

Multi-level Approaches for a Deep Analysis of Morphogenesis in Living Systems

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Ingegneria Due

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Outline

- ① The morphogenesis of living systems
 - ▶ the crucial role of the hierarchical organisation
- ② Requirement
 - ▶ multilevel large-scale tool
- ③ A new framework – MS-BioNet
 - ▶ computational model
 - ▶ specification language
 - ▶ simulation engine
- ④ The agent-based approach
- ⑤ The parameter optimisation
- ⑥ The analysis of *Drosophila Melanogaster* regionalisation
- ⑦ Conclusion and future works



Outline

- 1 On the morphogenesis of living systems
- 2 MS-BioNet
- 3 Agent-based model
- 4 Parameter tuning in Systems Biology
- 5 Evaluation on the Drosophila Melanogaster morphogenesis
 - Model and simulation on MS-BioNet
 - Model and simulation on Repast
- 6 Conclusion and future works



Biological Background

Developmental Biology researches the mechanisms of development, differentiation, and growth in animals and plants at the molecular, cellular, and genetic levels.

Animal developmental steps

- ① Fertilisation of one egg
- ② Mitotic division
- ③ Cellular differentiation
 - ▶ diverse gene expression
- ④ **Morphogenesis**
 - ▶ control of the organised spatial distribution of the cell diversity



Each region of the developing organism expresses a given set of genes

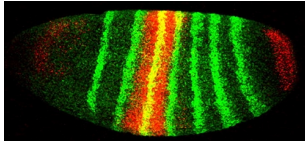


Figure: *Drosophila* M. segments

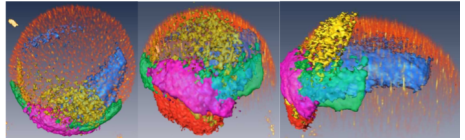


Figure: *Zebrafish* regionalisation

- Developmental Biology recognise as important actors in the emergence of embryonic patterning – self-organised structures
 - ▶ transcriptional control mechanisms
 - ▶ signalling pathways
 - ▶ cell-to-cell direct interaction
 - ▶ short and long range signals (*morphogenes*)
- **interplay between cells internal activity and cell-to-cell interactions**

Figure by:

[1] on-line [2] An Automatic Quantification and Registration Strategy to Create a Genetic Expression Atlas of Zebrafish Embryogenesis. C. Castro et al. Accepted at IEEE Engineering in Medicine and Biology Society (EMBC'09)

On the Need of Proper Tools

Tool requirements

- ① Multi-compartment / multi-scale model
 - ▶ for reproducing the interactions and integrations of the systems components at cellular and intracellular level
- ② Diffusion / Transfer
 - ▶ for studying the effects of short and long range signals
 - ▶ for modelling the compartment membrane
- ③ Stochasticity
 - ▶ for capturing the aleatory behaviour characteristic of those systems involving few entities



Two Approaches Based on Computational Models

MS-BioNet

- Ad-hoc Framework developed to tackle scenarios of dev. bio.
 - ▶ naturally supporting scenarios with many compartments
 - ▶ use state-of-the-art implem. techniques for the simulation engine
 - ▶ ground on Gillespie's characterisation of chemistry as CTMC

Agent-Based model (ABM)

- Built-in abstractions to capture the main aspects of complex systems
 - ▶ interactions, hierarchy, heterogeneity, locality



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An Ad-hoc Framework

MS-BioNet's Conceptual levels

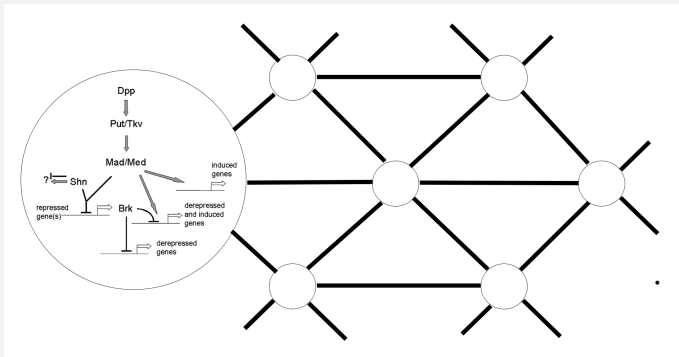
- ① **Computational Model:** graph of compartments, with transfer reactions
- ② **Surface Language:** systems as logic-oriented description programs
 - ▶ system structure
 - ▶ inner chemical behaviours
- ③ **Simulation Engine:** known $O(\log N)$ version of Gillespie SSA
 - ▶ reproducing the exact chemical evolution/diffusion of substances



Level 1: the Computational Model – Structure

A multi-compartment version of standard CMSB view

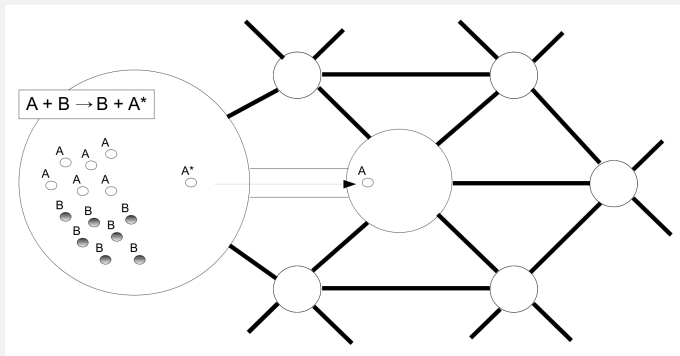
- A system is a graph-like network of compartments
- Each compartment hosts a chemical solution
- Mobility and mitotic division will be supported in future versions



Level 1: the Computational Model – Chemical Transfer

Transfer Model

- Some chemical reactions can produce so-called **firing molecules**
- They are sent to a neighbouring compartment picked probabilistically



Level 2: the Surface Specification Language

Structure

A program as a set of logic declarations

- Declaring molecules, reactions, compartments, links
- Configuring the simulation (initial state and parameters)
- Stating output commands

Declarations can have variables and be equipped with fully expressive preconditions, acting as constraints on declarations

- Supporting flexibility



Example Specification

Diffusion of a substance into a grid-like tissue

```
const size(20).
```

```
molecule M where (M in [pump,field]).
```

```
reaction r(pump) : [pump] --> [pump,field] rate 10.0.
```

```
reaction r(diff) : [field] --> [field,firing(field)] rate 0.2.
```

```
reaction r(decay) : [field] --> [] rate 0.1.
```

```
compartment c(X,Y) where (const size(N), X in {1..N}, Y in {1..N}).
```

```
link c(X,Y) >>> c(X,Y1) molecule field rate 10000.0 where ( Y1 in [Y-1,Y+1] ).
```

```
link c(X,Y) >>> c(X1,Y) molecule field rate 10000.0 where ( X1 in [X-1,X+1] ).
```

```
concentration 1 of pump into c(M,M) where (const size(N), M is N//2).
```

```
place AnyReaction into AnyCompartment.
```

```
final_steps 100000.
```

```
sample_steps 100.
```

```
out [molecule(c(X,Y),field),Delimiter] where (
```

```
const size(N),
```

```
inspect(compartment c(X,Y)),
```

```
(Y=N -> Delimiter=end_of_line ; Delimiter=space)
```

```
).
```

Level 3: the Simulation Engine – Under the hood

Main Elements

- An available chemical reaction in a compartment is picked up probabilistically based on its rate
- Exactly modelling chemical dynamics according to [1]

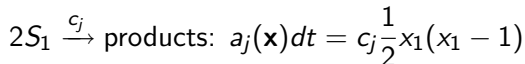
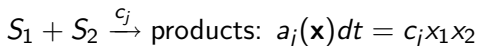
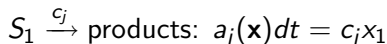
Based on:

[1] D. T. Gillespie. Exact stochastic simulation of coupled chemical reactions. J. Phys. Chem., 81(25), 1977.



The Gillespie's SSA: Premises

- *Well-stirred* system of molecules of N chemical species $\{S_1, \dots, S_N\}$
- The molecules interact through M reactions $\{R_1, \dots, R_M\}$
 - ▶ only *unimolecular* and *bimolecular* reactions are considered
 - ▶ *trimolecular, reversible...* are modelled as a sequence of reactions
- Let $\mathbf{X}(t) = (X_1(t), \dots, X_N(t))$ be the state of the system
 - ▶ $X_i(t)$ is the number of S_i molecules in the volume at time t
 - ▶ ν_j is the state change vector
- Let c_j be the reaction probability rate constant for R_j
- Let $a_j(\mathbf{x})dt$ be the *propensity function* for R_j as the probability, given $\mathbf{X}(t) = \mathbf{x}$, that an R_j will occur in $[t, t + dt)$



The Gillespie's SSA: the *Direct Method*

- ① Initialise the time $t = t_0$ and the system's state $\mathbf{x} = \mathbf{x}_0$
- ② With the system in state $\mathbf{x}$ at time t , evaluate
 - ▶ all the $a_j(\mathbf{x})$
 - ▶ their sum $a_0(\mathbf{x}) \equiv \sum_{j'=1}^M a_{j'}(\mathbf{x})$
- ③ Draw two random numbers r_1 and r_2 from the uniform distribution in the unit interval and take

$$\tau = \frac{1}{a_0(\mathbf{x})} \ln\left(\frac{1}{r_1}\right)$$

$$j = \text{the smallest integer satisfying } \sum_{j'=1}^j a_{j'}(\mathbf{x}) > r_2 a_0(\mathbf{x})$$

- ④ Effect the next reaction by replacing $t \leftarrow t + \tau$ and $\mathbf{x} \leftarrow \mathbf{x} + \nu_j$
- ⑤ Record $(\mathbf{x}, t)$ as desired
- ⑥ Return to step 2, or else stop



Level 3: the Simulation Engine – Output (1)

Produces a textual result from out commands

```
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 1 1 1 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 4 3 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 1 7 54 7 3 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 1 12 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
```

Level 3: the Simulation Engine – Output (2)

Produces a textual result from out commands

```
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 1 1 3 1 2 0 0 0 0 0 0 0 0
0 0 0 0 0 0 2 4 7 9 11 6 0 0 0 0 0 0 0 0
0 0 0 0 0 0 5 6 24 29 30 9 1 0 0 0 0 0 0 0
0 0 0 0 0 1 3 8 31 85 56 19 4 0 0 0 0 0 0 0
0 0 0 0 0 1 3 20 83 166 73 21 9 1 1 0 0 0 0 0
0 0 0 0 0 1 2 9 58 90 56 14 6 1 0 0 0 0 0 0
0 0 0 0 0 0 0 2 19 27 26 10 3 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 5 7 5 1 2 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
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0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
```

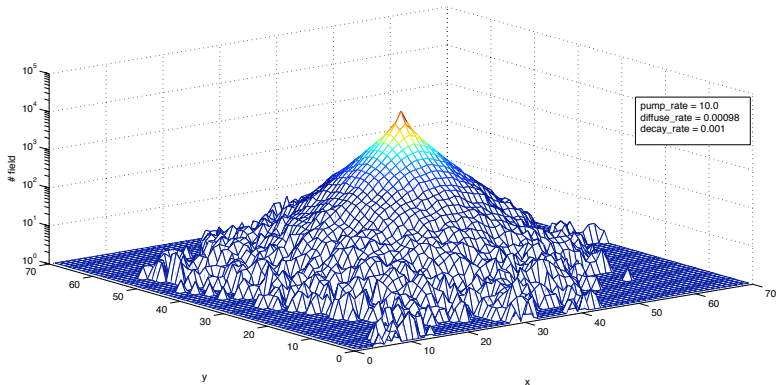
Level 3: the Simulation Engine – Output (3)

Produces a textual result from out commands

```
0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 1 0 0 1 1 1 0 0 0 0 0 0 0
0 0 0 0 0 0 0 2 1 3 6 5 2 0 1 0 0 0 0 0
0 0 0 0 0 2 6 11 11 14 12 2 0 1 3 2 0 0 0 0
0 0 0 1 4 8 17 36 64 57 46 20 7 5 2 1 0 0 0 0
0 0 0 3 9 15 31 77 120 142 98 47 36 16 5 1 0 0 0 0
1 1 2 6 20 28 78 162 217 238 221 145 78 43 14 6 1 0 0 0
0 1 1 12 33 83 171 261 401 497 419 265 130 52 16 3 1 0 0 0
1 5 9 20 52 93 227 399 658 779 587 381 228 84 29 5 2 0 0 0
0 0 6 16 44 100 243 460 768 966 737 495 269 98 38 10 4 4 0 0
0 0 3 11 44 106 191 385 638 803 677 431 234 94 36 11 0 0 0 0
0 0 3 2 32 51 120 251 412 466 445 338 160 61 23 16 1 0 0 0
0 0 2 1 8 27 48 117 205 289 246 171 75 39 15 11 5 1 0 0
0 0 1 2 2 11 25 46 86 134 117 64 36 14 5 5 7 1 0 0
0 0 0 0 0 2 6 24 31 37 26 23 9 4 0 0 0 0 0 0
0 0 0 0 0 0 1 4 6 10 4 7 4 2 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 3 2 1 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 1 0 0 1 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
```

Level 3: the Simulation Engine – Drawing Charts

Charting using any existing tool (Matlab, gnuplot,..)



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What is Agent-based Model

*Agent-based model is a specific **individual-based computational model** for studying macro emergent phenomena through the definition of the system **micro level** which is modelled as a collection of **interacting** entities.*

- MAS provides designers and developers with...
 - ▶ **Agents**
...a way of structuring a model around autonomous, heterogeneous, communicative, possibly adaptive, intelligent, mobile and... entities
 - ▶ **Society**
...a way of representing a group of entities whose behaviour emerges from the interaction among elements
 - ▶ **Environment**
...a way of modelling an environment characterised by a topology and complex internal dynamics
- MAS gives methods to...
 - ▶ model individual structures and behaviours of different entities
 - ▶ model local interactions among entities and entities-environment
 - ▶ model the environment structures and dynamics



An Agent-based System

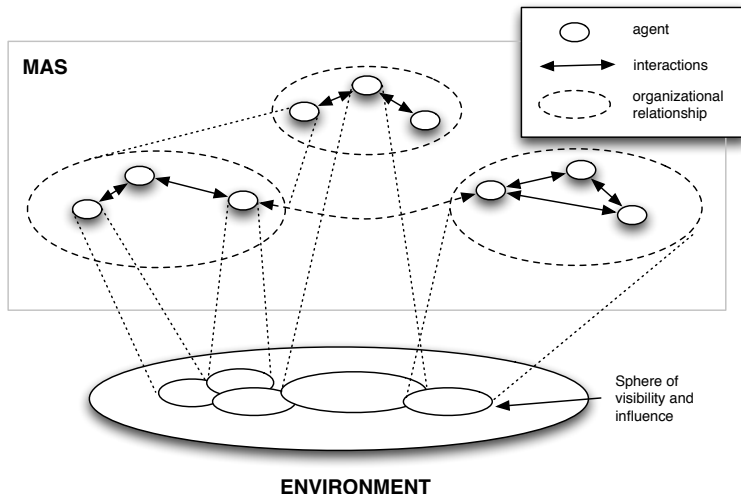


Figure: Interacting agents and environment

What is an Agent Based Simulation

Execute an ABM

- Running an ABM
- Study its evolution
 - ▶ observing individual and environment evolution
 - ▶ observing global system properties as emergent properties from the system's constituent units interactions (from the **bottom-up**)
 - ▶ making in-silico experiment

Platforms for realising agent-based simulation

- Repast, MASON, NetLogo ...



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Metaheuristics for parameter tuning in Systems Biology

Parameter tuning in Systems Biology

- Given the model structure and a set of target data
- Finding the values for model parameters so as to reproduce the system behaviour

The idea

- Transforming parameter tuning into an optimisation problem solved with metaheuristics

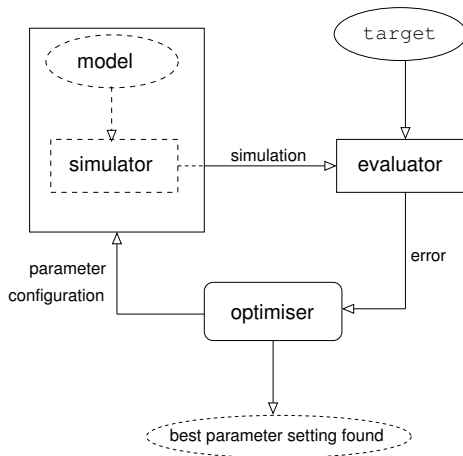


Architecture

- Simulator
- Evaluator
- Optimiser

Architecture

- Simulator
- Evaluator
- Optimiser



Evaluator

Measures of the distance between the attractor of the simulated system and the target attractor

In particular **Euclidean distance** of the vectors representing measures of the system dynamic such as:

- Average values of the output variables
- Periods
- Oscillation amplitude
- Peak frequency



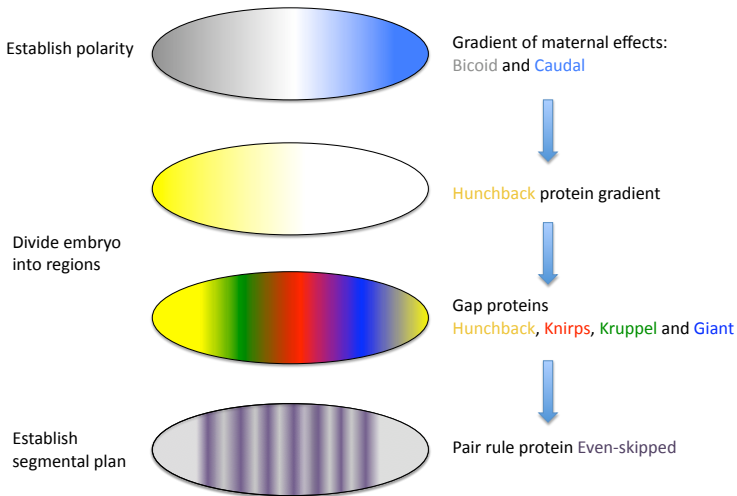
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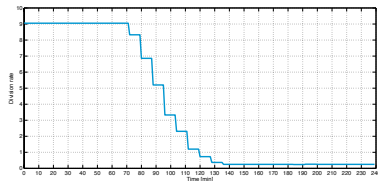
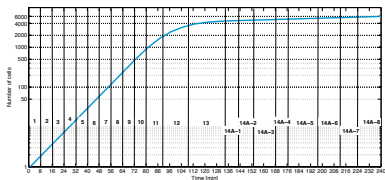
Biological Background - Gene Expression Pattern

- Egg of *Drosophila* already polarised by maternal effects



Biological Background - Cell Divisions

- Up to cleavage cycle 9
 - ▶ rapid and synchronous nuclear division and no zygotic transcription
- From cleavage cycle 9 to 13
 - ▶ rapid and synchronous divisions and few zygotic transcription
 - ▶ plasma membrane grow to enclose the nuclei
- From cleavage cycle 13
 - ▶ slow rate and asynchronous divisions and massive zygotic transcription



Goal of the Model

- Reproducing the gene expression pattern of the gap genes at **Cleavage Cycle 14A - temporal class 8...**
 - ▶ *hunchback* (hb), *Krüppel* (Kr), *knirps* (kni) and *giant* (gt)

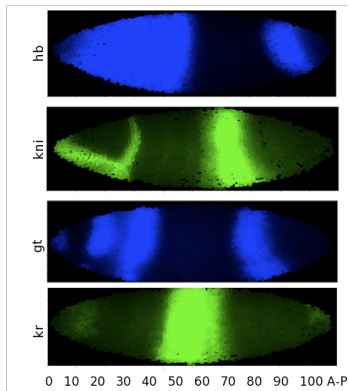


Figure: 2D data from the FlyEx database¹

¹ <http://flyex.ams.sunysb.edu/flyex/index.jsp>

Initial Condition

- ... Beginning with expression data at **Cleavage Cycle 11**

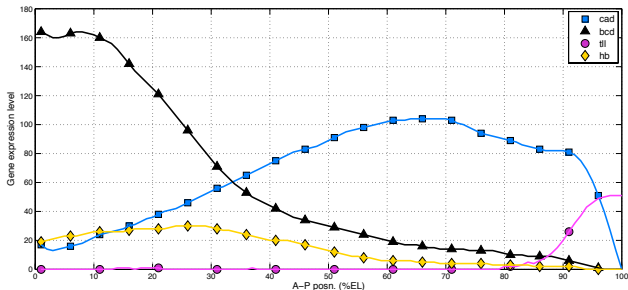


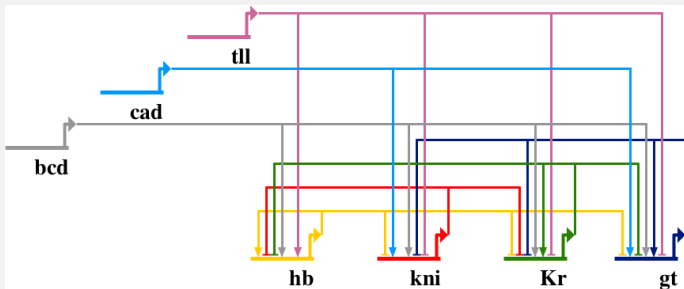
Figure: Experimental data from the FlyEx database of genes with non-zero concentration. The concentration of proteins are unitless, ranging from 0 to 255, at space point x , ranging from 0 to 100 % of embryo length.

The Intracellular Network Structure

- *caudal* and *bicoid* are maternal effectors
- They drive the expression of the gap genes *hunchback* (hb), *Krüppel* (Kr), *knirps* (kni) and *giant* (gt)
- *tailless* (tll) is a gap gene that we model as an input of the network

Intracellular Network from literature ^a

^aT. J. Perkins, J. Jaeger, J. Reinitz, and L. Glass. 2006. Reverse engineering the gap gene network of *Drosophila Melanogaster*. PLoS Comput Biol, 2(5)



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Model of the Cellular-System

- Each compartment is a cell that hosts chemical reactions
- The system size is 10×100
 - ▶ y corresponds to the central portion of D-V axis 45%-55%
 - ▶ x corresponds to the 0%-100% of the A-P axis
- Grid is fixed
- Hb, Kr, Kni and Gt are able to diffuse
- No concept of gradient
 - ▶ molecules can randomly go into one of the linked cells



The Model Specification (1/2)

Hunchback (hb) model

```
% Hb can be found in three different "forms"  
% Protein --> pHb  
% Gene active --> gHb1, gene inactive --> gHb0  
molecule M where (M in [pHb, gHb0, gHb1]).
```

```
% Hb reactions
```

```
reaction r(gHbAct00) : [pBcd, gHb0] --> [pBcd, gHb1] rate 0.1114.  
reaction r(gHbAct01) : [pTll, gHb0] --> [pTll, gHb1] rate 0.1.  
reaction r(gHbAct02) : [pHb, gHb0] --> [pHb, gHb1] rate 0.0293.  
  
reaction r(gHbDeAct00) : [pKni, gHb1] --> [pKni, gHb0] rate 0.3903.  
reaction r(gHbDeAct01) : [pKr, gHb1] --> [pKr, gHb0] rate 0.0124.  
  
reaction r(pHbSynth) : [gHb1] --> [gHb1, pHb] rate 32.03.  
  
reaction r(pHbDegr) : [pHb] --> [] rate 0.136.  
  
reaction r(pHbMove) : [pHb] --> [firing(pHb)] rate 2.25.
```

The Model Specification (2/2)

Setting the initial conditions

```
elem(1,[H|T],H).  
elem(I,[H|T],X) :- I1 is I-1, elem(I1,T,X).  
  
const size(10,100).  
  
const dataHb([19,20,21,22,23,23,23,24,25,26,26,26,26,26,26,27,28,28,28,28,28,28,  
29,30,30,30,30,30,30,29,28,27,27,26,25,24,23,22,21,20,20,20,20,19,18,17,16,15,  
14,13,12,11,10,9,9,8,8,7,6,6,6,6,6,5,5,5,5,4,4,4,4,4,4,4,4,4,3,3,3,3,3,3,3,2,  
2,2,2,2,2,2,2,1,0,0,0,0,0,0,0]).  
  
concentration C of pHb into c(X,Y) where  
( const dataHb(List), const size(K,L), X in {1..K}, Y in {1..L}, elem(Y,List,C) ).
```



Results

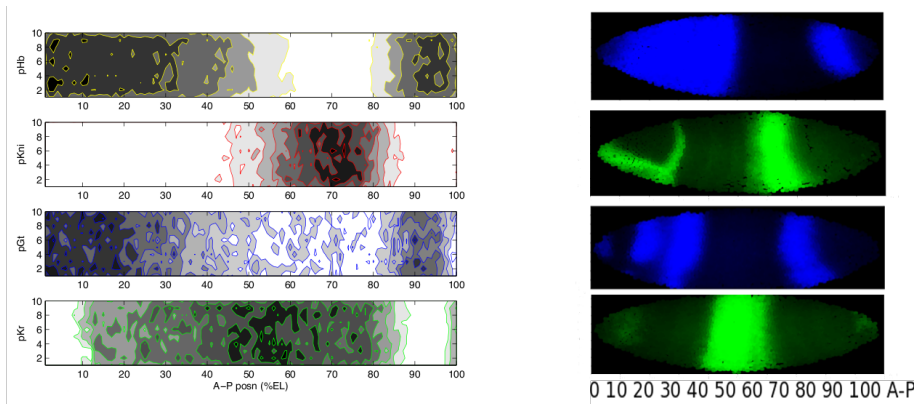


Figure: Simulation results for the four gap genes *hb*, *kni*, *gt*, *Kr* at a simulation time equivalent to the eighth time step of Cleavage Cycle 14A (left) and the corresponding experimental data (right)—% A-P length on the x and % D-V width on the y

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Model of the Cellular-System

- Each cell is modelled as an agent
 - ▶ agent internal behaviour models GRN
 - ▶ agent interactive capabilities model cell-to-cell / cell-environment communication
 - ▶ agent replicates so to model cell mitosis
- The extra-cellular environment is modelled as a grid-like environment
 - ▶ grid grows with the number of cells
 - ▶ Hb, Kr, Kni and Gt are able to diffuse
 - ▶ concept of gradient



Model of the Cell

- Gene regulatory network – agent behaviour
 - ▶ gene transcription might be activated or repressed
 - ▶ activation/inhibition is stochastic and depends on the concentration of transcription factors

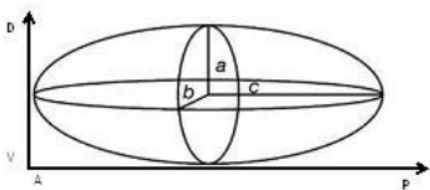
$$P_{hb} = f([Bicoid]) + f([Hunchback]) + f([Tailless]) - f([Knirps]) - f([Kruppel])$$

- ▶ f is a linear function with the proportionality constant representing the strength of interaction
 - ▶ if $P_{hb} > 0$ the protein is synthesised, otherwise the gene remains silent
- Mitosis
 - ▶ agents replicate according to the rate of cell division
- Chemical diffusion – agent interaction with the environment
 - ▶ chemicals are absorbed or released from/to the same location of the grid-like environment



Model of the Environment

- 3D tapered structure of the embryo $\rightarrow$ 2D section along the antero-posterior axis (c)
- Space is not continuous but grid-like
 - ▶ in each location a cell and/or morphogens
- Environment dynamic
 - ▶ diffusion of morphogens from region with bigger concentration to region with lower concentration, according to the *Fick's law*



Model Implementation and Simulation Procedure

- The model is implemented on top of Repast Simphony²
 - ▶ open-source agent-based modelling and simulation toolkit
 - ▶ abstraction for modelling the agent behaviour and the environment
 - ▶ multithreaded discrete event scheduler
- Simulations
 - ▶ are executed from the cleavage cycle 11
 - ▶ a time step corresponds to 4 seconds of the real system simulated

²<http://repast.sourceforge.net/index.html>



Qualitative Results

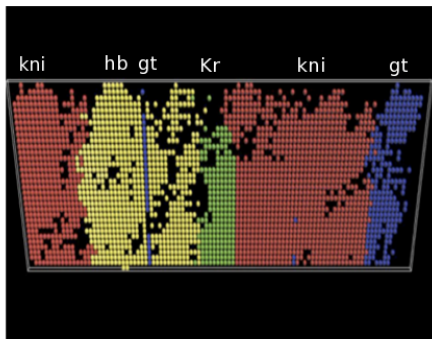
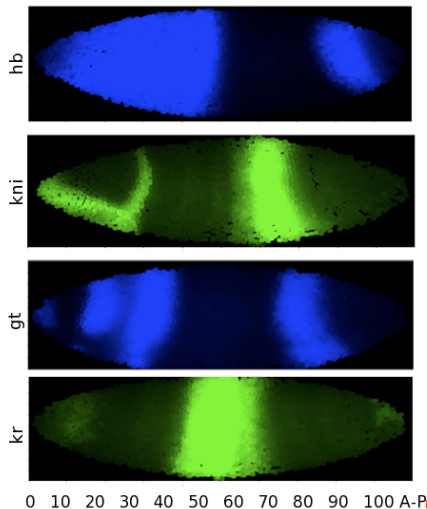


Figure: Qualitative results charted in 2D at the eighth time step of cleavage cycle 14A. The image shows for each cell of the embryo the genes with higher expression.



Quantitative Results

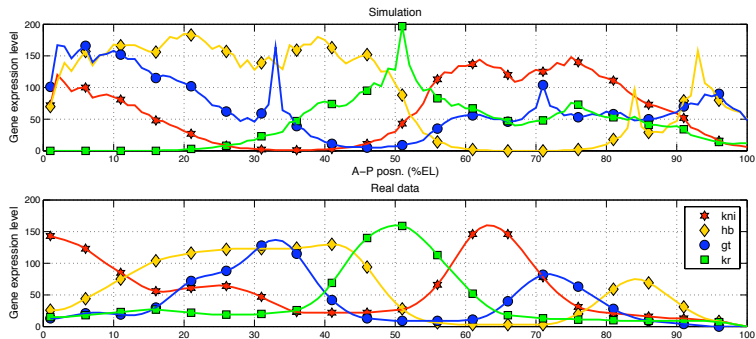


Figure: Quantitative simulation results for the four gap genes *hb*, *kni*, *gt*, *Kr* at a simulation time equivalent to the eighth time step of cleavage cycle 14A (top) and the corresponding experimental data (bottom)



Outline

- 1 On the morphogenesis of living systems
- 2 MS-BioNet
- 3 Agent-based model
- 4 Parameter tuning in Systems Biology
- 5 Evaluation on the Drosophila Melanogaster morphogenesis
 - Model and simulation on MS-BioNet
 - Model and simulation on Repast
- 6 Conclusion and future works**



Future Works

- Biological systems phenomena
 - ▶ studying the *even-skipped* stripes formation
 - ▶ introducing cellular phenomena driving the cell sorting
 - ★ chemotaxis
 - ★ cell adhesion
- MS-BioNet
 - ▶ re-engineer the tool towards a community release
 - ▶ support dynamic networks and mitotic division
 - ▶ improve chemical transfer model



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