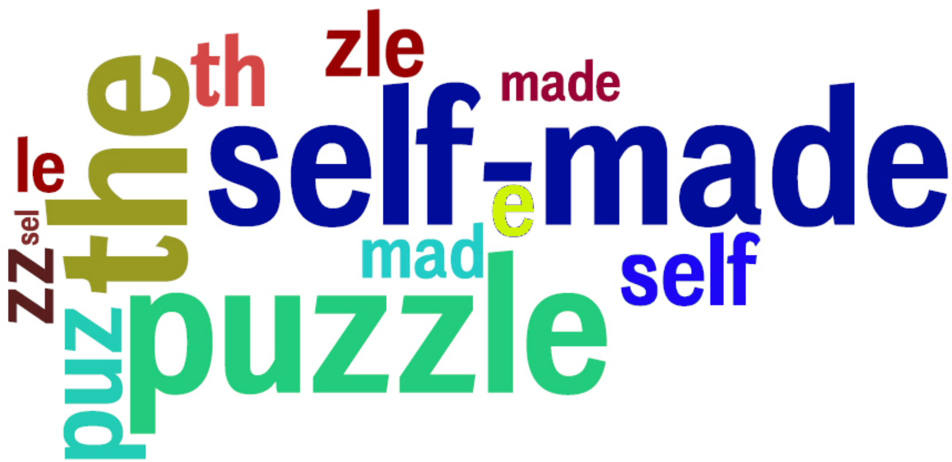
2nd Paris Workshop on MAS in Biology at meso or macroscopic scales

23 June 2009 — LPNHE, Campus Jussieu, T 43 RdC

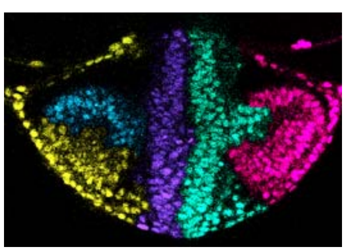
Heterogeneous collective motion or moving pattern formation?



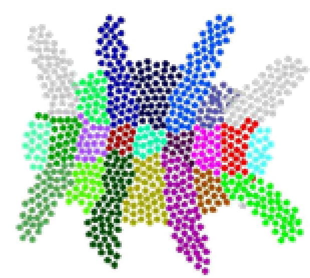
# of embryogenesis under the light of multi-agent modeling

René Doursat

http://www.iscpif.fr/~doursat



ISC PARIS ÎLE DE FRANCE — INSTITUT DES SYSTEMES COMPLEXES



Systems that are self-organized and architectured

the challenge for complex systems: integrate a true ***architecture***

the challenge for complicated systems: integrate ***self-organization***

free self-organization

deliberate design

designed self-organization / self-organized design

Toward programmed self-organization

Self-organized systems

- a myriad of self-positioning 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

---

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) approach to development

- ✓ as a fundamentally *spatial* phenomenon
- ✓ highlighting the *broad principles* – necessary to absorb and integrate the data – and proposing a *computational* model of these principles

➢ Broad principles

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

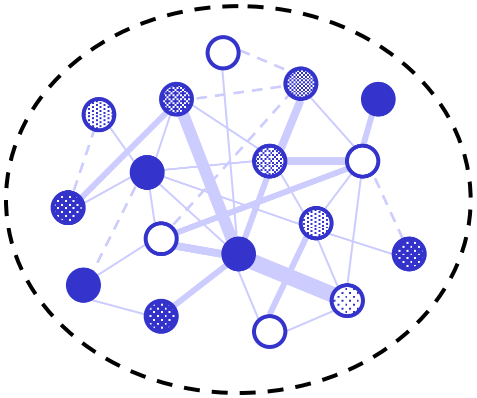
- ✓ best positioned to integrate both
- ✓ account for heterogeneity, modularity, hierarchy
- ✓ each agent carries a set of *biomechanical* and *regulatory* rules

The self-made puzzle of embryogenesis

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

Self-organized and structured systems

➢ Complex systems in many domains

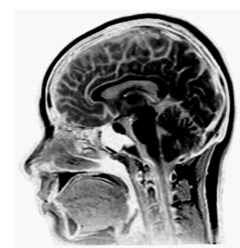


- large number of elementary **agents** interacting **locally**
- simple individual behaviors creating a complex **emergent** collective behavior
- *decentralized dynamics: no master blueprint or grand architect*

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

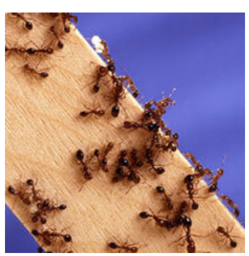
pattern
formation
○ = matter

biological
development
○ = cell

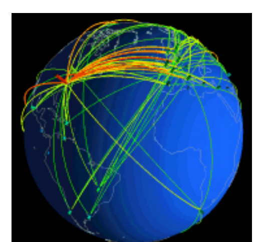


the brain
& cognition
○ = neuron

insect
colonies
○ = ant



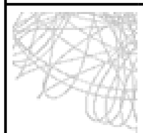
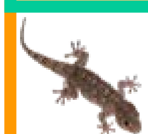
Internet
& Web
○ = host/page



social
networks
○ = person

“Statistical” vs. “morphological” complex systems

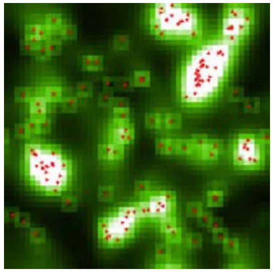
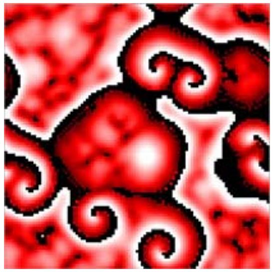
➤ A brief taxonomy of systems

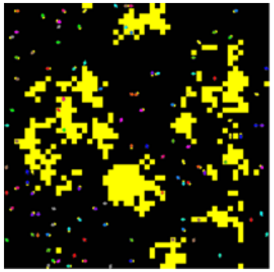
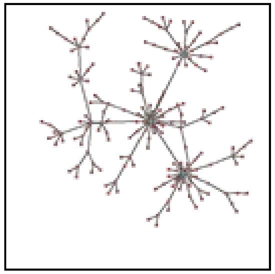
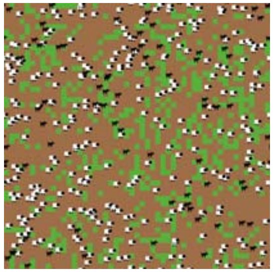
Category	Agents / Parts	Local Rules	Emergent Behavior	A “Complex System”?
two-body problem	*few*	*simple*	*simple*	*NO*
 three-body pb, low-D chaos	*few*	*simple*	*complex*	*NO – too small*
 crystal, gas	*many*	*simple*	*simple*	*NO – few params suffice to describe it*
 patterns, swarms, complex networks	*many*	*simple*	*“complex”*	*YES – but mostly random and uniform*
 structured morphogenesis	*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.*

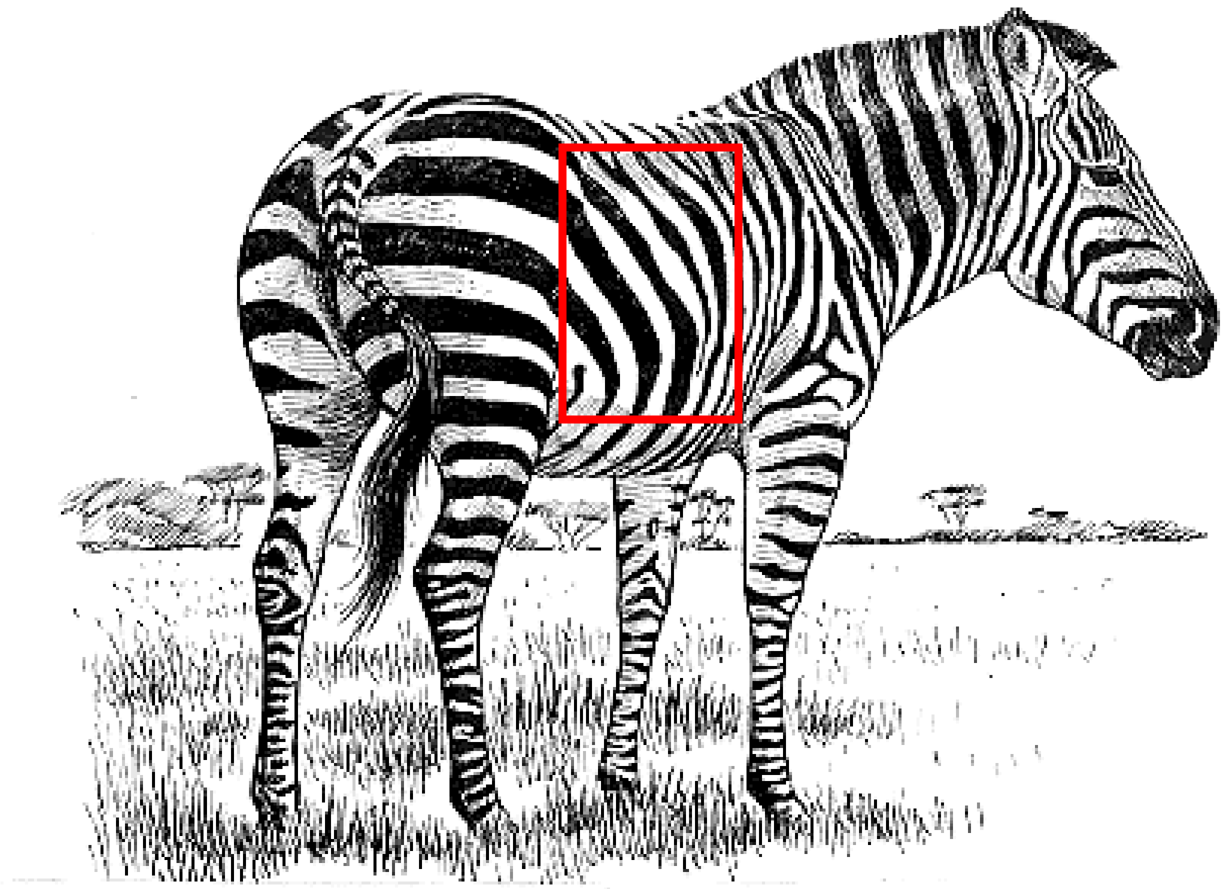
   

- ✓ yet, often like “textures”: repetitive, statistically ***uniform***, information-poor
- ✓ spontaneous order arising from amplification of ***random*** fluctuations
- ✓ ***unpredictable*** number and position of mesoscopic entities (spots, groups)

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

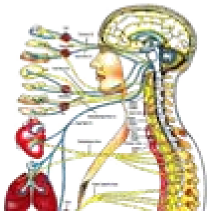
- Many agents, sophisticated rules, complex emergence

  → *natural ex: organisms (cells)*

plants

vertebrates

arthropods



humans

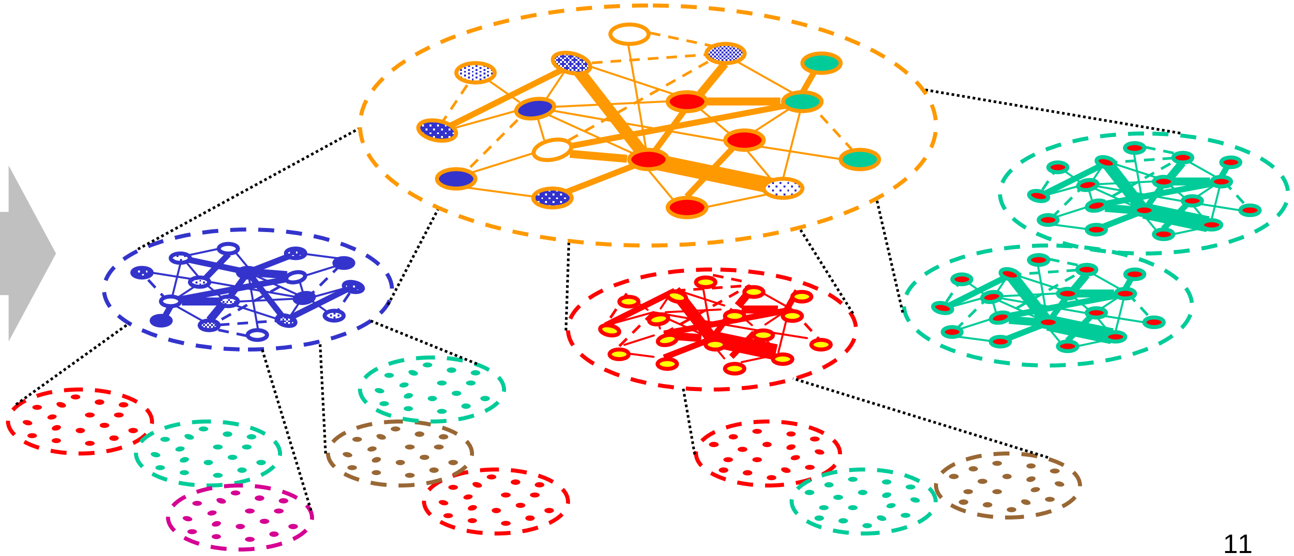
  - ✓ mesoscopic organs and limbs have intricate, ***nonrandom*** morphologies
  - ✓ development is highly ***reproducible*** in number and position of body parts
  - ✓ ***heterogeneous*** elements arise under information-rich genetic control

- 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

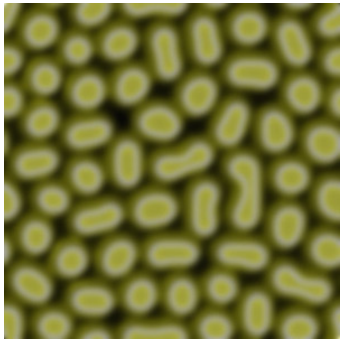
- Complex systems can be much more than a "soup"
  - ✓ "complex" doesn't necessarily imply "homogeneous"...
    → ***heterogeneous*** *agents and diverse patterns, via positions*
  - ✓ "complex" doesn't necessarily imply "flat" (or "scale-free")...
    → ***modular****, hierarchical, detailed architecture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



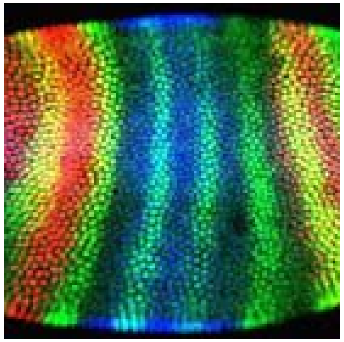
Statistical vs. morphological systems

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

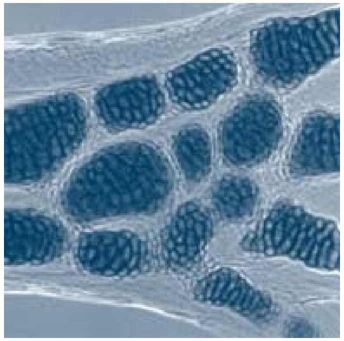
convection cells
www.chabotspace.org



reaction-diffusion
texturegarden.com/java/rd



fruit fly embryo
Sean Caroll, U of Wisconsin

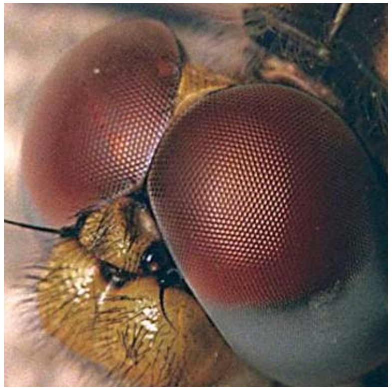


larval axolotl limb
Gerd B. Müller

Statistical vs. morphological systems

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

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



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

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

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

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

The self-made puzzle of embryogenesis

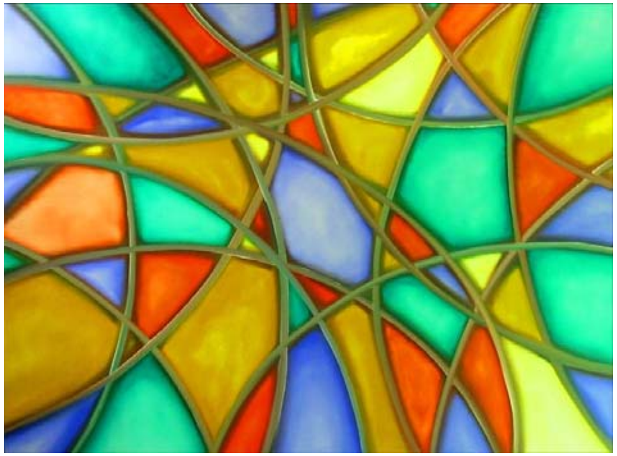
1. Self-organized and structured systems
2. Two-side challenge: heterogeneous motion / moving patterns
3. A multi-agent model of embryogenesis
4. Evolutionary development (evo-devo)

Morphogenesis couples assembly and patterning

➢ Sculpture → forms

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

➢ Painting → colors



"shape from patterning"

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

"patterns from shaping"

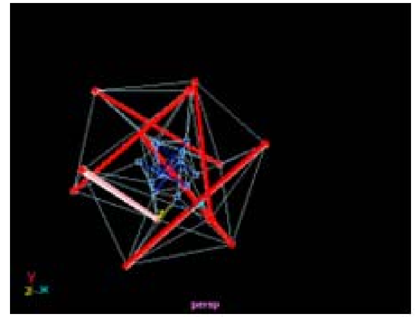
✓ new color regions appear (domains of genetic expression) triggered by deformations

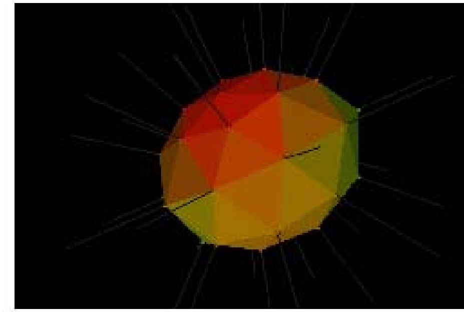
Niki de Saint Phalle

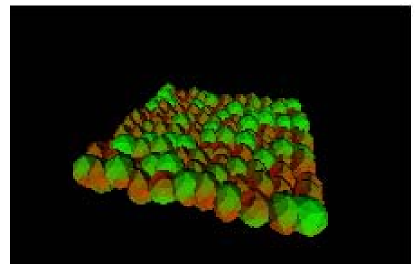
Embryogenesis couples mechanics and regulation

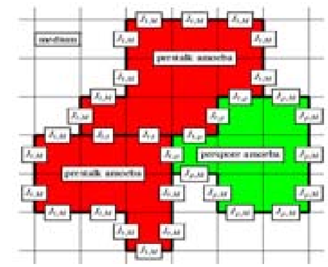
- ➤ **Cellular mechanics**
  - ✓ adhesion
  - ✓ deformation / reformation
  - ✓ migration (motility)
  - ✓ division / death

tensional integrity (Ingber)



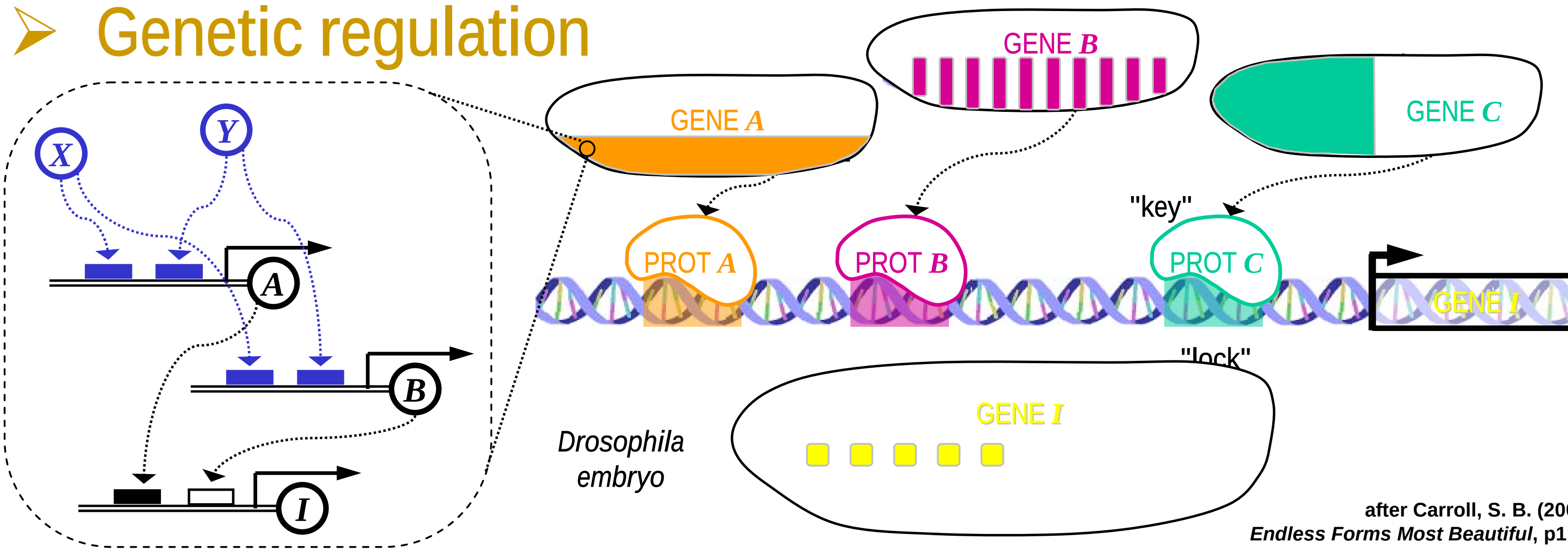






cellular Potts model (Graner, Glazier, Hogeweg)

- ➤ **Genetic regulation**

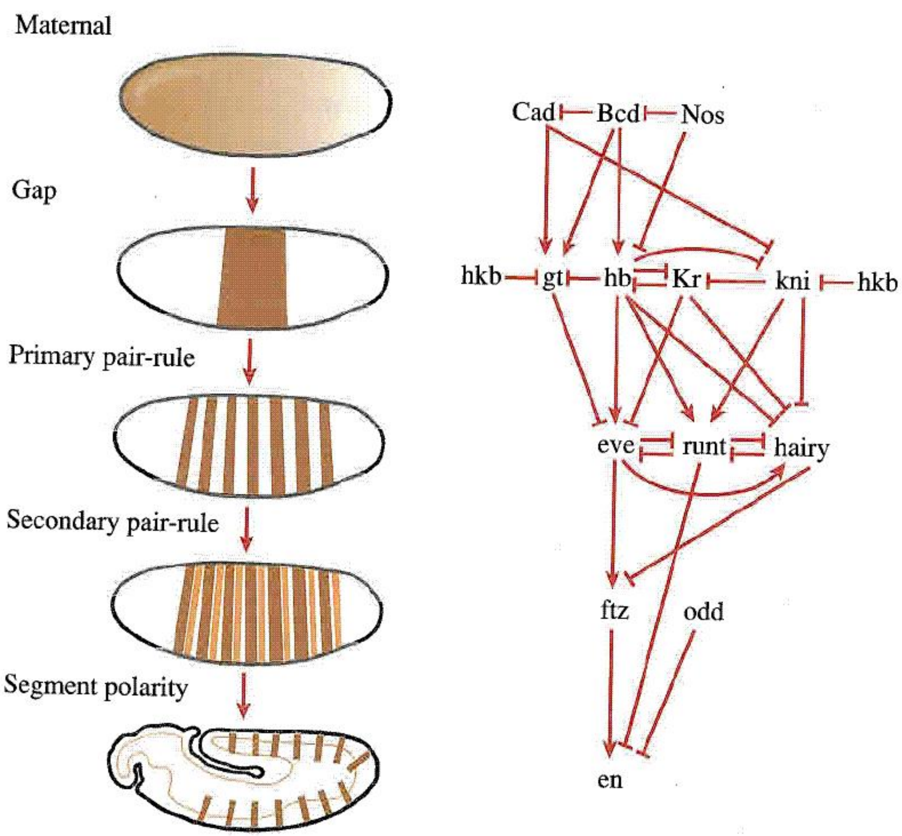


after Carroll, S. B. (2005)
Endless Forms Most Beautiful, p117

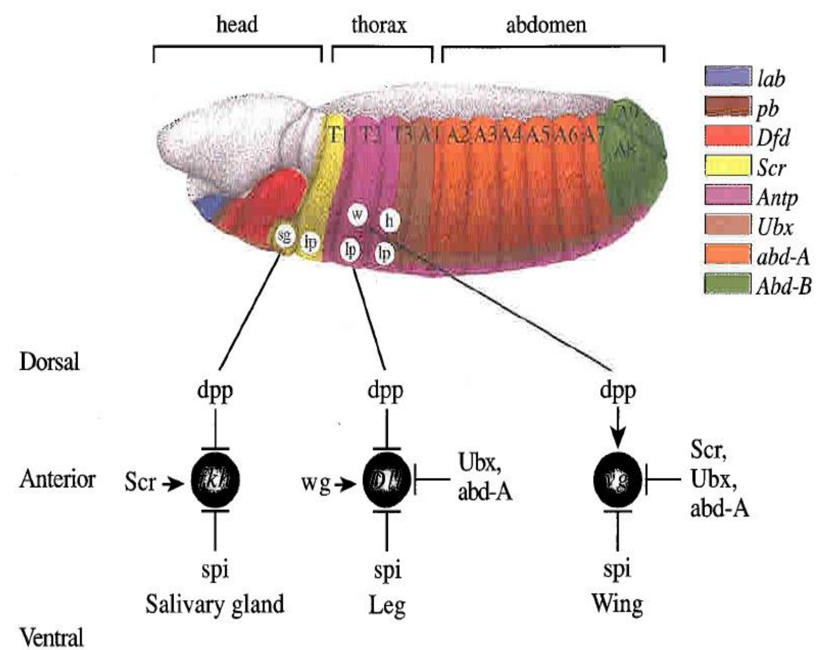
Gene regulatory pattern formation

➢ 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.)

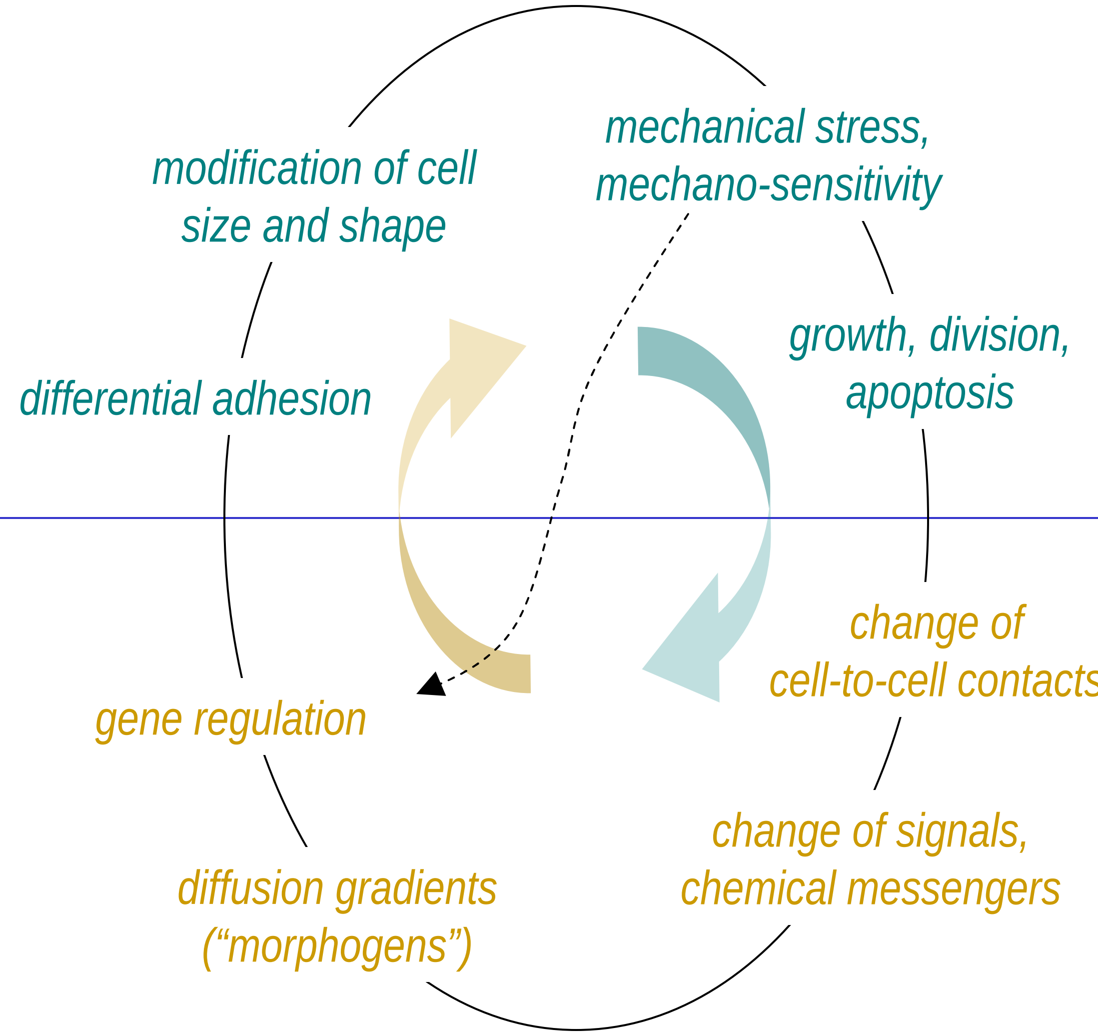


from Carroll, S. B., et al. (2001) *From DNA to Diversity*, p63

Embryogenesis couples mechanics and regulation

- Cellular mechanics

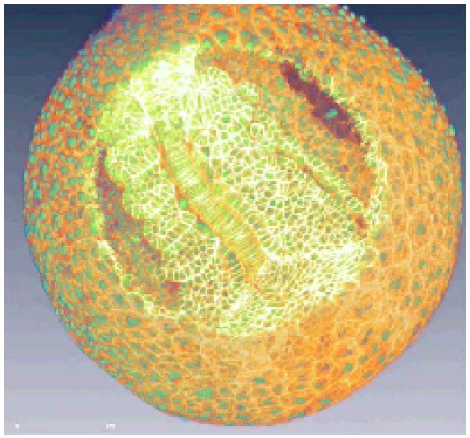
- Genetic regulation



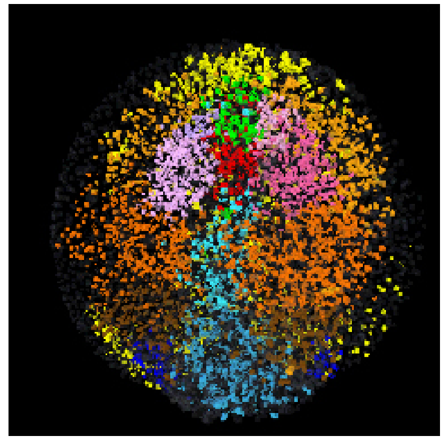
Embryogenesis couples motion and patterns

Nadine Peyriéras, Paul Bourgine, Thierry Savy, Benoît Lombardot, Emmanuel Faure et al.
Embryomics & BioEmergences

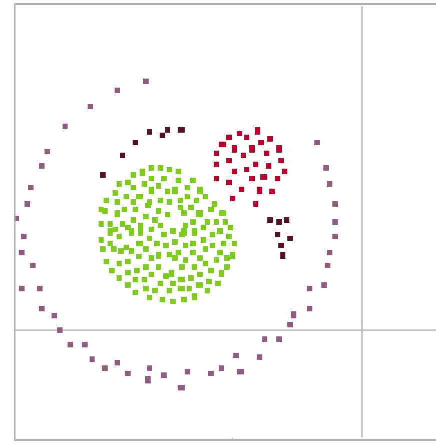
Collective motion regionalized into patterns



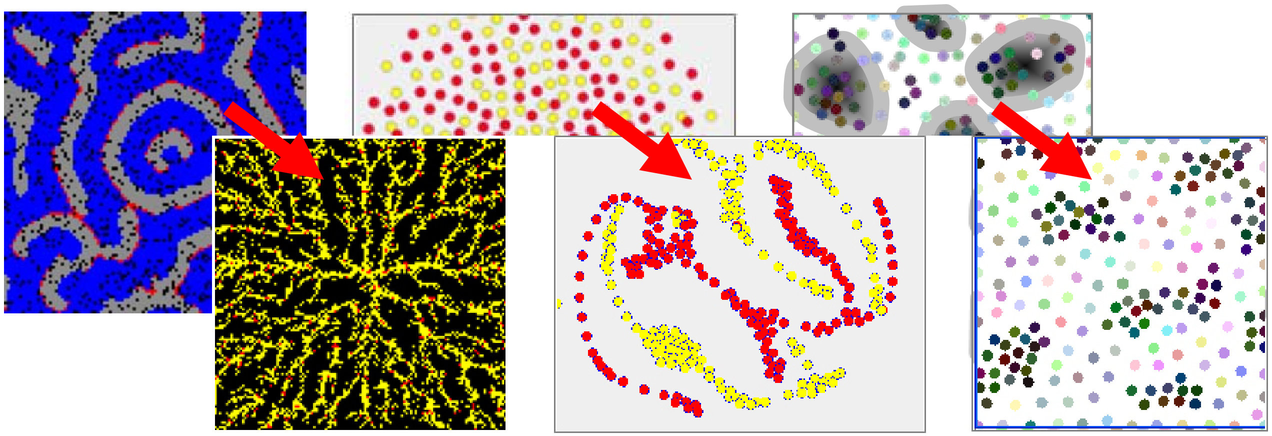
zebrafish



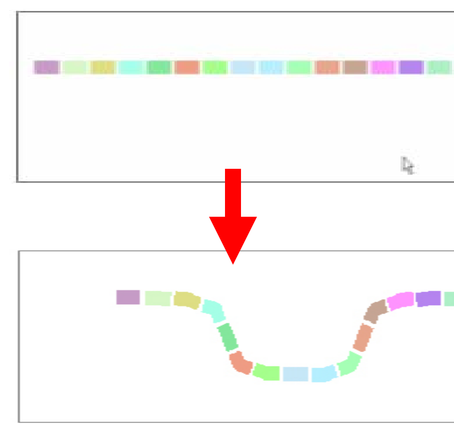
Hiroki Sayama (Swarm Chemistry)
http://bingweb.binghamton.edu/~sayama/SwarmChemistry/



Pattern formation that triggers motion



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



The self-made puzzle of embryogenesis

1. Self-organized and structured systems

2. Two-side challenge: heterogeneous motion / moving patterns

3. A multi-agent model of embryogenesis

4. Evolutionary development (evo-devo)

Why multi-agent modeling?

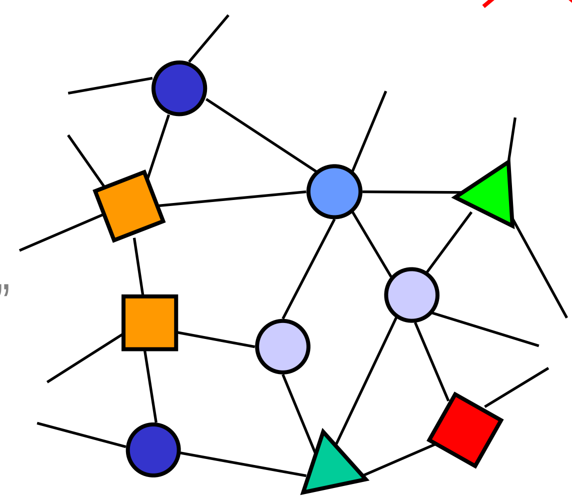
- Equations and laws can be hard or impossible to find...
  - ✓ *"The study of non-linear physics is like the study of non-elephant biology."* —Stanislaw Ulam
    - the physical world is a fundamentally *non-linear* and *out-of-equilibrium* process
    - focusing on linear approximations and stable points 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...

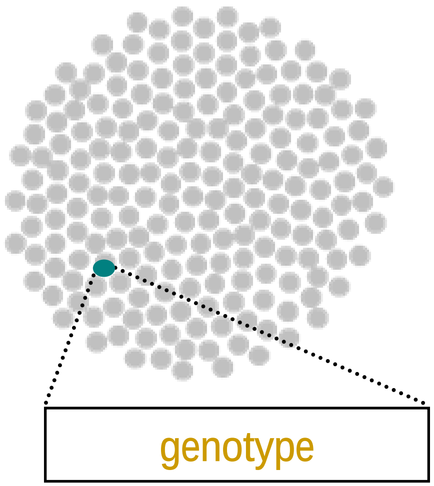
morphogenesis

- ✓ 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 (Bolean or real concentrations)
    - “amorphous computing”
  - ✓ focused on motion (little or no patterning)
    - (sub)cellular Potts model
    - self-assembly, aggregation
    - flocking, swarm formation, cellular sorting

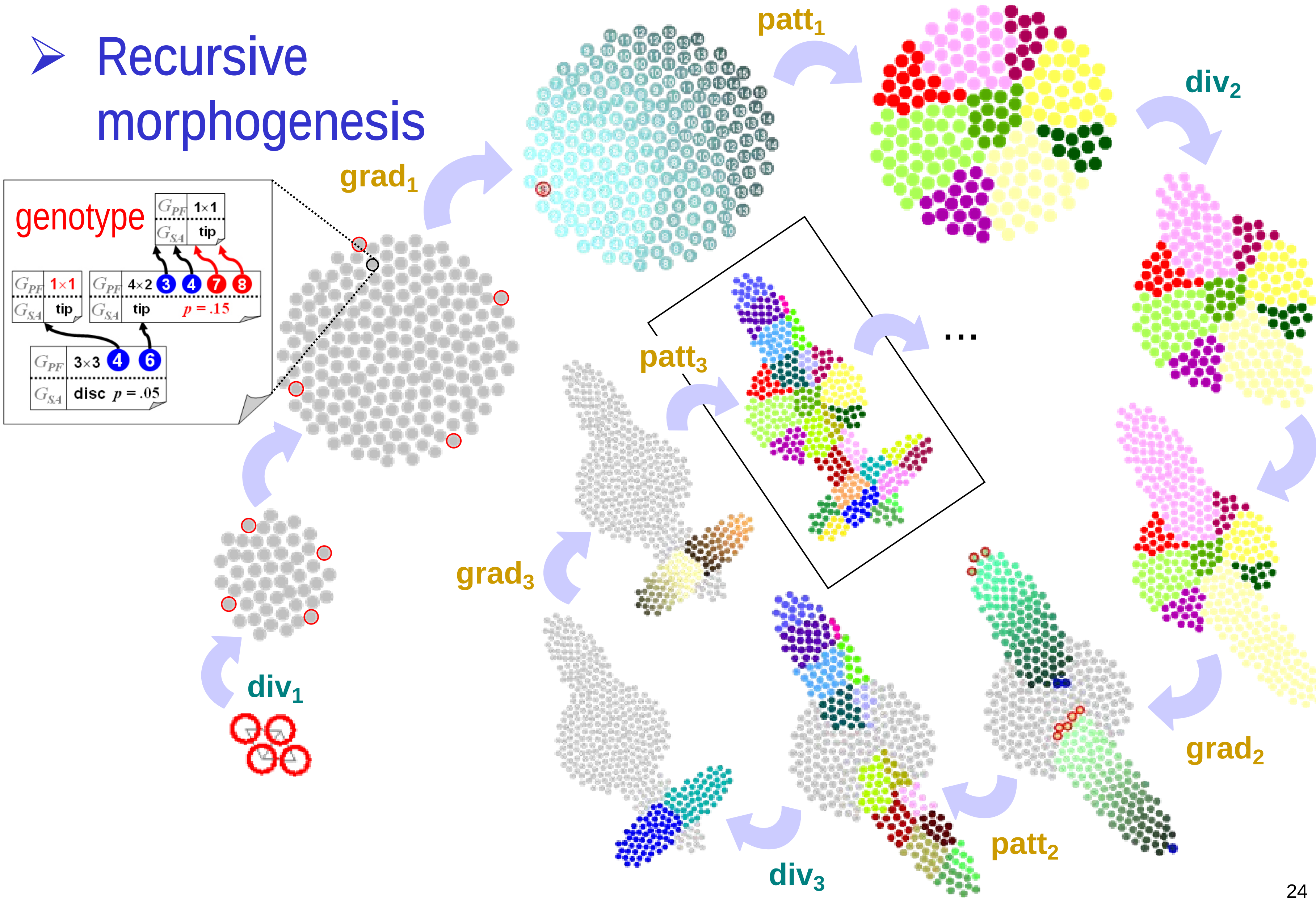


a combination that is still rare ; but see Hogeweg / Salazar-Ciudad / Mjolsness..

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

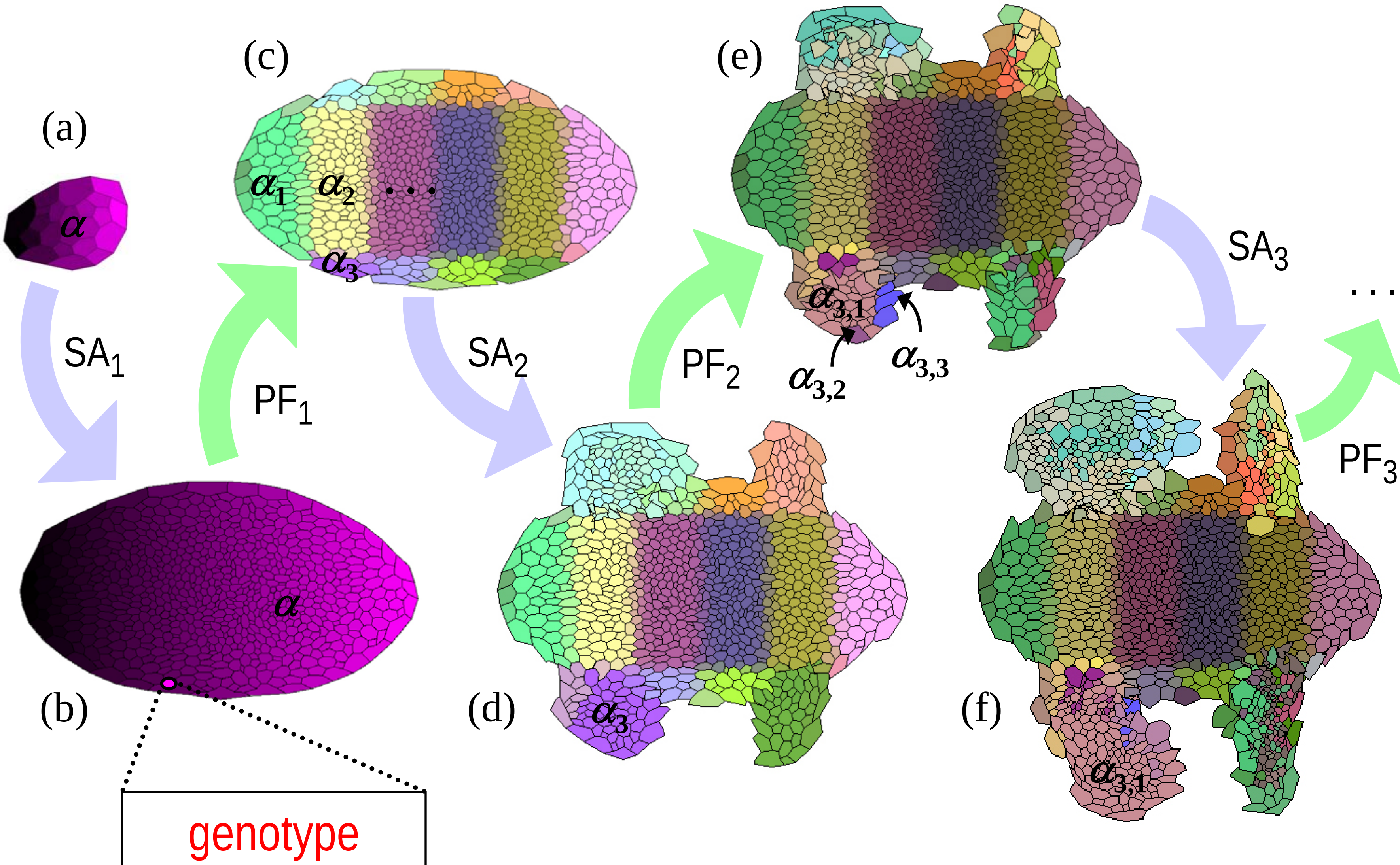
Exemple of hybrid mesoscopic model

- Recursive morphogenesis

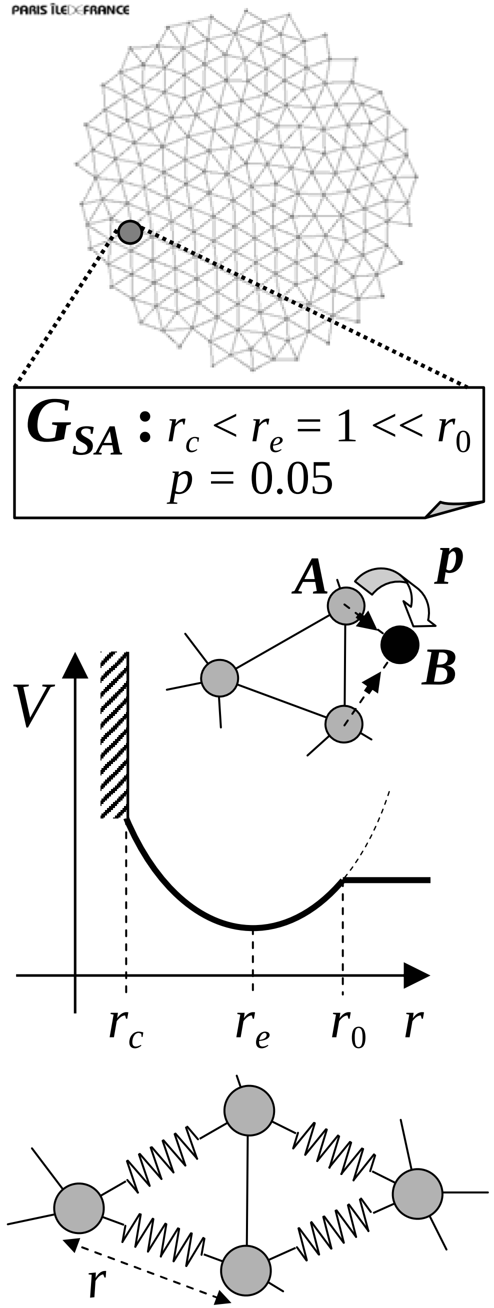


René Doursat, ALife XI (2008)

1. Self-Assembly + 2. Pattern Formation = 3. Morphogenesis

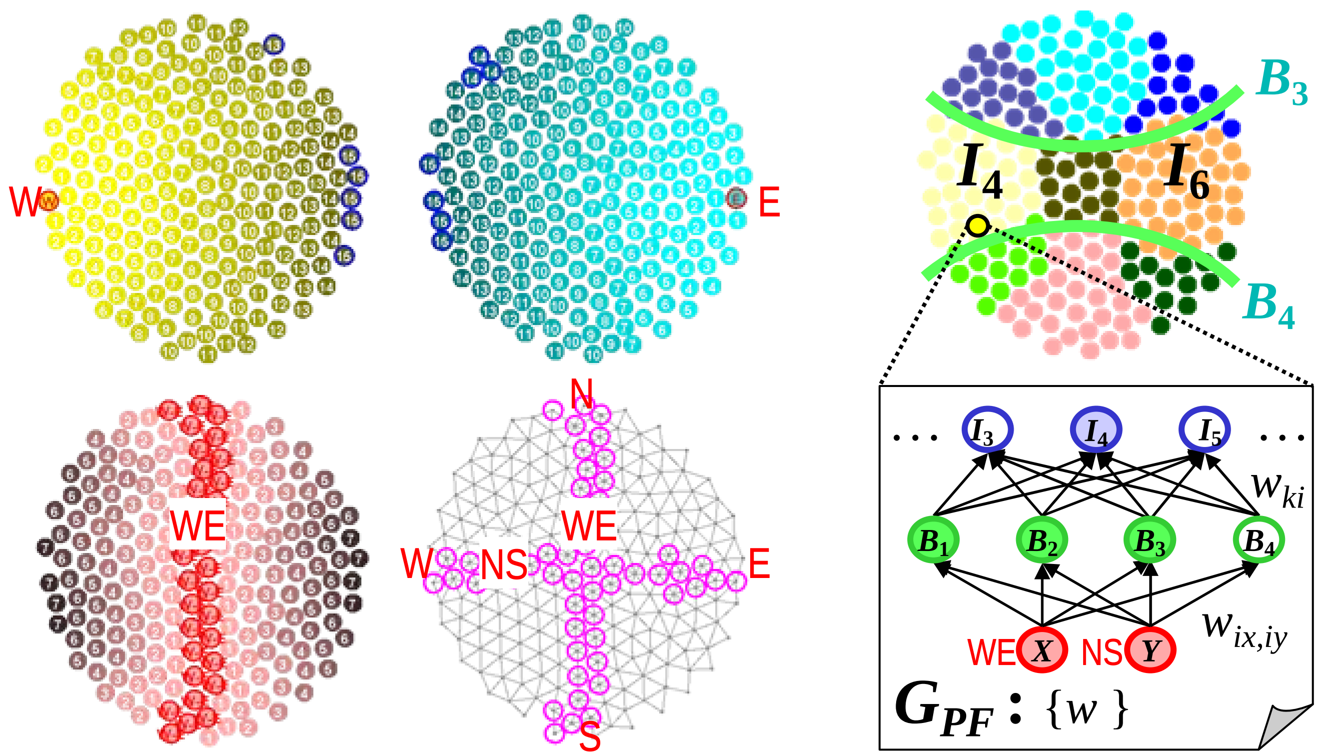


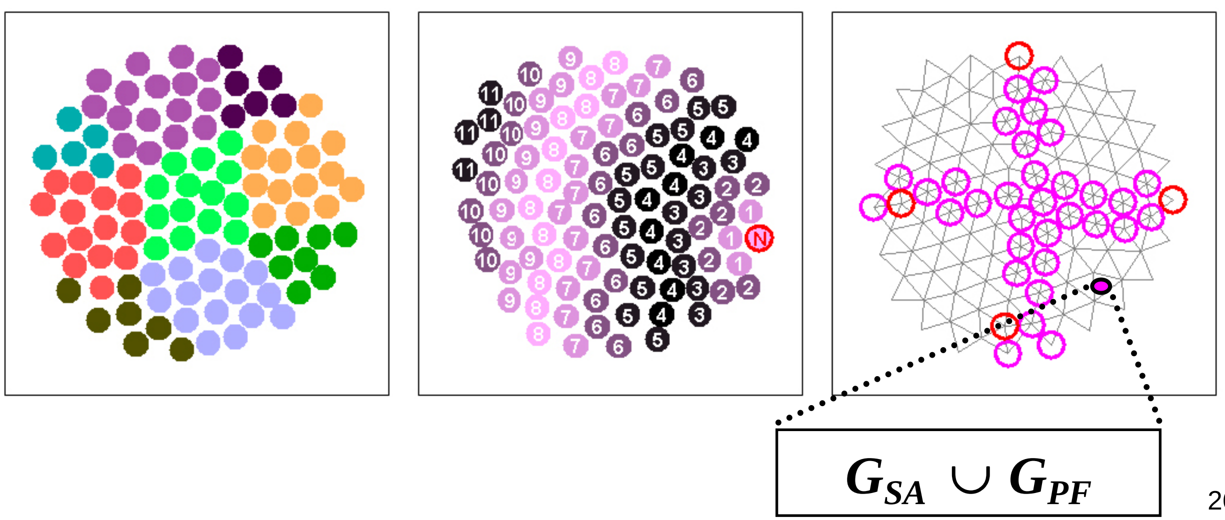
div



grad

patt





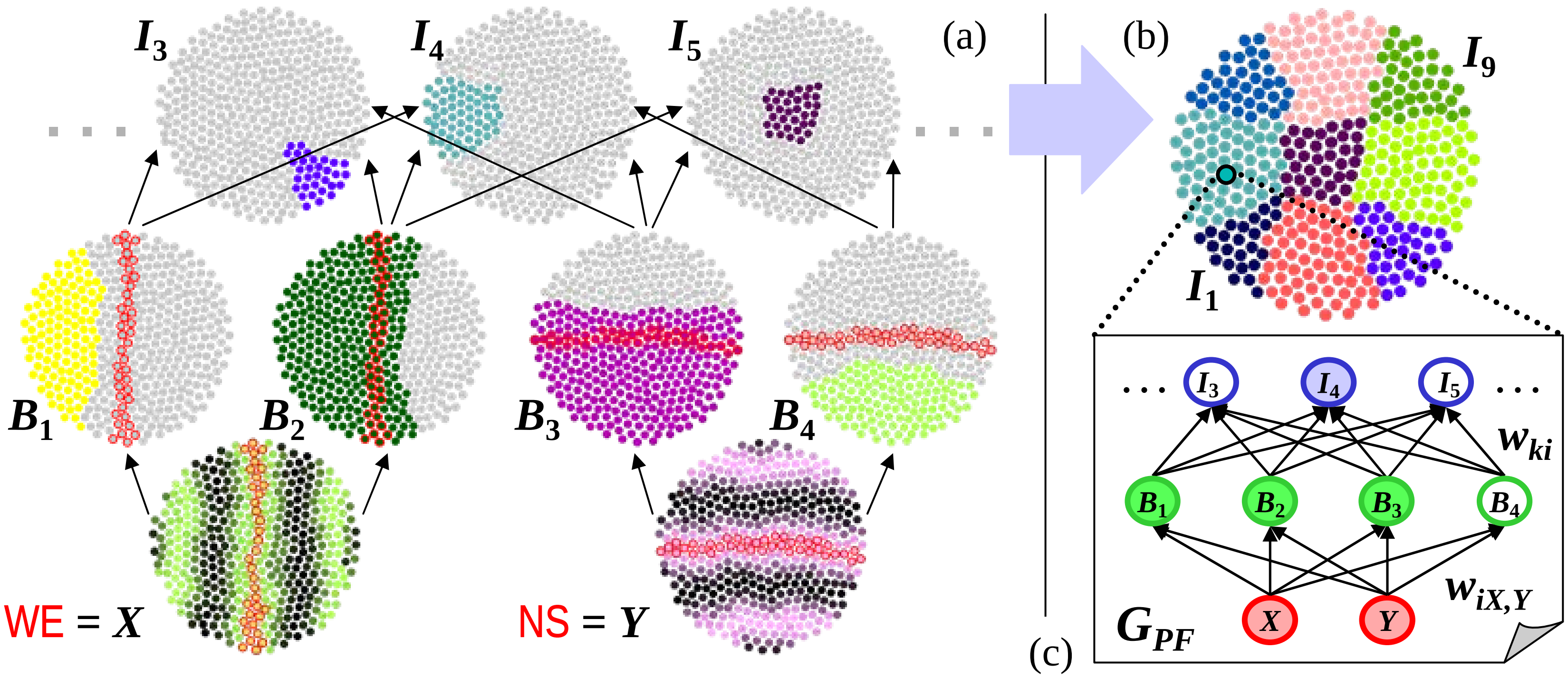
Virtual gene atlas

➢ 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 $k = 1...9$

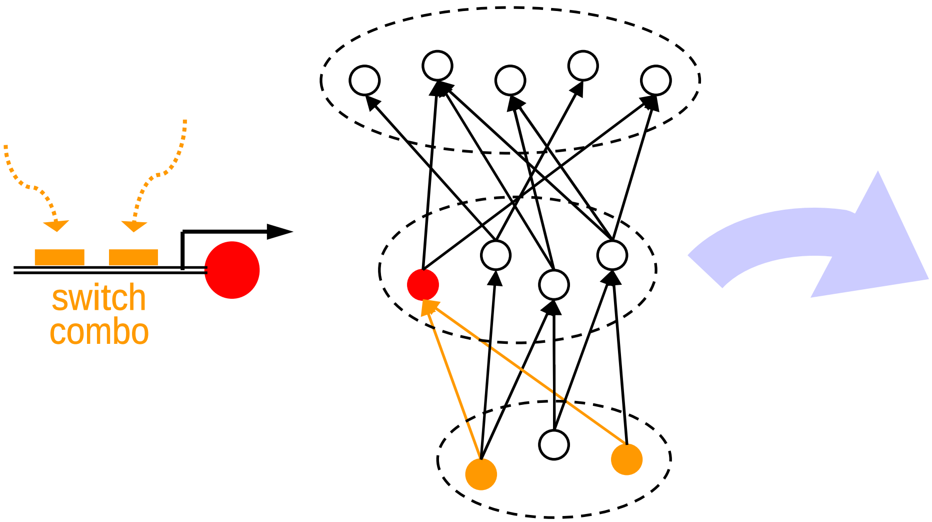
c) gene regulatory network used by each agent to calculate its expression levels, here: $B_1 = \sigma(1/3 - X)$, $B_3 = \sigma(2/3 - Y)$, $I_4 = B_1B_3(1 - B_4)$, etc.

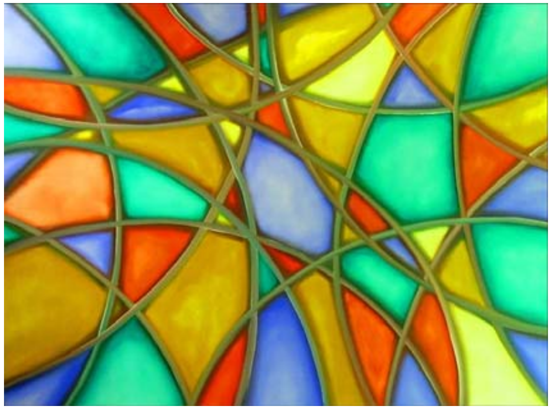


From feedforward to recurrent gene regulation

➢ 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

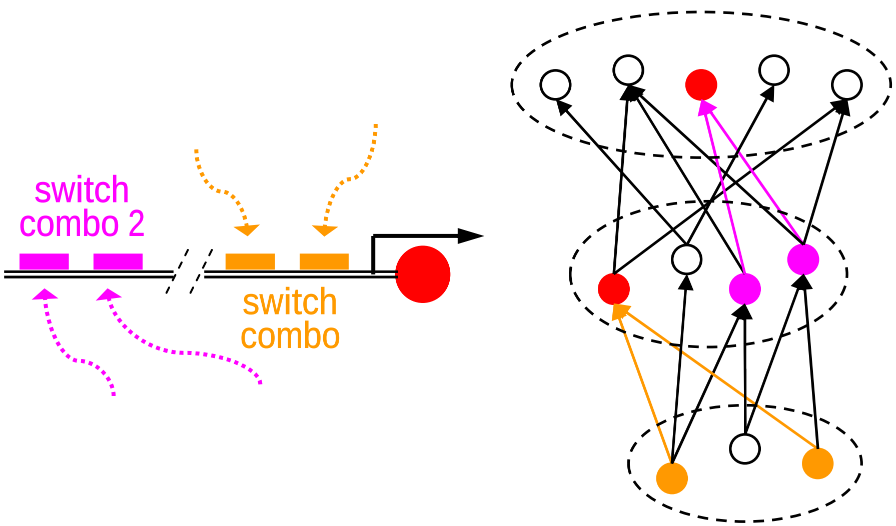


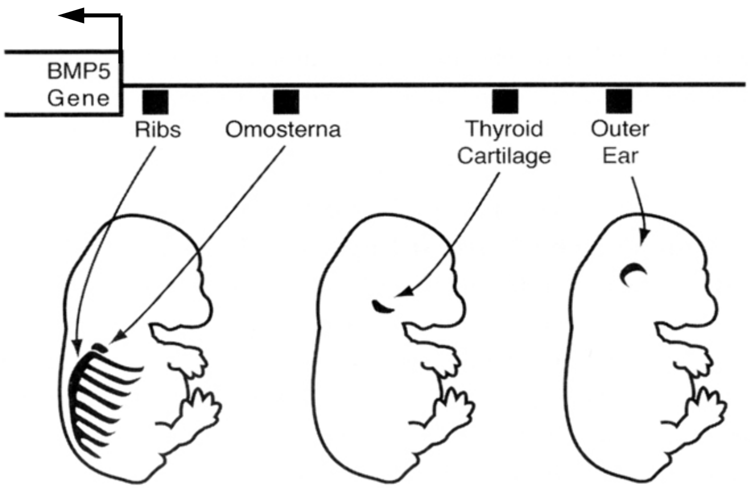


From feedforward to recurrent gene regulation

➢ Naturally, 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



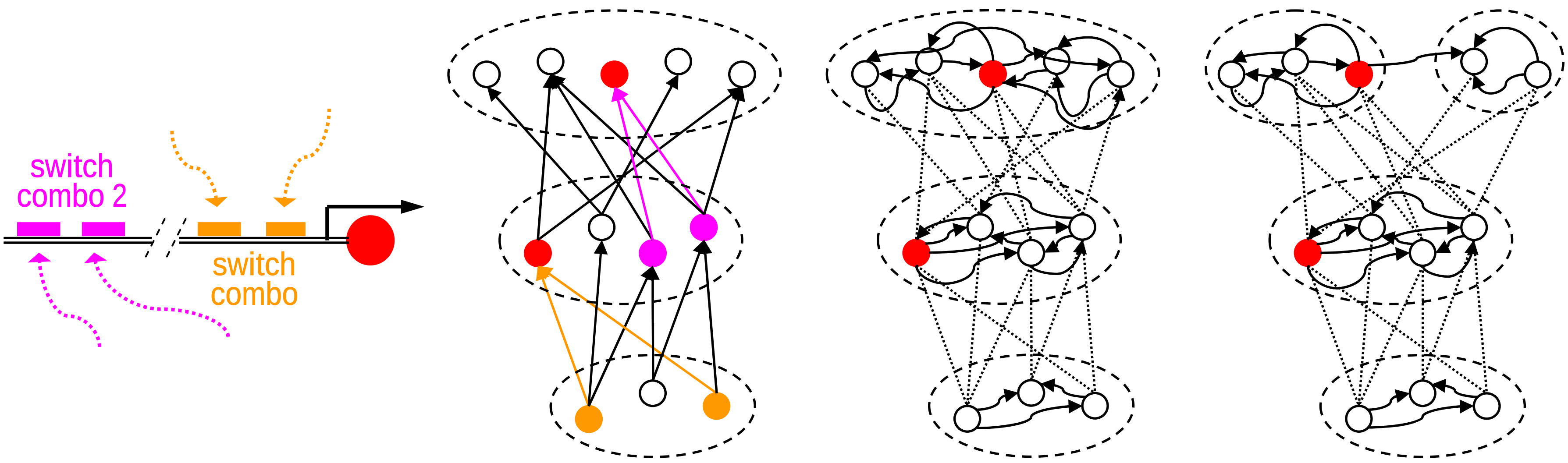


after David Kingsley, in Carroll, S. B. (2005)
***Endless Forms Most Beautiful*, p125**

From feedforward to recurrent gene regulation

➢ More realistic variants of GRNs

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



Hierarchical morphogenesis

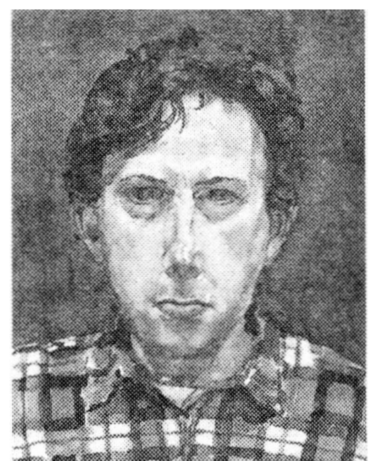
➢ Morphological refinement by iterative growth

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



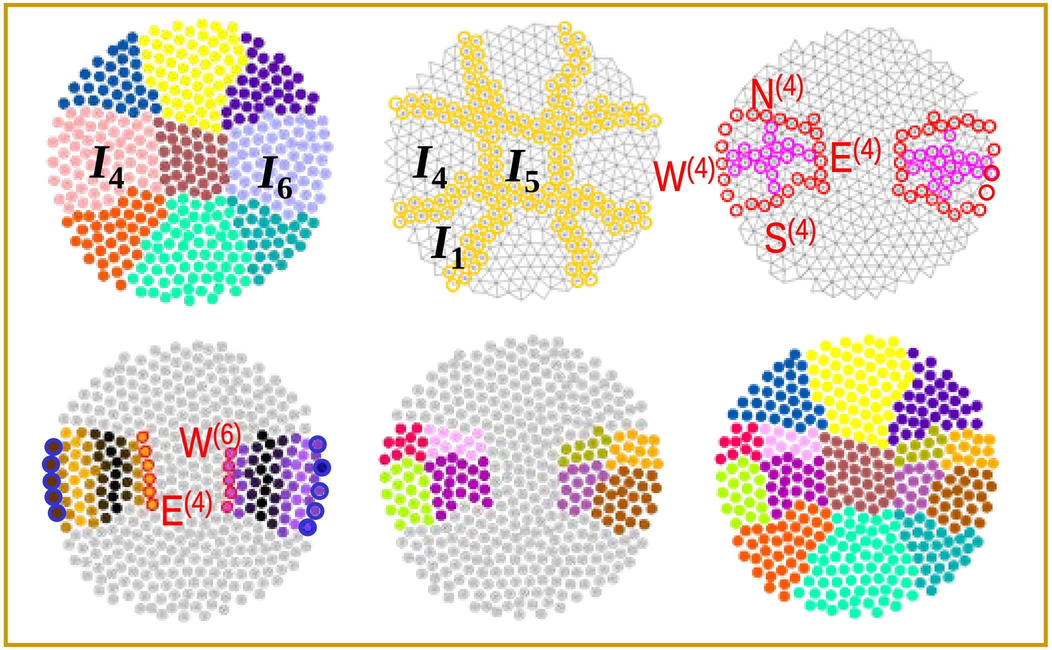
- ✓ . . . while, at the same time, the canvas grows

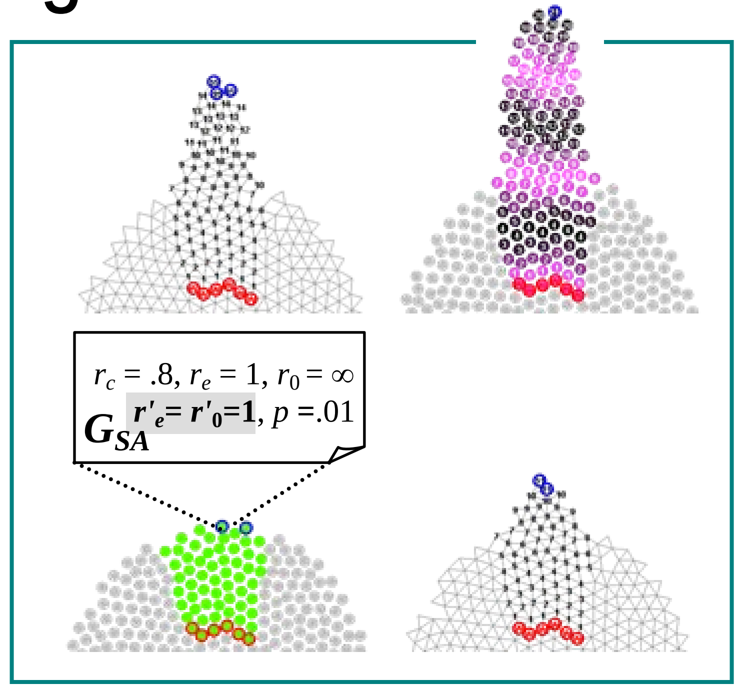


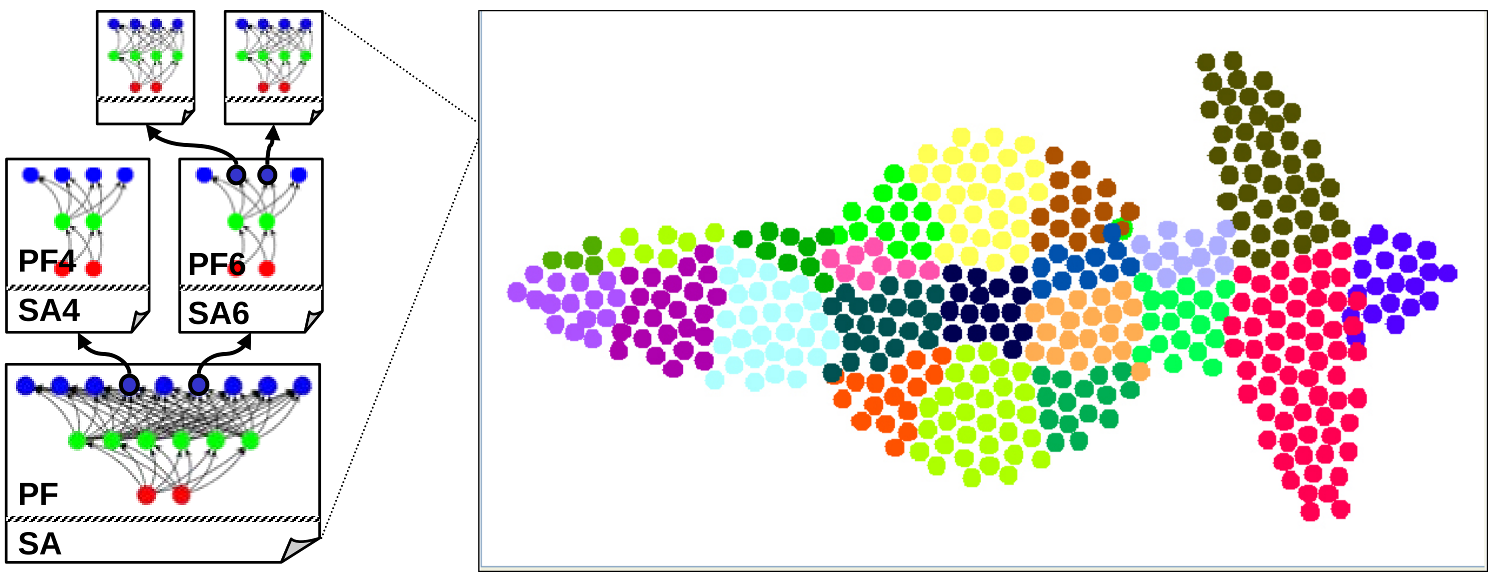


from Coen, E. (2000)
The Art of Genes, pp131-135

Hierarchical morphogenesis







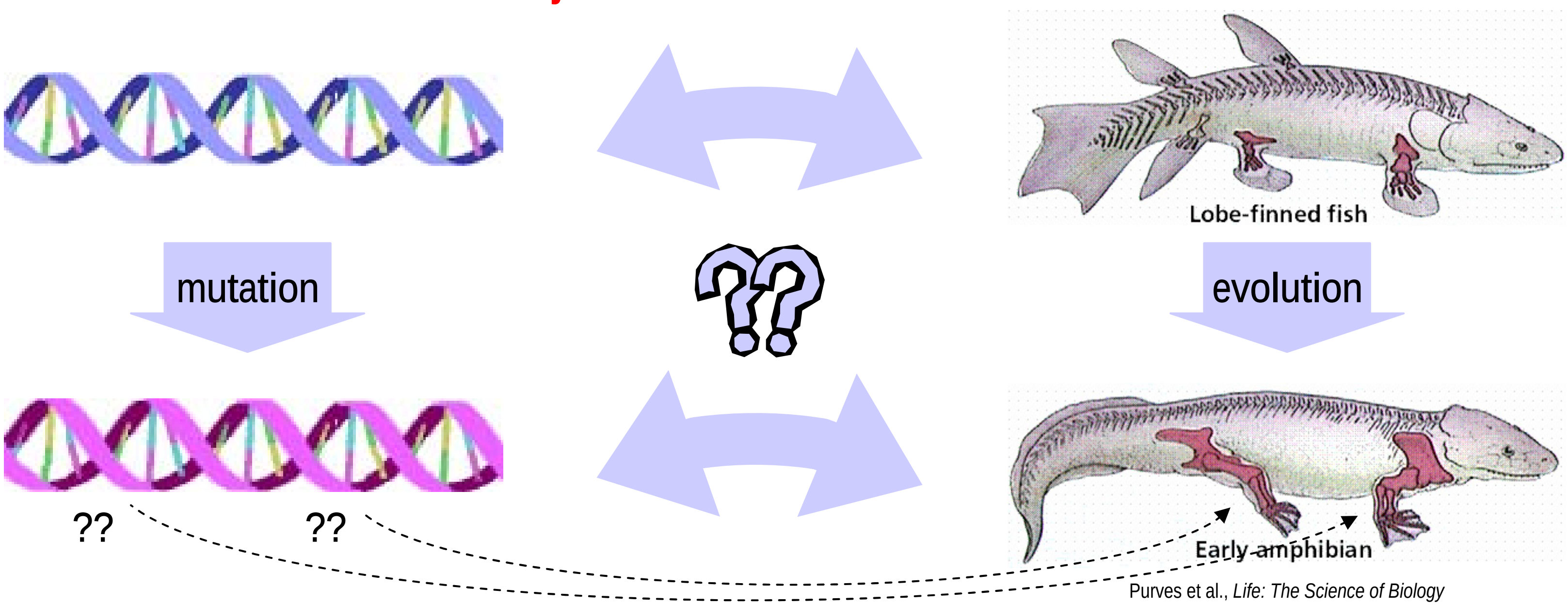
The self-made puzzle of embryogenesis

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

Evolutionary development (evo-devo)

➢ Development: the missing link of the Modern Synthesis

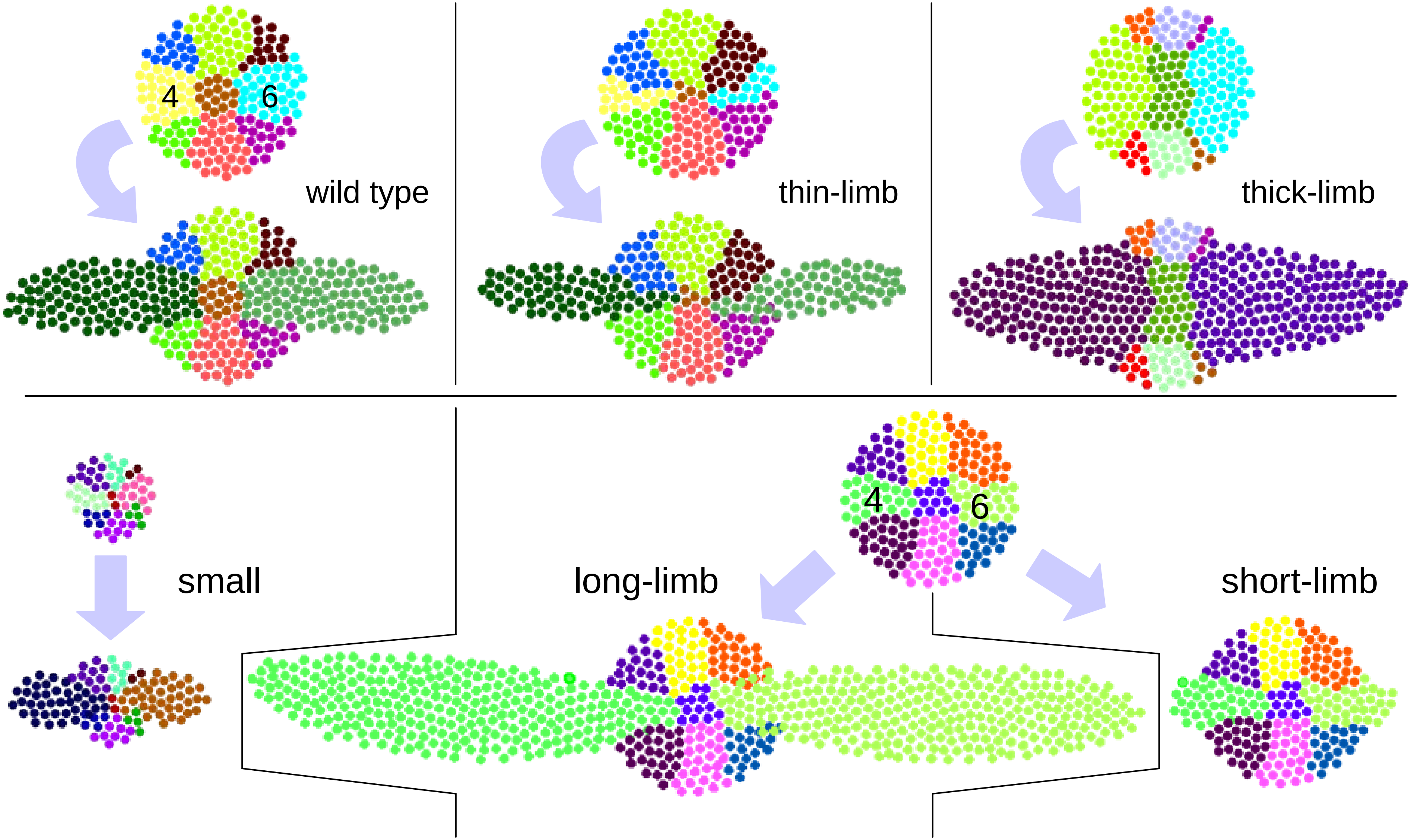
- ✓ biology's "Modern Synthesis" demonstrated a fundamental correlation between genotype and phenotype, yet the molecular and cellular mechanisms of development are still unclear
- ✓ the genotype-phenotype link cannot remain an abstraction if we want to understand evolution as ***producing innovation by variation*** and not just as a selection force



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

Multi-agent evolutionary development (evo-devo)

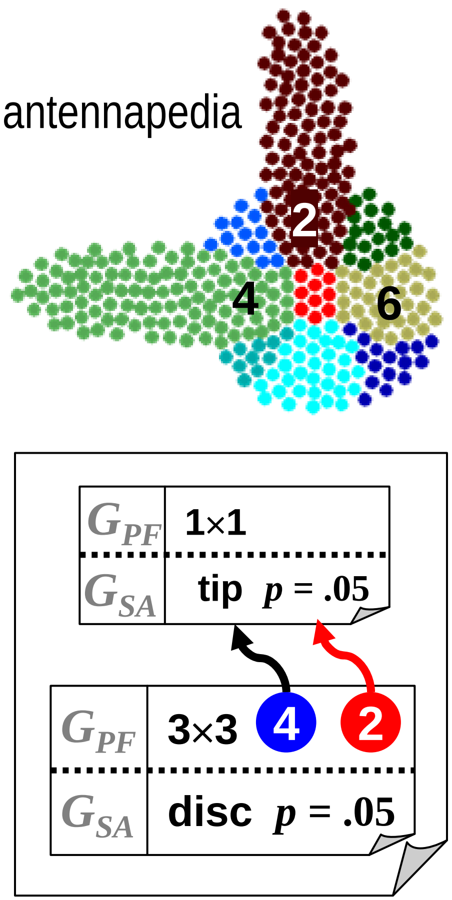
- Genotype mutations → phenotype variations (*quantitative*)



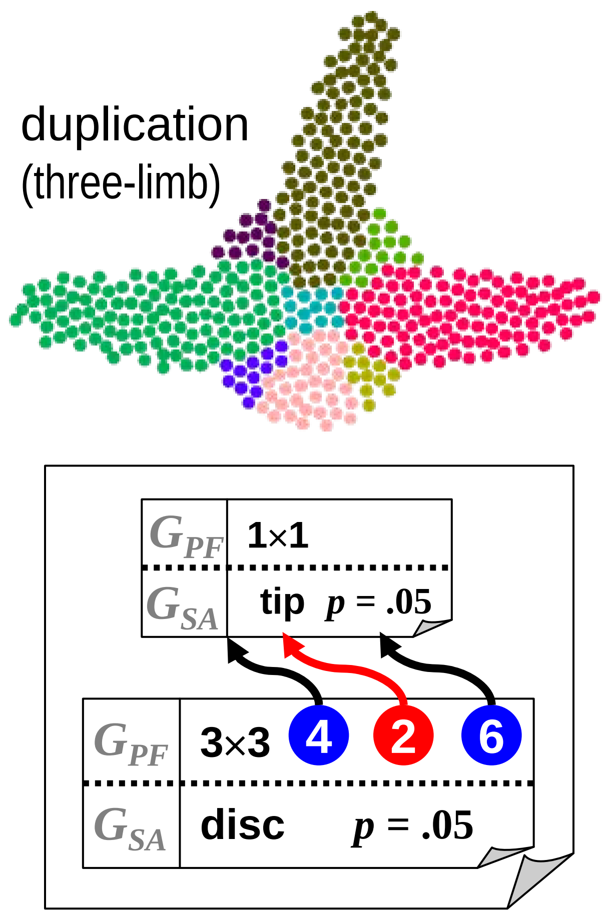
Multi-agent evolutionary development (evo-devo)

➢ Genotype mutations → phenotype variations (*qualitative*)

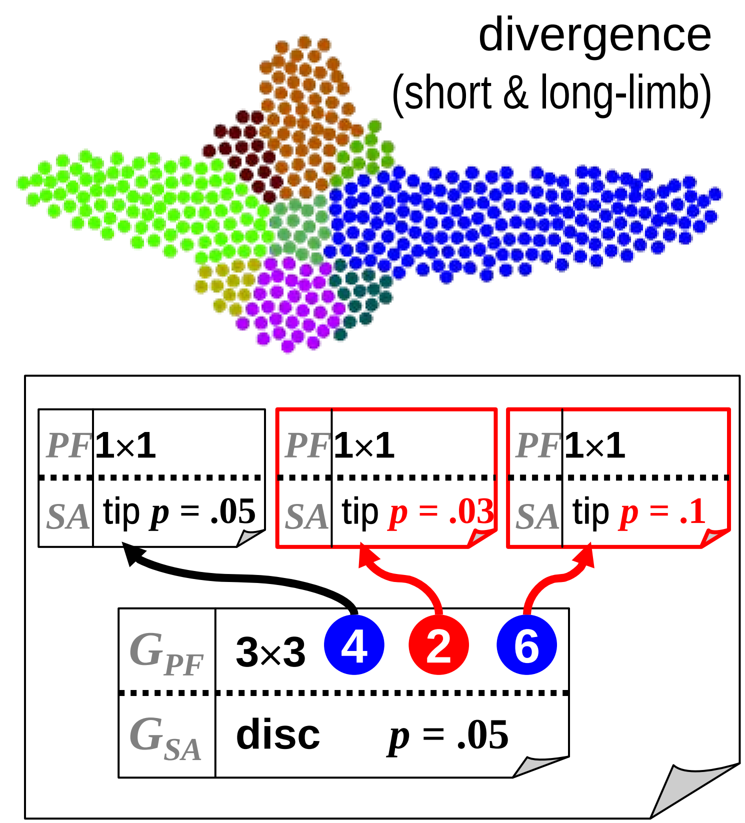
antennapedia



homology by *duplication*

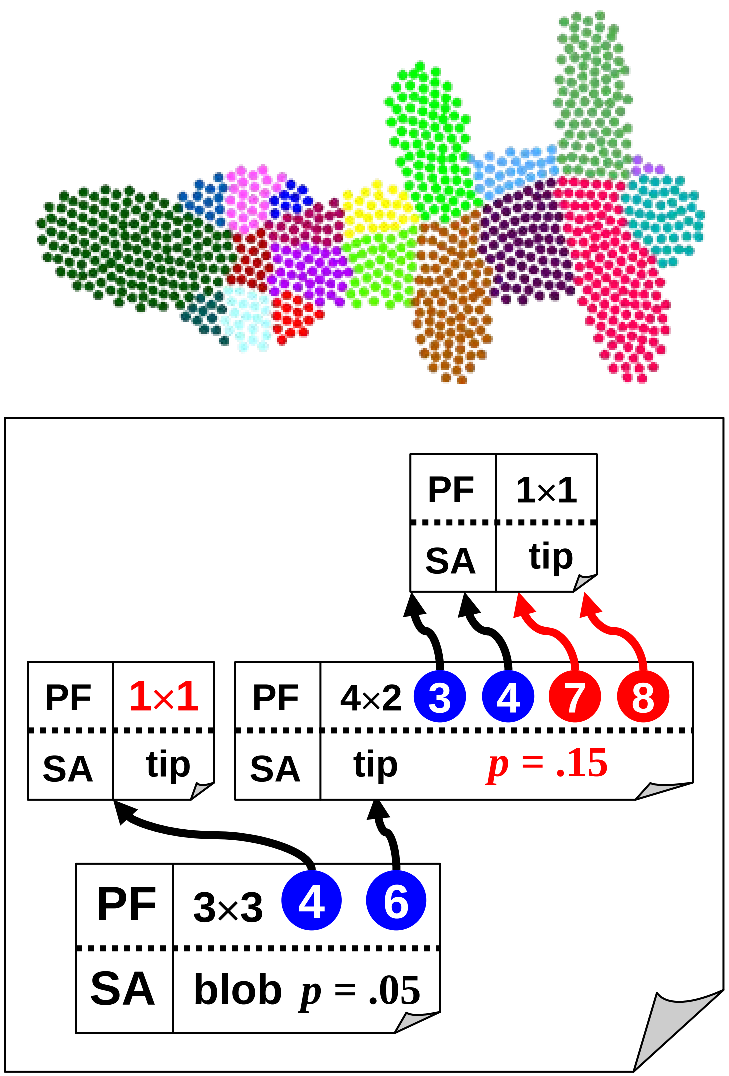


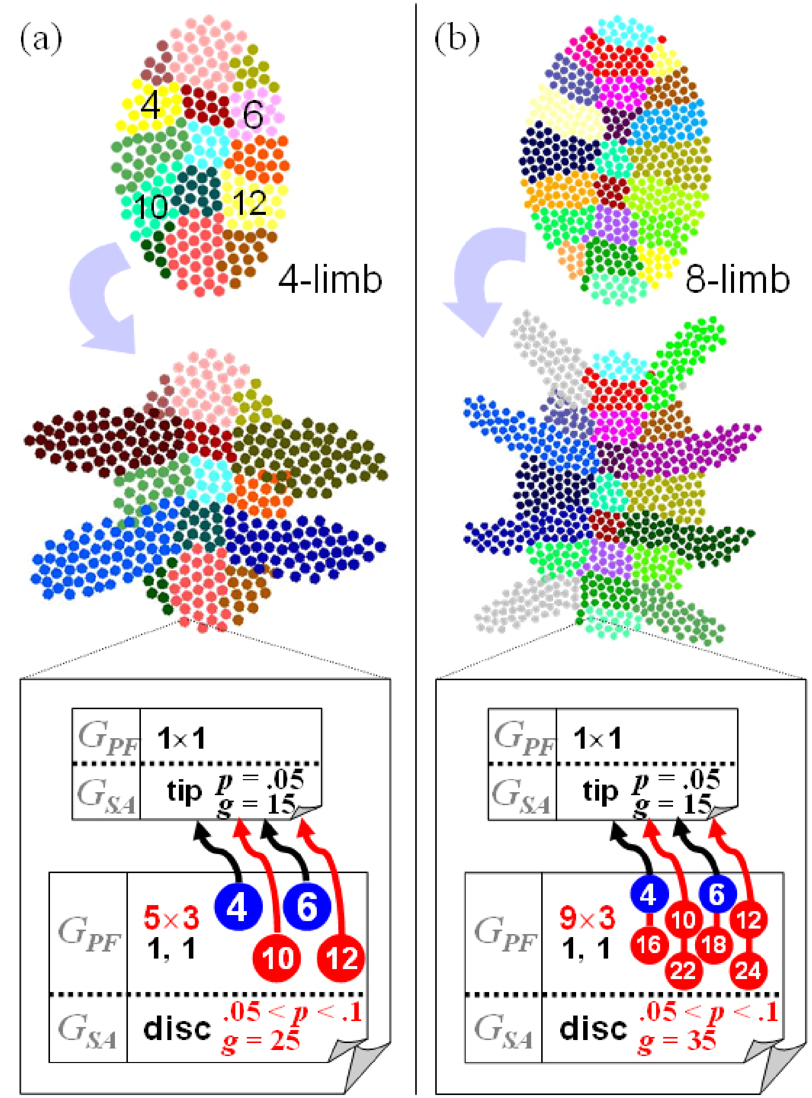
divergence of the homology



Multi-agent evolutionary development (evo-devo)

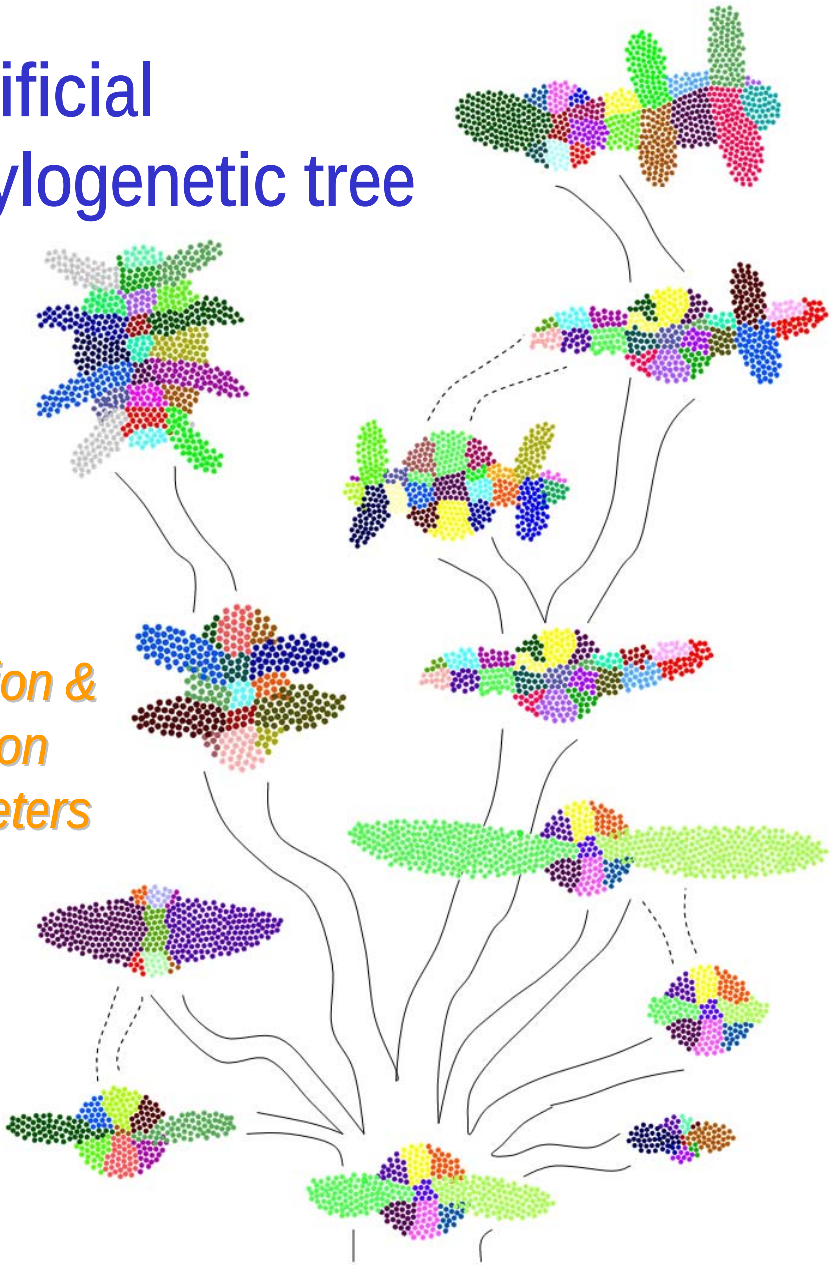
- Genotype mutations → phenotype variations (*qualitative*)





Multi-agent evolutionary development (evo-devo)

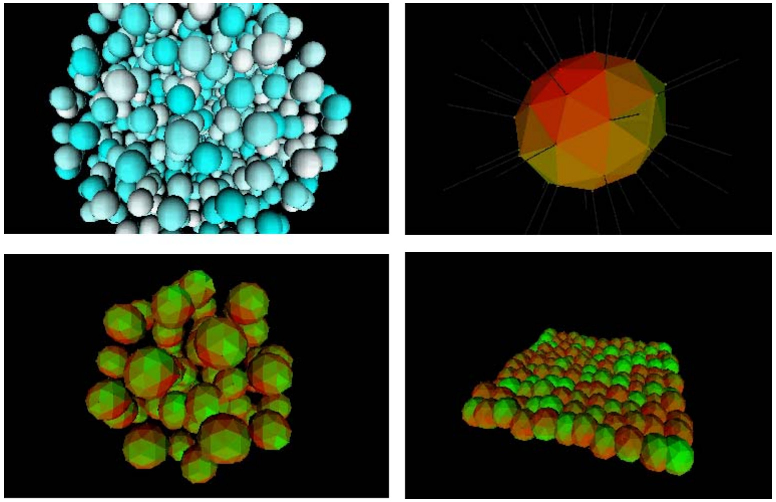
- ➢ Artificial phylogenetic tree



optimization & validation of parameters

future directions:

- better biomechanics (3D) : cytoskeleton, migration
- better gene regulation



The self-made puzzle of embryogenesis

1. Self-organized and structured systems

2. Two-side challenge: heterogeneous motion / moving patterns

3. A multi-agent model of embryogenesis

4. Evolutionary development (evo-devo)