A Model for Drosophila Melanogaster Development from a Single Cell to Stripe Pattern Formation

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Outline

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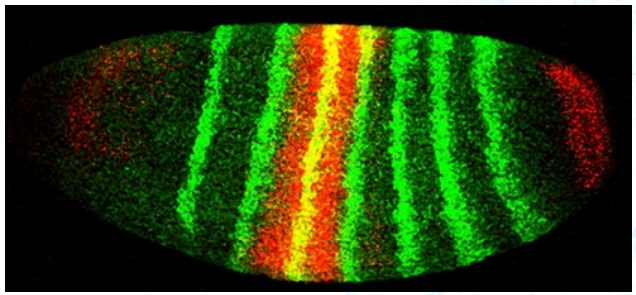
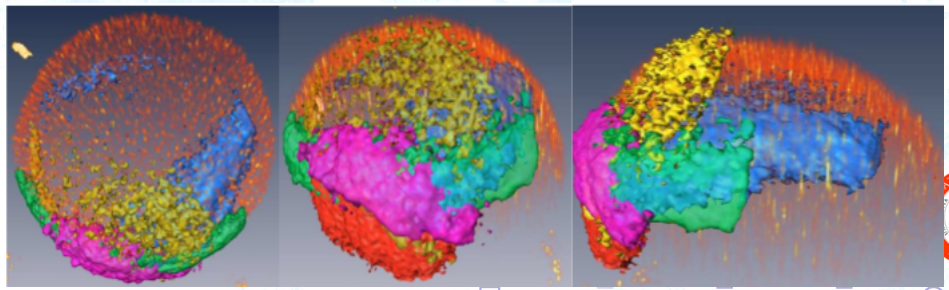
On the Morphogenesis of Living Systems

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

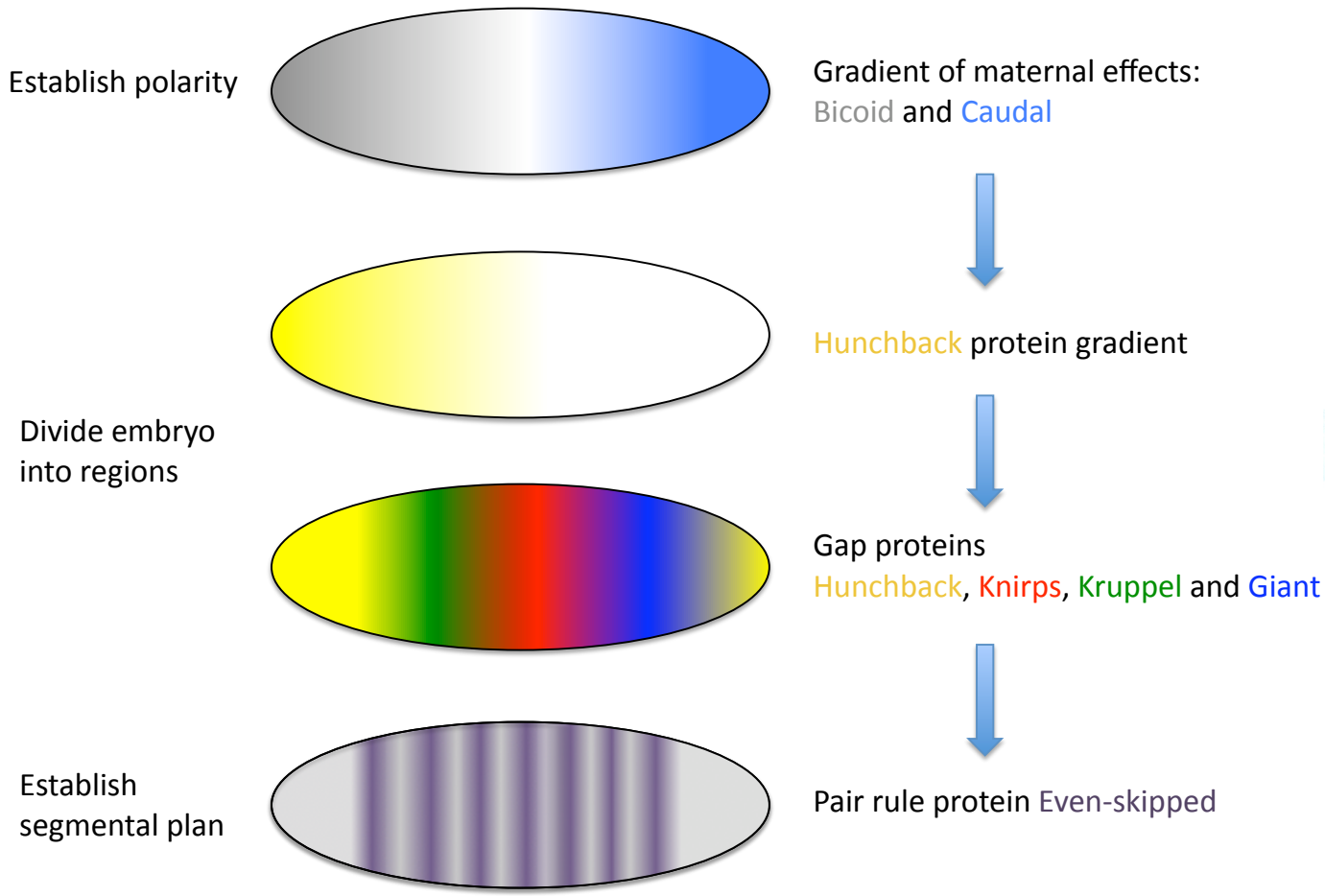
Animal developmental steps

1. Fertilisation of one egg
2. Mitotic division
3. Cellular differentiation
4. Morphogenesis
   - control of the organised spatial distribution of the cell diversity





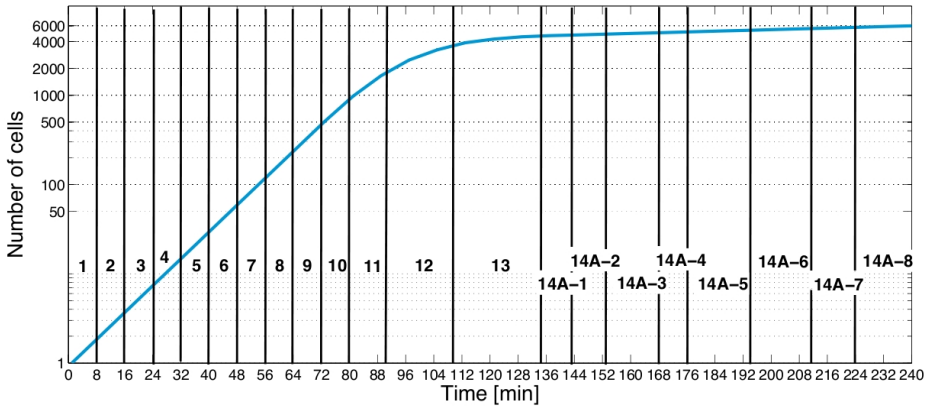
On the Drosophila Melanogaster Morphogenesis: Overview until Cleavage Cycle 14 temporal class 8

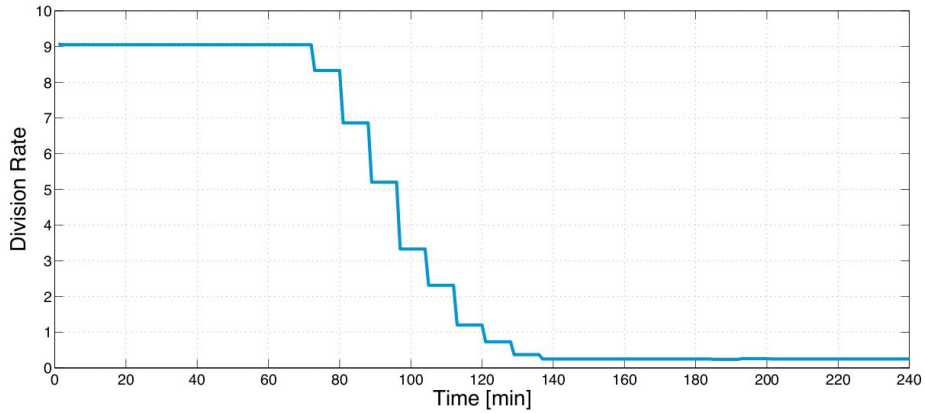


On the Drosophila Melanogaster Morphogenesis (1/2)

Fertilisation — Egg of Drosophila already polarised by maternal effects

Division and Movement — Nuclear and cellular divisions and movements

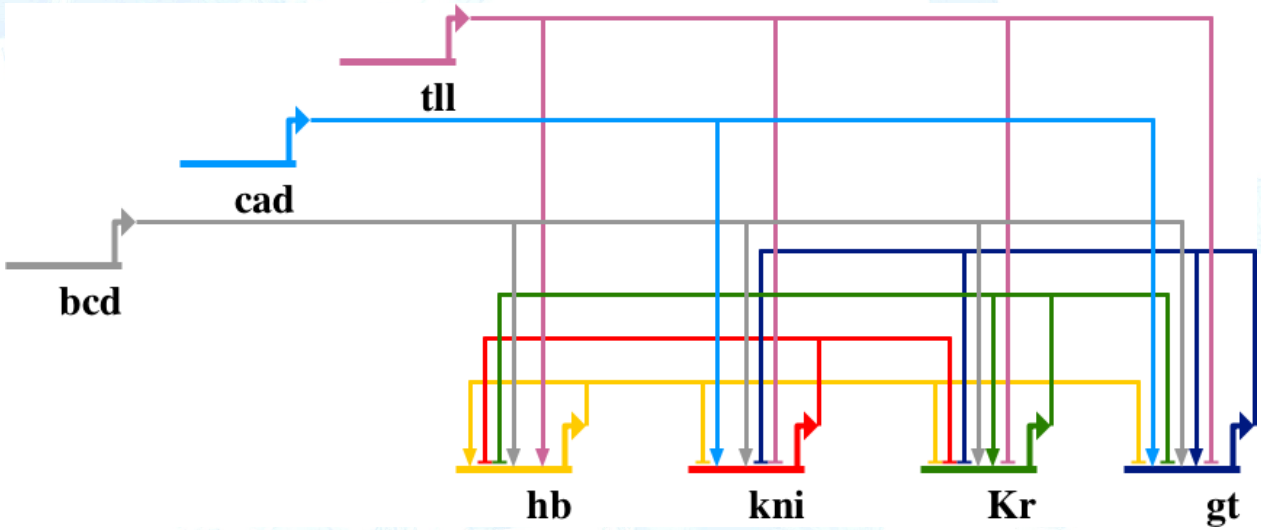




On the Drosophila Melanogaster Morphogenesis (2/2)

Molecule interaction Transcription factors inhibit or activate the expression of developmental genes

- Maternal effectors act over gap genes
- Gap genes interact among themselves



Molecule diffusion Transcription factors diffuse along the embryo

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A Computational Model for Addressing these Scenarios

Computational model requirements

1. Multi-compartment / multi-level model
   - for reproducing the interactions and integrations of the system 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. Dynamic topology
   - for modelling the compartment division and movement

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Brief Survey on Existing Work

Main modelling attempts

[Gursky et al., 2004] — continuous mathematical model based on a set of coupled nonlinear reaction-diffusion Partial Differential Equations

- $\surd$ protein synth./degr., gene inhibition and activation, protein diffusion
- x notion of compartments, stochasticity

[Montagna and Viroli, 2010] — multi-compartment, stochastic and discrete (Gillespie's SSA) version of [Gursky et al., 2004]

- $\surd$ interacting compartments with internal chemical reactions for [Gursky et al., 2004] processes
- x changes in network topology

[Lecca et al., 2010] — stochastic model of reaction-diffusion systems

- $\surd$ protein diffusion
- x gene interactions, protein synth./degr., cellular divisions

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Alchemist simulation approach

Base idea

- Start from the existing work with stochastic chemical systems simulation
- Extend it as needed to model multi-compartment dynamic networks

Goals

- Full support for Continuous Time Markov Chains (CTMC)
- Rich environments with mobile nodes, etc.
- More expressive reactions
- Fast and flexible SSA engine

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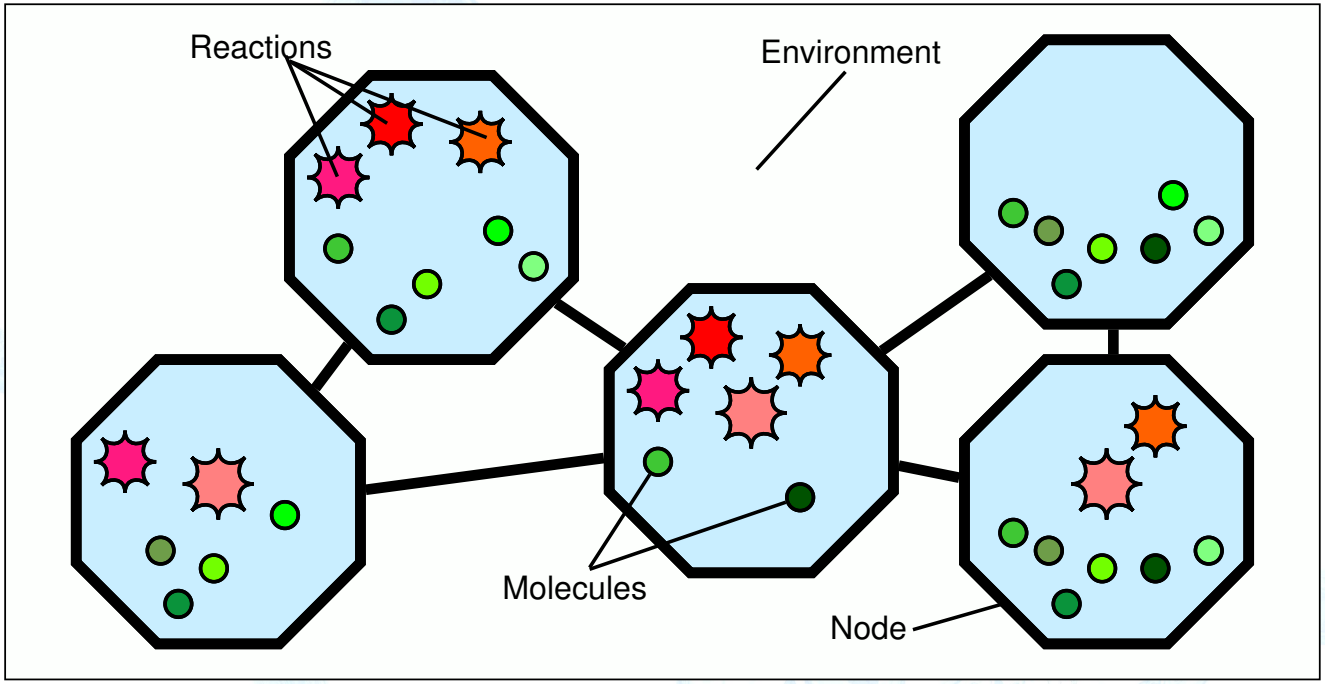
Enriching the environment description

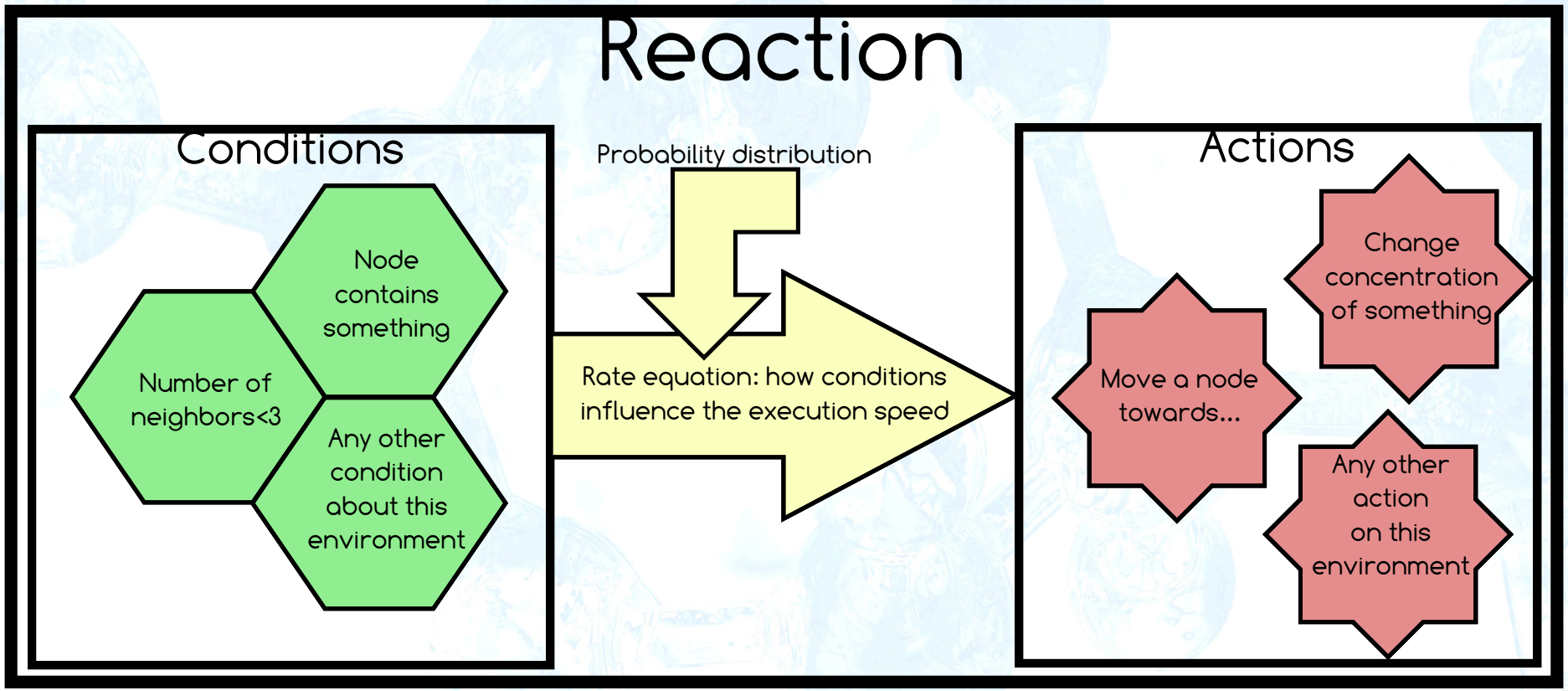


Alchemist world

- The `Environment` contains and links together `Nodes`
- Each `Node` is programmed with a set of `Reactions`
- `Nodes` contain `Molecules`

Extending the concept of reaction

From a set of reactants that combine themselves in a set of products to:



In Alchemist, every event is an occurrence of a Reaction

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Making efficient SSA Algorithms more flexible

Existing SSA algorithms

- Several versions, but same base schema [Gillespie, 1977]:
  1. Select next reaction to execute according to the markovian rates
  2. Execute it
  3. Update the markovian rates which may have changed
- Very efficient versions exist such as [Gibson and Bruck, 2000]

What they miss is what we added

- Reactions can be added and removed during the simulation
- Support for non-exponential time distributed events (e.g. triggers)
- Dependencies among reactions are evaluated considering their "context", speeding up the update phase

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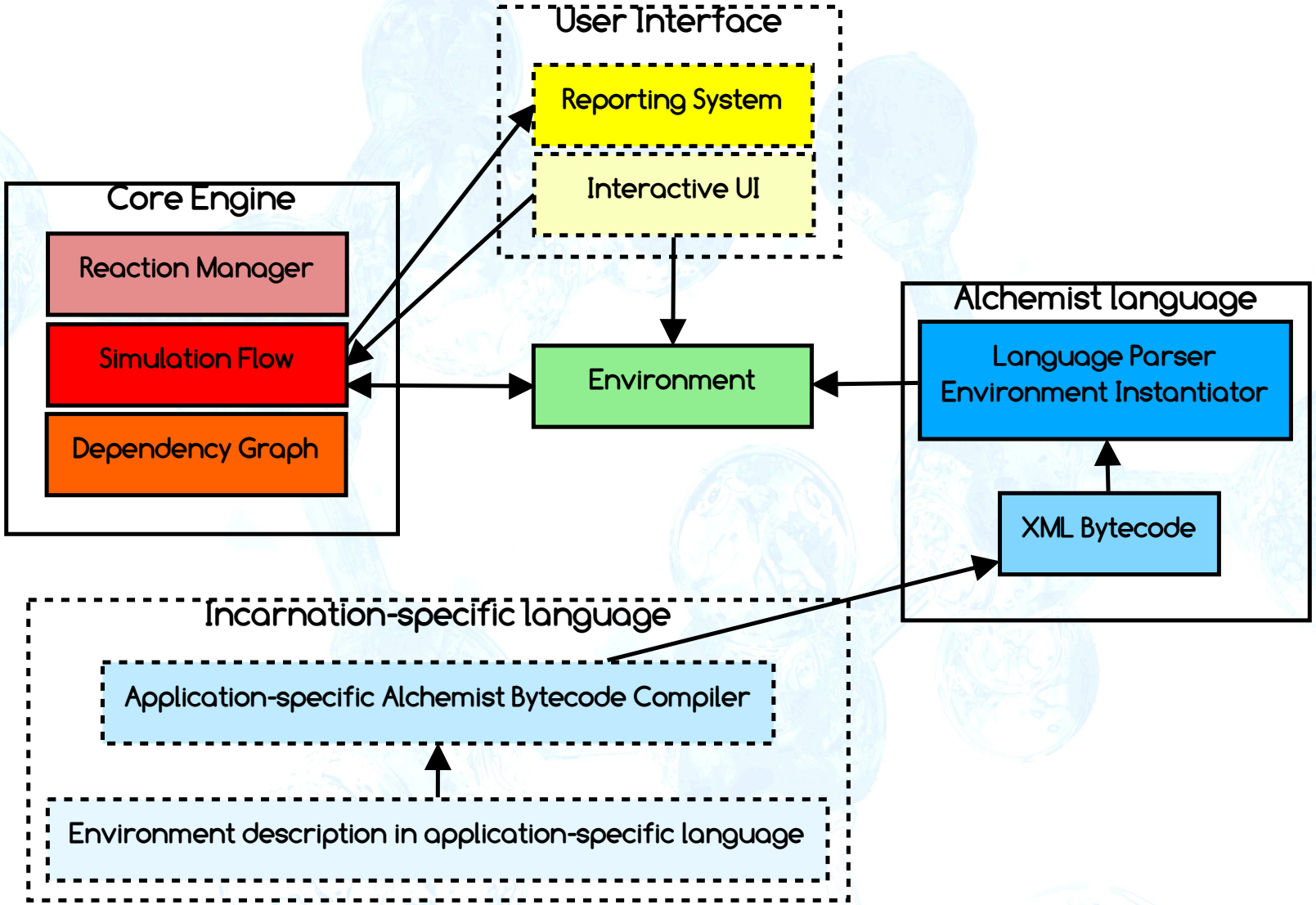
Alchemist is fully modular



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The Model

Taking in mind our *Drosophila* case study...

Goal of the model

- Reproducing the expression pattern of the gap genes at Cl. Cyc. 14 from the fertilised egg
- Validation over acquired images from the FlyEx database [a]

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

Model components

- Whole embryo as a 2D continuous cell
  - Environment composed by fixed nodes filled with morphogens
  - Nuclei/Cells as mobile nodes able to
    1. divide
    2. migrate
    3. interact via diffusing morphogens
    4. host gene expression regulation

The cell compartment

Each cellular process is modeled as a chemical like reaction with rate r

- Cellular division

  condition maximum number of other cells in the neighbourhood
  action create a new cell

- Cellular movement as a repulsion force

  condition position of cells in the neighborhood
  action move in a new position

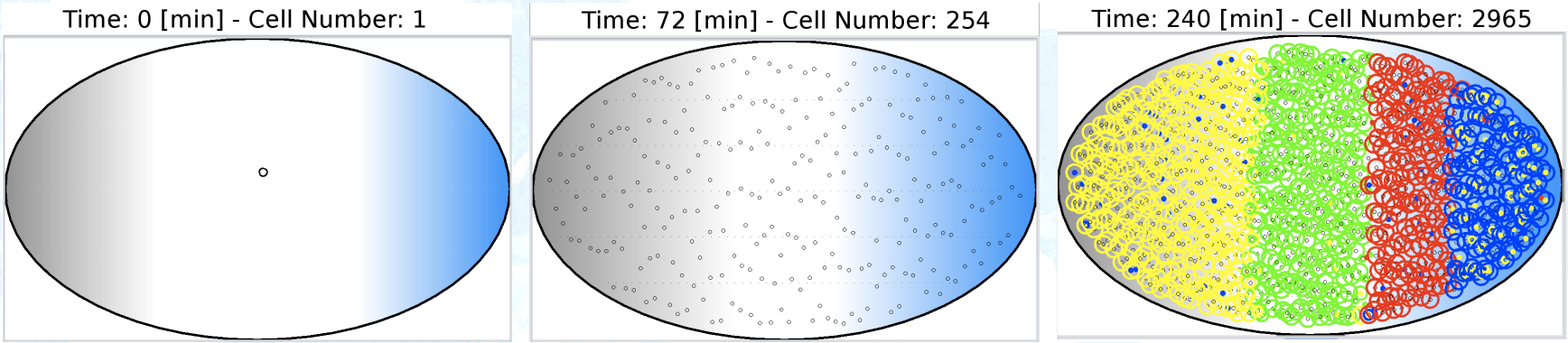
- Morphogen diffusion

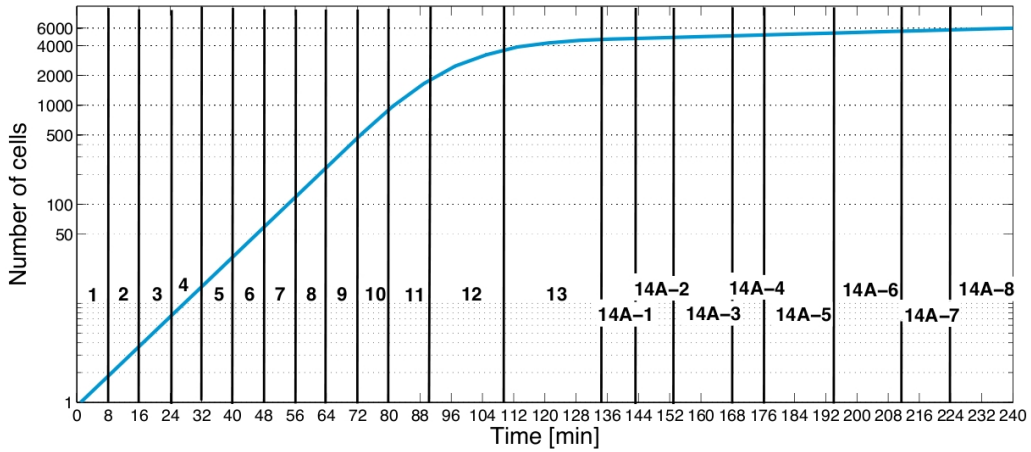
  condition morphogen a in node N
  action morphogen a moved in node $N1 \in neighbourhood(N)$

- Gene a regulation

  condition tr. factor (act) / tr. factor + gene a product ($inhib$)
  action tr. factor + gene a product (act) / tr. factor ($inhib$)

Simulation Results at the Cl. Cyc 14 tc 8: Cell Divisions





Simulation Results at the Cl. Cyc 14 tc 8

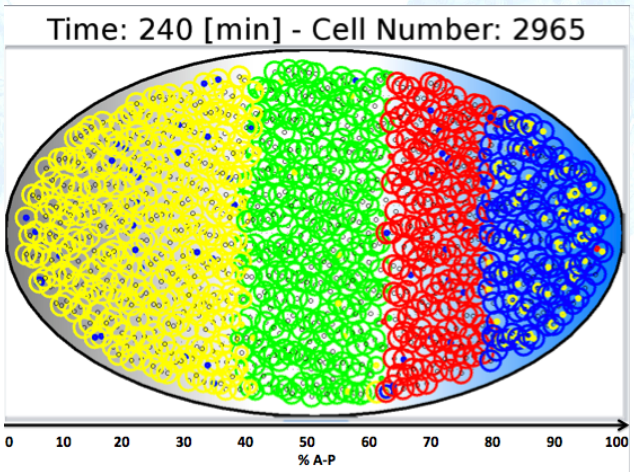


Figure: Gap gene expressions: *hb* (yellow), *kni* (red), *gt* (blue), *Kr* (green)

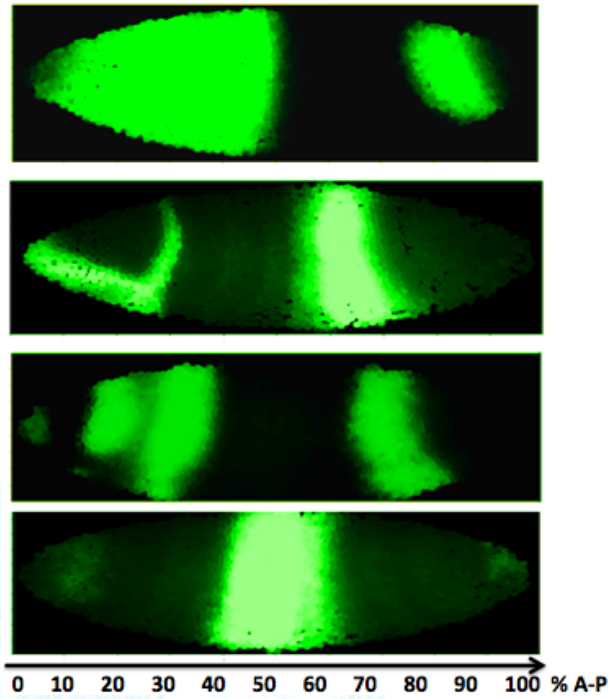


Figure: The experimental data for the expression of (from the top) *hb*, *kni*, *gt*, *Kr* ©Maria Samsonova and John Reinitz

Outline

Already developed...

- Model and framework for capturing mechanisms both at the cellular and molecular level
- Simulation reproducing the main characteristics of *Drosophila* development from one cell to cl. cyc. 14

To do...

- Quantitative comparison against experimental data is needed to validate the model more precisely
- Formation of eve-skipped stripes

Long term goal

- Provide a simulation framework able to support the Developmental Biology studies
  - providing a full-feature computational model and simulator engine
  - application at systems that present nowadays a bigger set of open questions

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