Agent-based and Chemical-inspired Approaches for Multicellular Models

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Alma Mater Studiorum—Università di Bologna a Cesena

Workshop on Multicellular Systems Biology
Laboratorio CINI InfoLife

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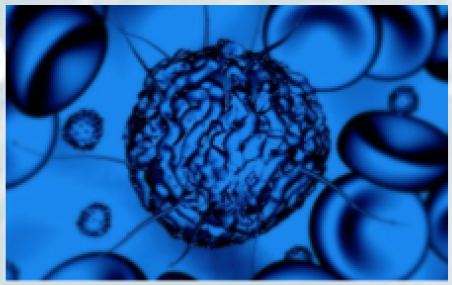
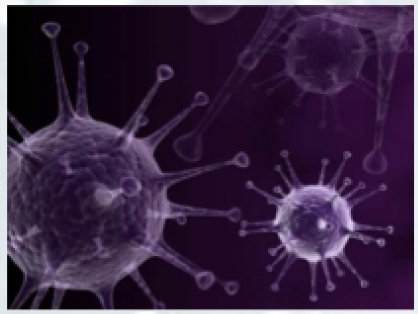
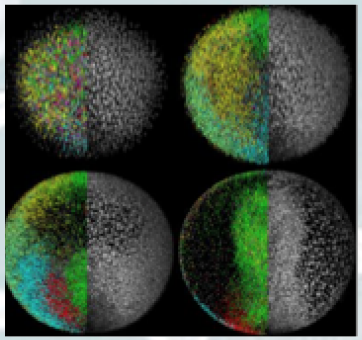
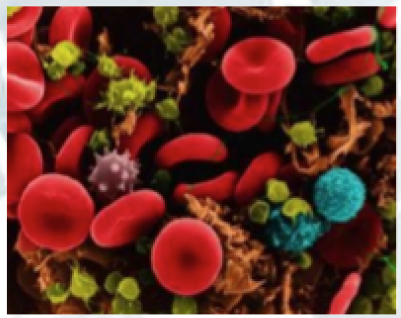
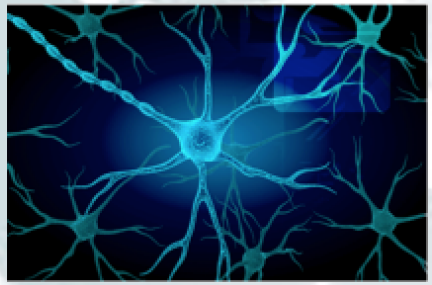
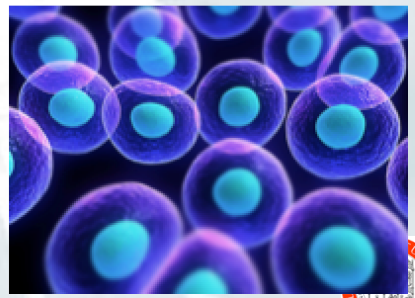
Outline

Outline

Multicellular Systems

Multicellular systems are living organisms that are composed of numerous interacting cells...[1]

- Immune System
- Neural System
- Embryogenesis
- Adult Stem Cells
- Tumor Growth
- ...

[1] www.nature.com

Levels of Biological Organisation[2]

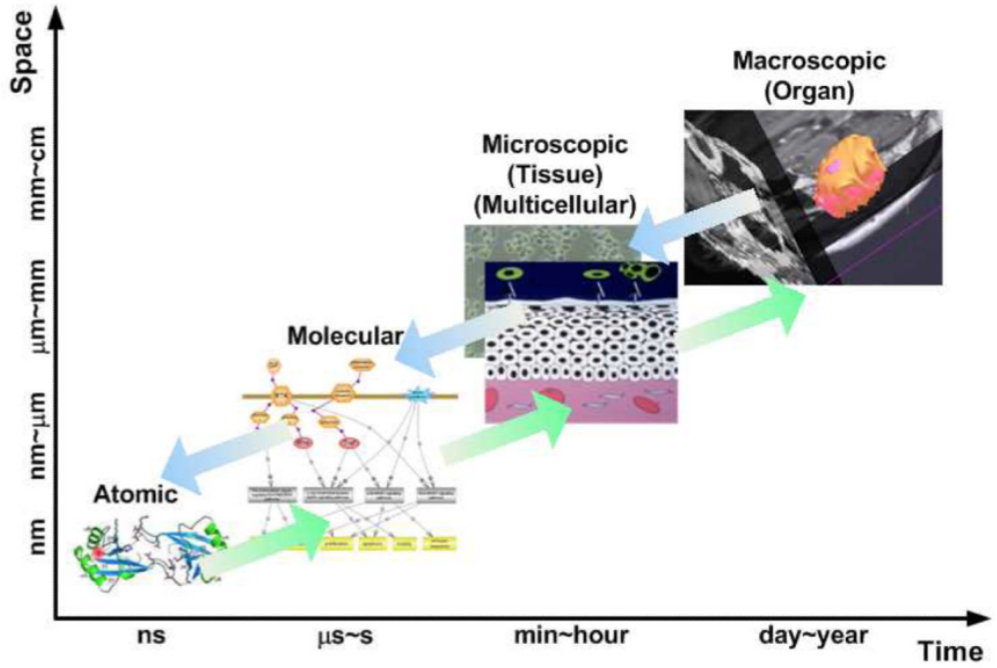


Figure 1.
Schematic illustration of the biological scales of significant relevance for cancer modeling including atomic, molecular, microscopic (tissue/multicellular), and macroscopic (organ) scales. Different scales represent different spatial and temporal ranges; the methods for modeling these distinct scales differ as well. Multiscale cancer modeling requires the establishment of a linkage between these scales.

[2] [DWMC11]

Multicellular Systems

Biological systems are inherently of multi-scale nature

- Global emergent behaviour by mechanisms happening across multiple space and time scales
- Each scale integrates information from strata above and below
  - *upward and downward causation*
- Interactions among components are the building block for the vast majority of mechanisms at each level

Three hierarchical scale for multicellular systems [Set12]

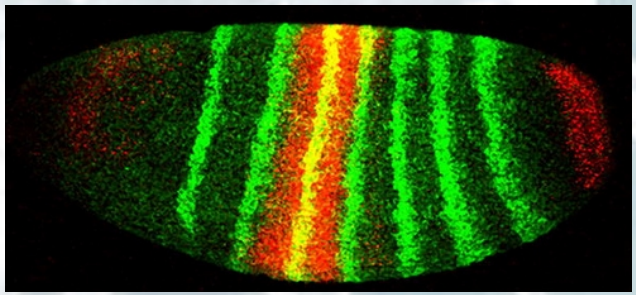
- Molecular, cellular and tissue
  - Intracellular regulatory network controls molecular mechanisms
    - gene expression, receptor activity and protein degradation
  - Individual cell decides on its next developmental step,
    - proliferation, fate determination and motility
  - Cell population acts in concert to develop its anatomy and function

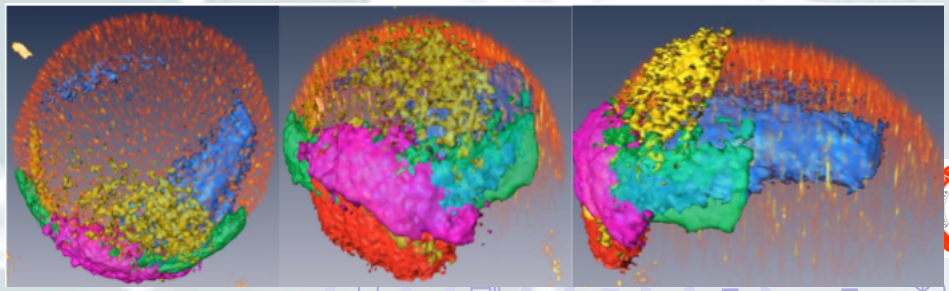
On the Morphogenesis of Living Systems

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





Outline

Multicellular Systems Biology

- Focus of research in systems biology is shifting from intracellular studies towards studies of whole cells or populations of cells

  → Multicellular Systems Biology
- Middle-out approach (nor bottom-up neither top-down)
  - it starts with an intermediate scale (the cell, the basic unit of life) and it is gradually expanded to include both smaller and larger scales
- It requires multiple data
  - molecular data such as gene expression profiles
  - image data such as spatial-temporal growth pattern

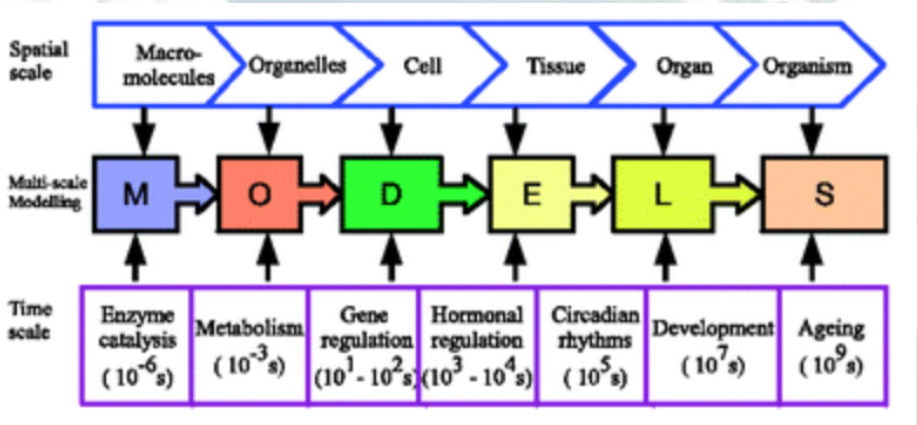


Figure: [DM11]

A Computational Model for Addressing these Scenarios

Computational model requirements

1. Multi-scale
   - for spamming several spatial and temporal scales
   - for reproducing the intra- and inter-scale interactions and integration
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
5. Heterogeneity
   - for modelling individual structures and behaviours of different entities of the biological system

Outline

Looking around...

Recently the trend of research strongly moved towards Multicellular Systems Biology. Many research groups:

DRESDEN — Research group multiscale modelling of multicellular systems[3]

INRIA / IZBI Joint Research Group — Multicellular systems biology[4]

SPECIAL ISSUE — Multiscale Modeling and Simulation in Computational Biology – deadline 30th September 2014 [5]

ESMTB — Multi-scale modeling platforms in multicellular systems biology[6], symposium at the European Conference on Mathematical and Theoretical Biology

[3] http://tu-dresden.de/

[4] http://ms.izbi.uni-leipzig.de

[5] http://www.mdpi.com/journal/computation/special_issues/multiscale-model

[6] http://www.math.chalmers.se/~torbjrn/ECMTB/Minisymposium/no3.pdf

Brief Survey on Multi-scale Methods

The interdependent nature of multicellular processes often makes it difficult to apply standard mathematical techniques to separate out the scales, uncouple the physical processes or average over contributions from discrete components.[CO13]

- Over the past decades several multi-scale methods developed [DM11]
  - Quasi continuum method, Hybrid quantum mechanics-molecular mechanics methods, Equation free multi-scale methods, Coarse projective integration, Gap-tooth scheme, Patch dynamic, Heterogeneus multi-scale method, Agent-based modelling, complex automata
- Some of these applied in biology

Brief Survey on Multi-scale Frameworks

Chaste — An open source C++ library for computational physiology and biology

CompuCell3D — Modelling tissue formation

EPISIM Platform — Graphical multi-scale modeling and simulation of multicellular systems

CellSys — Modular software for physics-based tissue modelling in 3D

VirtualLeaf — Towards an off-lattice Cellular Potts model

Biocellion — Accelerating multicellular biological simulation

Morpheus — User-friendly modeling of multicellular systems

Brief Survey on Related Work in Modelling Morphogenesis

Main modelling attempts

[GJK+04] — 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

[CHC+05] — combines discrete methods based on cellular-automata and continuous models based on reaction-diffusion equation

- $\surd$ interacting compartments (agents), protein diffusion
- x realistic model for cell internal behaviour

[LIDP10] — stochastic model of reaction-diffusion systems

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

...

Outline

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The coordination model approach

Base idea

- Coordination models explicitly deal with interaction in comp. sys.
- Simulation frameworks based on coordination are well-suited for the simulation of a complex system
  - as a special sort of multiagent-based simulation (MABS)
- *Nature-inspired coordination tuple-based models* are the most promising ones for the simulation of biological systems [Omi13]

Goals

- Experimenting the expressive power of coordination models in the simulation of molecular and cellular systems
- Empowering the environment as a first-class abstraction by the notion of *tuple spaces*
  - tuple-spaces are the coordination abstractions as shared distributed spaces, used by agents to synchronise, cooperate, and coordinate

Biochemical Tuple spaces for Self-Organising Coordination

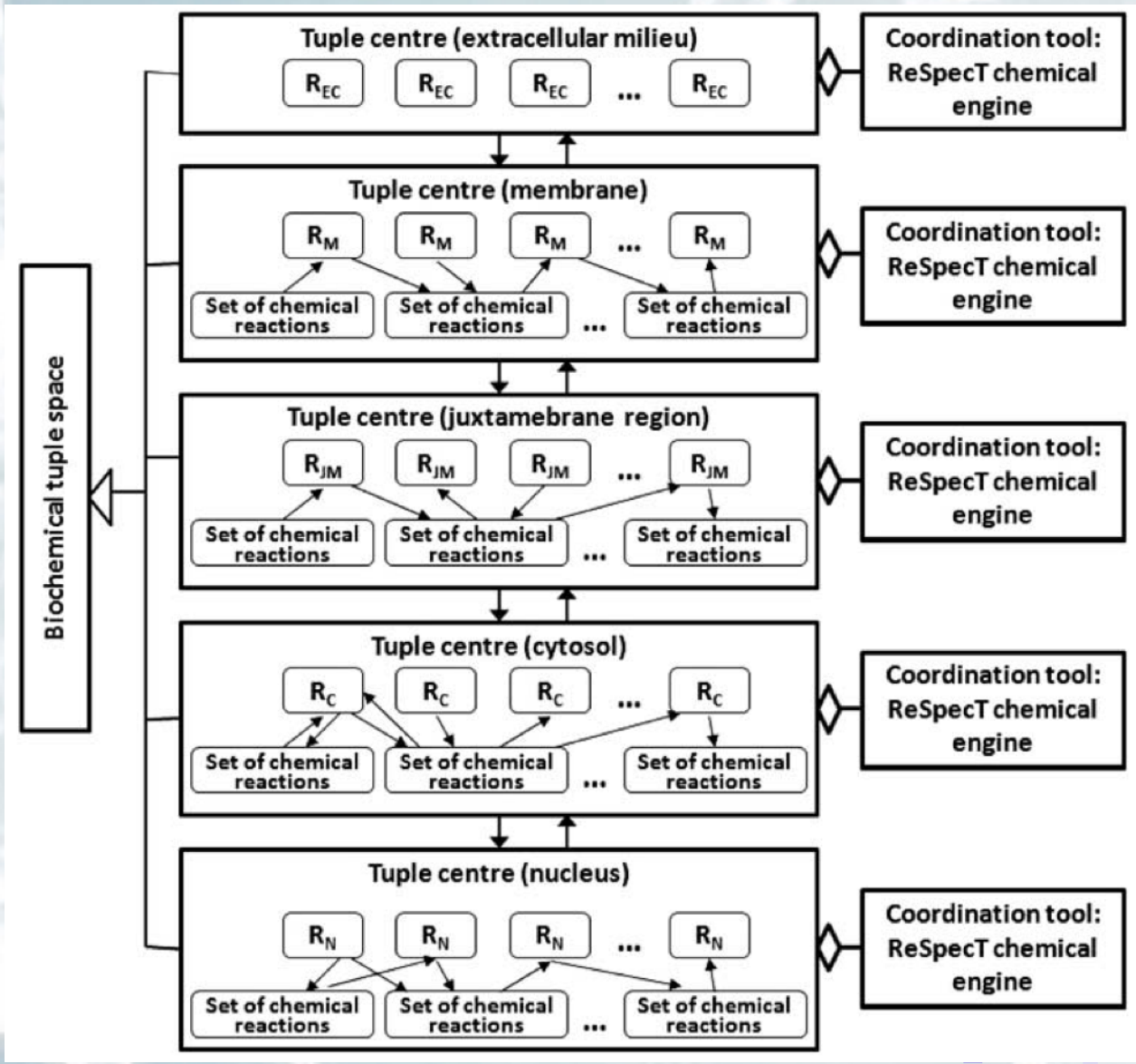
Computational model

- Based on BTS-SOC [VC09]
  - tuple space working as a compartment where biochemical reactions take place as coordination laws
  - which are actually stochastic
  - chemical reactants are represented as tuples
  - the environment has a structure – requiring a notion of locality, and allowing components of any sort to move through a topology

Simulation infrastructure

- Biochemical tuple spaces are built as ReSpecT tuple centres
- Simulations run upon a TuCSoN distributed coordination middleware
- Tuples are logic-based tuples
- Biochemical laws are implemented as ReSpecT specification tuples

A First Modelling Attempt [GPOS13]



Outline

Ad-hoc Framework to Tackle Scenarios of Dev. Bio.

MS-BioNet

- 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

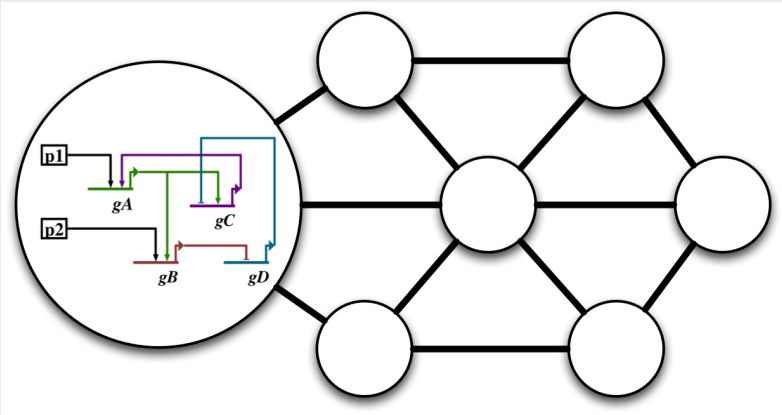
A module for parameter tuning

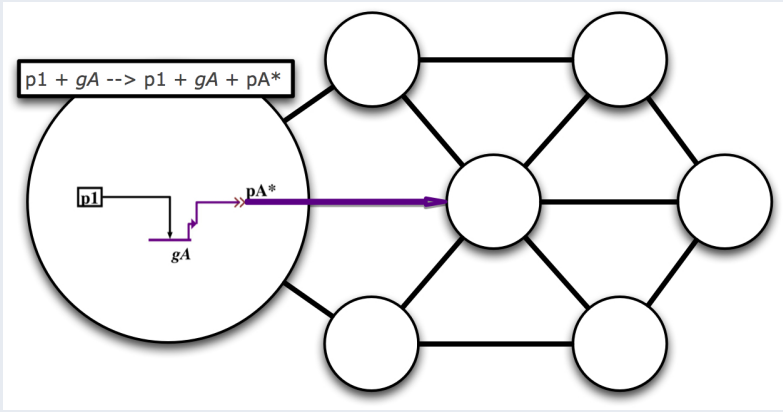
- Parameter tuning as an optimisation problem
  - searching the solution with metaheuristics

MS-BioNet

MS-BioNet's Conceptual levels [MV10]

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**: implementation of Gillespie SSA [Gil77]
   - reproducing the exact chemical evolution/diffusion of substances

Outline

Alchemist simulation approach

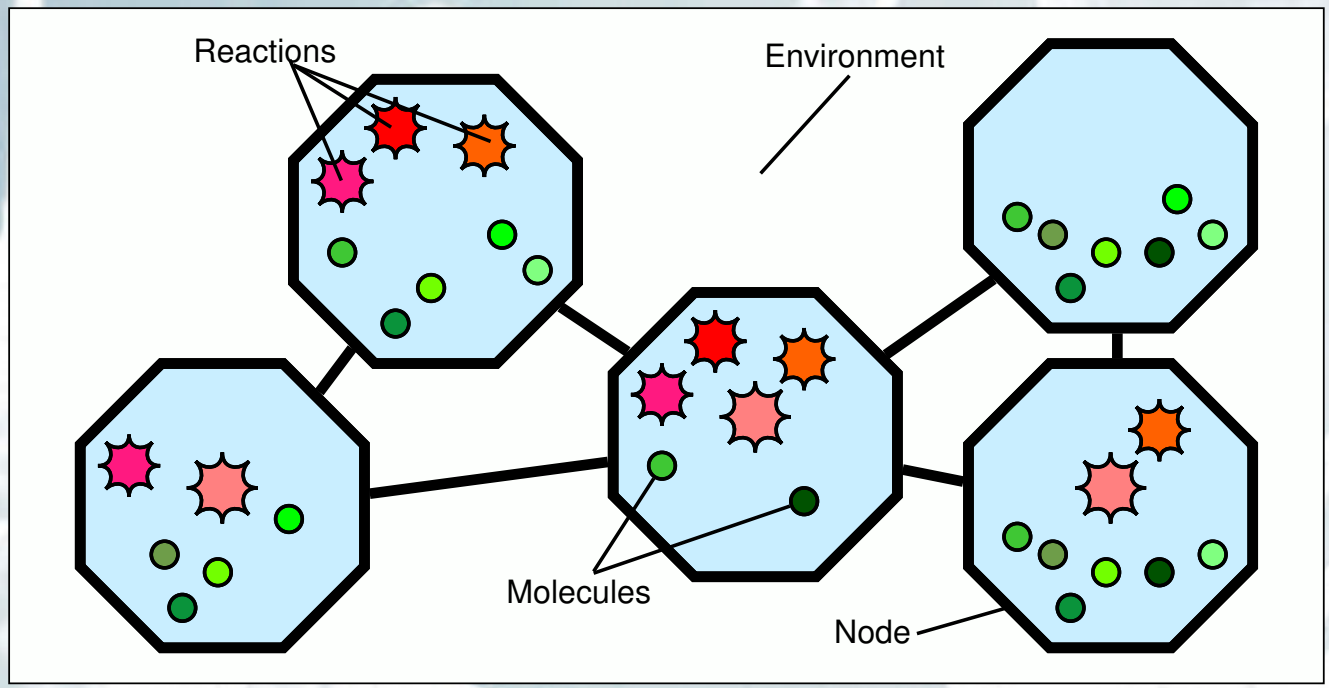
Base idea

- 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

Enriching the environment description

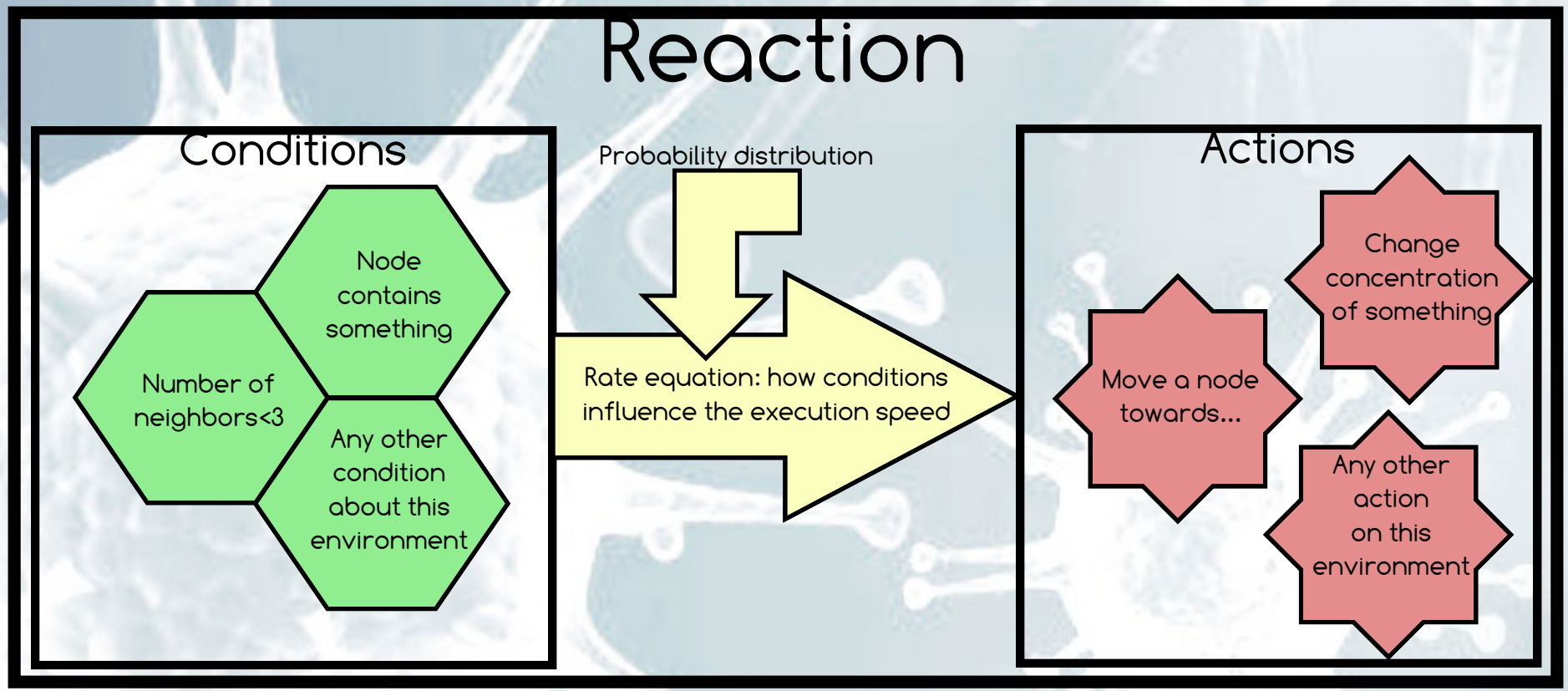


Alchemist world

- 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

Dynamic Engine: Making efficient SSA Algorithms more flexible

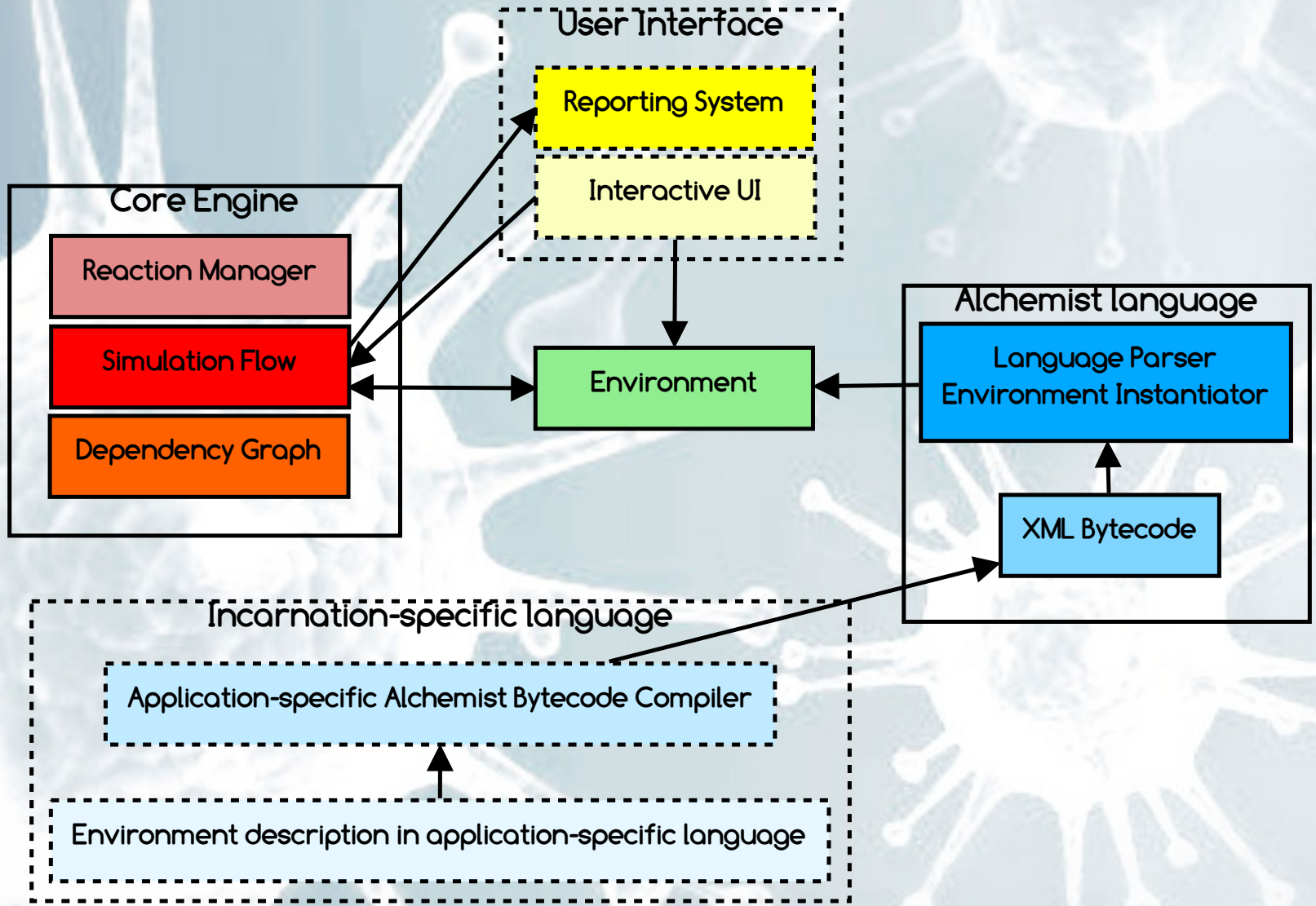
Existing SSA algorithms

- Several versions, but same base schema [Gil77]:
  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 [GB00]

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

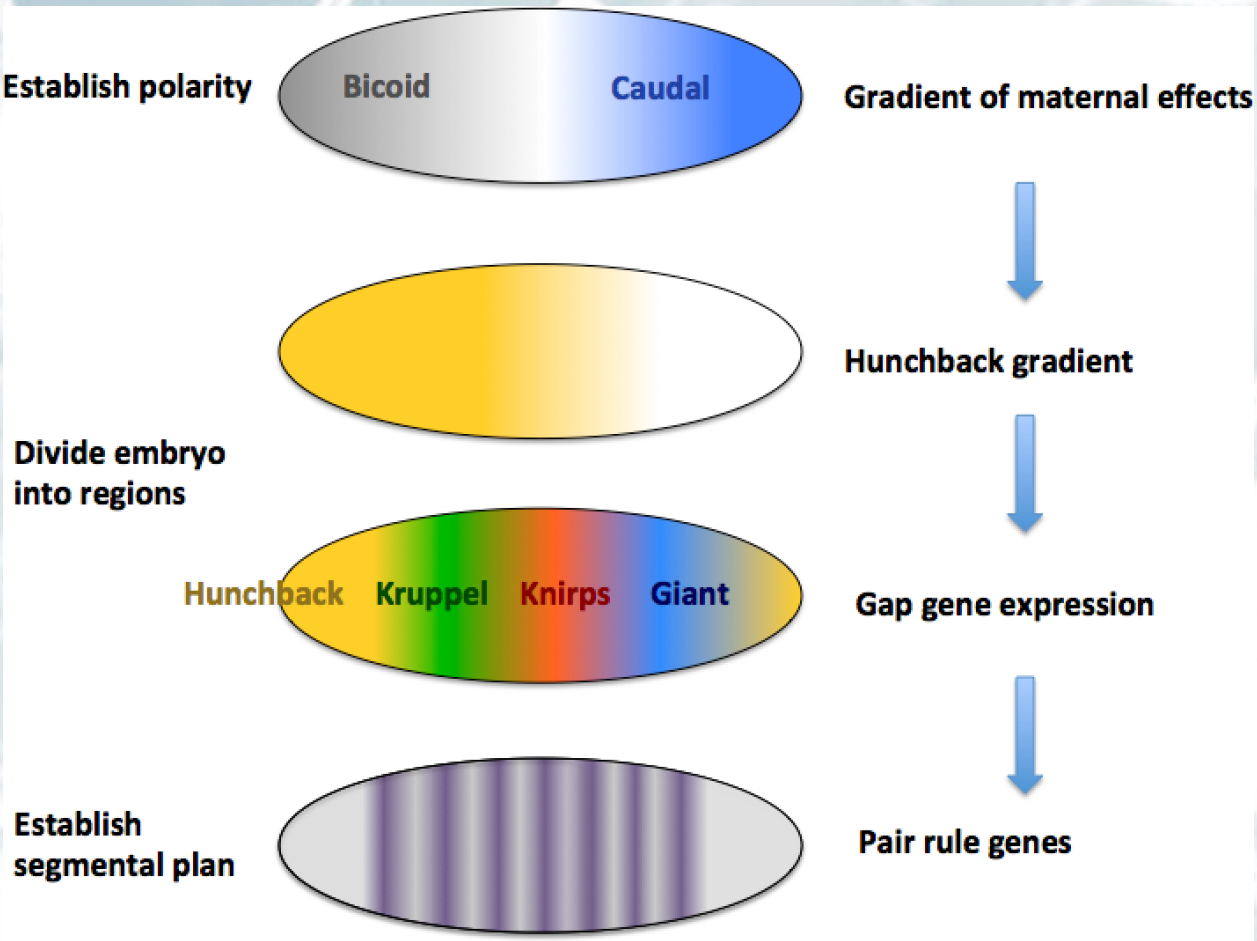
Alchemist Architecture: it is fully modular



Outline

On the Drosophila Melanogaster Morphogenesis

- Overview until Cleavage Cycle 14 temporal class 8



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

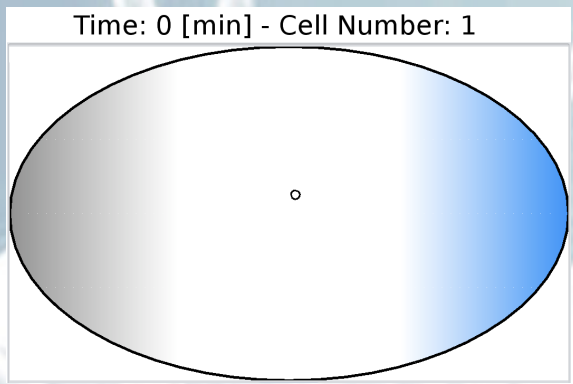
  condition morphogen a in node N
  action morphogen a moved in node $N1 \in neighbourhood(N)$

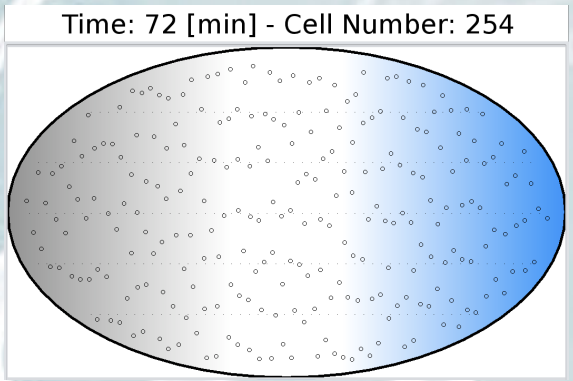
- Gene a regulation

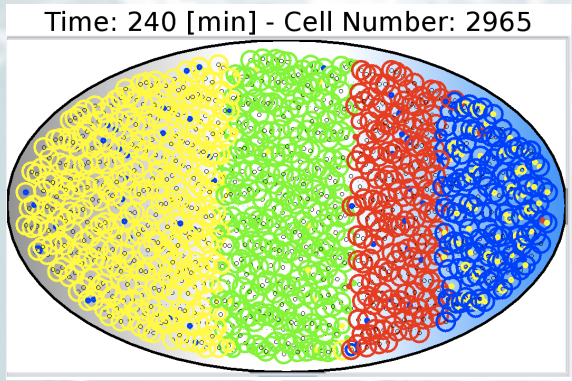
  condition tr. factor (act) / tr. factor + gene a product ($inhib$)
  action tr. factor + gene a product (act) / tr. factor ($inhib$)

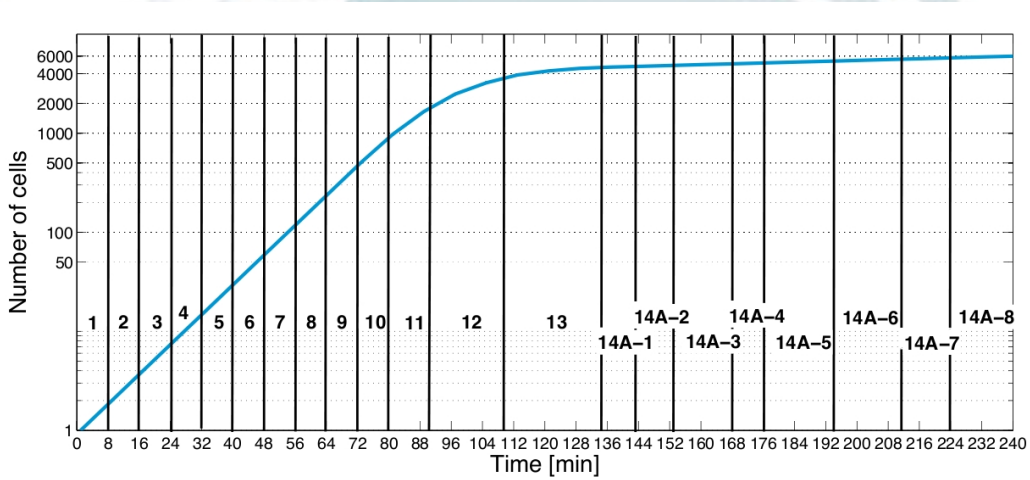
Simulation Results at the CI. Cyc 14 tc 8: Cell Divisions

- Simulations are conducted over the ALCHEMIST platform









Qualitative Simulation Results at the CI. Cyc 14 tc 8

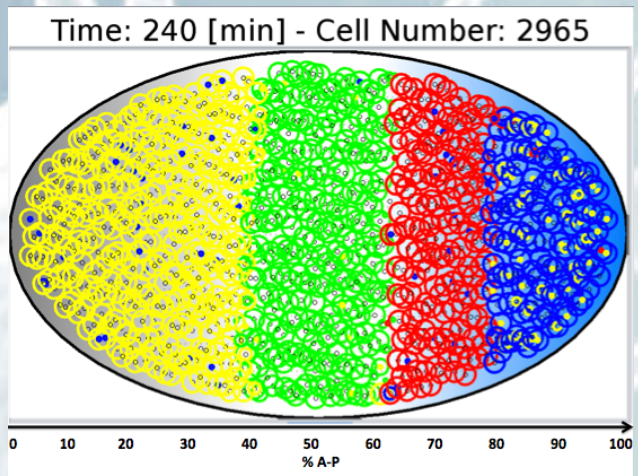


Figure: Gap gene expressions: *hb* (yellow), *kni* (red), *gt* (blue), *Kr* (green)

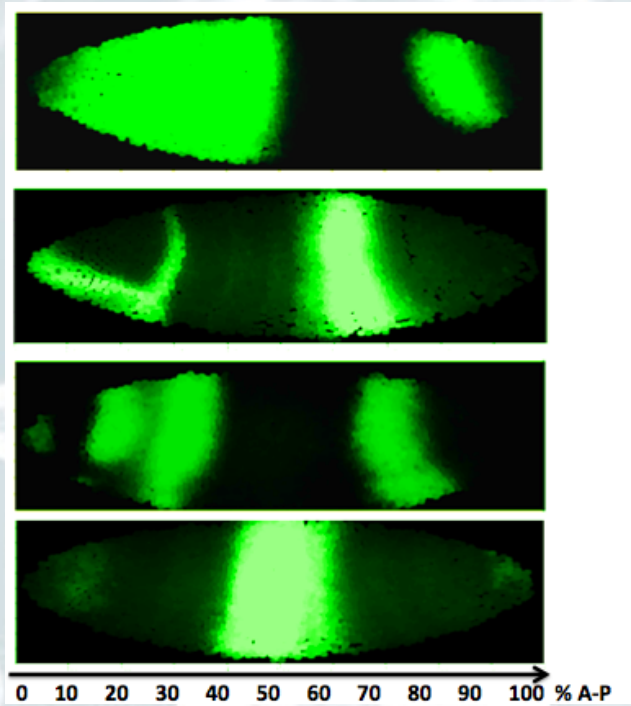
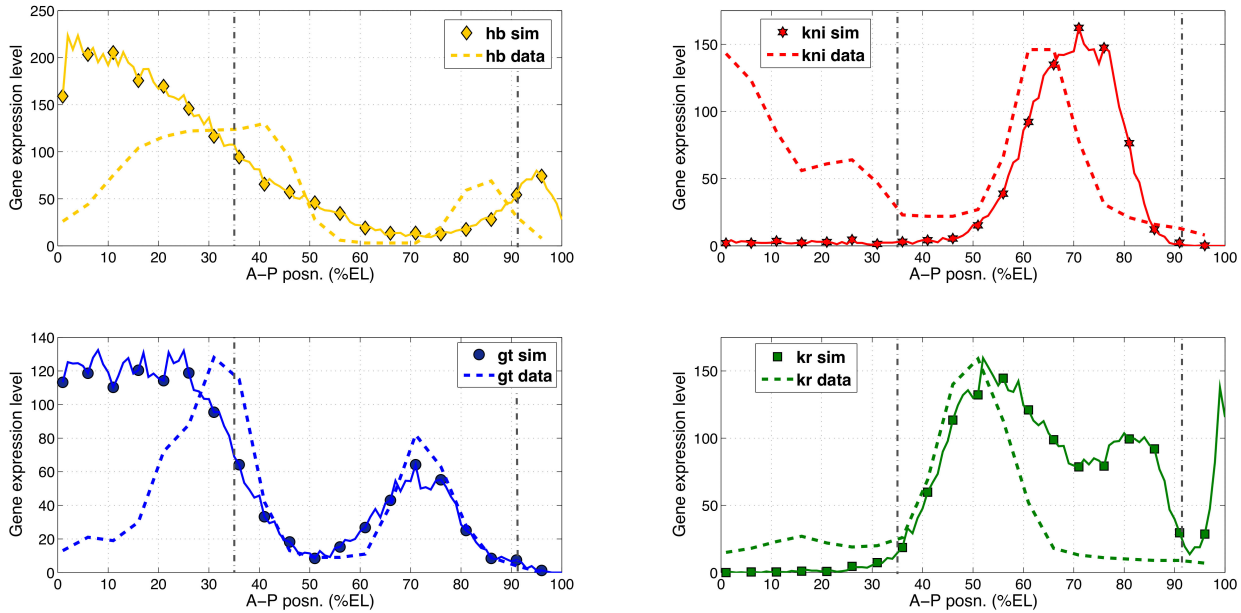


Figure: The experimental data for the expression of (from the top) *hb*, *kni*, *gt*, *Kr* ©Maria Samsonova and John Reinitz

Quantitative Simulation Results

- Simulations are conducted over the MS-BioNET platform

Results at the CI. Cyc 14 tc 8



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Projects we are/were in ...

1. SAPERE – Self-aware Pervasive Service Ecosystems
   - 2010–2013
   - EU Seventh Framework Programme (7FP), FP7-ICT-2009.8.5: Self-awareness in Autonomic Systems
   - Official Site: `http://www.sapere-project.eu/`
2. GALILEO – Ricostruzione e modellazione delle dinamiche molecolari e genetiche alla base della precoce regionalizzazione degli embrioni di zebrafish e di seaurchin
   - 2009–2010
   - Funding Body: Università Italo-Francese – Project Galileo 2008/2009
   - Official Site: `http://apice.unibo.it/xwiki/bin/view/Projects/GalileoNETSCALE`

Our Products

1. ALCHEMIST
   - Alchemist is now open source, GPL licensed, and the whole code base is publicly accessible on bitbucket
   - Official Site: `alchemist.apice.unibo.it`
2. MS-BioNET – MultiScale-Biochemical NETwork
   - Official Site: `ms-bionet.apice.unibo.it`
3. TuCSoN – Tuple Centres Spread over the Network
   - Official Site: `tucson.apice.unibo.it`

Outline

Objective of our research in Developmental Biology

- Provide an adequate simulation framework
  - full-feature computational model and simulator engine
  - virtual embryo
  - application at systems that present nowadays open questions
    - obtain a better understanding of some features of the system
    - verify hypothesis and theories underlying the model that try to explain the system behaviour
    - make prediction to be tested by in-vivo experiments
    - ask what if questions about real system

H2020 calls – PERSONALISING HEALTH AND CARE

- PHC-02-2015: Understanding disease: systems medicine
- PHC-28-2015: Self management of health and disease and decision support systems based on predictive computer modelling used by the patient him or herself
- PHC-30-2015: Digital representation of health data to improve disease diagnosis and treatment

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