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

Genomics and functional genomics

From top to bottom, left to right:
1) Genome (sequencing)  
2) Transcriptome (DNA arrays)  
3) Proteome (2D protein gels)  
4) Proteome (mass spectrometry)  
5) Interactome (double-hybrid)

Gene regulation in eukaryotes

Source: Klug & Cummings (1994)

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)

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

- ftz zebra element
- eve stripes 2 & 3+7 elements
- kni posterior element
- Ubx PBX element

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

Genetic data

Maternal mutants

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

Source: Wolpert et al. (1998)
Patterns of gene expression (mRNAs or proteins)

Numerisation + Normalisation + registration + integration → database FlyEx

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

Source: Sánchez & Thieffry (2001)
Multiple asynchronous transitions

**Input:**
- Initial maternal gradients

**Gap module Maternal inputs**

<table>
<thead>
<tr>
<th>gt</th>
<th>hb</th>
<th>kni</th>
<th>bcd</th>
<th>cad</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>(-3)</td>
<td>-2</td>
<td>0</td>
<td>(+1)</td>
</tr>
<tr>
<td>-1</td>
<td>s/3</td>
<td>0</td>
<td>-1</td>
<td>+1</td>
</tr>
<tr>
<td>-1</td>
<td>-2</td>
<td>0</td>
<td>-1</td>
<td>+1</td>
</tr>
</tbody>
</table>

**Output:**
- Four distinct gap gene expression combinations

**Logical parameters**

<table>
<thead>
<tr>
<th>gt</th>
<th>hb</th>
<th>kni</th>
<th>bcd</th>
<th>cad</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
</tr>
<tr>
<td>0</td>
<td>(+1)</td>
<td>-2</td>
<td>0</td>
<td>+1</td>
</tr>
<tr>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>+1</td>
<td>0</td>
</tr>
<tr>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>+1</td>
<td>0</td>
</tr>
</tbody>
</table>

**Simulation of perturbations**
- loss of giant expression in A
- loss of hunchback and Krüppel expressions in B and C
- activation of kni in A and B
- increase of Krüppel expression in C
- loss of kni expression in C
- loss of giant expression in D
- activation of giant in all regions
- activation of giant in B and C
- increase of Krüppel expression in C

**Source:** Sánchez & Thieffry (2001)

**Reverse engineering of the Gap regulatory matrix**

**Partial Differential Equation Model**
- Ordinary Differential Equation Model
- Kinetics Approximation
- Fit Model to Data
- Simulated Annealing
- Optimal Control Theory

**Data Analysis**
- Gene Expression Data
- Database Records, Numerical Test Files
- Images

**Synthesis**

\[
\frac{dv_i^a}{dt} = R_ag_a \left( \sum_{b=1}^{N} T_{ab} v_i^b + m_{i} a_{bcd} + h_{a} \right)
\]

**Transport**

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

**Decay**

\[-\lambda_a v_i^a\]

**Source:** Reinitz et al. (1998)
**Constraints on the cross regulatory matrix**

<table>
<thead>
<tr>
<th></th>
<th>bcd</th>
<th>cad</th>
<th>hb</th>
<th>Kr</th>
<th>gt</th>
<th>kni</th>
<th>tll</th>
</tr>
</thead>
<tbody>
<tr>
<td>hb</td>
<td>0/1/8</td>
<td>3/1/6</td>
<td>2/2/6</td>
<td>4/6/0</td>
<td>2/4/4</td>
<td>10/0/0</td>
<td>3/5/2</td>
</tr>
<tr>
<td>Kr</td>
<td>0/0/10</td>
<td>0/1/9</td>
<td>7/3/0</td>
<td>1/2/7</td>
<td>10/0/0</td>
<td>10/0/0</td>
<td>10/0/0</td>
</tr>
<tr>
<td>gt</td>
<td>1/0/9</td>
<td>2/1/7</td>
<td>8/2/0</td>
<td>10/0/0</td>
<td>2/6/2</td>
<td>3/7/0</td>
<td>10/0/0</td>
</tr>
<tr>
<td>kni</td>
<td>1/1/8</td>
<td>1/1/8</td>
<td>9/1/0</td>
<td>6/4/0</td>
<td>10/0/0</td>
<td>0/2/8</td>
<td>8/2/0</td>
</tr>
</tbody>
</table>

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

**Gap Gene Expression**

**Determination of the gap expression boundaries**

- **Anterior Boundaries**
  - Central Kr domain asymmetric repression by Bcd
  - Posterior kni domain asymmetric repression by Gt
  - Posterior hb domain asymmetric repression by Gt
  - Posterior kr domain follows sharpening of posterior boundary of anterior hb

- **Posterior Boundaries**
  - Posterior gt domain follows shift of posterior boundary of posterior kni
  - Posterior hb domain follows shift of posterior boundary of posterior kni

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

Bibliography