Modelling and simulation of Complex Biological Systems

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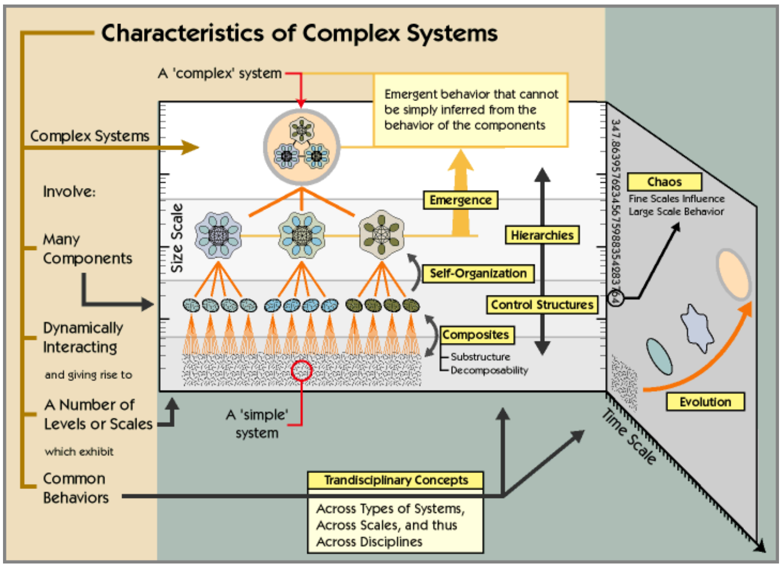
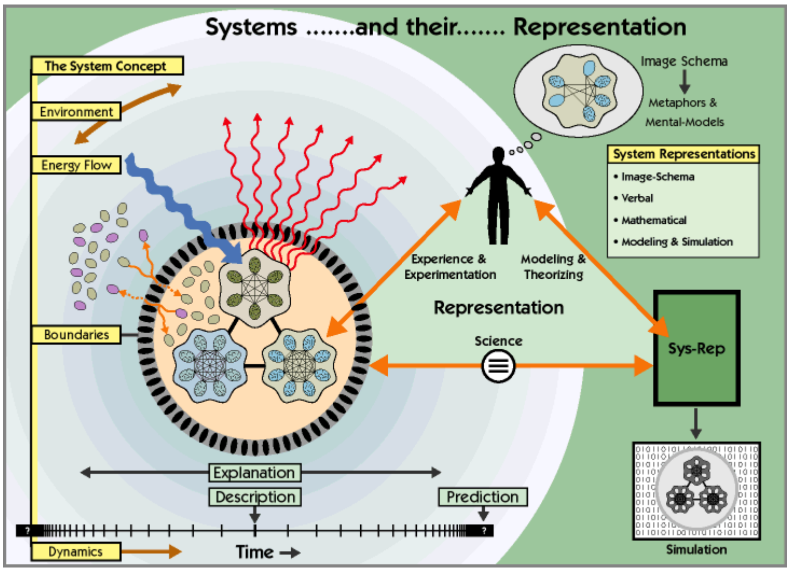
What is a complex system?

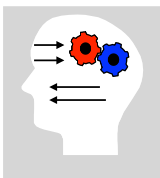


System… and their… Representation

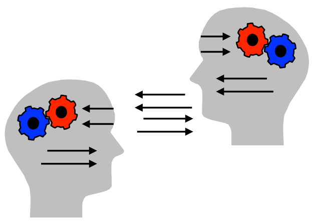


Distributed Artificial Intelligence (DAI)

DAI is concerned with systems in which artificial agents act collectively and in a decentralized way in order to perform a task



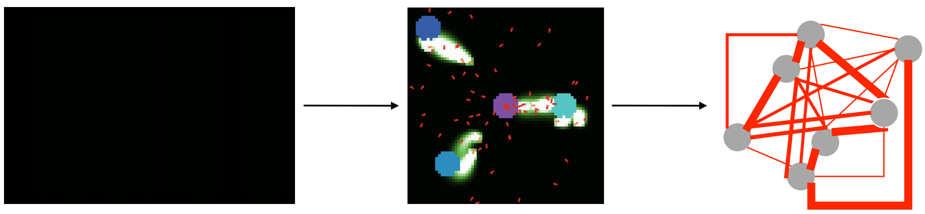
AI metaphor : the isolated thinker



DAI metaphor: the community of thinkers

Multiagent Systems (MAS): Problematics

- Two main objectives [Ferber 95]
  - "the theoretical and experimental analysis of self-organization processes that arise when several autonomous entities interact"
  - "the design of distributed artefacts capable of performing complex tasks through cooperation and interaction"
- Two complementary approaches
  - model and simulate natural phenomena; build self-organization models
  - design complex computerized systems based on the concepts of ***agent***, ***interaction*** and ***organisation***



What is an agent?

[Wooldridge et Jennings 1995]

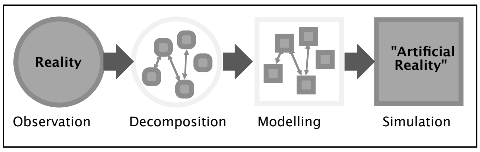
- Weak agency

  hardware or software-based computer system that enjoys the following properties:

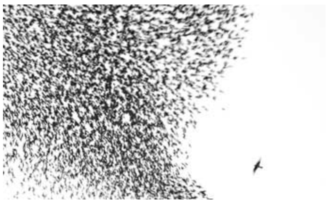
  - ***autonomy***: agents operate without the direct intervention of humans or others, and have some kind of control over their actions and internal state
  - ***social ability***: agents interact with other agents (and possibly humans) via some kind of *agent-communication language*
  - ***reactivity***: agents perceive their environment, (which may be the physical world, a user via a graphical user interface, a collection of other agents , the Internet, or perhaps all of these combined), and respond in a timely fashion to changes that occur in it;
  - ***pro-activeness***: agents do not simply act in response to their environment, they are able to exhibit goal-directed behavior by *taking the initiative*

Agent-based simulation: base principles

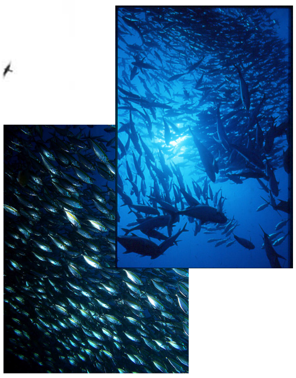
- Create an artificial world, composed of interacting agents
- Three components
  - the agents
  - the rules of behaviour
  - the environment
- The agents act in the environment and modify it
- One can observe the result of their interactions as if it was occurring in a laboratory (virtual lab)



Example – gregarious behaviours



in birds



in fishes

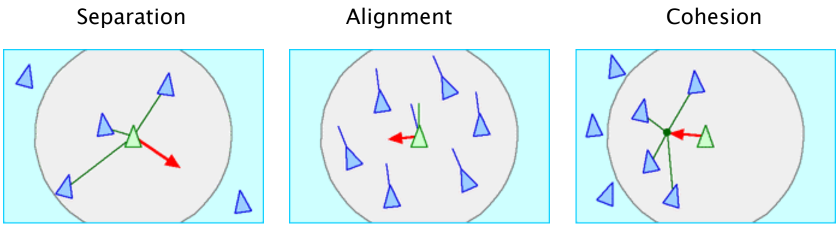
in mammals

Gregarious behaviours

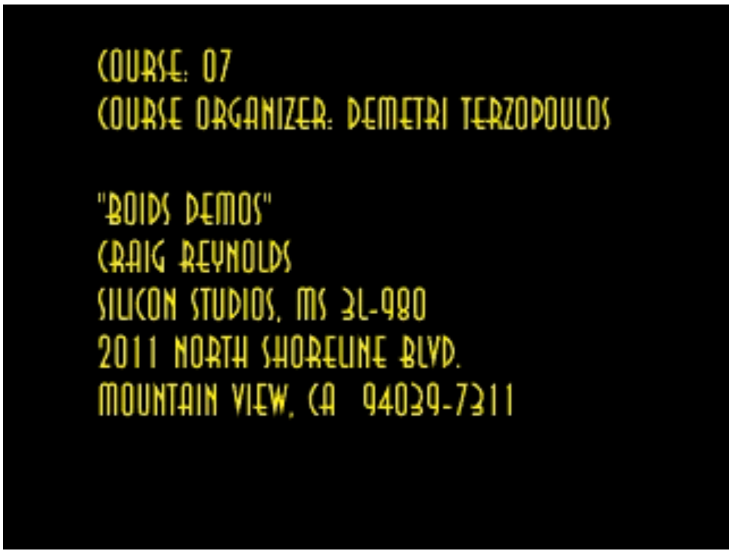
Gregarious behaviours

Example – the flocking model [C. Reynolds]

- model of group displacement in social animals (birds, fishes, social mammals, etc.)
  - 3D representation
  - model of behaviour based on 3 elementary behaviours that describe the maneuvers to achieve, depending on the local surroundings



C. Reynolds – The boids demo



Application to animation (1/3)

- 1987: **Stanley and Stella in: Breaking the Ice**, (short) Director: Larry Malone, Producer: Symbolics, Inc.
- 1988: **Behave**, (short) Produced and directed by Rebecca Allen
- 1989: **The Little Death**, (short) Director: Matt Elson, Producer: Symbolics, Inc.
- 1992: **Batman Returns**, (feature) Director: Tim Burton, Producer: Warner Brothers.
- 1993: **Cliffhanger**, (feature) Director: Renny Harlin, Producer: Carolco Pictures.
- 1994: **The Lion King**, (feature) Director: Allers / Minkoff, Producer: Disney.
- 1996: **From Dusk Till Dawn**, (feature) Director: Robert Rodriguez, Producer: Miramax.
- 1996: **The Hunchback of Notre Dame**, (feature) Director: Trousdale / Wise, Producer: Disney.
- etc.

Application to animation (2/3)

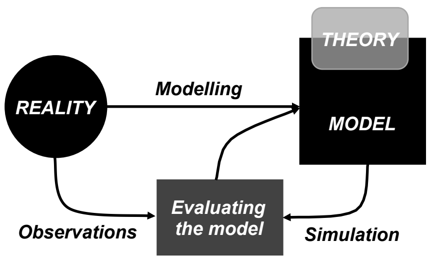
The Lion King (© Disney)

Application to animation (3/3)

MASSIVE (Multiple Agent Simulation System in Virtual Environment)

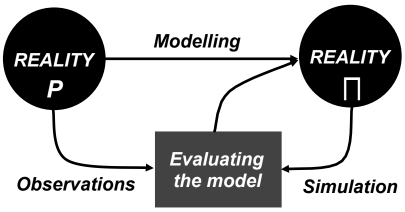
Simulation (1)

- Simulate: reproduce a given phenomenon in order to
  - Test hypothesises to explain the phenomenon
  - Predict the evolution of the phenomenon
- Any simulation is based on a pre-existing theory

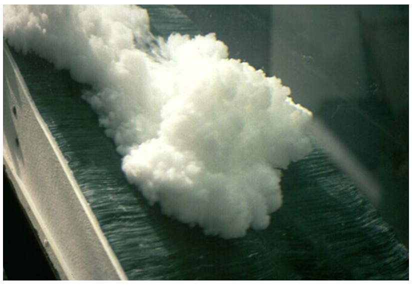


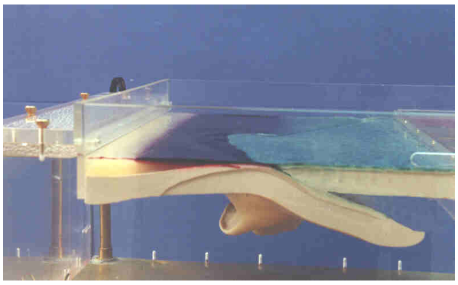
Simulation (2)

- Analog simulation
  - Aircraft models in wind tunnel
  - Electrical homeostatic models
  - Climate models



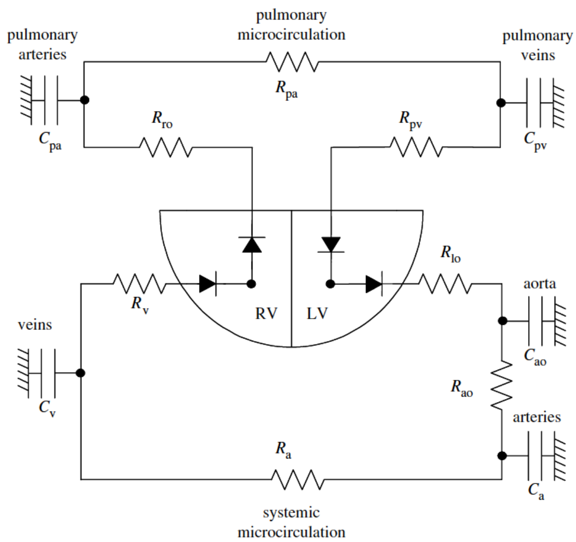
Examples of analog models (1/2)





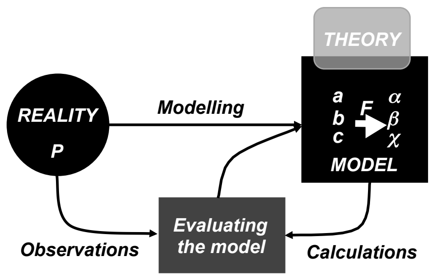
Examples of analog models (2/2)

Model of blood circulation [Shim et al. Phil. Trans. R. Soc. A, 2006]



Simulation (3)

- Numeric simulation
  - mathematical theories
  - introduction of stochastic phenomena (Monte-Carlo simulation)



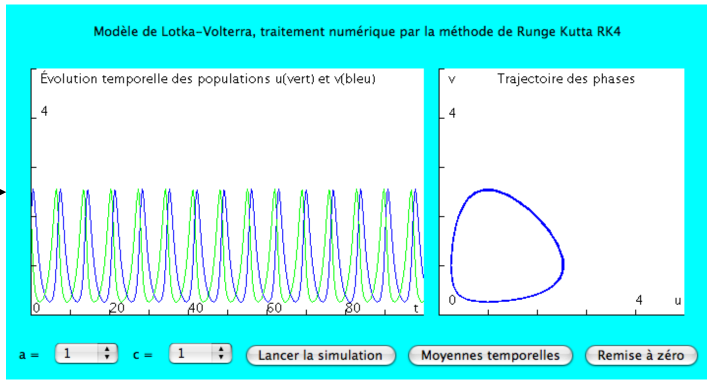
  - Example: Lotka-Volterra (1926)

$$\begin{cases} N(0) = N_0 \quad P(0) = P_0 \\ \frac{dN}{dt} = aN - bNP \\ \frac{dP}{dt} = -cP + dNP \end{cases}$$

N an P : preys and predators populations
a : fertility rate of preys
b : predation coefficient
c : efficiency with which predators convert food into progeny
d : mortality of predators

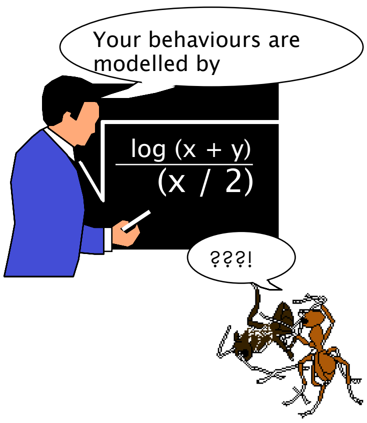
Lotka and Volterra predation model

$$\begin{cases} N(0) = N_0 \quad P(0) = P_0 \\ \dfrac{dN}{dt} = aN - bNP \\ \dfrac{dP}{dt} = -cP + dNP \end{cases}$$



Limits of numeric simulations

- Equational model with a large number of parameters, different theories used in biology, sociology, economy, etc.
- Difficulty of the micro/macro transition, difficulty to represent different levels
- No representation of the behaviours but only their overall result (number of offspring, amount of food, etc.)
- Doesn't account for the emergence of spatial and time structures (e.g. fish schools, columns of ants, etc.)



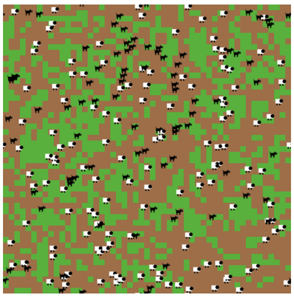
From numeric to agent-based simulation

- Desired properties
  - Model of **local** actions et interaction
  - Model of **space**
  - **Discrete** modelling

[Lotka-Volterra 1926]

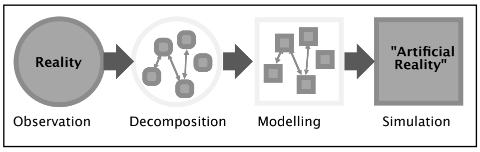
$$\begin{cases} N(0) = N_0 \quad P(0) = P_0 \\ \frac{dN}{dt} = aN - bNP \\ \frac{dP}{dt} = -cP + dNP \end{cases} \longrightarrow$$

[Wilensky 1997]



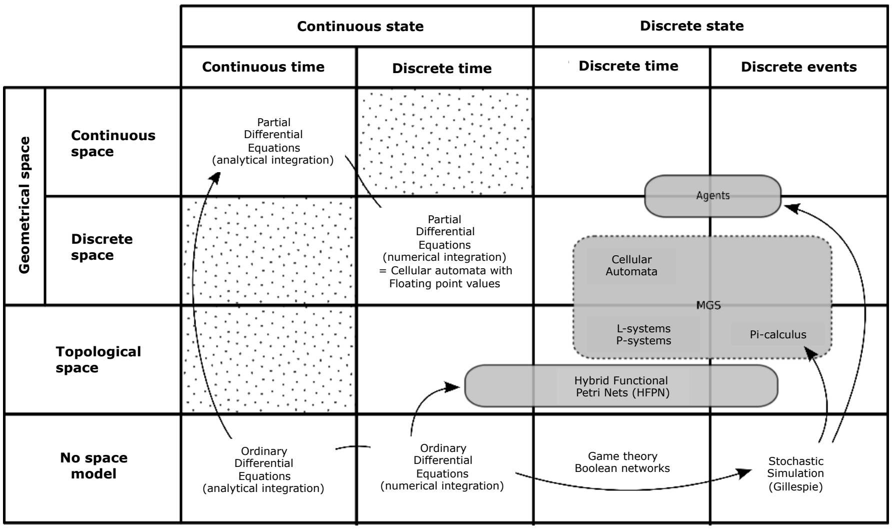
Agent-based simulation: base principles

- Create an artificial world, composed of interacting agents



- Three components
  - the agents
  - the rules of behaviour
  - the environment
- The agents act in the environment and modify it
- One can observe the result of their interactions as if it was occurring in a laboratory (virtual lab)

A tentative typology of simulation paradigms

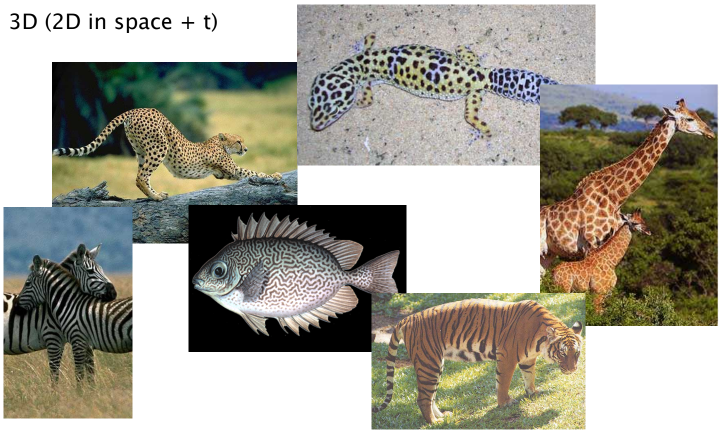


Why space does matter?

- Because some systems are the product of a morphogenetic process
  - in 2D (1D in space + t)

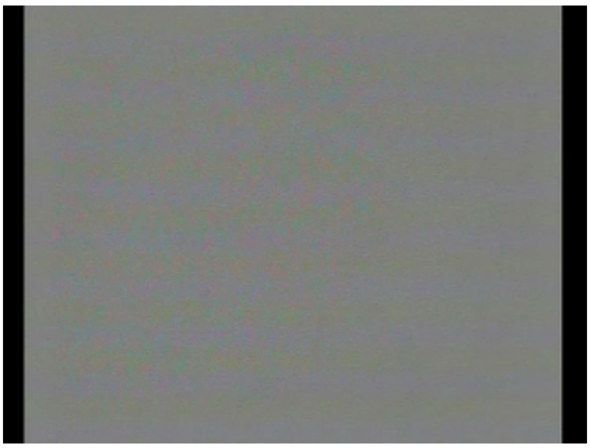
Why space does matter?

- Because some systems are the product of a morphogenetic process
  - in 3D (2D in space + t)



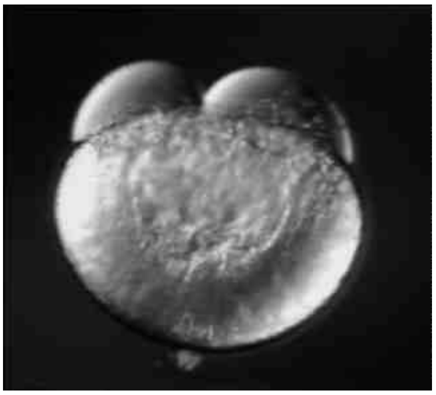
Why space does matter?

- Because some systems are the product of a morphogenetic process
  - in 3D



Why space does matter?

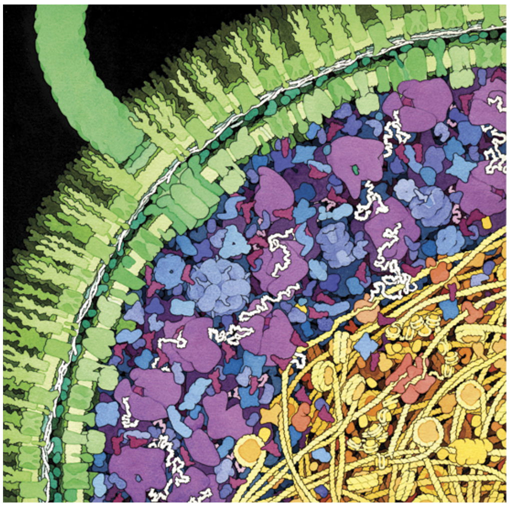
- Because some systems are the product of a morphogenetic process
  - in 4D (3D in space + t)



[R. Karlstrom & D. Dane, Development 123:461, 1996]

Why space does matter?

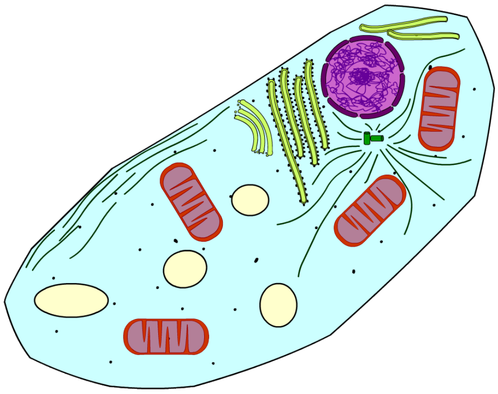
- Because cells are crowded with molecules!



[D. Goodsell]

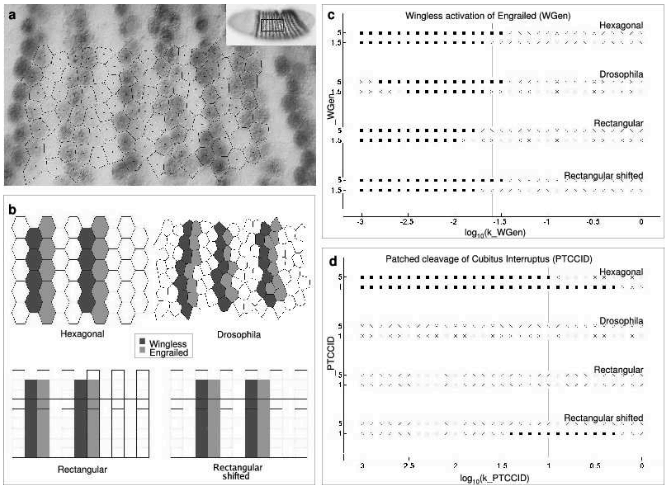
Why space does matter?

- Because some phenomena occur in interconnected compartments



Why space does matter?

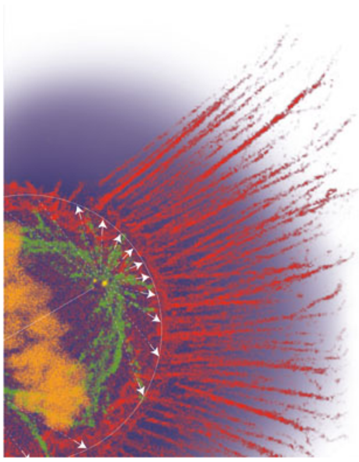
- Because the topology on which the reactions apply may matter



[Mallavarapu et al. 2007]

Why space does matter?

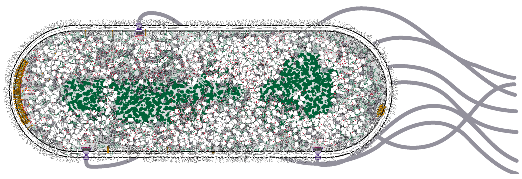
- Because cells are polarized



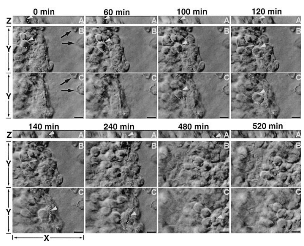
[M. Bornens]

Why space does matter?

- Because some behaviours or structures are oriented by the environment
  - Chemotaxis
  - Wound healing



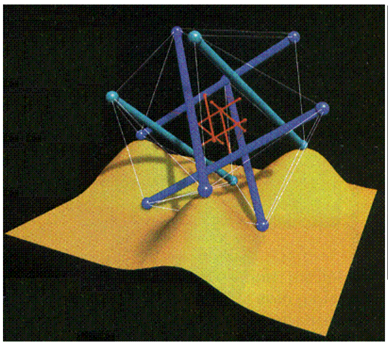
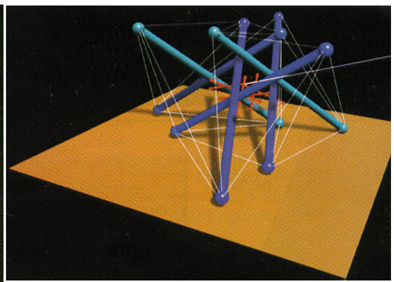
[D. Bray]



[M. Zhao]

Why space does matter?

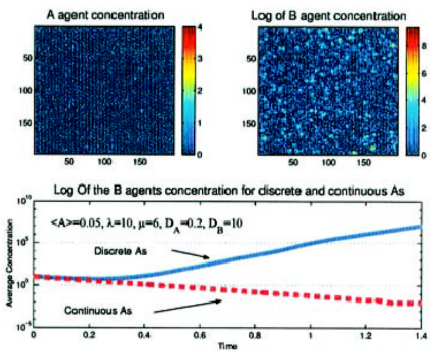
- Because the behaviour of cells is related to their dynamical mechanical structure (tensegrity)

[D. Ingber]

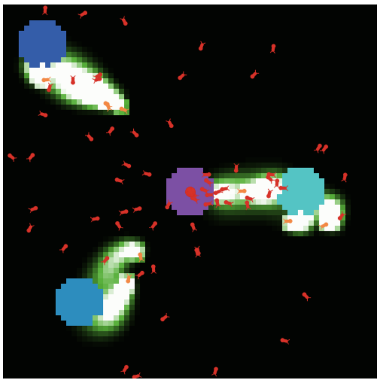
Why space does matter?

- Because compartments are heterogeneous
  - localized interactions vs. global computation can lead to qualitatively different dynamics
  - "In conditions in which the continuum equations predict the population extinction, the individuals self-organize in spatio-temporally localized adaptive patches, which ensure their survival and development." [Shnerb et al., PNAS 2000]



Why space does matter?

- Because some phenomena are the result of a stigmergic process
  - P.-P. Grassé « Stimulation of ant workers by the work already done »
  - collective organisation principle thanks to the local modification of and perception of the environment of the individuals



Cellular Automata (CA): a first example

- Conway's *Game of Life* (70)
  - the automaton is a regular grid of square cells that may be in two states: *on* and *off*
  - the evolution of a cell is determined by its own state and by the number of cells in the *on* state amongst the 8 adjacent cells N_v
    - a cell in the *on* state "dies"
      - if $N_v < 2$ (isolation)
      - or $N_v > 3$ (overcrowding)
    - a cell in the *off* state becomes "alive"
      - if $N_v = 3$ (reproduction)

Impossible d'afficher l'image. Votre ordinateur manque peut-être de mémoire pour ouvrir l'image ou l'image est endommagée. Redémarrez l'ordinateur, puis ouvrez à nouveau le fichier. Si le x rouge est toujours affiché, vous devrez peut-être supprimer l'image avant de la réinsérer.

Cellular Automata: a second example

- 1D automata
  - the automaton is an one-dimensional array of cells that may be in two states: *on* and *off*
  - the evolution of a cell is determined by its own state and by the state of its two neighbours

- e.g. rule 18
  - a cell in the *on* state "dies"
  - a cell in the *off* state becomes "alive" if it has exactly one neighbour in the *on* state
  - mimics a simple diffusion process [Meinhardt & Klingler 1987]

Cellular Automata: a general framework

- Introduced by J. von Neumann and S. Ulam as a way to study self-reproducing machines
- General properties
  - the CA space is a lattice of cells with a regular geometry
  - each cell is defined by its state, chosen from a limited range of values (e.g., 0 and 1)
  - the neighbourhood of the cells is defined in a uniform way as a finite set of indexes
  - time advances in discrete steps; all cells update synchronously, using the same updating rule or transition function (in uniform CA), depending only on local relations
- Applications for the modelling and simulation of complex systems in chemistry, physics, biology, ecology, economics, sociology

Cellular Automata: design choices

- Space dimension and lattice geometry
- Shape and size of the neighbourhood
- Boundary conditions
- Initial conditions
- State space
- Transition rules

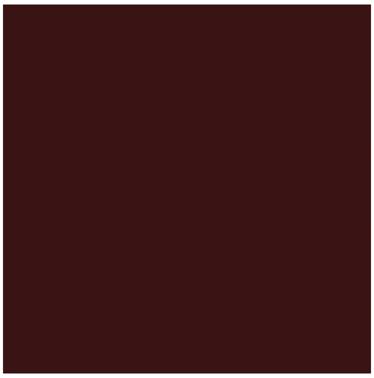
Reaction-diffusion systems

- Invented by A. Turing (early 50's)
  - proposed as a cause of various embryological patterns

Combination of

- a reaction in each cell between chemicals that behave as activators and inhibitors
- the diffusion of the chemicals between neighbouring cells

Meinhardt model of periodic patterns formation



$$\frac{\partial a}{\partial t} = \frac{\rho a^2}{h} - \mu_a a + D_a \frac{\partial^2 a}{\partial x^2} + \rho_0$$

$$\frac{\partial h}{\partial t} = \rho' a^2 - \mu_h h + D_h \frac{\partial^2 h}{\partial x^2}$$

CA modelling of a genetic switch

- « With these characteristics, cellular automata provide rather general discrete models for homogeneous systems with local interactions. They may be considered as idealizations of partial differential equations, in which time and space are assumed discrete, and dependent variables taken on a finite set of possible values. » [S. Wolfram]

- Proposition
  - CA = spatialized explicit Euler Scheme
  - make the correspondence between deterministic modelling and CA modelling
    - discretization of space
    - discretization of time
    - continuous variables

CA modelling of a genetic switch

Discretization of space

- In deterministic modelling, all the chemical species
  - are present in a single compartment
  - are able to react with each other without any restriction
- In the CA model
  - the global compartment is divided into a collection of smaller compartments (cells)
  - the state of the cells is composed of variables giving the concentration of the chemical species (X, Y)
  - reactions occur in each single cell
  - chemicals are exchanged between the cells according to :

$$dx = D_x\left(\frac{1}{|N(x)|}\sum_{i\in N(x)} x_i - x\right)$$

  - with D_x the proportion of x shared with the neighbouring cells
  - $N(x)$ the neighbourhood of the cell

Discretization of time

- Differential equations express small variations of the concentration of the chemical specie *x* on a small time-interval
  - *dx/dt=f(x)*
  - *x(t+dt) = x(t) + dt.f(x)*
- The general deterministic model

$$\frac{dX}{dt} = \frac{\alpha_1}{1+Y^{\beta_1}} - k_1 X$$

$$\frac{dY}{dt} = \frac{\alpha_2}{1+X^{\beta_2}} - k_2 Y$$

- The corresponding CA model

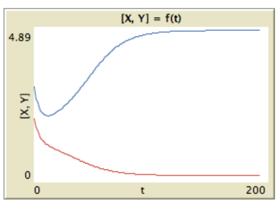
$\Delta X = \frac{\alpha_1}{1+Y^{\beta_1}} - k_1 X$ and $X(t+dt) = X(t) + dt\,\Delta X$

$\Delta Y = \frac{\alpha_2}{1+X^{\beta_2}} - k_2 Y$ and $Y(t+1) = Y(t) + dt\,\Delta Y$

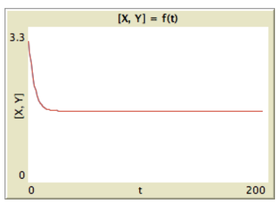
Initial parameterization

- In the deterministic model
  - two stable states using the following parameterization:

$$k_1 = k_2 = 1 \qquad \alpha_1 = \alpha_2 = 5$$
$$dt = 0.01 \qquad \beta_1 = \beta_2 = 2$$



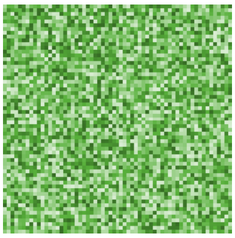
xinit > yinit



xinit = yinit

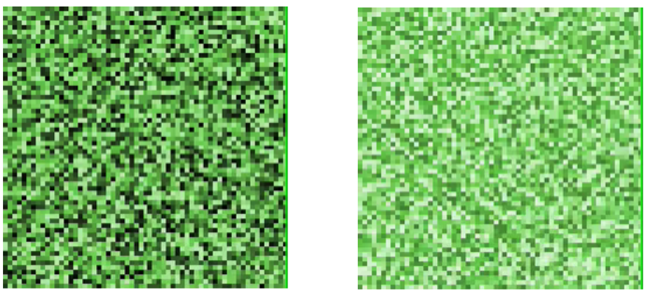
Adding heterogeneity

- the initial concentration of X and Y is not homogeneous in the cell
- to have a mean initial concentration of X_0, we randomly choose the initial value of each cell of the automata in the interval [0; 2 * X_0]



Adding diffusion

- if $D_X = 0$, each cell of the automaton is an individual system
- if $D_X = 1$, everything is mixed up and homogenized very quickly
- we chose an intermediate value of 0.1



Simulation process

1. **Initialization** : for each cell, choose the value of x in the interval $[x_0(1-h_x); x_0(1+h_x)]$, similarly for y

2. **Reaction** : for each cell of the automaton, compute

$$\Delta_{reaction} X = dt\left(\frac{\alpha_1}{1+Y^{\beta_1}} - k_1 X\right) \qquad \Delta_{reaction} Y = dt\left(\frac{\alpha_2}{1+X^{\beta_2}} - k_2 Y\right)$$

3. **Diffusion** : for each cell i of the automaton, compute

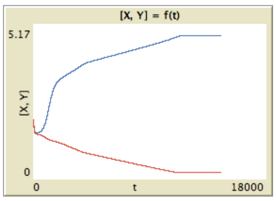
$$\Delta_{diffusion} X = D_X\left(\frac{1}{|N(i)|}\sum_{j\in N(X)} X_j - X_i\right) \qquad \Delta_{diffusion} Y = D_Y\left(\frac{1}{|N(i)|}\sum_{j\in N(Y)} Y_j - Y_i\right)$$

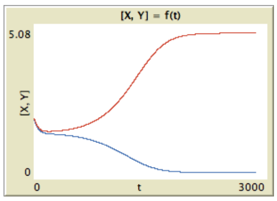
4. **Update** : for each cell of the automaton, compute

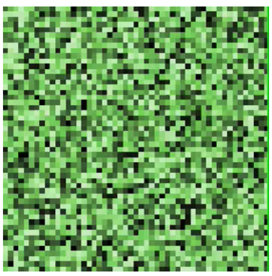
$$X = X + \Delta_{reaction} X + \Delta_{diffusion} X \qquad Y = Y + \Delta_{reaction} Y + \Delta_{diffusion} Y$$

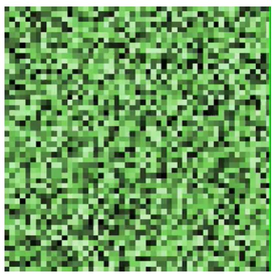
5. **Iteration** : go back to step 2

Different possible behaviors (1/2)

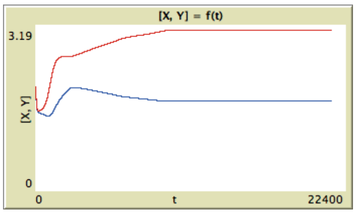


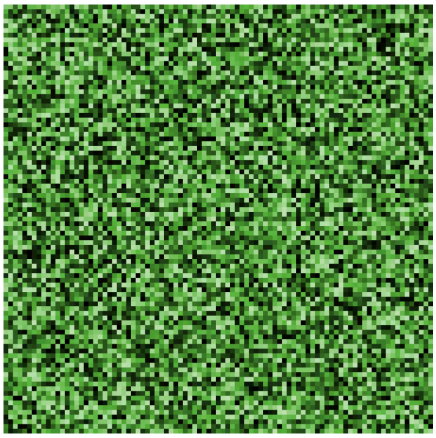




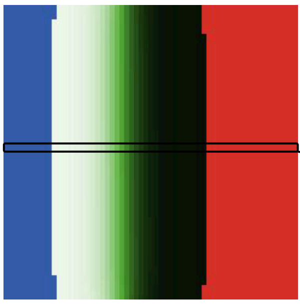


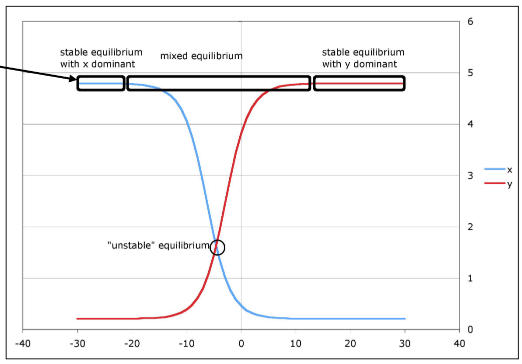
Different possible behaviors (2/2)





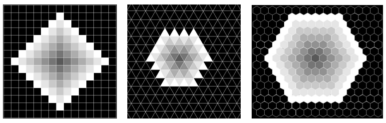
What do the transition looks like?



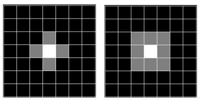


Border effects

- Observation
  - structures are always exactly vertical or horizontal
- Possible explanations
  - the structures are conditioned by the borders of the environment
  - the structures are conditioned by the topology of the cell lattice



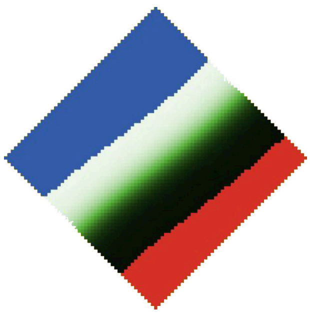
  - the structures are conditioned by the diffusion process



Border effects

Changing the shape of the environment

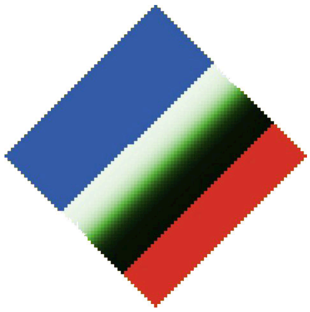
- Change
  - the environment is changed from a square to a diamond shape
- Observation
  - the structures remain roughly orthogonal to the borders
    - the geometry of the environment seems to be more important than the cell lattice
  - some distortion appears



Border effects

Changing the diffusion process

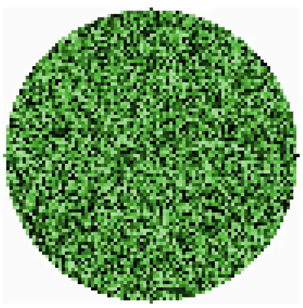
- Change
  - the diffusion is made with a von Neumann neighborhood (4 neighbors) instead of a Moore neighborhood (8 neighbors)
- Observation
  - the structures are again perfectly orthogonal to the borders of the environment



Border effects

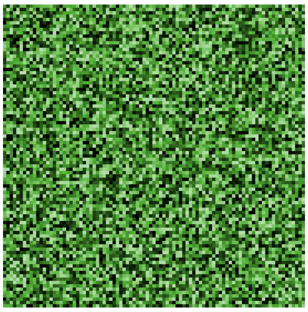
Changing the shape of the environment

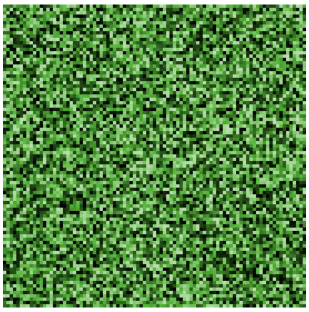
- Change
  - the environment is made circular
- Observation
  - the orientation of the structures can be arbitrary
  - the mixed equilibrium is no longer stable



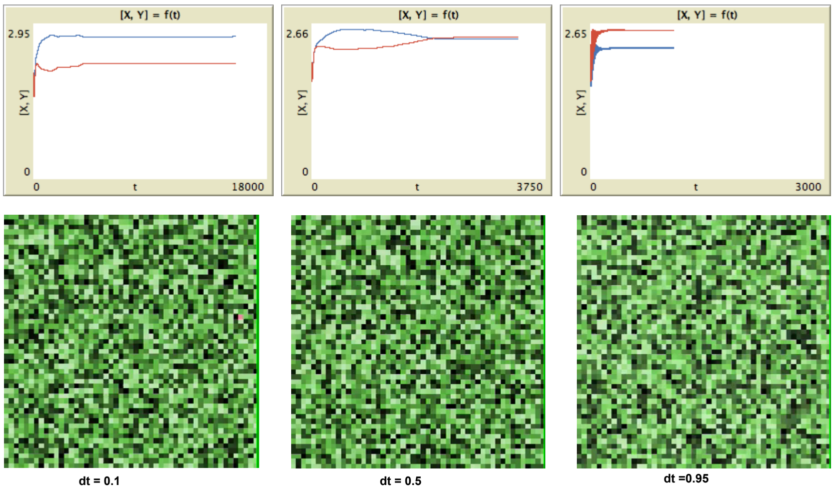
Border effects
Changing the shape of the environment

- Change
  - the environment is made toroidal
- Observation
  - either homogeneous steady state
  - or two stripes of X and Y





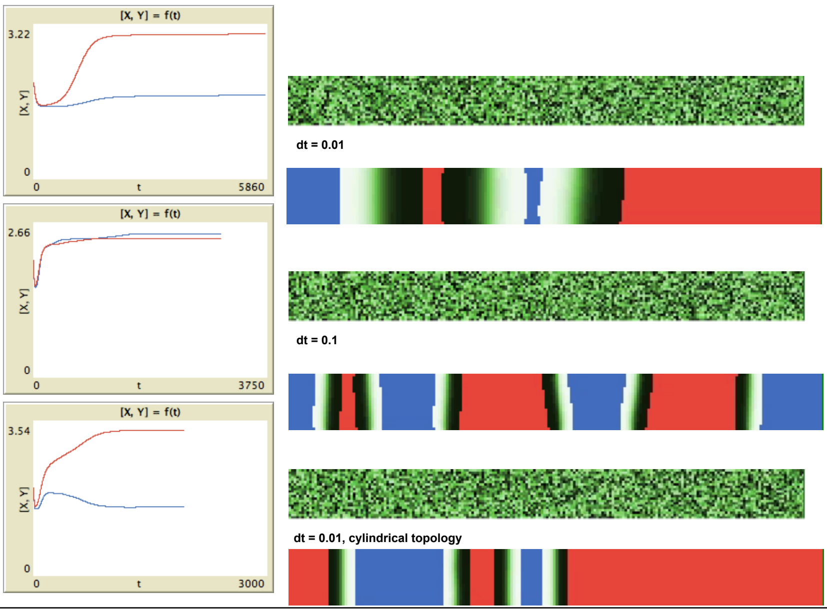
Playing with parameters (*dt*)



Playing with parameters (dt)

- the dt factor is applied to the reaction term but not to the diffusion term (as it should have been)
- increasing dt
  - gives more weight to the reaction term with respect to the diffusion term
  - leads to more fragmented patterns

Playing with topology



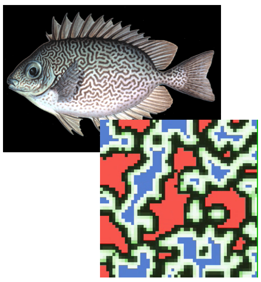
Discussion

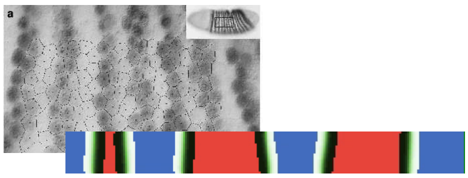
- Spatialization
  - ✔ allows to take heterogeneity into account
  - ✔ allows to take diffusion into account
  - ✔ allows to study the impact of the geometry of the system on the dynamics
  - ✔ allows to observe the way in which local interactions between entities may produce global spatio-temporal patterns
  - ✔ imposes to revisit the notion of steady-state

  - ✘ the exploration of the parameter space is very empirical
  - ✘ the geometry of the lattice may constrain the geometry of the structures that are produced (possible border effects)

Discussion

- Modelling a genetic switch
  - ✘ the activity of several molecules is abstracted as a small region with concentrations
    - not really a model of a genetic switch
    - rather a simplified model of animal skins or morphogenetic process





From CA to Agent-Based Modeling

- Switch to agent-based modeling
  - individual modeling of the entities of the system
  - modeling of the interactions between the entities
  - modeling of the environment in which the entities "live"

The "philosophy" behind agent-based models (ABM)

- Modeling entities of the real system as entities in the simulation
  - integrating models and theories of an application domain
- Modeling at a chosen level of abstraction (or granularity)
  - mixing several levels of description in the same model
  - expliciting the inter-relations between the different levels
- Modeling the behaviour of the entities, not only their result at the population level
  - reproducing the emergence of spatial and temporal structures
- Accounting for local heterogeneities in the system
  - because of a variability between the individuals
  - because of spatial variations
- Designing simulations that are kinds of virtual laboratories
  - conducting experiments just in the same way as in the real life
  - testing hypothesises about the dynamics of the system

From the biological question to an ABM

- The formulation of the problem
  - " *the gene x synthesizes the protein X which inhibits the expression of gene y, i.e. the synthesis of protein Y by the gene y. In turn, the protein Y inhibits the expression of gene x, i.e. the synthesis of protein X* "
- Design issues
  - Choosing the entities of the model
  - Choosing a model for the representation of space and time
  - Describing the behavior of the agents and their interactions
  - Choosing a computational model

A more detailed scenario

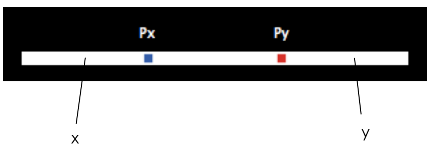
- **"*the gene x synthesizes the protein X…*":**
  - RNA Polymerase binds to the DNA promoter region of gene x and forms a complex;
  - this complex achieves the transcription of gene x and produces a mRNA transcript;
  - this transcript in turn forms a complex with a ribosome that achieves the translation and produces a X protein;
  - the mRNA transcript may be translated several times, producing as many proteins.
- **"*…which inhibits the expression of gene y, i.e. the synthesis of protein Y by the gene y*":**
  - two X proteins form a dimer, which binds to the promoter of gene y, thus preventing the transcription of gene y (and the synthesis of protein Y)

Choosing the entities of the model

- Deciding which of the entities of the real system will be represented as agents
  - close to the *reification* problem in OOP
  - closely linked to the choice of the level of abstraction used for the description of the system
- Criteria
  - depends on the aim of the simulation
    - what hypothesises do the modeler wishes to test and validate?
  - compromise between the expected level of detail or realism, and the computing resources
  - strongly conditioned by
    - the available data about the real system
    - the ontologies used by the experts of the domain
  - possibility of multi-level modeling

The entities in the genetic switch

- The molecules that participate in the reactions
  - X X2
  - Y Y2
  - pRNA
- The promoter regions
  - Px, Py



Representation of space and time

- The spatial environment
  - the geometrical structure of the system
  - the diffusion medium for the signals
  - the support for the movements of agents
- The representation of time
  - as a succession of time-steps (discrete time simulation)
  - as a succession of events (discrete events simulation)
- The scheduling of agents
  - activation in turn in fixed order
  - activation in turn in a random order
  - activation in parallel
  - other activation schema...

Space and time in the genetic switch

- Space
  - regular lattice of square cells
    - structure: phage DNA
    - signals: molecules have to be in the same cell to be able to interact with each other
  - movements in a continuous space
- Time
  - discrete-time simulation
  - scheduling handled by the simulation platform

The behaviour of the agents

- Can be abstracted as three successive steps
  - perception
    - the agent retrieves information in its environment
  - decision
    - the agent chooses which action to undertake (amongst a set of possible actions)
    - depends on its internal motivation(s) and its external perception(s)
  - action
    - the agent executes the chosen action, thus modifying its environment, the physical one or the other agents
- Very general behavioural model
  - enables to take into account such different entities as atoms or molecules, cells, organs, animals, human beings, enterprises, etc.

The behavior of the agents

- In the context of molecular biology
  - molecules may
    - participate in reactions with other molecules
    - get spontaneously transformed
  - stochasticity:
    - reaction = when two molecules are close enough, they have some probability to interact with each other
- Molecular behaviors
  - perception: identifying the molecules with which the agent may react
  - "decision": random choice depending on the reaction kinetics
  - action: depends on the type of reaction
    - if the reaction is a catalysis, and the agent is an enzyme, then the action would be to transform the substrate into a product
    - if the reaction is a dimerization, then the action would be to bind to the other molecule, etc.

Pseudo-brownian movement

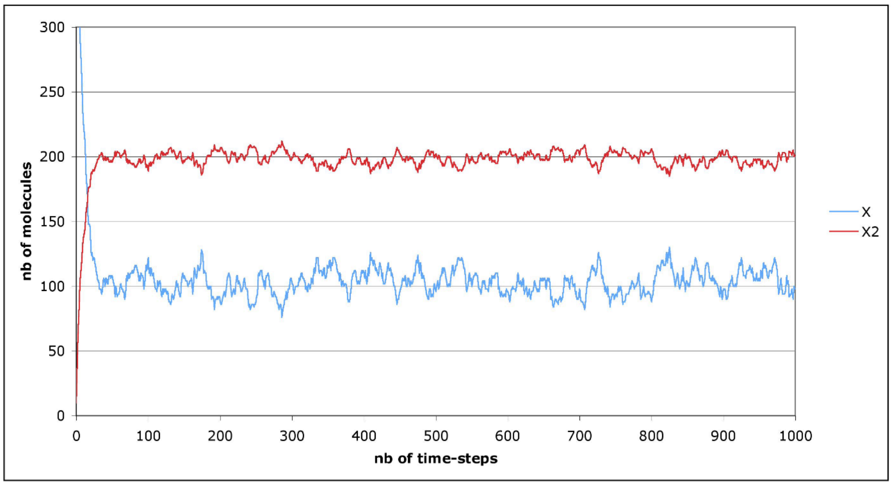
- Principle
  - choose a totally random direction
  - move by a distance of 1 unit

Dimerization and degradation

- Monomers form dimers (and back)
  - $X + X \rightarrow_{Kdim} X_2$
  - $X_2 \rightarrow_{Kdis} X + X$
  - $X \rightarrow_{Kdeg} *$
  - K_{dim} interpreted as the probability to dimerize when two *CI* molecules meet
    - "meeting" = presence in the same cell
  - K_{dis} interpreted as the probability that a dimer spontaneously dissociates at a given time-step (similarly for K_{deg})
  - dimerisation may be seen as
    - the creation of a binding between the two molecules

    or ...
    - the creation of a new dimer molecule and the destruction of the two monomers

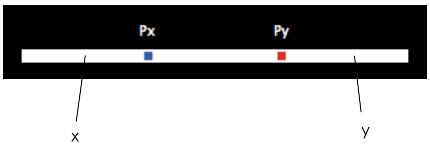
Dimerization and degradation



$K_{dim} = 0.1$ / $K_{dis} = 0.01$ / $K_{deg} = 5.10^{-4}$

DNA modelling

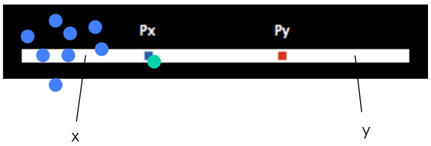
- Principle
  - modeling of each promoter site as an individual agent
  - DNA molecule considered as static
  - promoter agents may bind other molecules (*RNAp*, *X_2*, *Y_2*)
    - only the promoter agents check if the binding can be done



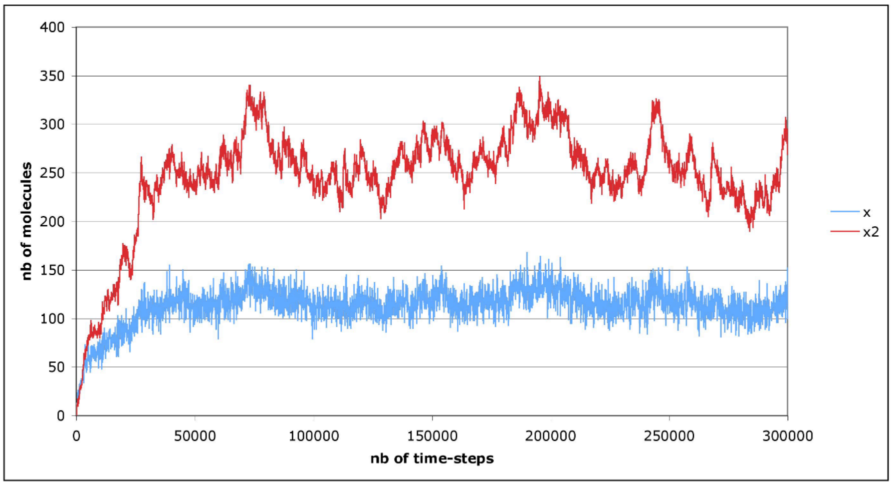
Promoters & RNA polymerase modeling

- Principle
  - when P_x "senses" the presence of a *RNAp*, it binds to it with the probability k_x
  - if *RNAp* gets bound to P_x,
    - this complex achieves the transcription of gene x and produces a mRNA transcript;
    - this transcript in turn forms a complex with a ribosome that achieves the translation and produces a X protein;
    - the mRNA transcript may be translated several times, producing as many proteins;

➜ we directly produce between 5 and 15 molecules of *X* or *Y*
➜ the *RNAp is released*



Synthesis and degradation of X

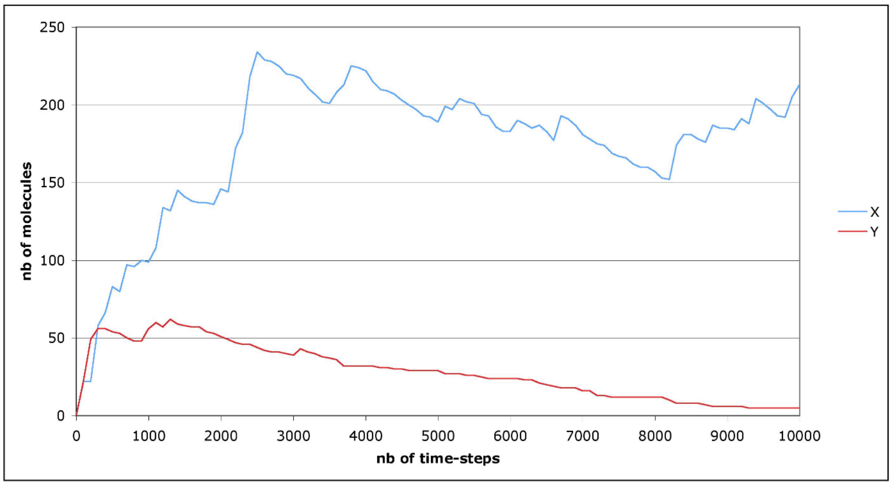


$K_{dim} = 0.1$ / $K_{dis} = 0.01$ / $K_{deg} = 5.10^{-4}$ / $K_x = 0.1$

Mutual inhibition

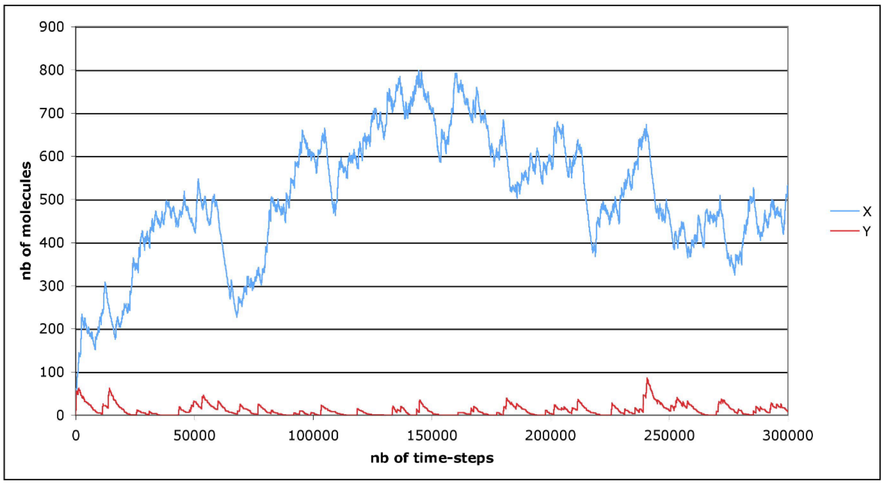
- Principle
  - when P_x is free and "senses" the presence of a Y_2 *molecule*, it binds to it with the probability k_{+inh}
  - if P_x gets bound to Y_2,
    - Y_2 inhibits its moving behavior
    - P_x inhibits its binding behavior (both with *RNAp* and with other Y_2 molecules)
    - Y_2 can be freed at each time step with probability k_{-inh}
  - ...and similarly for P_y and X_2

Sample evolutions : stable equilibrium



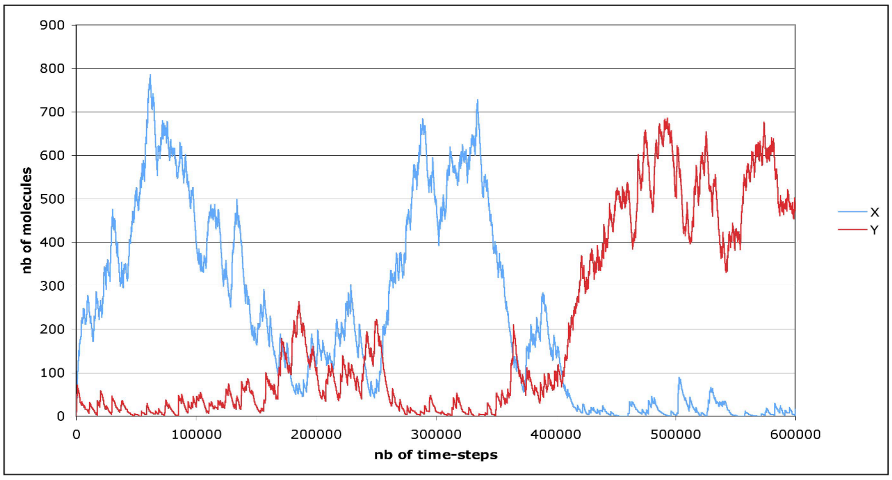
$K_{dim} = 0.1$ / $K_{dis} = 0.01$ / $K_{deg} = 5.10^{-4}$ / $K_x = 0.1$ / $K_{+inh} = 0.1$ / $K_{-inh} = 10^{-3}$

Sample evolutions : stable equilibrium



$K_{dim} = 0.1$ / $K_{dis} = 0.01$ / $K_{deg} = 5.10^{-4}$ / $K_x = 0.1$ / $K_{+inh} = 0.1$ / $K_{-inh} = 10^{-3}$

Sample evolutions : spontaneous switch

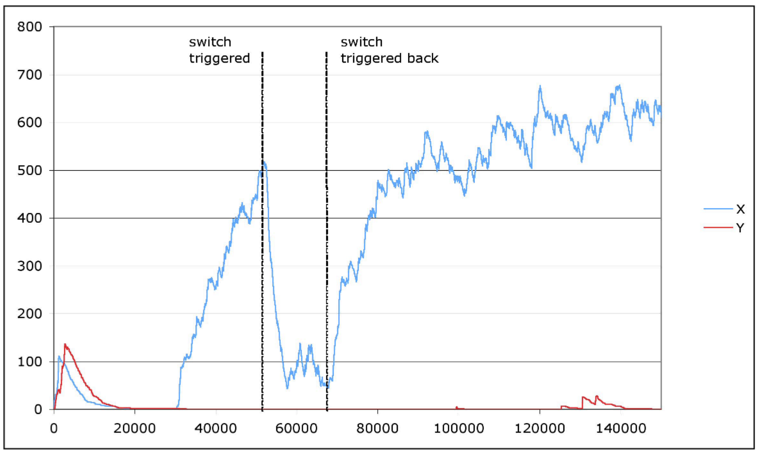


$K_{dim} = 0.1$ / $K_{dis} = 0.01$ / $K_{deg} = 5.10^{-4}$ / $K_x = 0.1$ / $K_{+inh} = 0.1$ / $K_{-inh} = 10^{-3}$

Triggering the switch

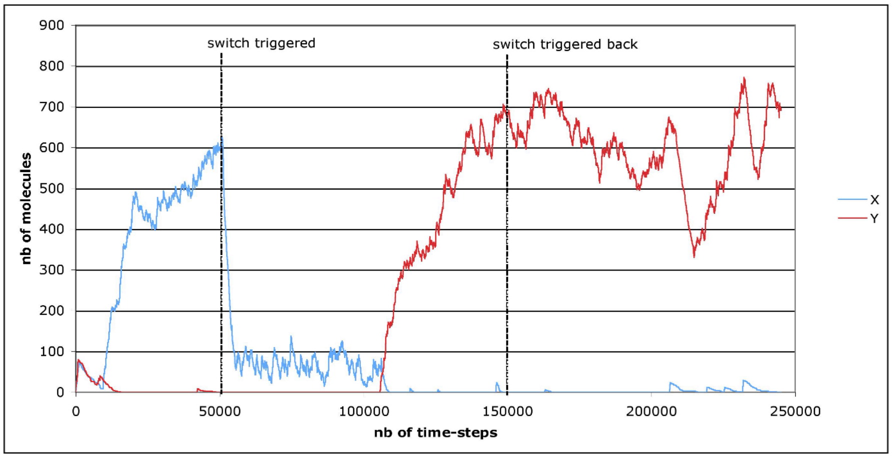
- External activation of the switch
  - mutation provoked by irradiation with UVs (or by temperature)
  - a new molecular type, *recA*, degradates *X* in monomer state

Sample evolutions: triggering the switch (1/2)



K_{dim} = 0.1 / K_{dis} = 0.01 / K_{deg} = 5.10^{-4} / K_x = 0.1 / K_{+inh} = 0.1 / K_{-inh} = 10^{-3}

Sample evolutions: triggering the switch (2/2)



$K_{dim} = 0.1$ / $K_{dis} = 0.01$ / $K_{deg} = 5.10^{-4}$ / $K_x = 0.1$ / $K_{+inh} = 0.1$ / $K_{-inh} = 10^{-3}$

Discussion (1/2)

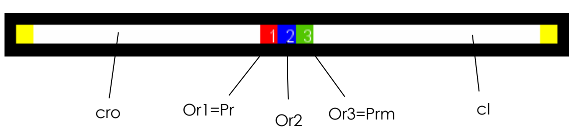
- Characteristics of ABM
  - explicit modelling of space
  - explicit modelling of entities behaviour
  - no need to simplify excessively the model to be able to study the system (incremental approach)
  - modelling at different levels of abstraction
- Interests
  - ✔ allows to study the spatial and temporal emergent phenomena in the system
  - ✔ allows to study the effects of stochasticity
  - ✔ allows to design artificial experiments that allow to make predictions

Discussion (2/2)

- It can sometimes be difficult to tune the model
  - ✔ generally fast to have a model that is approximately coherent
  - ✘ can be very long and tedious to tune the model precisely
- Difficult to characterize the different possible dynamics of the system depending on the parameters
  - ✘ has to be done by hand
- *New research directions*
  - automatic exploration of the parameter space of a model
  - automatic characterization of the emergent dynamics of the system
  - multi-scale and hybrid simulation

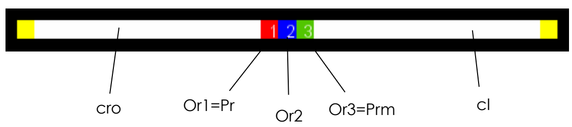
The entities in the λ switch

- The molecules that participate in the reactions
  - CI ● CI2 ●●
  - Cro ● Cro2 ●●
  - pRNA
  - recA
- The lambda operator
  - OR1, OR2, OR3
  - the genes that code for CI and Cro



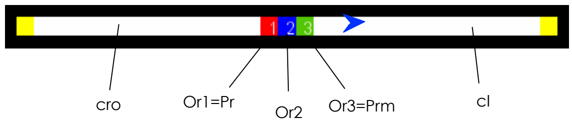
DNA modelling

- Principle
  - modelling of each operator site as an individual agent
  - DNA molecule considered as static
  - only the operator agents check if the binding can be done
    - when binding *CI*, *Or2* has to check if *Or1* is also bound to *CI*
  - no hypothesis about which reaction occurs first
    - all reactions are concurrent and may occur
    - some are more probable than others
  - when a dimer is bound
    - it inhibits its moving and dissociation behaviors
    - the operator inhibits its binding behavior

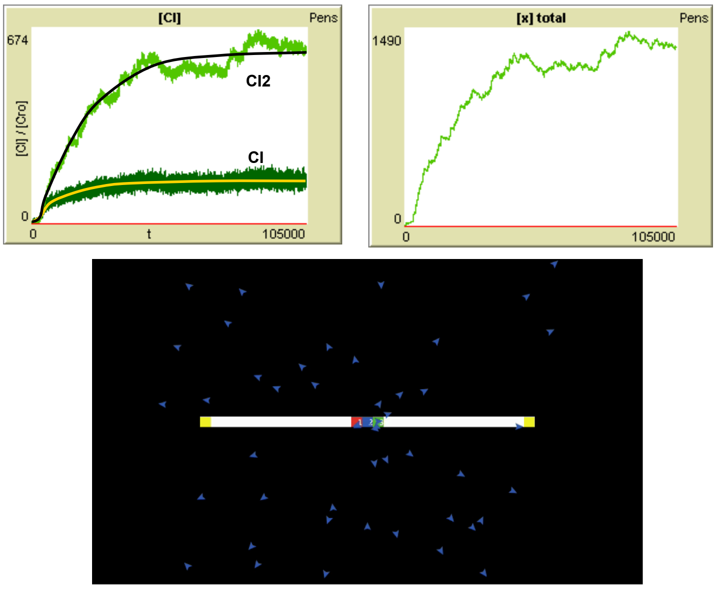


Promoters & RNA polymerase modelling

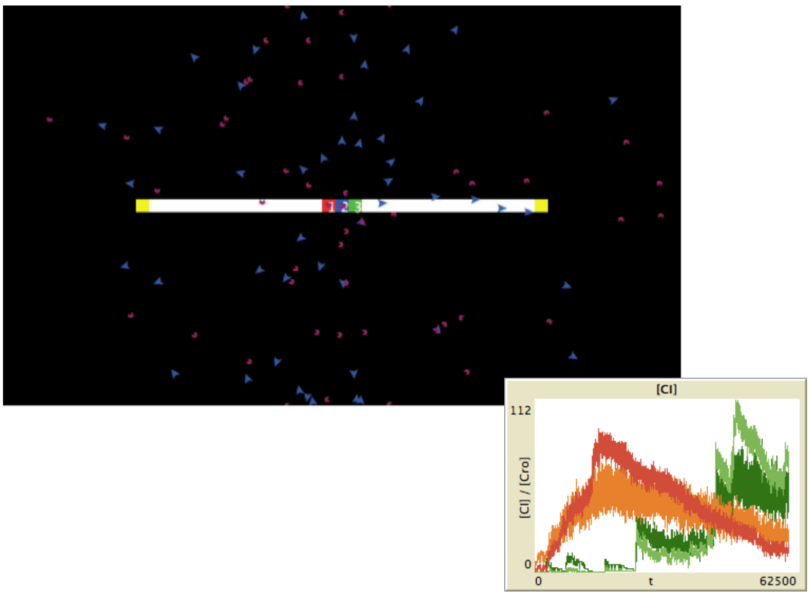
- Principle
  - promoters *Pr* and *Prm* are not modeled as separate agents
    - *Or1 = Pr*
    - *Or3 = Prm*
  - only *Pr* and *Prm* check if *RNAp* molecules are present
  - when *RNAp* is bound
    - its heading is changed to be colinear with DNA
    - *RNAp* moves forward until it reaches the "stop" codon
    - *RNAp* is released and creates *n* protein molecules



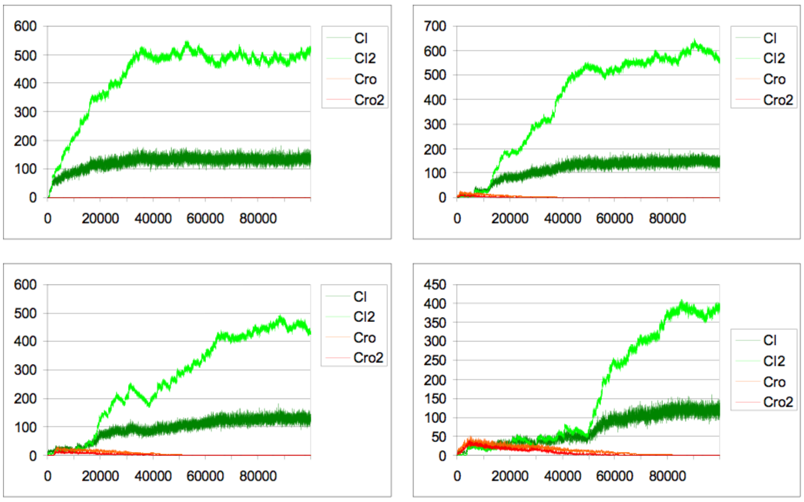
The model with CI only



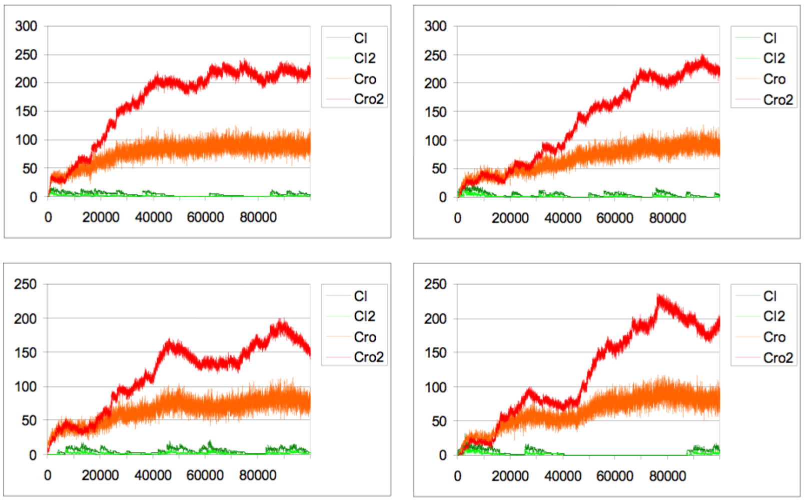
The model with both CI and Cro



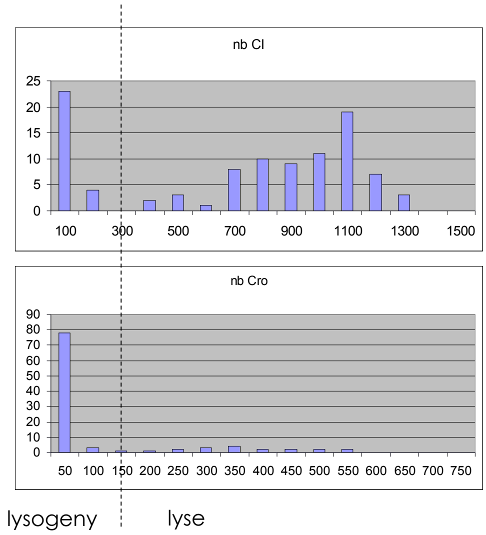
Sample lysogenic evolutions (~80%)



Sample lytic evolutions (~20%)

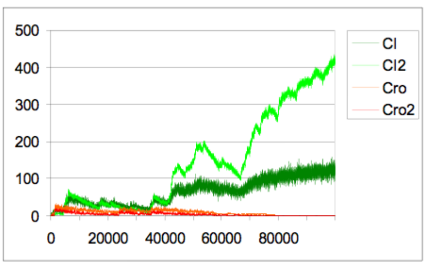


Distribution lysogeny vs. lyse



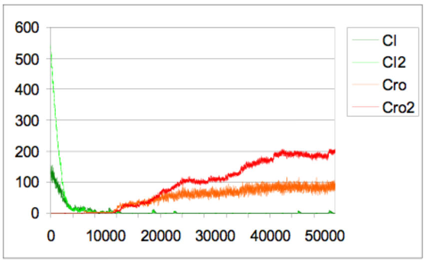
Triggering the lambda switch (1)

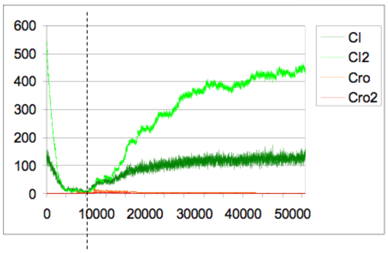
- Spontaneous evolution sometimes chaotic
  - may switch spontaneously in some cases from lysogeny to lyse



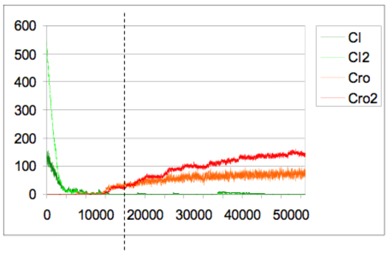
- External activation of the switch
  - mutation provoked by irradiation with UVs (or by temperature)
  - a new molecular type, recA, degrades CI in monomer state

Triggering the lambda switch (2)





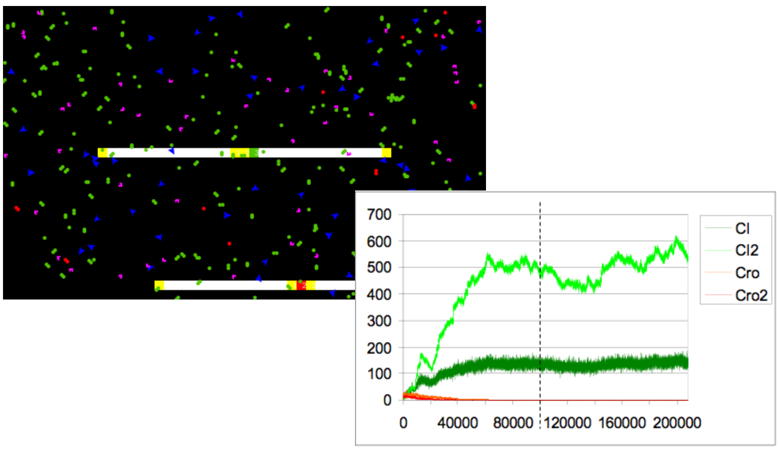
reverse mutation



reverse mutation

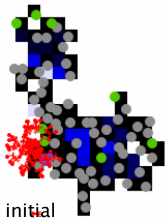
Immunity

- At t=100000, a new phage DNA enters the bacterium

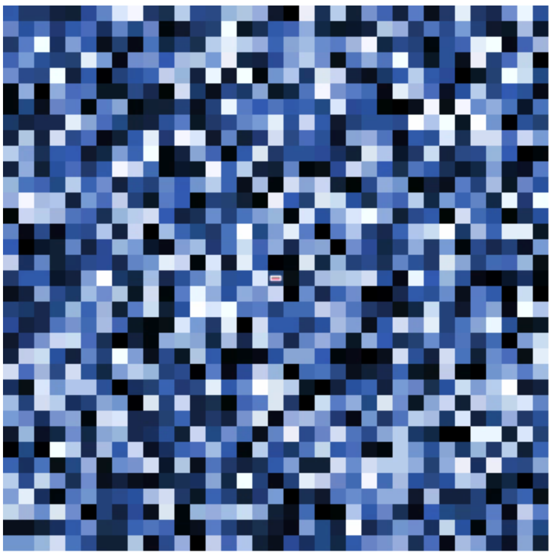


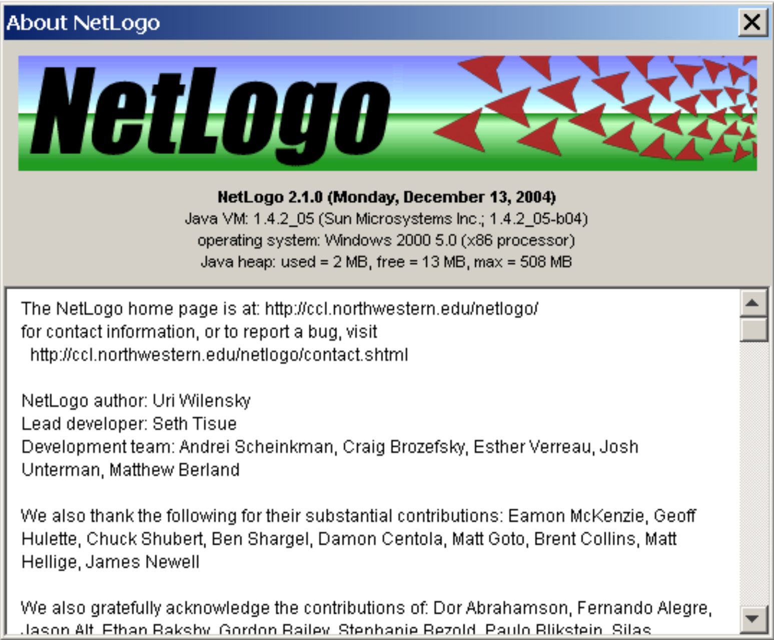
Crossing the levels of abstraction (1/2)

- Switch from the molecular level to the cellular level
  - either by enlarging the model to include several bacteria
  - ... or by modeling cells instead of molecules
- Abstraction of the cellular behavior
  - model cells
    - bacteria
    - λ phages
  - define cells' behavior
    - define the probability of lyse and lysogeny as a function of the initial conditions and of the parameters
    - include a cellular division behavior
    - include a lyse behavior



Crossing the levels of abstraction (2/2)




About NetLogo
NetLogo
NetLogo 2.1.0 (Monday, December 13, 2004)
Java VM: 1.4.2_05 (Sun Microsystems Inc.; 1.4.2_05-b04)
operating system: Windows 2000 5.0 (x86 processor)
Java heap: used = 2 MB, free = 13 MB, max = 508 MB
The NetLogo home page is at: http://ccl.northwestern.edu/netlogo/
for contact information, or to report a bug, visit
http://ccl.northwestern.edu/netlogo/contact.shtml
NetLogo author: Uri Wilensky
Lead developer: Seth Tisue
Development team: Andrei Scheinkman, Craig Brozefsky, Esther Verreau, Josh Unterman, Matthew Berland
We also thank the following for their substantial contributions: Eamon McKenzie, Geoff Hulette, Chuck Shubert, Ben Shargel, Damon Centola, Matt Goto, Brent Collins, Matt Hellige, James Newell
We also gratefully acknowledge the contributions of: Dor Abrahamson, Fernando Alegre,