A Multiscale Agent-based Model of Morphogenesis in Biological Systems

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Outline

1. The morphogenesis of living systems
   - the crucial role of hierarchical organisation
2. Requirement
   - multilevel large-scale tool
3. The agent-based approach
4. First results
   - the analysis of *Drosophila melanogaster* regionalisation as a case study
5. Conclusion and future works

Outline

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 cell diversity

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

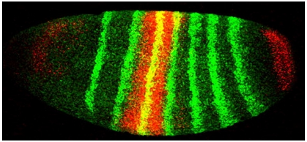


Figure: *Drosophila M.* segments

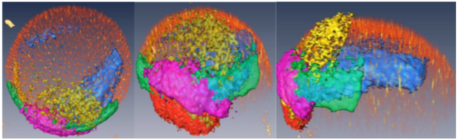


Figure: *Zebrafish* regionalisation

- 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*)

$\longrightarrow$ 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 all. 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
4. Heterogeneity
   - for modelling individual structures and behaviours of different entities of the biological system

Outline

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 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

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

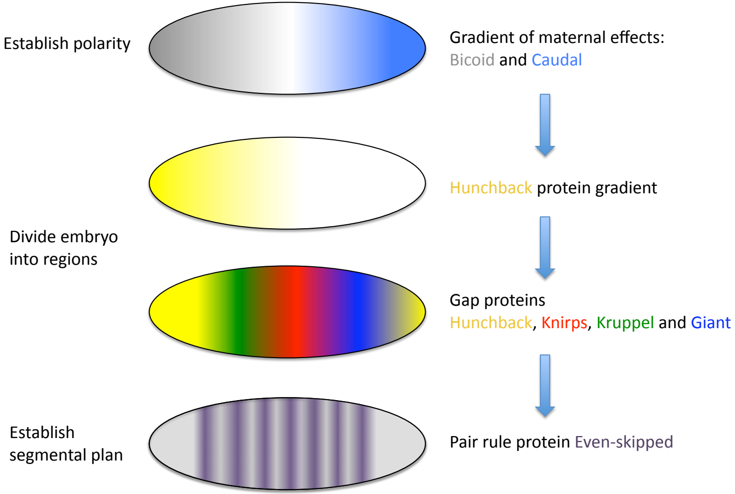
Platforms for realising agent-based simulation

- Repast, MASON, NetLogo . . .

Outline

Biological Background - Gene Expression Pattern

- Egg of Drosophila already polarised by maternal effects



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)

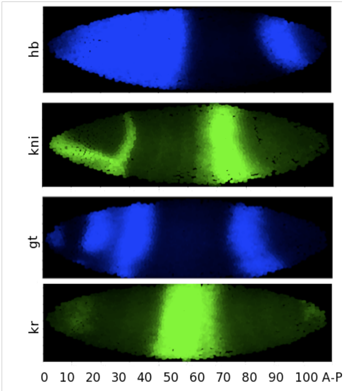


Figure: 2D data from the FlyEx database[1]

[1] http://flyex.ams.sunysb.edu/flyex/index.jsp

Initial Condition

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

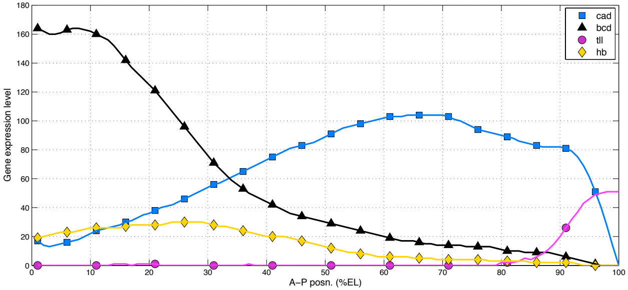


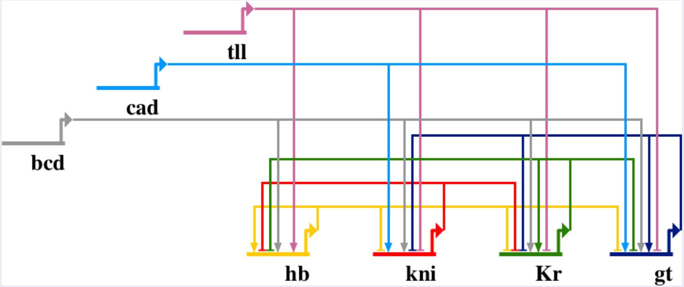
Figure: Experimental data from the FlyEx database of genes with non-zero concentration. The concentration of proteins are unitless, ranging from 0 to 255, at space point x, ranging from 0 to 100 % of embryo length.

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)
- *tailess* (tll) is a gap gene that we model as an input of the network

Intracellular Network from literature [a]

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



Outline

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

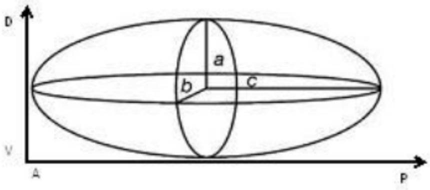
- Gene regulatory network – agent behaviour
  - gene transcription might be activated or repressed
  - activation/inhibition is stochastic and depends on the concentration of transcription factors. For instance:

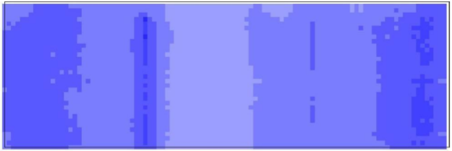
$$P_{hb} = f([Bicoid]) + f([Hunkbuck]) + f([Tailess]) - f([Knirps]) - f([Kruppel])$$

  - f is a linear function with the proportionality constant representing the strength of interaction
  - if $P_{gene} > 0$ 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

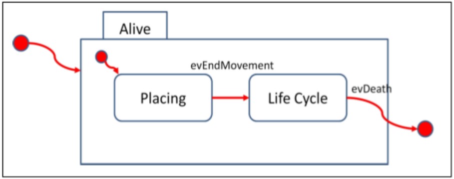
Model of the Environment

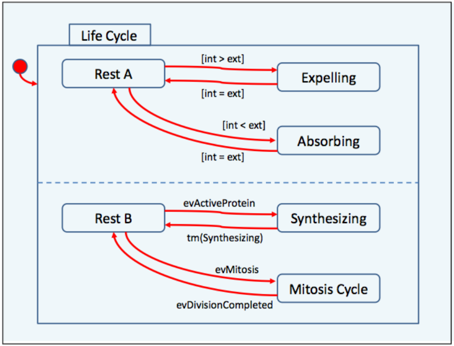
- 3D tapered structure of the embryo → 2D section along the antero-posterior axis (c)
- Space is not continuous but grid-like
  - in each location a cell and/or morphogens
- Environment dynamic
  - diffusion of morphogens from region with bigger concentration to region with lower concentration, according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





Model Formalisation with Statecharts





Formal model of the cell

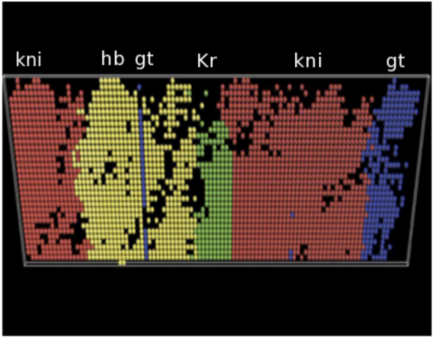
- Main macro state *Alive Placing* and *Life Cycle*
  - *Placing*, first movement of the cell to find its place inside the embryo
  - *Life Cycle*
    - *Rest A* (idle)– *Expelling* and *Absorbing* sub-states
    - *Rest B* (idle) – *Synthesizing* and *Mitosis Cycle* sub-states

Model Implementation and Simulation Procedure

- The model is implemented on top of Repast Simphony[2]
  - 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



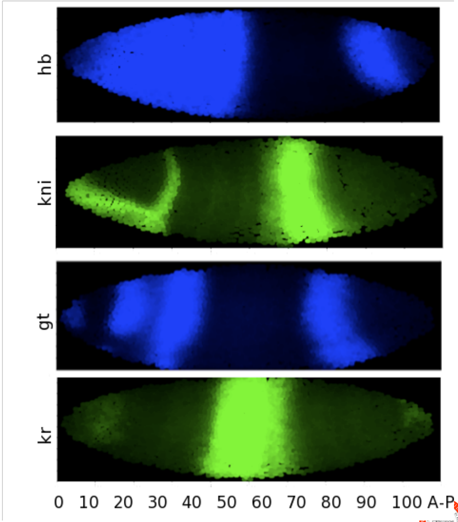


Figure: Qualitative results charted in 2D at the eighth time step of cleavage cycle 14A. The image shows for each cell of the embryo the genes with higher expression.

Quantitative Results

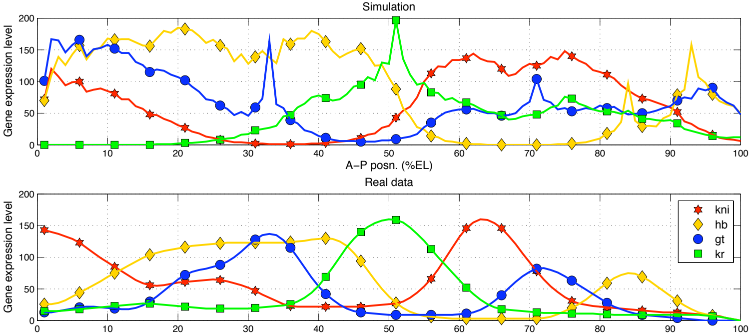


Figure: Quantitative simulation results for the four gap genes *hb*, *kni*, *gt*, *Kr* at a simulation time equivalent to the eighth time step of cleavage cycle 14A (top) and the corresponding experimental data (bottom)

Outline

Conclusion and Future Work

Conclusion

- ABM powerful tool for multiscale modelling
- Lack of a methodology for applying ABM to multicellular phenomena in general

Future work

- Biological systems phenomena
  - studying the *even-skipped* stripes formation
  - introducing cellular phenomena driving the cell sorting
    - chemotaxis
    - cell adhesion

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