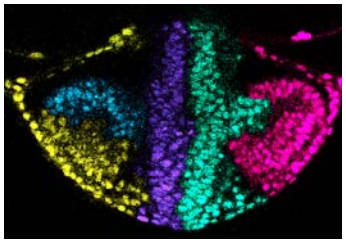
BIOCOMPLEXITY X
Quantitative Tissue Biology and Virtual Tissues

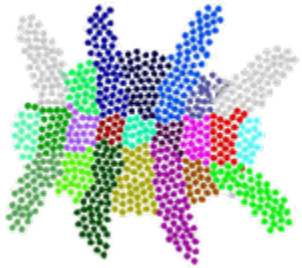
# *Heterogeneous* collective motion or *moving* pattern formation?

## The two sides of embryogenesis combined by multi-agent modeling into a


**René Doursat**
http://www.iscpif.fr/~doursat



PARIS ÎLE-DE-FRANCE
INSTITUT DES SYSTEMES COMPLEXES



# Systems that are self-organized and architectured

free self-organization

the scientific challenge of complex systems: how can they integrate a true ***architecture?***

Peugeot Picasso

deliberate design

the engineering challenge of complicated systems: how can they integrate ***self-organization?***

components evolve

Peugeot Picasso

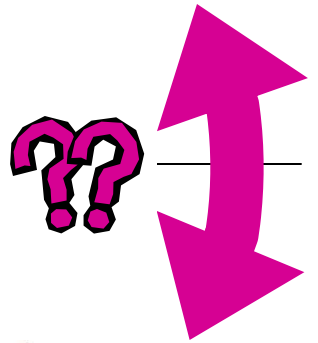
decompose the system

self-organized architecture / architectured self-organization

# Toward programmed self-organization

## ➢ Self-organized (complex) systems

- ✓ a myriad of self-positioning, self-assembling agents
- ✓ collective order is not imposed from outside (only influenced)
- ✓ comes from purely *local* information & interaction around each agent
- ✓ no agent possesses the global map or goal of the system
- ✓ but every agent may contain all the ***rules*** that contribute to it



eradicate any illusion of ID by *explaining* the *developmental* mechanisms of spontaneous architecture formation (not just evolutionary)

## ➢ Structured systems

- ✓ true *architecture*: non-trivial, complicated morphology
  - *hierarchical*, multi-scale: regions, parts, details, agents
  - *modular*: reuse, quasi-repetition
  - *heterogeneous*: differentiation & divergence in the repetition
- ✓ *random* at the microscopic level, ***but reproducible*** (quasi deterministic) at the mesoscopic and macroscopic levels

# Quick preview of multi-agent embryogenesis

## ➢ An *abstract* (computational), *top-down* approach

- ✓ development as a fundamentally ***spatiotemporal*** phenomenon
- ✓ JAG: "***start generically***, treat cells as black boxes, add details gradually"
- ✓ highlighting the ***broad principles*** necessary to integrate and make sense of the data; proposing a ***computational*** model of these principles

## ➢ And the broad principles are...

1. *biomechanics* → collective motion → "sculpture" of the embryo
2. *gene regulation* → gene expression patterns → "painting" of the embryo

\+ ***coupling*** between shapes and colors

## ➢ Multi-agent models

- ✓ best positioned to integrate both
- ✓ account for heterogeneity, modularity, hierarchy
- ✓ each agent carries a combined set of *biomechanical* and *regulatory* rules

# The self-made puzzle of embryogenesis

1. Self-organized *and* structured systems

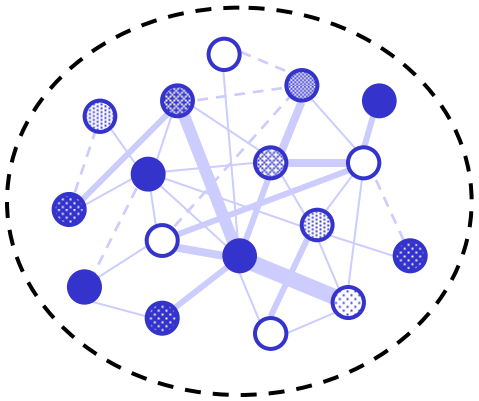
2. A two-side challenge: heterogeneous motion / moving patterns

3. A multi-agent model of embryogenesis

4. Evolutionary development (evo-devo)

# Self-organized *and* structured systems

## ➢ Natural and human-made complex systems everywhere

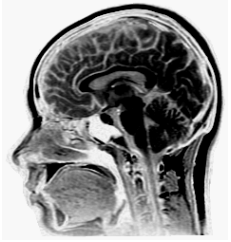


- large number of elementary **agents** interacting **locally**
- simple individual behaviors creating a complex **emergent** collective behavior
- *decentralized dynamics: no master blueprint or grand architect*

✓ physical, biological, technical, social systems (natural or artificial)

pattern formation
○ = matter

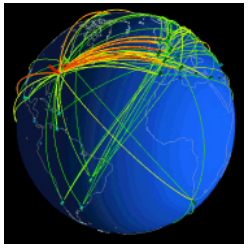
biological development
○ = cell



the brain & cognition
○ = neuron

insect colonies
○ = ant

Internet & Web
○ = host/page



social networks
○ = person

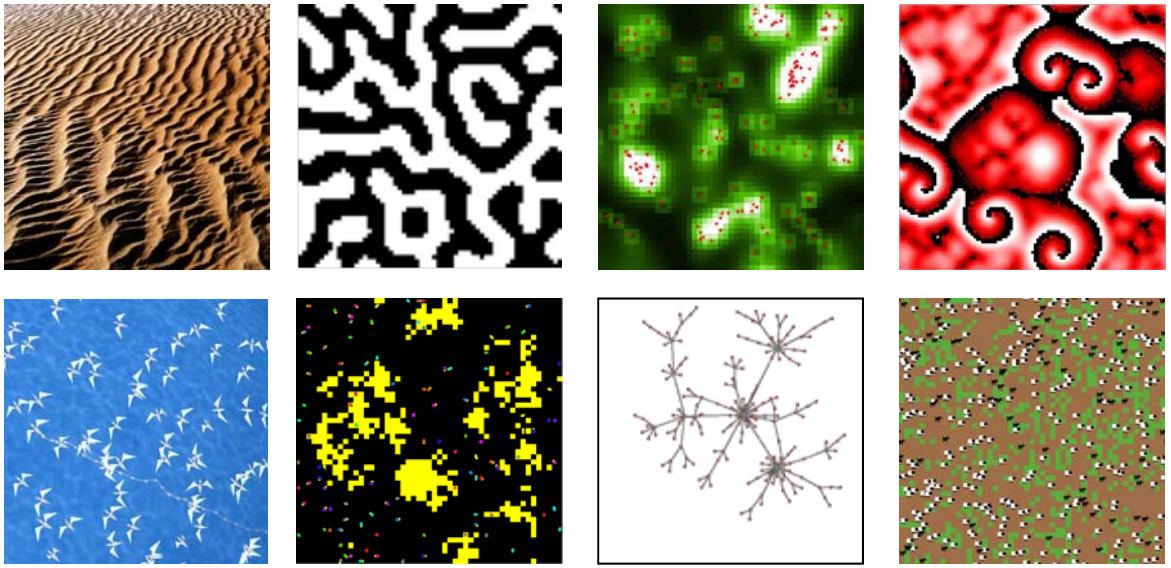
# "Statistical" vs. "morphological" complex systems

## ➢ A brief taxonomy of systems

| Category | *Agents / Parts* | *Local Rules* | *Emergent Behavior* | *A "Complex System"?* |
|---|---|---|---|---|
|  2-body problem | *few* | *simple* | *simple* | *NO* |
|  3-body problem, low-D chaos | *few* | *simple* | *complex* | *NO – too small* |
|  crystal, gas | *many* | *simple* | *simple* | *NO – few params suffice to describe it* |
|  patterns, swarms, complex networks | ***many*** | ***simple*** | ***"complex"*** | ***YES – but mostly random and uniform*** |
|  embryogenesis | ***many*** | ***sophisticated*** | ***complex*** | ***YES – reproducible and heterogeneous*** |
|  machines, crowds with leaders | *many* | *sophisticated* | *"simple"* | *COMPLICATED – not self-organized* |

# Statistical (self-similar) systems

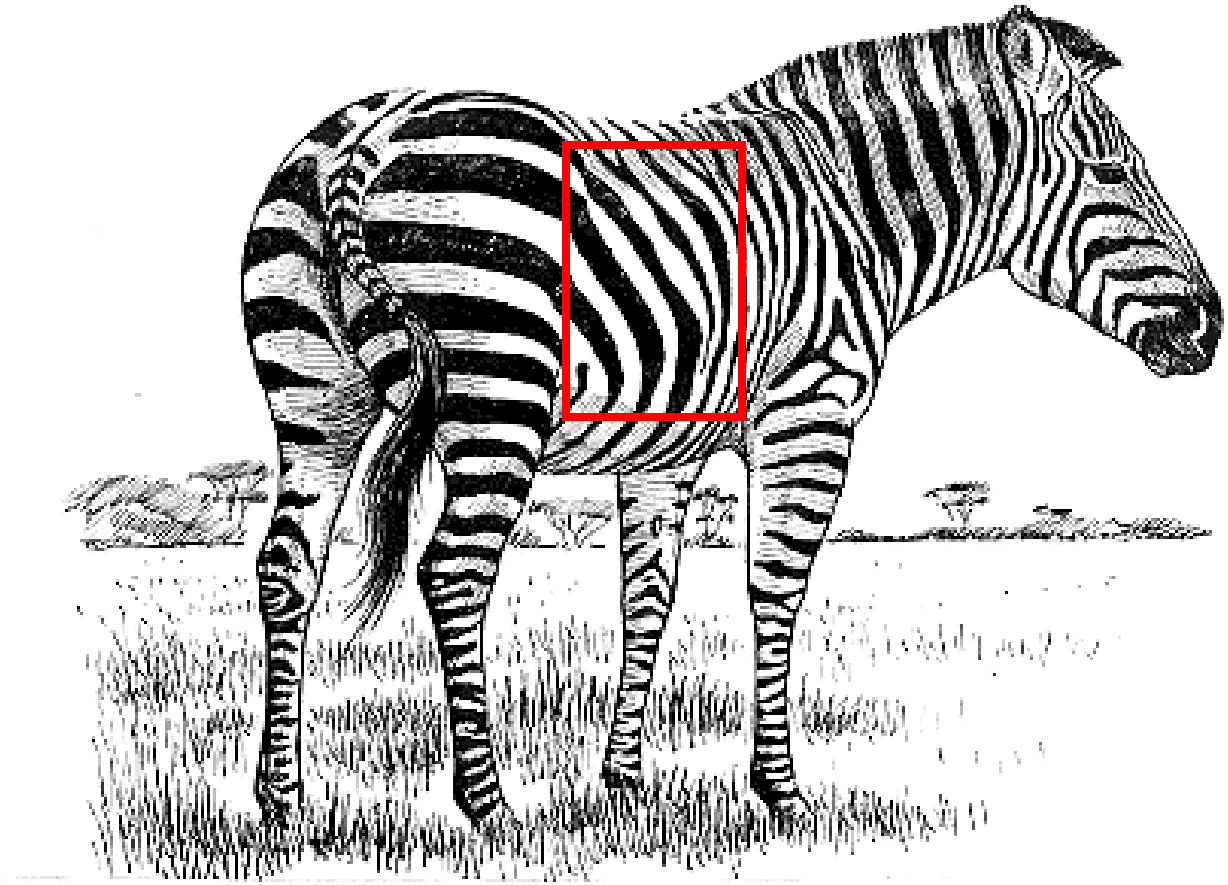
- Many agents, simple rules, "complex" emergent behavior
  - → *the "clichés" of complex systems: diversity of pattern formation (spots, stripes), swarms (clusters, flocks), complex networks, etc.*



- ✓ yet, often like "textures": repetitive, statistically *uniform*, information-poor
- ✓ spontaneous order arising from amplification of *random* fluctuations
- ✓ *unpredictable* number and position of mesoscopic entities (spots, groups)

# Morphological (self-dissimilar) systems

## compositional systems: pattern formation ≠ morphogenesis



*"I have the stripes, but where is the zebra?"* OR

*"The stripes are easy, it's the horse part that troubles me"*

—attributed to A. Turing, after his 1952 paper on morphogenesis

# Morphological (self-dissimilar) systems

- **Many agents, sophisticated rules, complex emergence**
  - → *natural ex: organisms (cells)*


*plants*


*vertebrates*

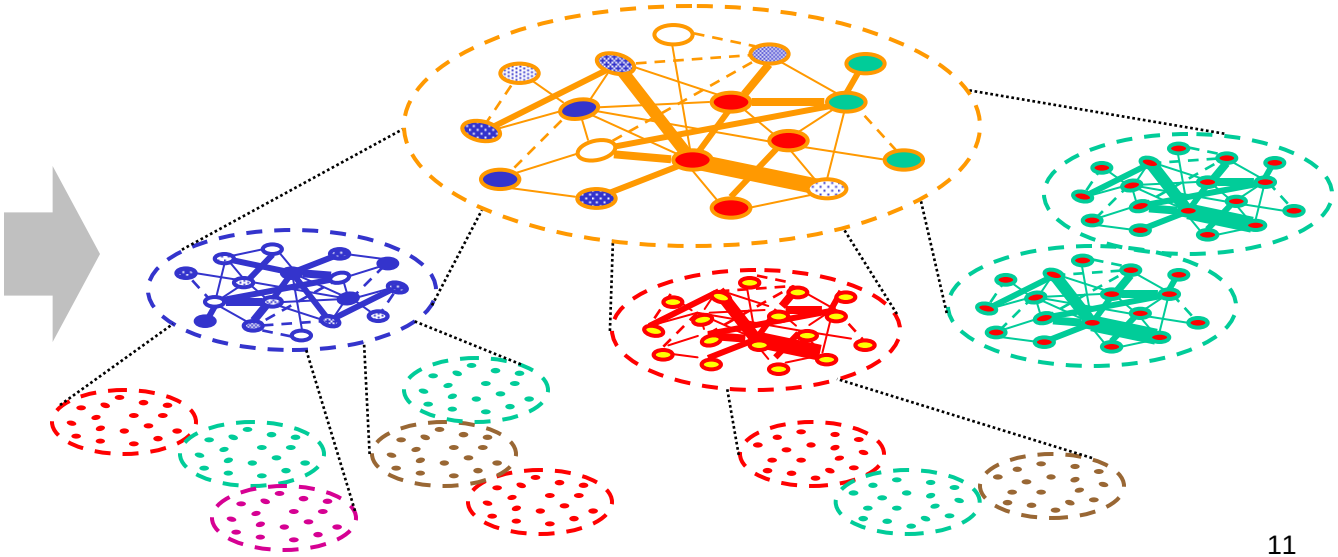

*arthropods*


*humans*

  - ✓ mesoscopic organs and limbs have intricate, ***nonrandom*** morphologies
  - ✓ development is highly ***reproducible*** in number and position of body parts
  - ✓ ***heterogeneous*** elements arise under information-rich genetic control
- **Biological organisms are self-organized *and* structured**
  - ✓ because the pieces of the puzzle (agent rules) are more "sophisticated" (than inert matter): depend on agent's ***type*** and/or ***position*** in the system
  - ✓ the outcome (development) is truly complex but, paradoxically, can also be more ***controllable*** and ***programmable***

# Beyond statistics: heterogeneity, modularity, reproducibility

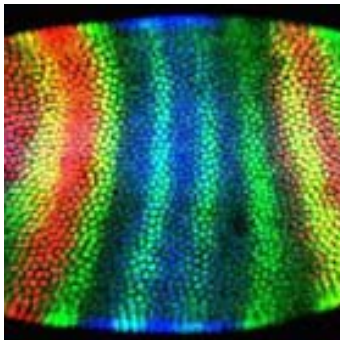
- Complex systems can be much more than a “soup”
  - ✓ “complex” doesn’t necessarily imply “homogeneous”...
    → *heterogeneous agents and diverse patterns, via positions*
  - ✓ “complex” doesn’t necessarily imply “flat” (or “scale-free”)...
    → *modular, hierarchical, detailed architecture (at specific scales)*
  - ✓ “complex” doesn’t necessarily imply “random”...
    → *reproducible patterns relying on programmable agents*



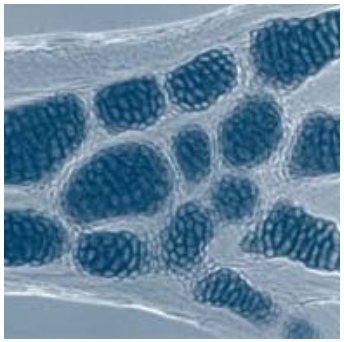
# Statistical vs. morphological systems

- Physical pattern formation is “free” –
  Biological (multicellular) pattern formation is “guided”

reaction-diffusion
with NetLogo



fruit fly embryo
Sean Caroll, U of Wisconsin



larval axolotl limb condensations
Gerd B. Müller

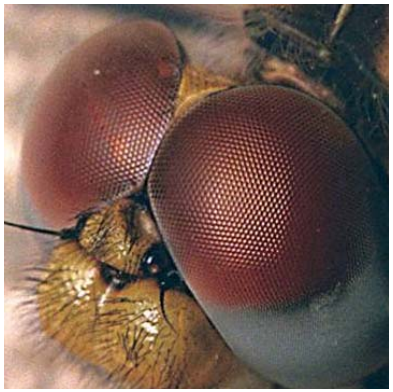
**Fig. 8.2.**

# Statistical vs. morphological systems

- Multicellular forms = a bit of "free" + a lot of "guided"
  - ✓ domains of free patterning embedded in a guided morphology

unlike Drosophila's stripes, these pattern primitives are *not* regulated by different sets of genes depending on their position

spots, stripes in skin
angelfish, www.sheddaquarium.org



ommatidia in compound eye
dragonfly, www.phy.duke.edu/~hsg/54

  - ✓ repeated copies of a guided form, distributed in free patterns

entire structures (flowers, segments) can become modules showing up in random positions and/or numbers

flowers in tree
cherry tree, www.phy.duke.edu/~fortney

segments in insect
centipede, images.encarta.msn.com

# The self-made puzzle of embryogenesis

1. Self-organized and structured systems

2. A two-side challenge: heterogeneous motion / moving patterns

3. A multi-agent model of embryogenesis

4. Evolutionary development (evo-devo)

# Embryogenesis couples assembly and patterning

## ➢ Sculpture → forms

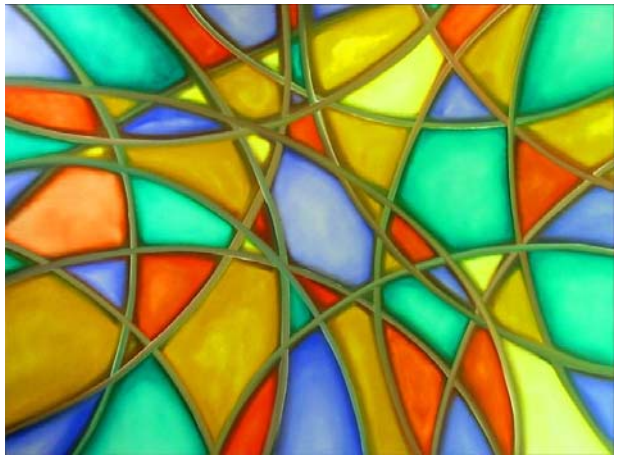
Ádám Szabó, *The chicken or the egg* (2005)
http://www.szaboadam.hu

## “shape from patterning”

✓ the forms are “sculpted” by the self-assembly of the elements, whose behavior is triggered by the colors

Niki de Saint Phalle

## ➢ Painting → colors

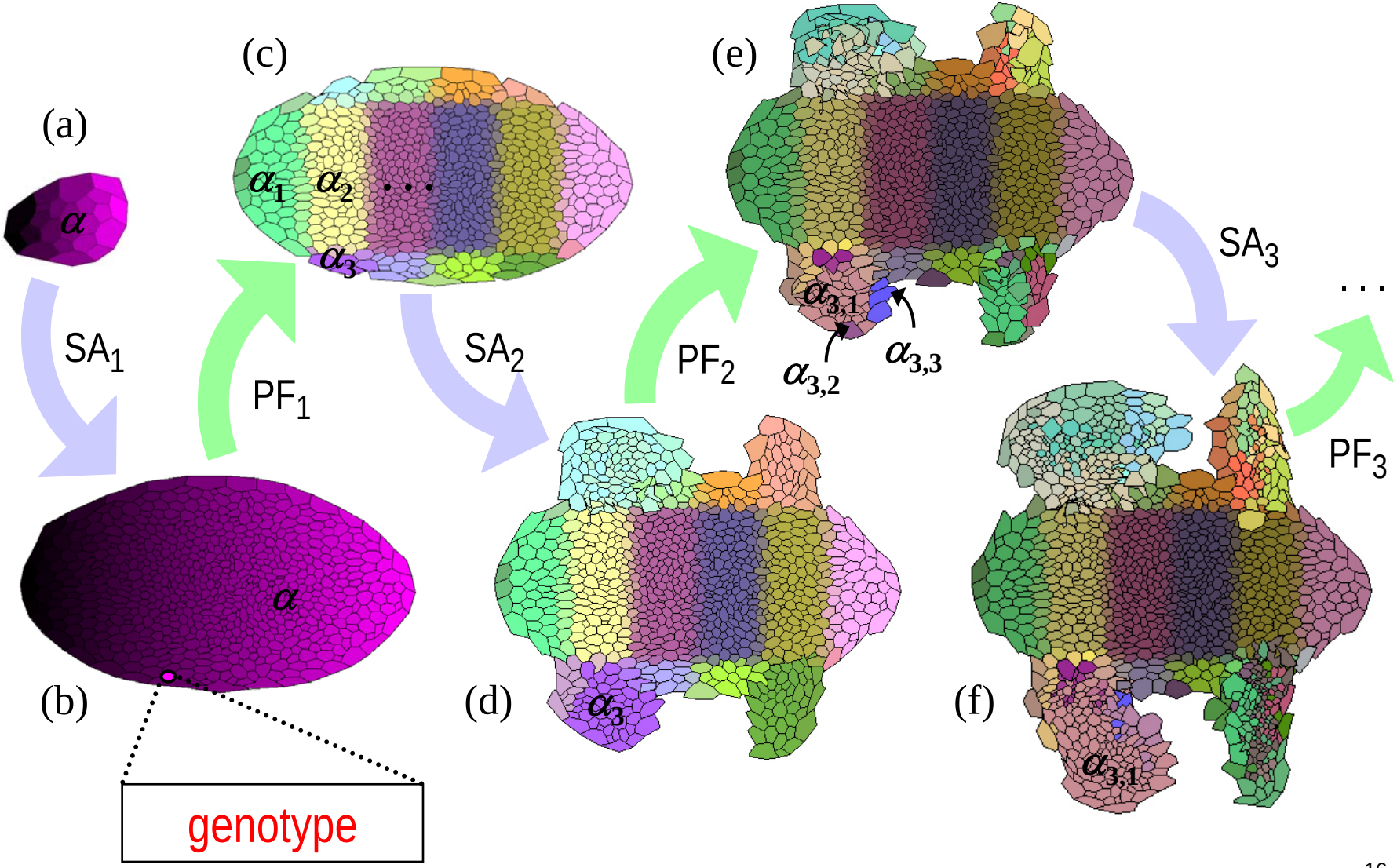


## “patterns from shaping”

✓ new color regions appear (domains of genetic expression) triggered by deformations

# Embryogenesis couples assembly and patterning

SA = self-assembly (“sculpture”)
PF = pattern formation (“painting”)

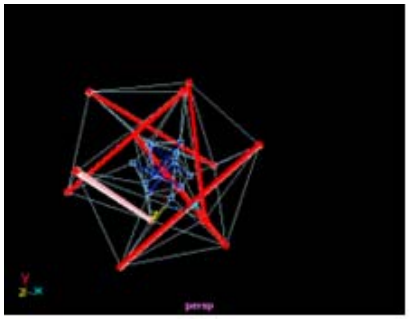


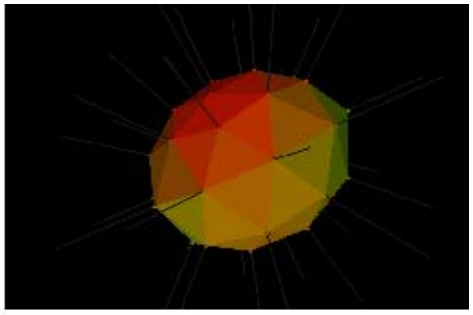
# Embryogenesis couples mechanics and regulation

## Cellular mechanics

- ✓ adhesion
- ✓ deformation / reformation
- ✓ migration (motility)
- ✓ division / death

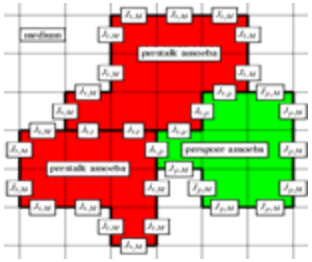
tensional integrity (Ingber)

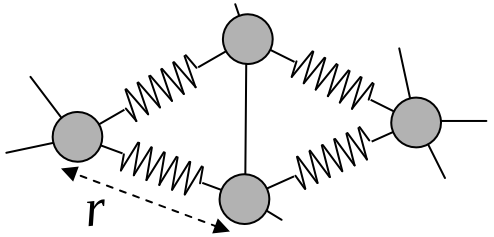




(Delile & Doursat)

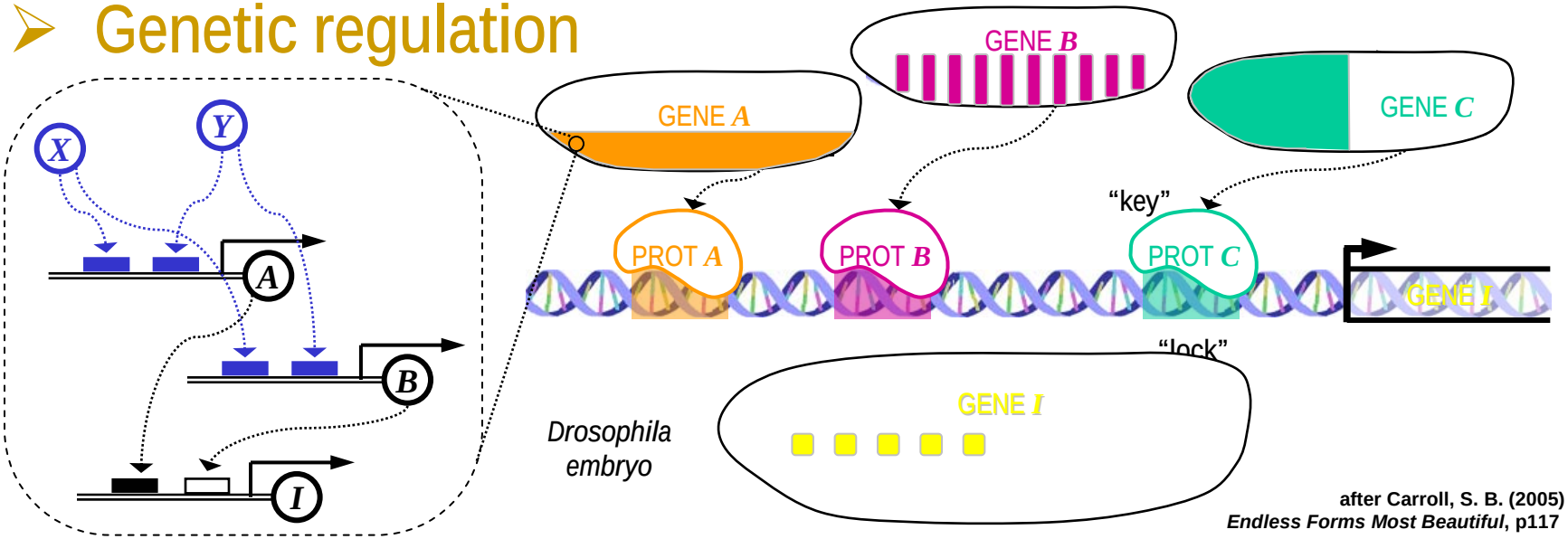
cellular Potts model (Graner, Glazier, Hogeweg)






(Doursat)

## Genetic regulation

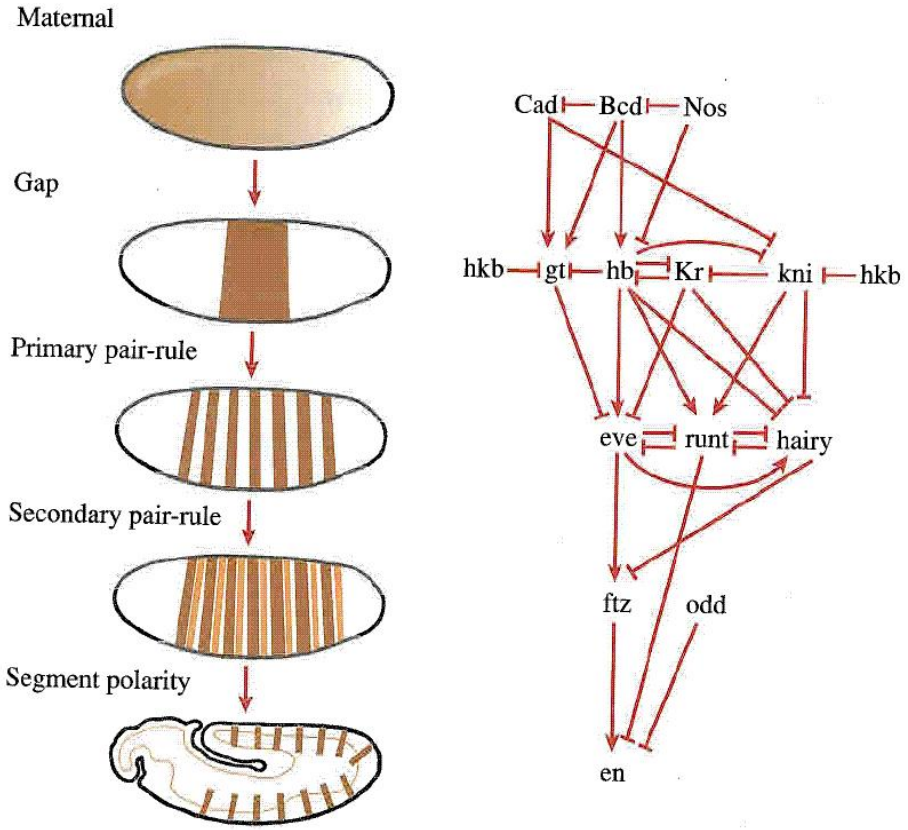



after Carroll, S. B. (2005) *Endless Forms Most Beautiful*, p117

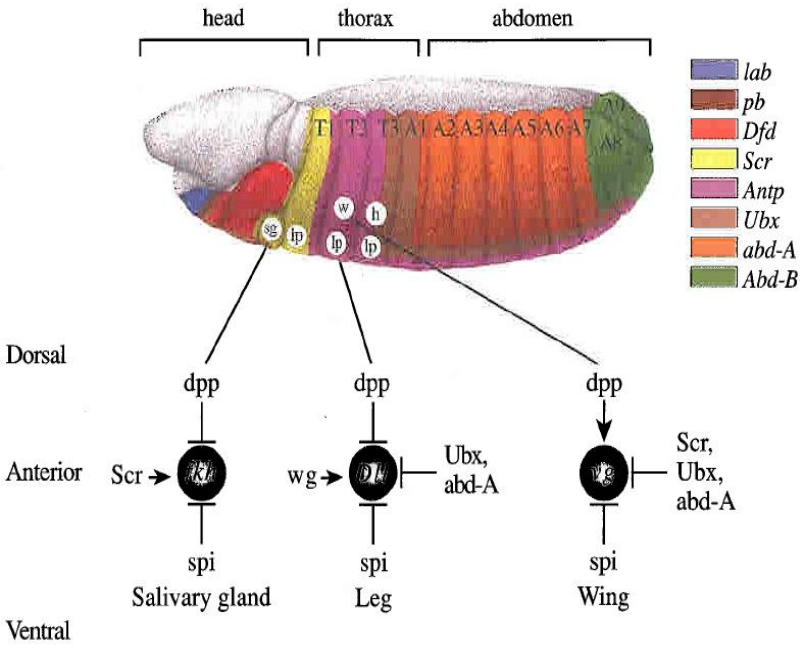
# Gene regulatory pattern formation

## ➢ Segmentation & identity domains in *Drosophila*

- ✓ periodic A/P band patterns are controlled by a 5-tier gene regulatory hierarchy



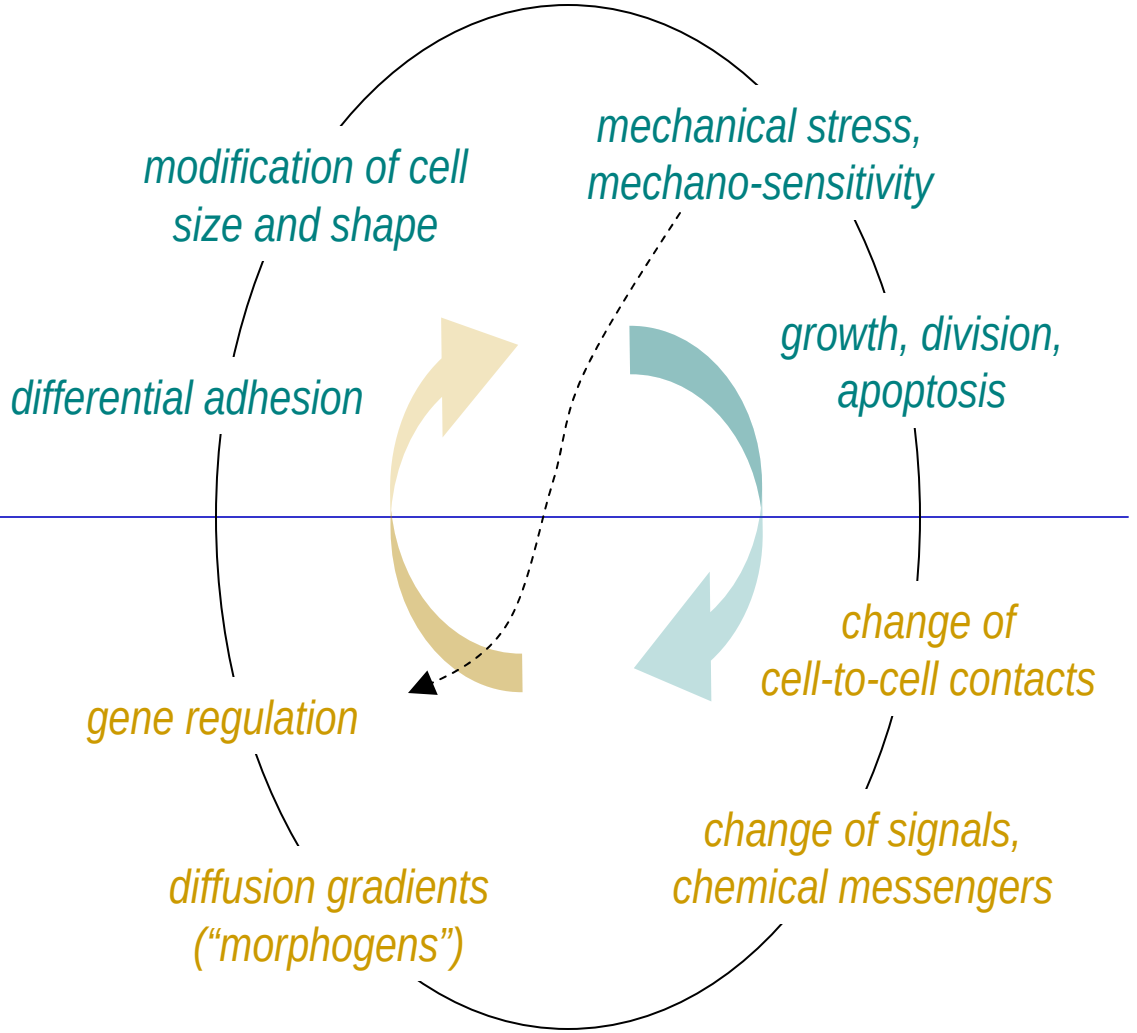

- ✓ intersection with other axes creates organ primordia and imaginal discs (identity domains of future legs, wings, antennae, etc.)




**from Carroll, S. B., et al. (2001)**
***From DNA to Diversity*, p63**

# Embryogenesis couples mechanics and regulation

- Cellular mechanics



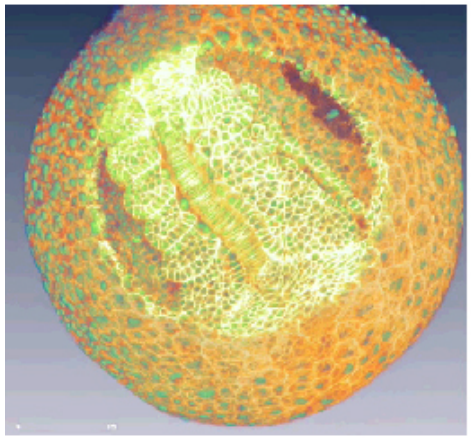

- Genetic regulation

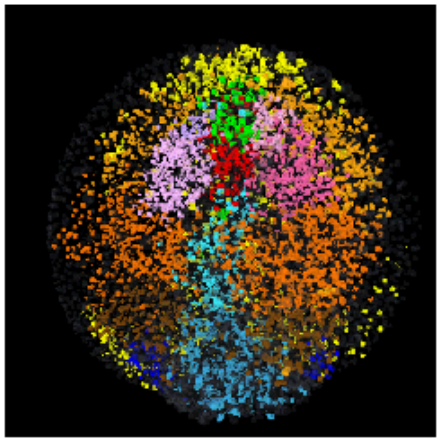
# Embryogenesis couples motion and patterns

## Collective motion regionalized into patterns

**Nadine Peyriéras, Paul Bourgine,** Thierry Savy, Benoît Lombardot, Emmanuel Faure et al.

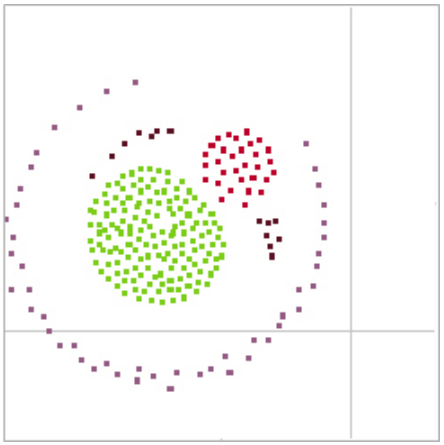
**Embryomics & BioEmergences**



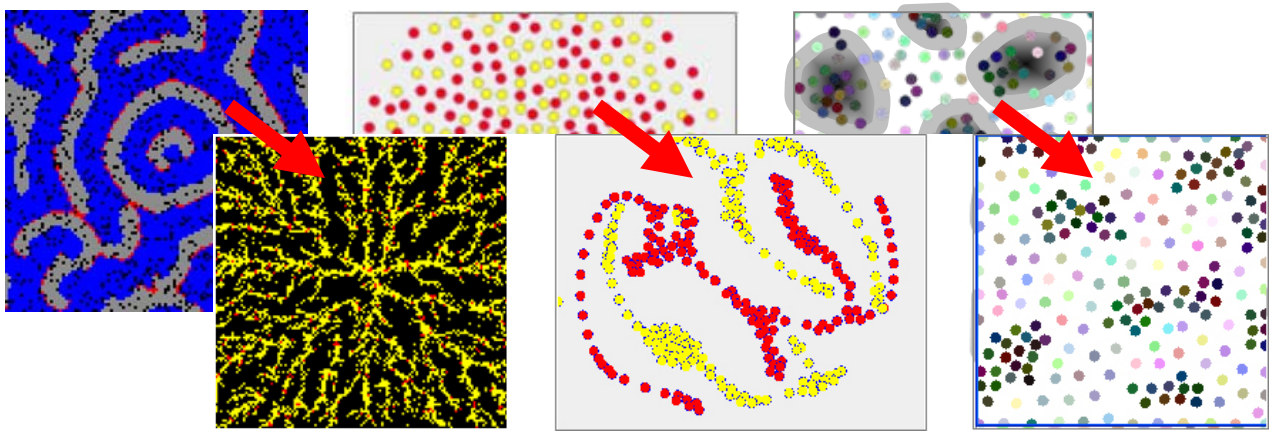


zebrafish

**Hiroki Sayama** (Swarm Chemistry) http://bingweb.binghamton.edu/~sayama/SwarmChemistry/

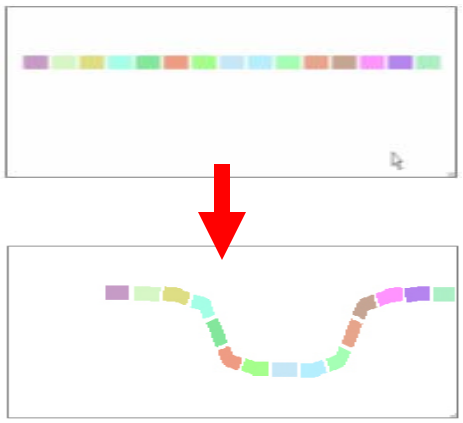


## Pattern formation that triggers motion



http://zool33.uni-graz.at/schmickl

Doursat



# The self-made puzzle of embryogenesis

1. Self-organized and structured systems
2. A two-side challenge: heterogeneous motion / moving patterns
3. **A multi-agent model of embryogenesis**
4. Evolutionary development (evo-devo)

# Why multi-agent modeling?

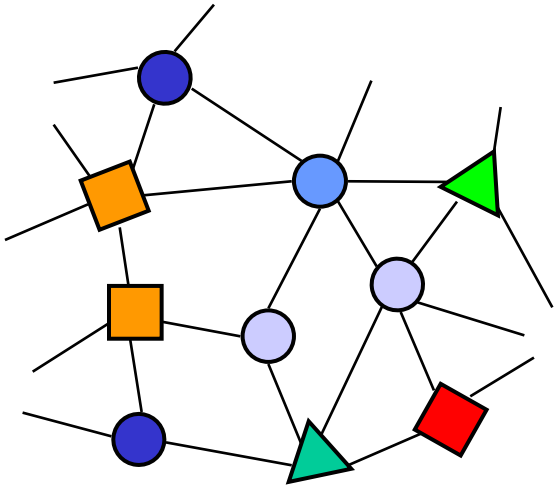
- Equations and laws can be hard or impossible to find...
  - ✓ *"The study of non-linear physics is like the study of non-elephant biology."* —Stanislaw Ulam
    - the physical world is a fundamentally *non-linear* and *out-of-equilibrium* process
    - focusing on linear approximations and stable points is missing the big picture in most cases
  - ✓ let's push this quip: *"The study of non-analytical complex systems is like the study of non-elephant biology."* —??
    - complex systems have their own "elephant" species, too: dynamical systems that can be described by diff. eqs or statistical laws
    - many real-world complex systems do not obey neat macroscopic laws

# Why multi-agent modeling?

➢ Equations and laws can be hard or impossible to find in...

morphogenesis

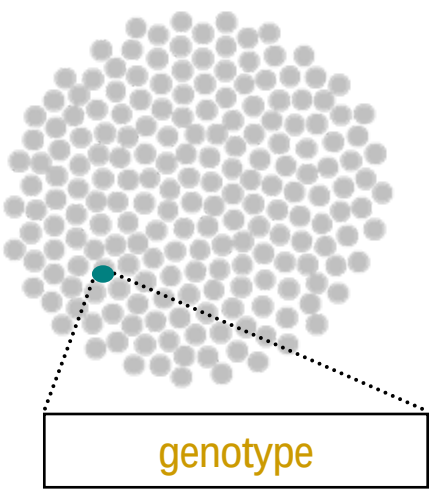
- ✓ systems that *no macroscopic quantity* suffices to explain ~~(ODE)~~
  - no law of “concentration”, “pressure”, or “gross domestic product”
  - even if global metrics can be designed to give an indication about the system’s dynamical regimes, they rarely obey a given equation or law
- ✓ systems that require a *non-Cartesian* decomposition of space ~~(PDE)~~
  - network of irregularly placed or mobile *agents*
- ✓ systems that contain *heterogeneity*
  - segmentation into different *types of agents*
  - at a fine grain, this would require a “patchwork” of regional equations
- ✓ systems that are dynamically *adaptive*
  - the topology and strength of the interactions depend on the short-term activity of the agents and long-term “fitness” of the system in its environment



# Different approaches and families of models

## ➢ Biological, bio-inspired or artificial models

- ✓ focused on spatial differentiation patterns (little or no motion)
  - reaction-diffusion (PDEs, cellular automata)
  - gene networks (Boolean or concentrations) on a fixed lattice
  - "amorphous computing"
- ✓ focused on motion (little or no patterning)
  - Cellular Potts Model (on predefined cell types)
  - aggregation, self-assembly
  - collective motion, flocking, cellular sorting

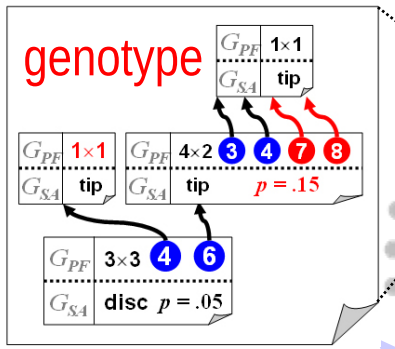


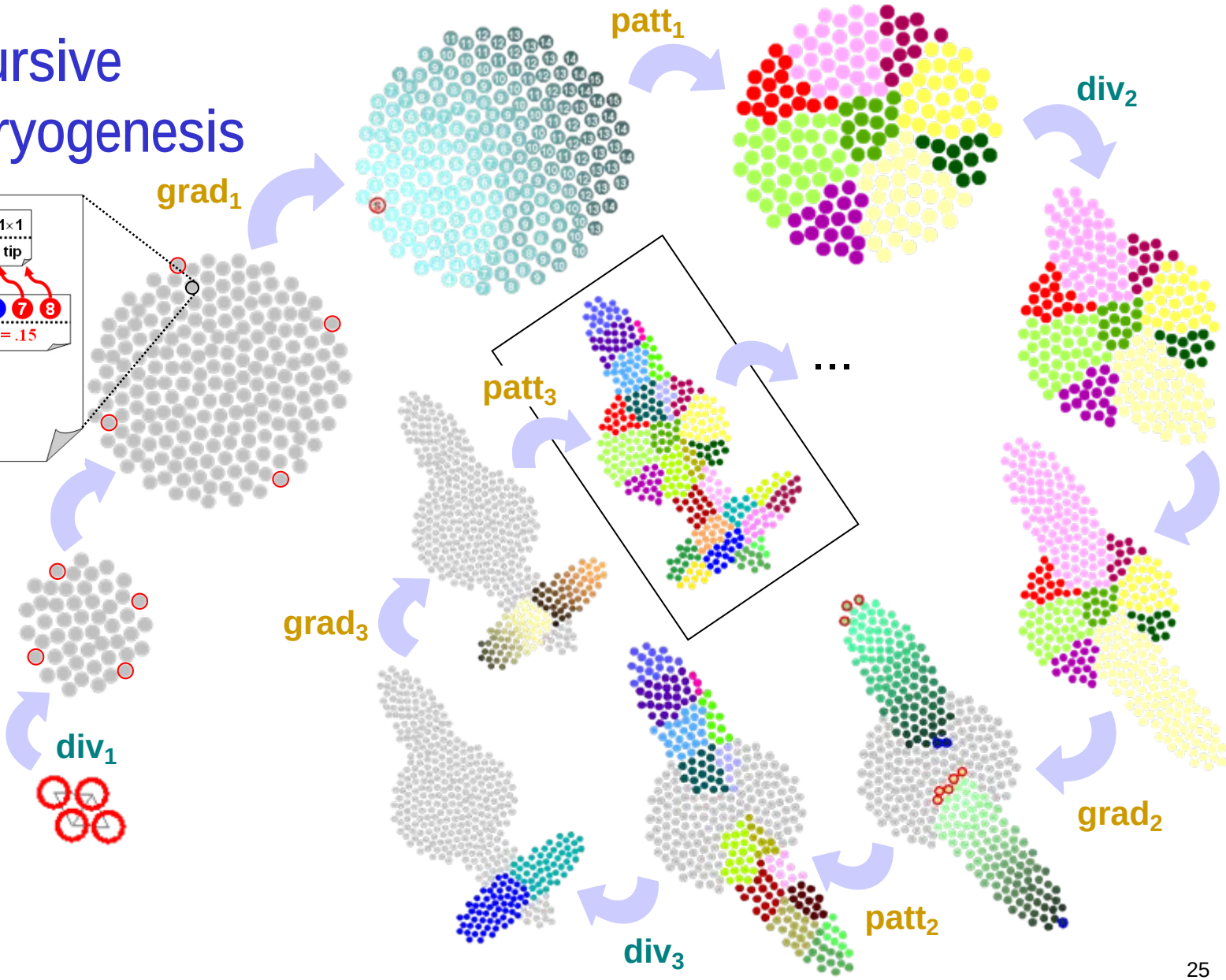

*a combination that is still rare ; but see Hogeweg / Salazar-Ciudad / Mjolsness..*

- ✓ at different scales
  - macroscopic models (densities, differential geometry) → no individual information
  - mesoscopic models (cellular centers, Potts) → no membrane geometry or nuclei
  - microscopic models (elastic polyedra, drop models) → cellular deformations

# Example of hybrid mesoscopic model

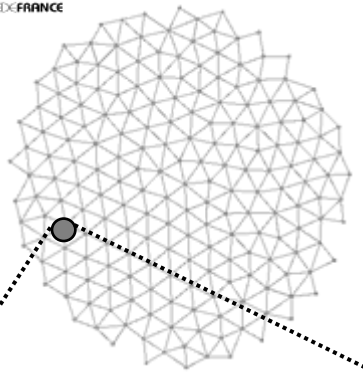
- Recursive embryogenesis



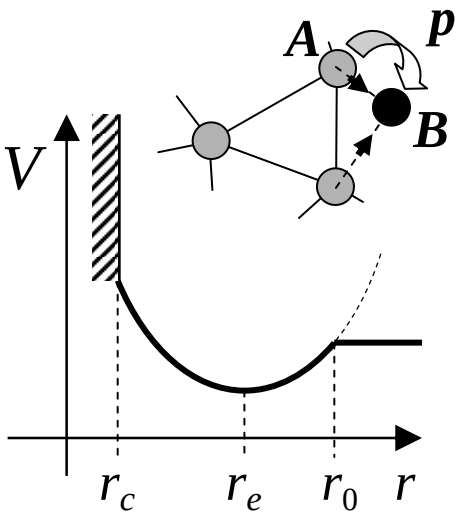



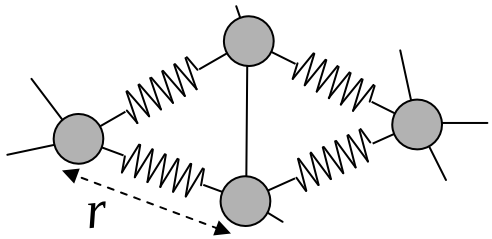

René Doursat, ALife XI (2008)

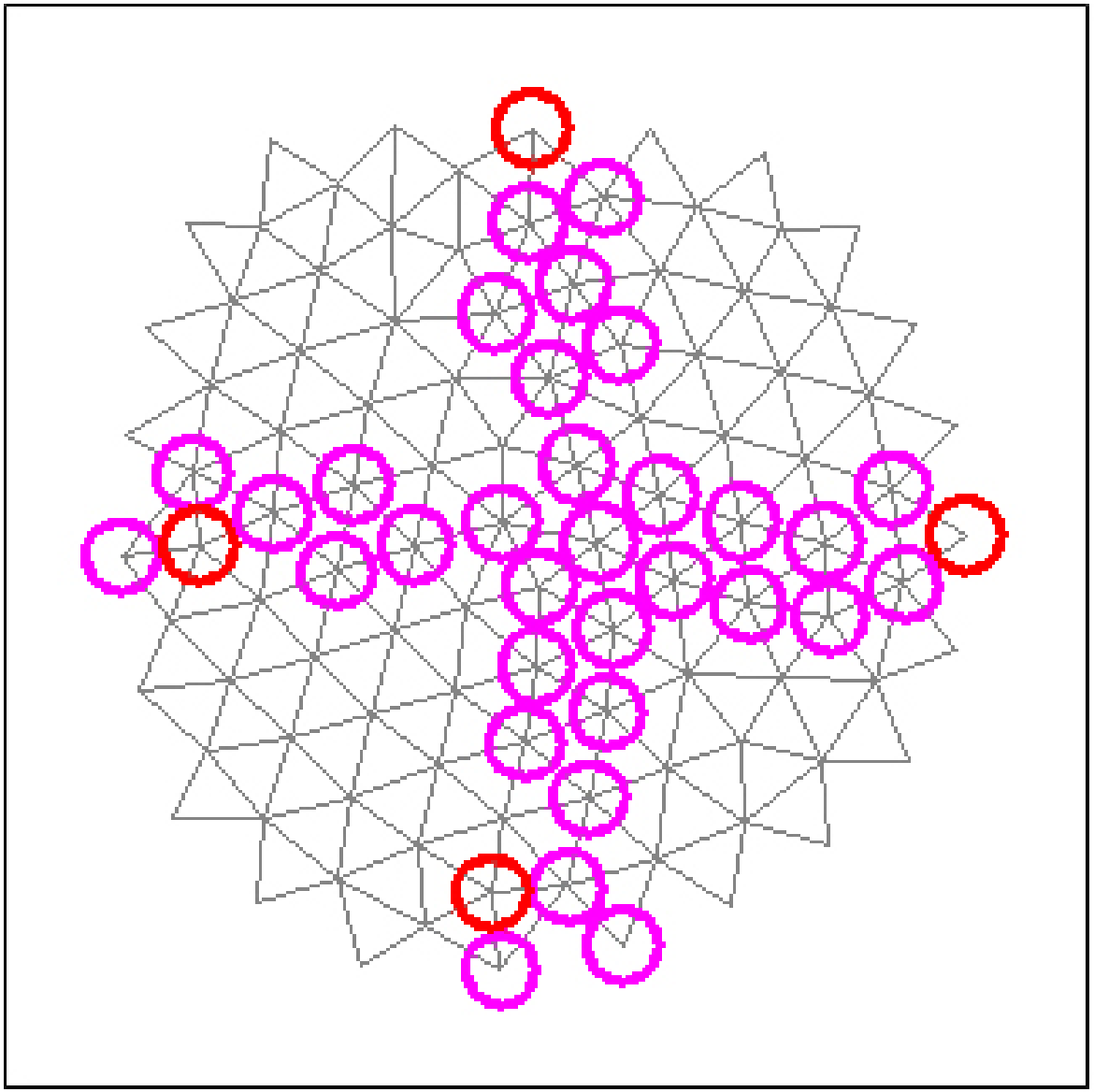
div

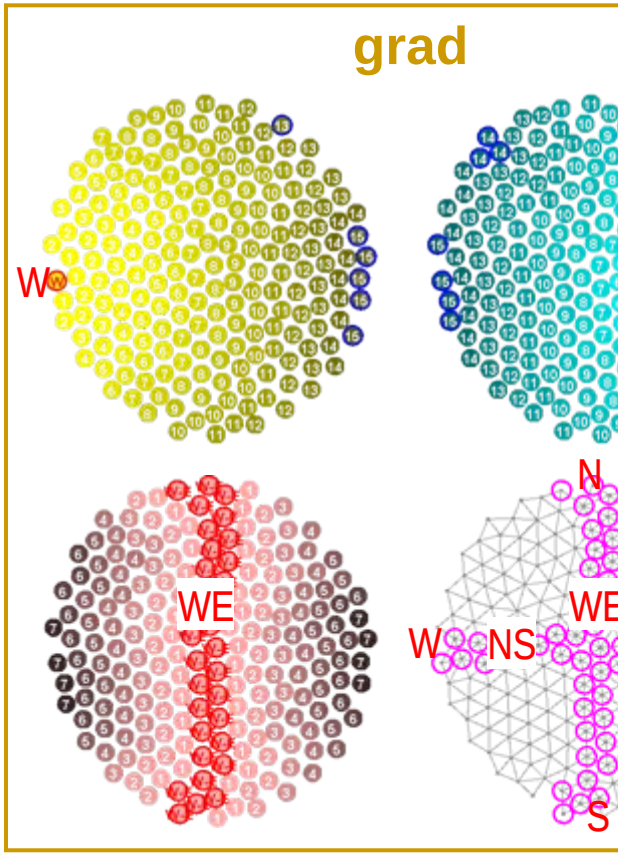


$G_{SA}$: $r_c < r_e = 1 << r_0$
$p = 0.05$

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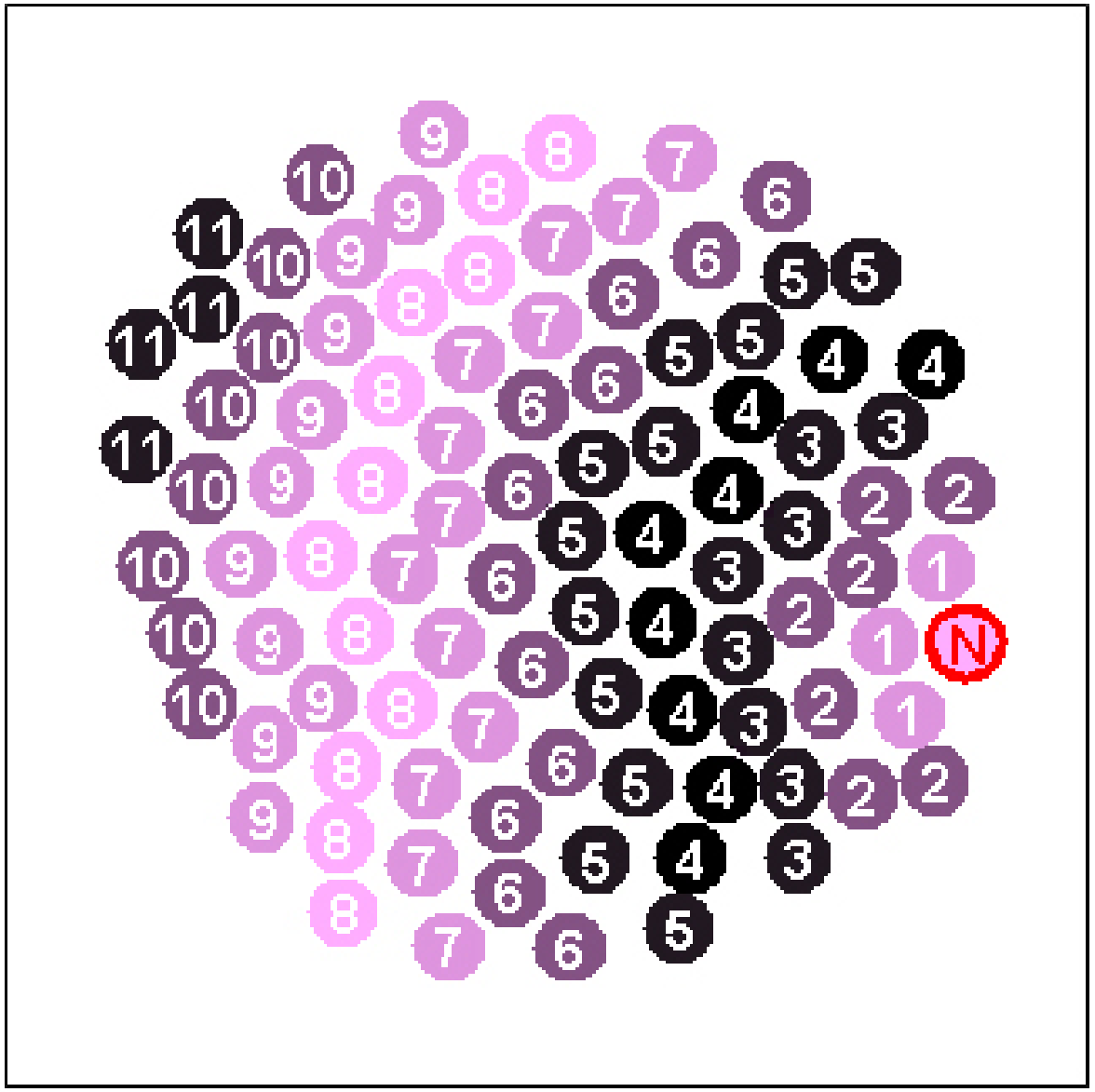
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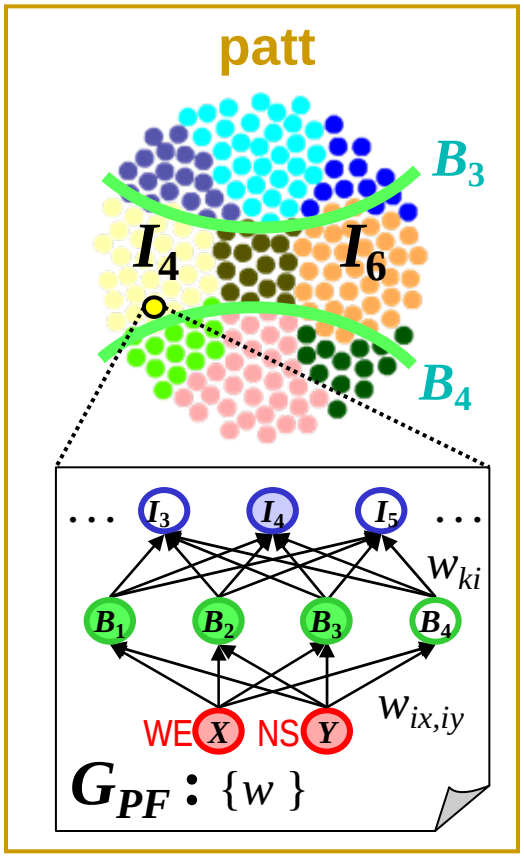
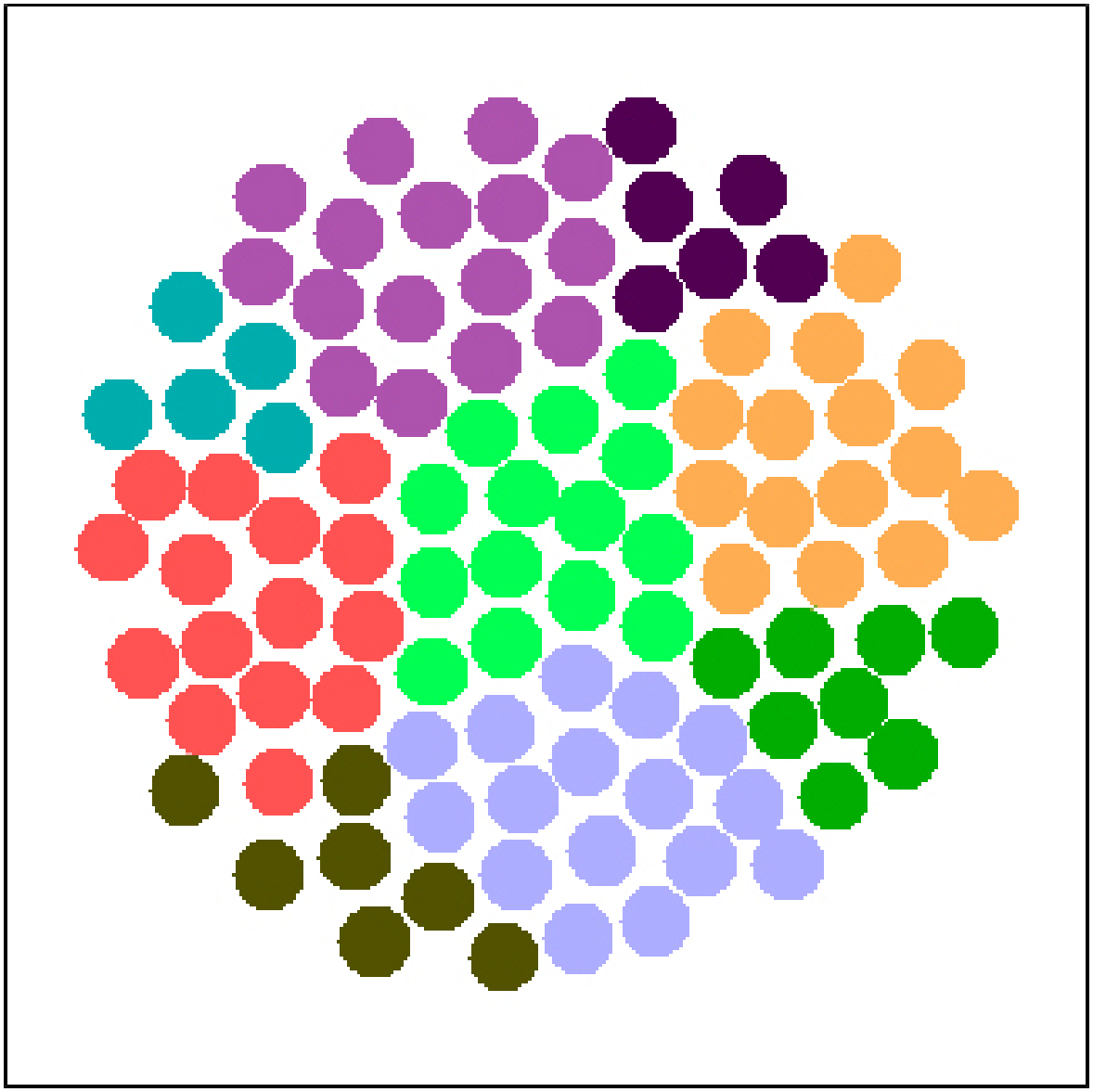
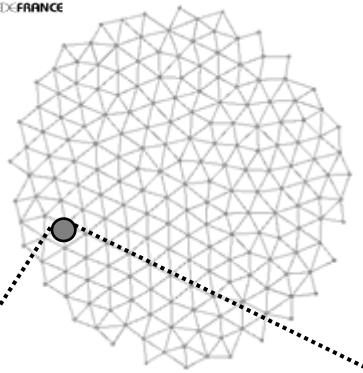
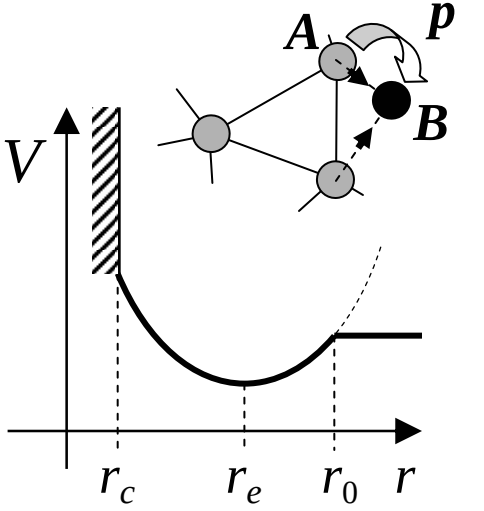

patt
$B_3$
$I_4$
$I_6$
$B_4$
$I_3$
$I_4$
$I_5$
$w_{ki}$
$B_1$
$B_2$
$B_3$
$B_4$
$w_{ix,iy}$
WE
X
NS
Y
$G_{PF}$ : {w }

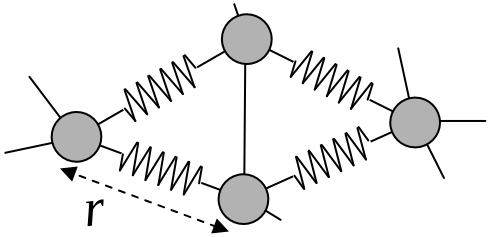


## div



$G_{SA}$ : $r_c < r_e = 1 << r_0$
$p = 0.05$

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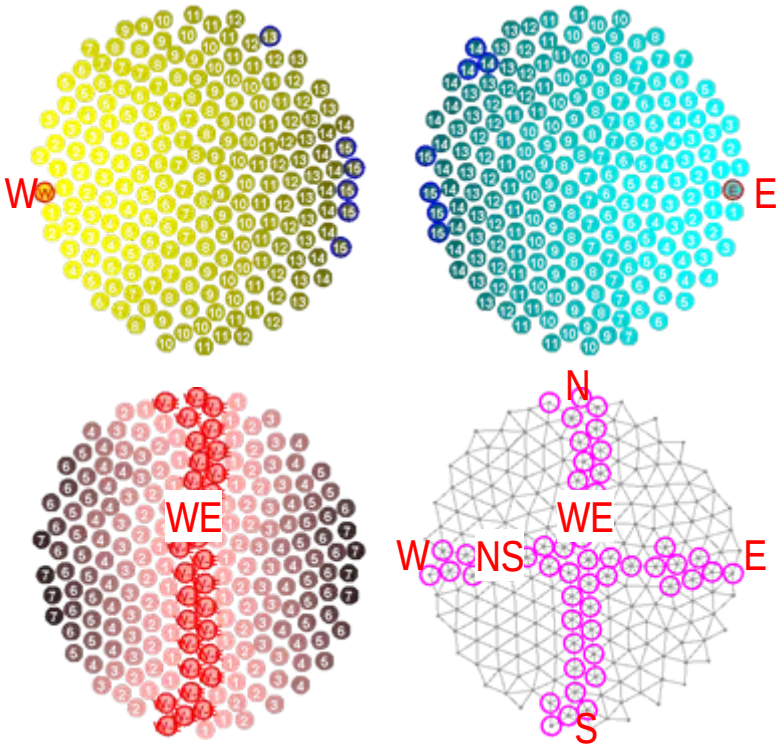
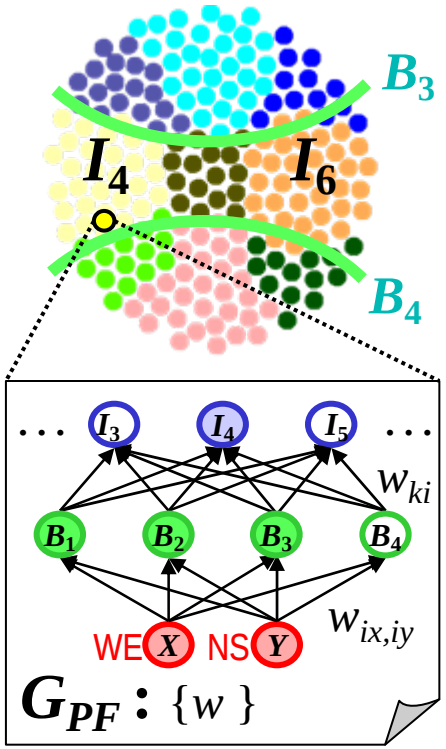
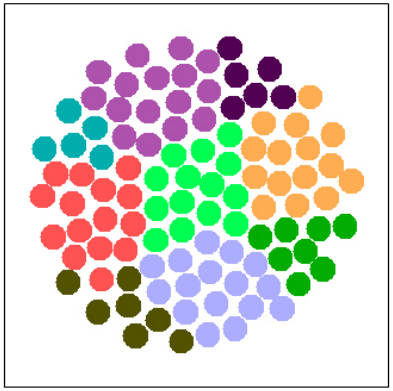
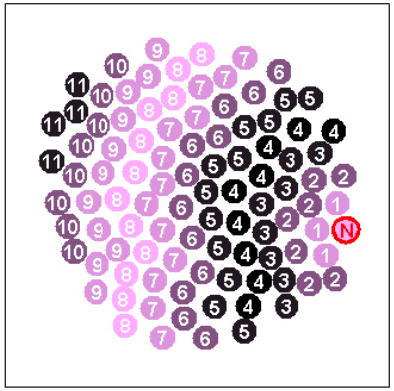
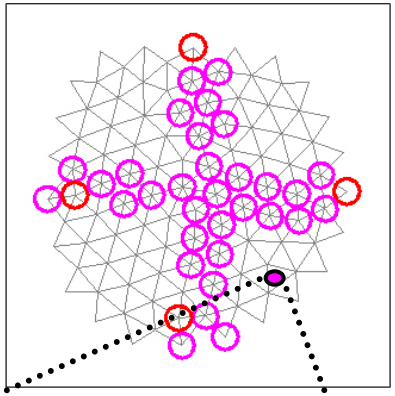



## patt



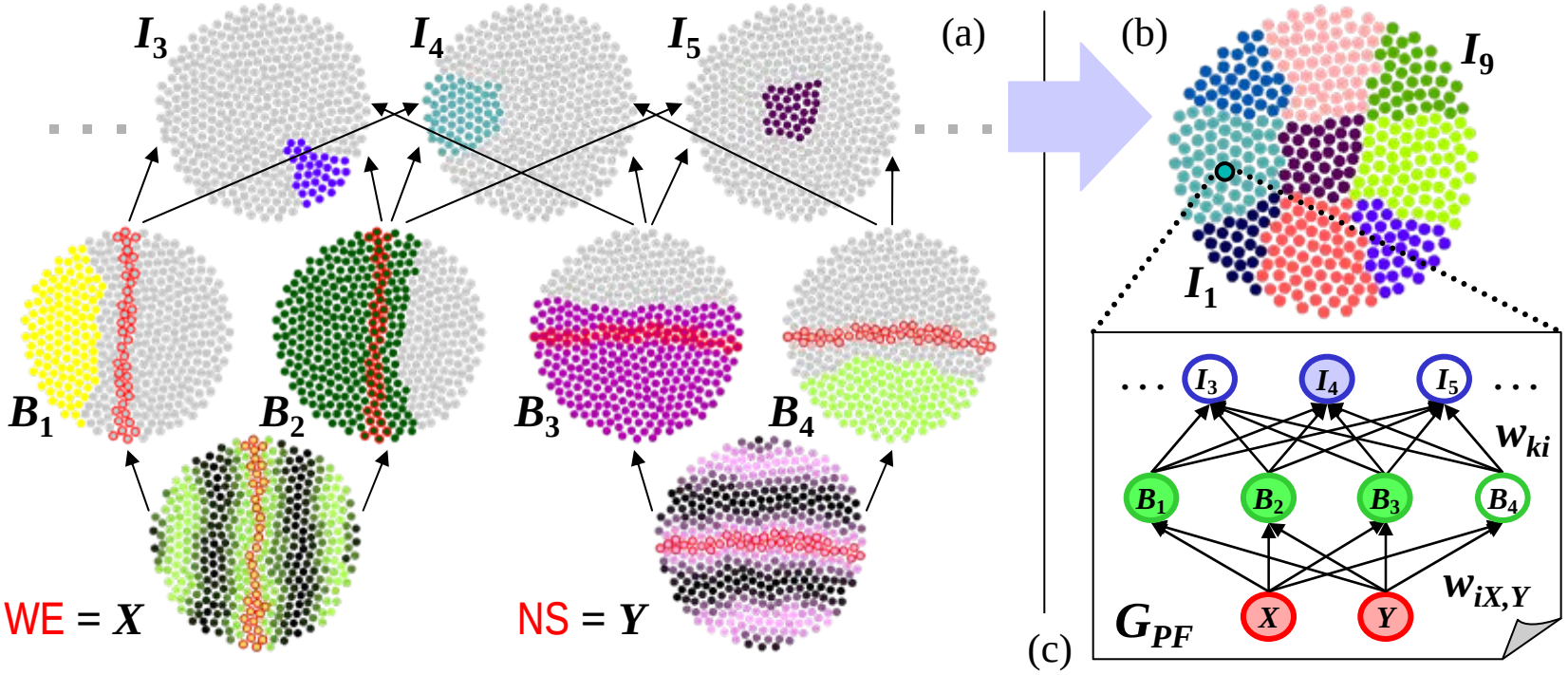




$G_{SA} \cup G_{PF}$

# Virtual gene atlas

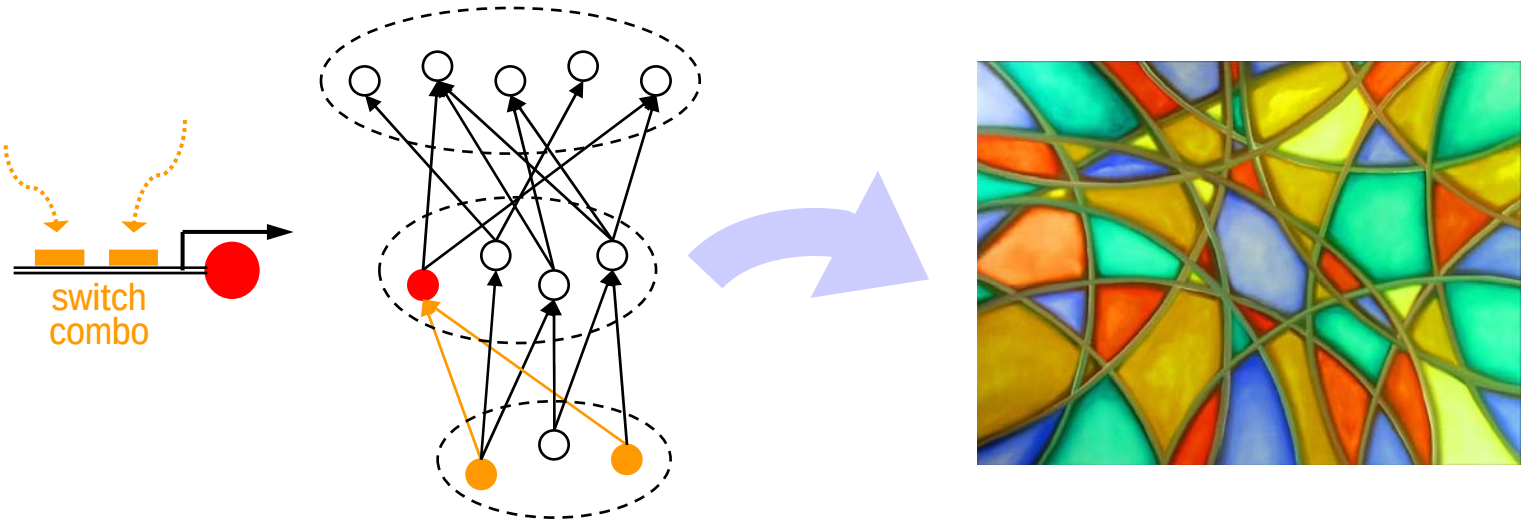
- **Programmed patterning (patt): the hidden embryo map**
  a) same swarm in different colormaps to visualize the agents' internal patterning variables $X$, $Y$, $B_i$ and $I_k$ (virtual *in situ hybridization)*
  b) consolidated view of all identity regions $I_k$ for $k = 1...9$
  c) gene regulatory network used by each agent to calculate its expression levels, here: $B_1 = \sigma(1/3 - X)$, $B_3 = \sigma(2/3 - Y)$, $I_4 = B_1 B_3(1 - B_4)$, etc.



# From feedforward to recurrent gene regulation

## ➢ Summary: simple feedforward hypothesis

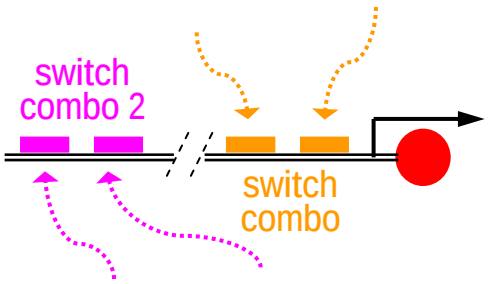
- ✓ developmental genes are broadly organized in tiers, or “generations”: earlier genes map the way for later genes
- ✓ gene expression propagates in a directed fashion: first, positional morphogens create domains, then domains intersect

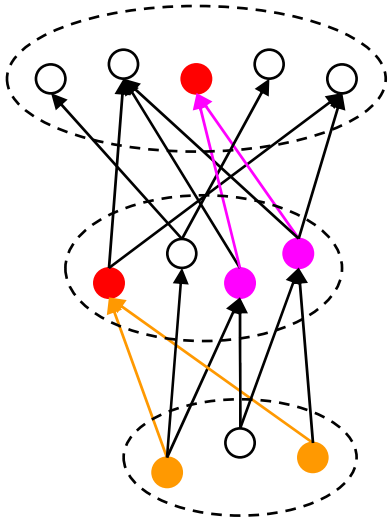


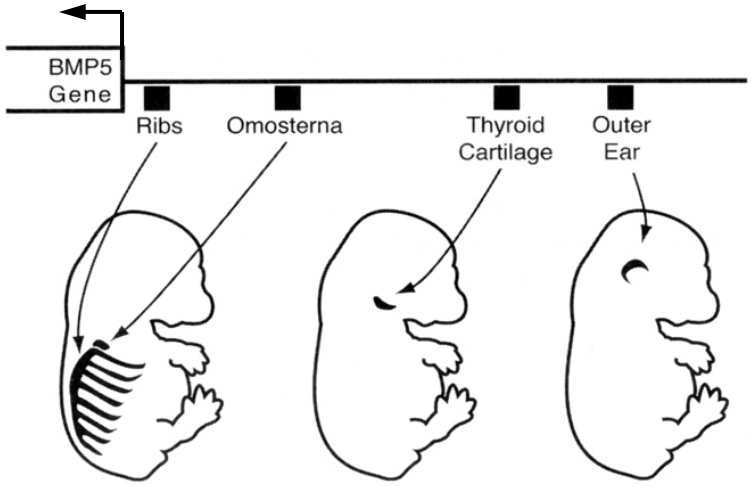
# From feedforward to recurrent gene regulation

## ➢ Toolkit genes are often multivalent

- ✓ exception to the feedforward paradigm: “toolkit” genes that are reused at different stages and different places in the organism
- ✓ however, a toolkit gene is triggered by different switch combos, which can be represented by duplicate nodes in different tiers



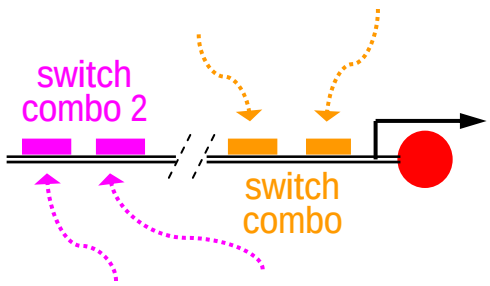


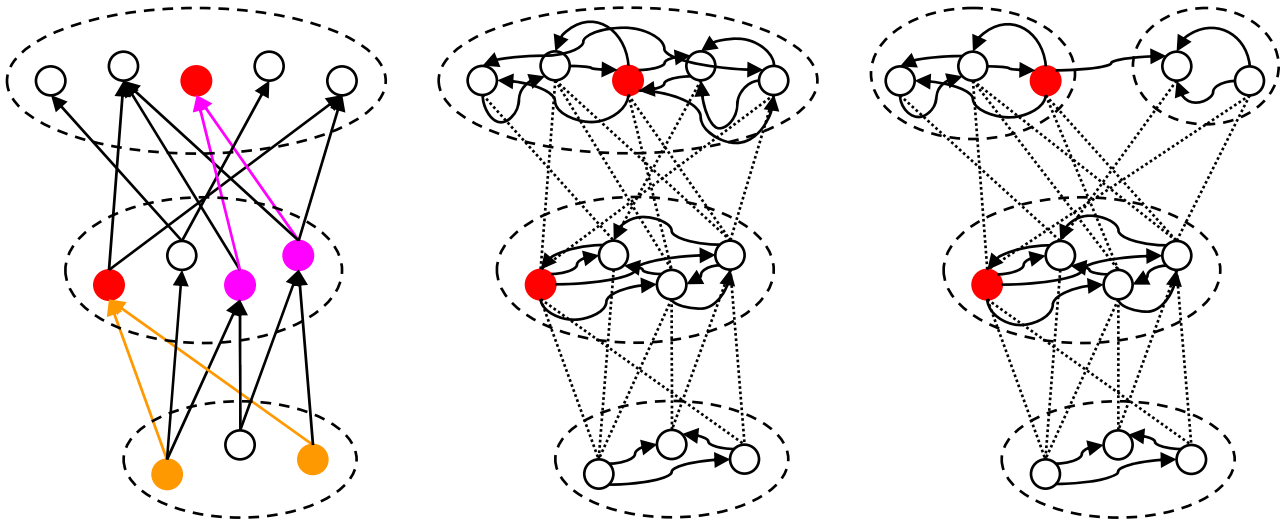

**after David Kingsley, in Carroll, S. B. (2005)**
***Endless Forms Most Beautiful*, p125**

# From feedforward to recurrent gene regulation

## More realistic variants of GRNs

- ✓ add recurrent links within tiers → domains are not established independently but influence and sharpen each other
- ✓ subdivide tiers into subnetworks → this creates **modules** that can be reused and starts a hierarchical architecture



# Multiscale embryogenesis

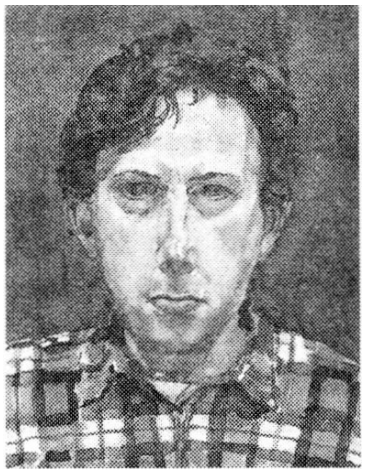
## ➢ Morphological refinement by iterative growth

- ✓ details are not created in one shot, but gradually added. . .



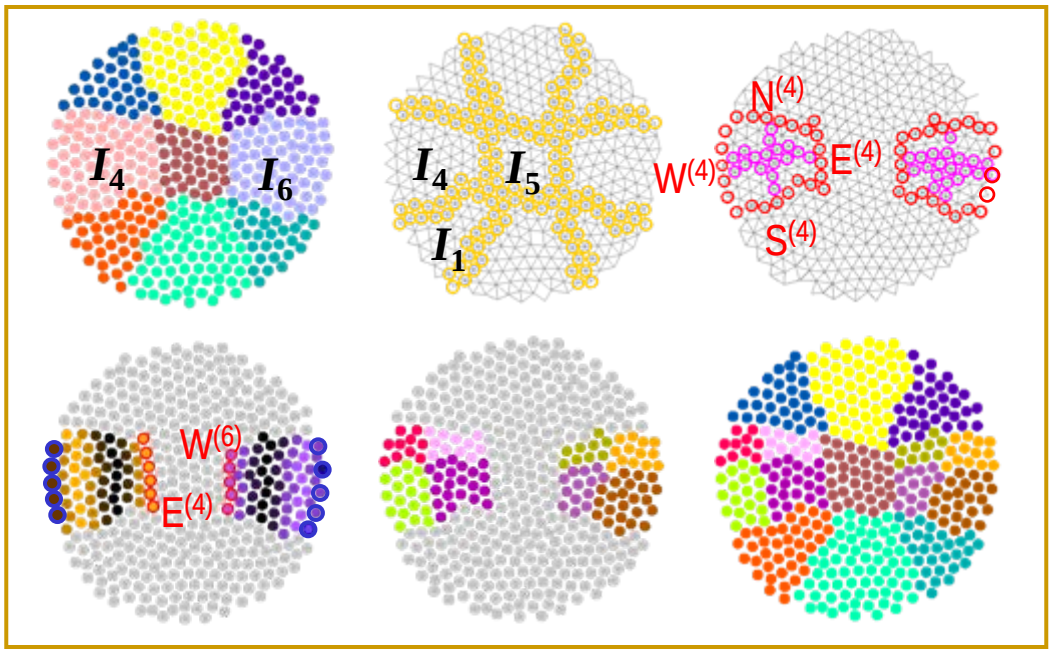
- ✓ . . . while, at the same time, the canvas grows



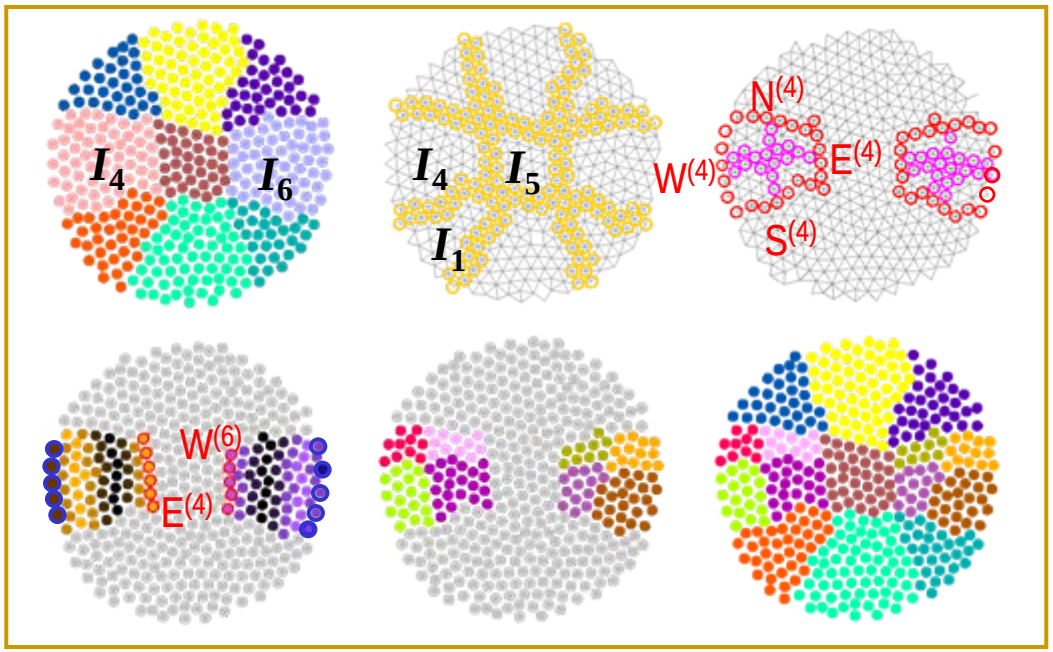


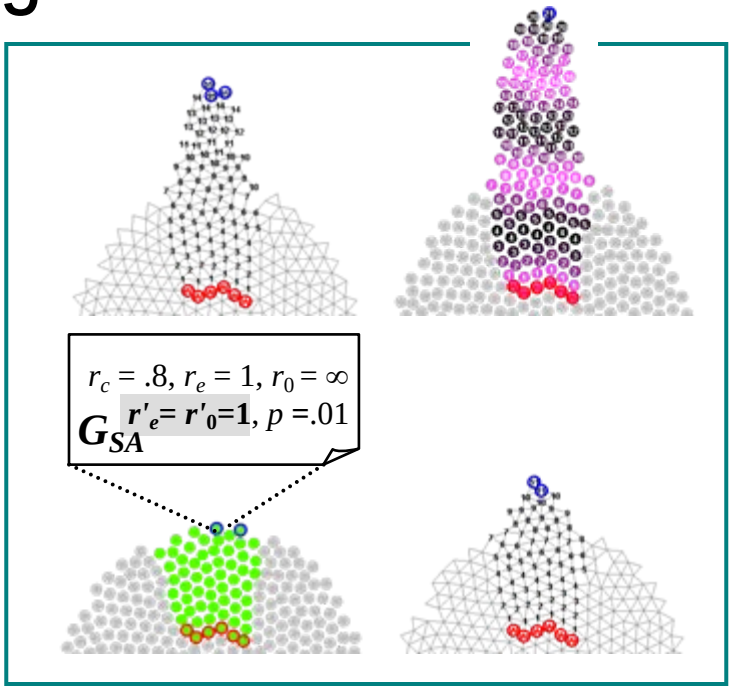
from Coen, E. (2000)
*The Art of Genes*, pp131-135

# Multiscale embryogenesis

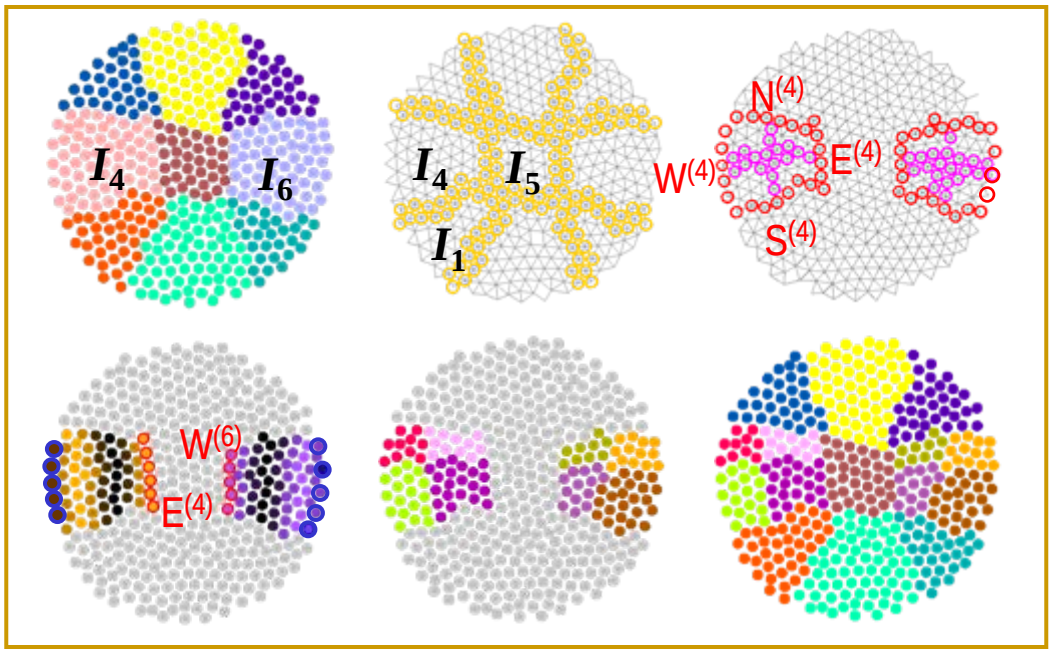


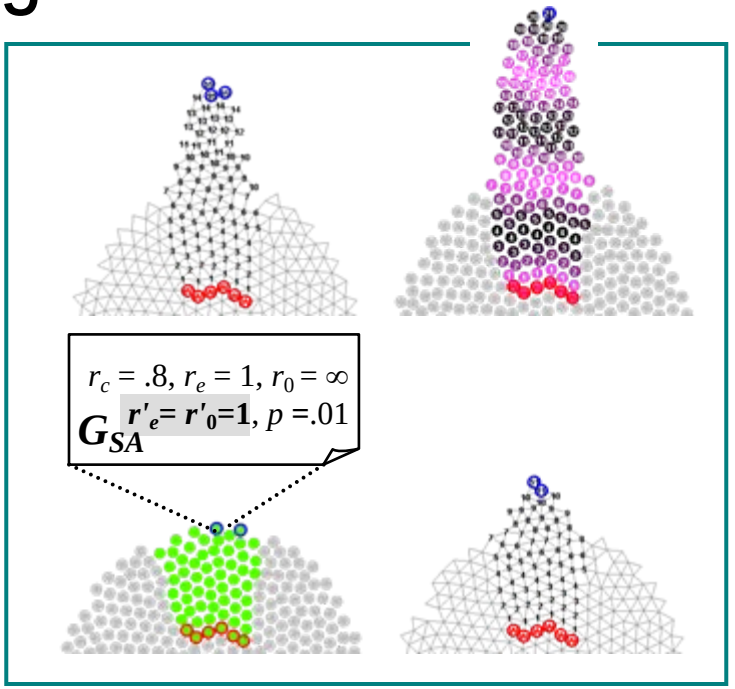
# Multiscale embryogenesis

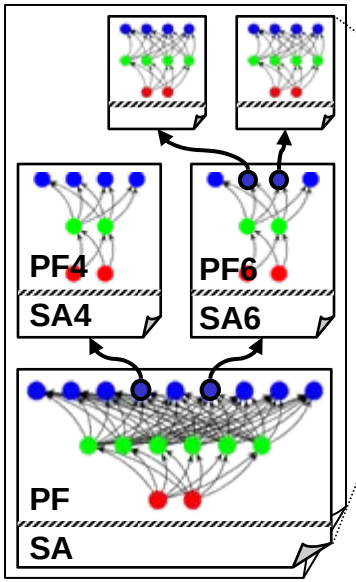


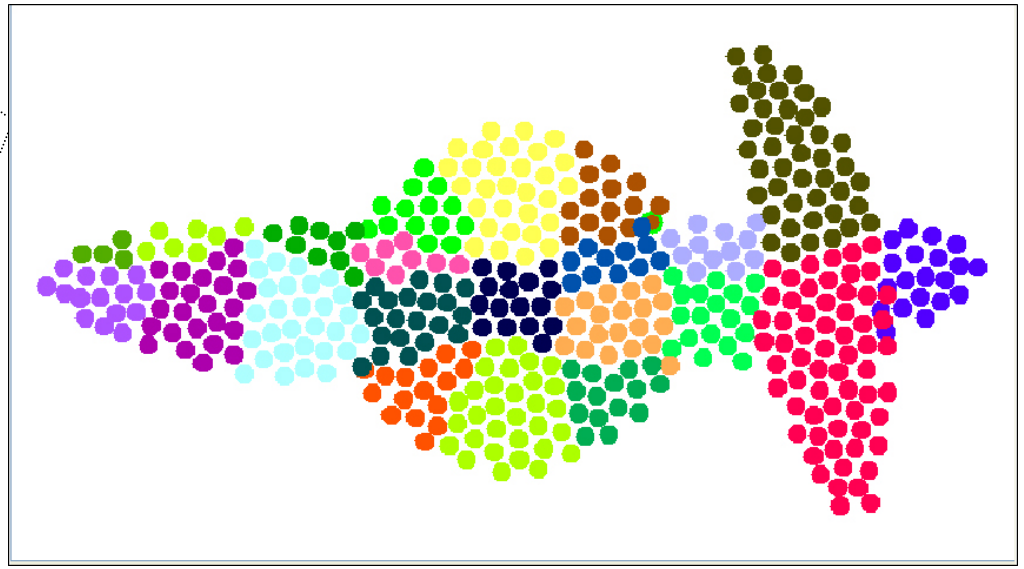



# Multiscale embryogenesis

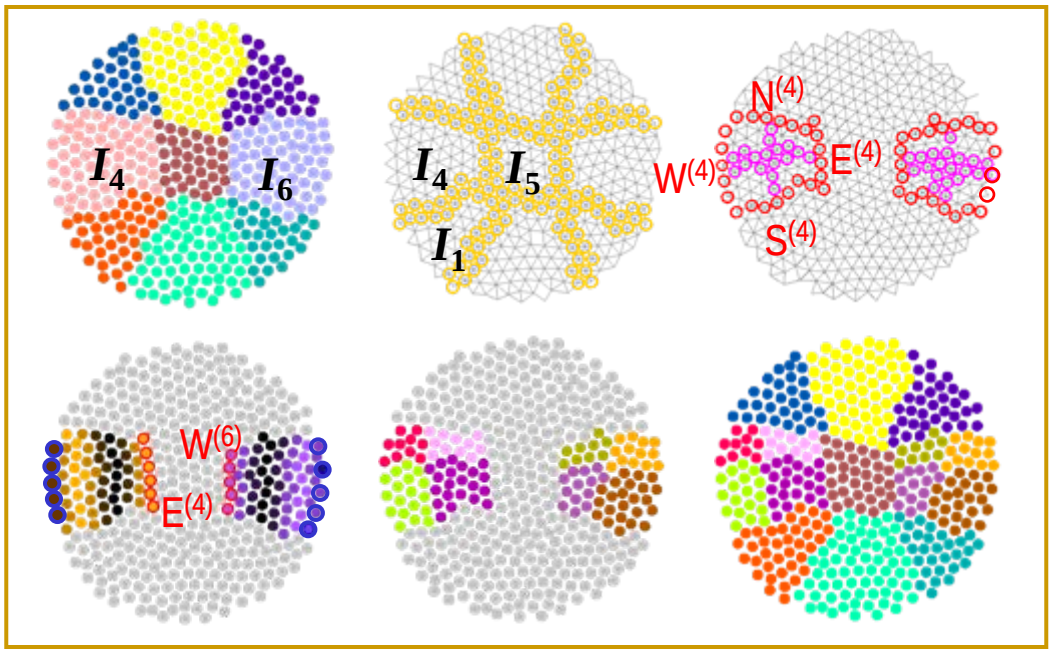


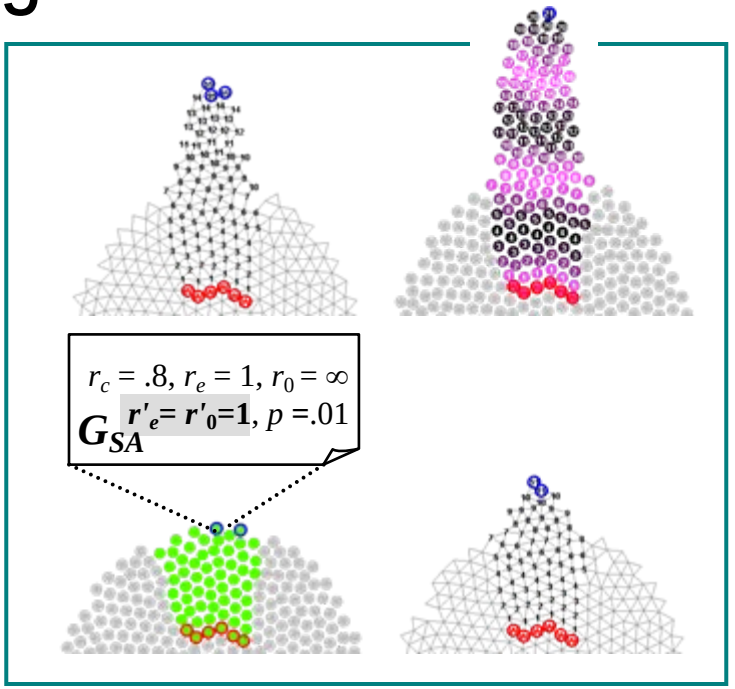



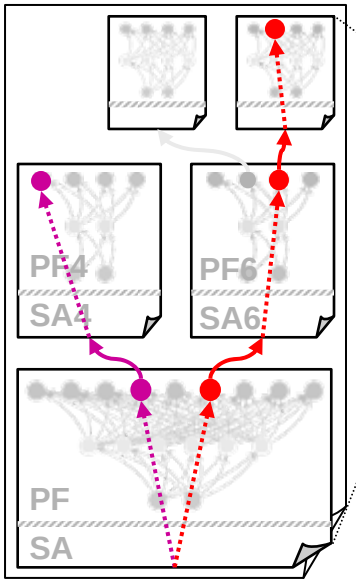



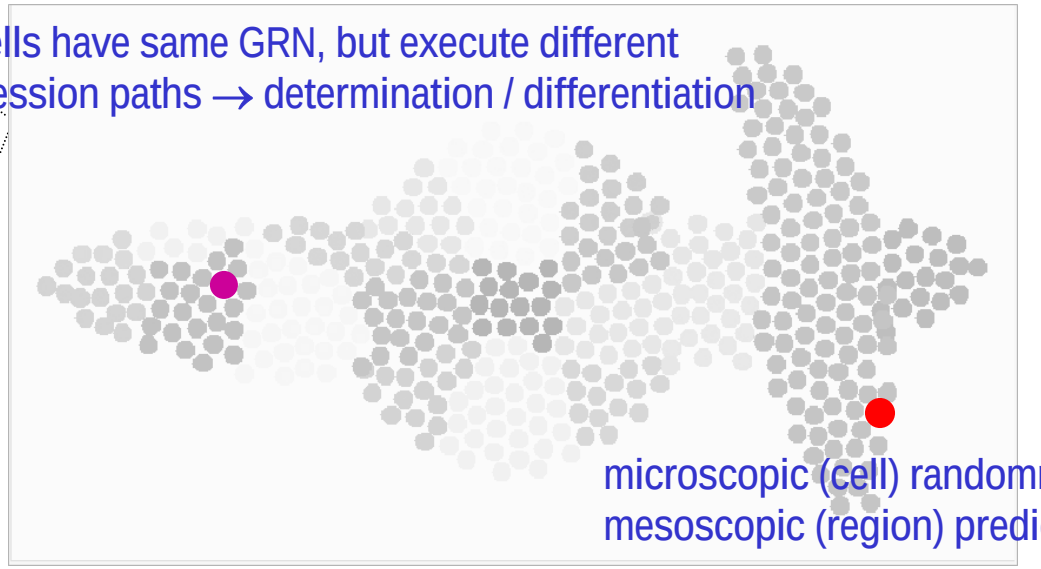
# Multiscale embryogenesis




all cells have same GRN, but execute different expression paths → determination / differentiation



microscopic (cell) randomness, but mesoscopic (region) predictability

# The self-made puzzle of embryogenesis

1. Self-organized and structured systems
2. A two-side challenge: heterogeneous motion / moving patterns
3. A multi-agent model of embryogenesis
4. Evolutionary development (evo-devo)

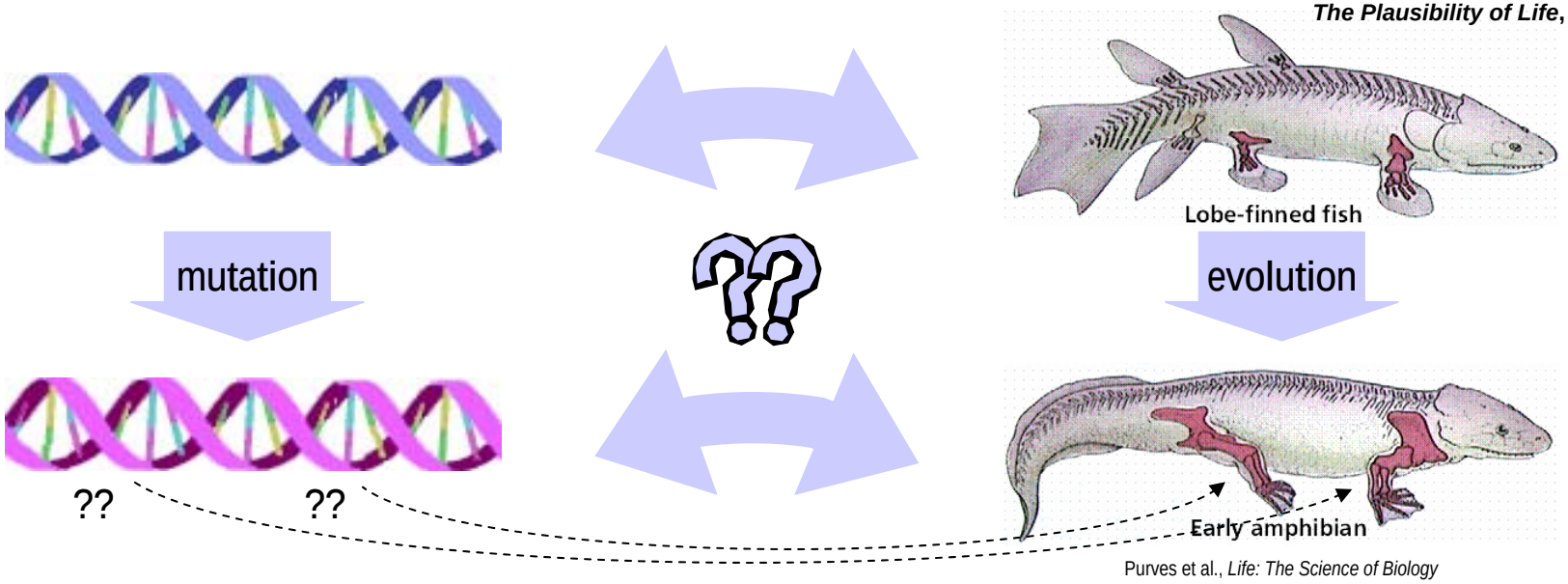
# Evolutionary innovation by development

## ➢ Development: the missing link of the Modern Synthesis

*"When Charles Darwin proposed his theory of evolution by variation and selection, explaining selection was his great achievement. He could not explain variation. That was Darwin's dilemma."*

*"To understand novelty in evolution, we need to understand organisms down to their individual building blocks, down to their deepest components, for these are what undergo change."*

**—Marc W. Kirschner and John C. Gerhart (2005)**
***The Plausibility of Life*, p. ix**



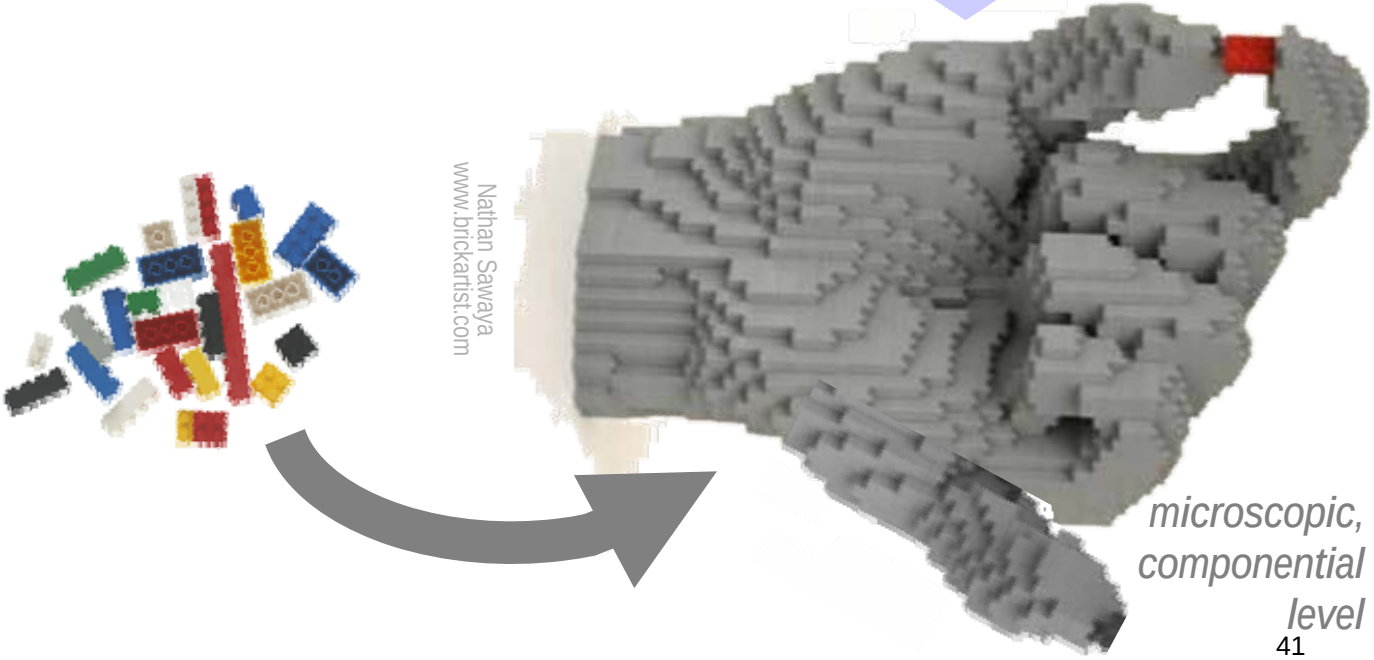

Purves et al., *Life: The Science of Biology*

# The self-made puzzle of “evo-devo” engineering

## ➢ Development: the missing link of the Modern Synthesis


*macroscopic, emergent level*

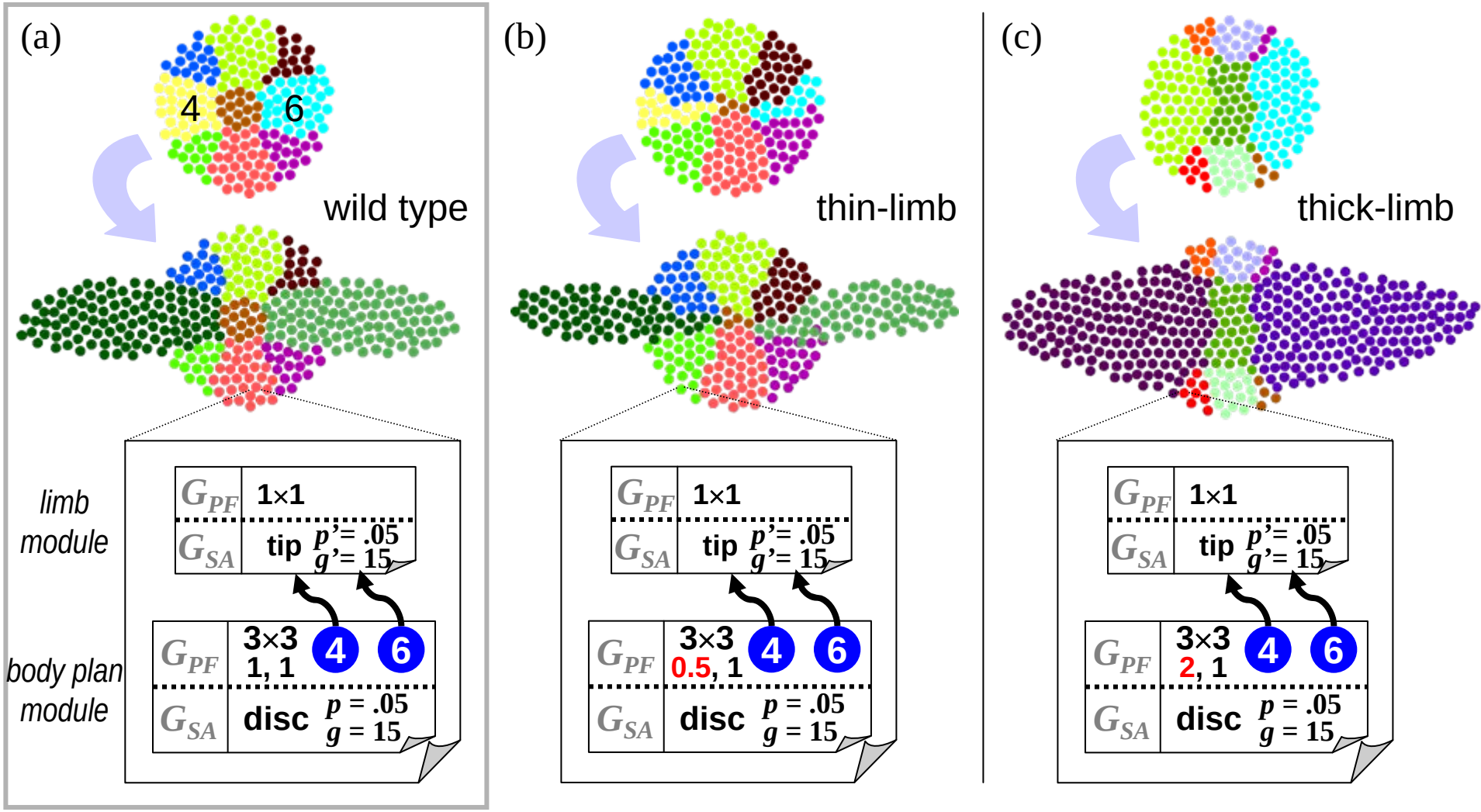
*“To understand novelty in evolution, we need to understand organisms down to their individual building blocks, down to their deepest components, for these are what undergo change.”*




*microscopic, componential level*

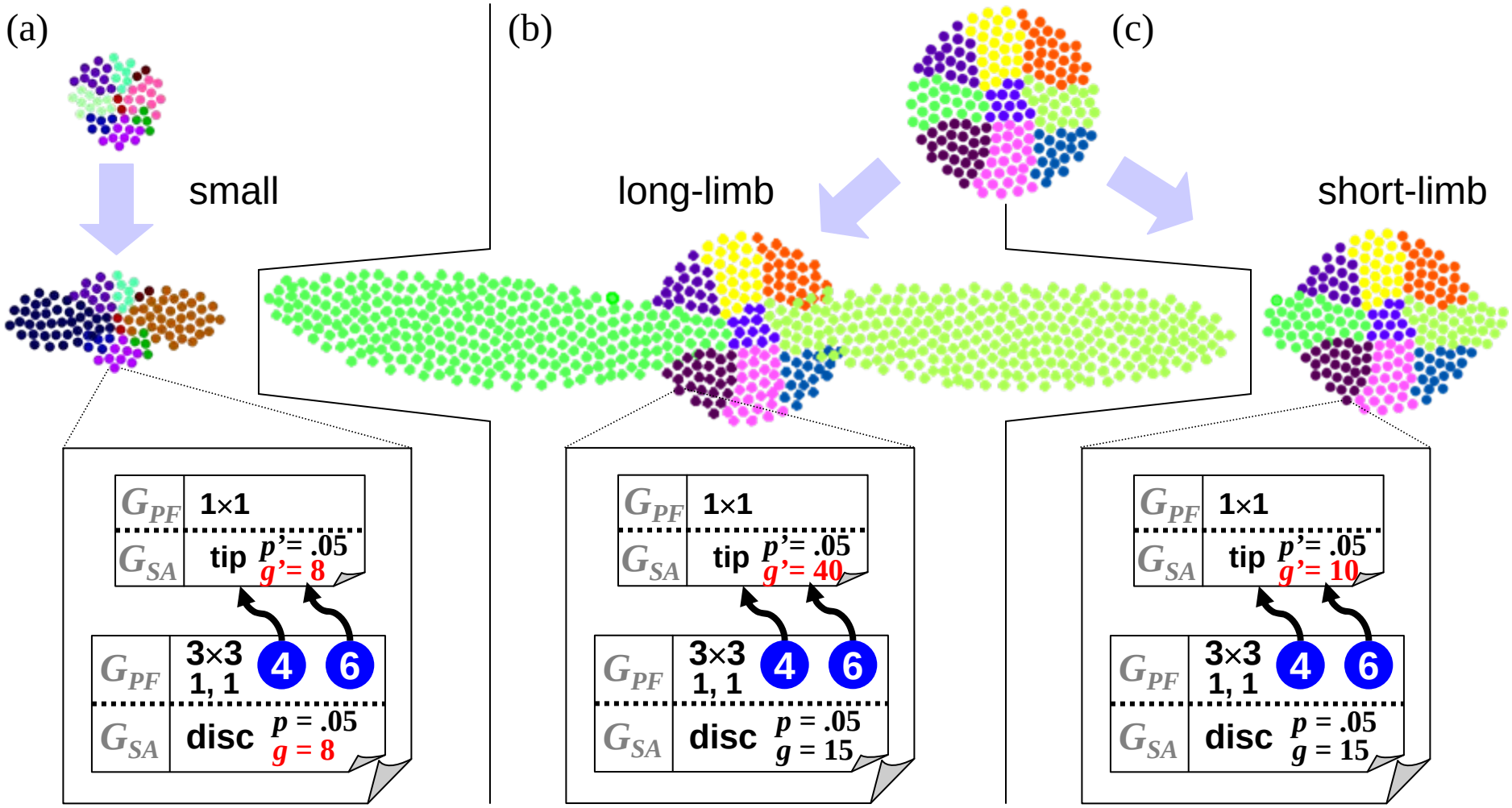
# Multi-agent evolutionary development (evo-devo)

## ➢ Quantitative mutations: limb thickness



# Multi-agent evolutionary development (evo-devo)

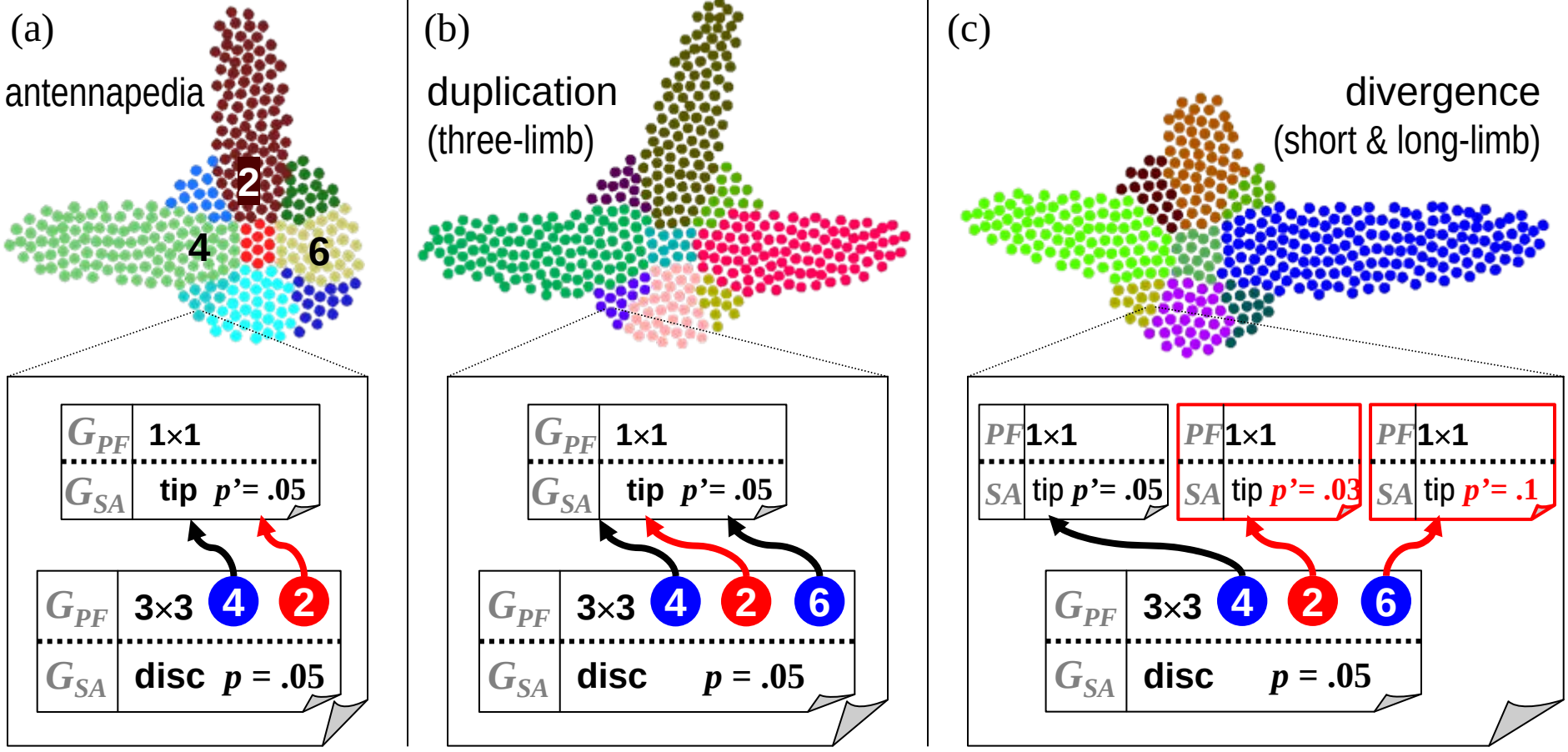
- Quantitative mutations: body size and limb length



# Multi-agent evolutionary development (evo-devo)

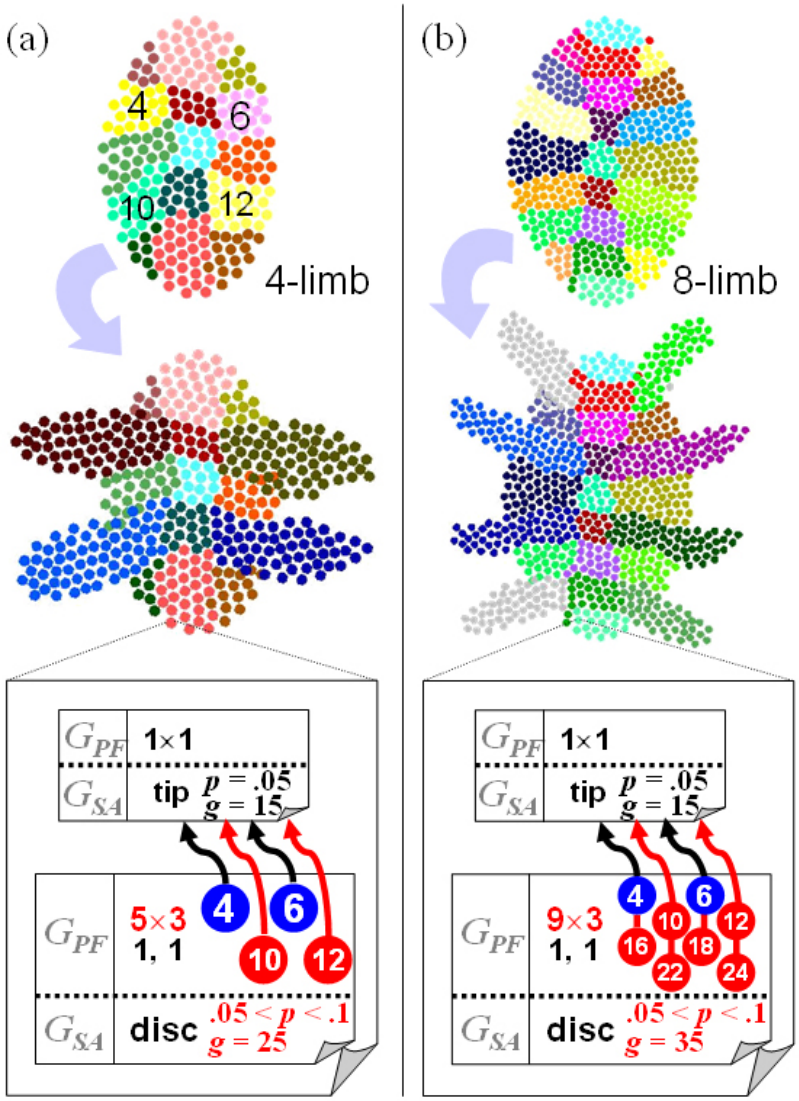
## ➢ Qualitative mutations: limb position and differentiation

antennapedia | *homology* by *duplication* | *divergence* of the homology



# Multi-agent evolutionary development (evo-devo)

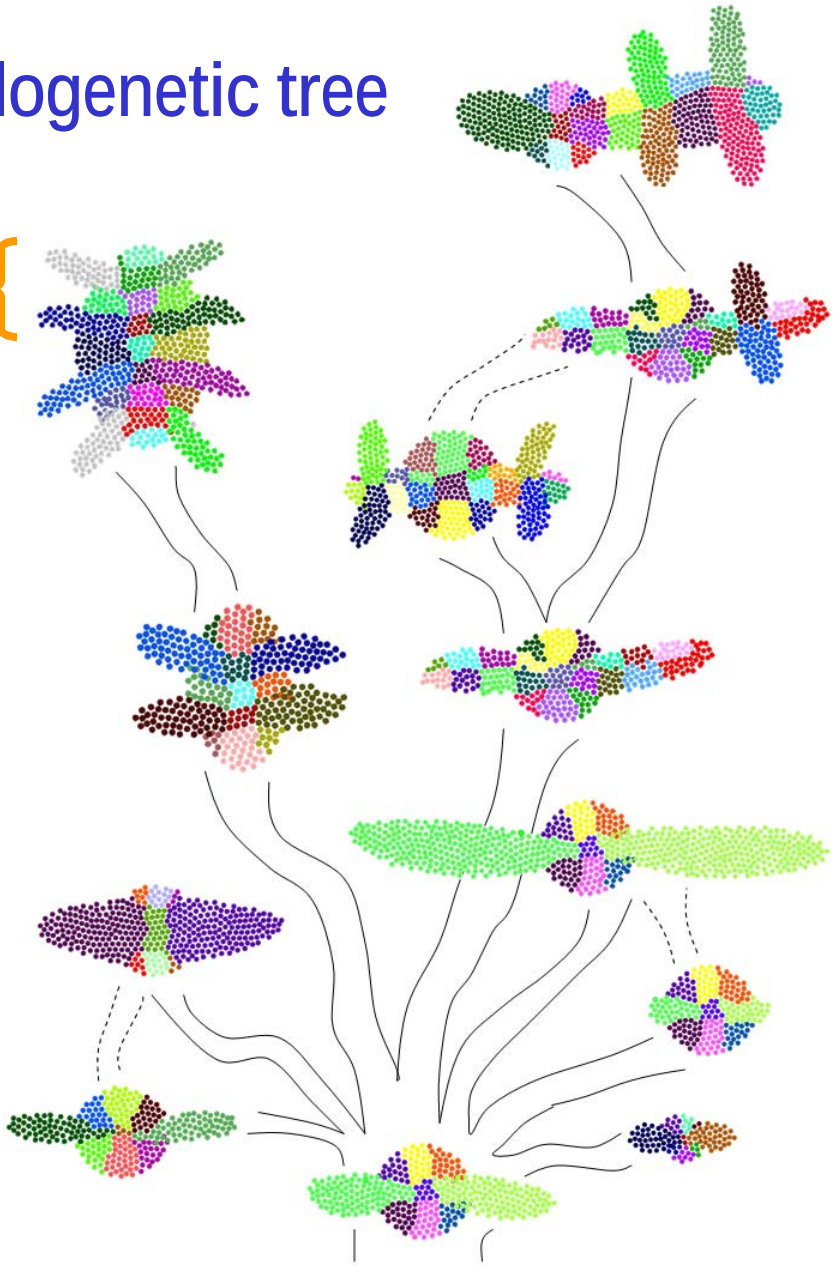
- Qualitative mutations: number of limbs



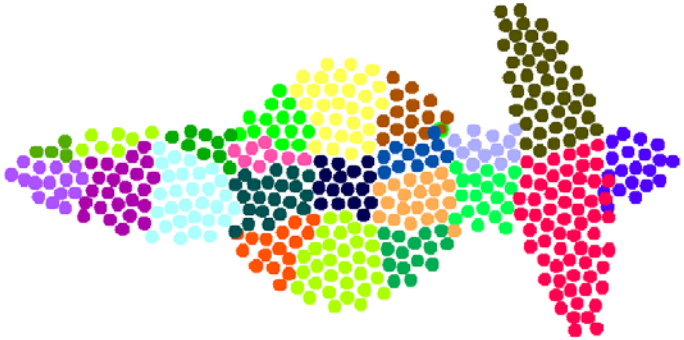
# Multi-agent evolutionary development (evo-devo)

- Artificial phylogenetic tree

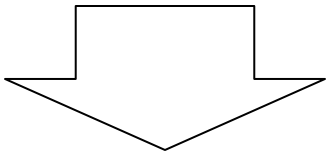
*production of structural innovation*



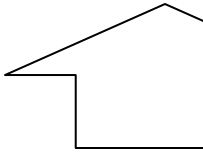
# Work toward more accurate biological modeling

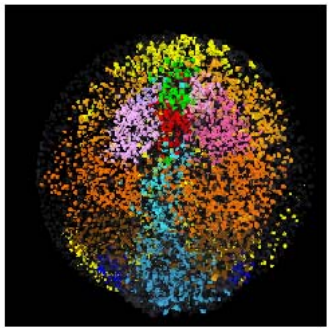


top-down, abstract,
heuristic approach



bottom-up, data-driven,
induction approach

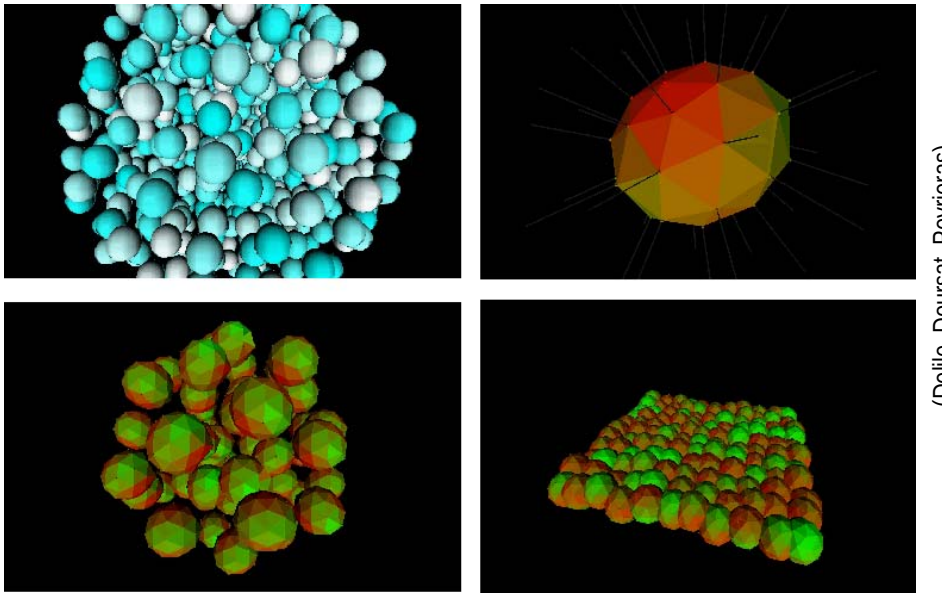




# Work toward more accurate biological modeling

## More accurate mechanics

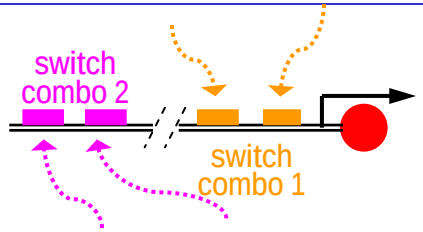
- ✓ 3-D
- ✓ individual cell shapes
- ✓ collective motion, migration
- ✓ adhesion

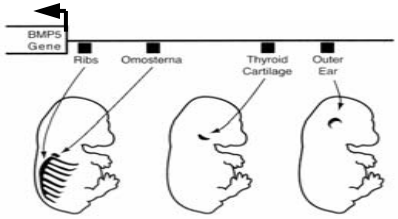


(Delile, Doursat, Peyrieras)

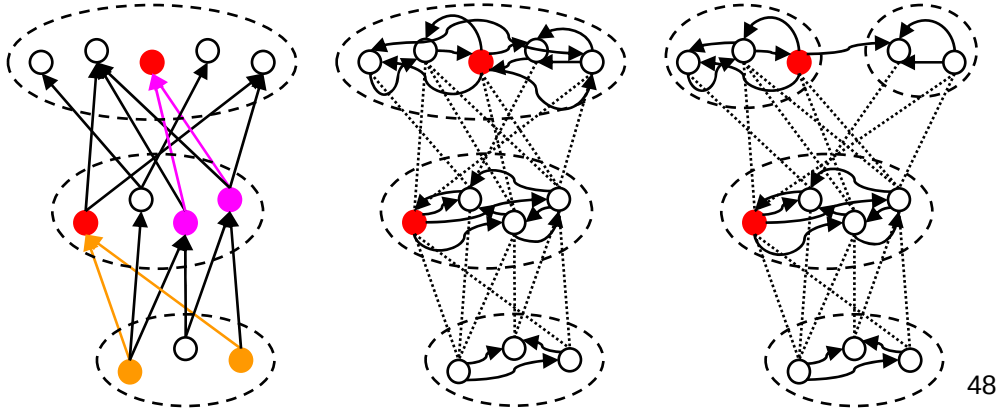
## Better gene regulation

- ✓ recurrent links
- ✓ gene reuse
- ✓ kinetic reaction ODEs
- ✓ attractor dynamics




after David Kingsley, in Carroll, S. B. (2005) *Endless Forms Most Beautiful*, p125



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