Evolving networks *in silico*

Goals:

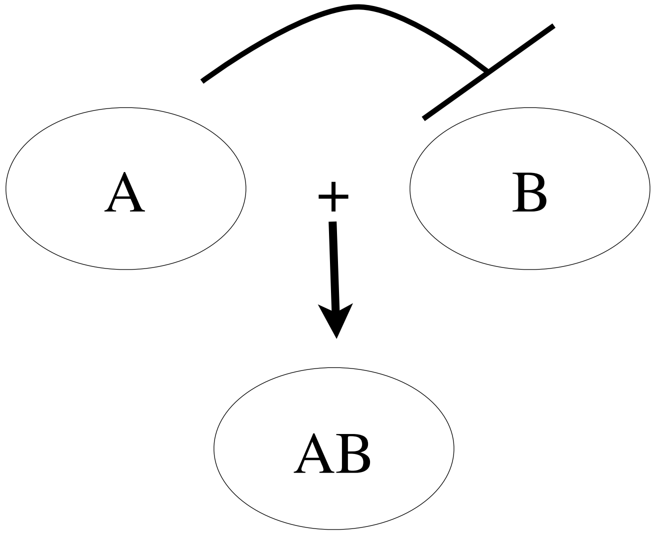
use mutation-selection to numerically evolve networks of differential equations that perform a specified phenotype

We change both topologies and kinetic parameters

See PF, V. Hakim (2004) and multiple publications since then

Equations

Mass-action laws
+
Hill functions for transcription

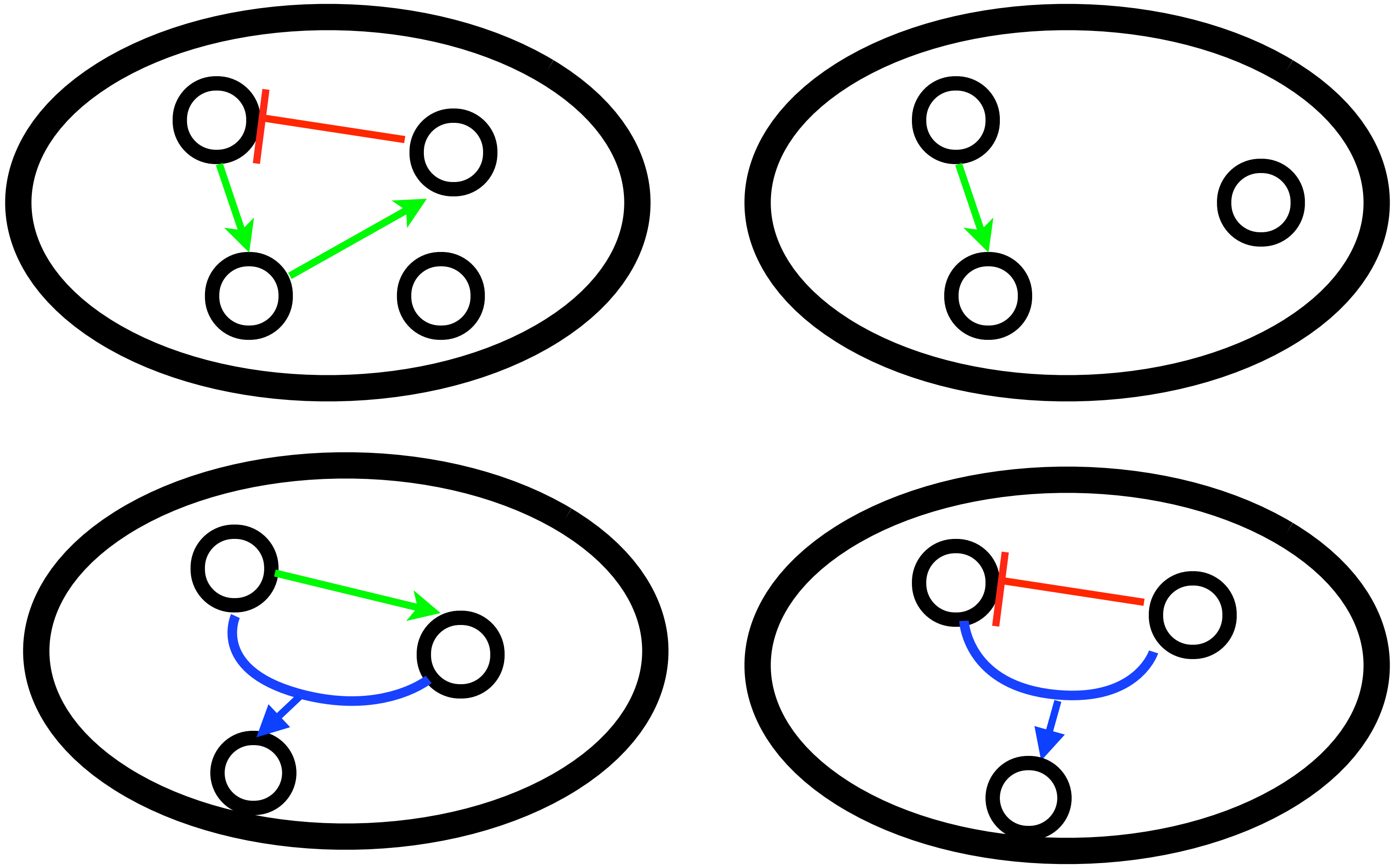


$$\frac{d[A]}{dt} = \dots$$

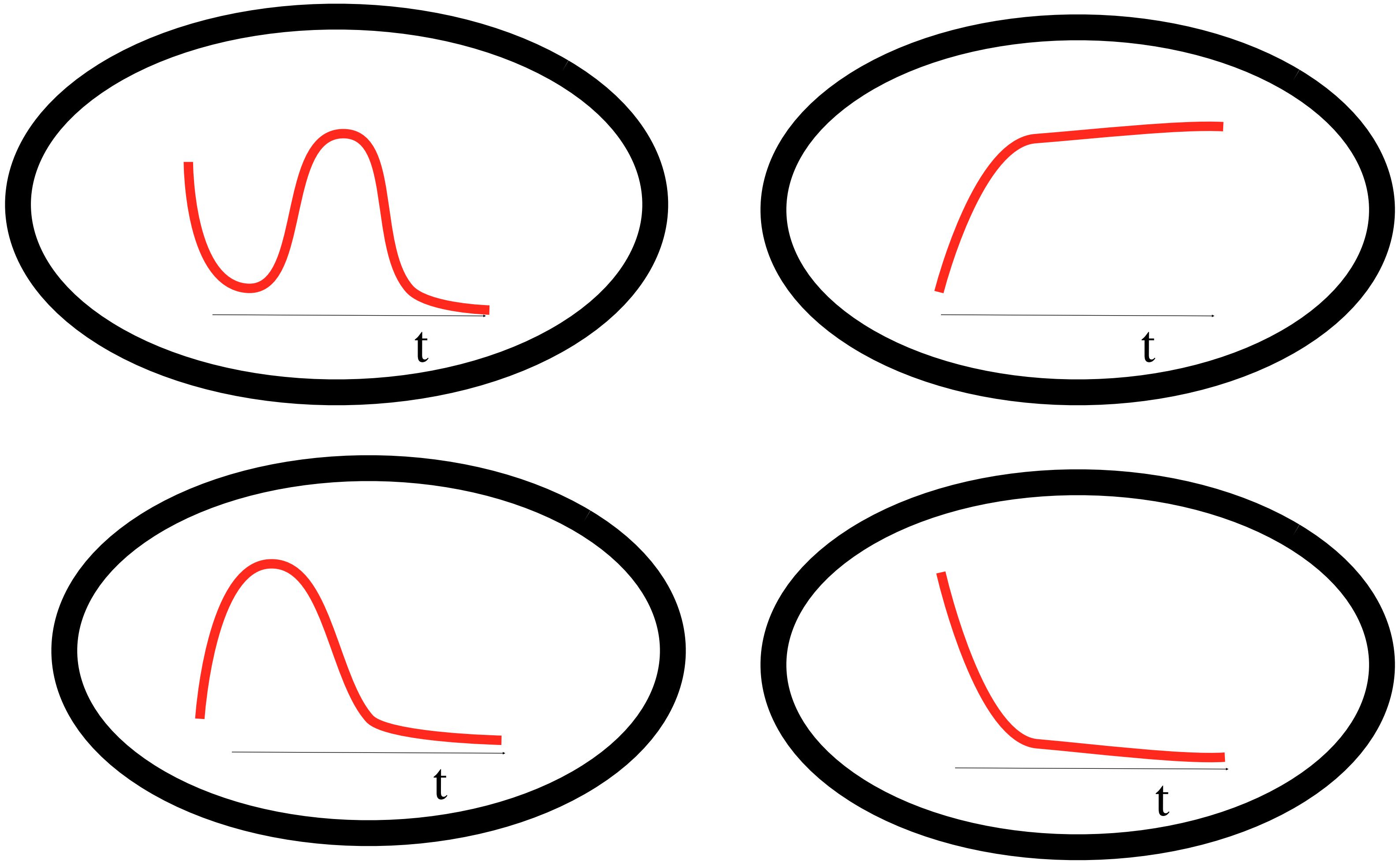
$$\frac{d[B]}{dt} = \frac{\rho}{1 + ([A]/A_0)^n} - \gamma[A][B] + \theta[AB] - \delta_B[B]$$

$$\frac{d[AB]}{dt} = \dots$$

Population of different networks

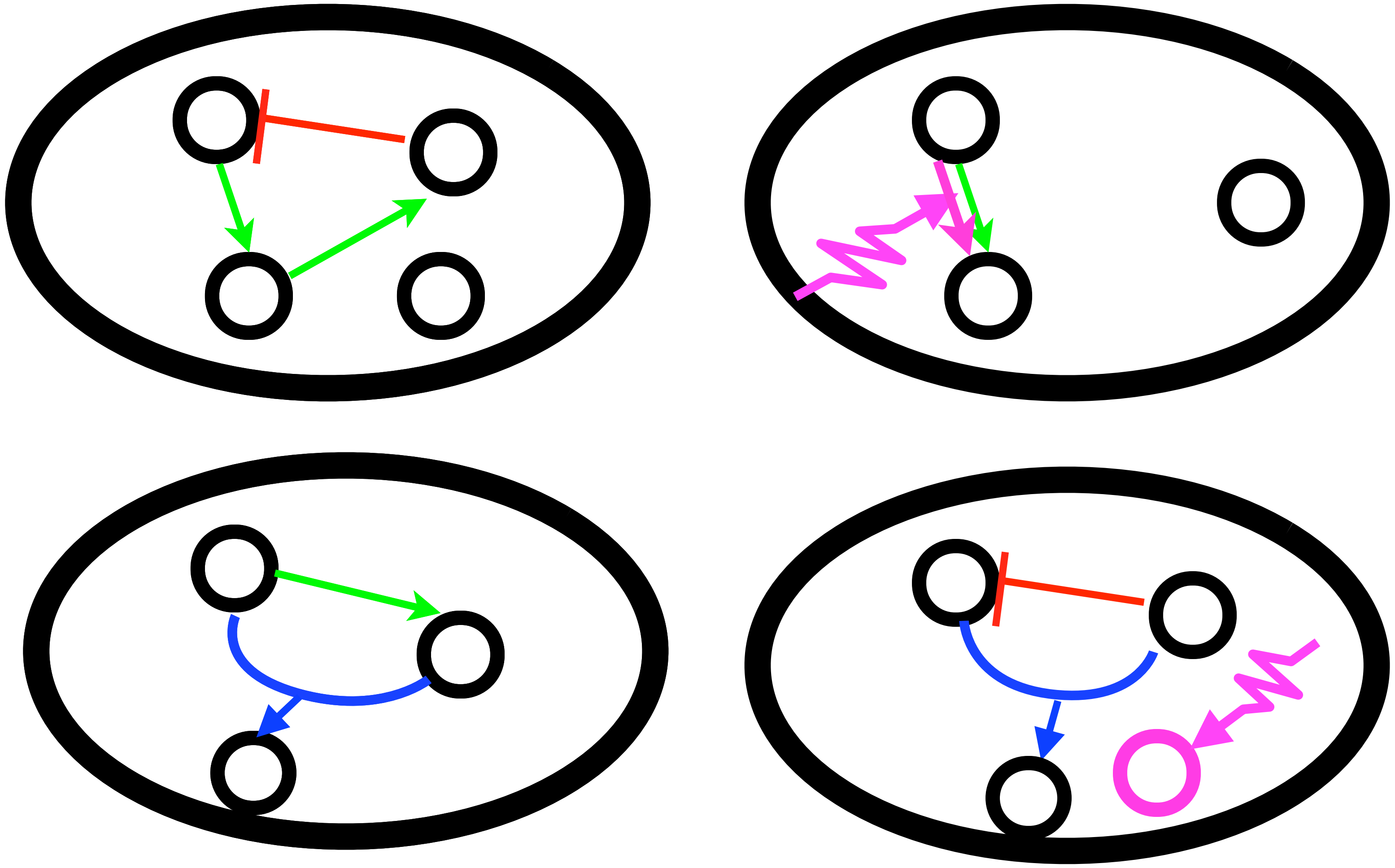


Time integration : selection for oscillators ...

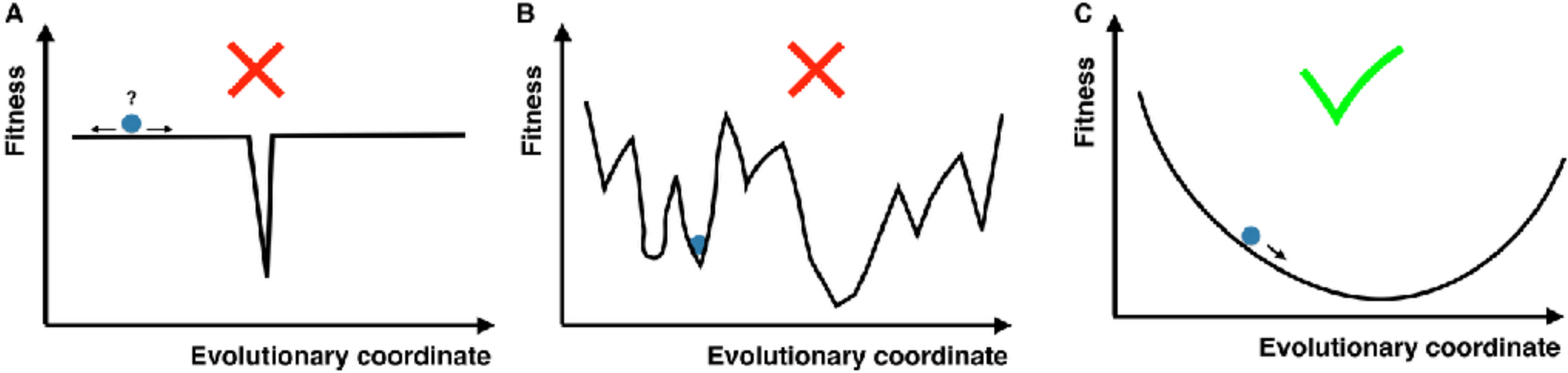


One reporter, here we compare its dynamics to an “ideal” behaviour

Population of different networks



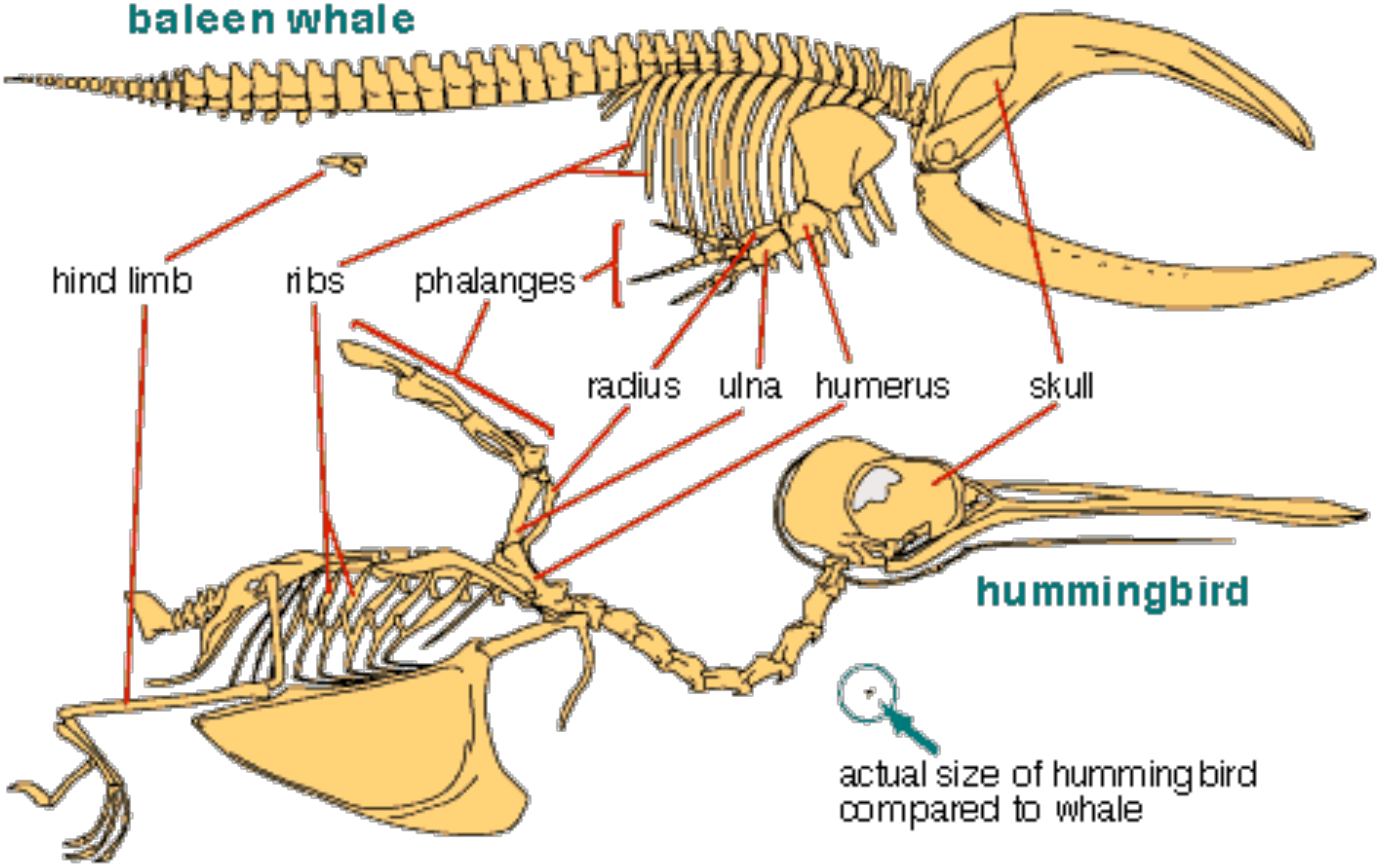
How to define a good “fitness” ?



Stragegy: coarse-grained description of phenotypes.
Multidimensional problem: mutual information based fitness works pretty well
Also: Pareto evolution (Warmflash, PF, Siggia, 2012)

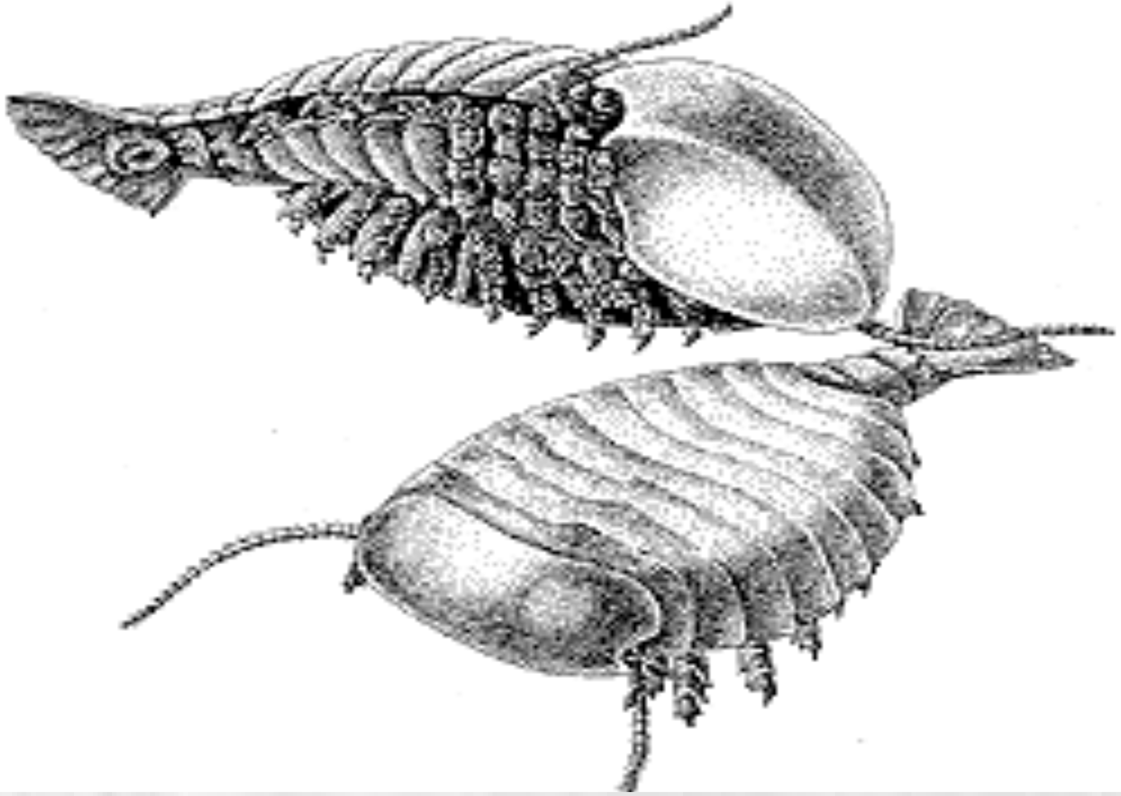
http://phievo.readthedocs.io/en/latest/

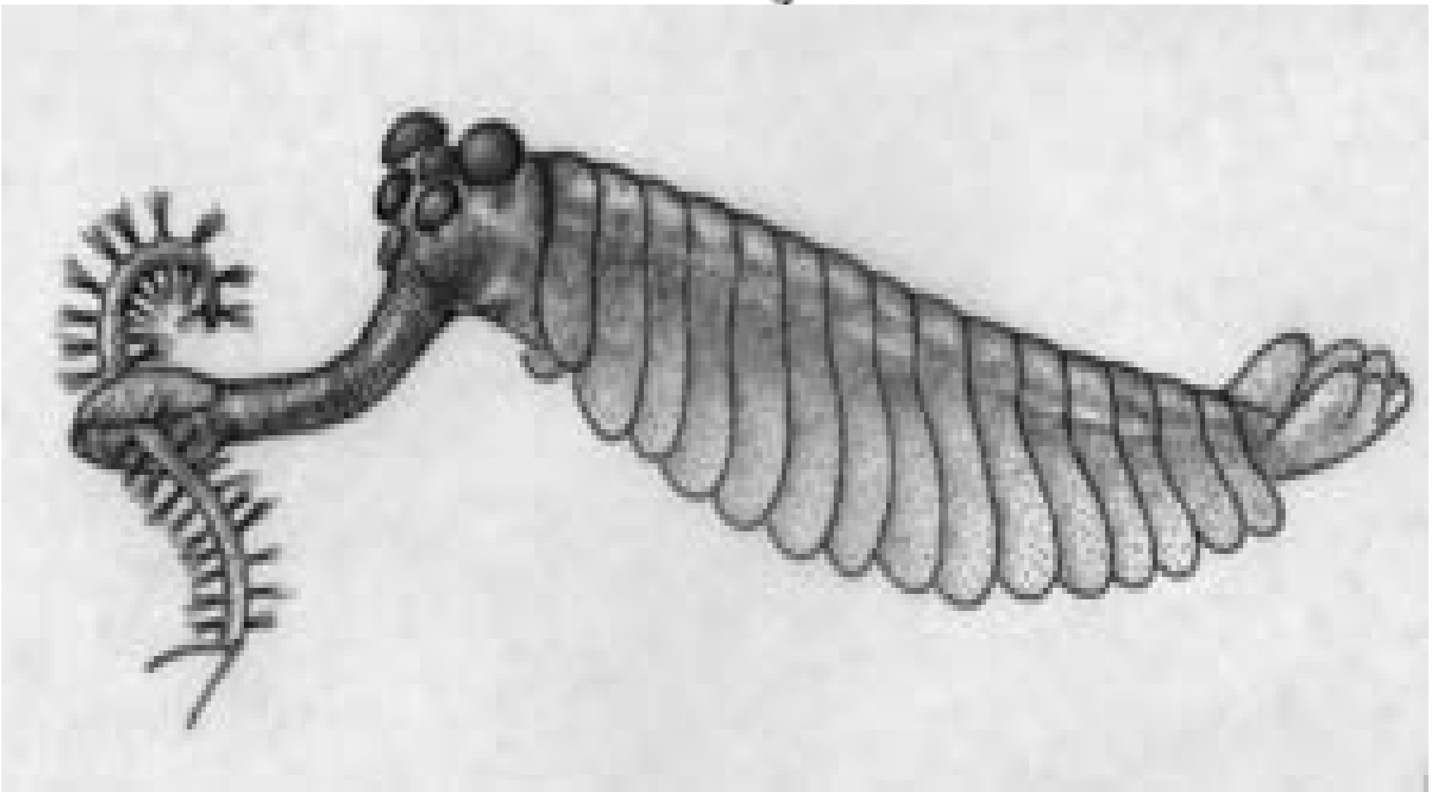
https://www.youtube.com/watch?v=FRPc_hWm_JI

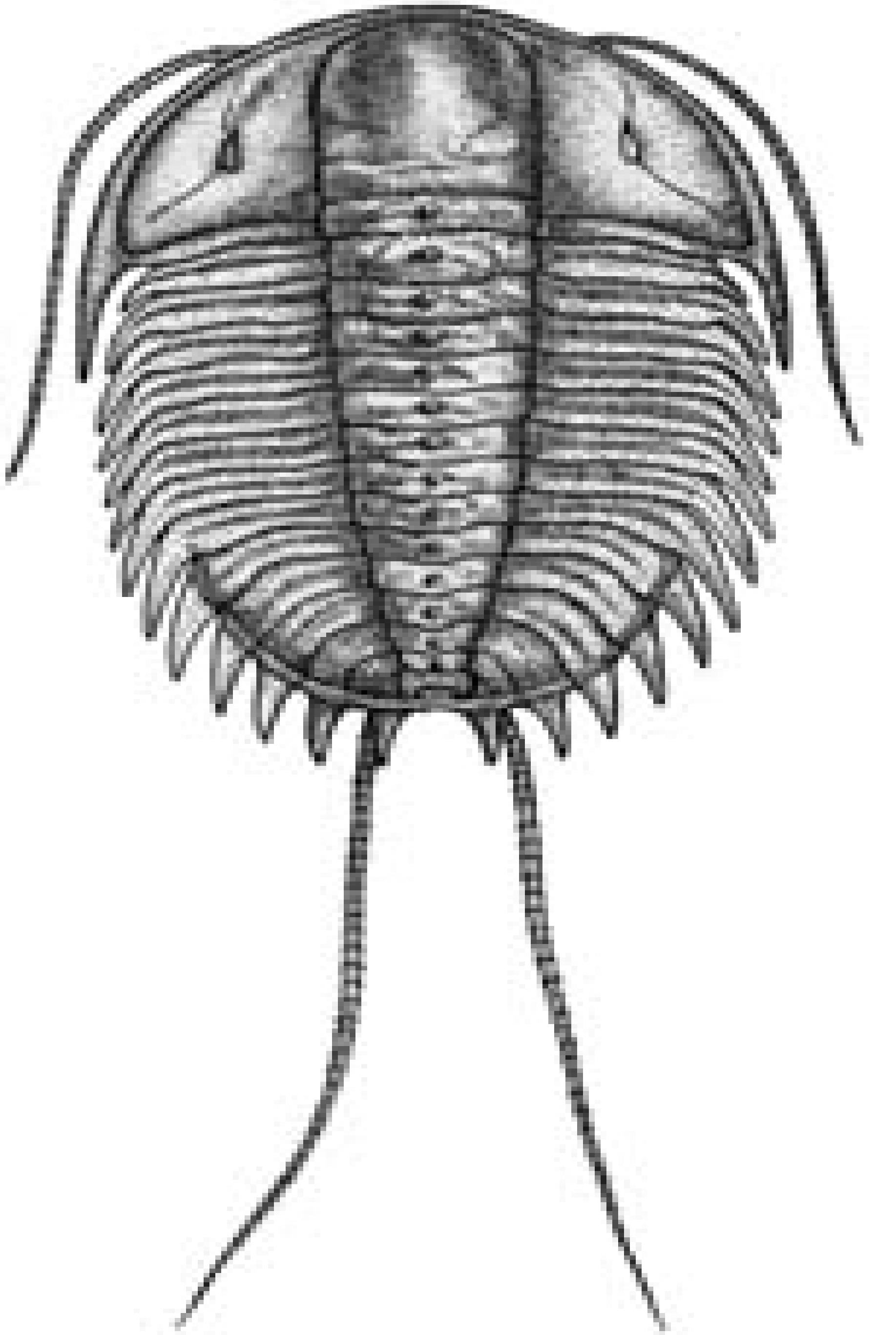


source: evolution.berkeley.edu

Segmentation almost as old as animals (Cambrian)

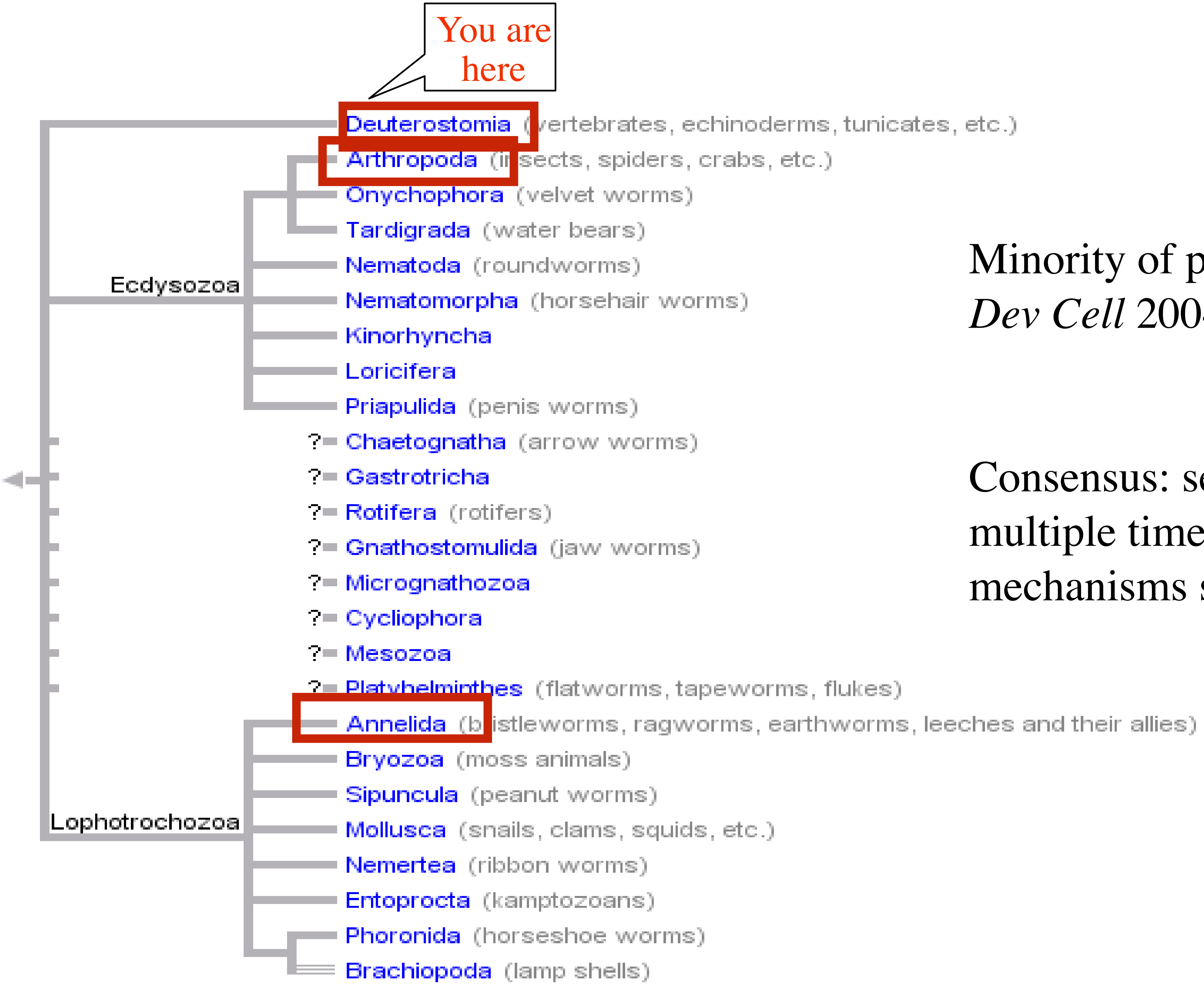






http://www.usask.ca/diefenbaker/gallery.html

Bilaterians (tolweb.org)



You are here

Deuterostomia (vertebrates, echinoderms, tunicates, etc.)

Ecdysozoa
- Arthropoda (i sects, spiders, crabs, etc.)
- Onychophora (velvet worms)
- Tardigrada (water bears)
- Nematoda (roundworms)
- Nematomorpha (horsehair worms)
- Kinorhyncha
- Loricifera
- Priapulida (penis worms)

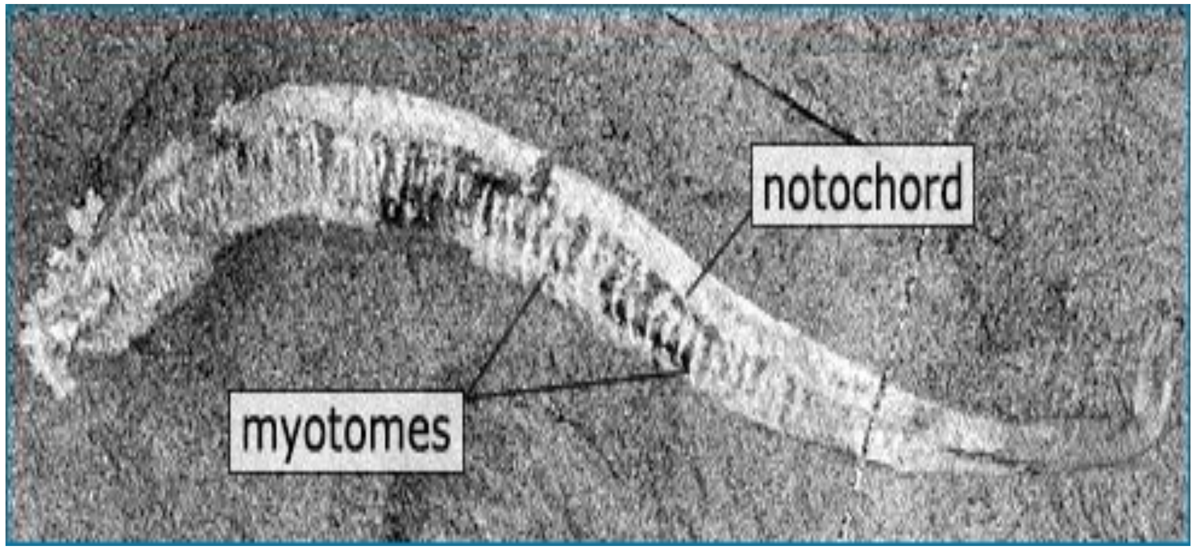
?= Chaetognatha (arrow worms)
?= Gastrotricha
?= Rotifera (rotifers)
?= Gnathostomulida (jaw worms)
?= Micrognathozoa
?= Cycliophora
?= Mesozoa
?= Platyhelminthes (flatworms, tapeworms, flukes)

Lophotrochozoa
- Annelida (b istleworms, ragworms, earthworms, leeches and their allies)
- Bryozoa (moss animals)
- Sipuncula (peanut worms)
- Mollusca (snails, clams, squids, etc.)
- Nemertea (ribbon worms)
- Entoprocta (kamptozoans)
- Phoronida (horseshoe worms)
- Brachiopoda (lamp shells)

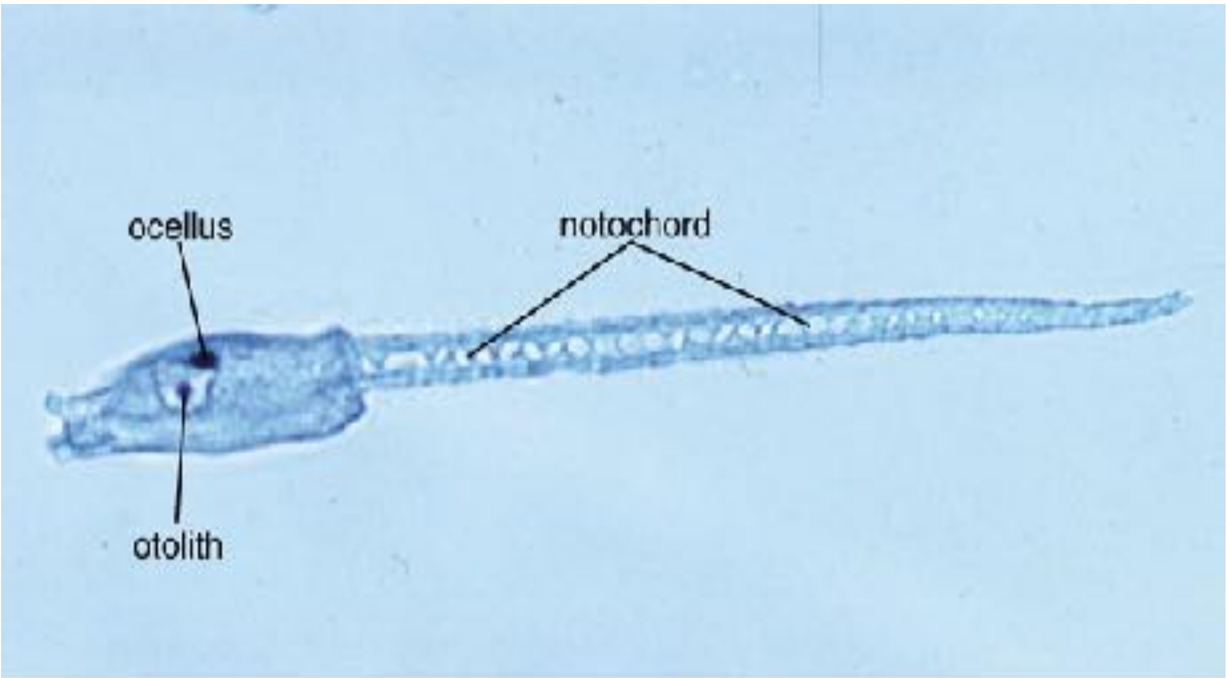
Minority of phyla segmented (Tautz *Dev Cell* 2004)

Consensus: segmentation evolved multiple times, molecular mechanisms similar within phyla

Chordate segmentation



Pikia possible cambrian ancestor of ascidians (//evolution.berkeley.edu)



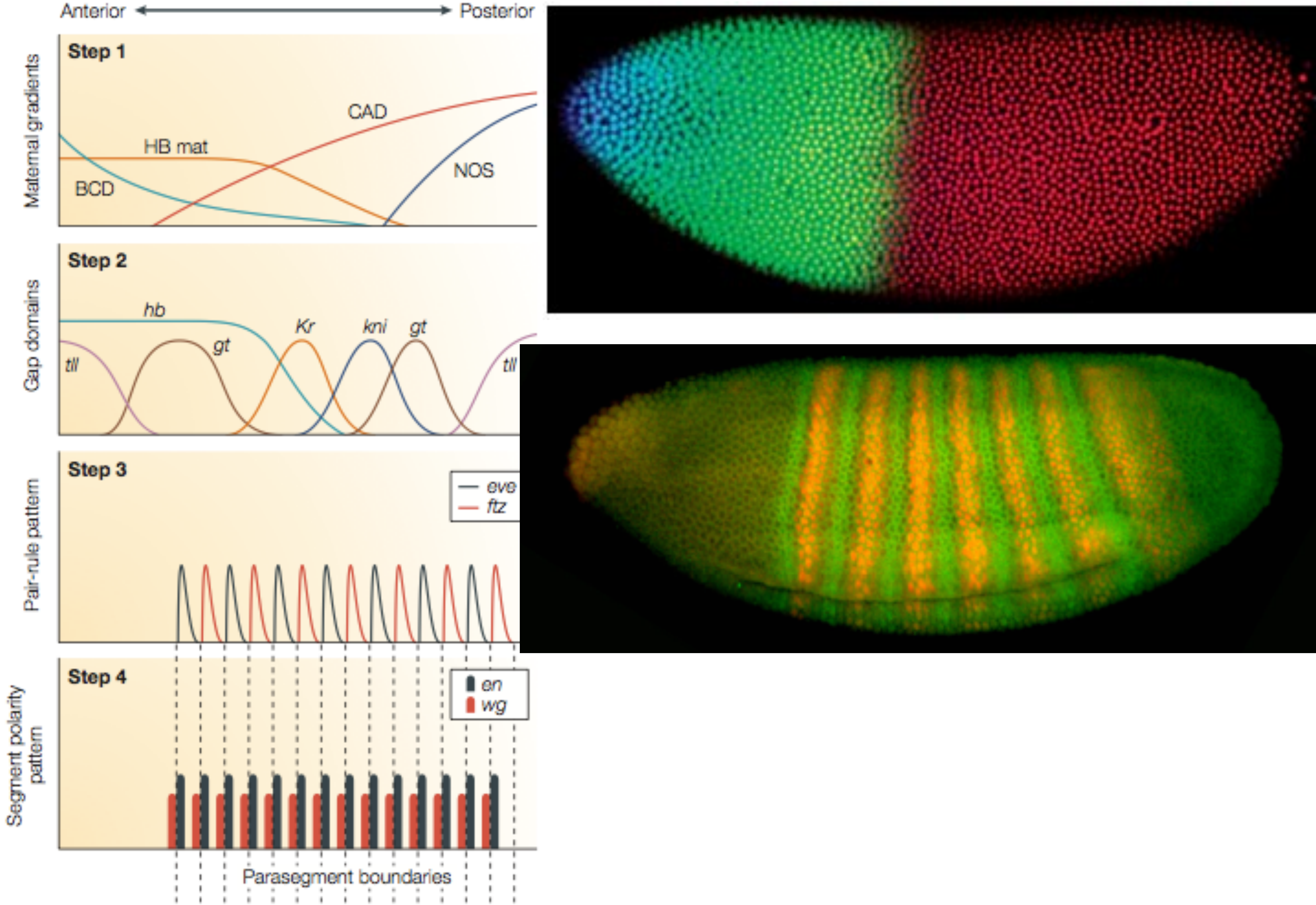
→

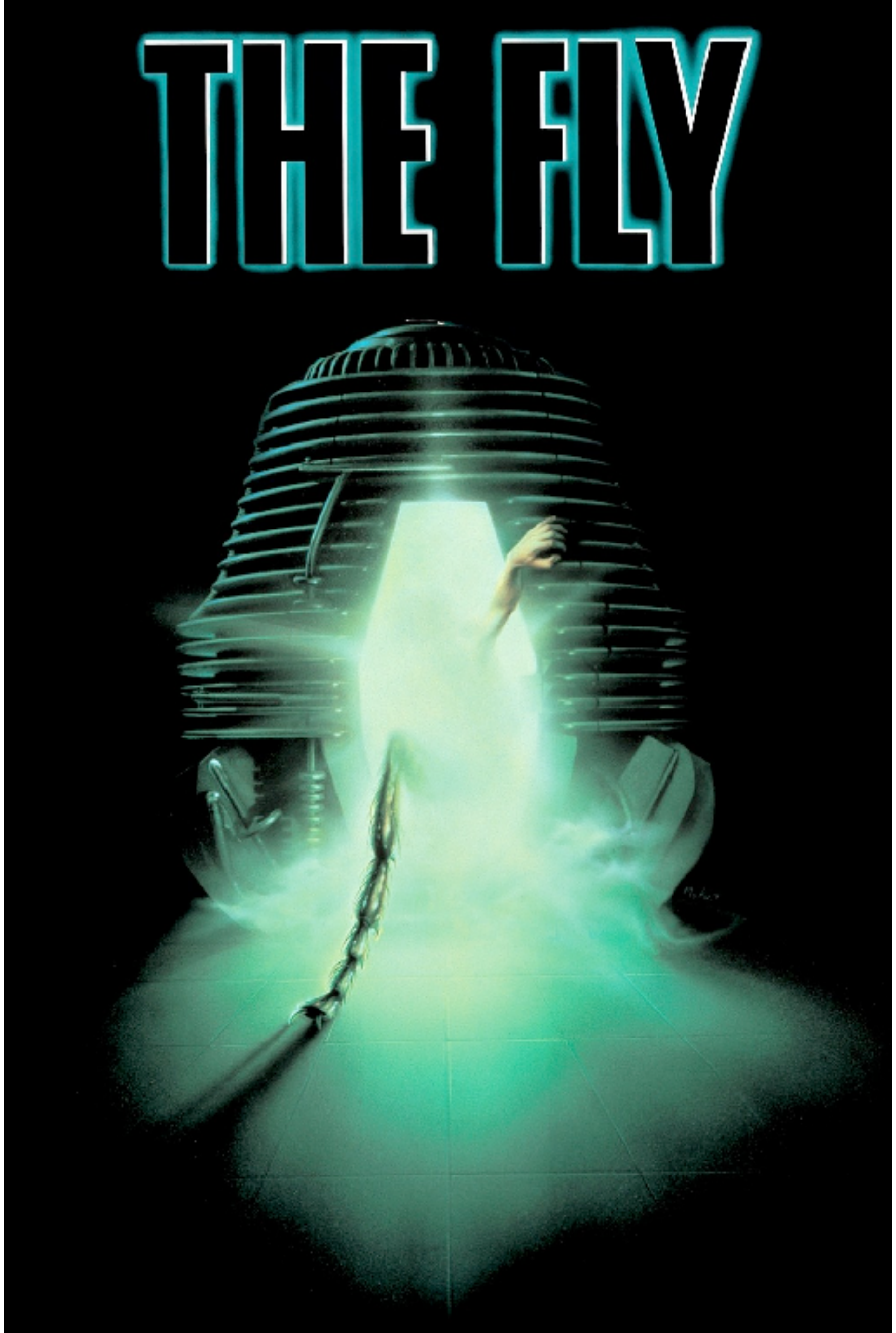
Ascidians, non-vertebrate chordates: tadpole larvae

Lemaire, *Science* 2006

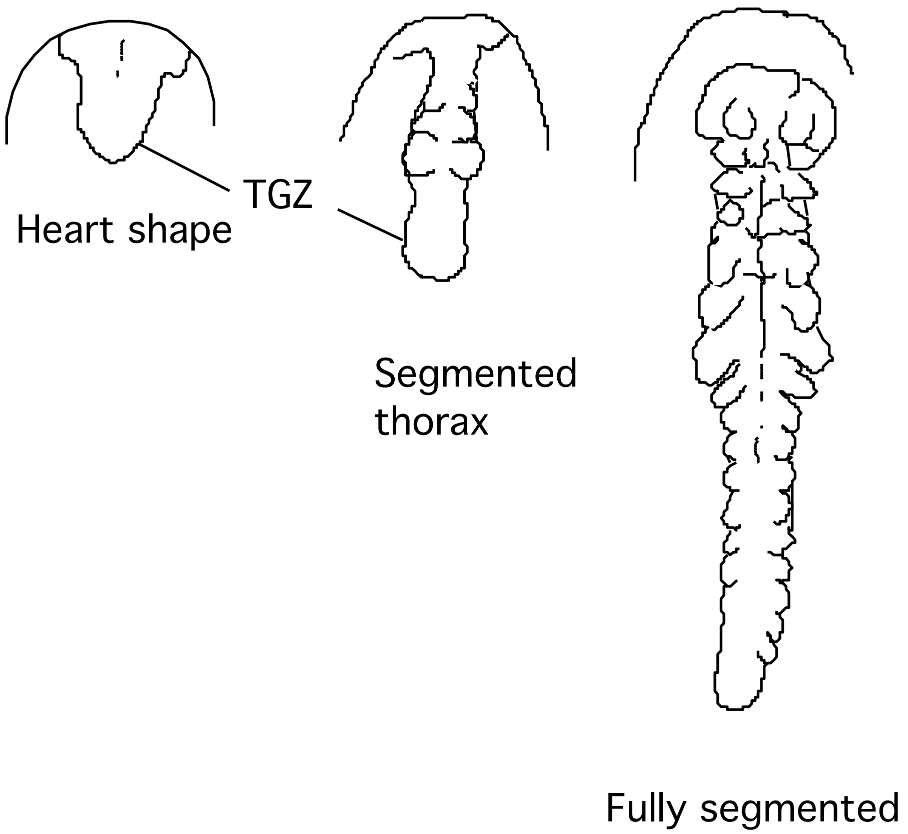
Frog tadpole

A classical paradigm: fly

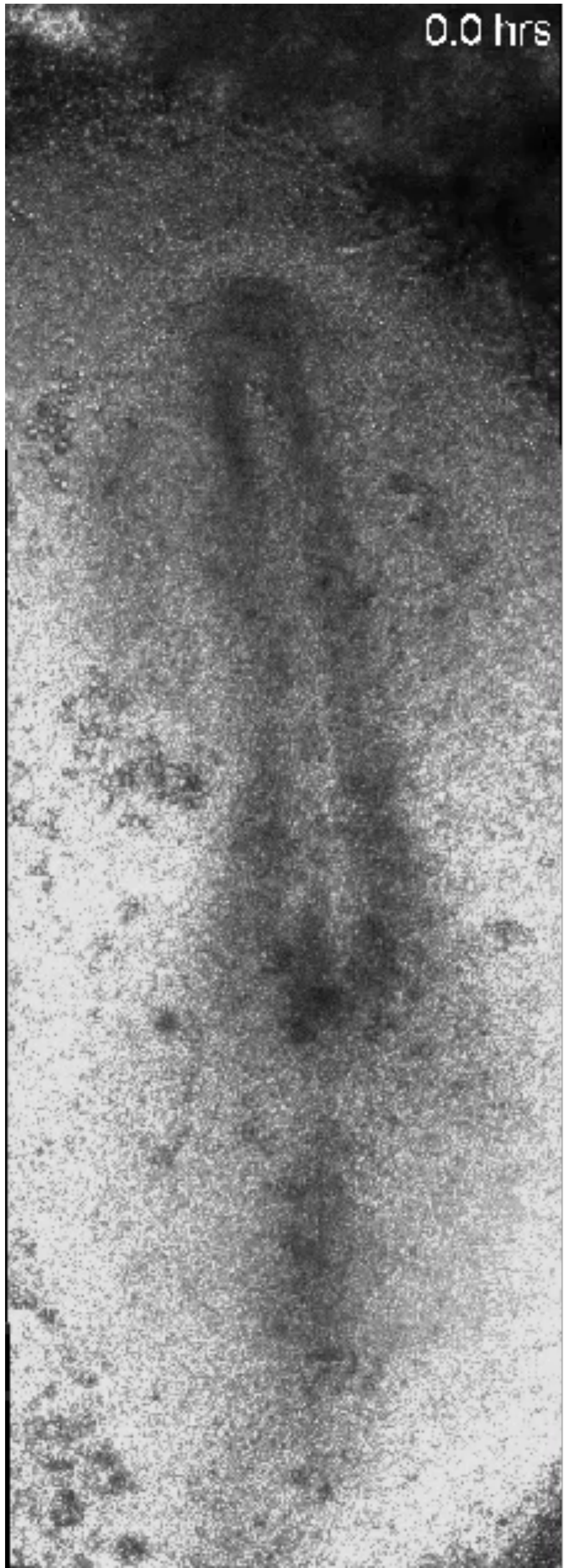



THE FLY

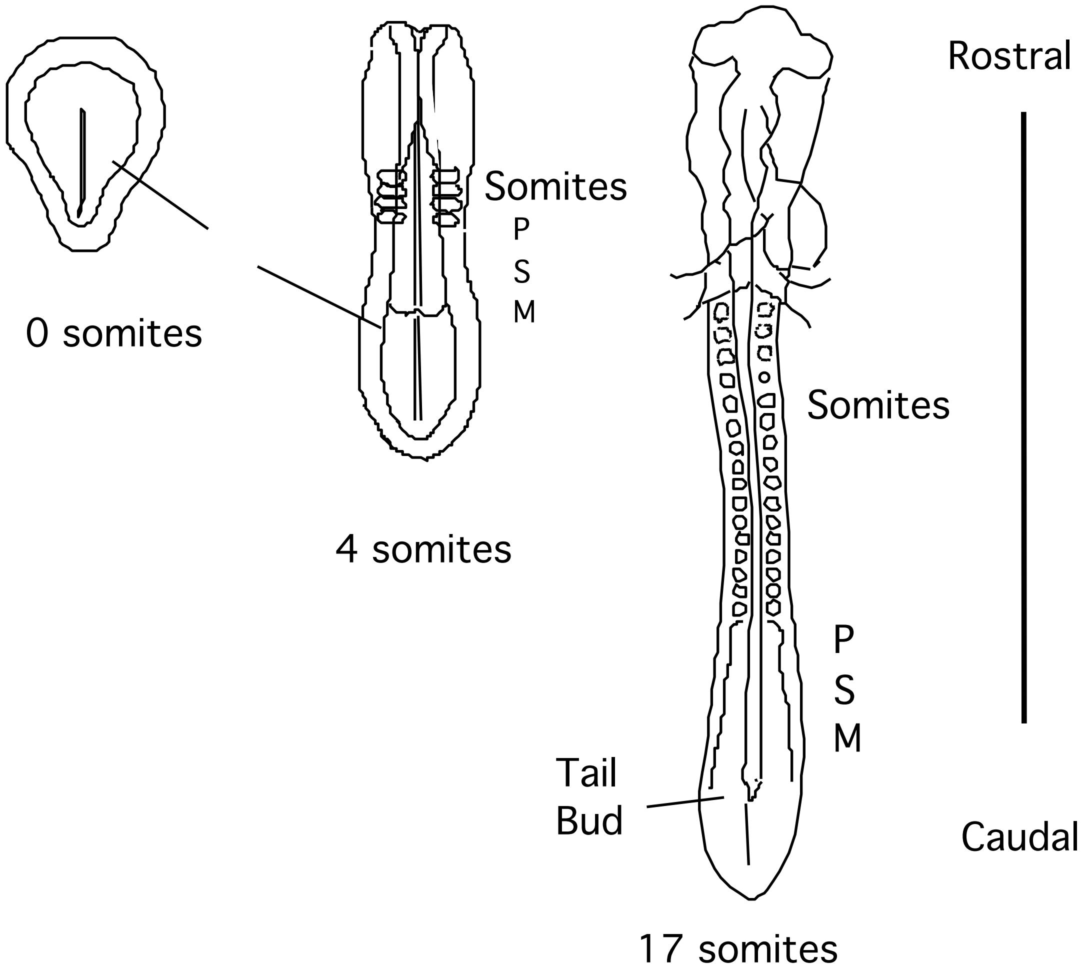
In most animal species, the body axis progressively forms by posterior elongation



Most arthropods

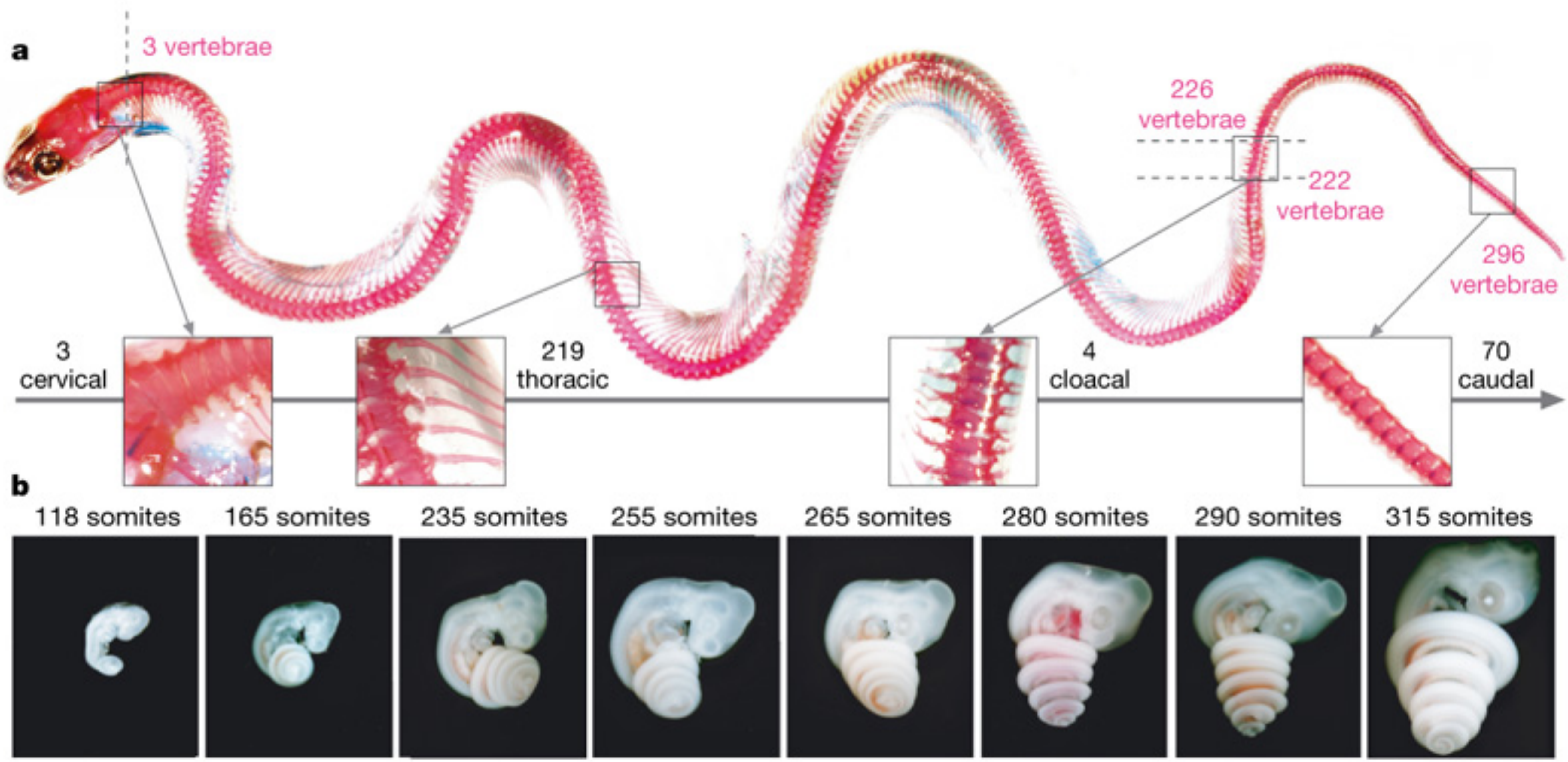


Chick

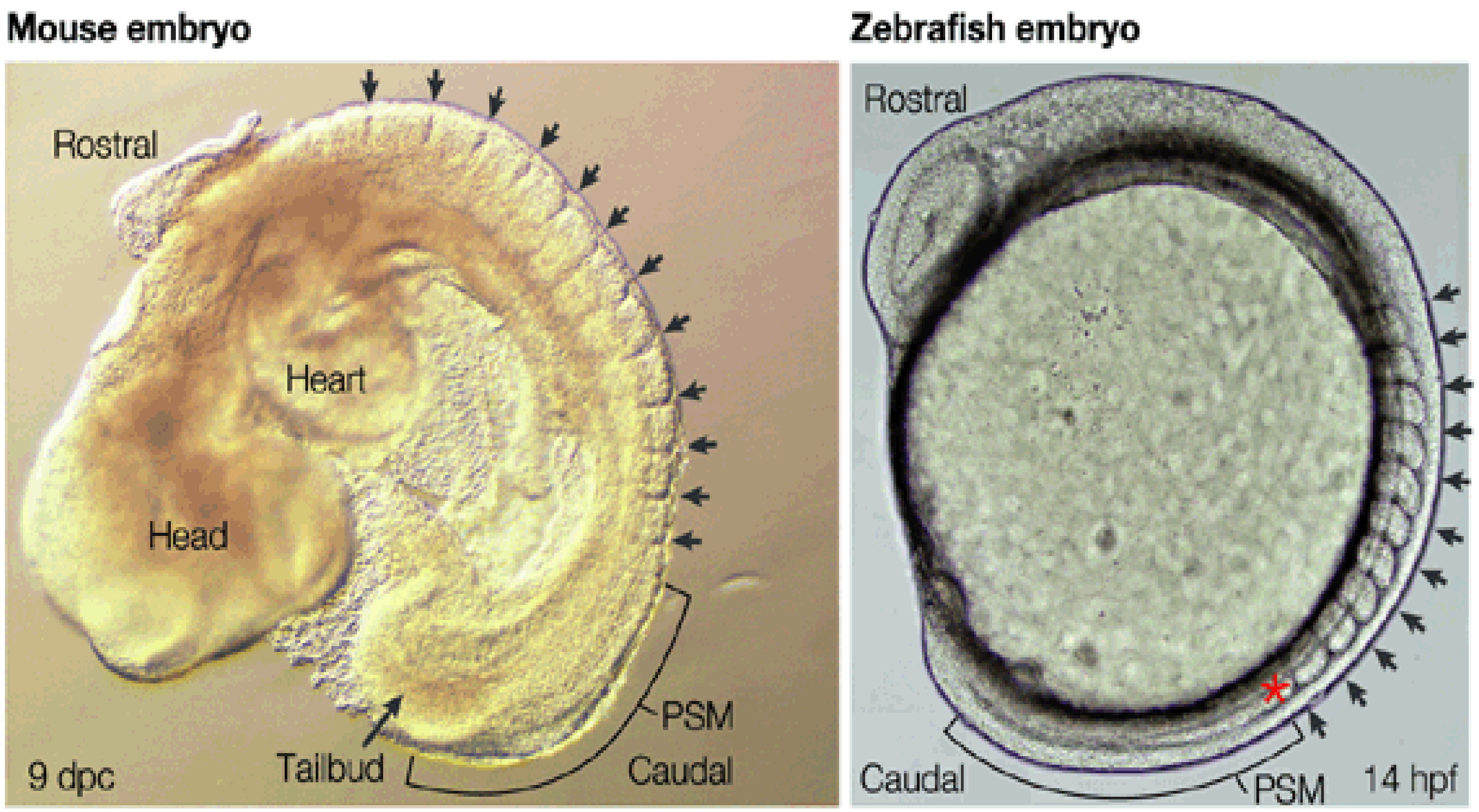


(Movie : Pourquié's lab)

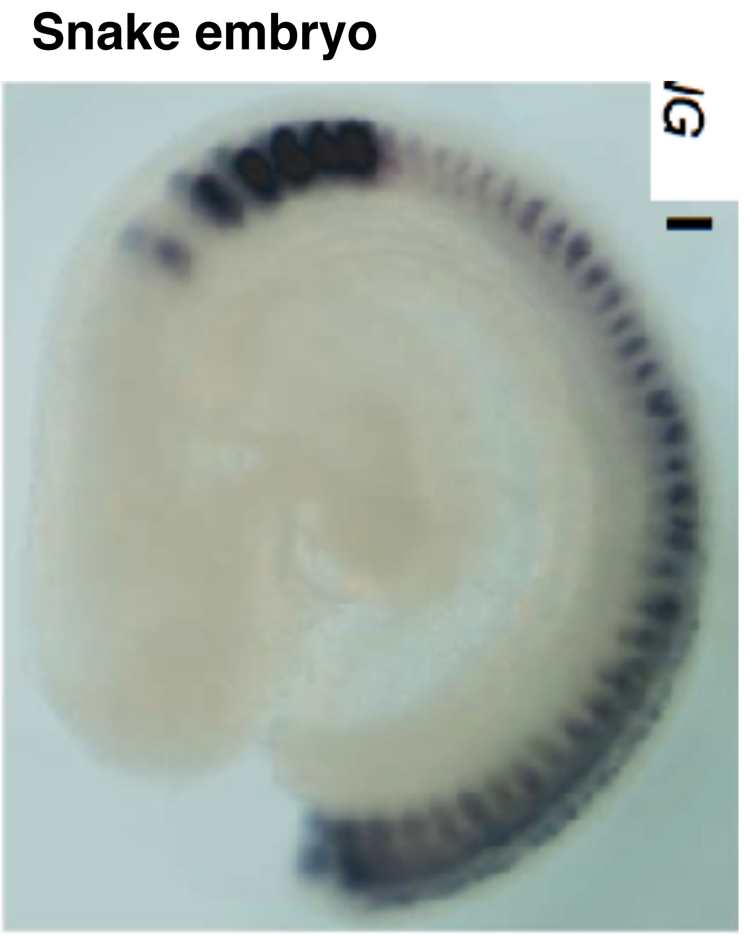
Gomez et al. Nature, 2008



Somitogenesis : sequential segmentation from PSM



Nature Reviews | Genetics

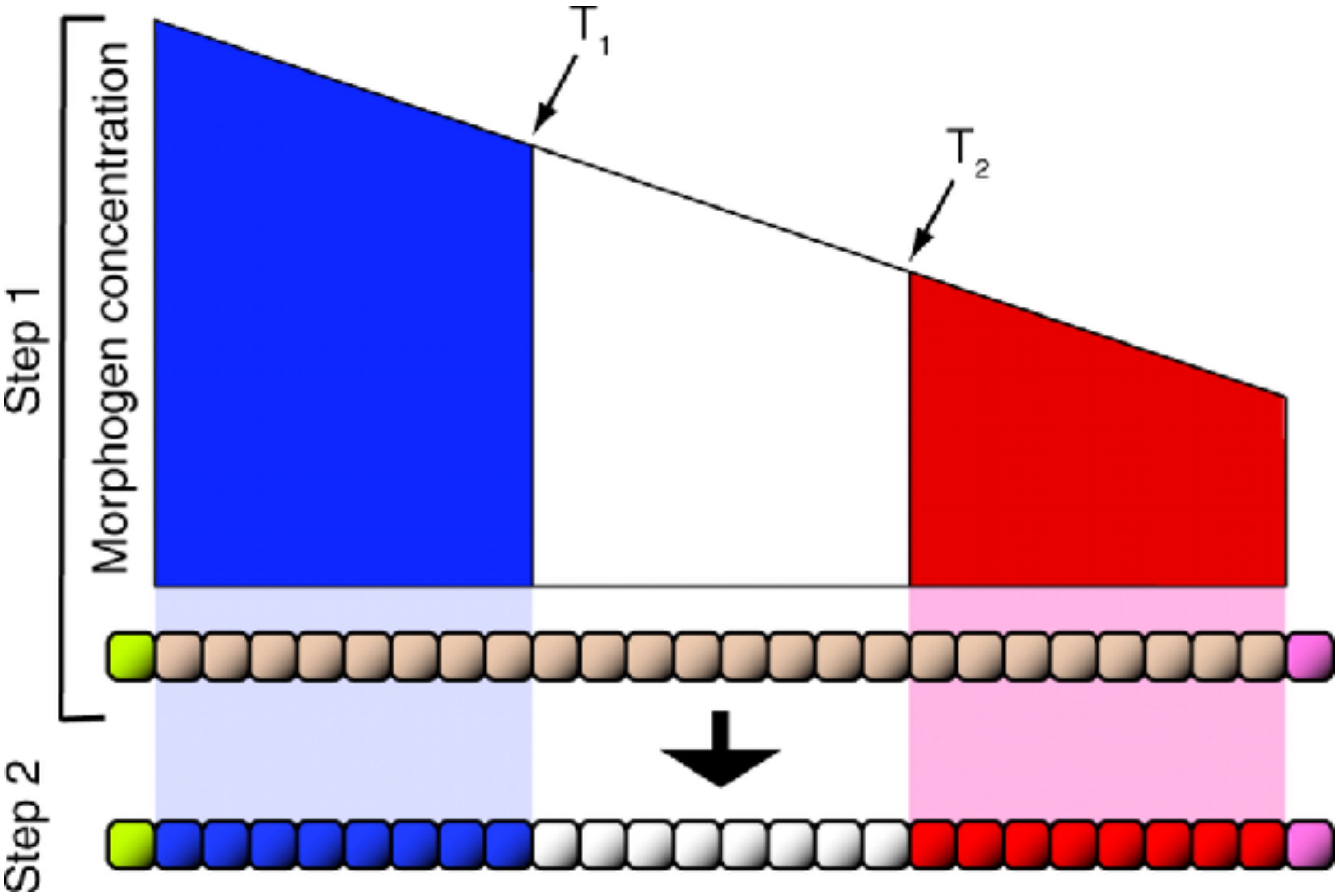


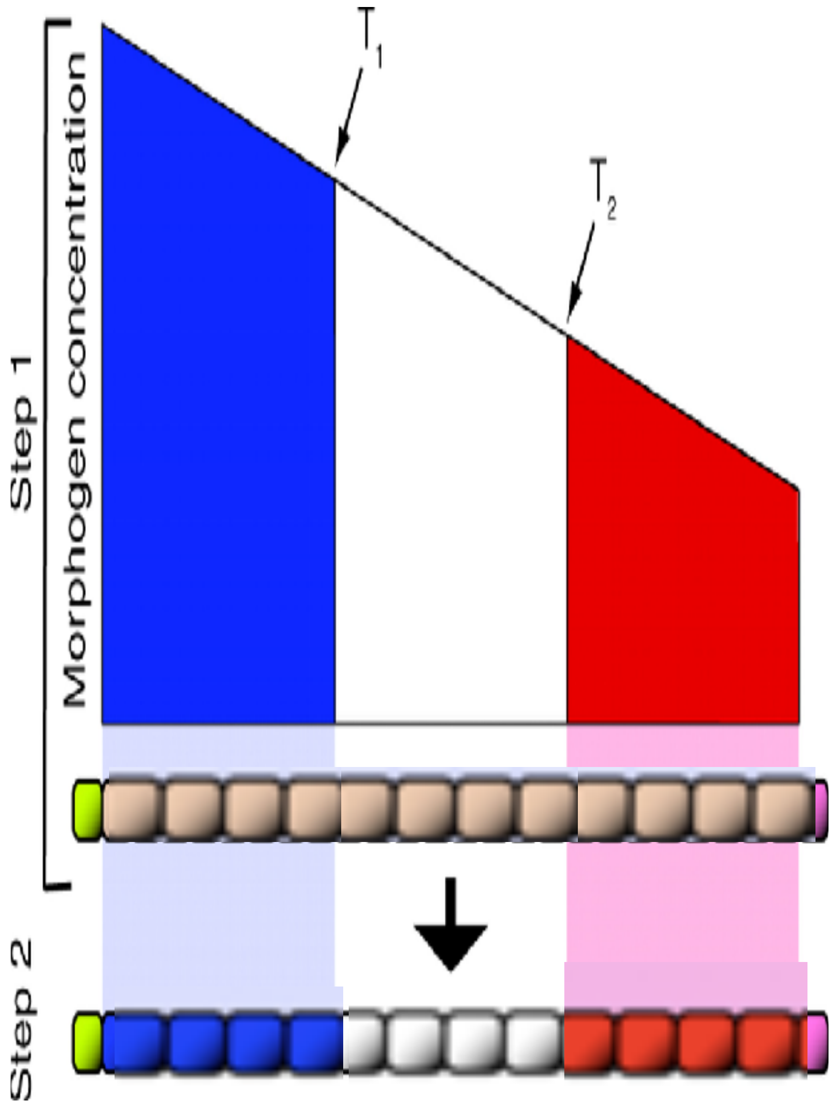
Saga & Takeda 2001

Gomez et al 2008

PSM= Pre Somitic Mesoderm

A solution ? French Flag Model (~ fly)

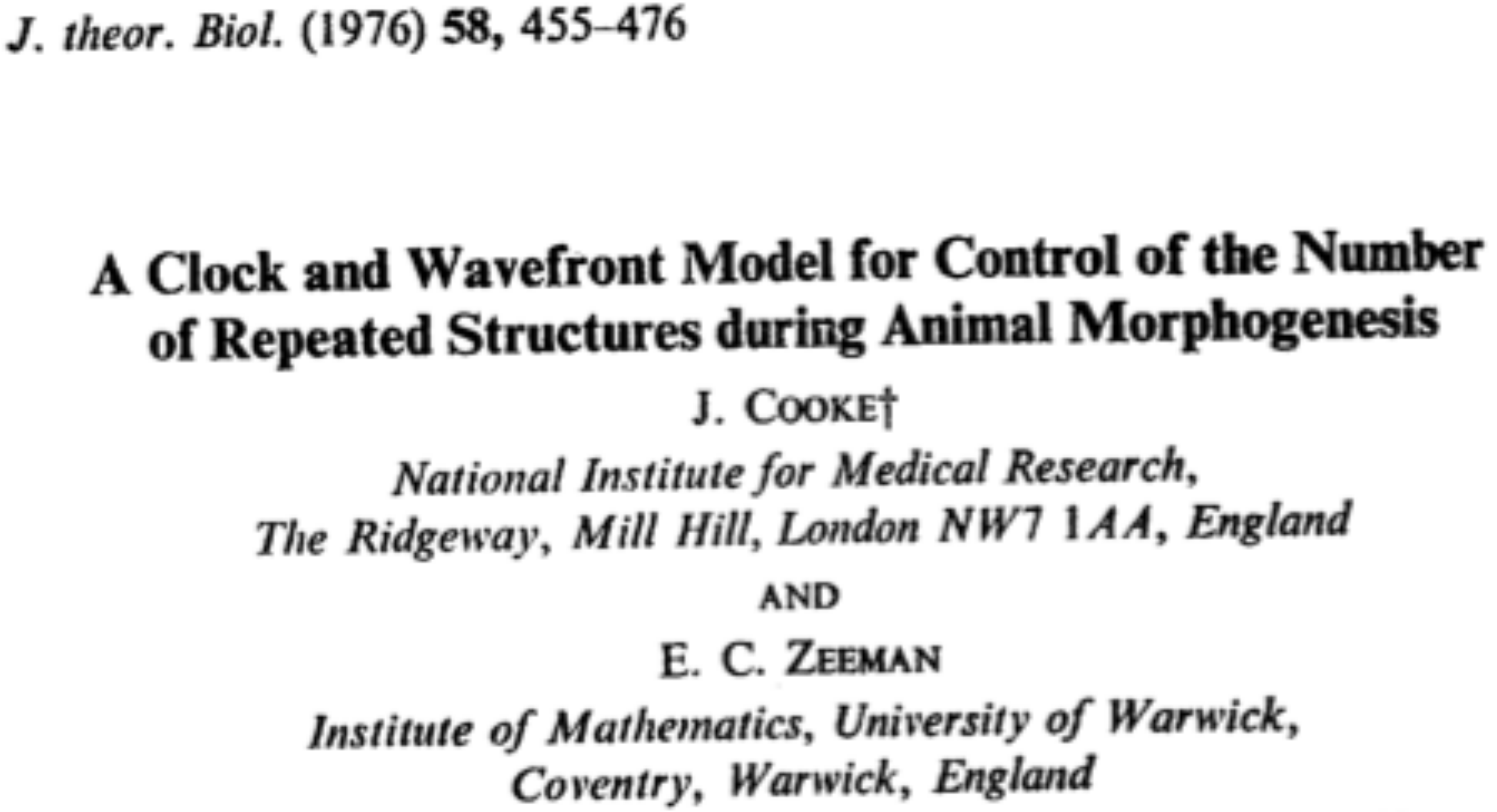




Cooke and Zeeman consider it implausible: too many thresholds to define (think about the snake !),

number of somites not so strongly controlled within body regions, etc..

The Clock and Wavefront model



J. theor. Biol. (1976) **58,** 455–476

A Clock and Wavefront Model for Control of the Number of Repeated Structures during Animal Morphogenesis

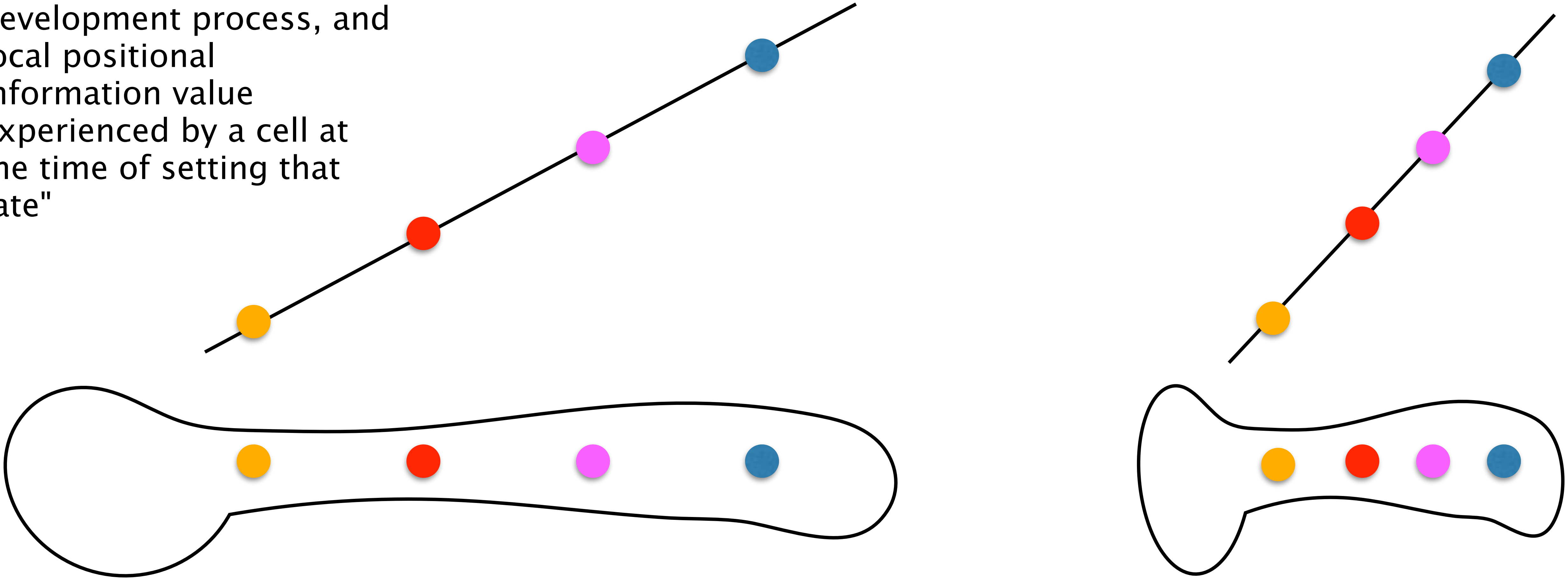
J. COOKE†
National Institute for Medical Research,
The Ridgeway, Mill Hill, London NW7 1AA, England

AND

E. C. ZEEMAN
Institute of Mathematics, University of Warwick,
Coventry, Warwick, England

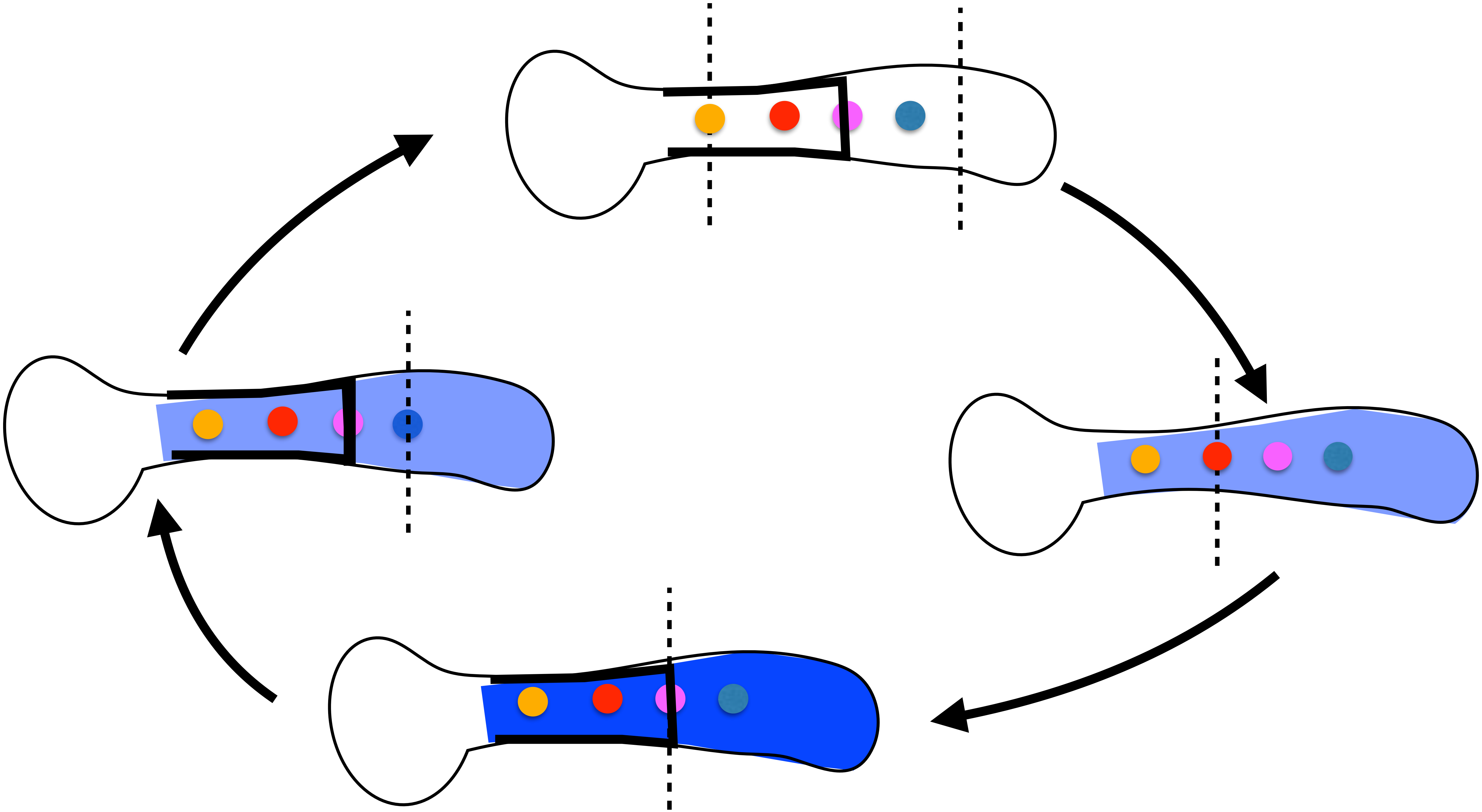
Idea 1: French Flag Model on a continuous dynamical variable

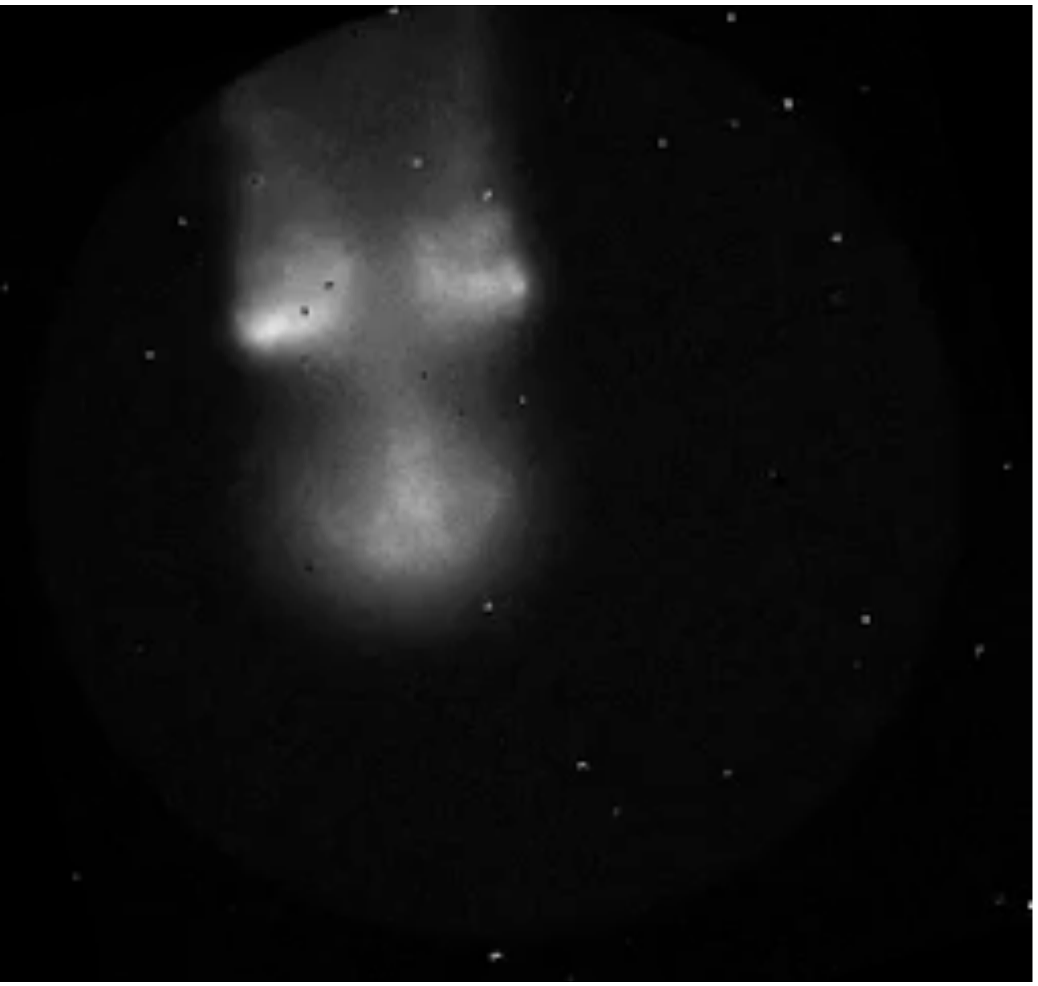
"We shall assume a fixed monotonic relation between **RATE** of an intracellular evolution of development process, and local positional information value experienced by a cell at the time of setting that rate"

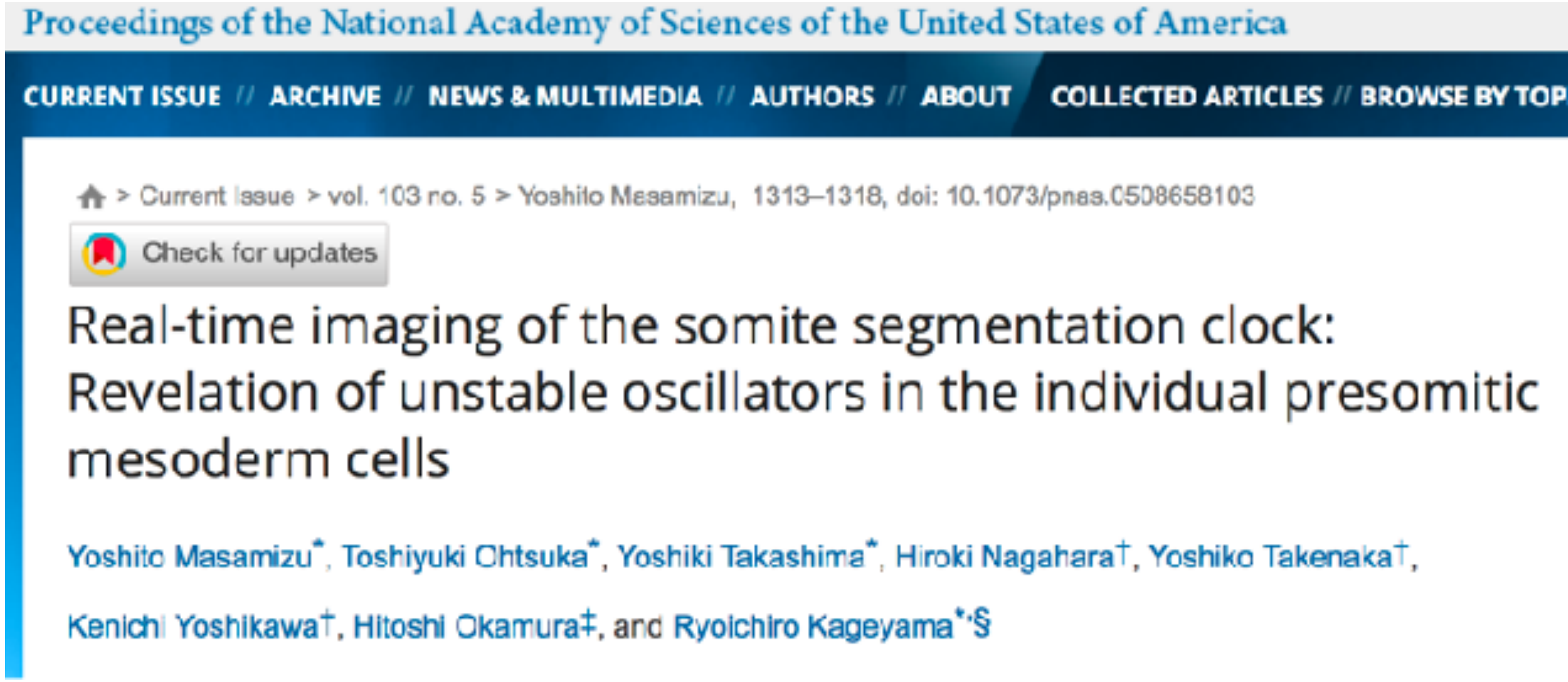


A cell exposed to concentration c is "committed" at time t(c)
This defines a temporal coordinate along the embryo called "wavefront".

The original picture







Proceedings of the National Academy of Sciences of the United States of America

> Current Issue > vol. 103 no. 5 > Yoshito Masamizu, 1313–1318, doi: 10.1073/pnas.0508658103

Real-time imaging of the somite segmentation clock: Revelation of unstable oscillators in the individual presomitic mesoderm cells

Yoshito Masamizu[*], Toshiyuki Ohtsuka[*], Yoshiki Takashima[*], Hiroki Nagahara[†], Yoshiko Takenaka[†], Kenichi Yoshikawa[†], Hitoshi Okamura[‡], and Ryoichiro Kageyama[*,§]

nature
International journal of science

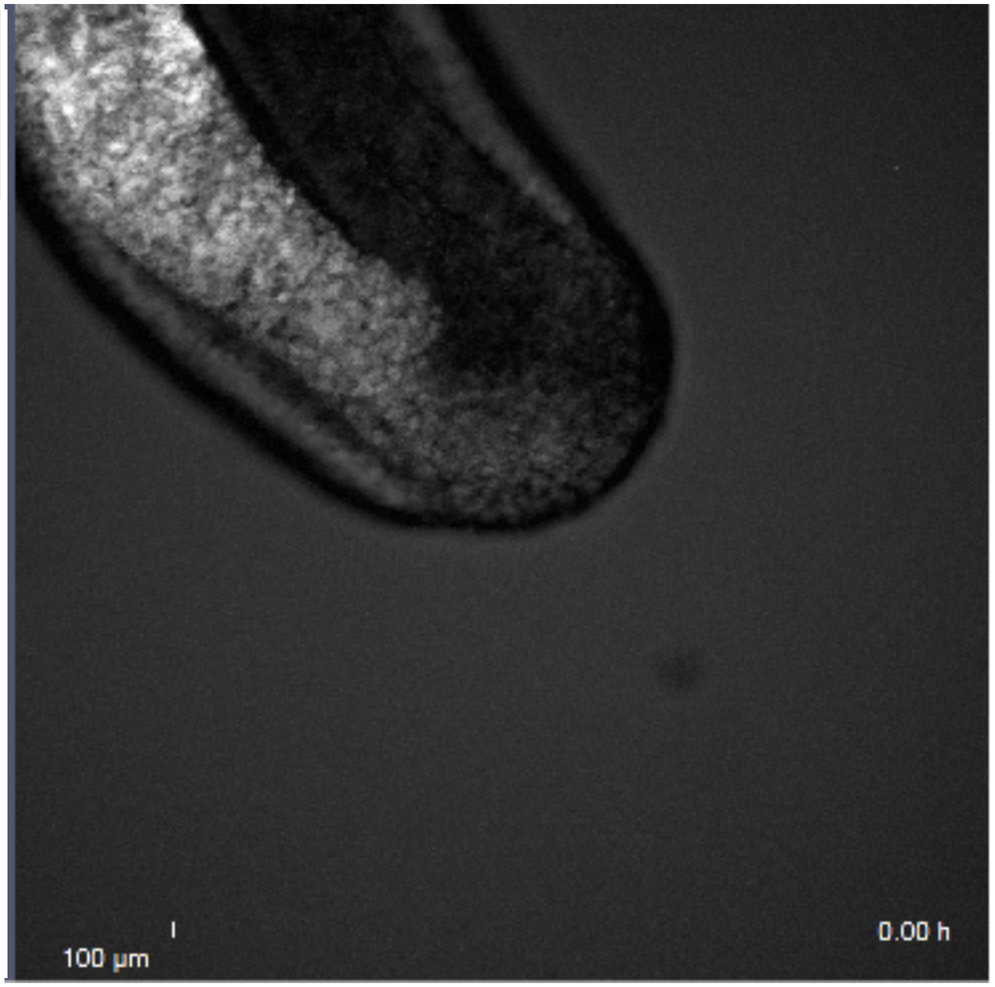
Access provided by NIH Library

Altmetric: 19 Citations: 57

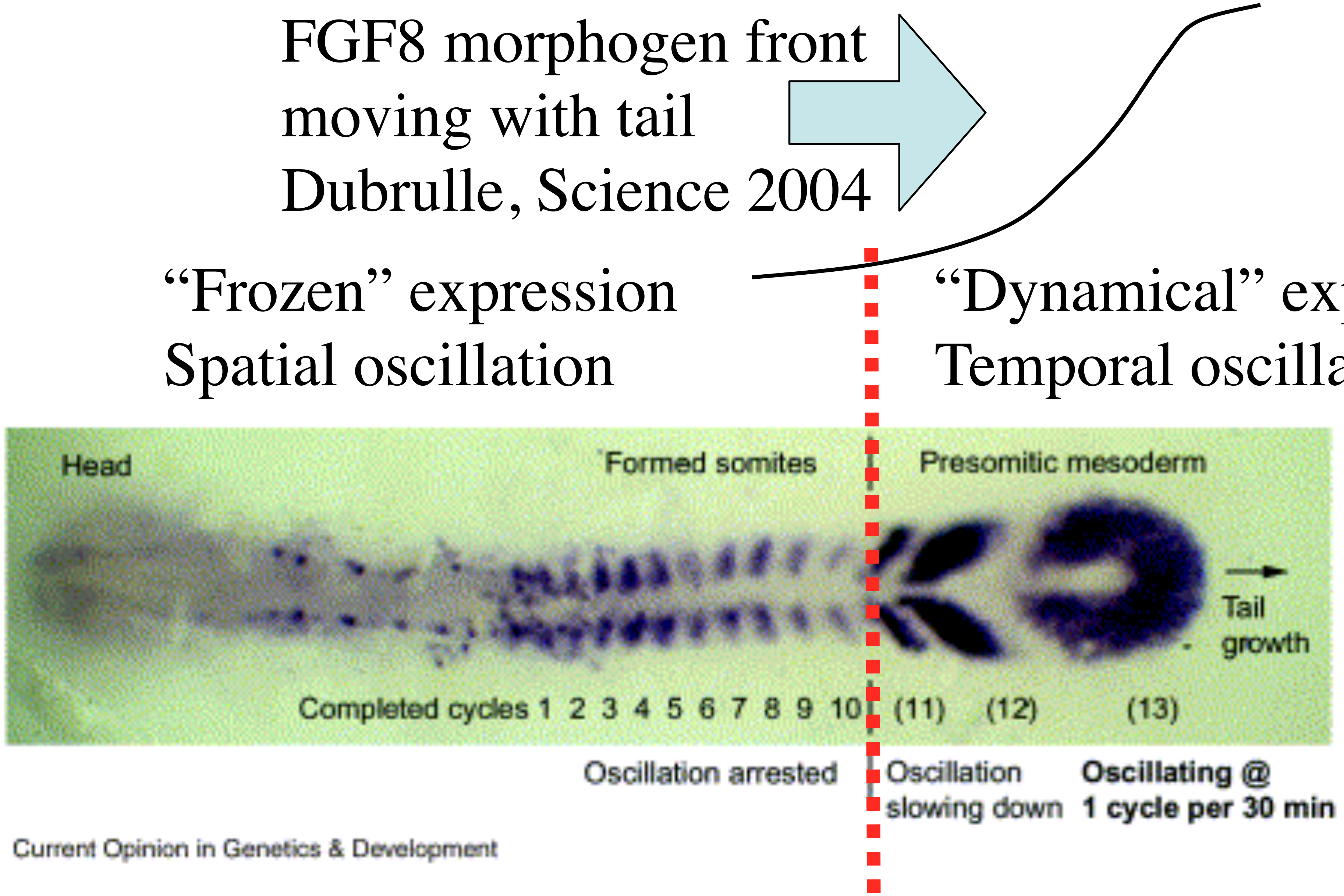
Letter

Scaling of embryonic patterning based on phase-gradient encoding

Volker M. Lauschke, Charisios D. Tsiairis, Paul François & Alexander Aulehla



Segmentation in zebrafish



FGF8 morphogen front
moving with tail
Dubrulle, Science 2004

“Frozen” expression
Spatial oscillation

“Dynamical” expression
Temporal oscillation

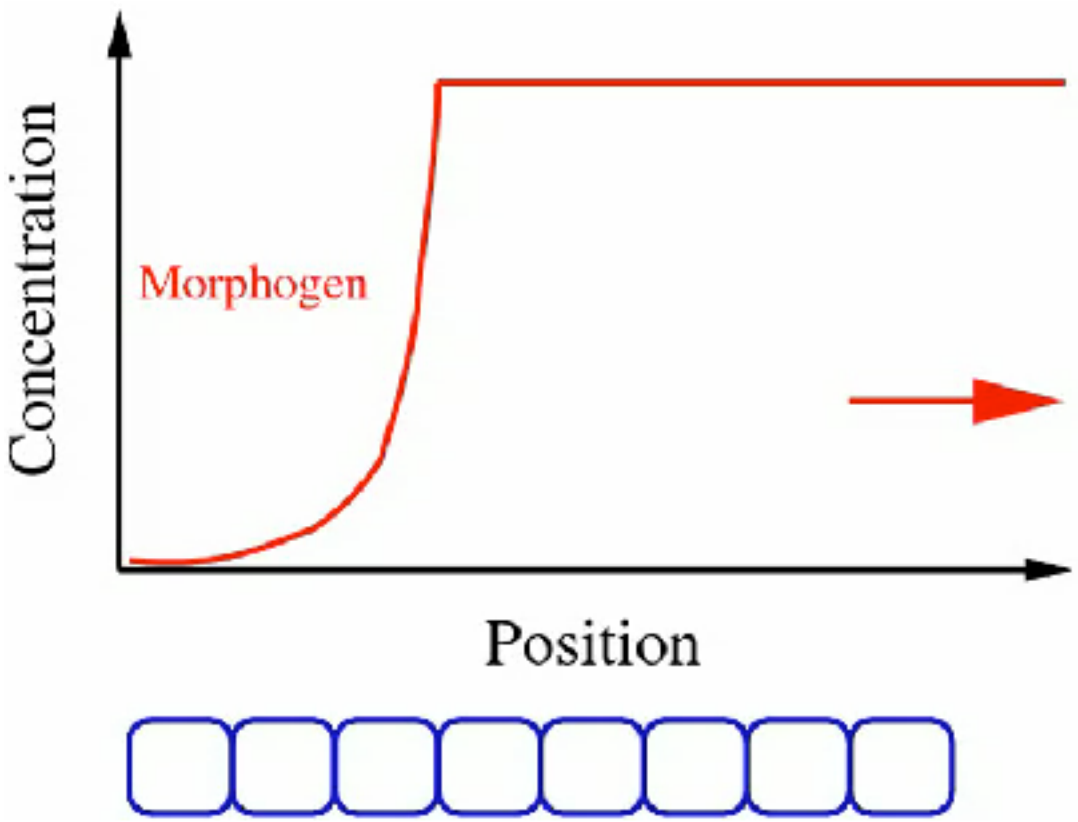
Current Opinion in Genetics & Development

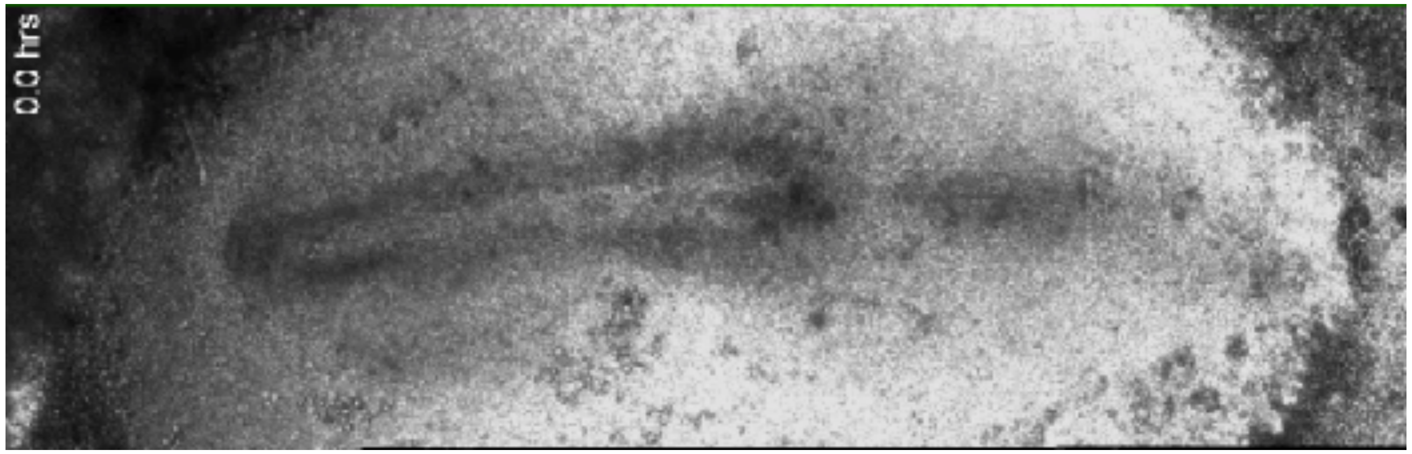
J Lewis,
Curr Bio 2003

Speed of the front x Period of the clock=
Typical size of the pattern (Cooke & Zeeman 1976)

Evolving segmentation

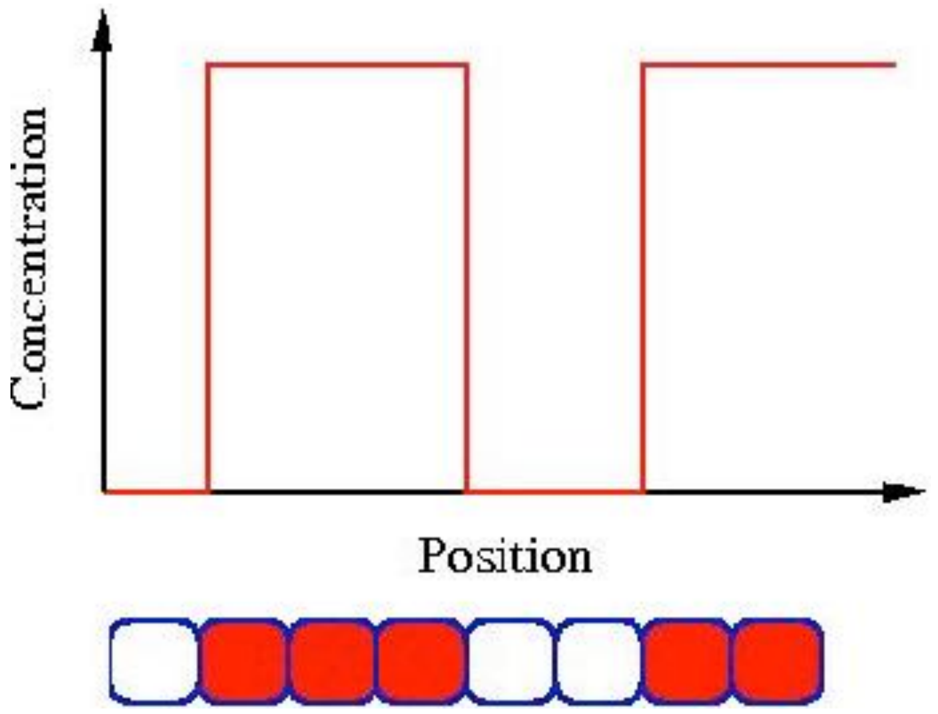
- Embryo: a line of identical cells with common network
- Imposed morphogen translating to model growth zone
- Interactions: regulation of transcription + degradation, cell autonomous



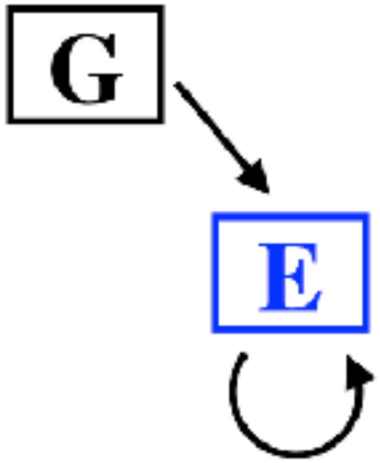


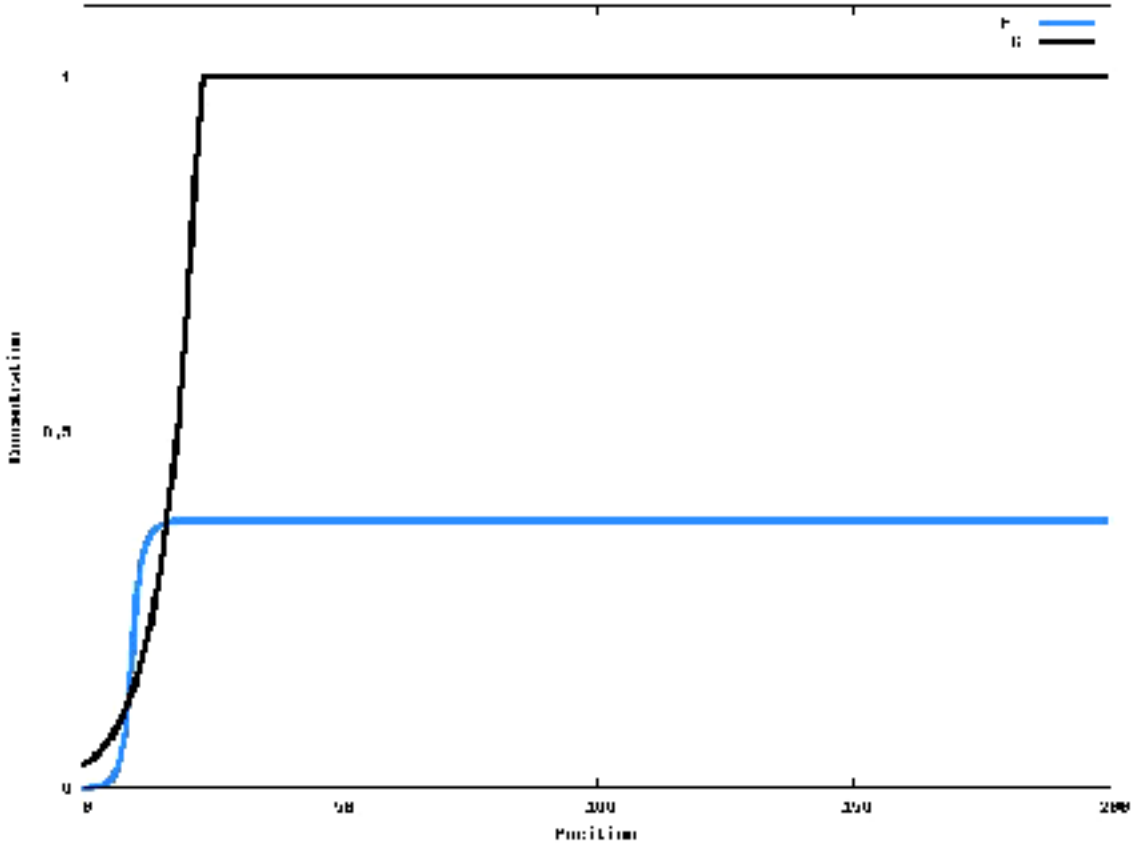
Fitness function : “More is better”

Level of protein E defines segments
Fitness = number of up or down transitions in E at end of development.
e.g. here, F=3



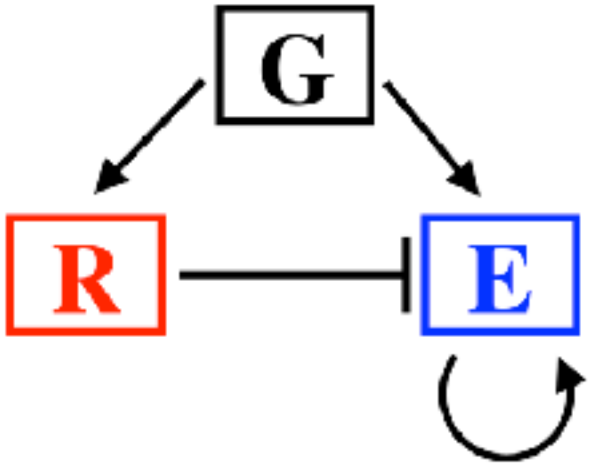
Dynamic gradient : main pathway 1

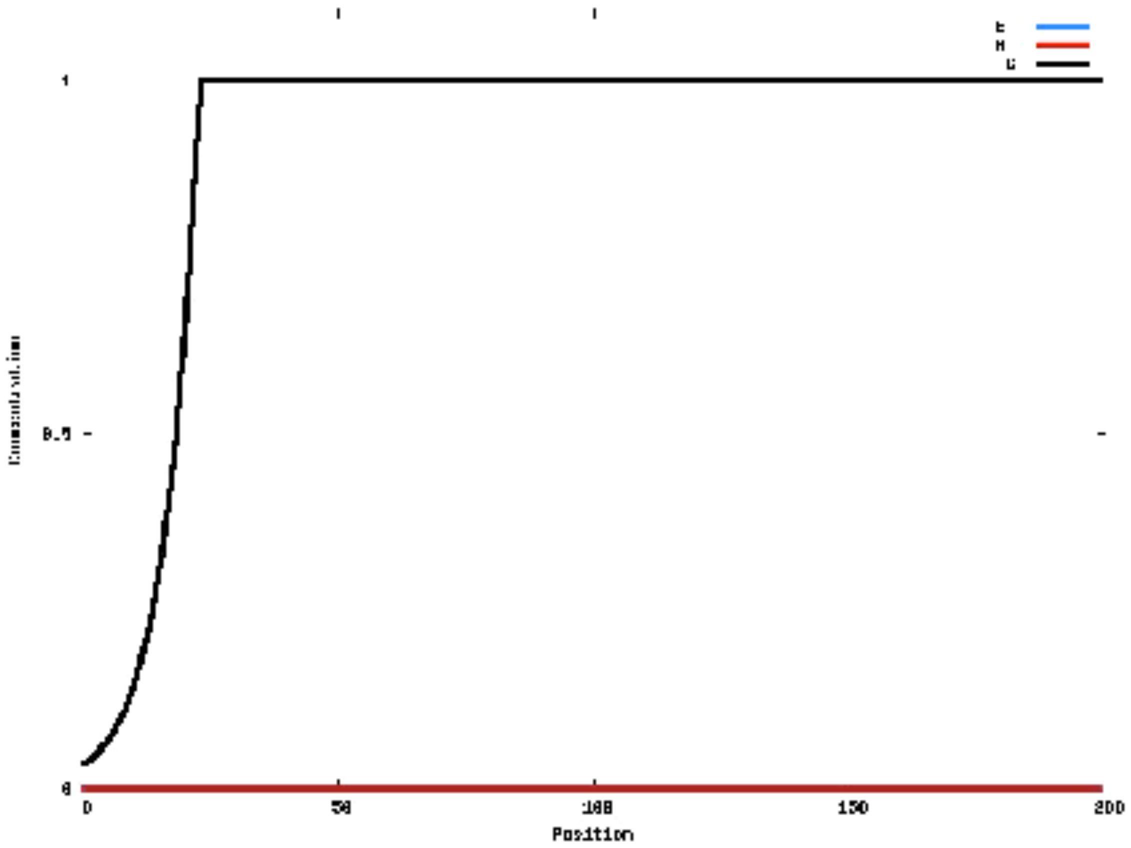




F=1

Dynamic gradient : main pathway 2

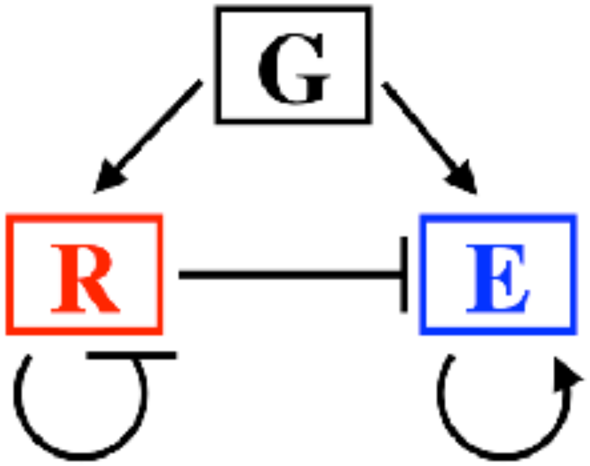


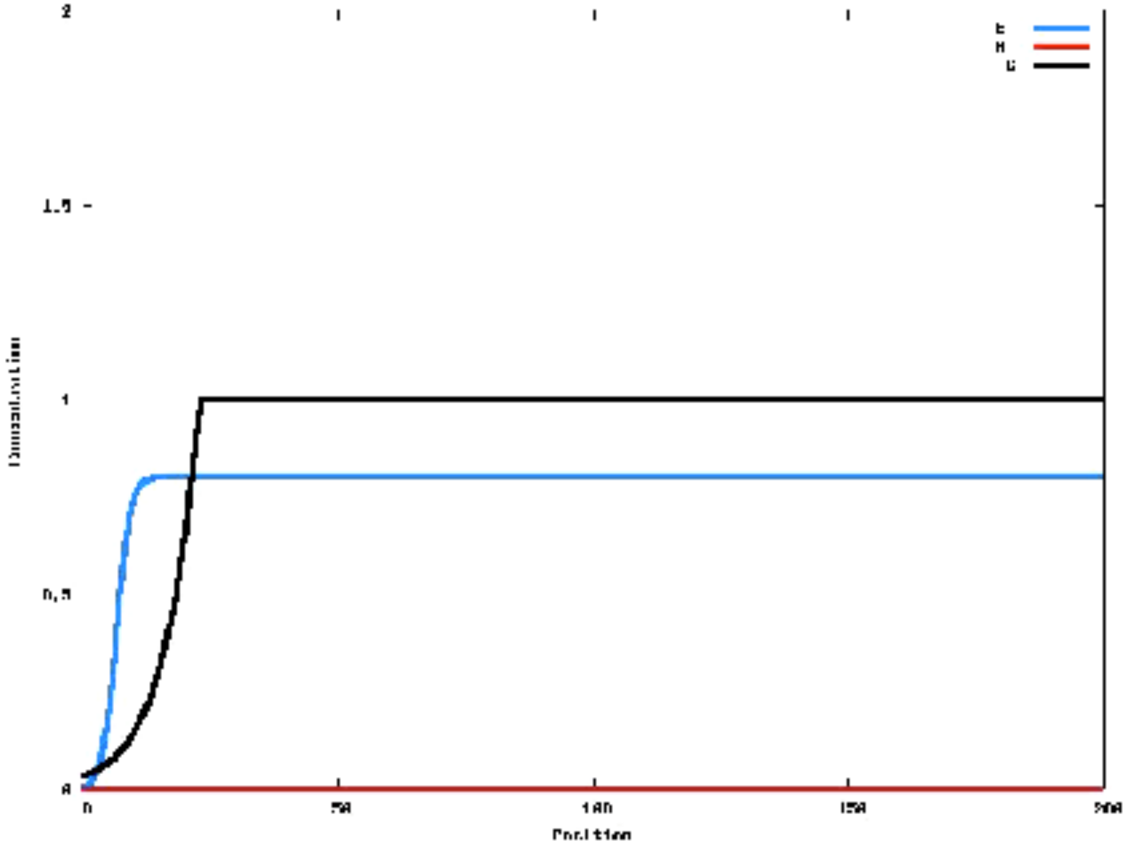


F=2

Dynamic gradient : main pathway 3

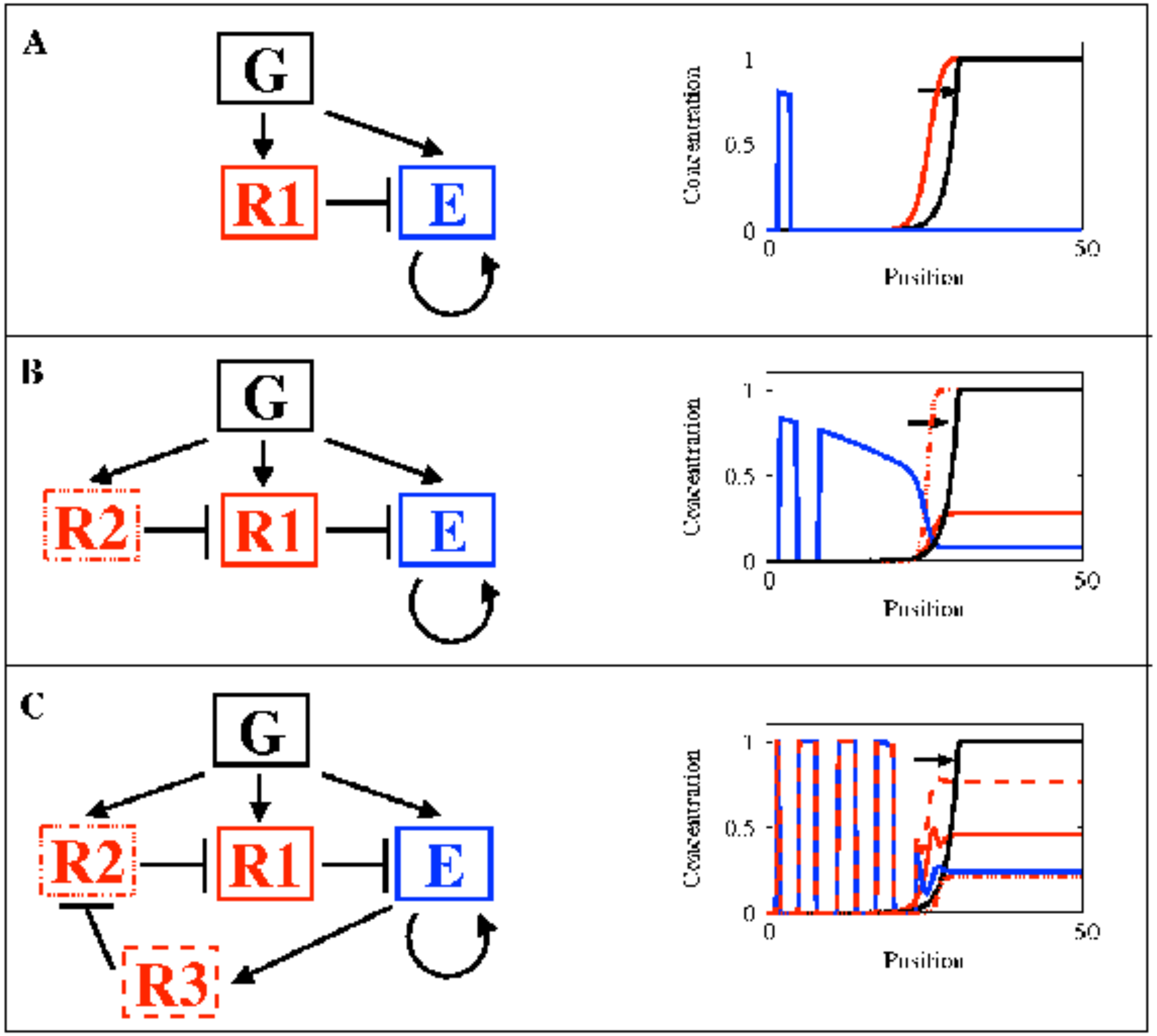
Gradient G, Repressor R, Output E





F=N

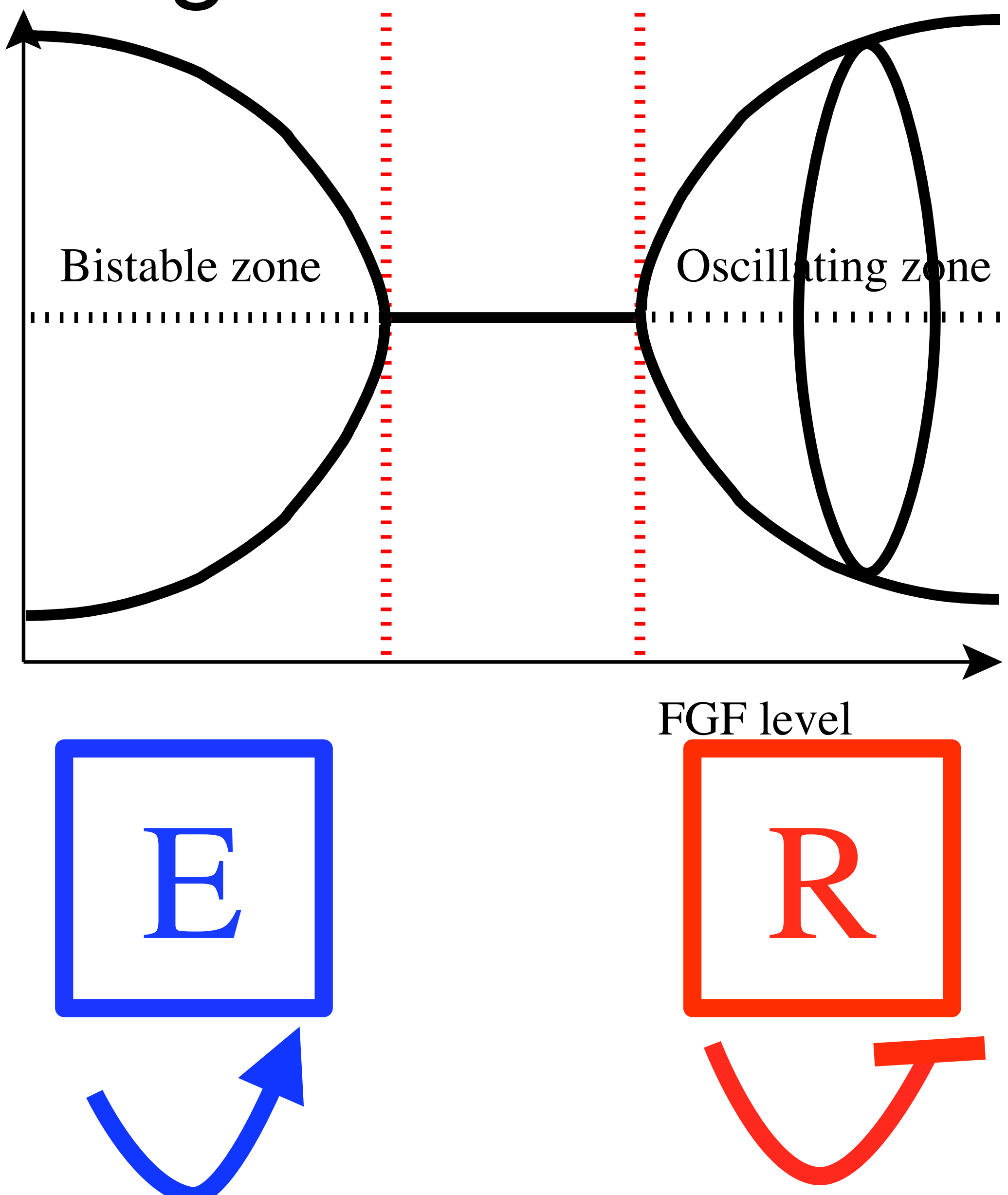
Similar dynamics, but different topology



Instead of creating oscillator by neg. feedback of R1 on itself, make chain of repressors.. and finally oscillator via E -> R3

Stochasticity vs determinism

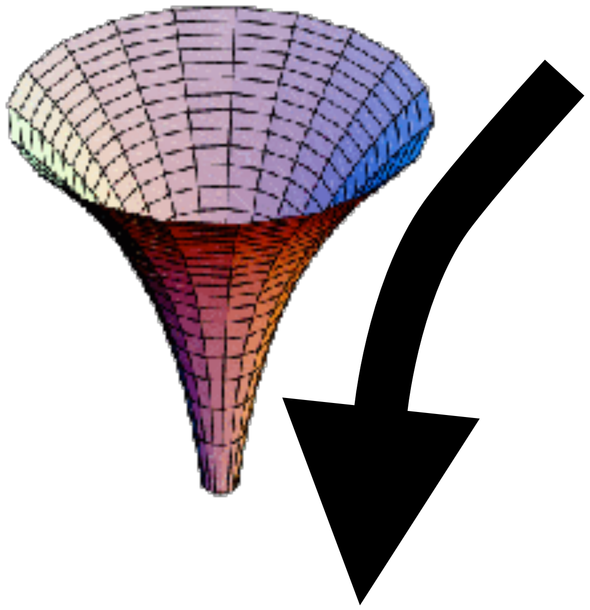
- Stochastic : network topology
- Reproducible (deterministic ?) : bifurcation diagrams



This means that the bifurcation level might be the “right” one to make predictions on evolution in that case.

(how to build a theory of this ?)

Property of these evolutionary simulations

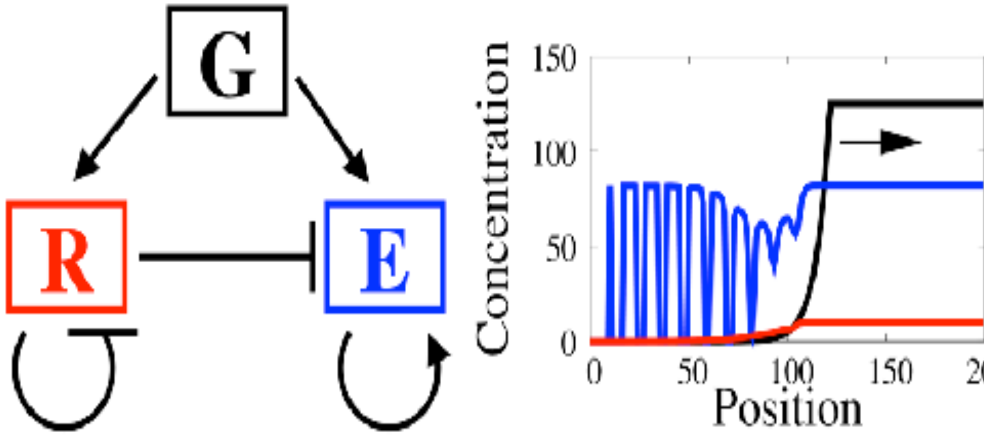


Evolution is reproducible from one simul. to the other

- “Parallel” evolution, a unique path :
  Step 1 : bistable E to remember initial value.
  Step 2 : Repressor added after E
  Step 3 : Oscillator built from repressor

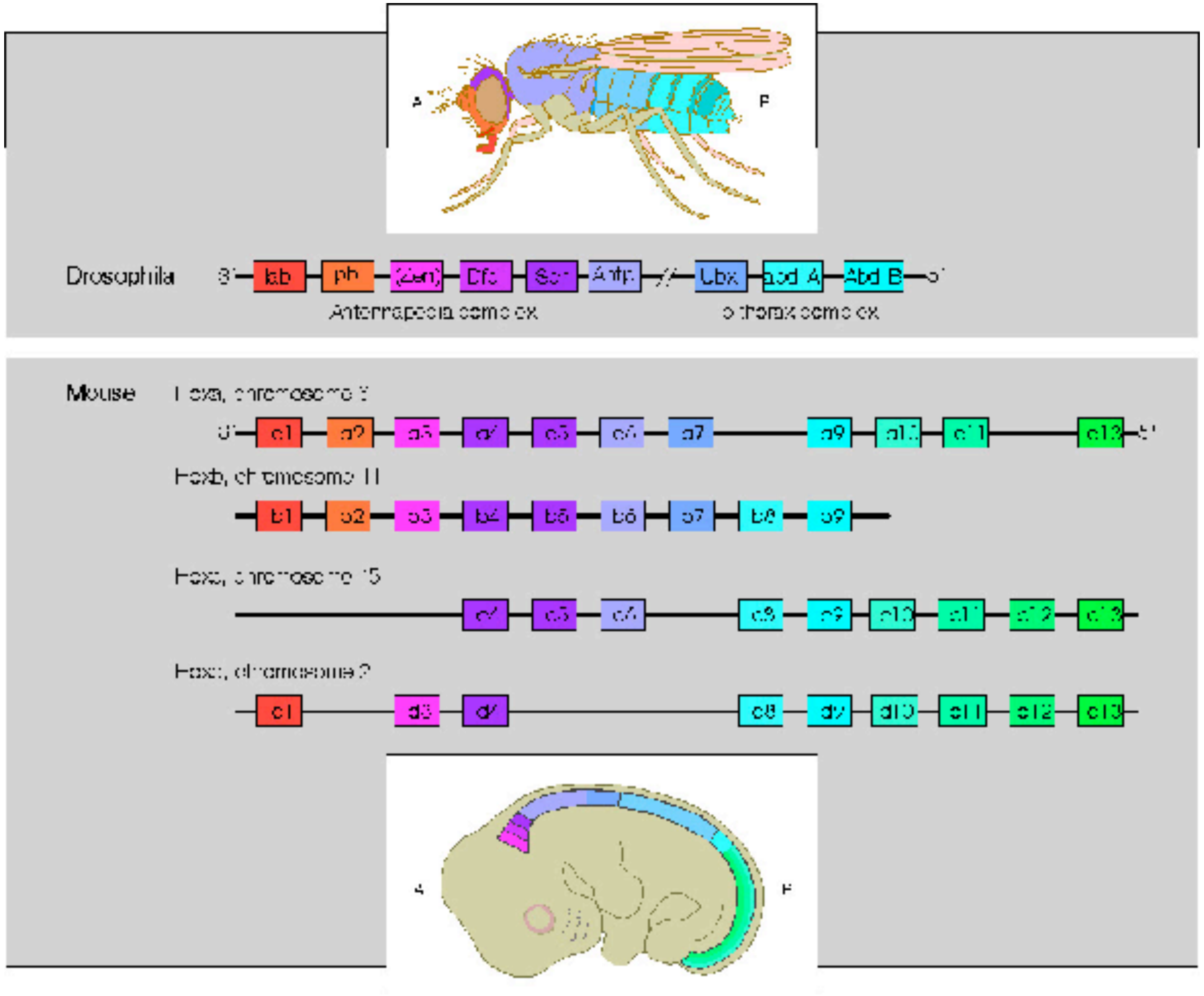
- Several solutions but similar phenotype.
- Clock and wavefront model comes “free”

- First model of the complete system.



PF, Vincent Hakim, Eric D. Siggia,
Molecular Systems Biology (2007)

Can we “guess” anything on hox patterning ?



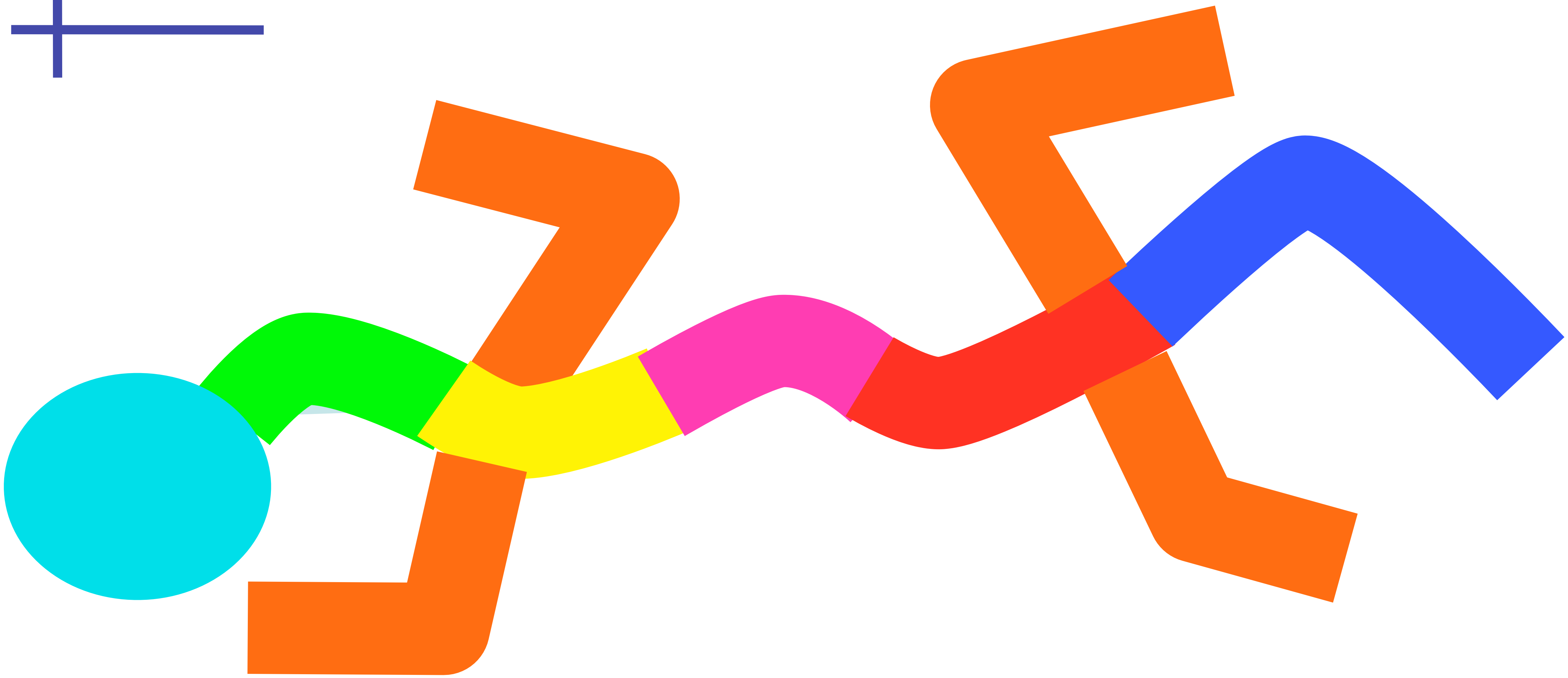
Hox genes : different parts of the body are defined by different hox genes.

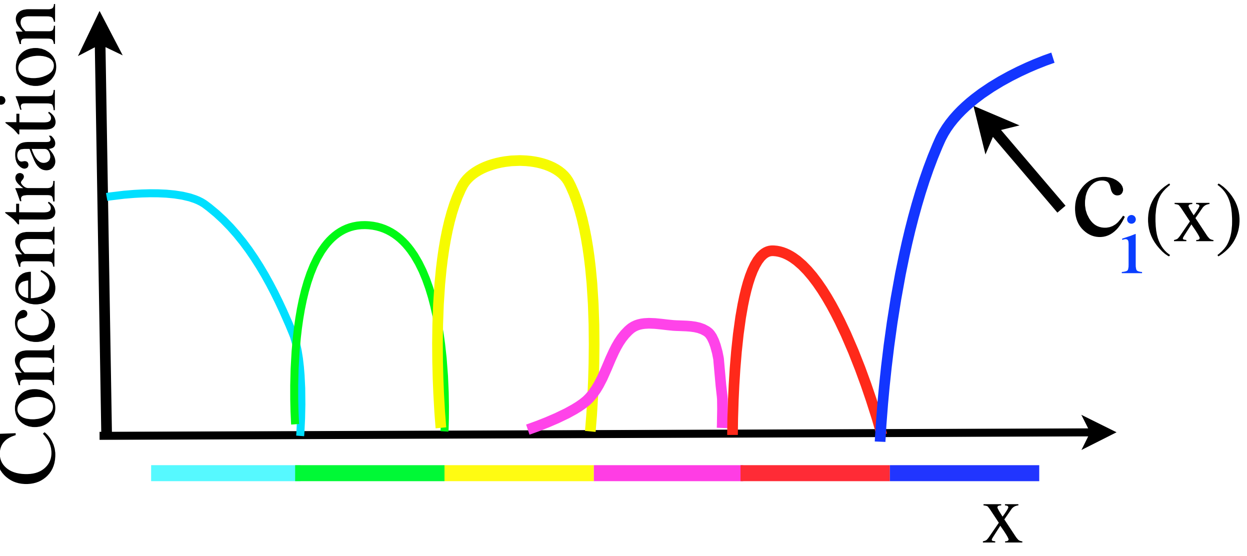
“Cellular Zip Code”

Very complex system

Does any network structure emerge ?

Patterning a field of cells





Selector genes hypothesis

Sox2 for neurons, MyoD for muscles…

Patterning and entropy

Connecting patterning to entropy

- Rich patterning ->high **global** disorder, high entropy at the global level

- Precision of patterning -> high **local** order, low *conditional* entropy

Fitness I

$$p_{ij} = \frac{c_i(j)}{\sum_k c_k(j)}$$

i : selector gene
j : position

sum over i=1 -> we normalize by 1/N, N being the number of cells

Fitness II Mutual information

Maximizing variability : $\sum p_i log(p_i) = -H(State)$

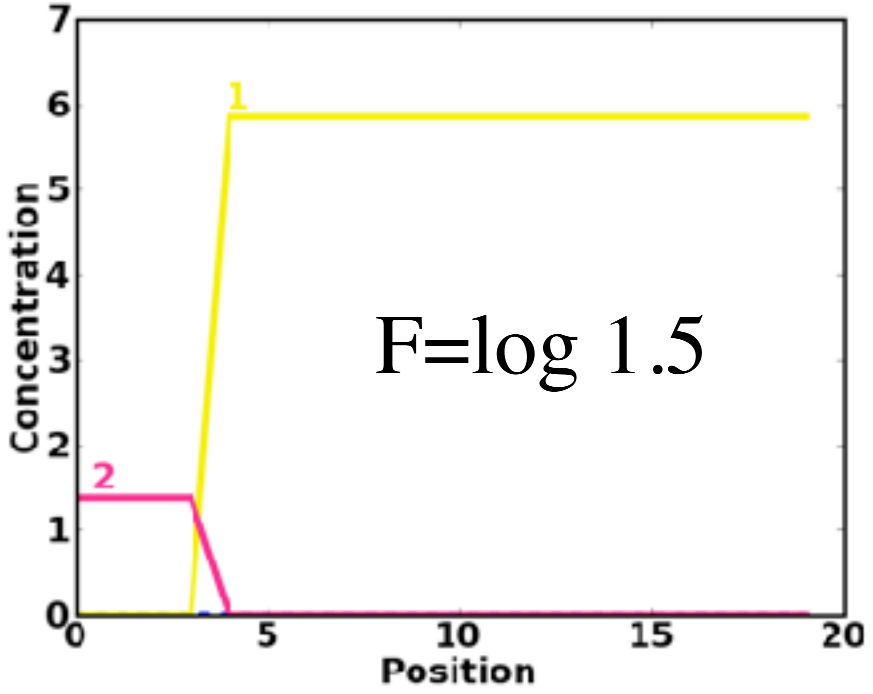
Minimizing entropy of State knowing Position :

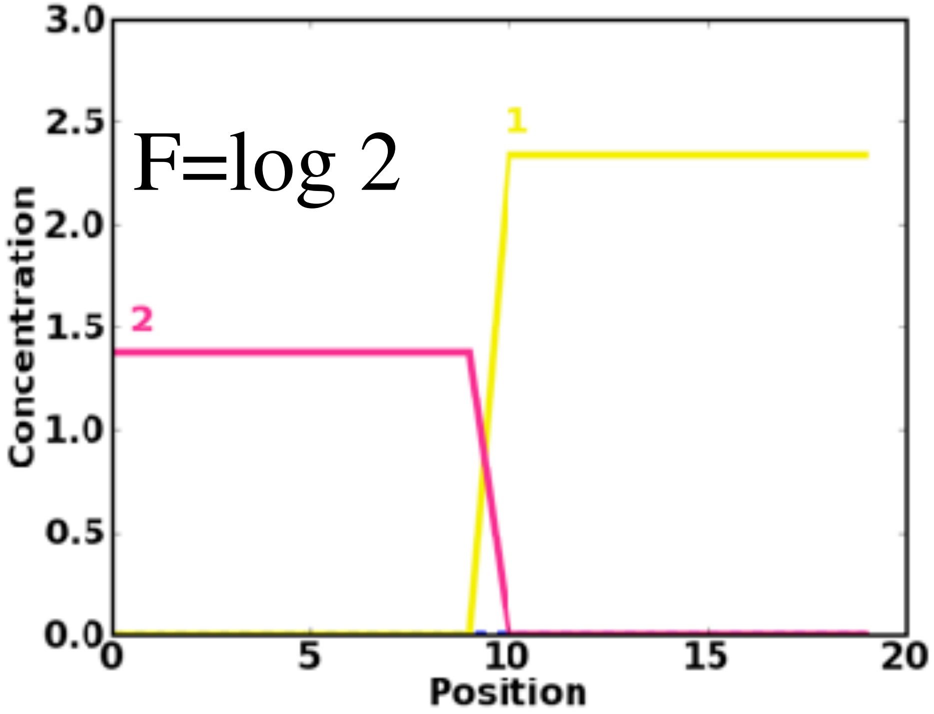
$$\sum p_{ij} log(p_{ij}) - \sum p_j log(p_j) = -H(State|Position)$$

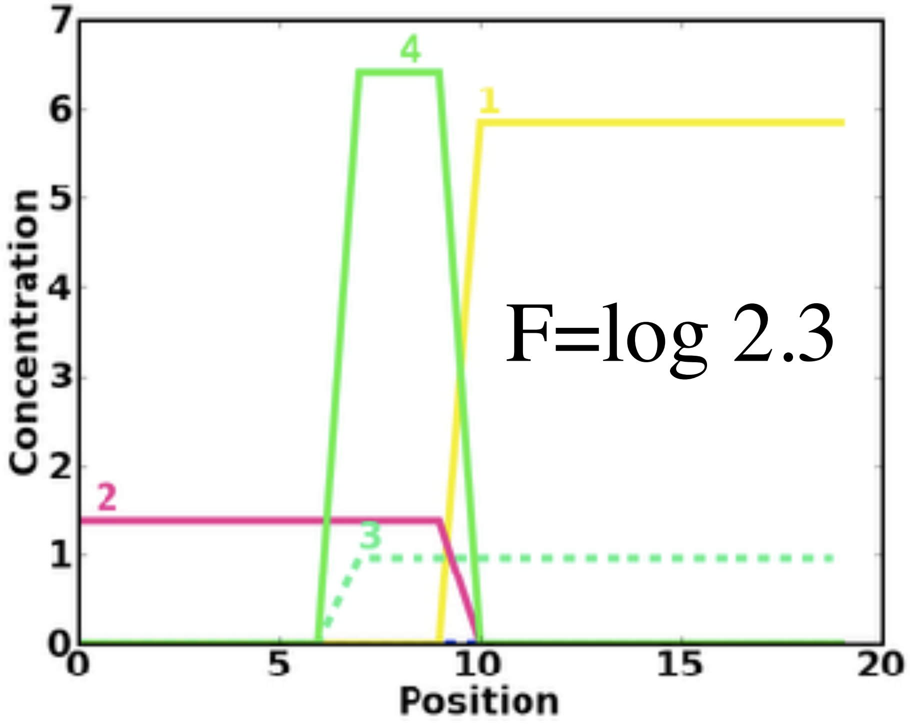
One Possible Fitness : $\sum p_i log(p_i) + \sum p_j log(p_j) - \sum p_{ij} log(p_{ij})$

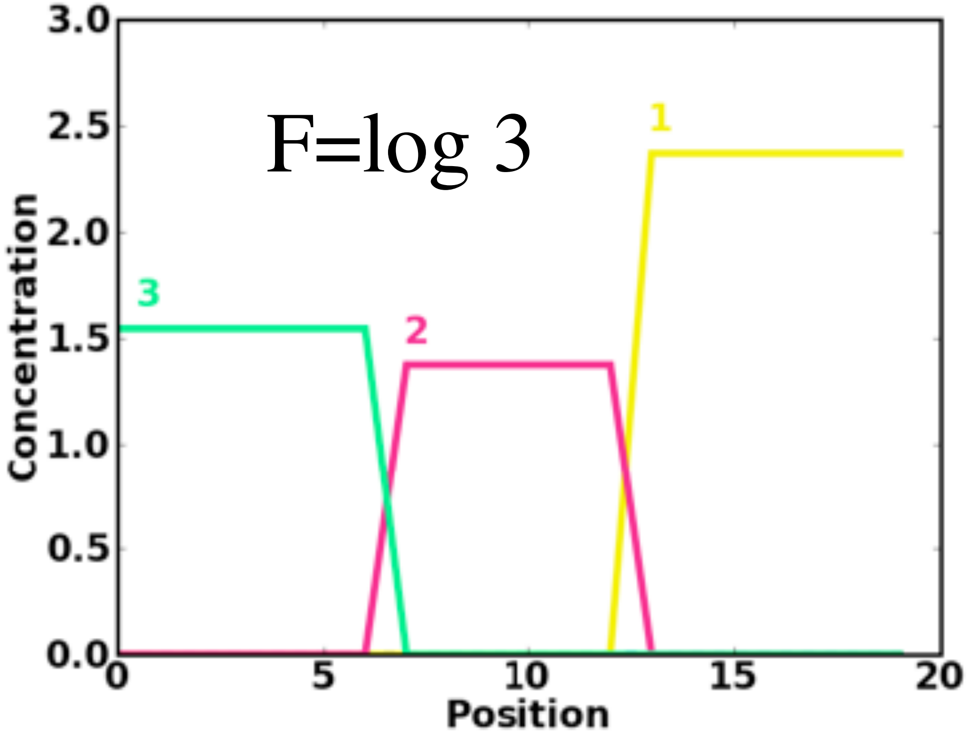
"From its fate, the cell can determine position, and vice-versa"

Quantifying “patterning” : mutual info between expression and position

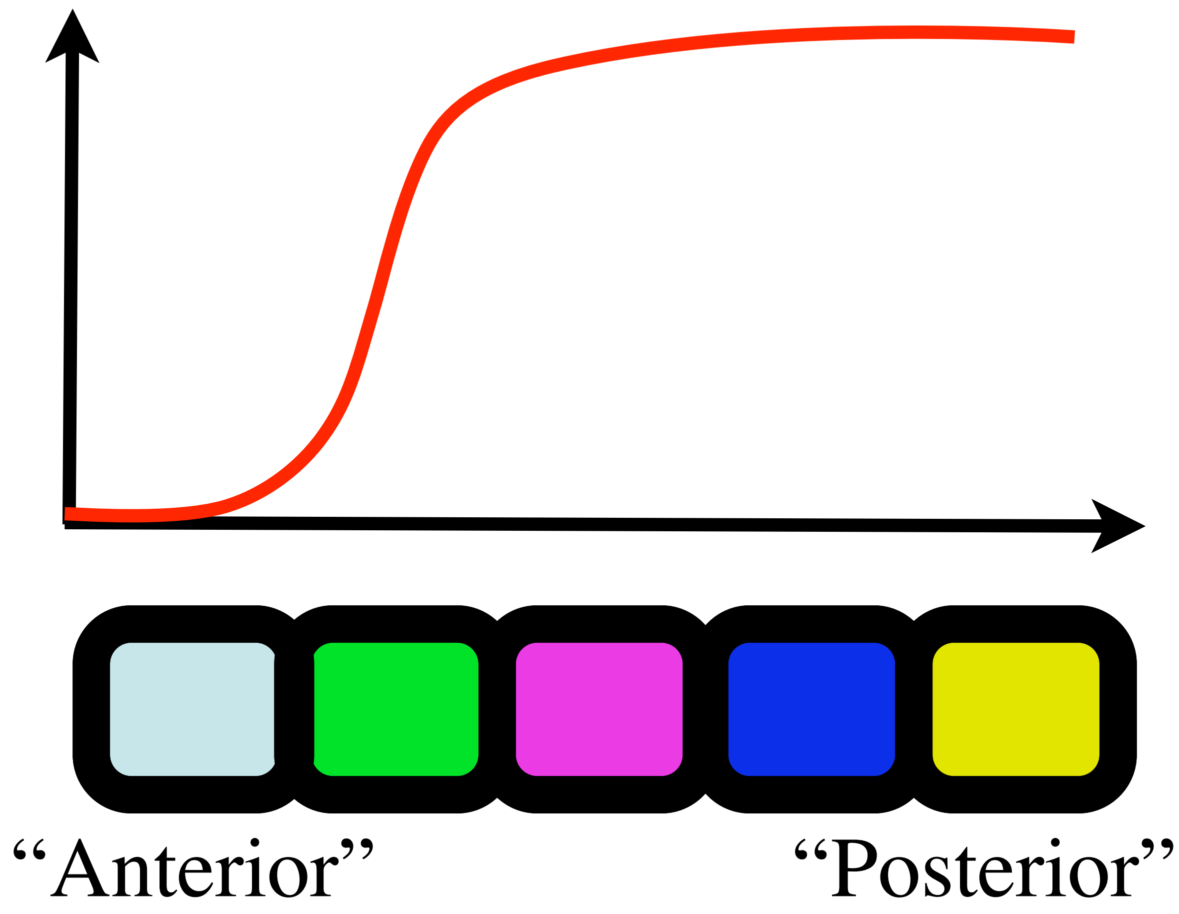




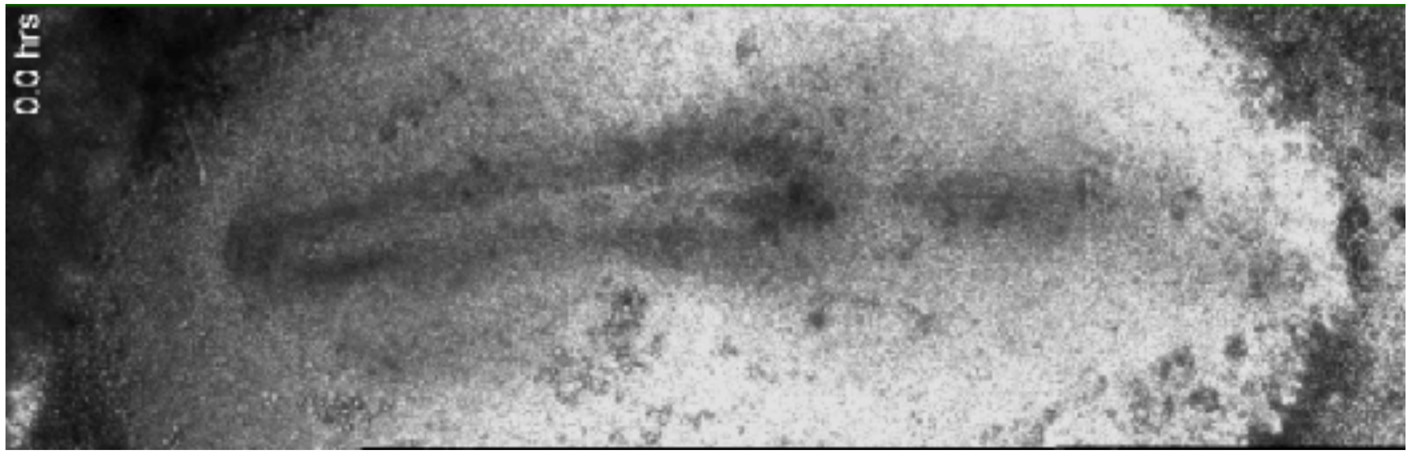




Patterning a field of cells : AP growth



- Impose translating morphogen defining growth zone (or frog organizer)
- Gene duplication possible (“creates” a selector gene)



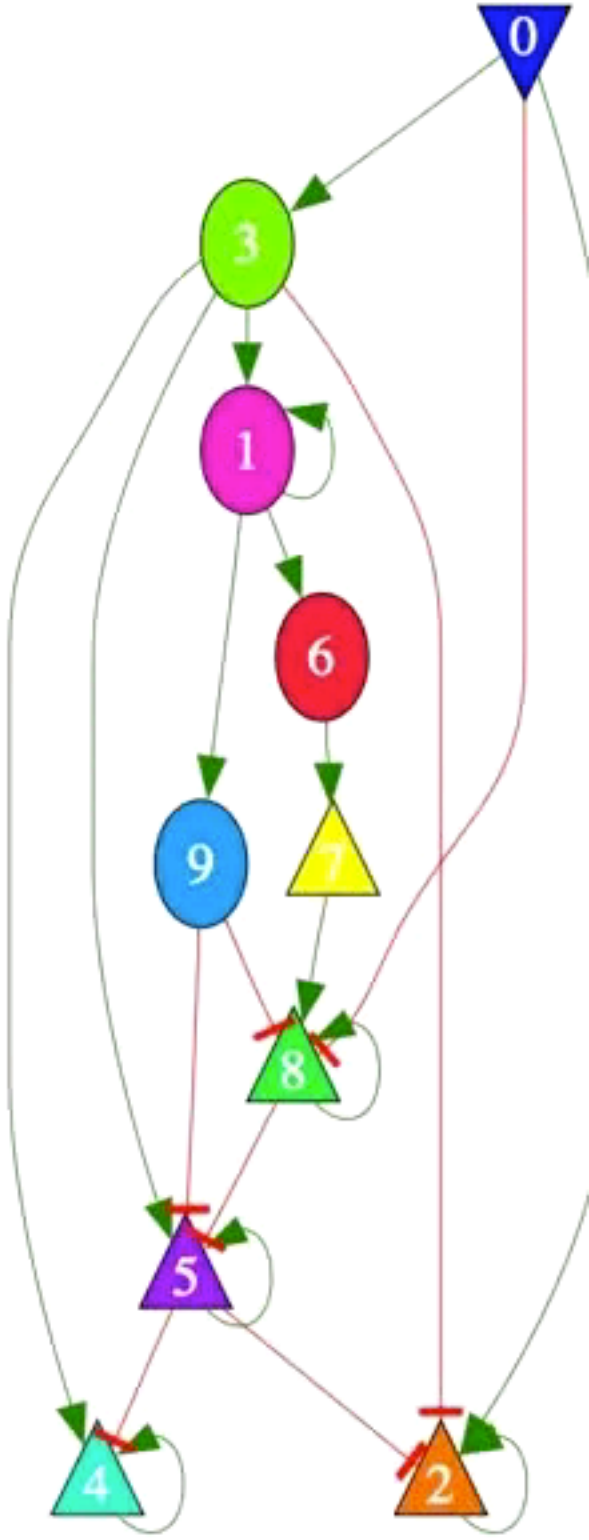
Difference between cells =
time spent before involuting

Patterning a field of cells

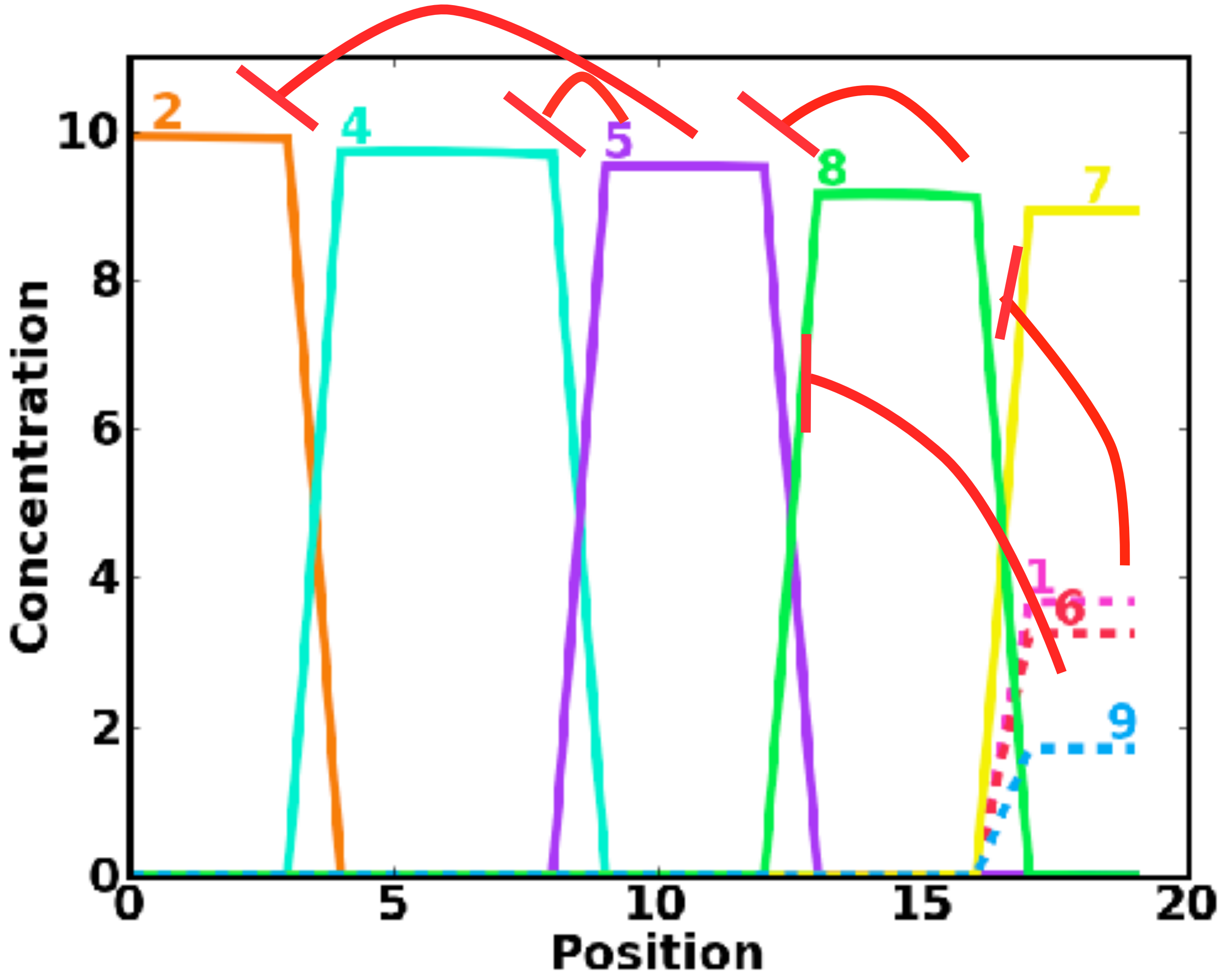
Dynamics of the network topology displayed on Fig.5

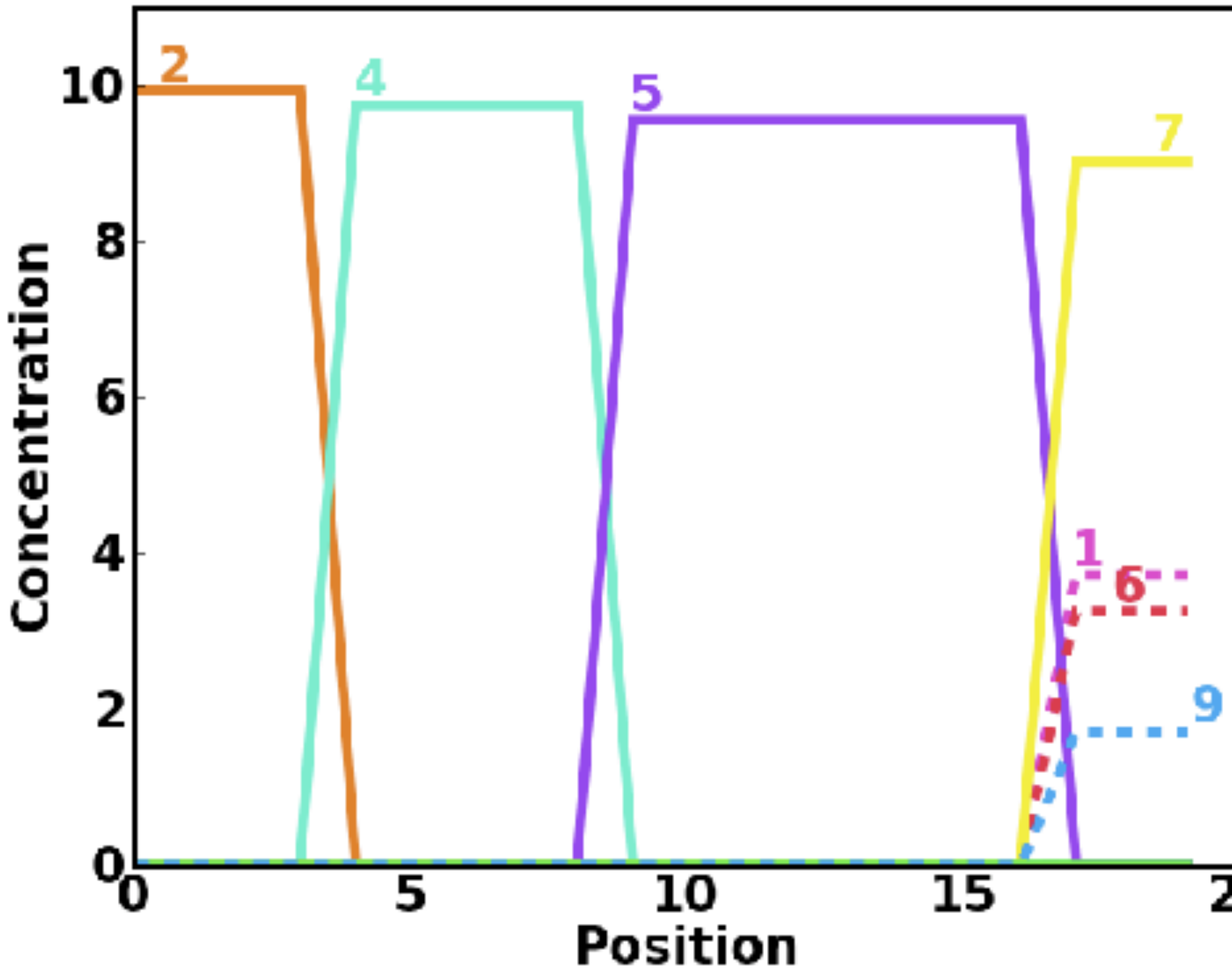
Sliding input is in dashed blue,
simulating the presence of cells
in a growth zone

P. François, E. Siggia
pfrancois@rockefeller.edu

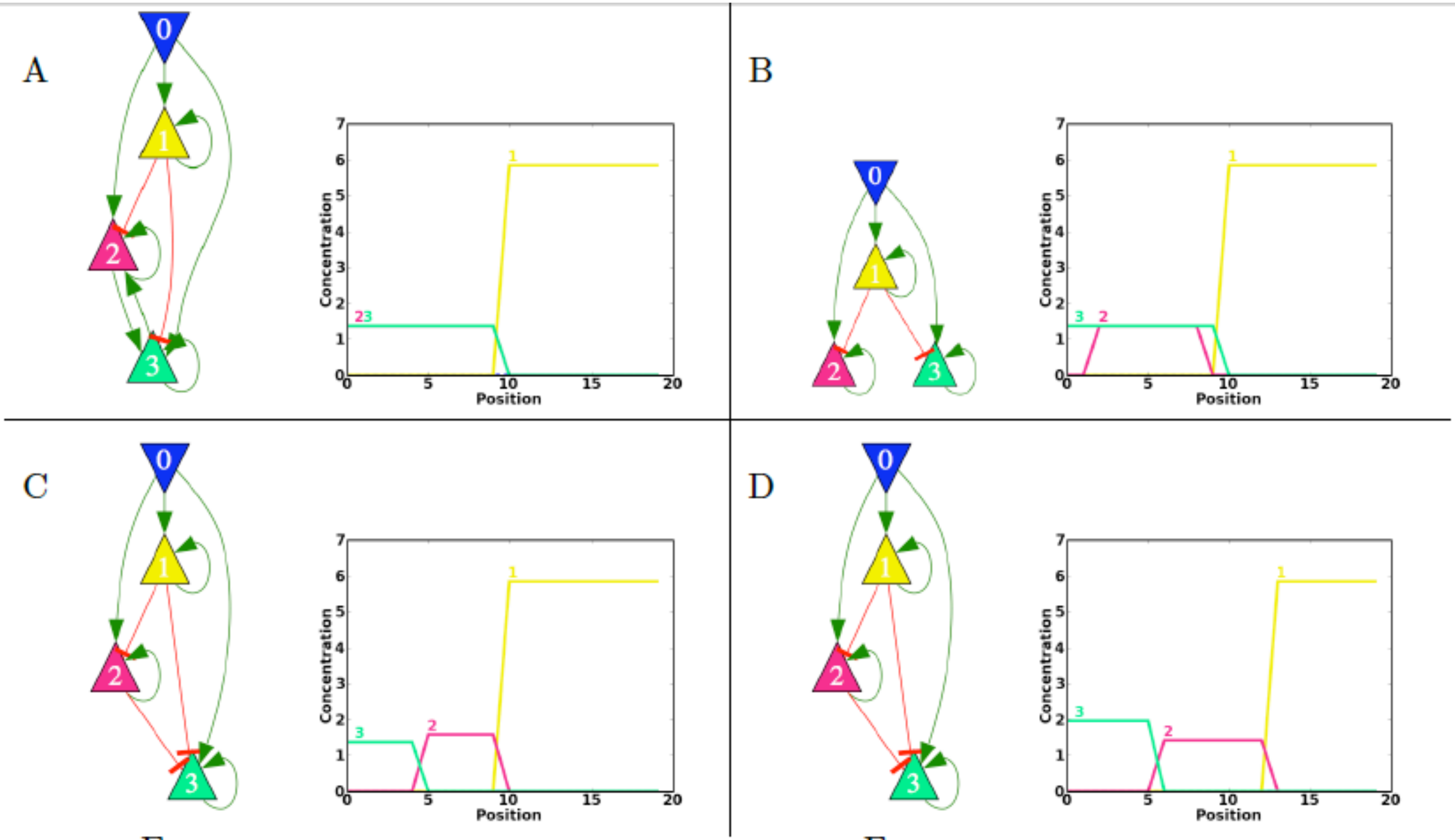


‘Anterior homeotic transformation’ : removal of gene 8 -> similar to posterior prevalence



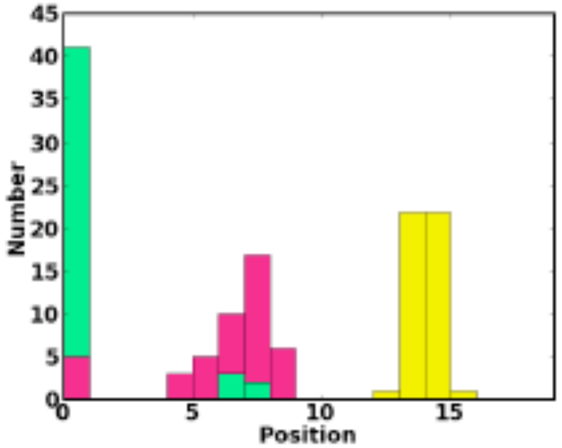


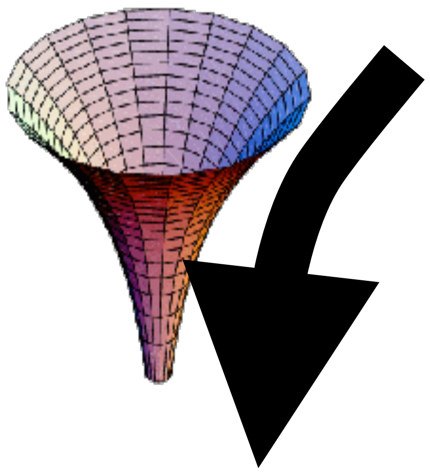
Typical evolutionary pathways



E

F





Conclusions hox-like patterning

- A mutual information fitness can be defined to quantify "diversity" and "precision" in patterning
- Evolutionary steps can be understood mathematically
- Computational evolution suggests transitory forms

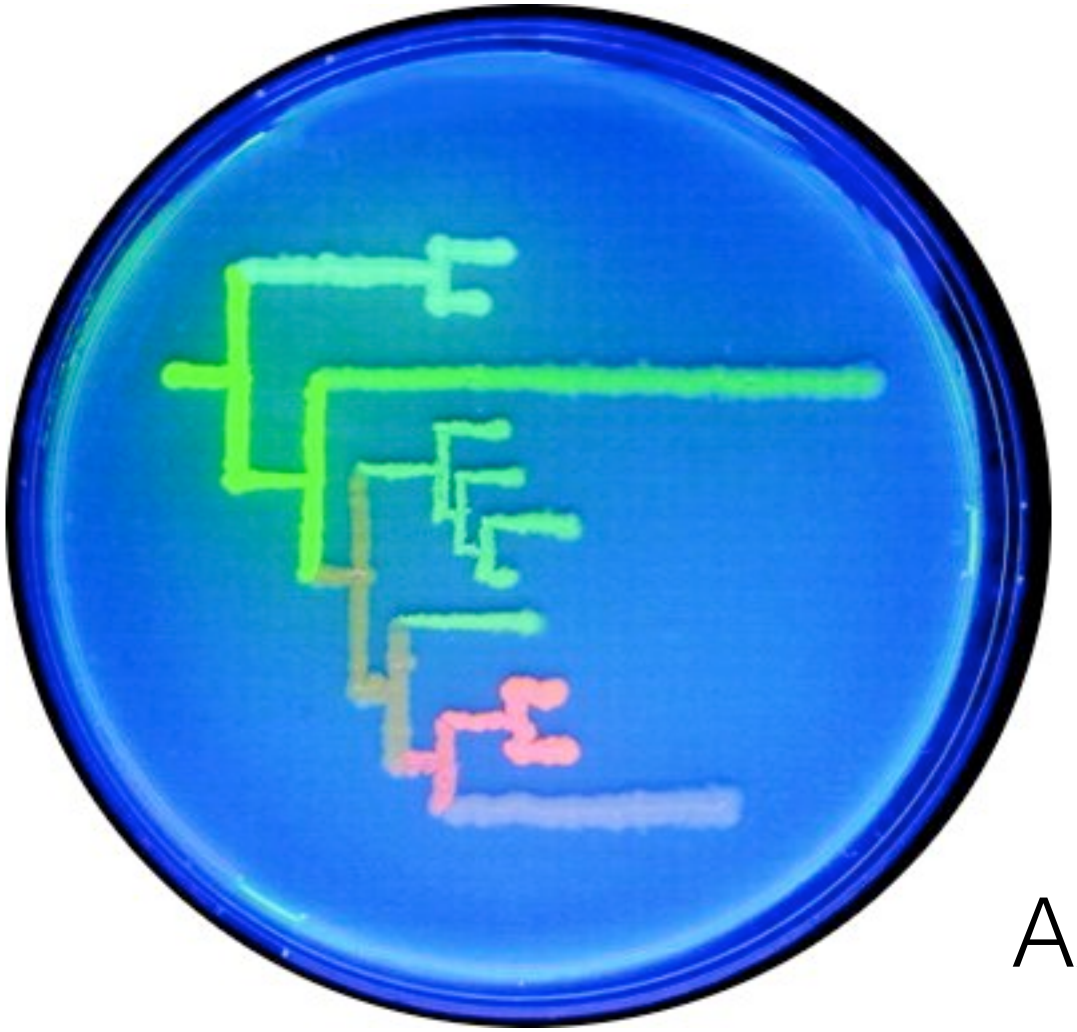
Reproducible aspects of evolution :

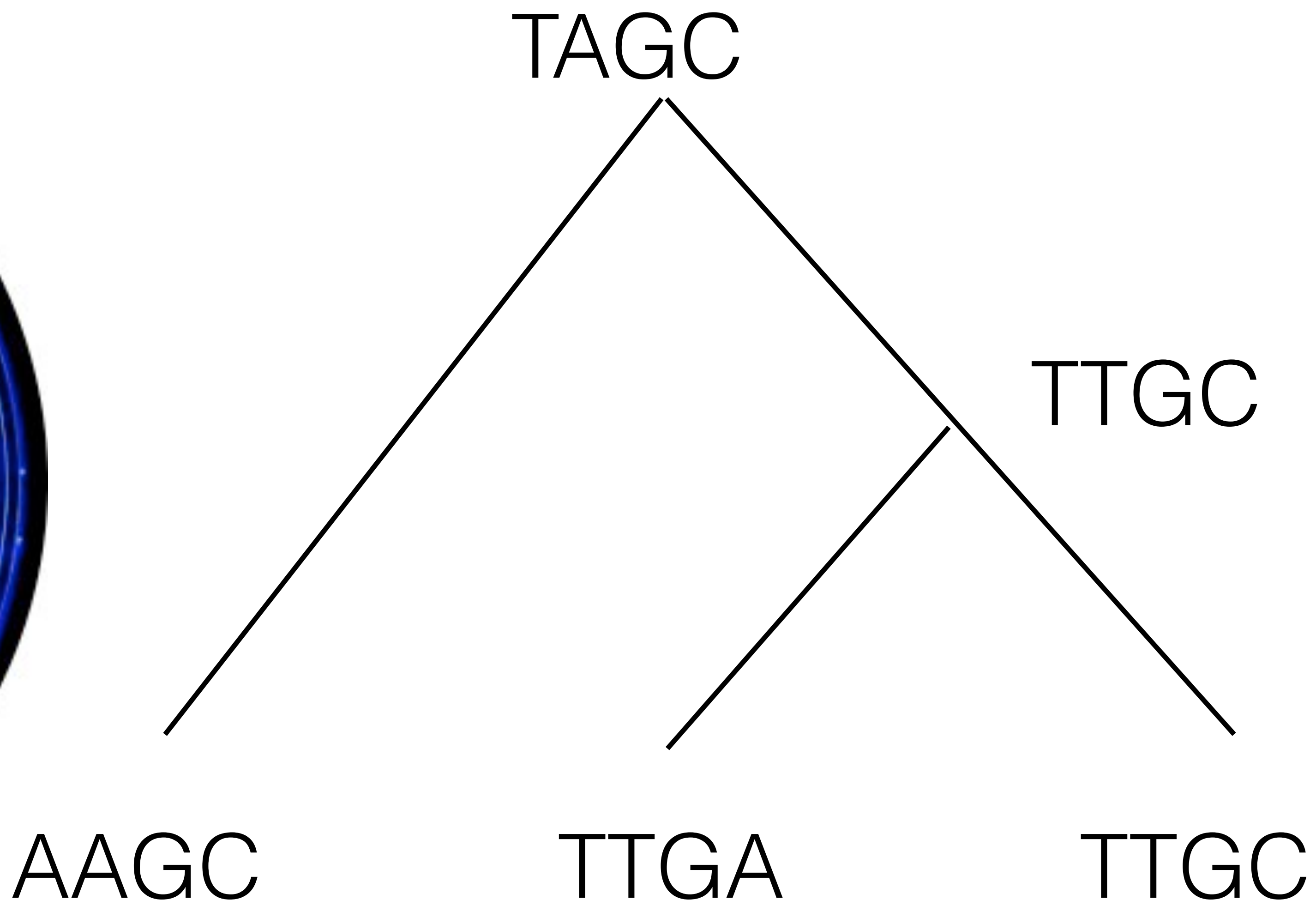
- Networks evolve by successive gene duplications
- Networks are complex in general, but some clear rules evolve :
    - anterior boundaries set up by activation threshold by timer, we predict "timer gene" acting like morphogen
    - posterior boundaries set up by repression by posterior/ late genes

-> "posterior dominance" + temporal colinearity as consequences

PF, Eric D. Siggia, Development (2010)

Reconstructing evolutionary history





TAGC

TTGC

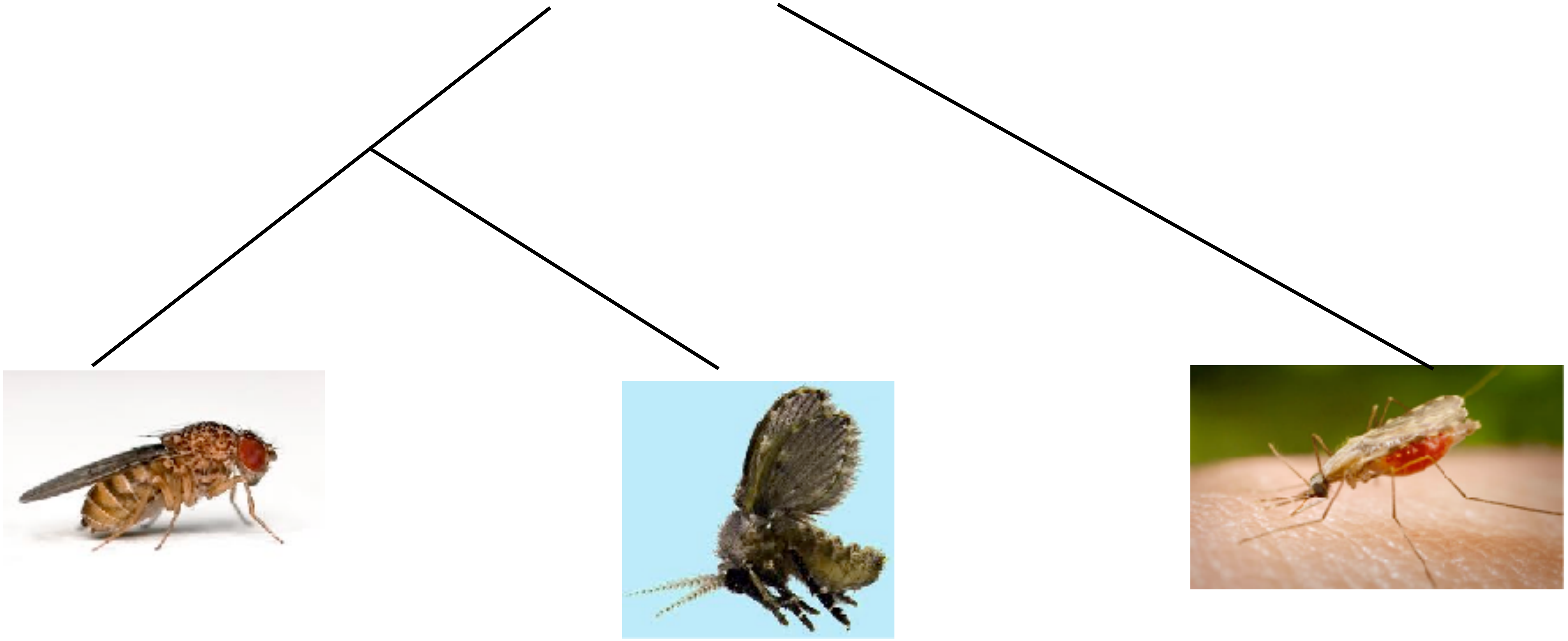
AAGC

TTGA

TTGC

Evolution of Coral Pigments Recreated
Juan A. Ugalde, Belinda S. W. Chang and Mikhail V. Matz
(September 2, 2004)
Science **305** (5689), 1433. [doi: 10.1126/science.1099597]

Predicting ancestral species ?



Ur-Dipteran ?

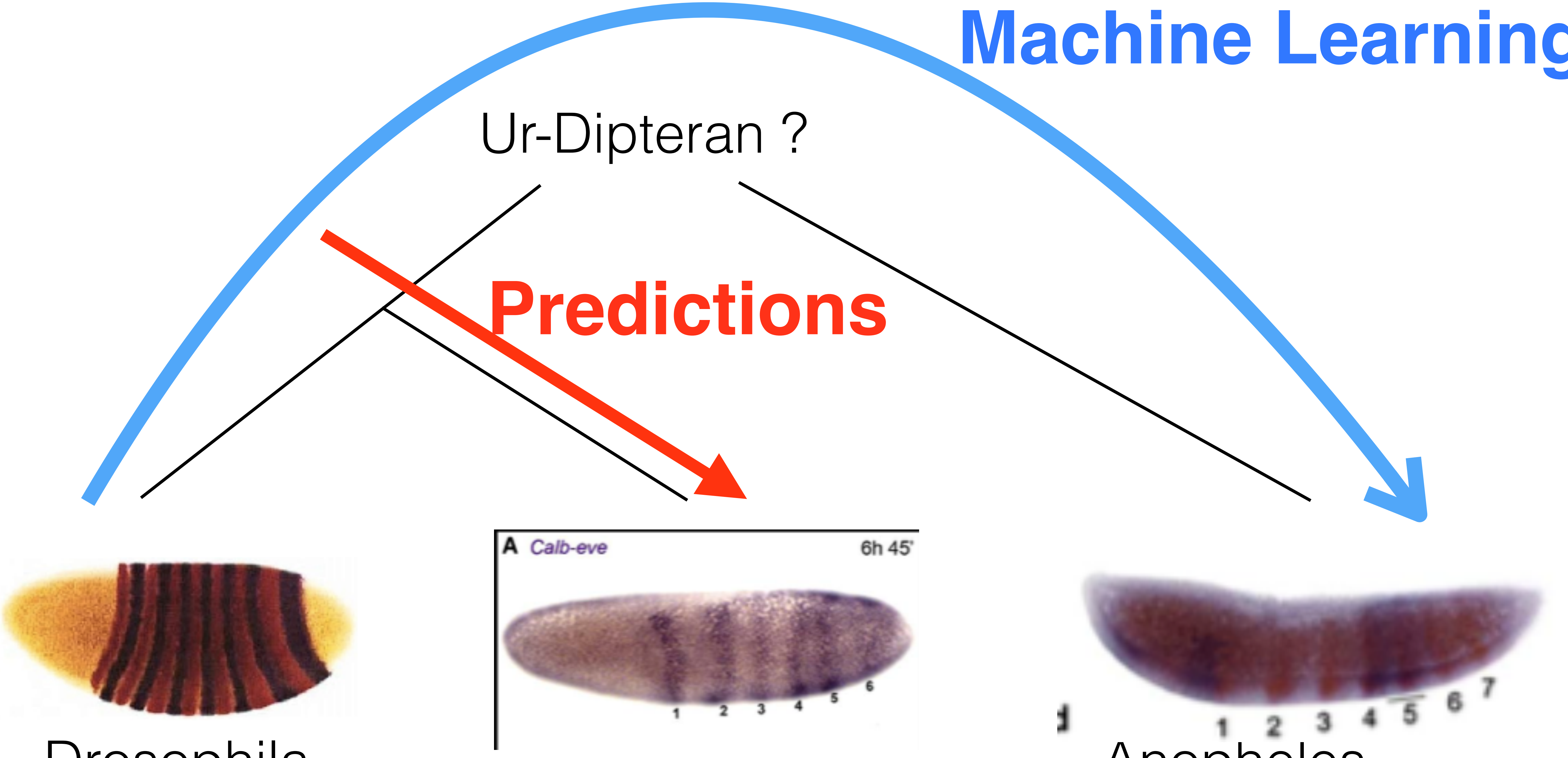
Drosophila

Clogmia

Anopheles

Not really clear what the cost function should be

Predicting ancestral species



(Evolutionary) Machine Learning

Ur-Dipteran ?

Predictions

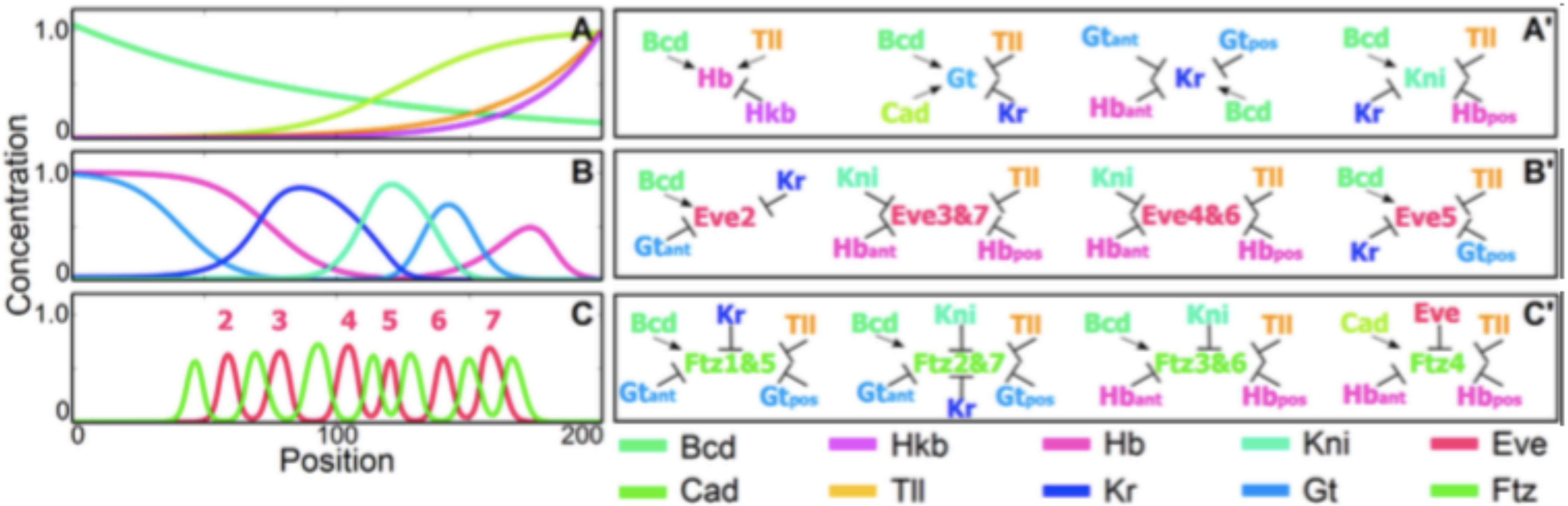
Drosophila

Clogmia

Anopheles

Score: conservation of “some” striped pattern

A minimum semi-phenomenological model of the fly cascade

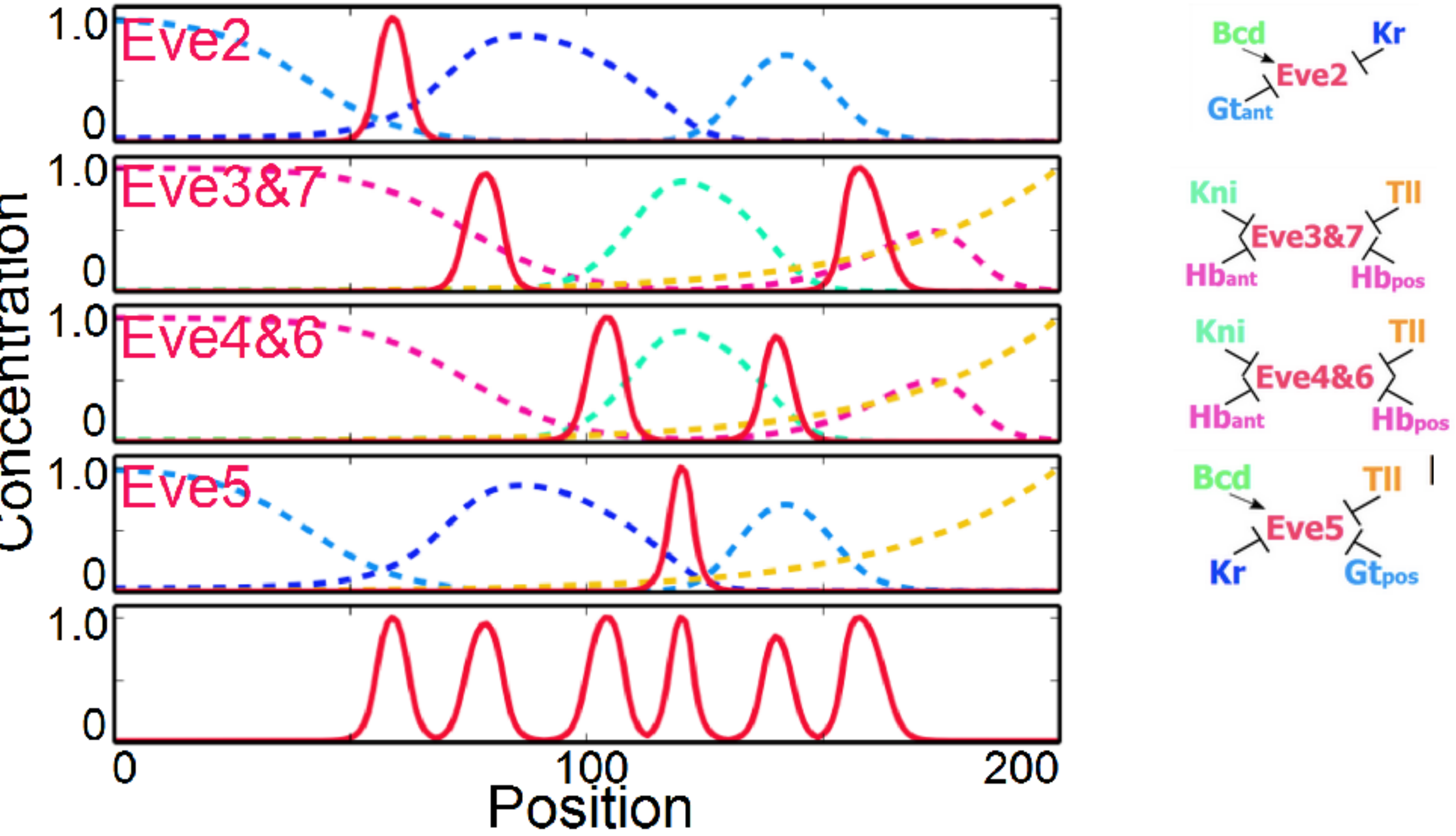


- gap genes repress each other
- eve stripes are sandwiched between local gap genes
- standard biochemical kinetics

$$\frac{dGt}{dt} = \frac{Bcd^n}{Bcd^n + b^n}\frac{k^m}{Kr^m + k^m} - \delta Gt$$

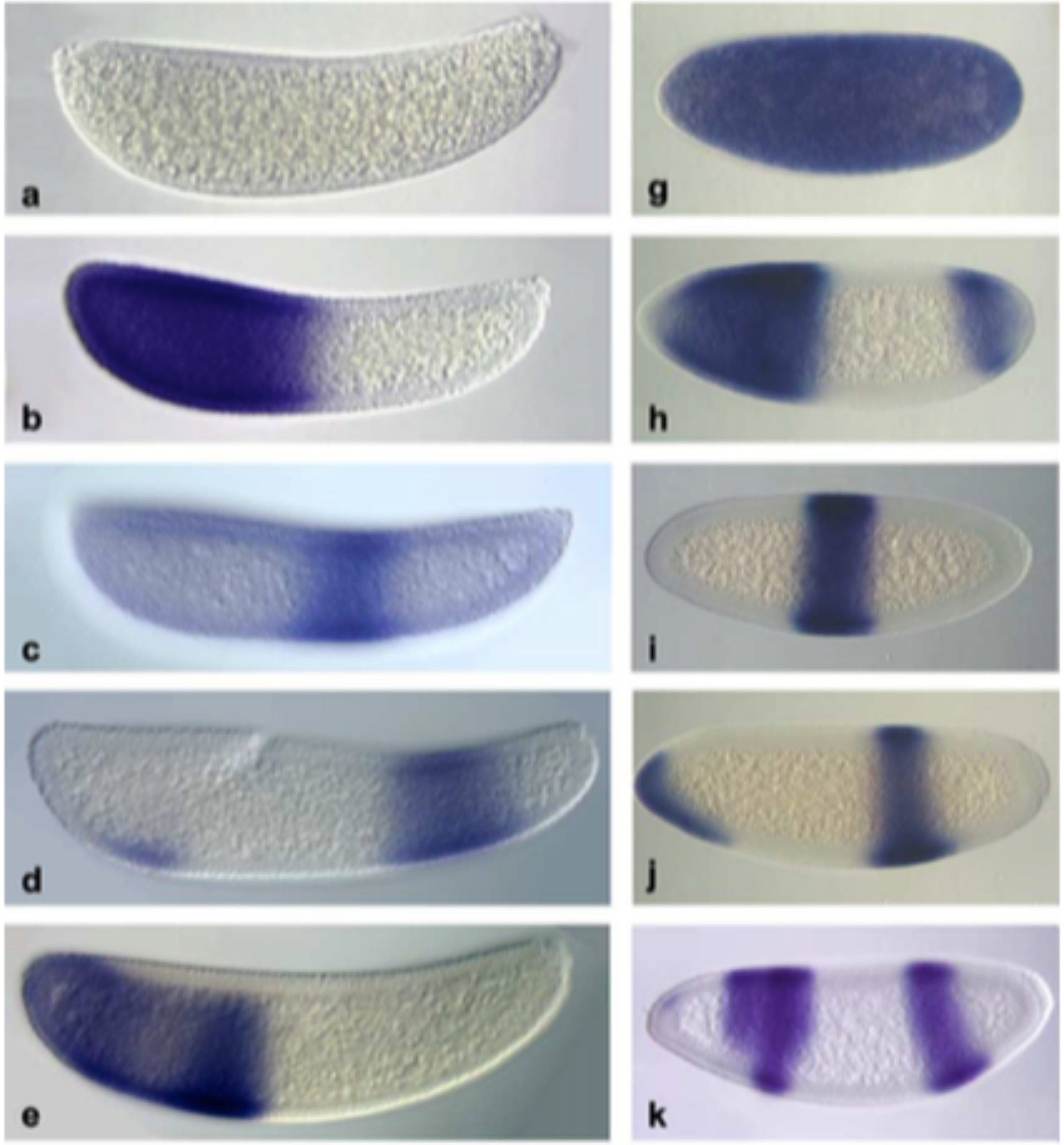
Eve regulations (from both genetics and bioinformatics)

1A



Mosquito side: Goltsev et al., 2004

Mosquito Fly



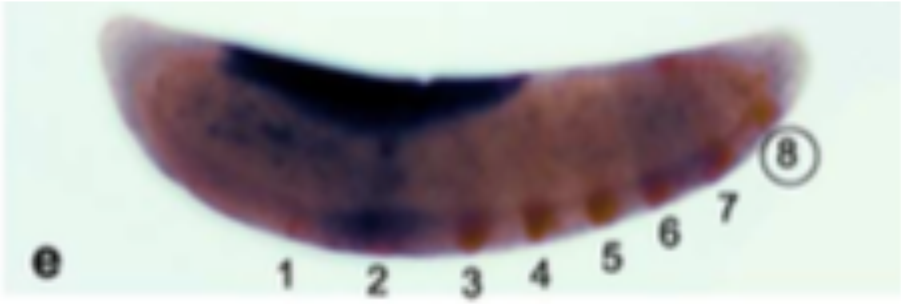
hb

Kr

kni

gt

Posterior gap genes different

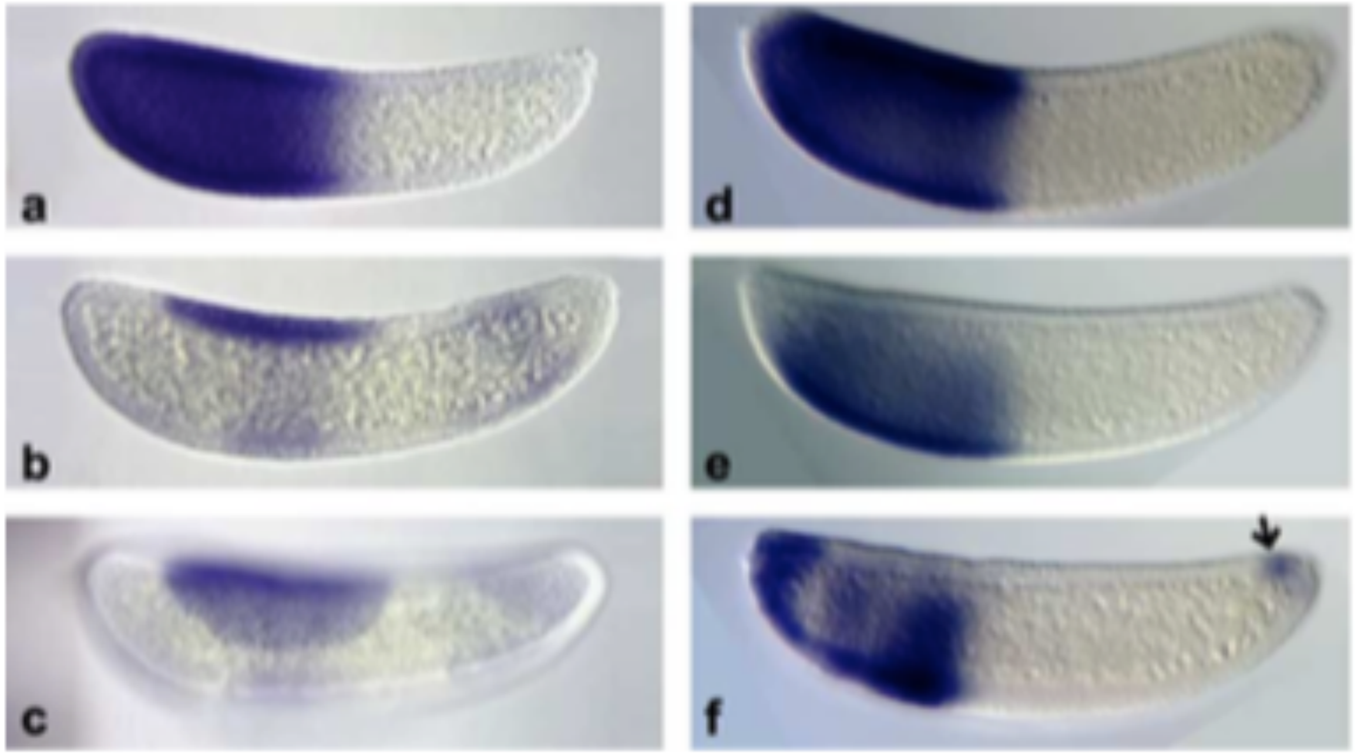


Up to 8 eve stripes !

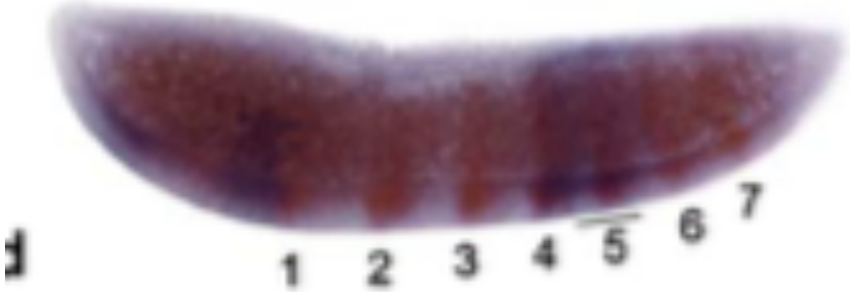
Later patterning in the posterior

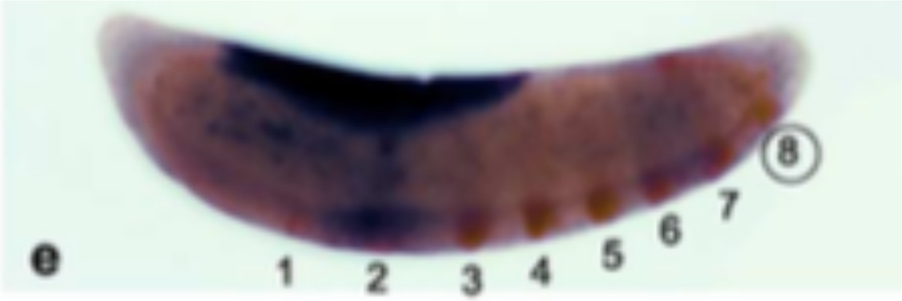
hb

gt



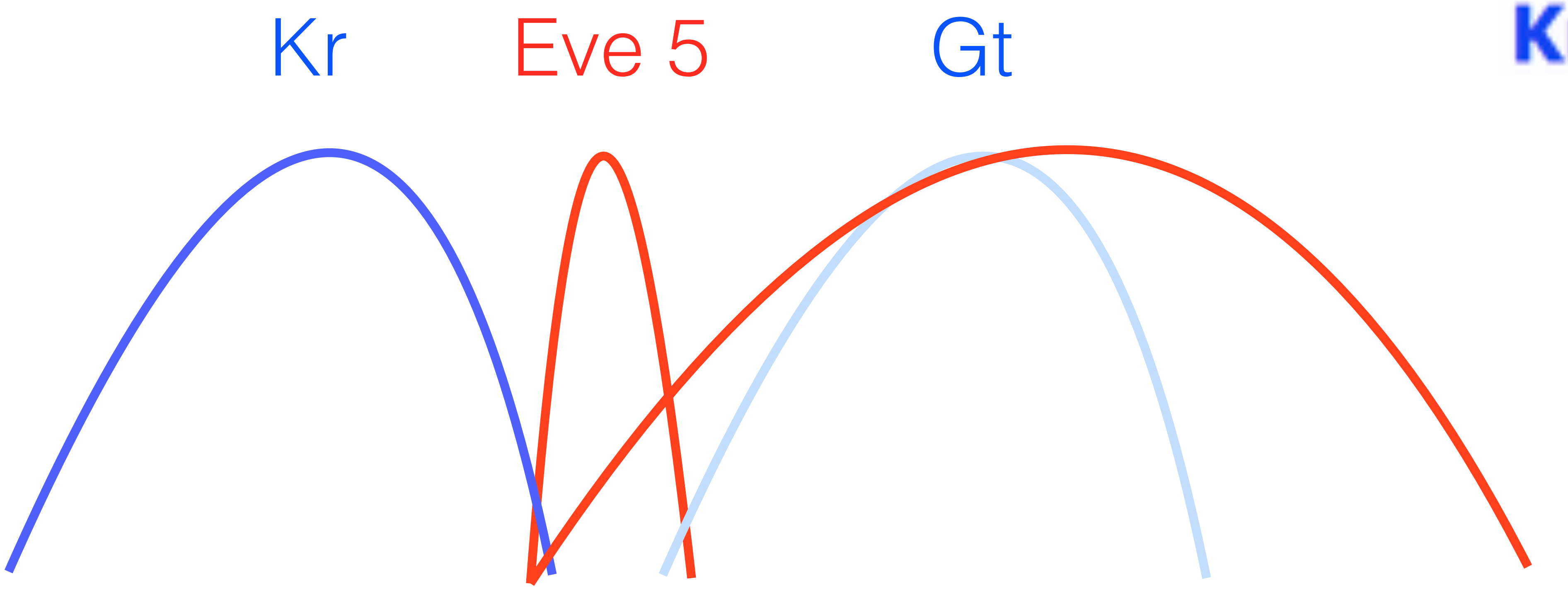
eve





hb+eve

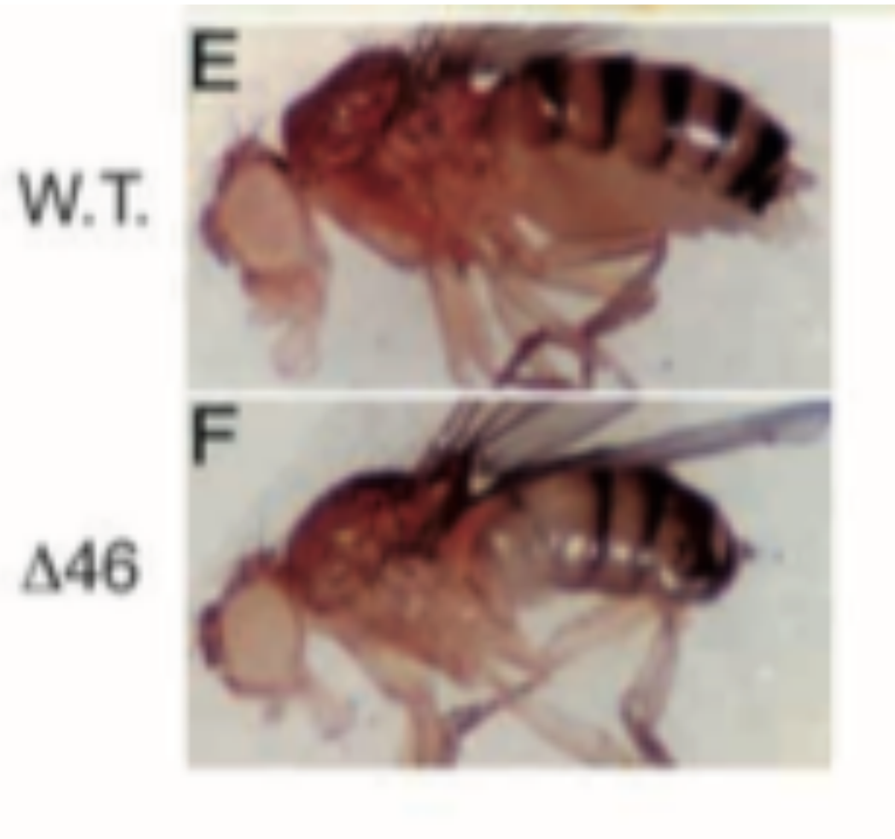
The “eve 5 conundrum”



Eve regulations can not be conserved.
However some of the anterior stripes look the same ->
some enhancers must be functionally conserved

Score computation

There is surprising plasticity regarding stripes !



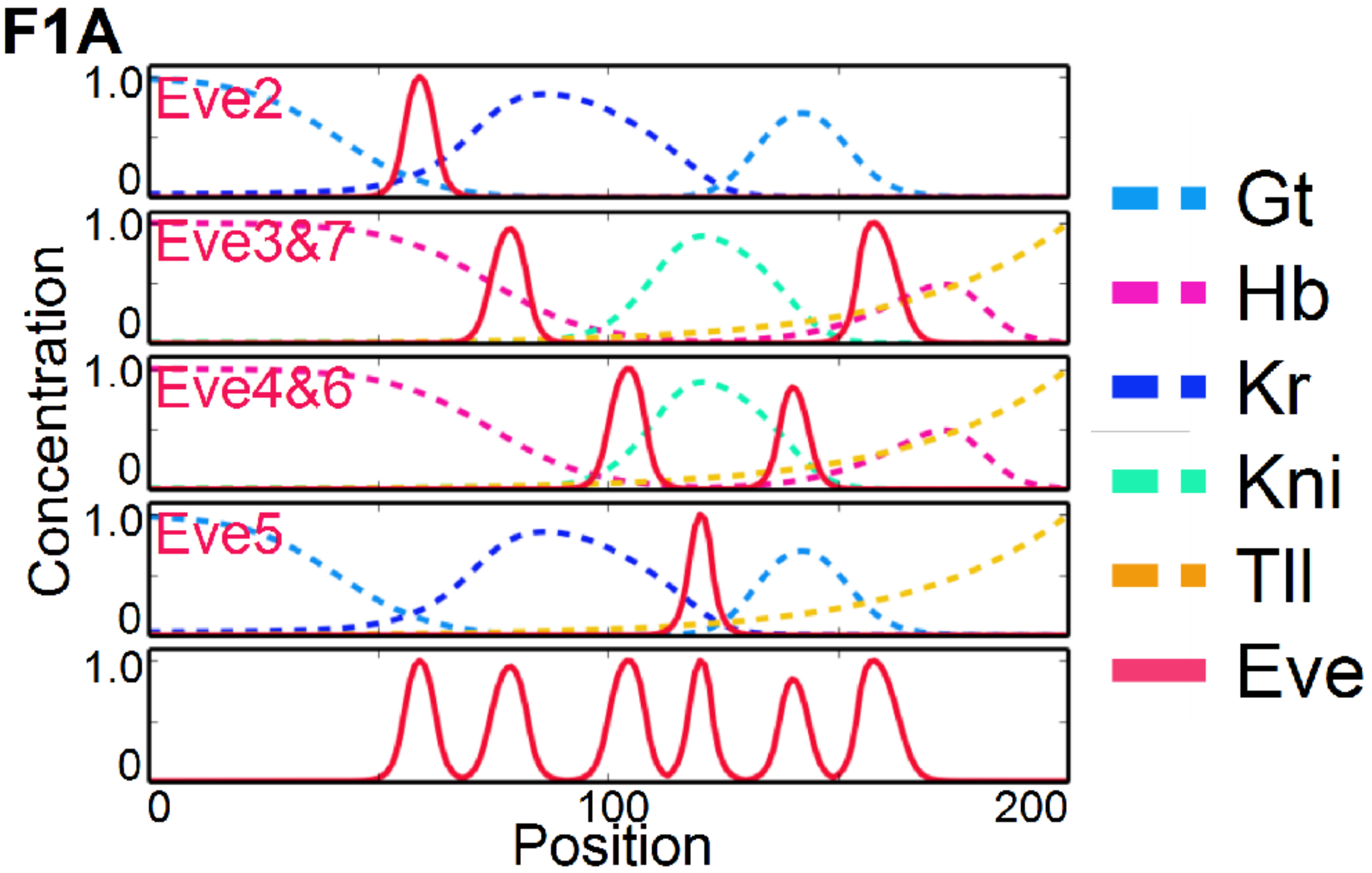
Fujioka et al, Development, 2002

- Score 2: simply counting Eve stripes and making sure we have **at least** 7. “Coarse-grained” fitness. We assume some compensatory mechanism can adjust problems with exact size positioning.

No constraint on size, etc…

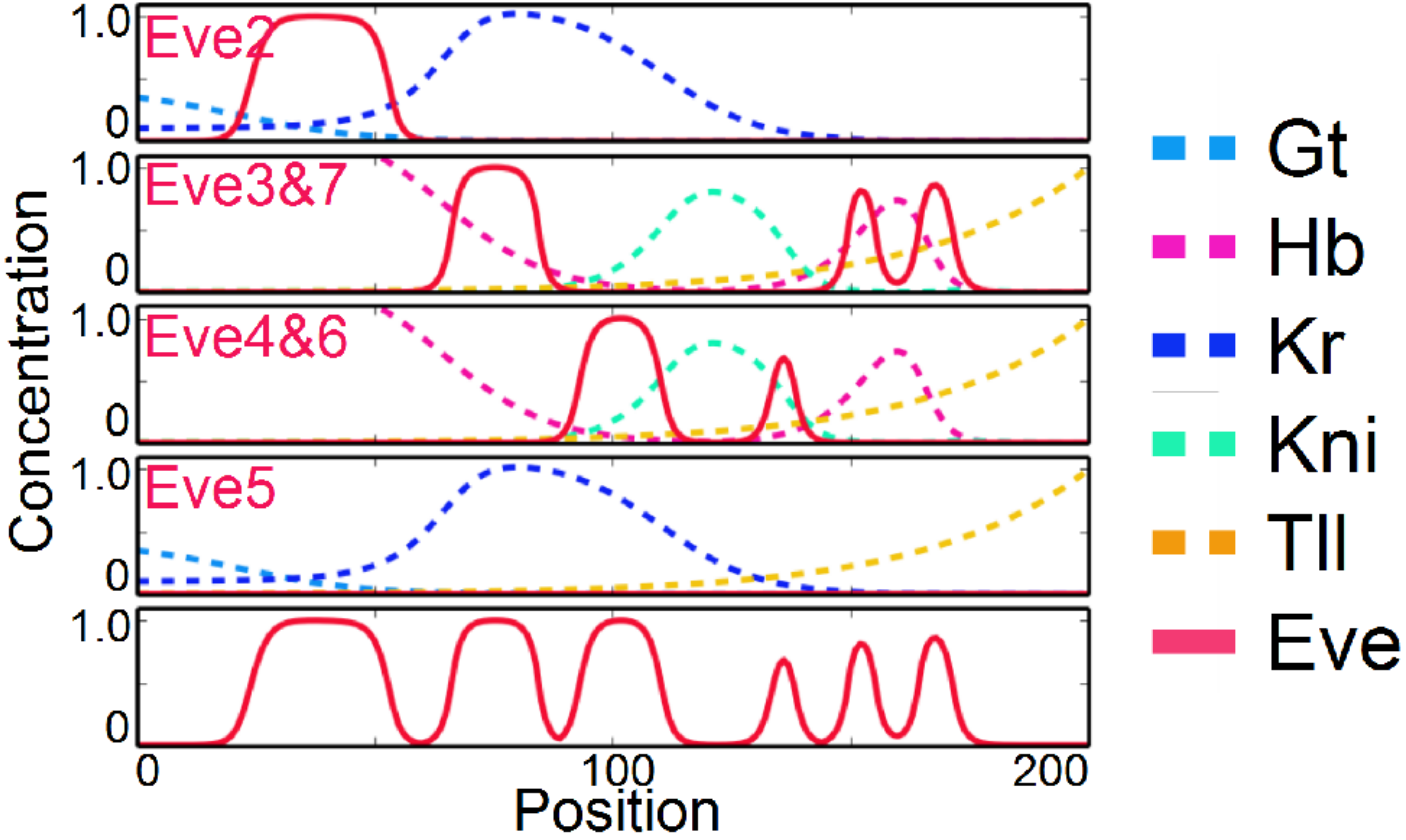
Evolutionary scenario

F1A



Evolutionary scenario 1

F1C

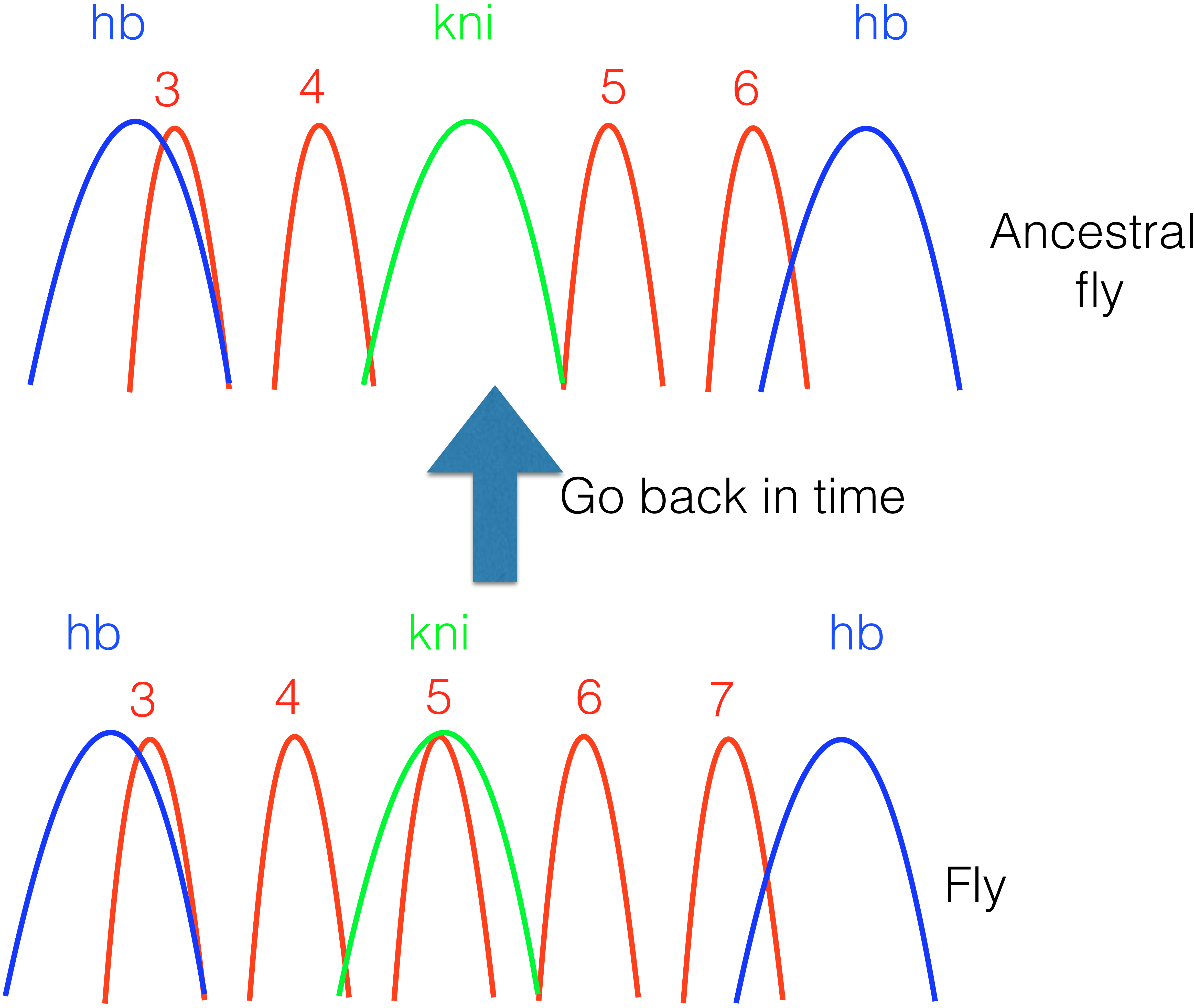


Evolutionary scenarios

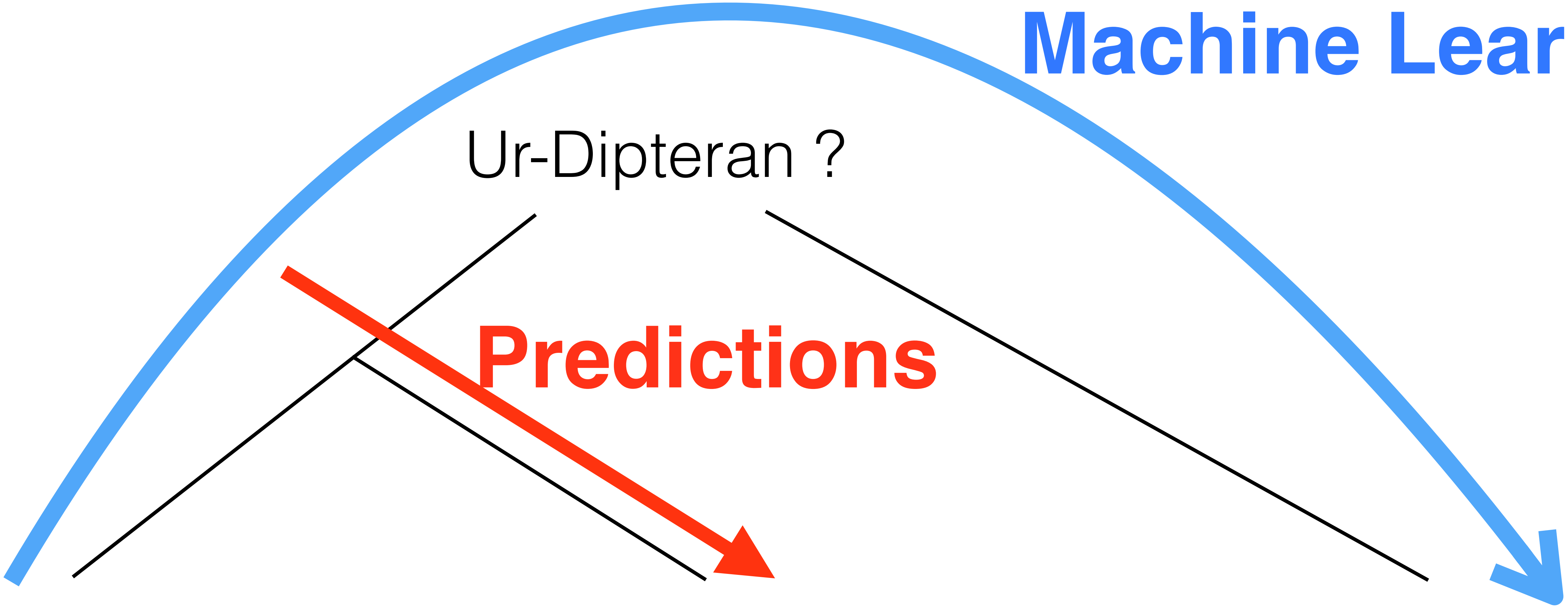
(from fly to mosquito)

- Creates an extra stripe in the posterior because hb getting more anterior
- Suppress eve 5

PREDICTION
eve 4-5 stripes in mosquito homologous to eve 4-6 in fly


hb
kni
hb
3
4
5
6
Ancestral fly
Go back in time
hb
kni
hb
3
4
5
6
7
Fly

Predicting ancestral species



(Evolutionary) Machine Learning

Ur-Dipteran ?

Predictions

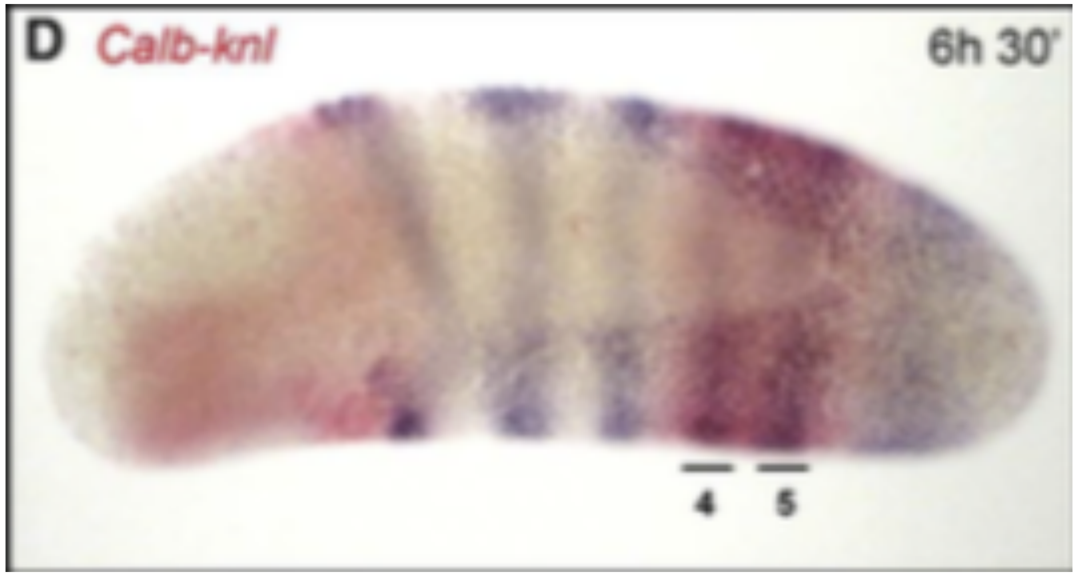
Drosophila

Clogmia

Anopheles

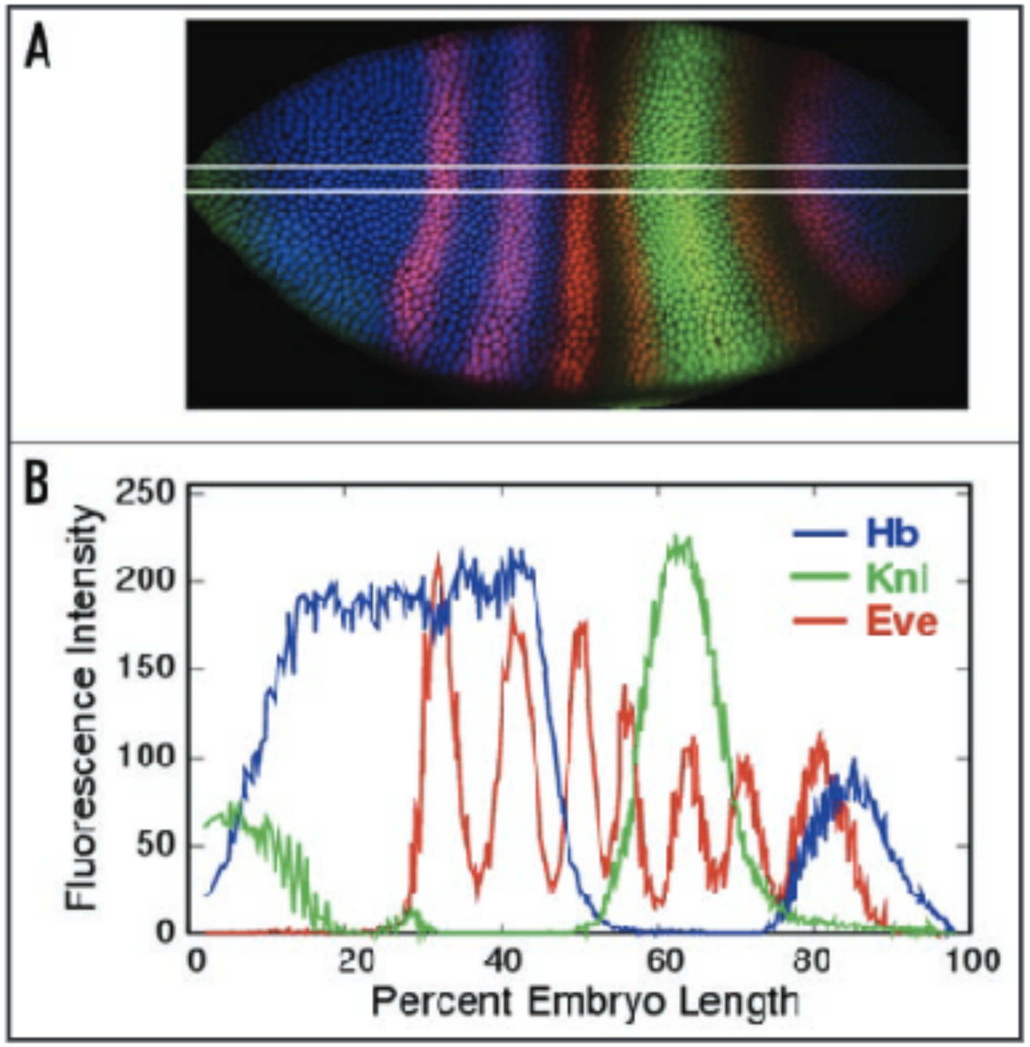
Clogmia

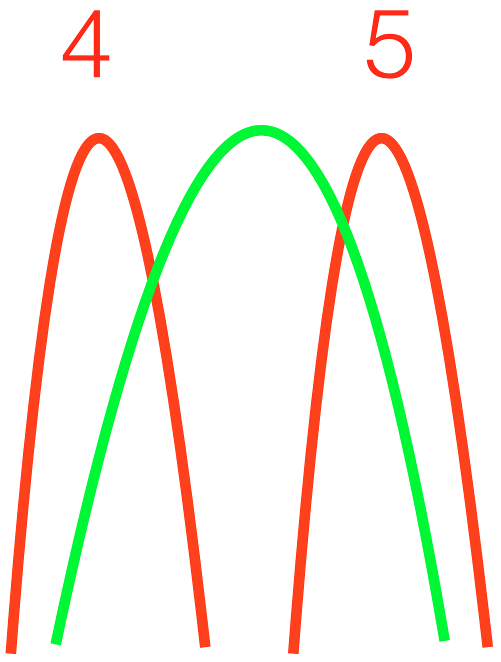
Garcia-Solache et al,
Dev Biol 2014



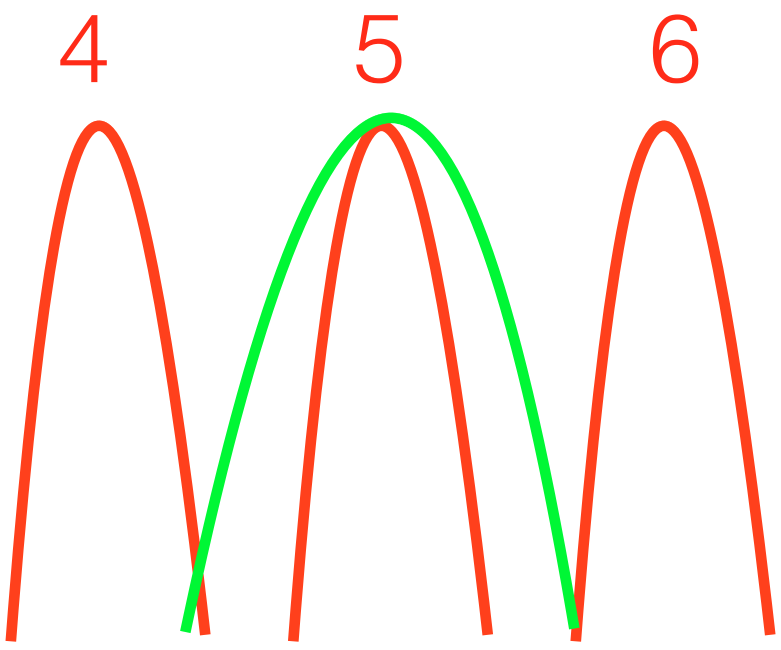
Drosophila

Surkova et al, Fly, 2008

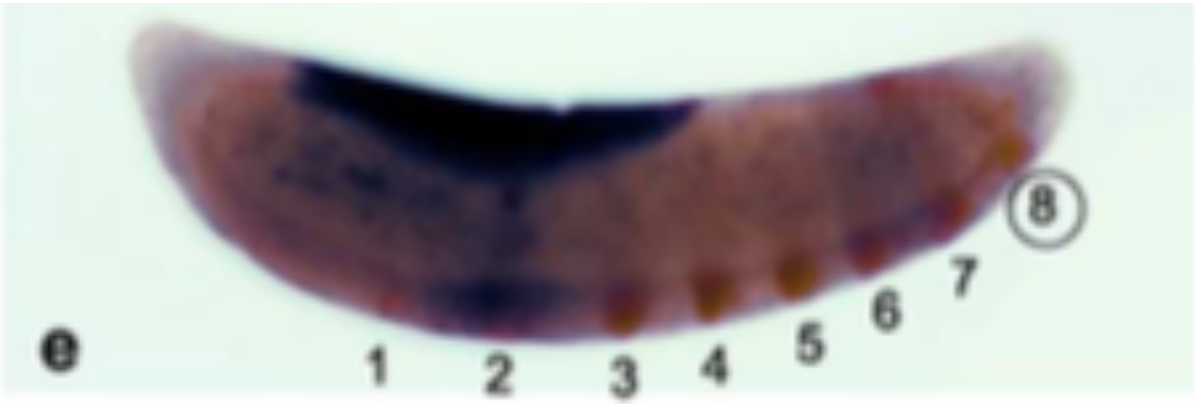




kni

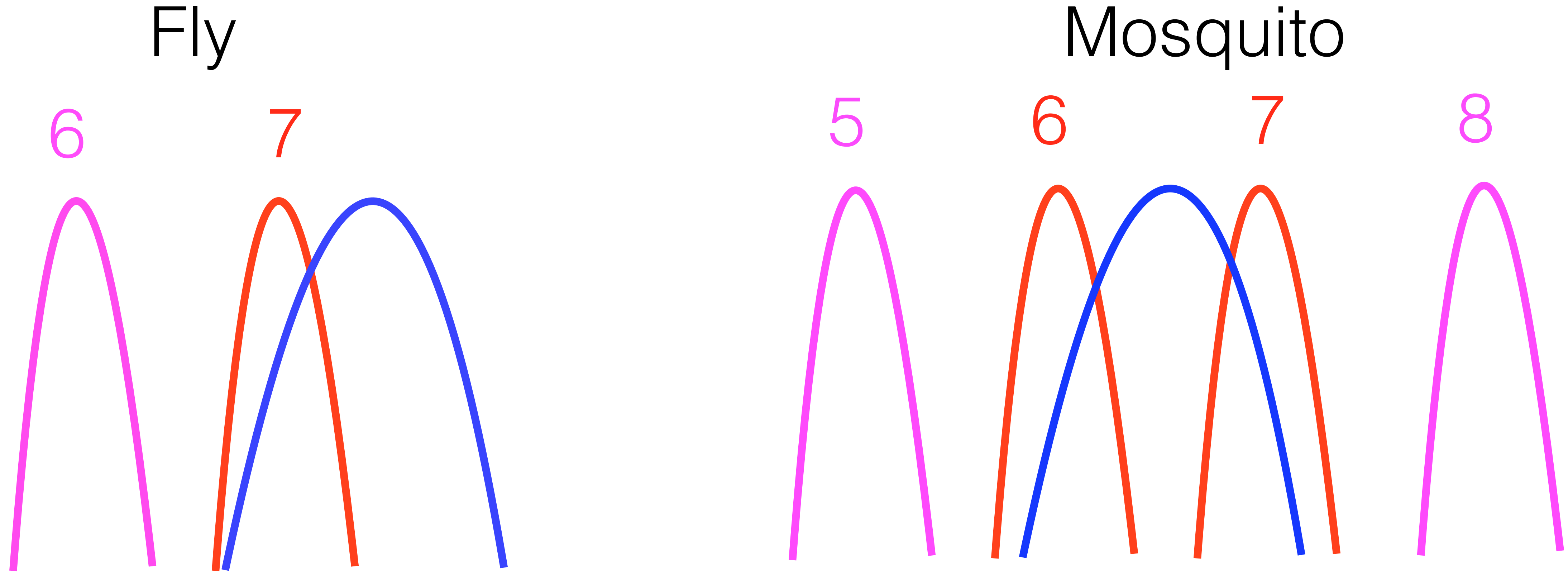


Another prediction: a proposal for mosquito Eve 8 stripe



hb+eve

Either eve 6 or 7 are reused during our simulations.
What if both are reused in the posterior?
Prediction: mosquito eve 5/6 are mirror images of eve 7/8 w.r. to hb ***(you can see it on in situs !)***



- You find “more than you put” (e.g. you correctly predict positions of eve stripes relative to gap genes even though that was unconstrained by design !!) - “spandrel”

- Computational evolution is surprisingly efficient and reproducible

- Evolutionary machine learning on sparse data works very well to generate predictions/

Rothschild et al, PLoS Genetics, 2016