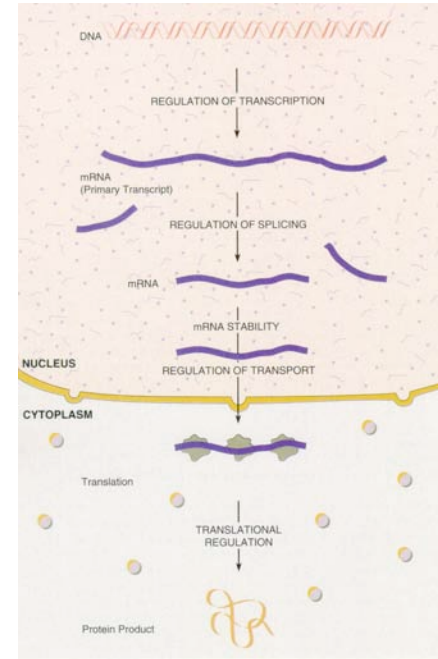


Towards the dynamical modelling of the regulome

Denis THIEFFRY (LGPD-IBDM, Marseille)

Contents

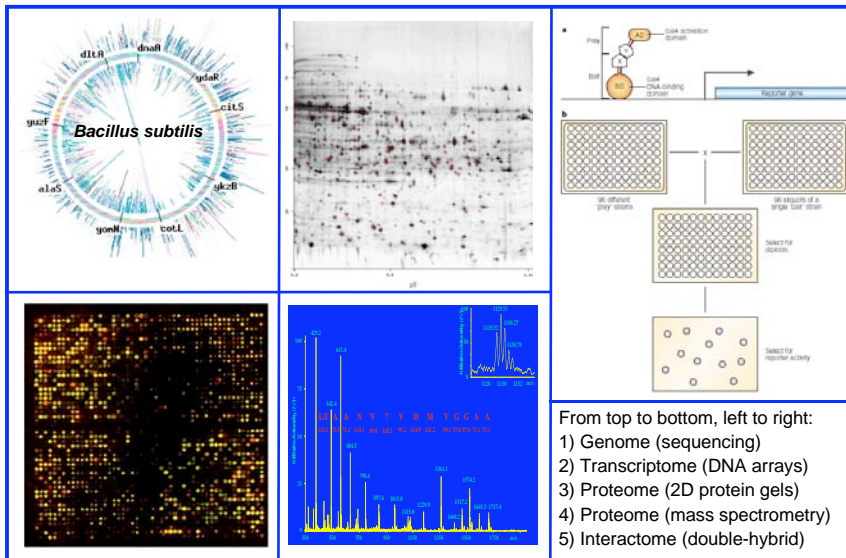
1. Biological introduction
2. Dynamical modelling: network inference/simulation
3. Conclusions and prospects



Gene regulation in eukaryotes

Source: Klug & Cummings (1994)

Genomics and functional genomics



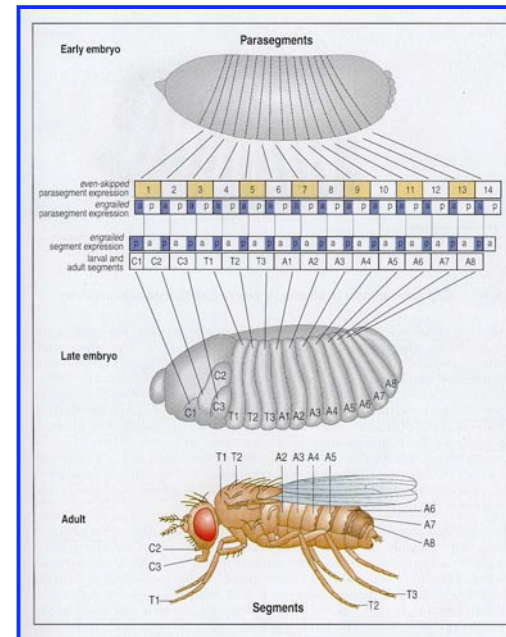
Functional genomics

The "**genome**" is defined as all the **DNA** (and thus all the genes) of an organism

Similarly, one can define :

- the "**transcriptome**"
- the "**proteome**"
- the "**metabolome**"
- the "**interactome**"
- the "**regulome**"

The challenge remain to understand how biological function emerges from these "omes" !

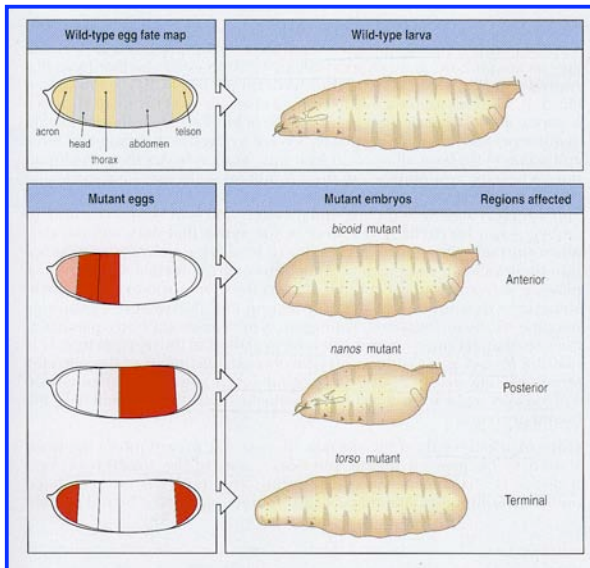


Drosophila Segmentation

Complexity :

- Spatial organisation
- Temporal organisation
- Number and diversity of mechanisms
- Variety/quantity of experimental data

Source: Wolpert *et al.* (1998)



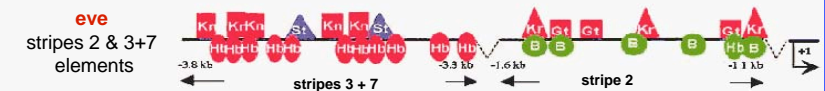
Genetic data

Maternal mutants

High throughput functional arrays:
LOF mutants, RNAi...

Source: Wolpert *et al.* (1998)

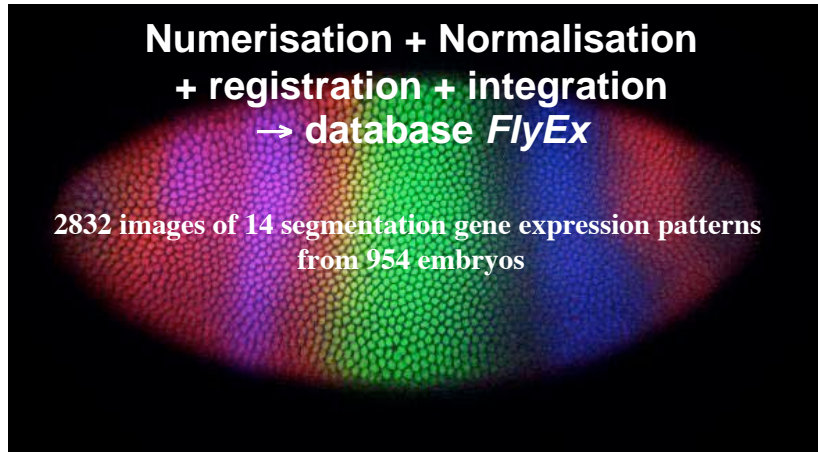
Information on cis-regulatory elements in *D. melanogaster*



+ interspecies comparisons + X-ChIP (on chip) data...



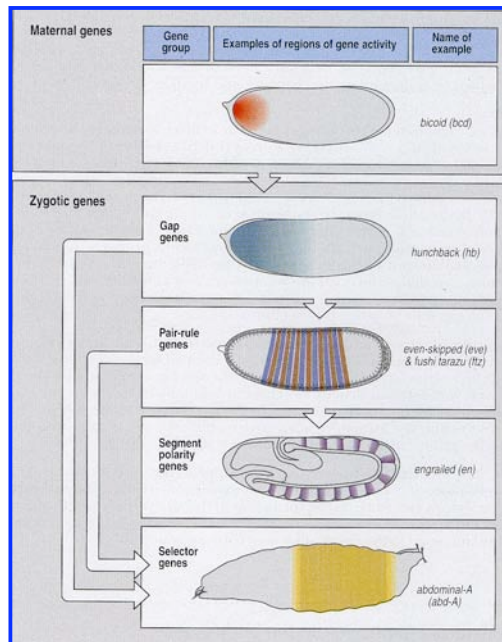
Patterns of gene expression (mRNAs or proteins)



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

Questions

- Correct **regulatory graph** for a given biological process ?
- What **relationships** between **cross-regulatory structures** and **spatio-temporal expression patterns** ?
 - From regulatory data to gene expression: **simulations**
 - From gene expression data to regulatory scheme: **inverse problem**
- Which **abstraction level** to answer specific biological questions ?
 - Molecular level: **biochemical network**
 - Gene cross-regulation level: **genetic network**
 - Tissue level: **inter-cellular network**
- **Qualitative** approaches (logical equations) versus **quantitative** approaches (differential or stochastic equations)
- How to **connect different levels of abstraction** ?



Qualitative analysis of the *Drosophila* anterior-posterior patterning system

Collection and integration of regulatory data



Graph analysis

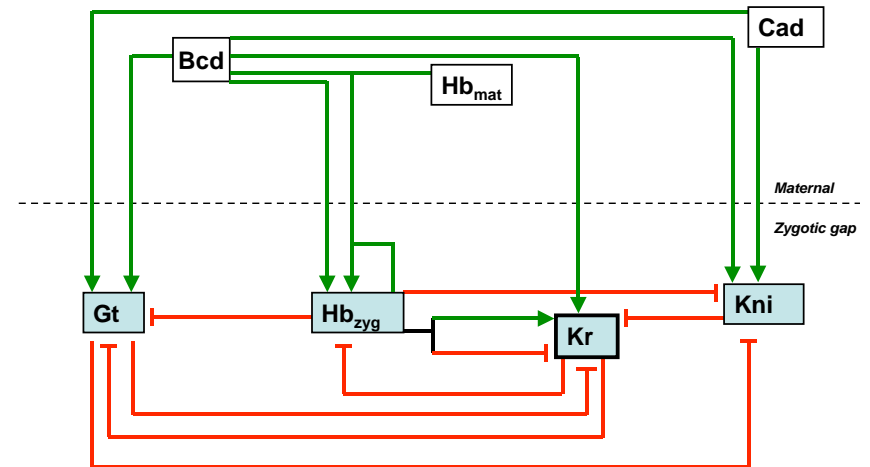


Three strongly connected components:

Gap
Pair-rule
Segment-polarity
“cross-regulatory modules”

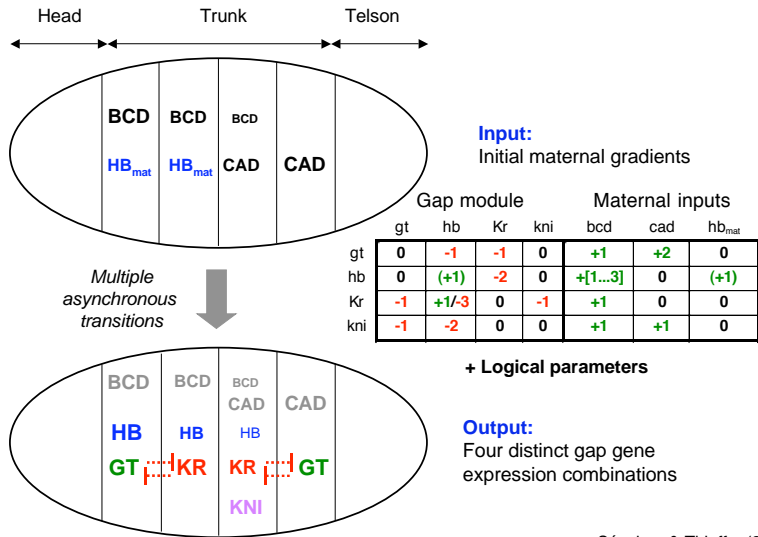
Source: Wolpert *et al.* (1998)

A qualitative model for the Gap regulatory Module



Sánchez & Thieffry (2001)

Logical simulation of the Gap Module



Sánchez & Thieffry (2001)

Simulation of perturbations (loss-of-function mutants, cis-regulatory mutations, ectopic gene expression)

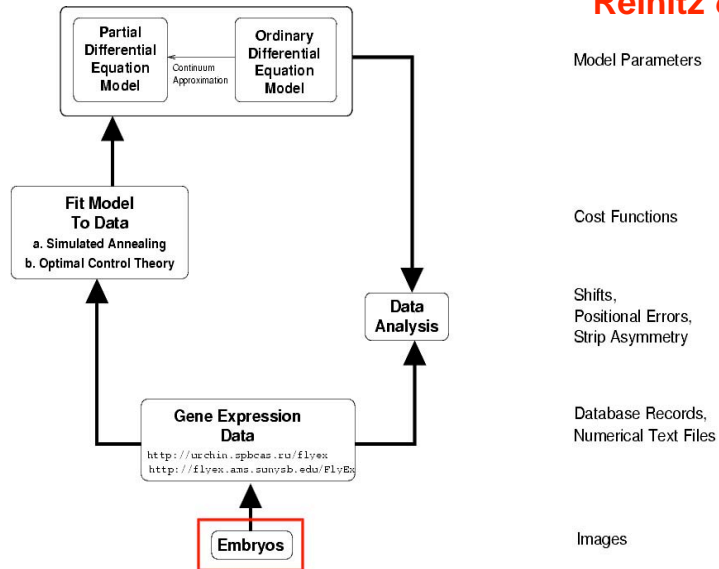
Genetic background (loss of function)	« Final state » GHRN (giant, hunchback, Krüppel, knirps)				Functional predictions
	A	B	C	D	
wildtype	1300	0220	0111	1000	
Bicoid	0001	0001	0001	1000	loss of <i>giant</i> expression in A loss of <i>hunchback</i> and <i>Krüppel</i> expressions in B and C activation of <i>knirps</i> in A and B
<i>hunchback</i> _{mat}	1300	0220	0111	1000	-
caudal	1300	0220	0120	0000	increase of <i>Krüppel</i> expression in C loss of <i>knirps</i> expression in C loss of <i>giant</i> expression in D
<i>giant</i>	0300	0220	0111	0001	activation of <i>knirps</i> in D
<i>Krüppel</i>	1300	1200	1100	1000	expression of <i>giant</i> in B and C
<i>knirps</i>	1300	0220	0120	1000	increase of <i>Krüppel</i> expression in C
<i>Hunchback</i> _{mat+2yg}	1000	1000	1000	1000	activation of <i>giant</i> in all regions
<i>giant-Krüppel</i>	0300	0200	0101	0001	activation of <i>knirps</i> in D
<i>Krüppel-knirps</i>	1300	1200	1100	1000	activation of <i>giant</i> in B and C
<i>giant-knirps</i>	0300	0220	0120	0000	increase of <i>Krüppel</i> expression in C

A — 4 domains —> P

Source: Sánchez & Thieffry (2002)

Reverse engineering of the Gap regulatory matrix

Reintz *et al.*



Courtesy: Maria Samsonova (2004)

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

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

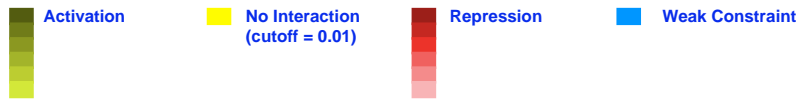
Decay

$$-\lambda_a v_i^a$$

Source: Reintz *et al.* (1998)

Constraints on the cross regulatory matrix

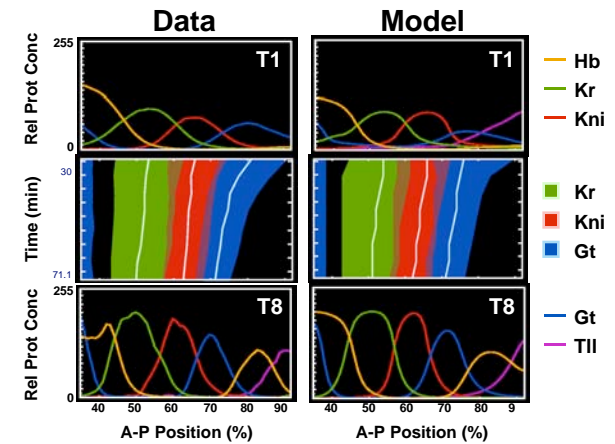
	<i>bcd</i>	<i>cad</i>	<i>hb</i>	<i>Kr</i>	<i>gt</i>	<i>kni</i>	<i>tll</i>
<i>hb</i>	0/1/9	3/1/6	2/2/6	4/6/0	2/4/4	10/0/0	3/5/2
<i>Kr</i>	0/0/10	0/1/9	7/3/0	1/2/7	10/0/0	10/0/0	10/0/0
<i>gt</i>	1/0/9	2/1/7	8/2/0	10/0/0	2/6/2	3/7/0	10/0/0
<i>kni</i>	1/1/8	1/1/8	9/1/0	6/4/0	10/0/0	0/2/8	8/2/0



(# negative / # nil / # positive interactions; total # = 10)

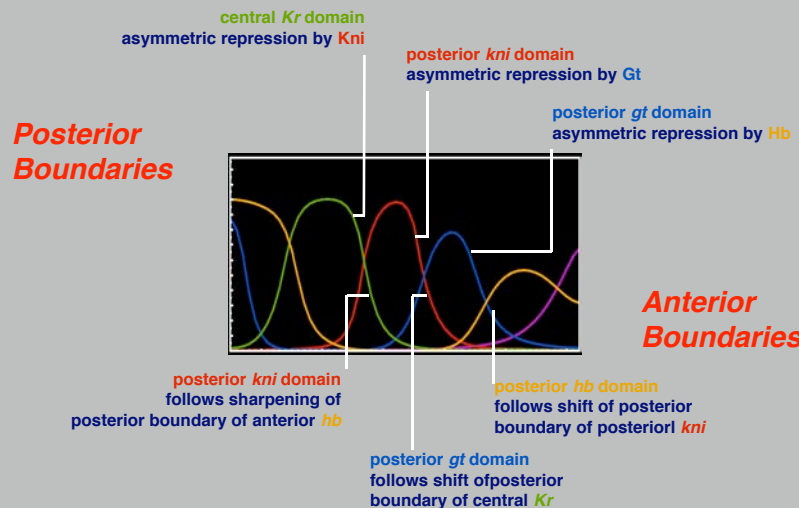
Source: Jaeger *et al.* (2004)

Gap Gene Expression

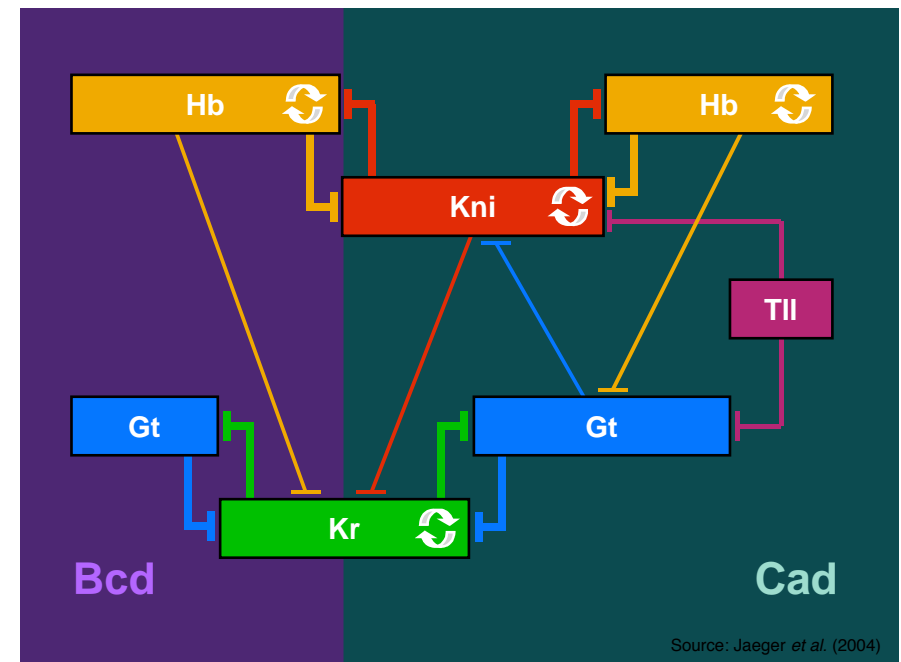


Source: Jaeger *et al.* (2004)

Determination of the gap expression boundaries



Source: Jaeger *et al.* (2004)

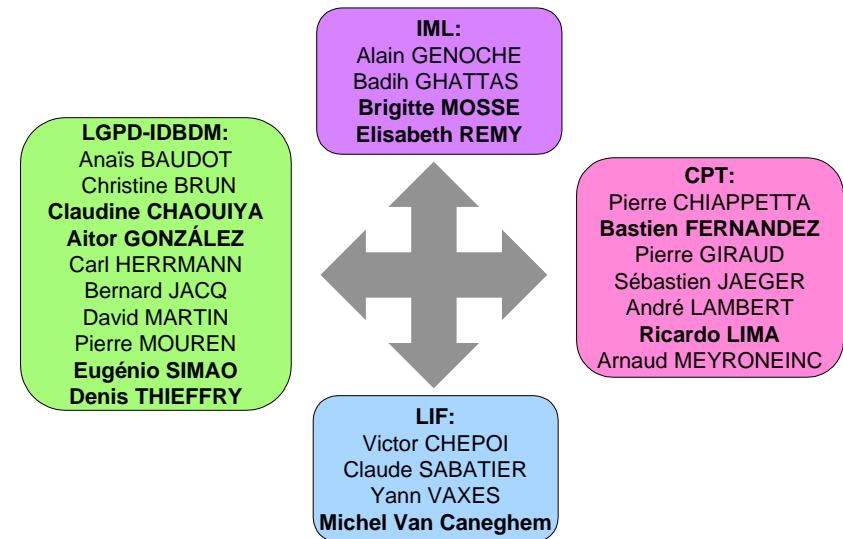


Source: Jaeger *et al.* (2004)

Conclusions and prospects

- Choice of **model definition** and **analysis tools** depends on **experimental data** and **questions**
- No **right models** but **useful models**
- **Explanatory** versus **predictive** insights
- **Complementarity** of different **model analyses** → ≠ **insights**
- Towards a rational **combination of different model analyses**
- **Interplay** between **modelling** and **experiment design**
- Role of **multidisciplinary collaborations**
- Designing of rational and user-friendly **computational modelling and analysis frameworks**

Multidisciplinary collaborations on the dynamical modelling of genetic networks at Luminy



Bibliography

- Albert R, Othmer HG (2003). The topology of the regulatory interactions predicts the expression pattern of the segment polarity genes in *Drosophila melanogaster*. *Journal of theoretical Biology* **223**: 1-18.
- Jaeger J, Blagov M, Kosman D, Kozlov KN, Manu, Myasnikova E, Surkova S, Vanario-Alonso CE, Samsonova M, Sharp DH, Reinitz J (2004). Dynamical analysis of regulatory interactions in the gap gene system of *Drosophila melanogaster*. *Genetics* **167**: 1721-1737.
- Jaeger J, Surkova S, Blagov M, Janssens H, Kosman D, Kozlov KN, Manu, Myasnikova E, Vanario-Alonso CE, Samsonova M, Sharp DH, Reinitz J (2004). Dynamic control of positional information in the early *Drosophila* embryo. *Nature* **430**: 368-371.
- Kauffman SA (1981). Pattern formation in the *Drosophila* embryo. *Philosophical transactions of the Royal Society of London, Series B, Biological sciences* **295**: 567-594.
- Meinhardt H (1986). Hierarchical inductions of cell states: a model for segmentation in *Drosophila*. *Journal of Cell Science* **4** (Suppl): 357-381.
- Poustelnikova E, Pisarev A, Blagov M, Samsonova M, Reinitz J (2004). A database for management of gene expression data in situ. *Bioinformatics* **20**: 2212-2221.
- Reinitz J, Kosman D, Vanario-Alonso CE, Sharp DH (1998). Stripe forming architecture of the gap gene system. *Developmental Genetics* **23**: 11-27.
- Sánchez L, Thieffry D (2001). A logical analysis of the *Drosophila* gap gene system. *Journal of theoretical Biology* **211**: 115-141.
- Thieffry D, Sánchez L (2002). Alternative epigenetic states understood in terms of specific regulatory structures. *Annals of the New York Academy of Sciences* **981**: 135-153.
- Sánchez L, Thieffry D (2003). Segmenting the fly embryo: a logical analysis of the pair-rule cross-regulatory module. *Journal of theoretical Biology* **224**: 517-537.
- Thieffry D, Sánchez L (2003). Dynamical modelling of pattern formation during embryonic development. *Current Opinion in Genetics and Development* **13**: 326-330.
- 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.