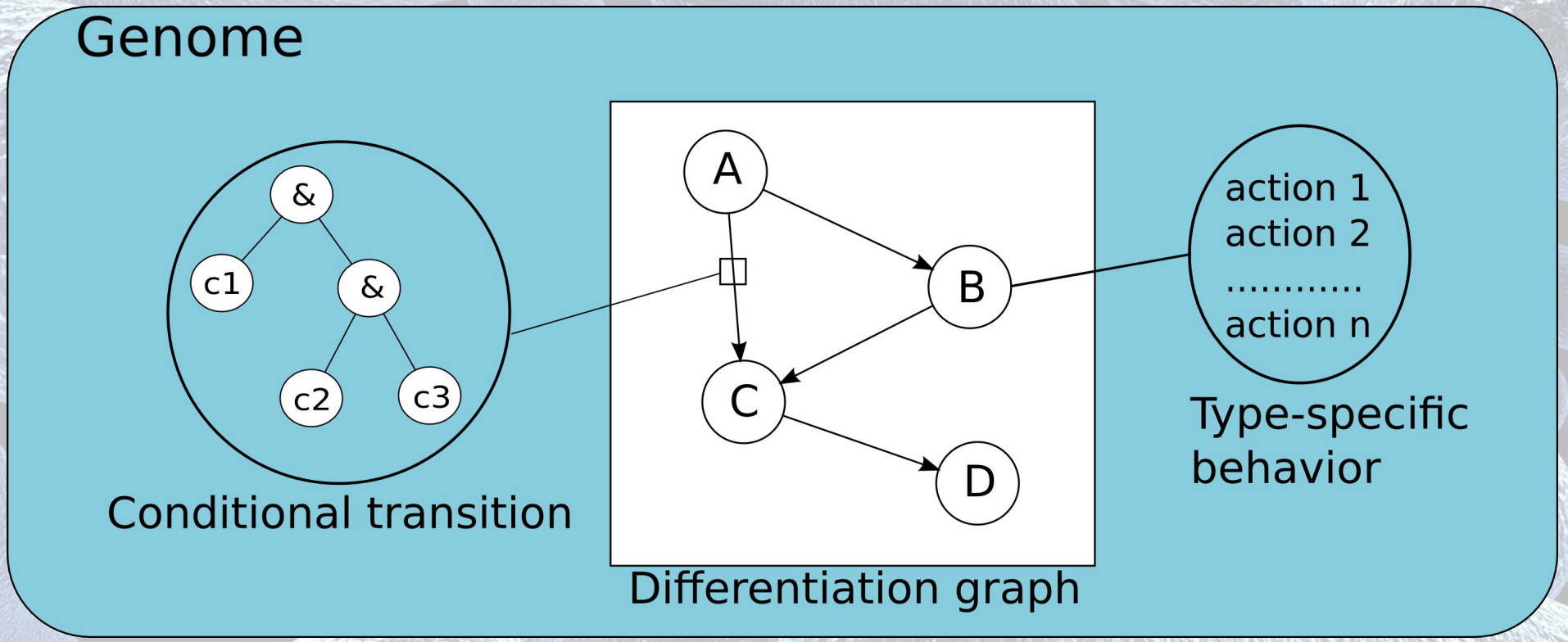
Our Model – Virtual *E. coli*

- Our model of *E. coli* includes a set of sensors/effectors



Our Model – Genome

- Bacterial dynamics is encapsulated in a finite state machine:
  - ✔ Nodes (states) are the types into which bacteria differentiate
    - Each state corresponds to a set of actions executed by the bacteria
  - ✔ Edges (transitions) describe the conditions of differentiation
    - Conditions pertain to protein concentrations and time



Genomic Representation – SBGP

- The **Synthetic Biology Genetic Programming** (SBGP) declarative language describes bacterial dynamics and environmental chemistry

```
"signals" : [
  ["A", 3, 0.4],
  ["B", 5, 0.01],
  ["C", 6, 0.5],
  ["D", 6, 0.5],
  ["E", 6, 0.5],
  ["F", 6, 0.5],
  ["G", 6, 0.5]
],

"reactions" : [
  [["A", "B"], ["C"], 0.5],
  [["D", "E"], ["F"], 0.5]
],

"type" : [
  "INIT",
  "INTER",
  "CENTRAL",
  "EMIT",
  "DEAD"
],

"parameters" : {
  "P1" : 250,
  "P2" : 35
},
```

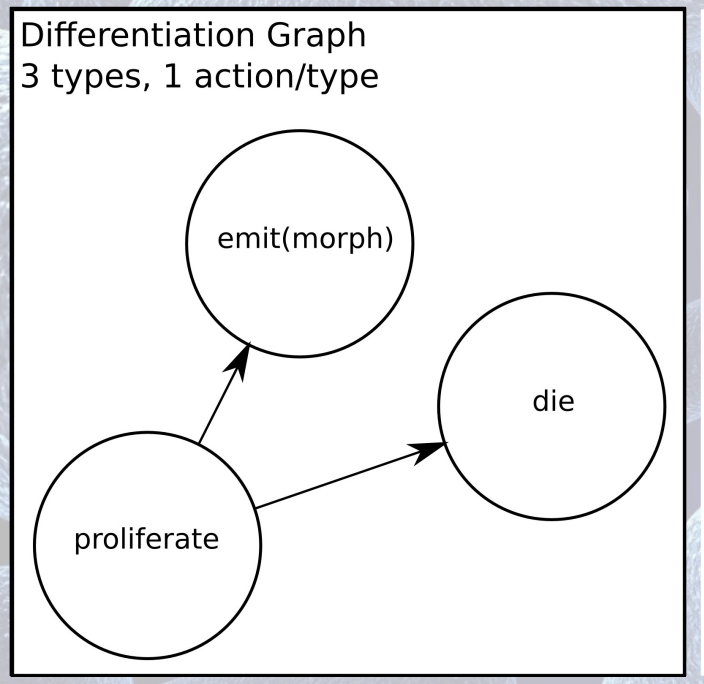
```
"behavior" : {
  "INIT" : [{"EmitSignal" : ["A", "50"]}],
  "INTER" : [{"Ungrowth" : []}],
  "CENTRAL" : [{"Growth" : []}],
  "EMIT" : [{"EmitSignal" : ["A", "35"]}],
  "DEAD" : [{"EmitSignal" : ["B", "750"]},
            {"Die" : []}]
},

"transition" : [
  ["NA", "NA", "C1", "NA", "NA"],
  ["NA", "NA", "NA", "NA", "C2"],
  ["NA", "C3", "NA", "C4", "NA"],
  ["NA", "C5", "NA", "NA", "C2"],
  ["NA", "NA", "NA", "NA", "NA"]
],

"cond_transition" :  {
  "C1" : {"AfterCond" : ["0.01"]},
  "C2" : {"OR" : [
            {"LessThreshold" : ["A", "5"]},
            {"GreaterThreshold" : ["B", "0.2"]}
          ]}
  "C3" : {"GreaterThreshold" : ["B", "0.2"]},
  "C4" : {"GreaterThreshold" : ["A", "25"]},
  "C5" : {"LessThreshold" : ["A", "25"]},
}
```

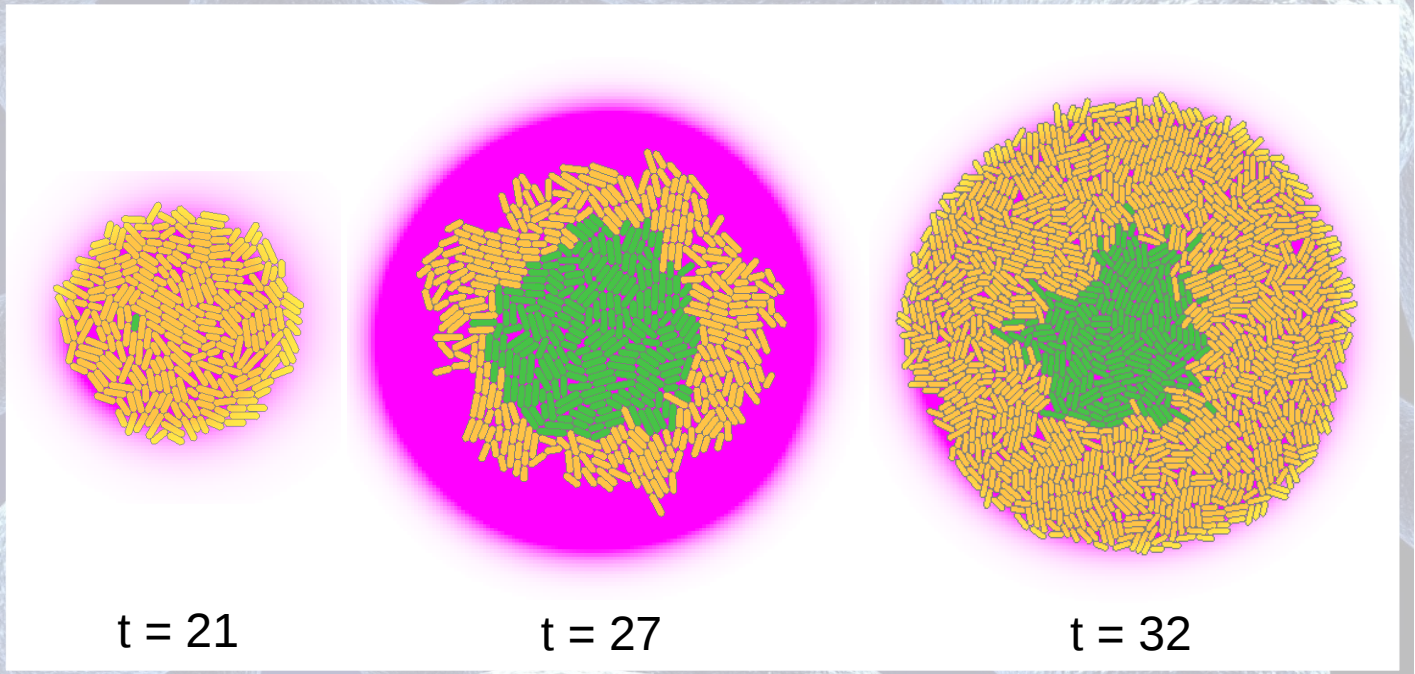
Rational Design

- In a first step we experimented with fundamental mechanisms that could generate collective behaviors typical of a cell assembly, i.e. homeostasis, shape formation, etc.
- The goal was to find the simplest genome for a given mechanism
- Examples with homeostatic growth and self-architecture

Example: Homeostatic Growth

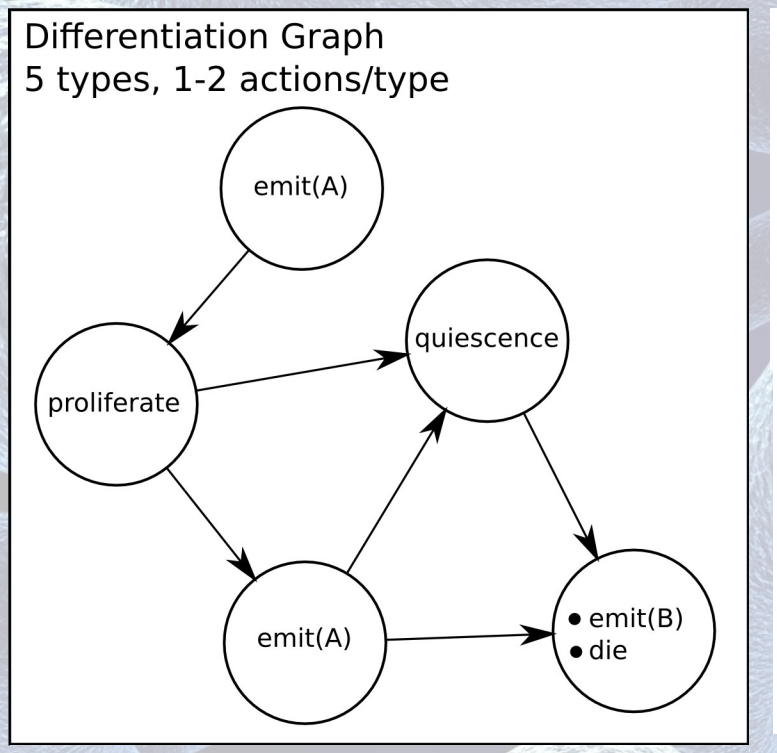
- A leader cell (green cell) emits a diffusive morphogen
- Followers cells (yellow) divide while above a certain threshold
- Death occurs if followers detect morphogens below the threshold

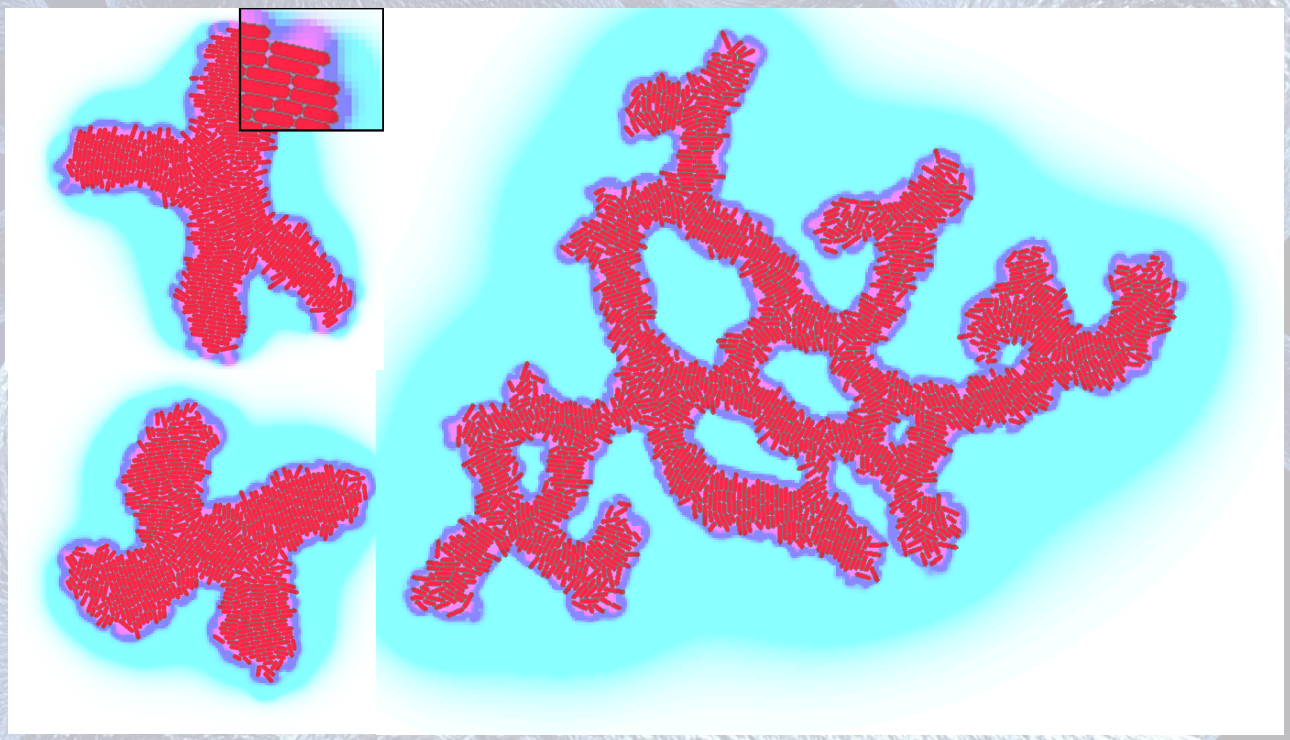




Example: Shape Formation

- Cells emit a slowly diffusive morphogen
- Cells die if morphogen concentration falls below a certain threshold
- Dying cells also send a faster diffusive signal that reacts with the morphogen and degrades it.
- This rate difference creates a mechanism of border reinforcement
- Mechanical forces induced by contacts between bacteria support *branching* structures





SEED Exploration

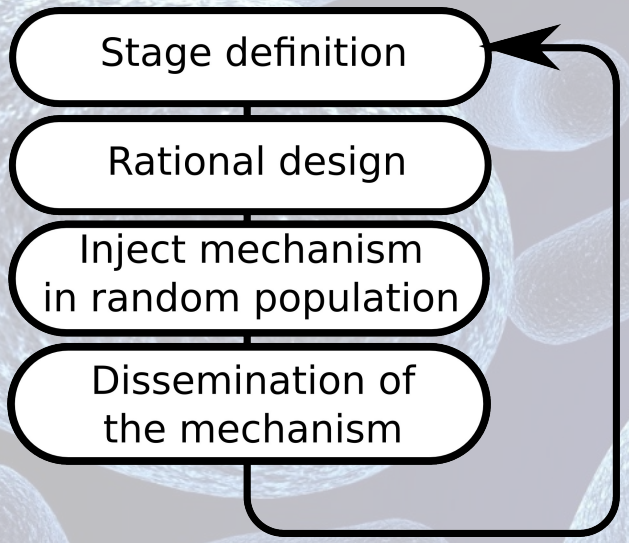
- Rational design faces its limits with an infinite number of possible gene regulation and molecular signaling networks.

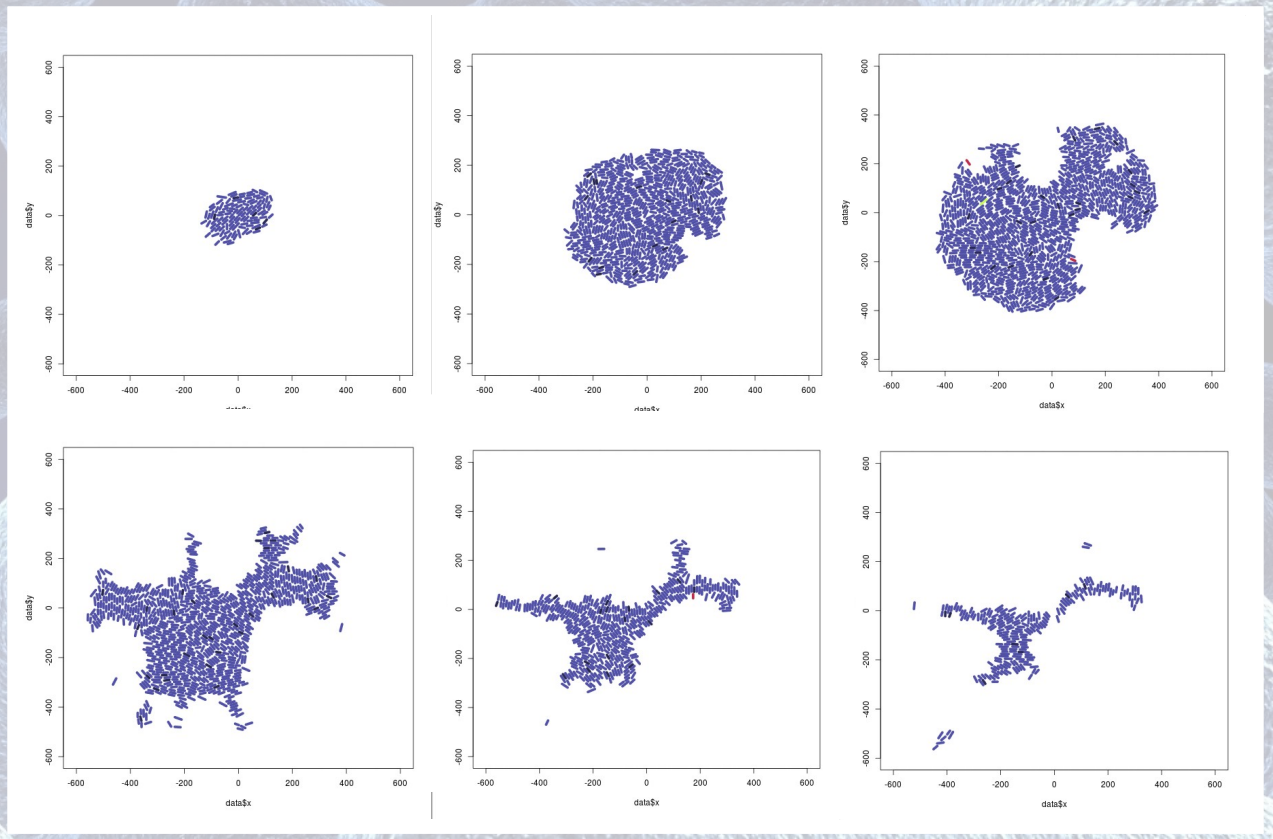
- Virtual Evolution is difficult to harness when exploring huge genotype spaces toward specific goals.

- **Staged Evolutionary Engineering of Development** (SEED) proposes to use human mediation as a tool for exploration and as a means of refining evolutionary goals between stages.

Evolutionary Scheme

- The idea behind SEED is to inject at each stage hand-designed mechanisms in the population,
- For example, branching mechanism is injected in randomly generated population
- Human mediation leads to a new kind of branching structure after spheroidal growth





Future Work

- Combine homeostatic and branching mechanisms to build complex stable structures
- Combine interactive and automatic selection in the SEED process
- Evaluate SEED vs classical evolution

Acknowledgements

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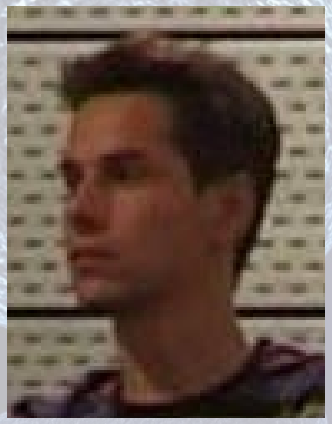

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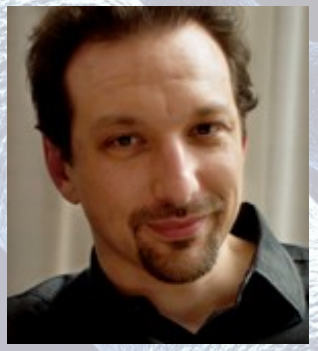

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