Logical dynamical modelling of developmental regulatory networks

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Contents

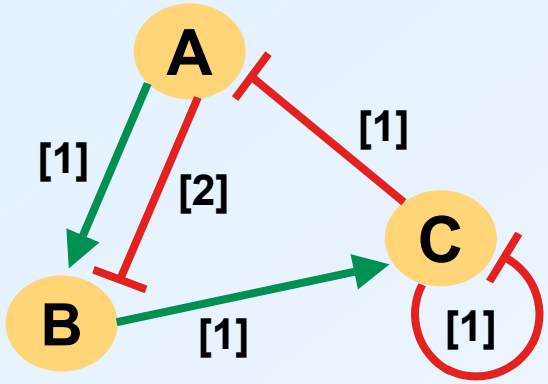
- Asynchronous, logical, multi-level dynamical modelling
- Drosophila segmentation
- Logical modelling of Drosophila segmentation
- Quantitative modelling of Drosophila segmentation

Biological regulatory networks

Abstraction levels *versus* biological questions:

- Molecular level: biochemical networks, signal transduction
- **Genetic level: genetic regulatory networks**
- Inter-cellular level: cell differentiation, tissues, patterns
- Macroscopic levels (organs, physiology...)

Logical modelling of regulatory networks



✓ A **graph** describes the interactions between genes or regulatory products

✓ **Discrete levels** of expression associated to each gene (logical variables) and interaction

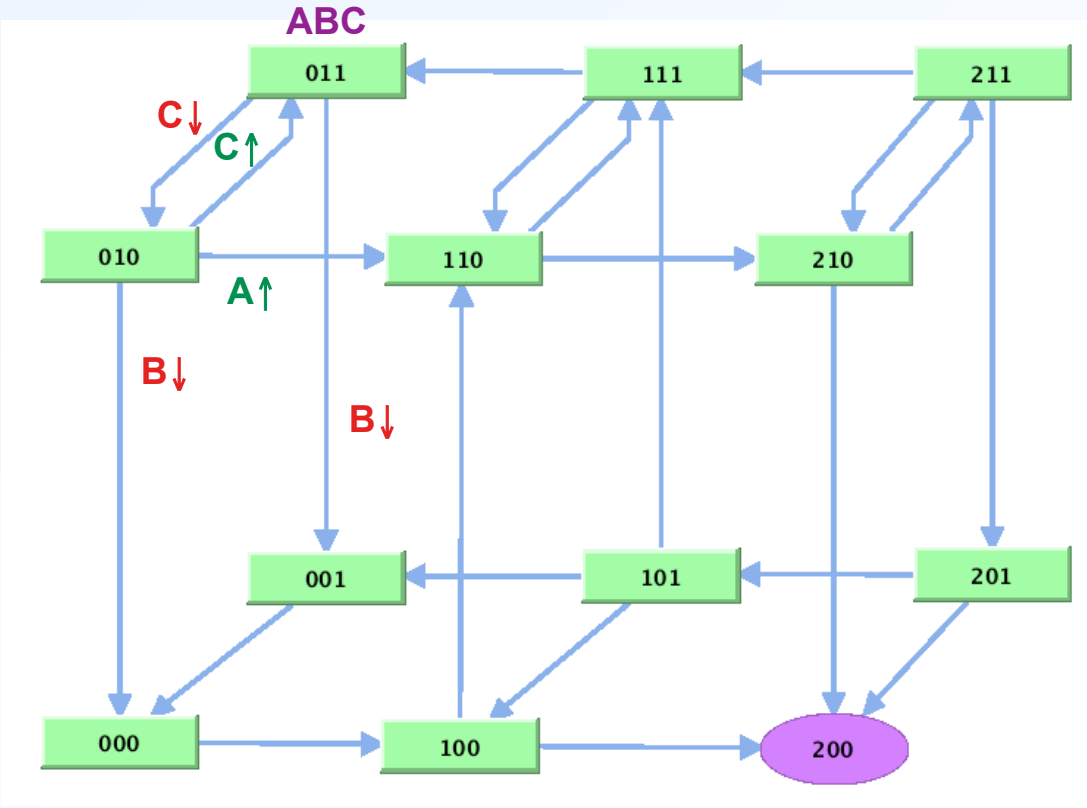
✓ **Logical parameters**
define the effect of combinations of incoming interactions

$K_B(\varnothing)=0$

$K_B(\{A,1\})=1$

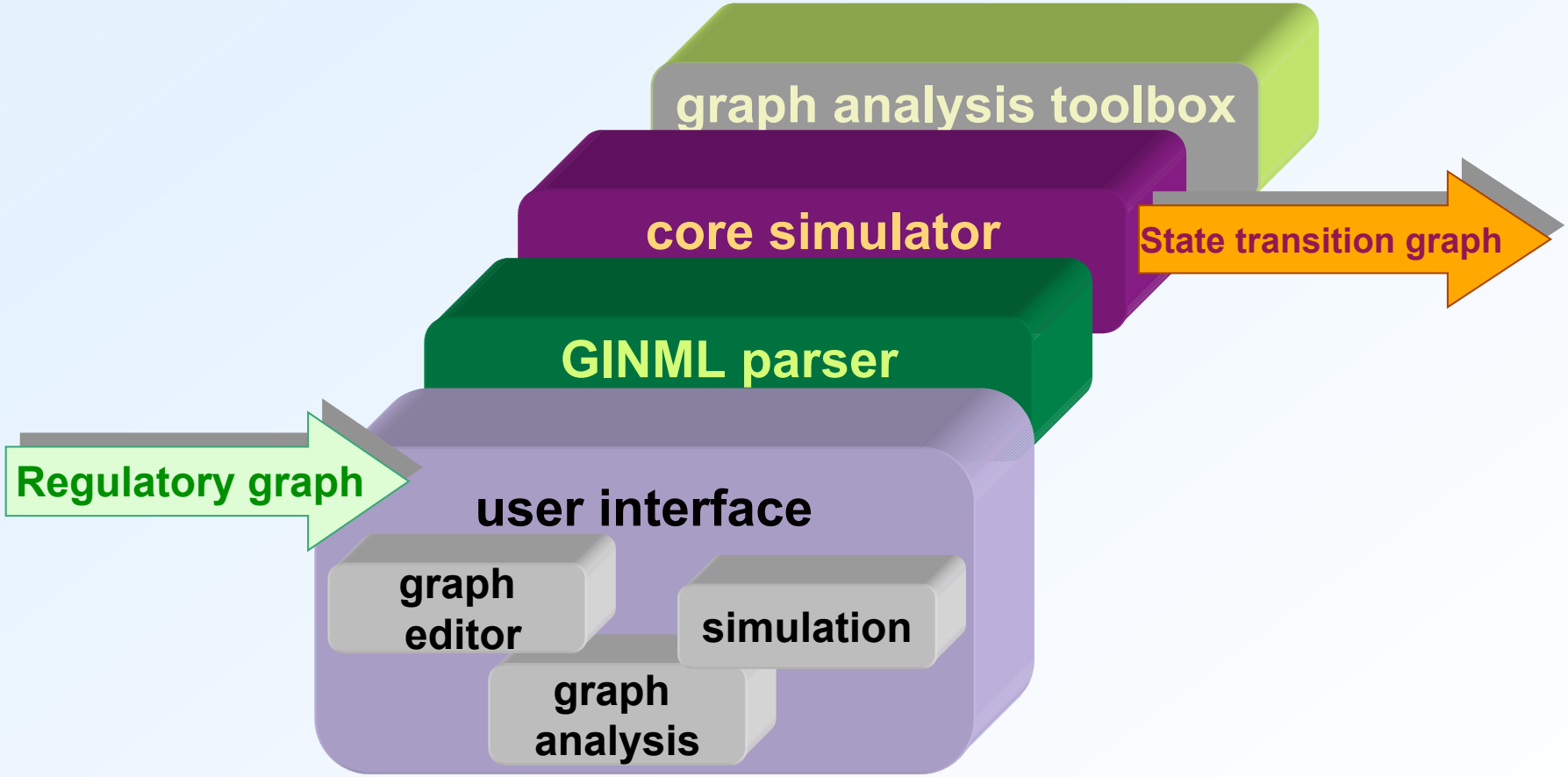
$K_B(\{A,2\})=0$

✓ The dynamics is represented by a **State Transition Graph** (here, all possible trajectories)



Chaouiya C, Remy E, Mossé B, Thieffry, D (2003). *LNCIS* **294**: 119-26.

GINsim (Gene Interaction Networks simulation)

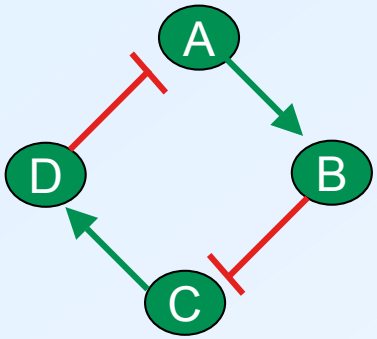


Available at **http://gin.univ-mrs.fr/GINsim**

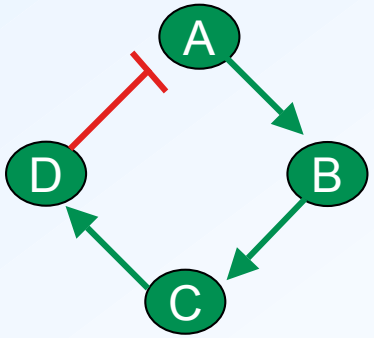
Gonzalez A, Naldi A, Sánchez L, Thieffry D, Chaouiya C (2006). *Biosystems* **84**: 91-100.

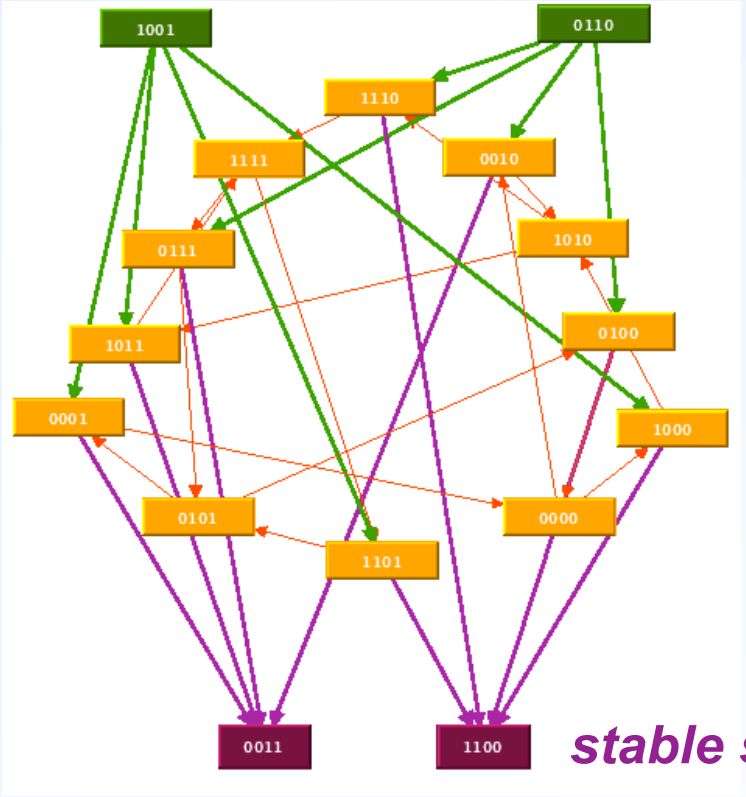
Discrete dynamics of simple feedback circuits

Positive circuit

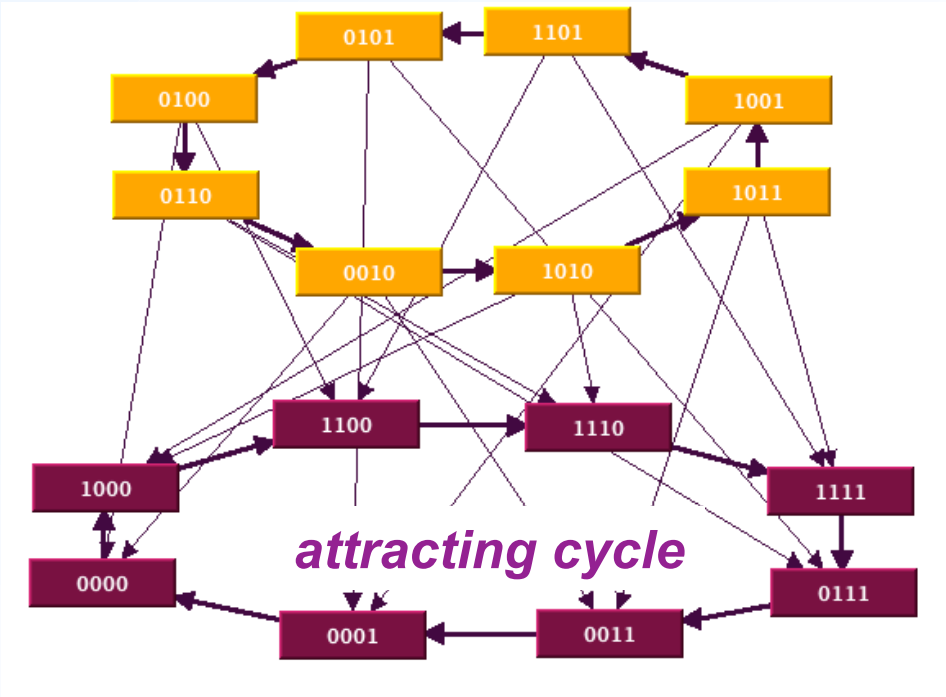


Negative circuit





stable states



attracting cycle

Remy E, Mosse B, Chaouiya C, Thieffry D (2003). *Bioinformatics* **10**: ii172-8.

Feedback circuits & Thomas' rules

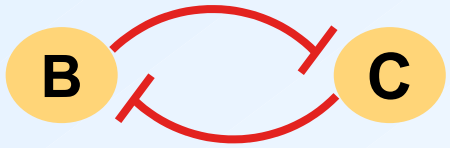
- ✓ A **positive feedback circuit** is **necessary** to generate **multiple stable states or attractors**
- ✓ A **negative feedback circuit** is **necessary** to generate **homeostasis or sustained oscillatory behaviour**

Thomas R (1988). *Springer Series in Synergics* **9**: 180-93.

Mathematical theorems and demonstrations:

- ✓ **In the differential framework:**
  - Soulé C (2005). *ComPlexUs* **1**: 123–33.
- ✓ **In the discrete framework:**
  - Remy E, Ruet P, Thieffry D (2006). *LNCIS* 341: 263-70.
  - Richard A (2006). *PhD thesis*, University of Evry, France.

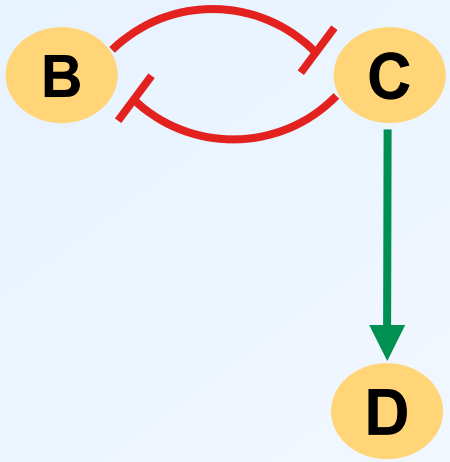
Circuit functionality context



This system typically gives two stable states

01 and **10**

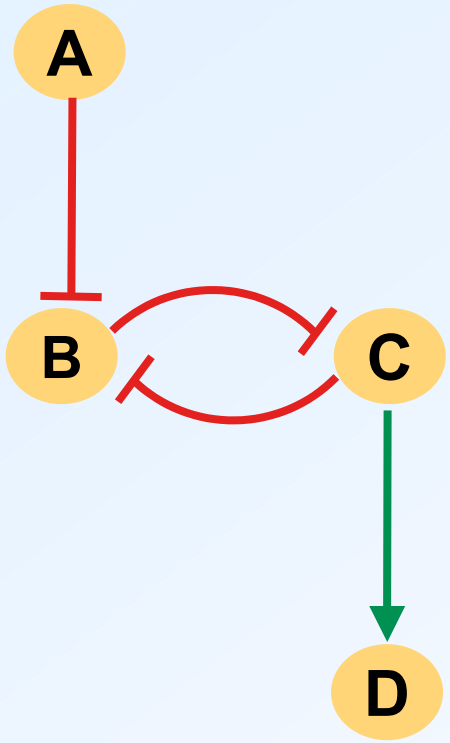
Circuit functionality context



This system typically gives two stable states,

now {B,C,D} = **011** and **100**

Circuit functionality context



Circuit behaviour depends on the effect of A on B

If A alone is able to switch OFF B:

- In the **presence** of **A**:

→ only **one stable state** with {A,B,C,D}= **1011**

- In the **absence** of **A**:

→ **two** stable states **0100** and **0011**

- The **positive cross-inhibitory circuit**

involving **B** and **C** is thus **functional**

only in the **absence of A**.

Development of a **computational algorithm** enabling the **analysis** of the **functionality** of **feedback circuits** in the **discrete case** (Naldi *et al*, 2007).

Dynamical analysis tools

- **Priorities**
  - Mixed a/synchronous simulations
    [Fauré *et al* (2006) *Bioinformatics* **22**: e124-31]
- **Decision diagrams (Aurélien NALDI)**
  - Stable state identification
  - Feedback circuit analysis
    [Naldi *et al* (2007) *LNCS* 4695: 233-47]
- **Petri nets (Claudine CHAOUIYA)**
  - Standard Petri nets [Remy *et al* (2006). *LNCS* **4230**: 56-72]
  - Coloured Petri nets [Chaouiya *et al* (2006) *LNCS* **4220**: 95-112]
- **Logical programming**
  - Attractor identification and reachability analysis

Applications

Drosophila development

- Genetic network controlling embryonic segmentation (with L Sanchez, Madrid)
- Compartment formation in imaginal disks
- Embryonic muscle and heart development (with E Furlong)

Cell cycle (DIAMONDS STREP, FP6) and **Apoptosis** (APOSYS, FP7)

- Yeast (*S. cerevisiae*) (with A Cilliberto, IFOM, Milano)
- Mammalian cells
- Drosophila (with L Calzone, B Novak, J Tyson)

Lymphoid cell differentiation and activation (ACI IMPbio & ANR BioSys)

- Th0/1/2, Tregs, Th17 (with J Carneiro, Lisbon)
- TCR signalling and T cell activation (with P Ferrier & R Lima, Marseille)
- Specification of haematopoietic lineages (with T Graf, Barcelona)

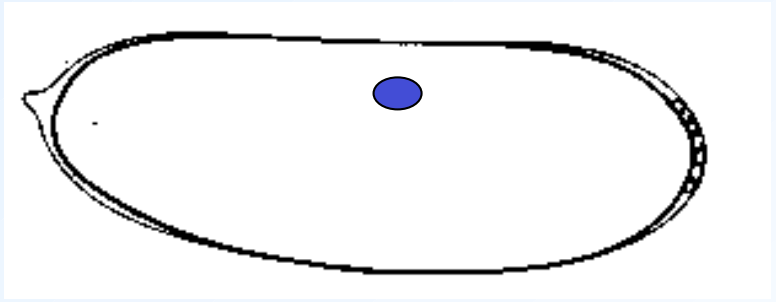
Staring: *D. melanogaster*

Courtesy: J. Reinitz

Drosophila Development

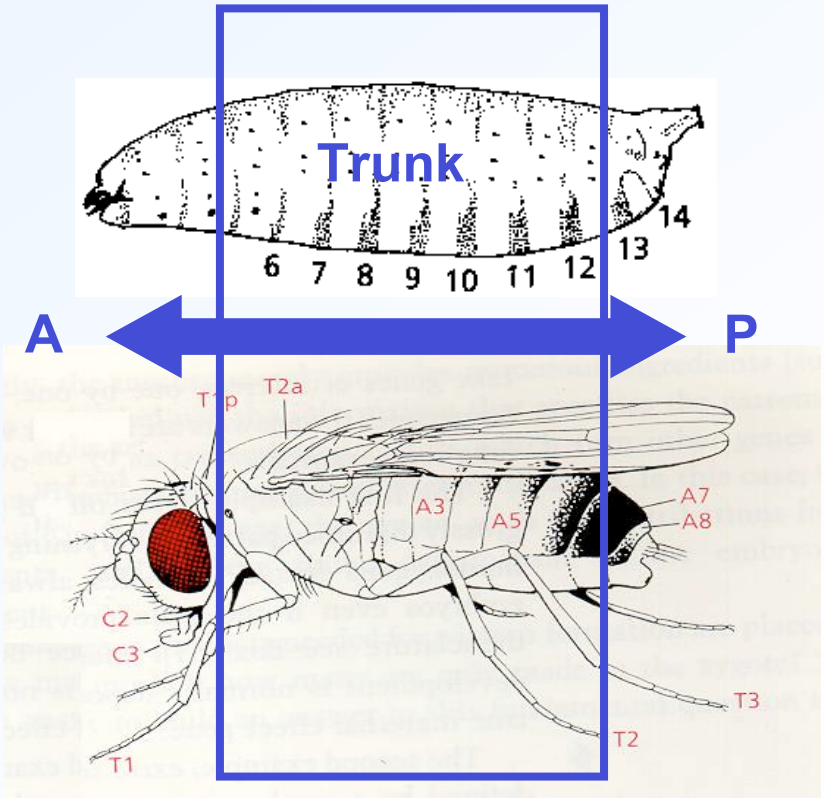
Zygote

24 hours

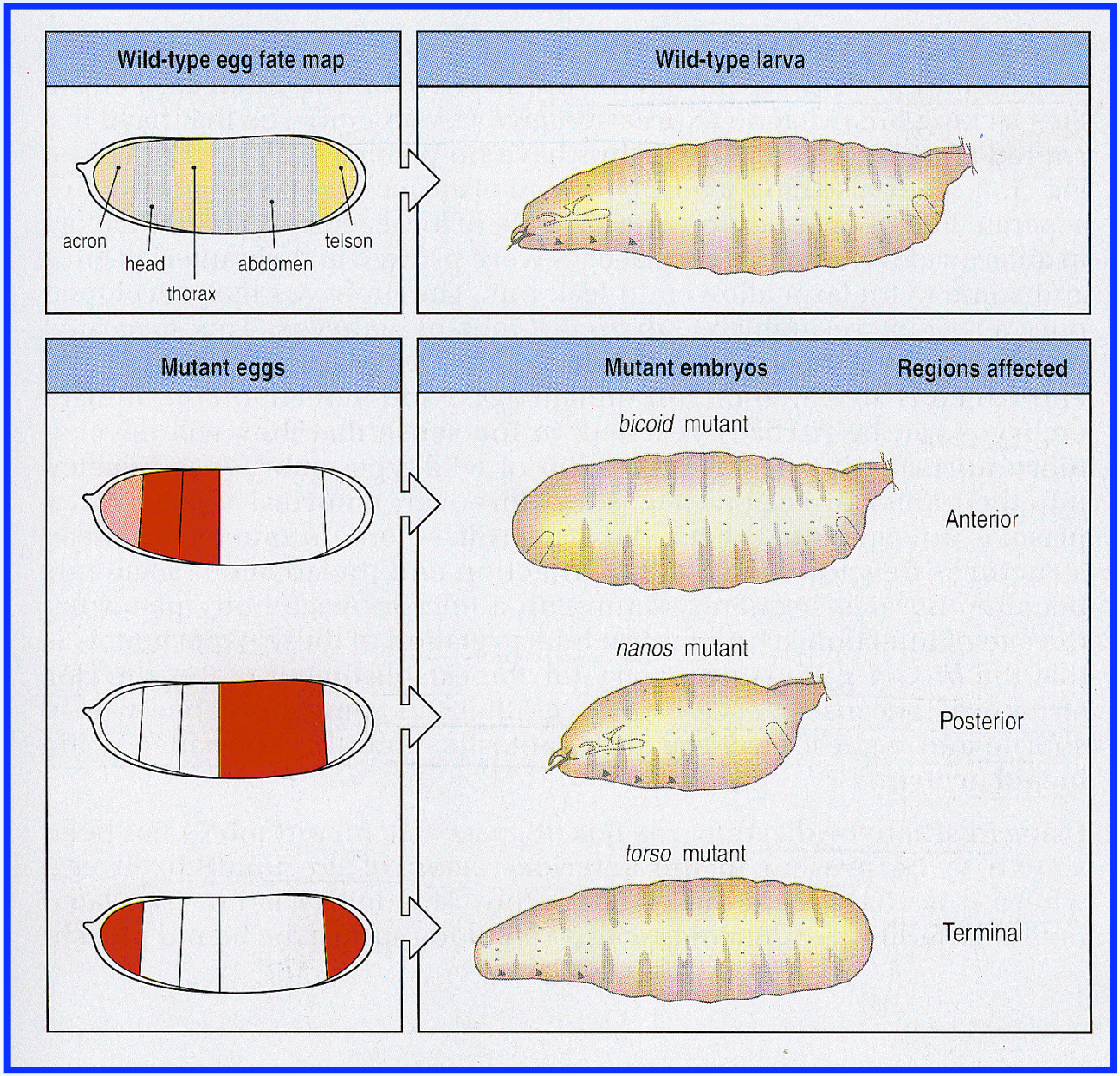


Larva

9 days



Adult



Genetic data

Maternal mutants

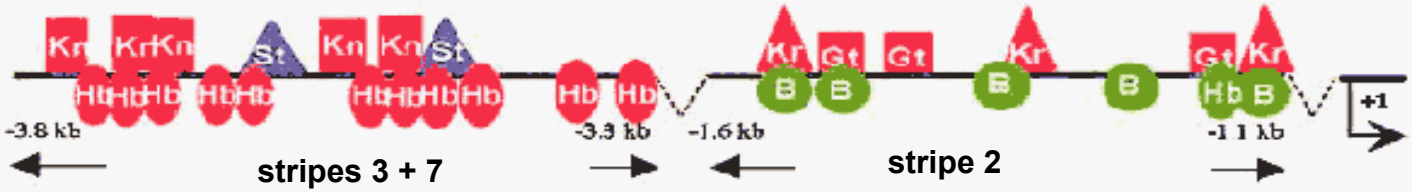
High troughput functional arrays: lof mutants, RNAi...

Source: Wolpert *et al.* (1998)

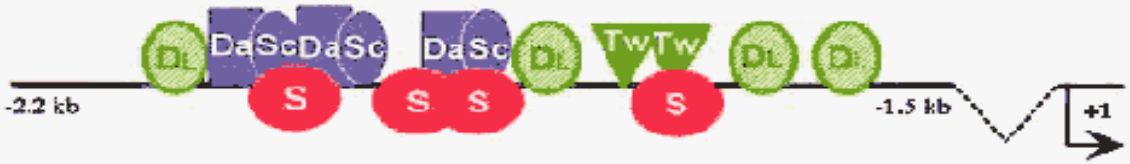
Information on *cis*-regulatory elements in *D. melanogaster*

ftz
zebra element

eve
stripes 2 & 3+7
elements

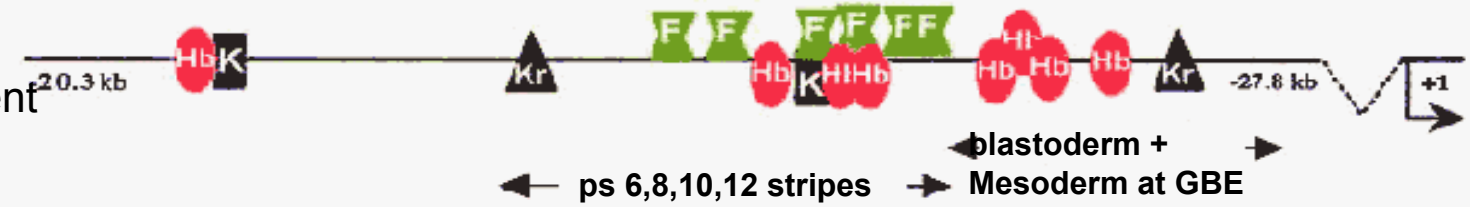


rho
lateral neurectoderm
stripe element

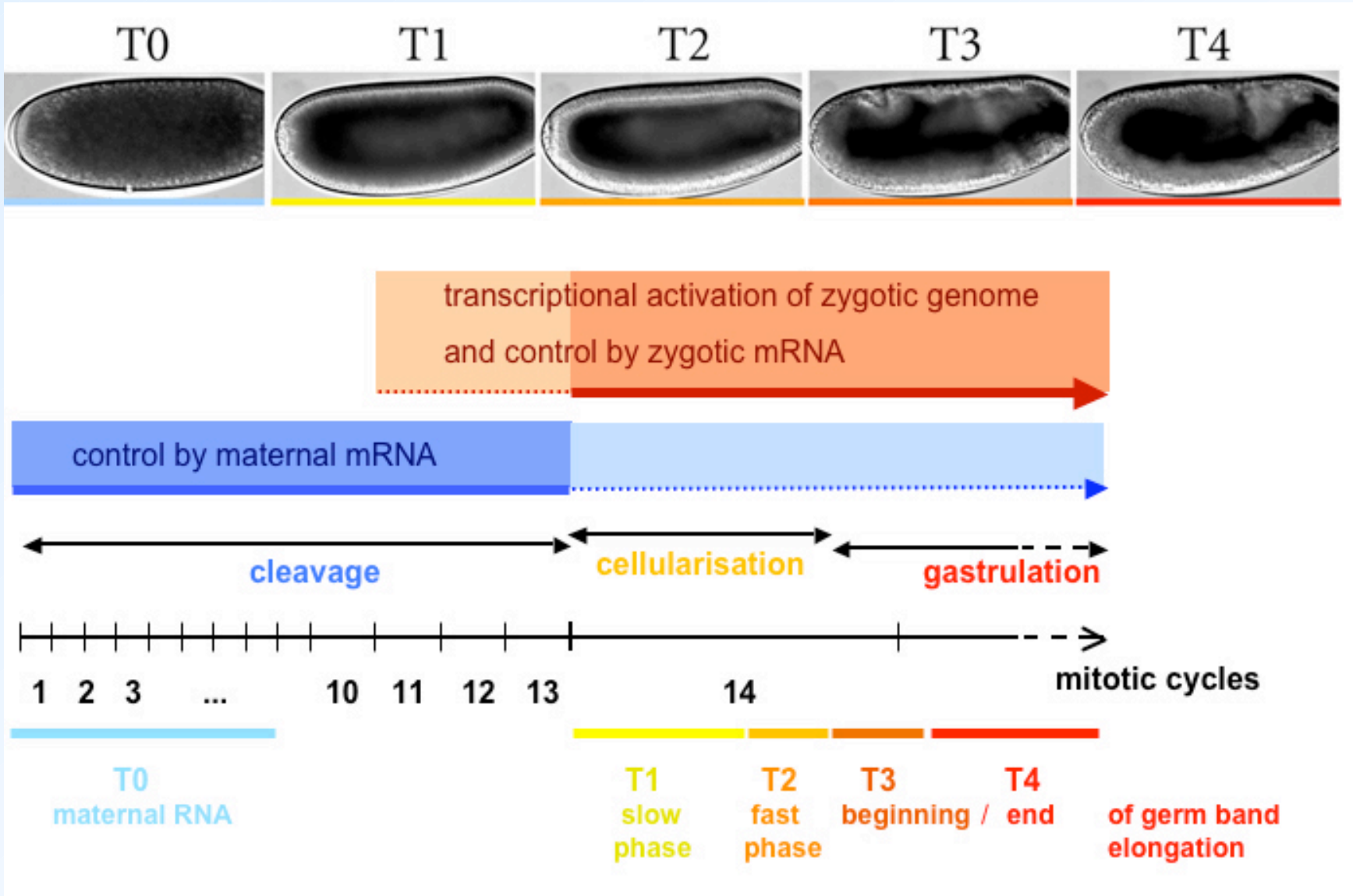


kni
posterior element

Ubx
PBX element

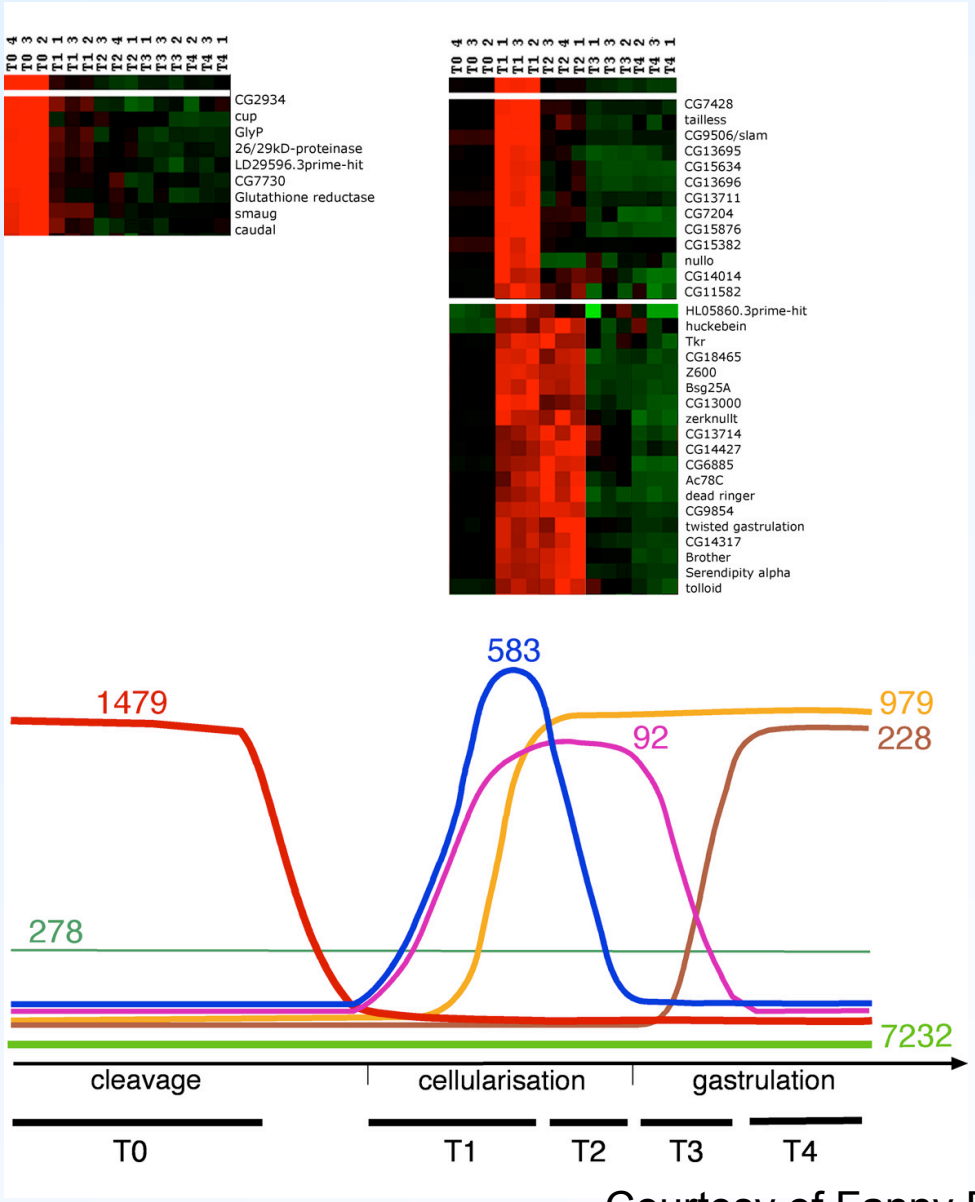


DNA array experiments



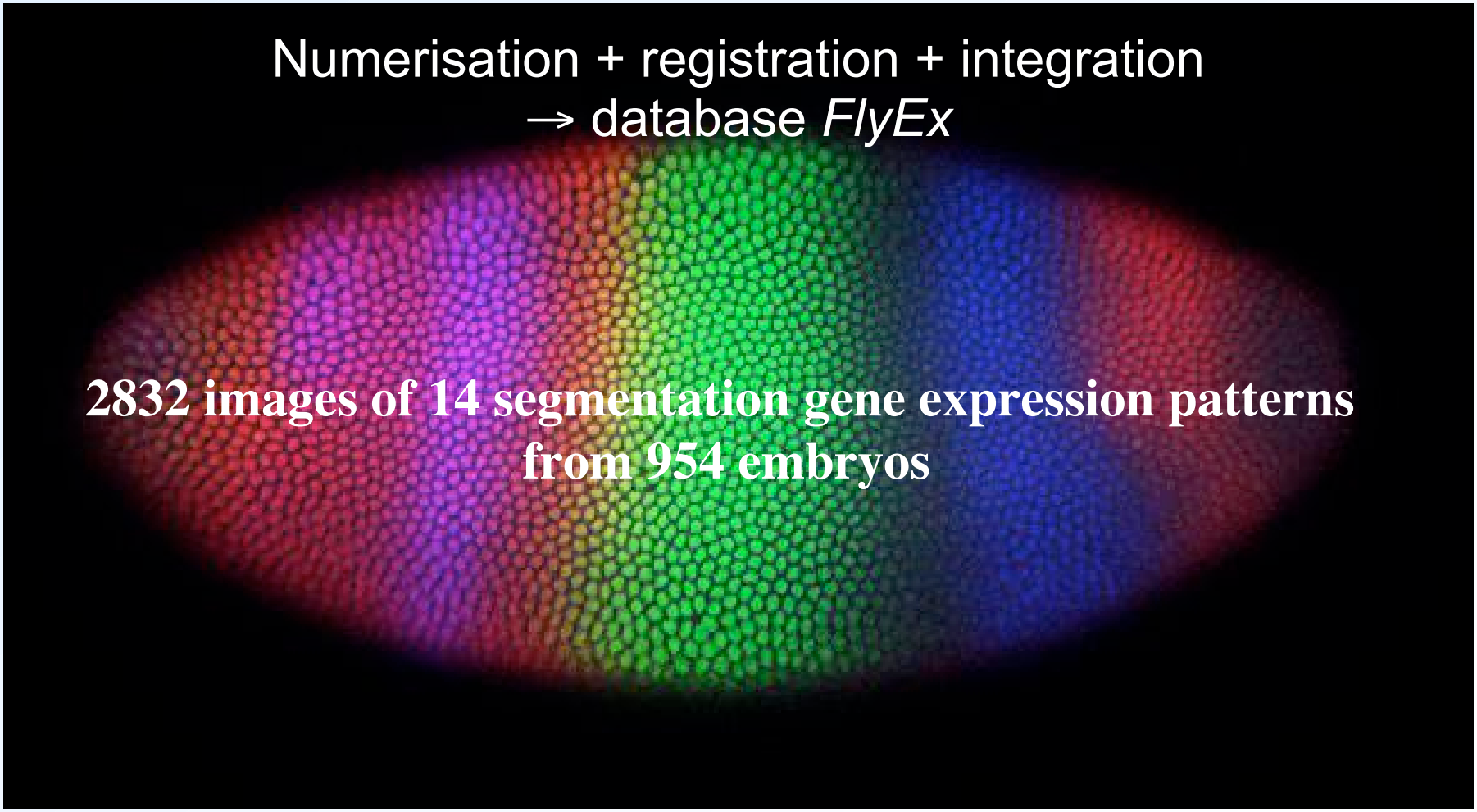
Courtesy of Fanny Pilot & Thomas Lecuit (IBDML, Marseille)

DNA array experiments

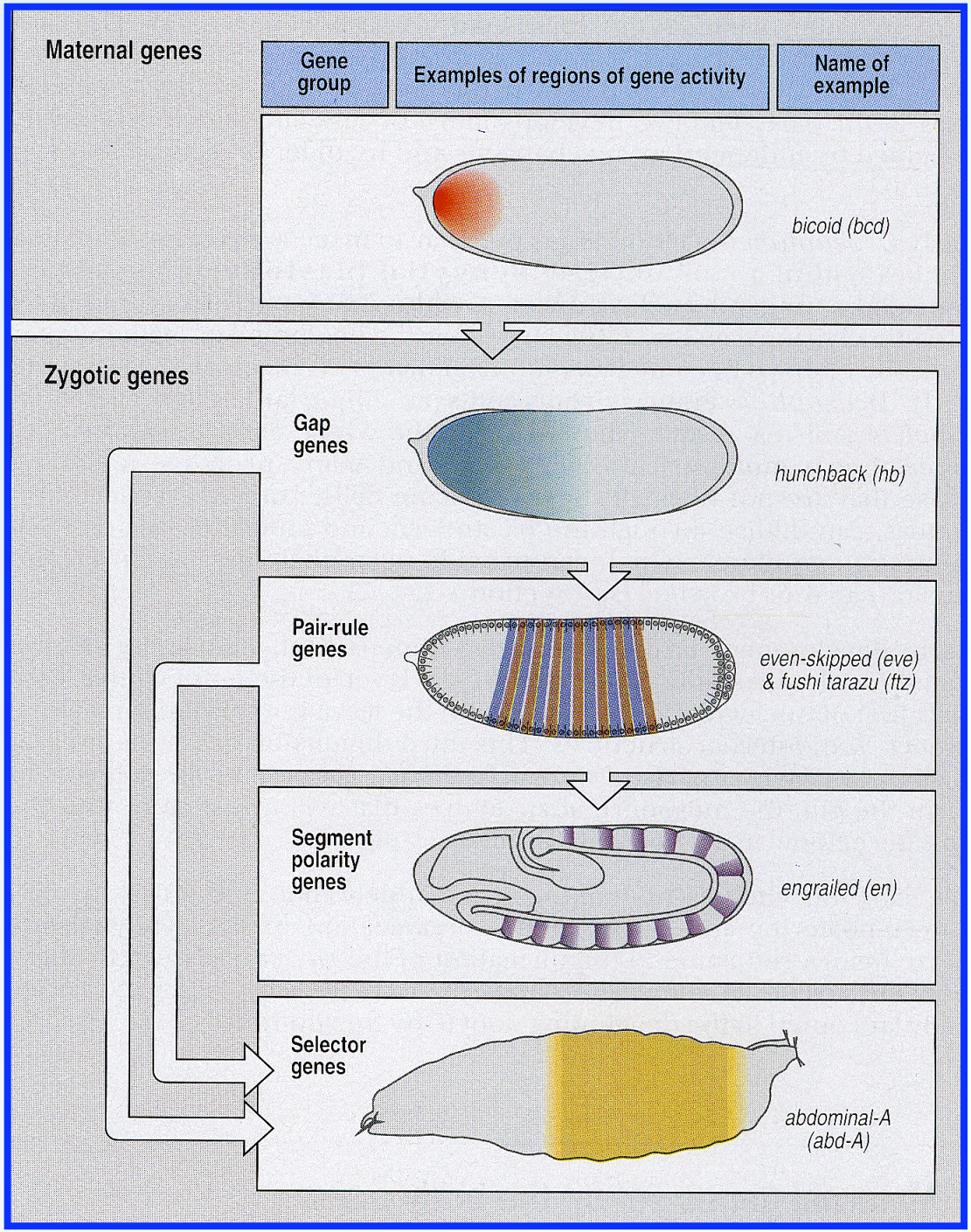


Courtesy of Fanny Pilot & Thomas Lecuit (IBDML, Marseille)

Patterns of gene expression (mRNAs or proteins)



Simultaneous labelling of **HB**, **KR** & **GT** Proteins in *Drosophila* embryo around cell cycle 13 (courtesy of John Reinitz, SUNY).



Anterior-posterior patterning system

Collaboration with

Lucas SANCHEZ

Collection and integration of regulatory data

Graph analysis

Three strongly connected components:

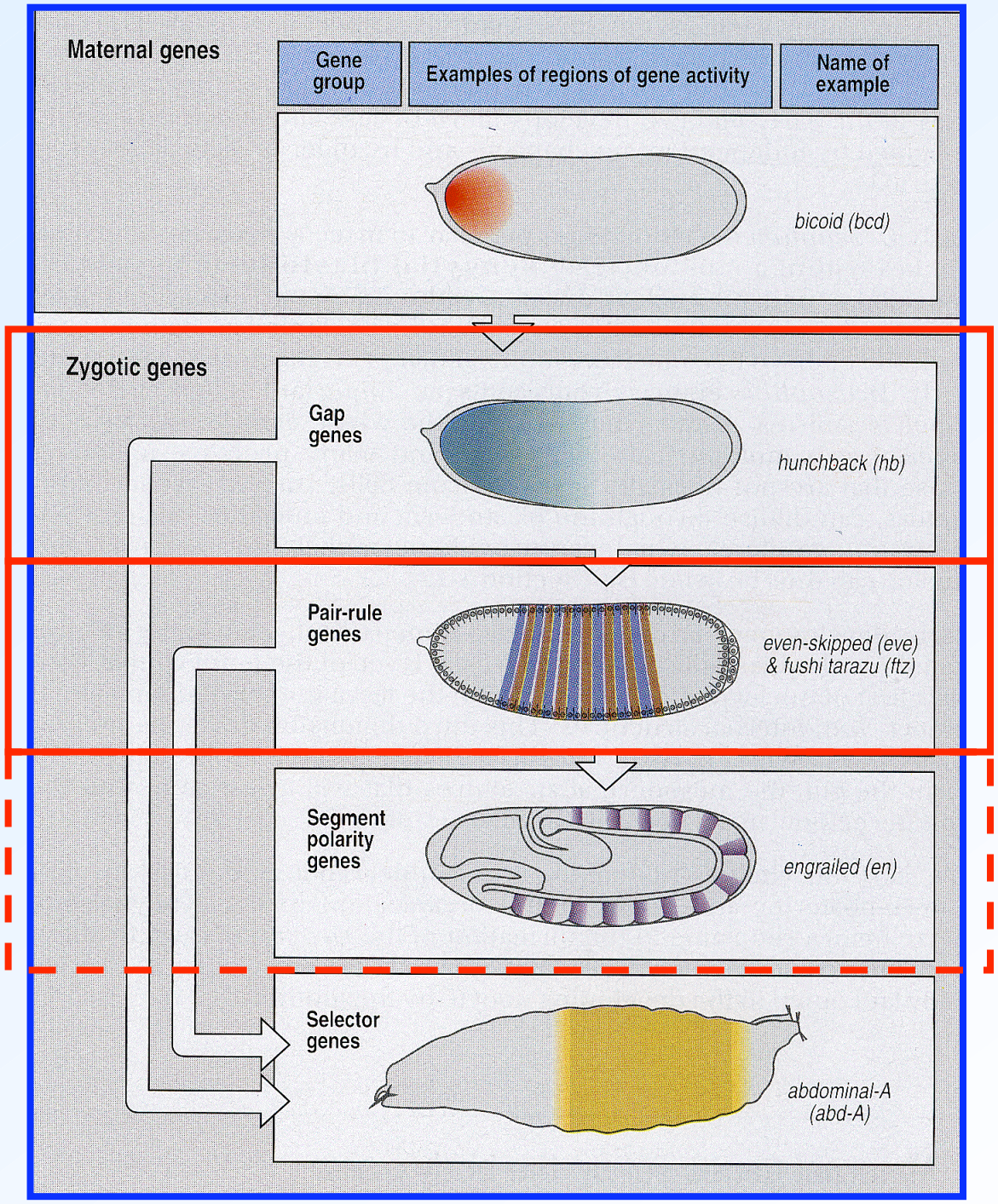
Gap

Pair-rule

Segment-polarity

"cross-regulatory modules"

Source: Wolpert *et al.* (1998)



Drosophila segmentation

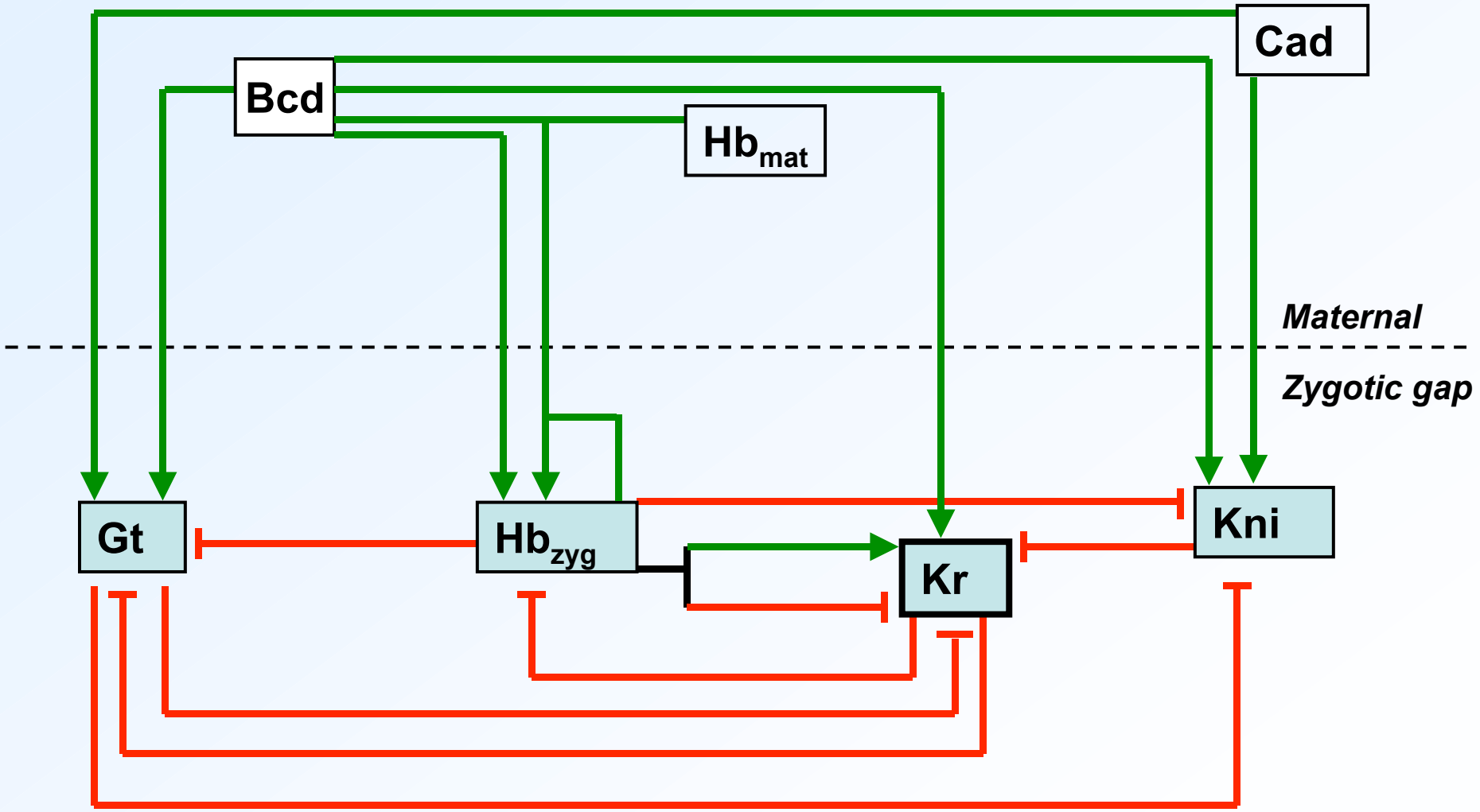
Sánchez L & Thieffry D (2001)
J theor Biol **211**: 115-41

Thieffry D & Sánchez L (2002)
An NY AcadSci **981**: 135-53

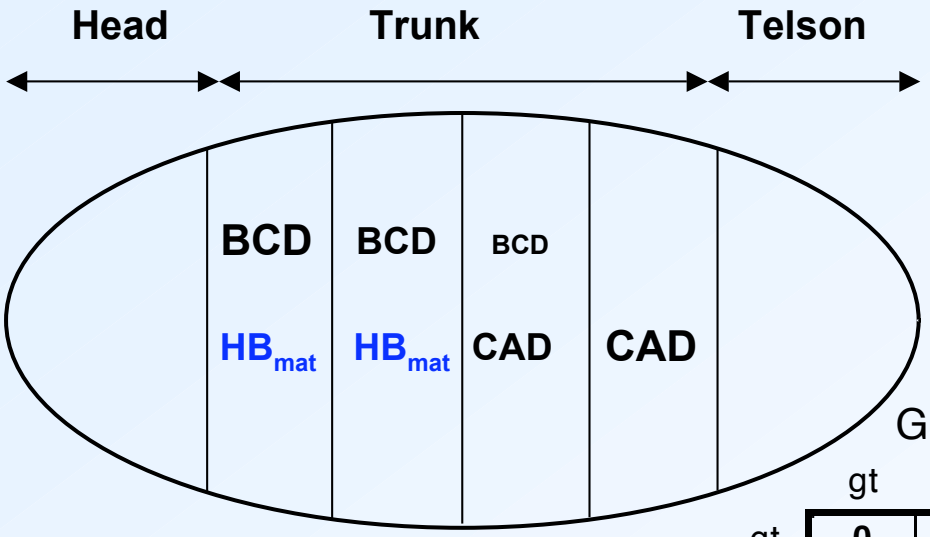
Sánchez L & Thieffry D (2003)
J theor Biol **224**: 517-37

Sánchez L, Chaouiya C
& Thieffry D (accepted)
Int J Dev Biol

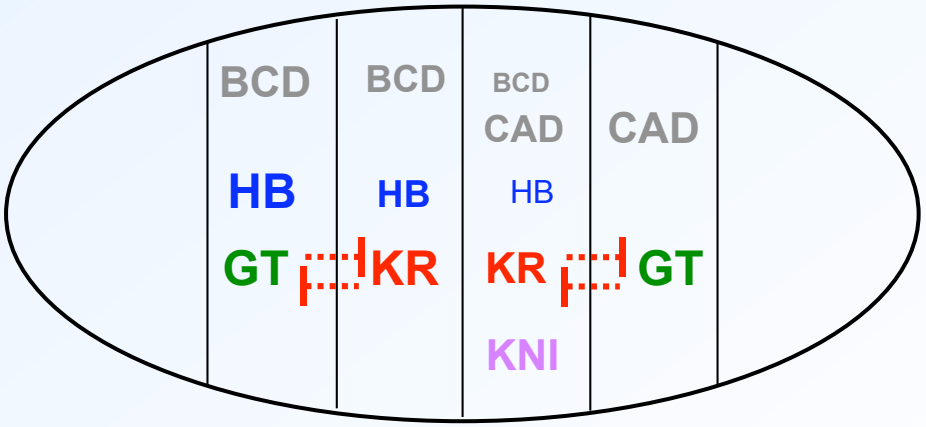
Gap Module



Simulation of the Gap Module



Multiple asynchronous transitions



Input:
Initial maternal gradients

	Gap module				Maternal inputs		
	gt	hb	Kr	kni	bcd	cad	hb_{mat}
gt	0	-1	-1	0	+1	+2	0
hb	0	(+1)	-2	0	+[1...3]	0	(+1)
Kr	-1	+1/-3	0	-1	+1	0	0
kni	-1	-2	0	0	+1	+1	0

+ Logical rules (parameters)

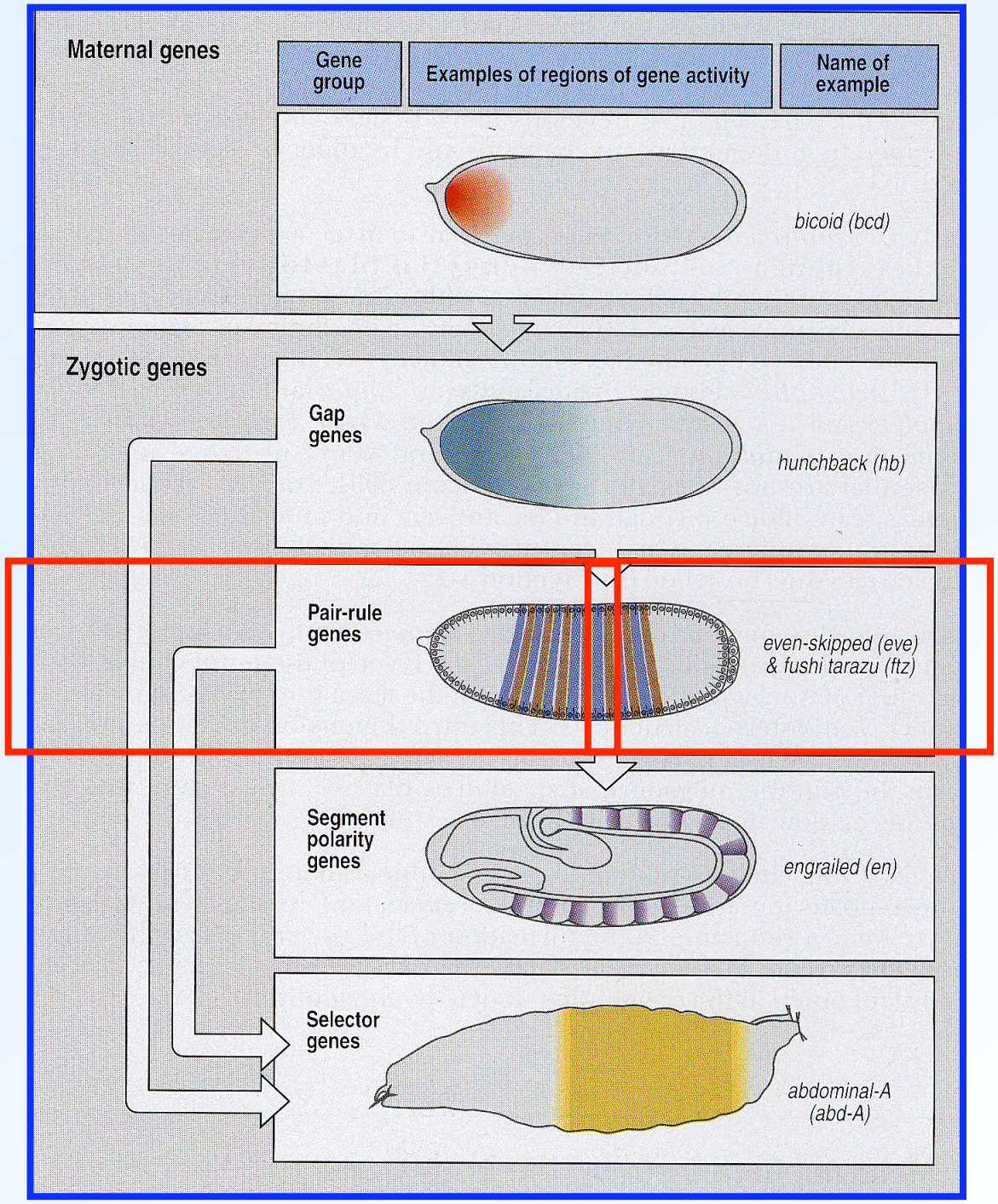
Output:
Four distinct gap gene expression combinations

Simulation of maternal and gap loss-of-function mutations

Genetic background	Final state (GT, HB, KR, KNI)				Observations/predictions
	A	B	C	D	
Wildtype	1300	0220	0111	1000	
Bicoid	**00**0**1**	0**000**1	0**00**1	1000	loss of GT in region A loss of HB in ABC and of KR in BC KNI expands anteriorly into region AB
Hunchback$_{mat}$	1300	0220	0111	1000	no significant effect
caudal	1300	0220	01**20**	**0**000	increase of KR in region C loss of KNI in region C loss of GT in region D
giant	**0**300	0220	0111	**000**1	KNI expands posteriorly into D
Krüppel	1300	1**2**00	1**1**00	1000	GT expands into regions B and C Loss of KNI in region C
knirps	1300	0220	01**2**0	1000	increase of KR in region C
Hunchback$_{mat\&zyg}$	1**0**00	1**00**0	1**00**0	1000	GT expands into regions B and C loss of KR in regions B and C loss of KNI in region C
giant-Krüppel	**0**300	0**2**00	0**1**01	**000**1	KNI expands posteriorly into region D
Krüppel-knirps	1300	1**2**00	1**10**0	1000	GT expands into regions B and C
giant-knirps	**0**300	0220	01**2**0	**0**000	increase of KR in region C

4 trunk domains

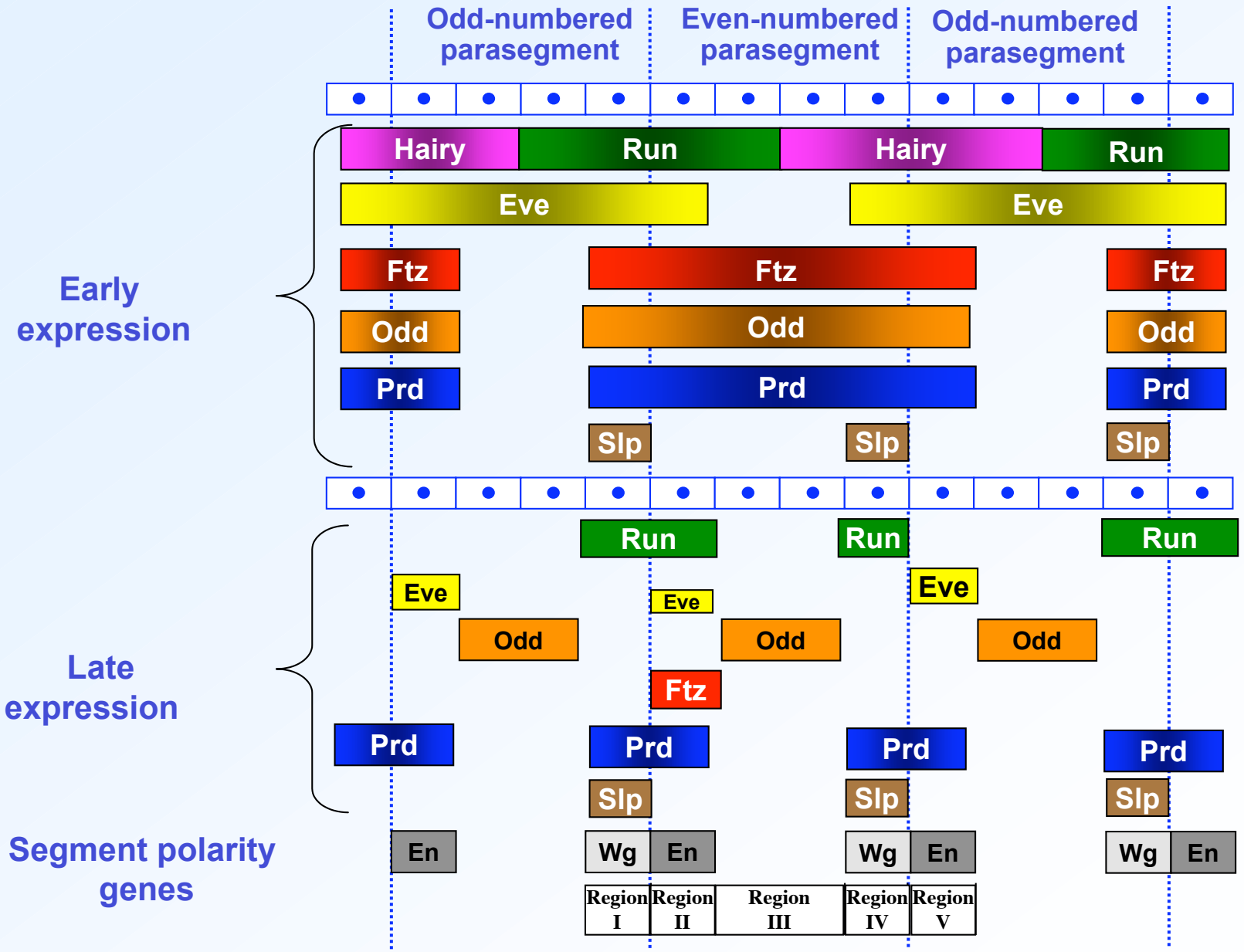
Anterior pole ⟷ Posterior pole



Drosophila segmentation

Sánchez L & Thieffry D (2003)
J theor Biol **224**: 517-37

Expression patterns of pair-rule genes



Pair-rule logical model

Input
(ubiquitous expression)

Ouputs (Segment polarity genes)	eve	prd	ppa	run	slp	ftz	odd	opa
eve	+1	+1	0	-1	-1	0	-1	0
prd	-3	0	-1	0	0	+1	-1	0
ppa	-2	0	0	0	0	0	0	0
run	-2	+1	0	0	0	0	-1	0
slp	-2	0	0	0	0	-1	-1	0
ftz	-2	0	0	0	-1	+1	-1	0
odd	-1	-1	0	0	0	+1	0	0
en	0	+2	0	-1	-1	+2	-1	+1
wg	-1	+1	0	0	+1	-1	-1	+1

Gene	value 1	value 2	value 3
eve	$K_{v.vrs}$ $K_{v.psd}$ $K_{v.vsd}$ $K_{v.prsd}$ $K_{v.vpsd}$ $K_{v.vprs}$ $K_{v.vrsd}$		$K_{v.vprsd}$
prd	$K_{p.d}$ $K_{p.vd}$ $K_{p.zd}$ $K_{p.zvd}$	$K_{p.ad}$ $K_{p.vad}$ $K_{p.azd}$ $K_{p.zvad}$	
ppa	$K_{a.v}$		
run	$K_{r.pvd}$		
slp	$K_{s.vzd}$		
ftz	$K_{z.vsd}$	$K_{z.zvsd}$	
odd	$K_{d.vp}$ $K_{d.zvp}$		
en	$K_{e.yzs}$ $K_{e.yprsd}$ $K_{e.yzrsd}$ $K_{e.ypzsd}$ $K_{e.ypzrsd}$		
wg	$K_{w.ypsvzd}$		

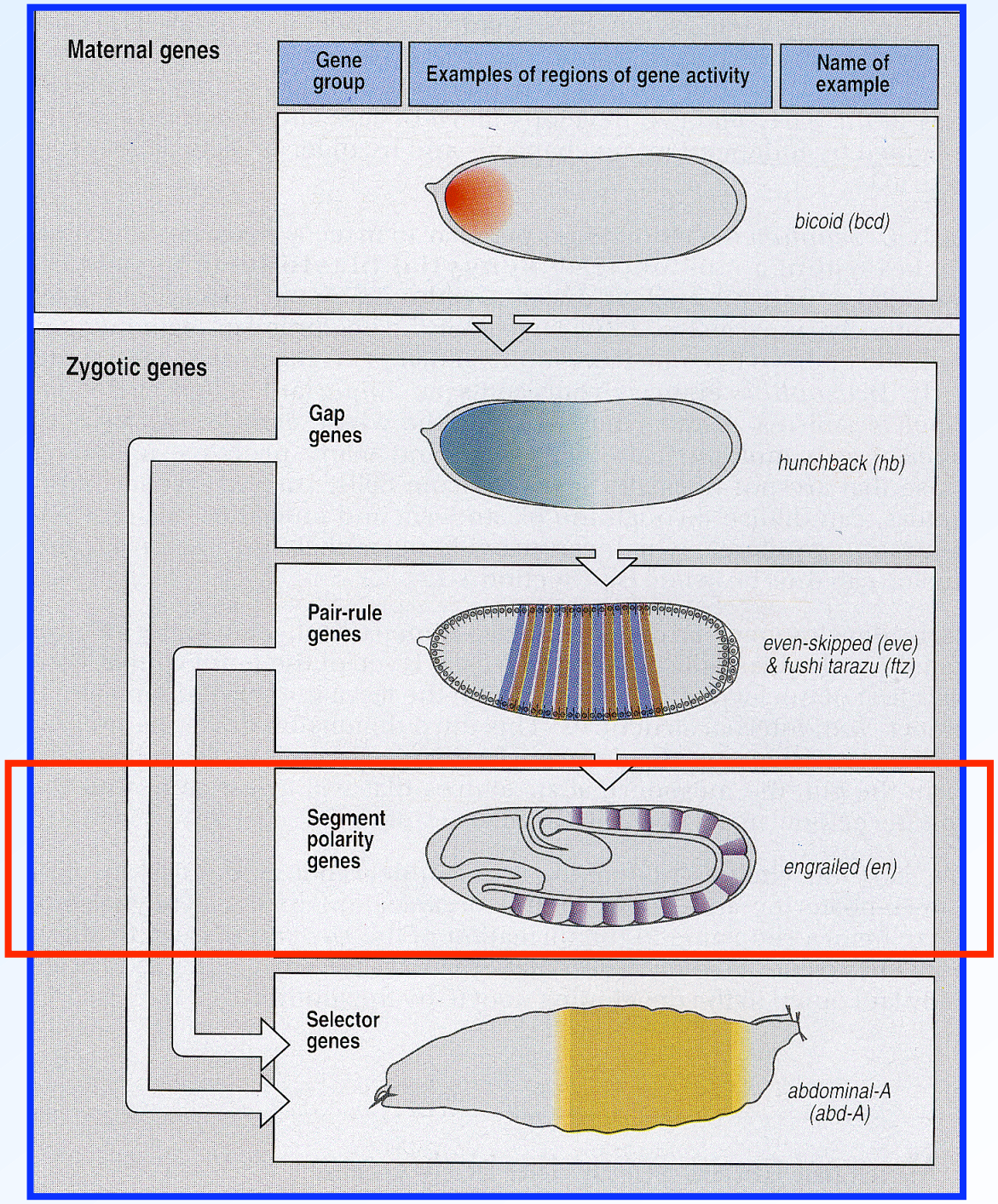
Four stables states :

- One **Wg** expressing state
- Two different **En** expressing states
- One state with no Wg, nor EN, but **Odd** expression

Prediction of pair-rule *cis*-regulatory mutants

Genetic background	stable states							Embryo regions	EN/WG expression	(partially) functional circuits	Comments
	v	**p**	**a**	**r**	**s**	**z**	**d**				
wild-type	0	0	1	0	0	0	1	III	-	eve (+), eve/run (+), eve/slp (+), prd/odd (+), slp/ftz (+), eve-ftz-slp (-), prd/odd/ftz (+)	
	0	1	1	1	1	0	0	I, IV	Wg		
	1	1	1	1	0	2	0	II	En		
	3	2	0	0	0	0	0	V	En		
eve auto-regulation	0	0	1	0	0	0	1	III	-	prd/odd (+), slp/ftz (+), prd/odd/ftz (+)	Replacement of odd **En**-stripes by **Wg**-stripes
	0	1	1	1	1	0	0	I, IV, (V)	Wg		
	1	1	1	1	0	2	0	II, (V)	En		
Ftz auto-regulation	0	0	1	0	0	0	1	III	-	eve (+), eve/run (+), eve/slp (+), prd/odd (+), slp/ftz (+), eve-ftz-slp (-), prd/odd/ftz (+)	Loss of even **En**-stripes
	0	1	1	1	1	0	0	I, IV	Wg		
	1	1	1	1	0	**1**	0	II	-		
	3	2	0	0	0	0	0	V	En		

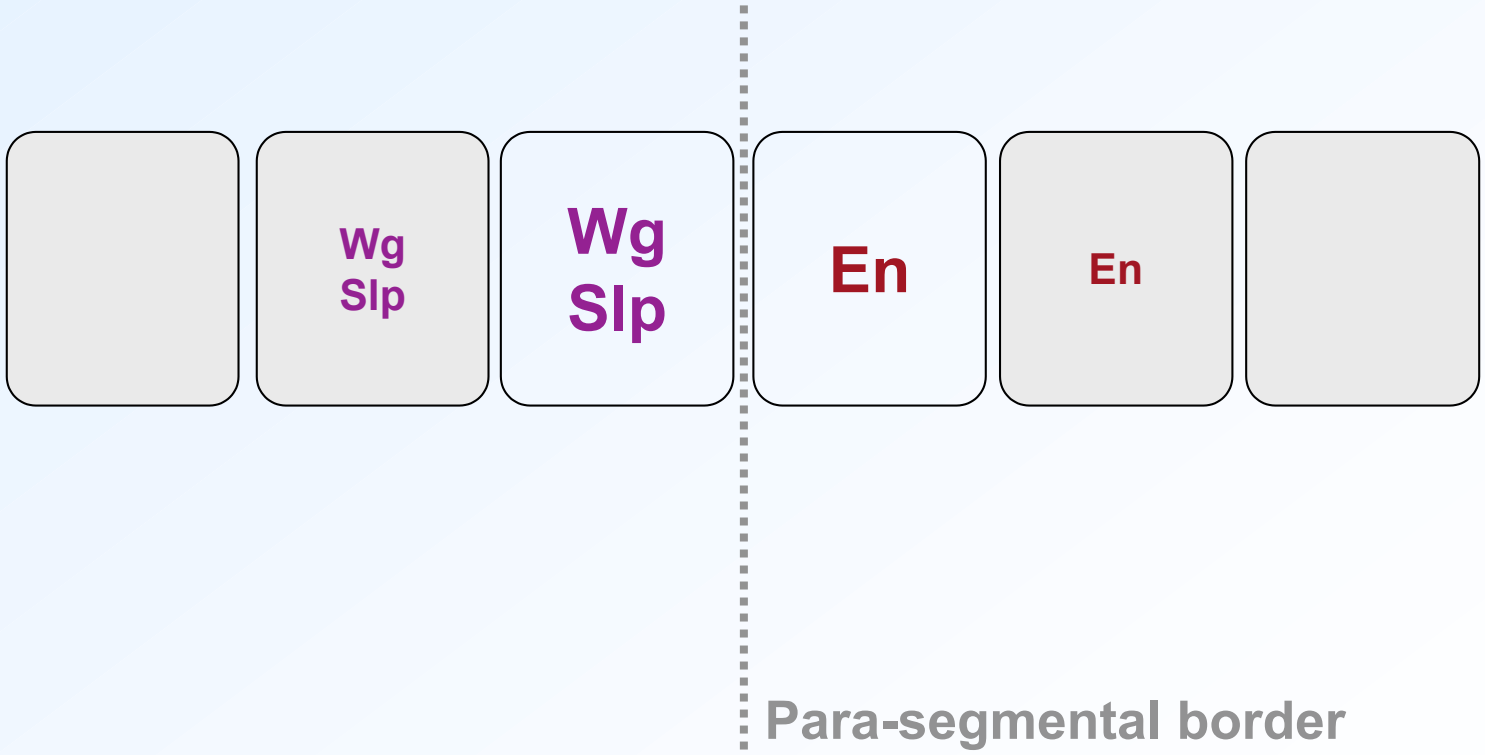
Eve Prd Ppa Run Slp Ftz Odd



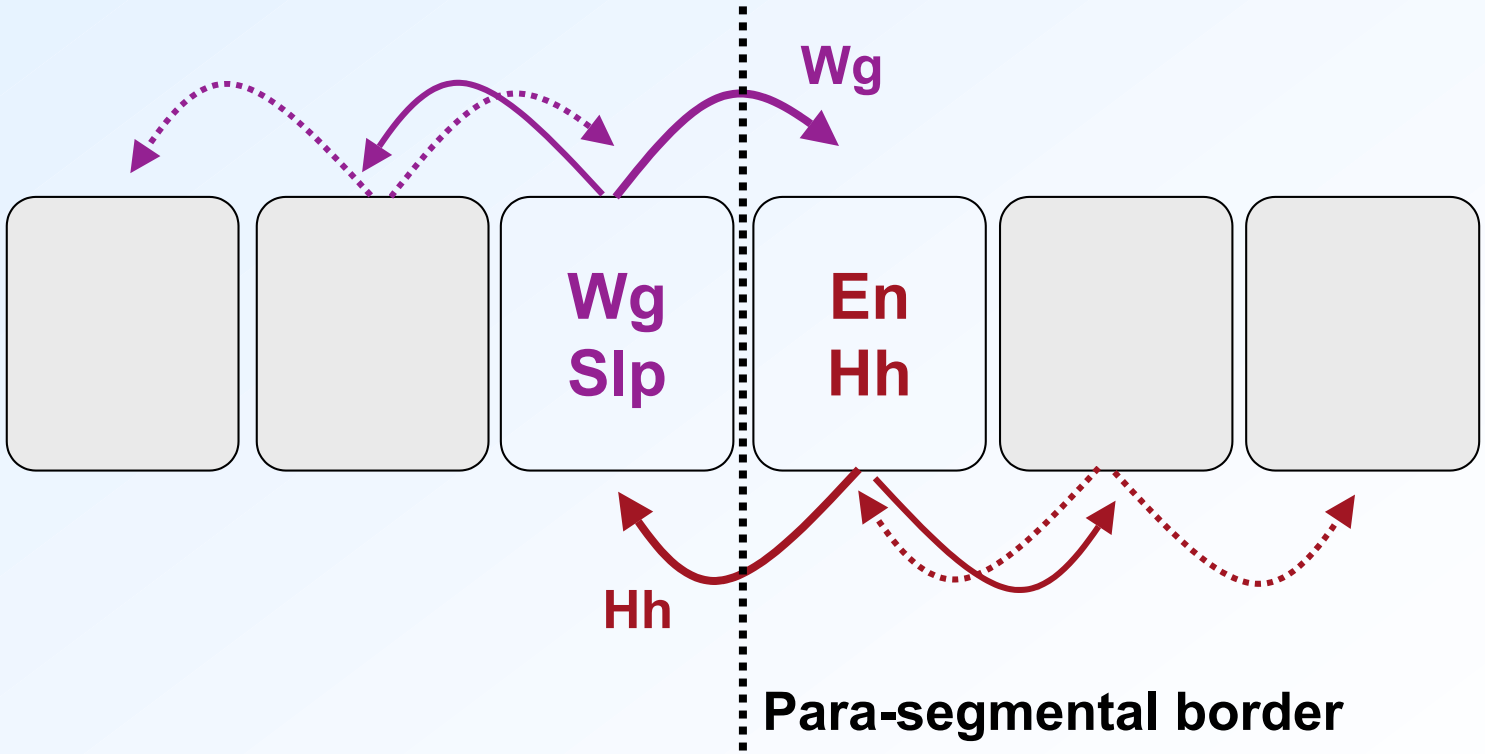
Drosophila segmentation

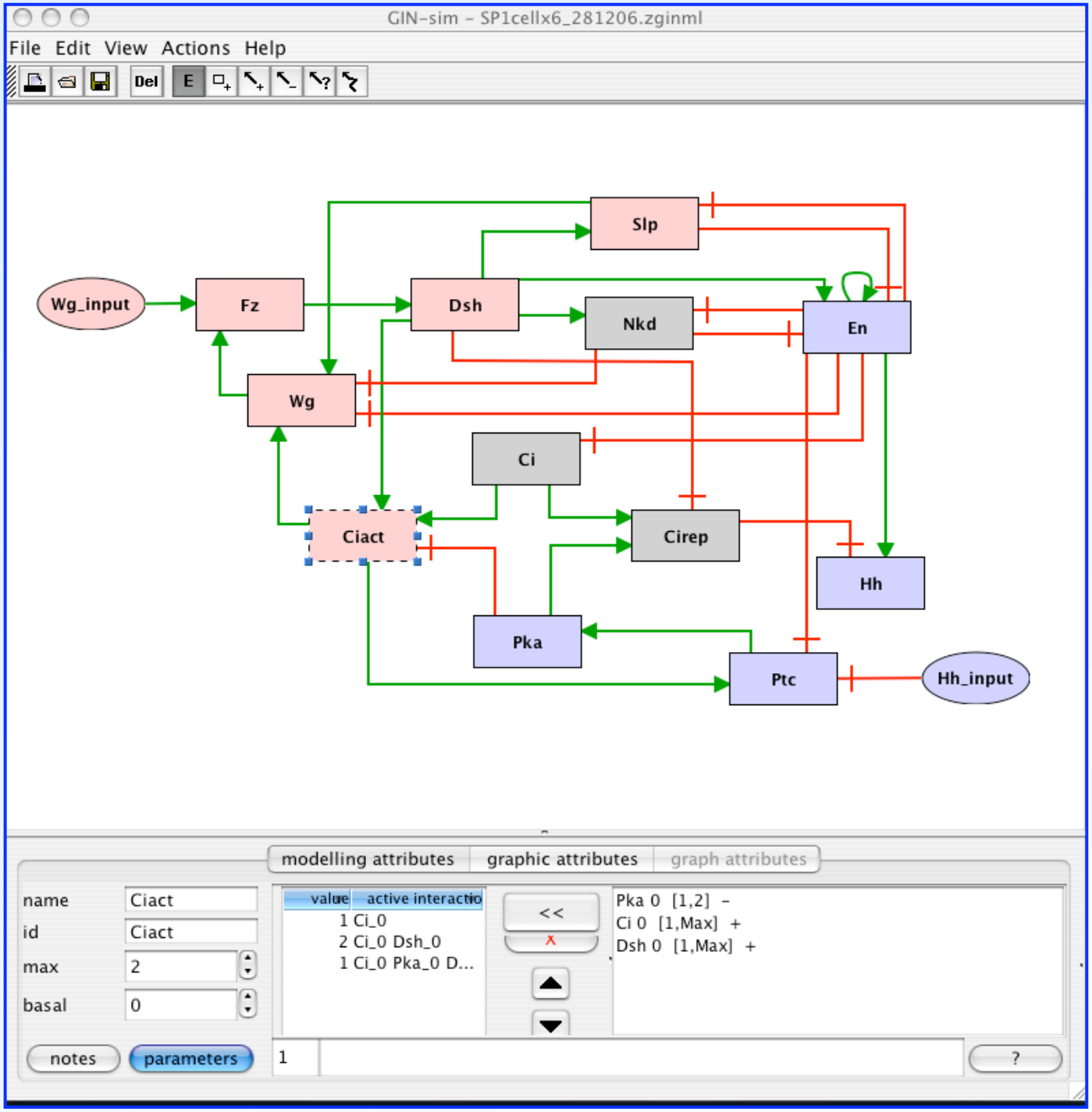
Sánchez L, Chaouiya C & Thieffry D (accepted) *Int J Dev Biol*

Segment Polarity system: pair-rule input



Segment Polarity system: inter-cellular signalling





Logical modelling of the Segment Polarity module

Collaboration with
Lucas SANCHEZ
(CIB, Madrid)

Dynamical analysis: strategy

- **Single cell** analysis -> delineation of possible **stable states** (= cellular states) for different Hh and Wg input configurations
- **Chaining of 6 cells** trough Wg and Hh signalling.
- Use of **constraint programming** to identify all **multi-cellular stable states**
- **Classification** of multi-cellular stable patterns (symmetries)
- Use of **Model checking** and **Petri net tools** to assess the **reachability** of relevant differentiation states **from relevant initial conditions**
- **Feedback circuit analysis**

Wild-type encapsulated cell

5 differentiation states depending on inputs combinations:

Wg	Hh	Wg	Fz	Dsh	Slp	Nkd	En	Hh	Ci	Ciact	Cirep	Pka	Ptc	State
0	0	0	0	0	0	1	0	0	1	0	1	2	1	**T**rivial
0	1	0	0	0	0	1	0	0	**1**	**1**	0	0	0	**C**i+Ci_act
0	1	**2**	1	1	1	2	0	0	1	2	0	0	0	**W**g
1	0	0	1	1	0	0	**1**	1	0	0	0	0	0	**E**n
1	0	0	1	1	1	2	0	0	1	1	0	2	2	**N**kd
1	1	**2**	1	1	1	2	0	0	1	2	0	0	0	**W**g
1	1	0	1	1	0	0	**1**	1	0	0	0	0	0	**E**n

Inputs coming from neighbouring cells

Wild type multi-cellular behaviour

- A priori, there are 5^6 possible combinations of the 5 unicellular stable states
- The intercellular constraints enable only **59** possible combinations
- **37** remaining combinations after discarding the symmetrical ones (eg TTTTEW <=>EWTTTT)
- **Reachability analysis** -> two multi-cellular outcome accessible from a relatively broad range of initial conditions:

T	N	W	E	C	T
T	T	T	T	T	T

Simulation of genetic perturbations

- Single **loss-of-functions** of Wg, En, Hh, or Ci give rise to a unique trivial (like) pattern:

- **Double loss-of function** of Wg/Ptc gives rise to a unique pattern:

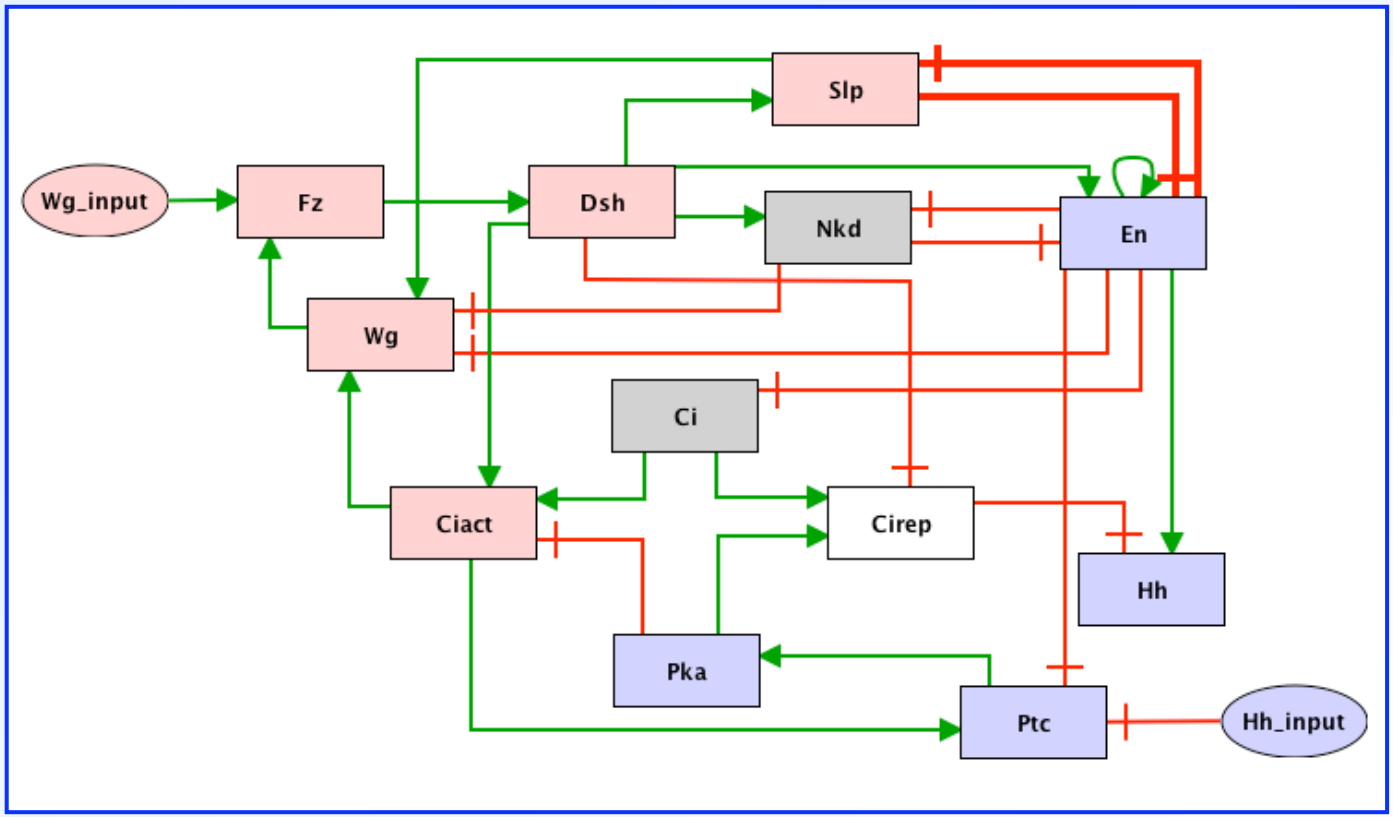
- **Ectopic En expression** gives also rise to a unique pattern:

Wg	Fz	Dsh	Slp	Nkd	En	Hh	Ci	Ciact	Cirep	Pka	Ptc
0	0	0	0	0	1	1	0	0	0	0	0

More complex genetic perturbations

- Single **Ptc loss-of-function** gives rise to several possible multi-cellular stable states, including a pattern with Wg posterior extension and posterior ectopic En expression

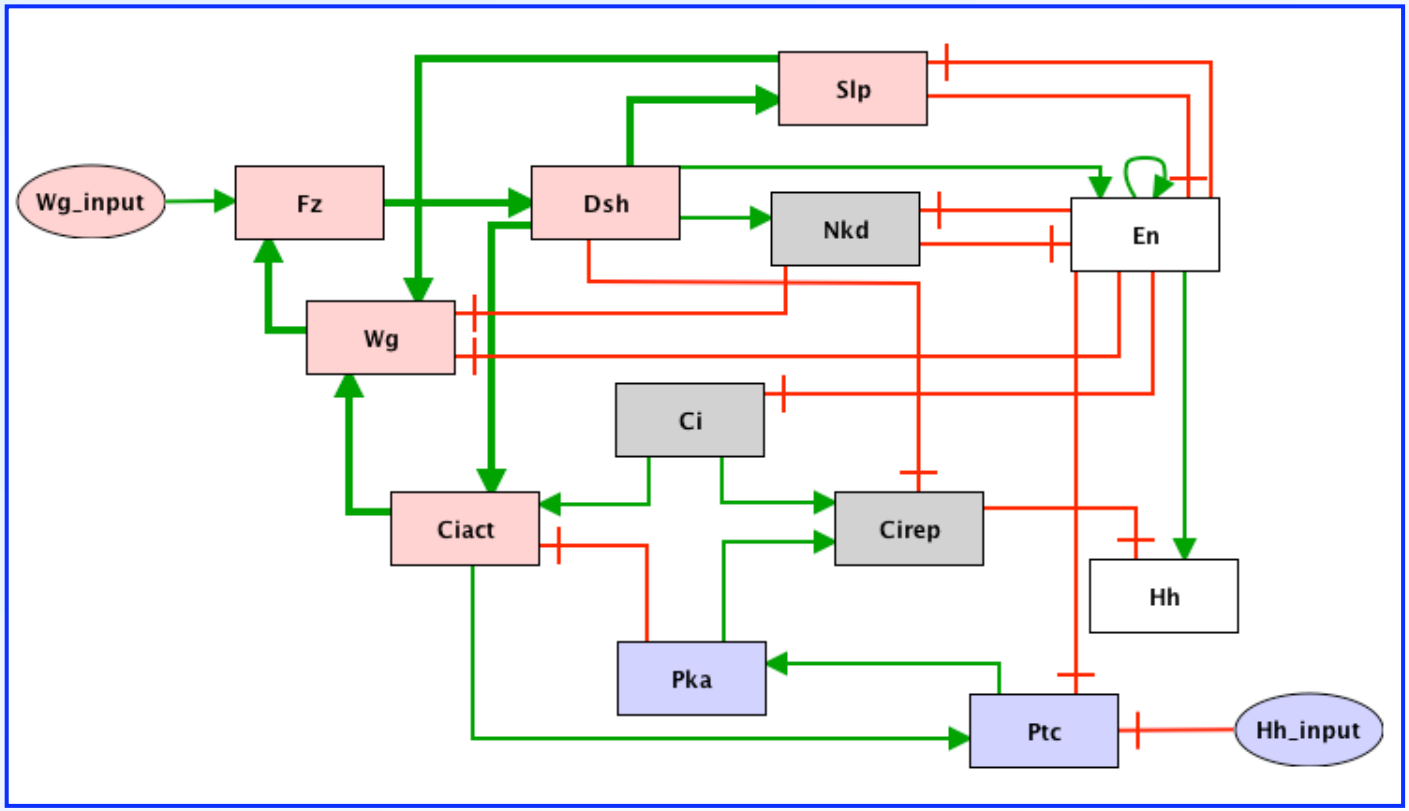
Feedback circuit analysis: functional intracellular circuits (1)



En-Slp circuit functional when Dsh=1

Enables **two different cellular states** in the presence of Wg signalling, one with En ON and Slp OFF, the other with En OFF and Slp ON

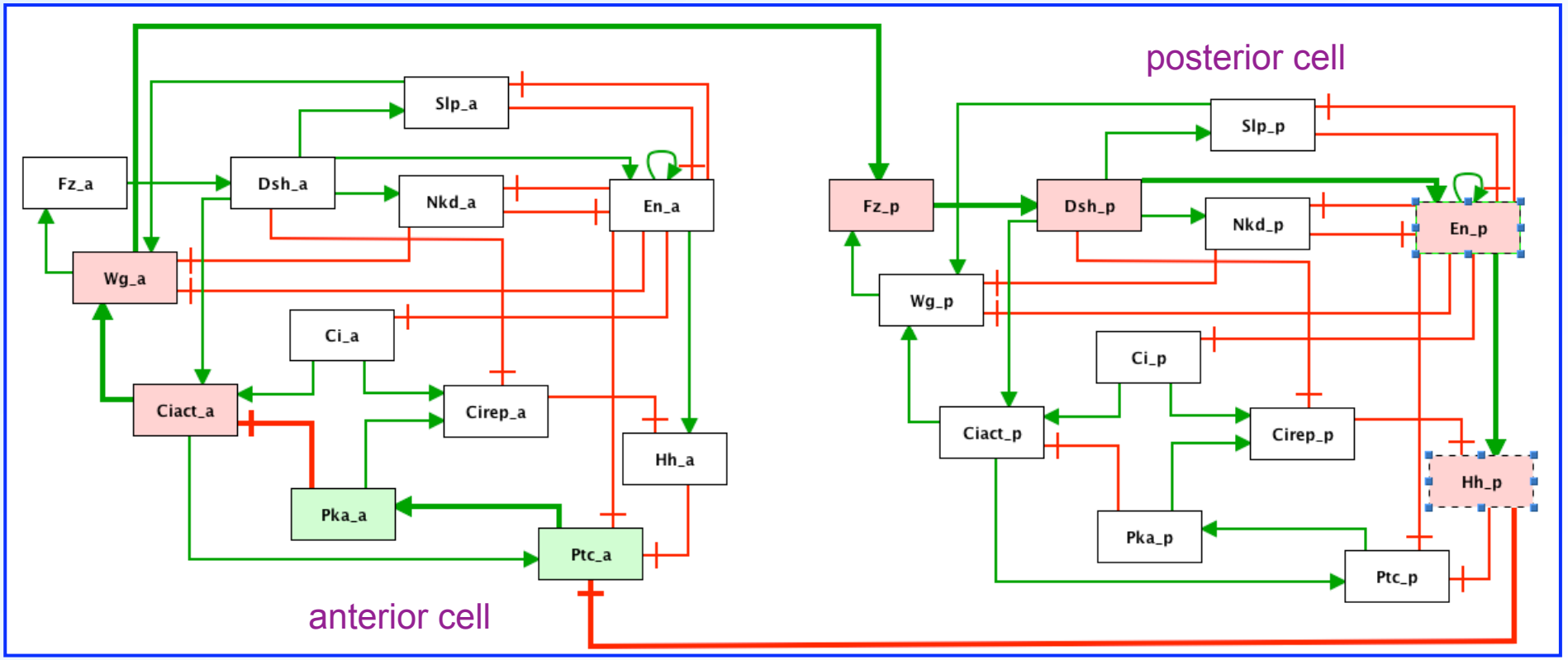
Feedback circuit analysis: functional intracellular circuits (2)



Wg circuits functional when En=0

Enables **different stable states**
with no, low or high Wg expression when En is OFF

Feedback circuit analysis: functional inter-cellular circuit



Forces the **combination** of specific neighbouring cellular states

Novel insights

- The **pair-rule signal** needs to be **operative** until the inter-cellular circuit become functional
- The **consolidation** of **Wg** and **En** expression pattern require the proper activity of both **autocrine** and **paracrine Wg pathways**
- **Dual role** played by the **Protein kinase A** (Pka) through phosphorylation of Cubitus interruptus, effector of Hh Pathway
- Important roles of **Slp** and **Nkd** during the transition from pair-rule to segment polarity expression patterns
- Novel insights in the roles of the various **feedback circuits**, in particular **positive circuits**, at the basis of **differentiation decisions**
- Consistency between the results of the **simulation of altered expression** of segment polarity genes with published data

Prospects

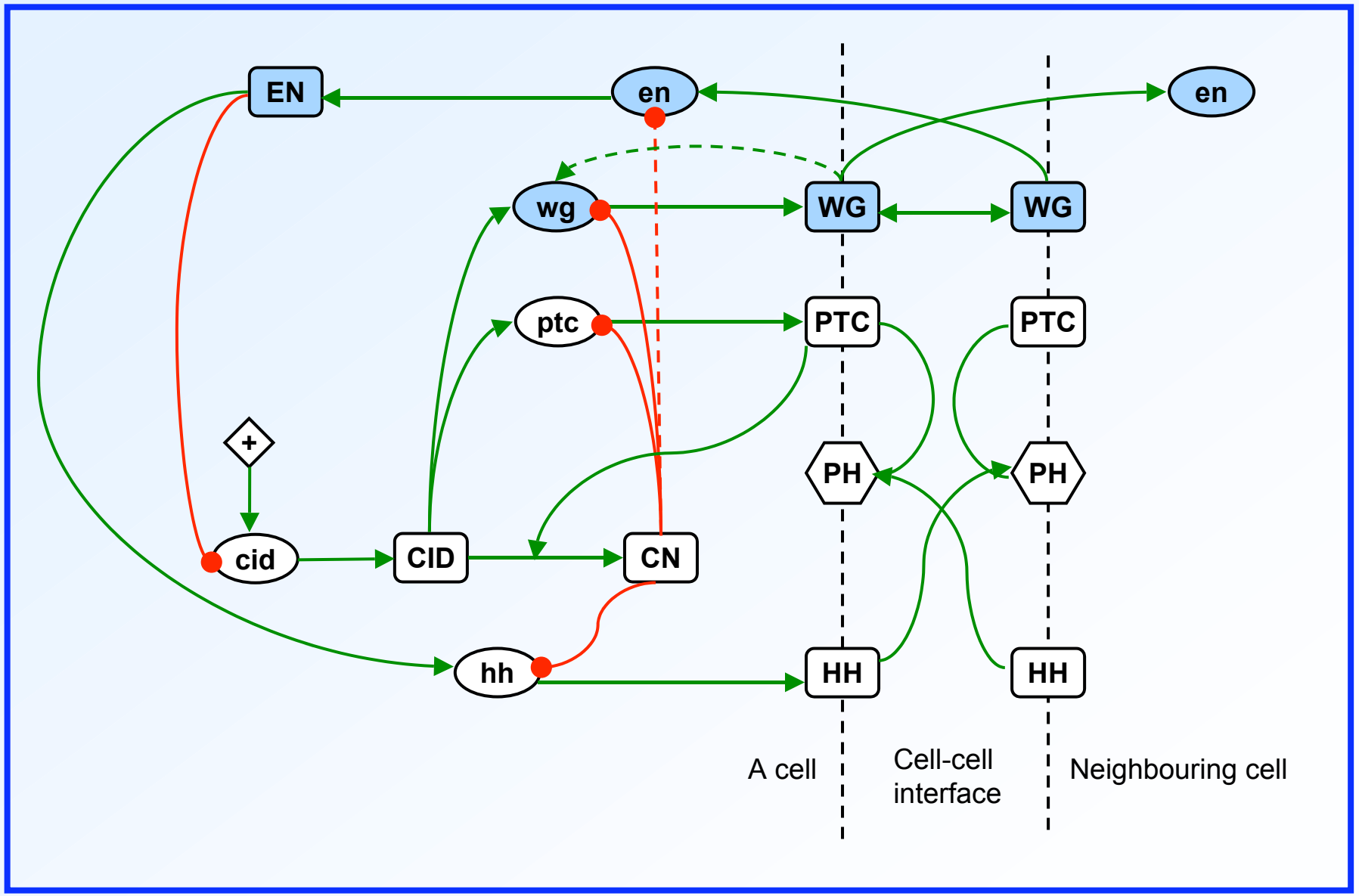
- **Coupling between the gap, pair-rule and segment polarity modules**
  → **towards a model of the whole segmentation hierarchy**
- **Modelling of control of the formation of the anterior-posterior boundary in wing imaginal disks**
  → **comparative analysis of segment polarity network variants**
- Modelling of the molecular network controlling embryonic **cell cycle**
  → analysis of the **coupling between cell cycle and cell differentiation**
- **Comparative and evolutionary analysis** of homologous regulatory networks (**graph topology**, **qualitative dynamics**, **redundancy**)

Quantitative modelling of pair-rule module

von Dassow G, Meir E, Munro EM & Odell GM (2000).
The segment polarity network is a robust developmental module.
Nature **406**: 188-192.

von Dassow G & Odell GM (2002).
Design and constraints of the Drosophila segment polarity module: robust spatial patterning emerges from intertwined cell state switches.
Journal of Experimental Zoology **294**: 179-215.

The segment-polarity module according to von Dassow *et al.* (2000)



$$Notation: X_{n,j+3} = amount\ of\ X\ on\ apposite\ cell\ face;\ X_{i,T} = \sum_{j=1}^{6} X_{i,j};\ X_{n,T} = \sum_{j=1}^{6} X_{n,j+3};\ X_{i,lr} = X_{i,j-1} + X_{i,j+1}$$

$$a)\ \frac{d\,en_i}{d\tau} = \frac{T_\circ}{H_{en}}\left(\frac{EWG_{n,T}\left(1-\frac{CN_i^{\nu_{CNen}}}{\kappa_{CNen}^{\nu_{CNen}}+CN_i^{\nu_{CNen}}}\right)^{\nu_{WGen}}}{\kappa_{WGen}^{\nu_{WGen}}+EWG_{n,T}\left(1-\frac{CN_i^{\nu_{CNen}}}{\kappa_{CNen}^{\nu_{CNen}}+CN_i^{\nu_{CNen}}}\right)^{\nu_{WGen}}}-en_i\right)$$

$$b)\ \frac{d\,EN_i}{d\tau} = \frac{T_\circ}{H_{EN}}\left(en_i - EN_i\right)$$

$$c)\ \frac{d\,wg_i}{d\tau} = \frac{T_\circ}{H_{wg}}\left(\frac{\alpha_{CIwg}\cdot\left(\frac{CI_i\left(1-\frac{CN_i^{\nu_{CNwg}}}{\kappa_{CNwg}^{\nu_{CNwg}}+CN_i^{\nu_{CNwg}}}\right)^{\nu_{CIwg}}}{\kappa_{CIwg}^{\nu_{CIwg}}+CI_i\left(1-\frac{CN_i^{\nu_{CNwg}}}{\kappa_{CNwg}^{\nu_{CNwg}}+CN_i^{\nu_{CNwg}}}\right)^{\nu_{CIwg}}}\right)+\alpha_{WGwg}\cdot\left(\frac{IWG_i^{\nu_{WGwg}}}{\kappa_{WGwg}^{\nu_{WGwg}}+IWG_i^{\nu_{WGwg}}}\right)}{1+\alpha_{CIwg}\cdot\left(\frac{CI_i\left(1-\frac{CN_i^{\nu_{CNwg}}}{\kappa_{CNwg}^{\nu_{CNwg}}+CN_i^{\nu_{CNwg}}}\right)^{\nu_{CIwg}}}{\kappa_{CIwg}^{\nu_{CIwg}}+CI_i\left(1-\frac{CN_i^{\nu_{CNwg}}}{\kappa_{CNwg}^{\nu_{CNwg}}+CN_i^{\nu_{CNwg}}}\right)^{\nu_{CIwg}}}\right)+\alpha_{WGwg}\cdot\left(\frac{IWG_i^{\nu_{WGwg}}}{\kappa_{WGwg}^{\nu_{WGwg}}+IWG_i^{\nu_{WGwg}}}\right)}-wg_i\right)$$

$$d)\ \frac{d\,IWG_i}{d\tau} = \frac{T_\circ}{H_{IWG}}\left(wg_i - IWG_i\right) + T_\circ\left(r_{EndoWG}EWG_{i,T} - r_{ExoWG}IWG_i\right)$$

$$e)\ \frac{d\,EWG_{i,j}}{d\tau} = T_\circ\left(\frac{r_{ExoWG}IWG_i}{6} - r_{EndoWG}EWG_{i,j} - r_{MxferWG}EWG_{i,j} + r_{MxferWG}EWG_{n,j+3} - 2r_{LMxferWG}EWG_{i,j} + r_{LMxferWG}EWG_{i,lr}\right) - \frac{T_\circ EWG_{i,j}}{H_{IWG}}$$

$$f)\ \frac{d\,ptc_i}{d\tau} = \frac{T_\circ}{H_{ptc}}\left(\frac{CI_i\left(1-\frac{CN_i^{\nu_{CNptc}}}{\kappa_{CNptc}^{\nu_{CNptc}}+CN_i^{\nu_{CNptc}}}\right)^{\nu_{CIptc}}}{\kappa_{CIptc}^{\nu_{CIptc}}+CI_i\left(1-\frac{CN_i^{\nu_{CNptc}}}{\kappa_{CNptc}^{\nu_{CNptc}}+CN_i^{\nu_{CNptc}}}\right)^{\nu_{CIptc}}}-ptc_i\right)$$

$$g)\ \frac{d\,PTC_{i,j}}{d\tau} = \frac{T_\circ}{H_{PTC}}\left(\frac{ptc_i}{6} - PTC_{i,j}\right) - T_\circ k_{PTCHH}[HH]_\circ HH_{n,j+3}\cdot PTC_{i,j} + T_\circ\left(r_{LMxferPTC}PTC_{i,lr} - 2r_{LMxferPTC}PTC_{i,j}\right)$$

$$h)\ \frac{d\,ci_i}{d\tau} = \frac{T_\circ}{H_{ci}}\left(\frac{B_i\left(1-\frac{EN_i^{\nu_{ENci}}}{\kappa_{ENci}^{\nu_{ENci}}+EN_i^{\nu_{ENci}}}\right)^{\nu_{Bci}}}{\kappa_{Bci}^{\nu_{Bci}}+B_i\left(1-\frac{EN_i^{\nu_{ENci}}}{\kappa_{ENci}^{\nu_{ENci}}+EN_i^{\nu_{ENci}}}\right)^{\nu_{Bci}}}-ci_i\right)$$

$$i)\ \frac{d\,CI_i}{d\tau} = \frac{T_\circ}{H_{CI}}\left(ci_i - CI_i\right) - T_\circ C_{CI}CI_i\left(\frac{PTC_{i,T}^{\nu_{PTC\cdot CI}}}{\kappa_{PTC\cdot CI}^{\nu_{PTC\cdot CI}}+PTC_{i,T}^{\nu_{PTC\cdot CI}}}\right)$$

$$j)\ \frac{d\,CN_i}{d\tau} = T_\circ C_{CI}CI_i\left(\frac{PTC_{i,T}^{\nu_{PTC\cdot CI}}}{\kappa_{PTC\cdot CI}^{\nu_{PTC\cdot CI}}+PTC_{i,T}^{\nu_{PTC\cdot CI}}}\right) - \frac{T_\circ CN_i}{H_{CI}}$$

$$k)\ \frac{d\,hh_i}{d\tau} = \frac{T_\circ}{H_{hh}}\left(\frac{EN_i\left(1-\frac{CN_i^{\nu_{CNhh}}}{\kappa_{CNhh}^{\nu_{CNhh}}+CN_i^{\nu_{CNhh}}}\right)^{\nu_{ENhh}}}{\kappa_{ENhh}^{\nu_{ENhh}}+EN_i\left(1-\frac{CN_i^{\nu_{CNhh}}}{\kappa_{CNhh}^{\nu_{CNhh}}+CN_i^{\nu_{CNhh}}}\right)^{\nu_{ENhh}}}-hh_i\right)$$

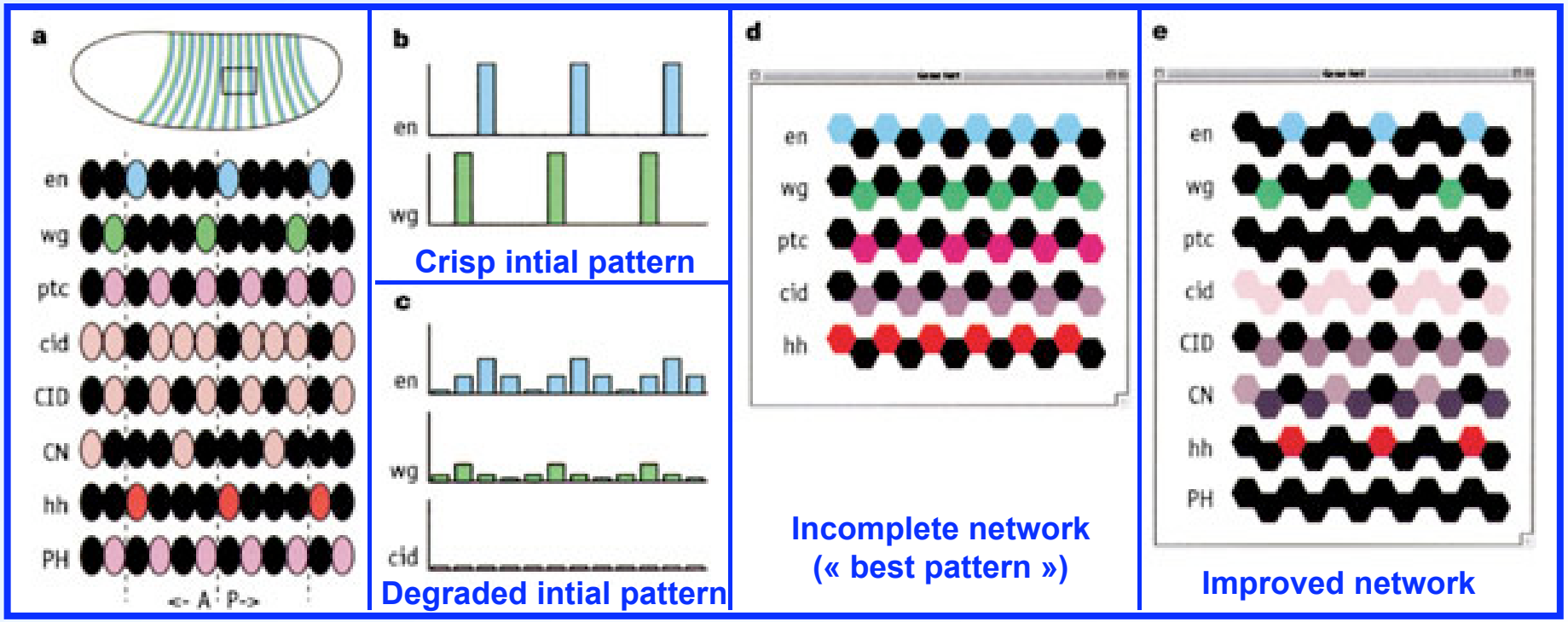
$$l)\ \frac{d\,HH_{i,j}}{d\tau} = \frac{T_\circ}{H_{HH}}\left(\frac{hh_i}{6} - HH_{i,j}\right) - T_\circ k_{PTCHH}[PTC]_\circ PTC_{n,j+3}\cdot HH_{i,j} + T_\circ\left(r_{LMxferHH}HH_{i,lr} - 2r_{LMxferHH}HH_{i,j}\right)$$

$$m)\ \frac{d\,PH_{i,j}}{d\tau} = T_\circ k_{PTCHH}[HH]_\circ HH_{n,j+3}\cdot PTC_{i,j} - \frac{T_\circ PH_{i,j}}{H_{PH}}$$

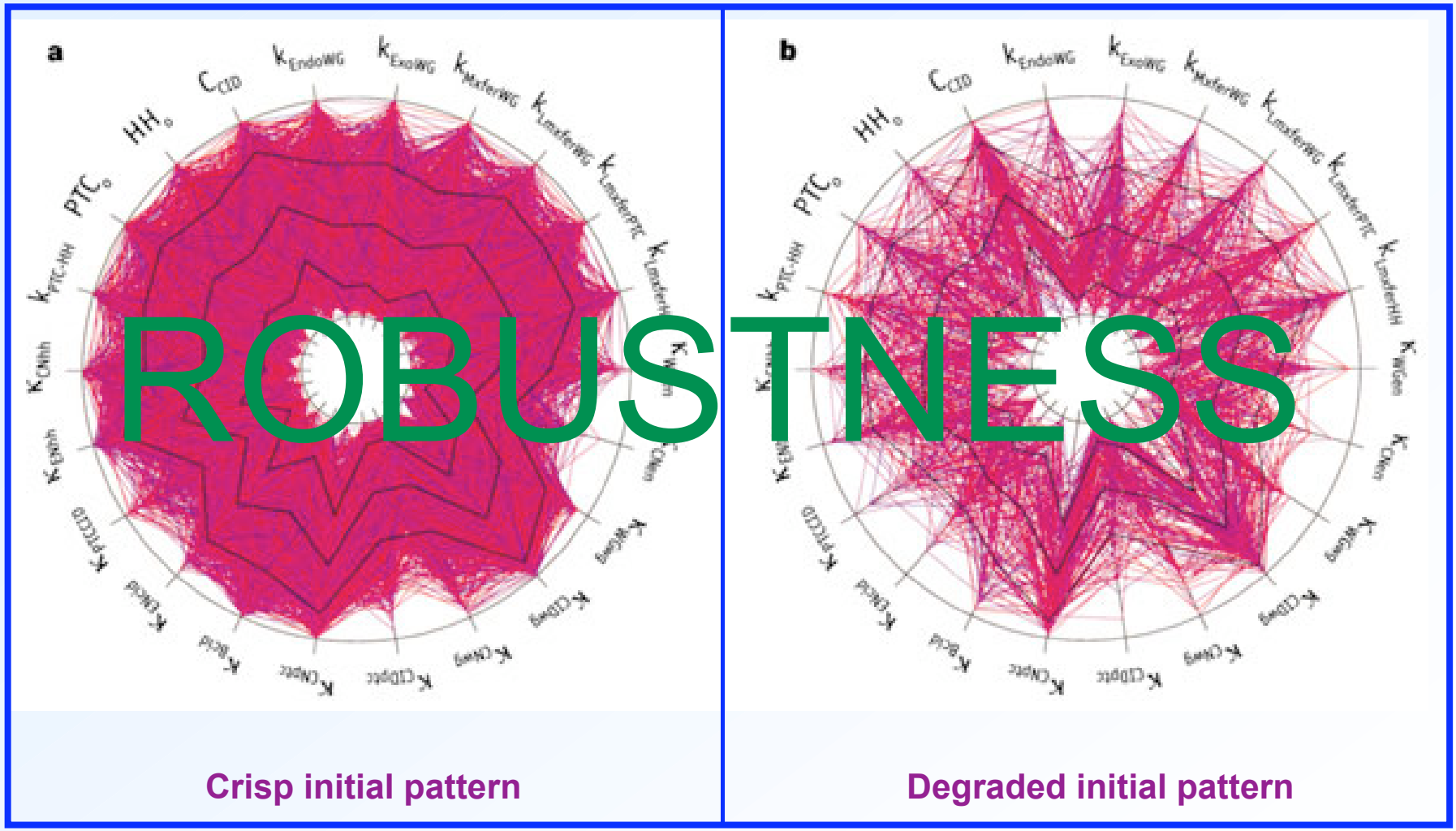
The mathematical model of von Dassow *et al.* (2000)

- Dictionary of mathematical terms, each associated with a specific biochemical interaction
- **9** equations and **48** parameters, describing the temporal evolution of [mRNA], [proteins] and [complexes]
- No direct access to parameter values. → random exploration of parameter space

Probing multicellular segment-polarity patterning ability



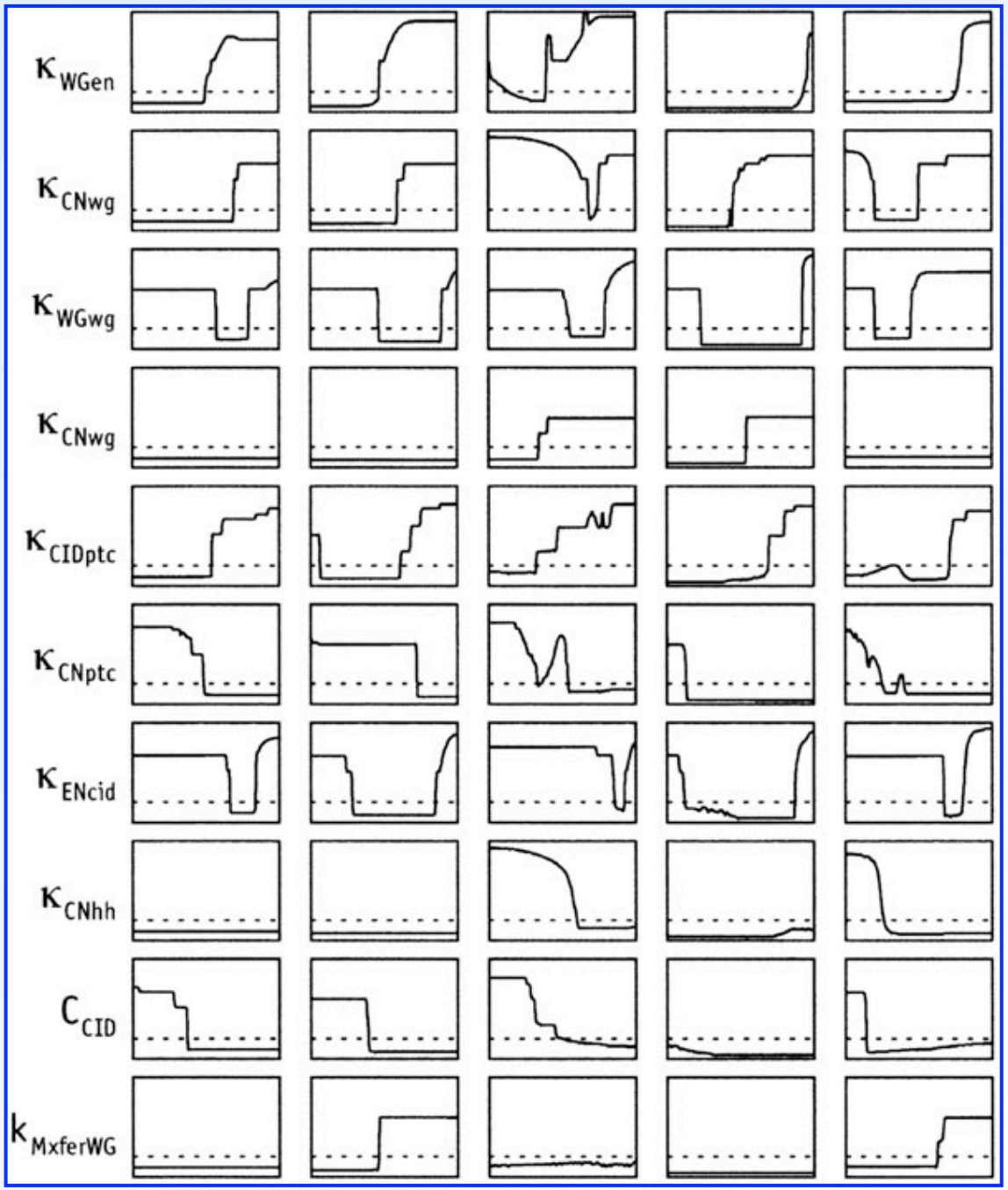
Probing the parameter space



Crisp initial pattern

Degraded initial pattern

“We asked: is there any set of parameter values for which the network exhibits the desired behaviour, given realistic initial conditions?”



Probing the parameter space

Different solutions

Summing up on Von Dassow *et al* (2000)

"We used computer simulations to investigate whether the ***known interactions*** *among segment polarity genes* ***suffice to confer the properties expected of a developmental module****."*

"Here we suggest, using computer simulations, that ***the*** **Drosophila** ***segment polarity genes constitute […] a module [..] resistant to variations in the kinetic constants*** *that govern its behaviour."*

"The most striking systems-level property we report is ***robustness to parameter variation****."*

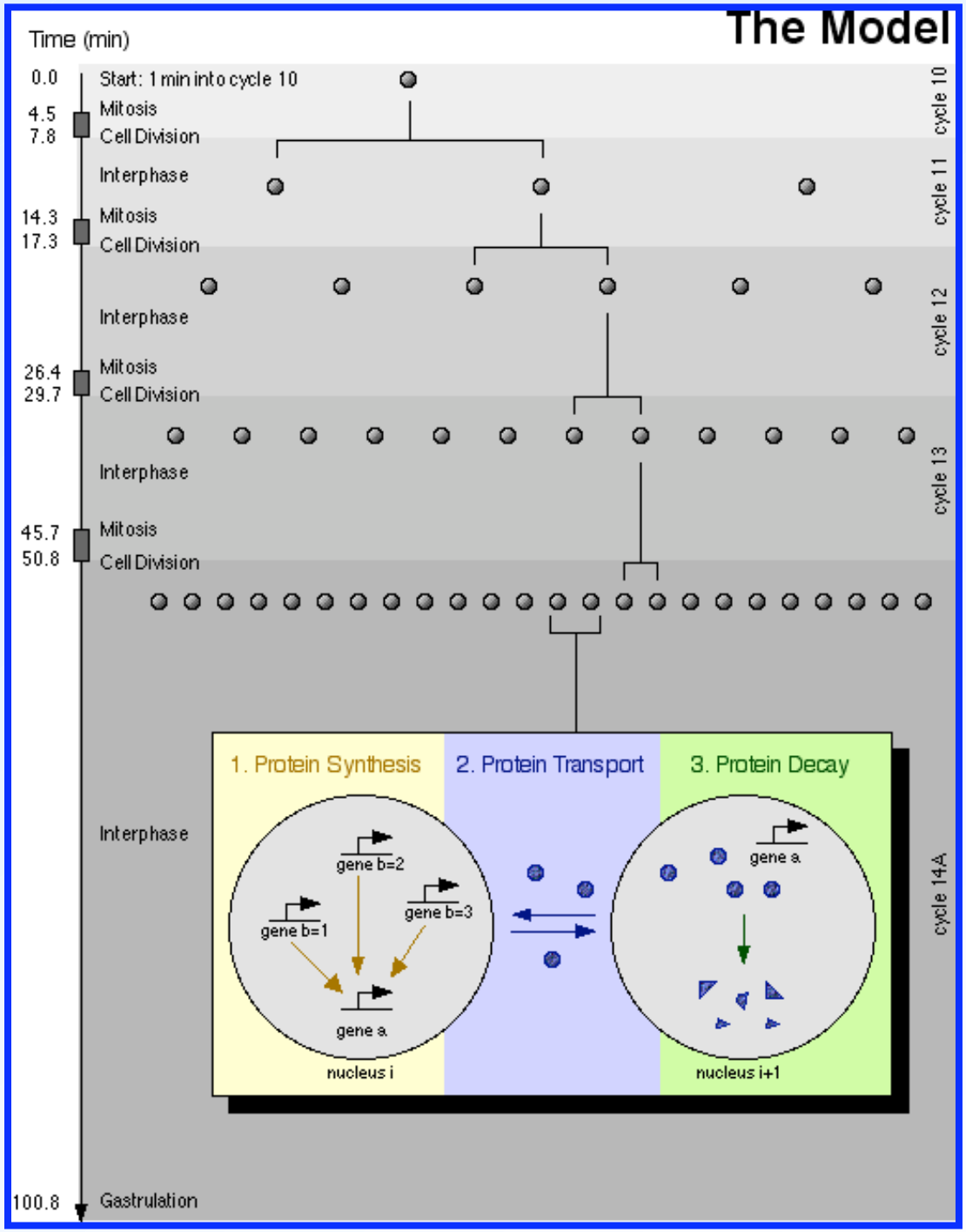
"Varying parameter is proxy for ***mutations*** *of small effect, and variation in initial conditions mimics one aspect of* ***developmental 'noise'****."*

Subsequent work on a comparative analysis of alternative wiring diagrams with respect to robustness.

Reverse engineering and fitting of coarse grain ODEs

Reinitz J, Kosman D, Vanario-Alonso C. E & Sharp DH (1998).
Stripe forming architecture of the gap gene system.
Developmental Genetics **23**: 11-27.

Jaeger J *et al*. (2004).
Dynamic control of positional information in the early Drosophila embryo.
Nature **430**: 368-71.



Reinitz *et al.*

Reinitz's generic equations

synthesis

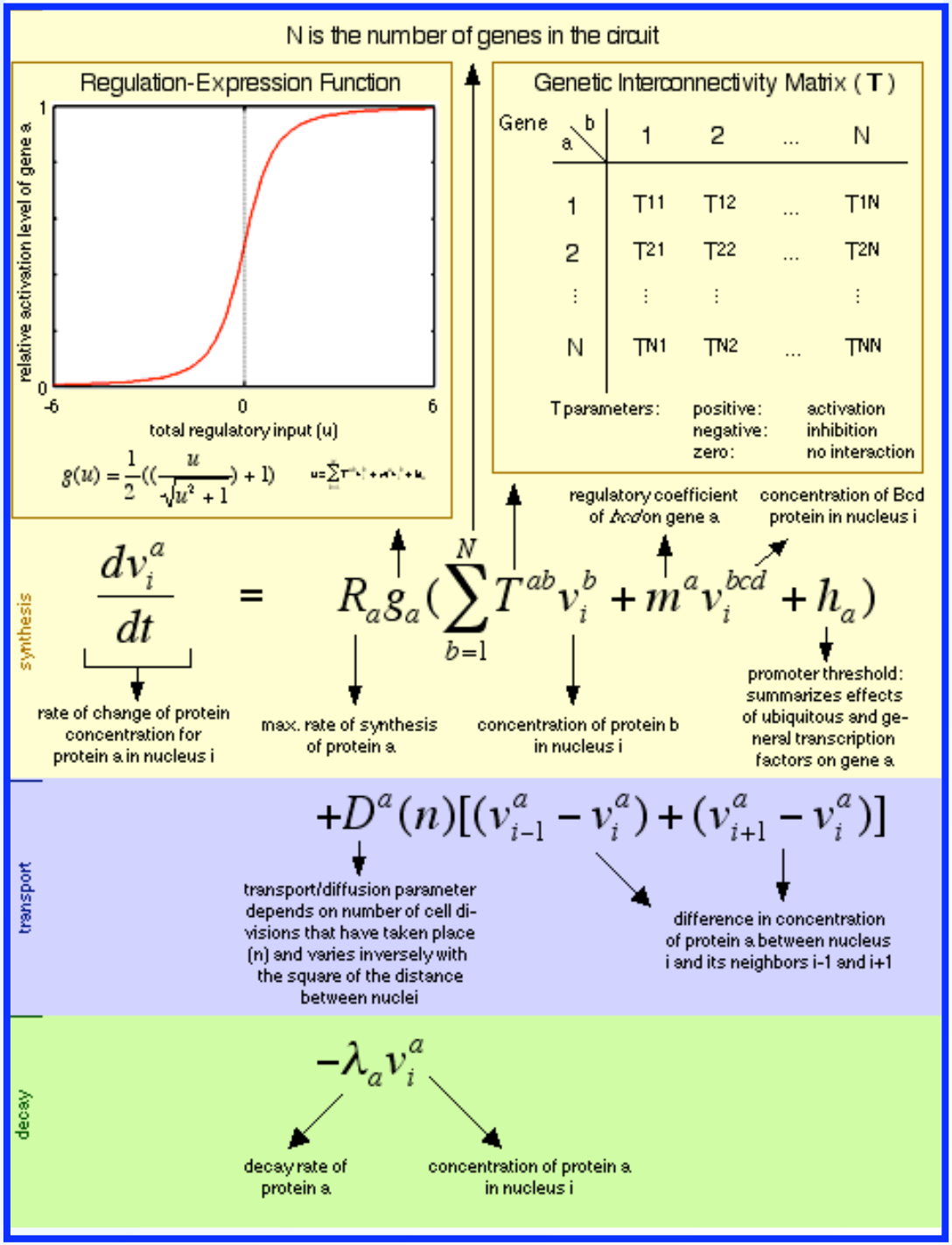
$$\frac{dv_i^a}{dt} = R_a g_a \left(\sum_{b=1}^{N} T^{ab} v_i^b + m^a v_i^{bcd} + h_a \right)$$

transport

$$+D^a(n)\left[\left(v_{i-1}^a - v_i^a\right) + \left(v_{i+1}^a - v_i^a\right)\right]$$

decay

$$-\lambda_a v_i^a$$



Reinitz's
***Gene Circuits* method**
Mechanism of Development
49: 133-158.

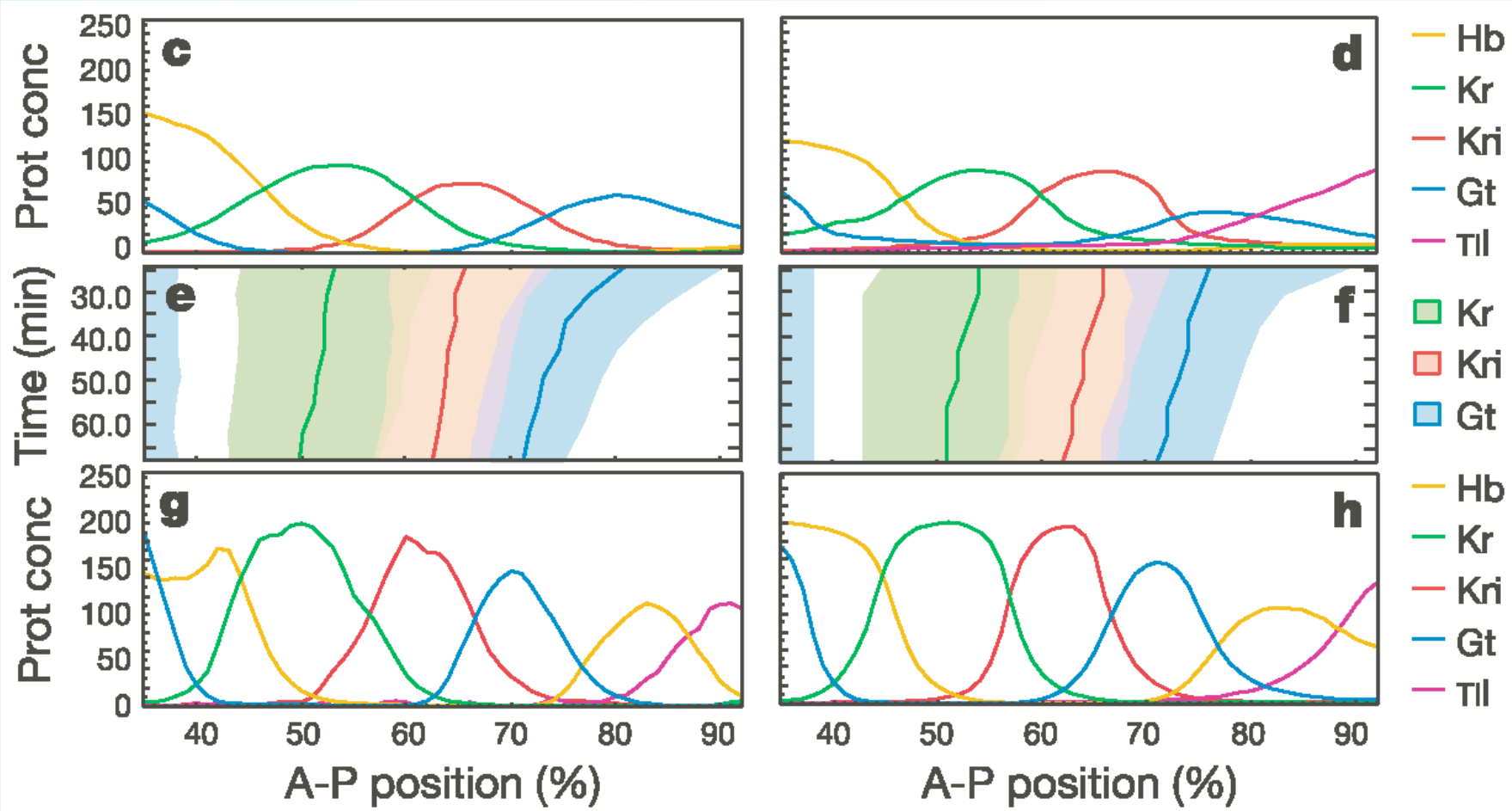
Reinitz's *et al* - Summing up

- Use of computational optimisation techniques to fit the parameters with self-produced *in situ* data

→ **matrix of interactions** (signs and weights of regulatory inputs)

- Outcome: several **novel biological insights**:
  - Gap genes (alone) specify a **unique set of pair-rule stripes**
  - Striking **diffusion coefficients** for some regulatory factors
  - Mechanism of the **control of stripe borders**
  - Uncovering of the **temporal shift** of gap gene expression domains

Jaeger *et al* (2004)



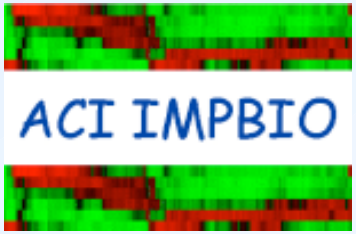
Dynamical shifts in gap gene domains are reproduced by gap gene circuits. Gene expression data (c, g) and gap gene circuit model output (d, h) at early (T1; c, d) and late (T8; g, h) cycle 14A. Vertical axes represent relative protein concentrations, horizontal axes represent position along the A–P axis (where 0% is the anterior pole). e, f, Gap domain shifts for Kr, kni and gt covering the time between patterns shown in c, d and g, h. Lines indicate the position of maximum concentration for each domain. Coloured areas represent regions in which protein concentration is above the half-maximum value. Positional values for data were obtained by approximation with quadratic splines.

	Von Dassow *et al* (2000)	Reinitz *et al* (1998) Jaeger *et al* (2004)	Sánchez *et al* (2001, 2003)
Formalism	Specified set of ODEs (continuous)	Generic set of ODEs (continuous)	Logical relationships Graphs (discrete)
Methodology	Simulations Random/directed parameter space exploration	Reverse engineering and model fitting (simulated annealing)	Logical analysis simulations
Initial data	Detailed knowledge of all components + interactions	List of key actors: the four gap genes + input + output genes	List of actors + qualitative characterisation of the interactions
Emphasis	Generic properties in relations with parameters values	Extracting interactive features from the knowledge of the dynamics	Role of specific feedback structures Simulations of mutants
Insights	Core interactions Robustness with respect to parameters and initial conditions	Gap genes specify one set of pair-rule stripes Diffusion coefficients Dynamics of stripe border setting	Delineation of the roles of crucial feedback circuits Prediction of new mutant phenotypes
Limitations	Variation of one parameter at a time Scaling up difficult	Standardisation of regulatory terms Scaling up difficult	Less standard maths… Transition towards more quantitative models?

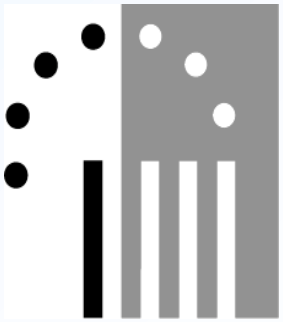
Main recent publications

- Calzone L, Thieffry D, Tyson JJ, Novak B (2007). *Mol Syst Biol* **3**: 131.
- Chaouiya C, Remy E, Ruet P, Thieffry D (2004). *LNCS* **3099**: 137-156.
- Chaouiya C, Remy E, Mossé B, Thieffry D (2004). *LNCIS* **294**: 119-126.
- Chaouiya C, Remy E, Thieffry D (2006). *LNCS* **4220**: 95-112.
- Fauré A, Naldi A, Chaouiya C, Thieffry D (2006). *Bioinformatics* **22**: e124-31.
- Gonzalez A, Chaouiya C, Thieffry D (2006). *Genetics* **174**: 1625-34.
- Gonzalez A, Naldi A, Sánchez L, Thieffry D, Chaouiya C (2006). *Biosystems* **84**: 91-100.
- Grange T, Imbert J, Thieffry D (2005). *BioEssays* **27**: 1203-5.
- Naldi A, Thieffry D, Chaouiya C (2007). *LNCS* **4695**: 233-47.
- Remy E, Mossé B, Chaouiya C, Thieffry D (2003). *Bioinformatics* **10** : ii172-8.
- Remy E, Ruet P, Thieffry D (2006). *LNCIS* 341: 263-70.
- Remy E, Ruet P, Mendoza L, Thieffry D, Chaouiya C (2006). *LNCS* **4230**: 56-72.
- Sánchez L, Thieffry D (2003). *J theor Biol* **224**: 517-37.
- Sánchez L, Chaouiya C, Thieffry D (2008). *Int J Dev Biol*, accepted.
- Simão E, Remy E, Thieffry D, Chaouiya C (2005). *Bioinformatics* **21**: ii190-6.
- Thieffry D, Sánchez L (2002). *Ann NY Acad Sci* **981**: 135-153.
- Thieffry D, Sánchez L (2003). *Curr Op Genet Dev* **13**: 326-30.
- Thieffry D (2007). *Brief Bioinfor* **8**: 220-5.

Current supports



CONTRAINTES Project



Interuniversity Attraction Poles

Bioinformatics and Modeling :

from Genomes to Networks