

COM3001
Modelling natural systems
Agent-based modelling

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Complex systems

- Many natural complex systems share a number of characteristics:
 - They comprise many different interacting components in a changing environment
 - These components communicate in various ways
 - The structure and behaviour of the overall system emerges from all of this activity
 - There is inherent noise and uncertainty in the system
 - Biological systems (and to an extent Economics) exist within a physical world

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Social insects

QuickTime™ and a
DV-PAL decompressor
are needed to see this picture.

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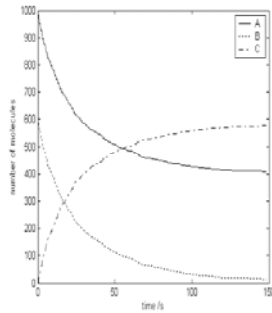
Components

- The components that make up a complex system are themselves systems
- They have internal state

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Simple reaction chemicals A and B make C

QuickTime™ and a
Creative Commons™
plugin are needed to see this picture.



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Agents

- A popular new way to model such systems is to use *agents*
- They are each individually implemented as a software component
- Simulations then involve creating a software environment where they can all interact and the overall system evolves and is observed
- Experiments can be carried out, research questions investigated

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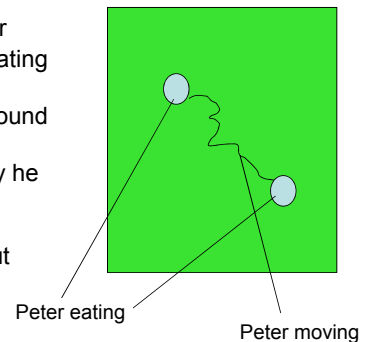
Defining agents

- Agents have a set of states
- Agents have a set of functions
- Agents have a location
- Agents send messages to other agents
- What agents do depends on their
 - current state,
 - where they are,
 - what they can sense
 - and what functions they possess that are enabled at that moment

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A simple agent

- A duck - Peter
- He is either eating the grass
- or moving around randomly
- If he is hungry he stops to eat
- Otherwise he waddles about



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Defining Peter

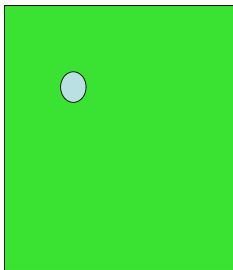
- He has two states: *eating* and *waddling*
- He is either *hungry* or *full*
- *If he is hungry he stops and eats*
- *If he is full he waddles until he is hungry again*
- We need to track where he is in space
- His x-coordinates (xpos) and y-coordinates (ypos)

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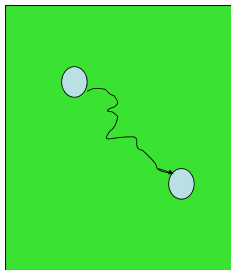
Internal Memory

- We define his internal memory to have 3 parts:
- (xpos, ypos, hungry/full)
- We now put Peter into the field at some position and start the model with him in an initial memory value.
- Depending on what this is he will do something.
- We record what he does.
- We visit him again shortly after and update his state and memory

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Time t = 0; (x,y,full)

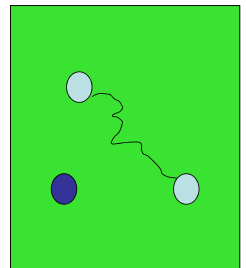


Time t = 1; (x',y',hungry)

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Peter has a friend

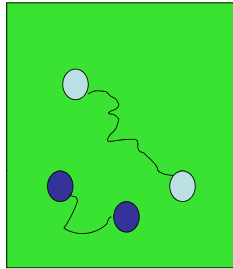
- Jane is at another position
- She also eats or waddles
- She has a memory
- Now we have two agents we have to remember which is which
- Define a new internal memory:
- (name, xpos, ypos, hungry/full)



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Now, at each time point we look at each duck and see what it does.

We need to see what its position is and then update that position if it moves, i.e. update its memory

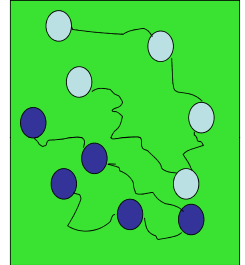


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We keep doing this at each iteration

- Is there a problem with this system?

They may collide - that is try to occupy the same co-ordinates at the same time



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Avoidance strategy

- Each agent needs to be able to see the other ducks
- We arrange for this by asking each agent to post its new position on a *message board*
- All the agents can read the message board and do this before they move
- Then they can avoid going to an occupied position

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X-agents

QuickTime™ and a decompressor are needed to see this picture.

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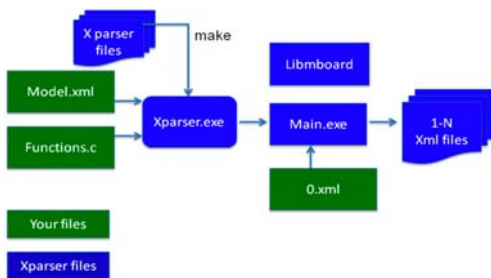
Computational model

- During each iteration each agent is visited once
- The order of visit changes each time
- Each agent is updated -
 - This involves looking at its current memory and seeing what the message board says
 - Then the agent will decide to do something (a *function* can be carried out, e.g. eating/moving etc.)
 - Then the memory is updated
 - And the new position is posted on the message board (the old position is deleted from the board)
- We move on to the next agent

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- Produced at the University of Sheffield, UK.
- Flexible Large-scale Agent-based Modelling Environment
- Based on X-machine architecture for agents
- Being used in a wide number of projects (Modelling of cells, tissues, biological and economic scenarios or networking models)
- Specify the agents in XML – FLAME then *generates* the C code
- Automatically produces parallelisable code for models

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FLAME manual

http://www.dcs.shef.ac.uk/~wmlh/FLAME_manual.pdf

<http://www.dcs.shef.ac.uk/~mariam/flametutorial.html>

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How to define agents?

```

<!--***** X-machine Agent - Rabbit *****-->
<xagent>
  <name>Rabbit</name>
  <!-- Variables for the Rabbit -->
  <memory>
    <variable><type>int</type><name>rabbitID</name><description></description></variable>
    <variable><type>double</type><name>rabbitX</name><description></description></variable>
    <variable><type>double</type><name>rabbitY</name><description></description></variable>
  </memory>
  <!-- Defining functions -->
  <functions>
    <function>
      <name>rabbitLocation</name>
      <currentState>0</currentState>
      <nextState>01</nextState>
      <outputs><output><messageName>rabbitInformation</messageName></output></outputs>
    </function>
    <function>
      <name>rabbitMove</name>
      <currentState>01</currentState>
      <nextState>02</nextState>
    </function>
  </functions>
</xagent>
<!--***** End of Agent - Rabbit *****-->

```

Design language: XMML

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..and now a fox turns up!

- This fox will chase rabbits and eat any it catches
- We need a new type of agent - fox
- It moves around so it looks on the message board to see where they are
- We need to update the rabbit agent to allow them to run away

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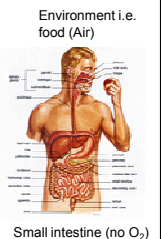
Some model examples

- Oxygen metabolism in *E. coli*
- Molecular basis of immune system
- Epithelial tissue - wound repair
- Social insects - foraging
- European economic model - policy design

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Why Escherichia coli?

- Most strains are beneficial to humans (gut flora); a few cause disease (*E. coli* O157).
- The most genetically and metabolically defined organism known.
- *E. coli* can live in places either with lots of O₂ or none by changing its metabolism to survive.
- The presence/absence of O₂ is a key signal during *E. coli* infection!
- *E. coli* is used as a "cell factory" for making many drugs & chemicals.

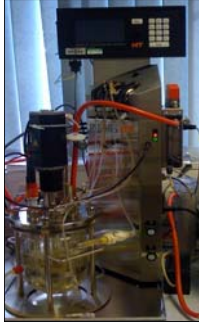


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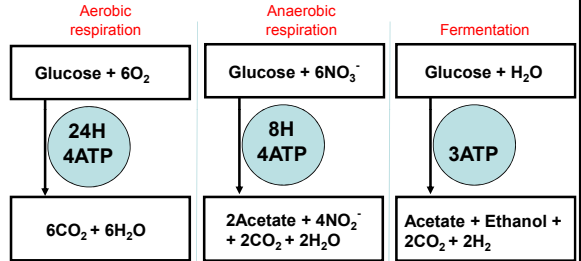
The Chemostat Approach

A chemostat is a device which can be used to grow microorganisms at a steady rate. In steady state, growth occurs at a constant growth rate and all culture parameters remain constant (culture volume, dissolved oxygen concentration, nutrient and product concentrations, pH, cell density, etc.)

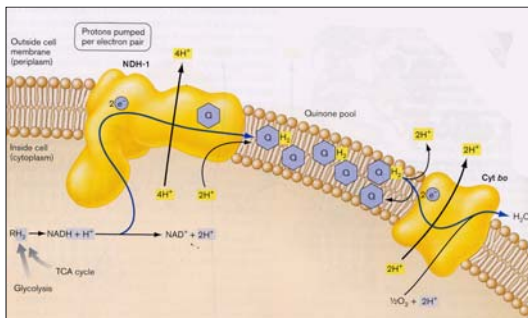
- ✓ Control and measurement of all key operating conditions, *including growth rate*
- ✓ Establish aerobic or anaerobic steady-states and perturb by removal or introduction of oxygen
- ✓ **Sample during transition for transcript profiling**
- ✓ Strictly defined conditions can be replicated in different laboratories



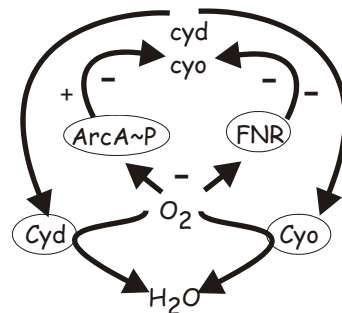
E. coli K-12: Growth Modes



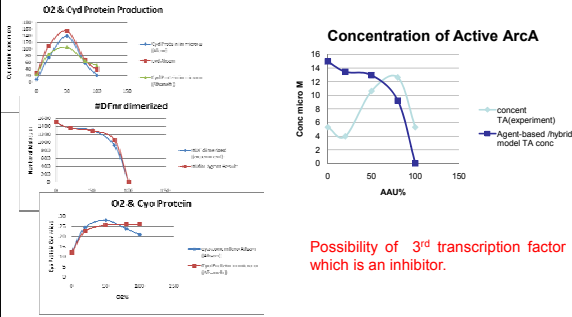
Spatial organization: the NADH→cytochrome *bo* segment



Schematic model of oxidase regulation



ArcA Agent-Based Model Result



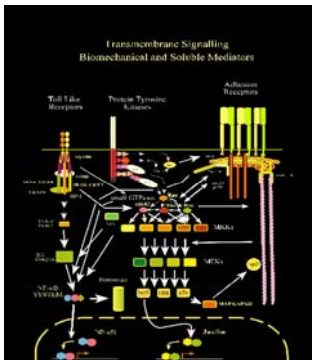
Possibility of 3rd transcription factor which is an inhibitor.

Another complex example:

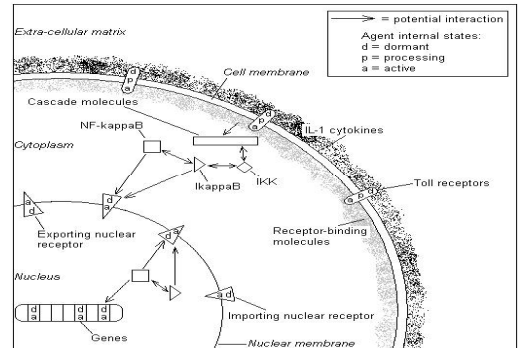
- Innate immune system - deals with basic infections and inflammation
- Adaptive immune system - learns from exposure to diseases - bacteria, virus, etc.
 - Basis of vaccination
- Very complex systems - still not fully understood
- Major research area

NF-κB system

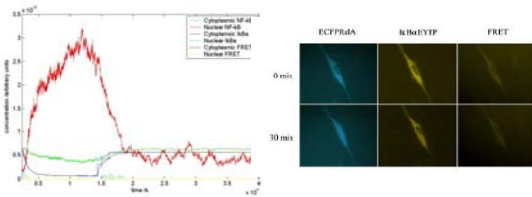
Part of the innate immune system



Agent model of NF-κB



Simulation data and experimental data

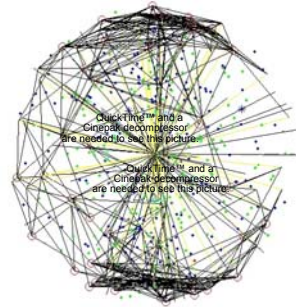


GFP Transfected single cell data using confocal microscopy (HeLa cells)

M Pogson et al BioSystems, 2006

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M Pogson
BioSystems 2006



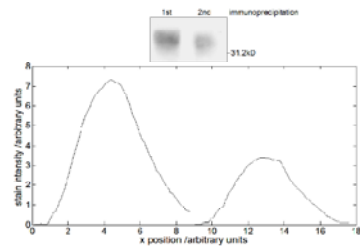
Actin IκBα simulation

New discovery

- There had been some evidence that the ratio of IκBα to NFκB was 3 times what was 'needed'
- Where was all this excess IκBα?
- The model predicted that if it was sequestered with the actin filaments this would explain where it was
- We can track every molecule at all times and thus model the full pathway in detail
- Recent experiments have produced very significant data that confirms this

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Immunoprecipitation of IκBα and secondary actin immunoprecipitation



Results of Western blot experiments

PLOS 2009

M Pogson et al PLOSOne 3(6): (2008)

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A new receptor -TILLR

QuickTime™ and a decompressor are needed to see this picture.

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Results

QuickTime™ and a decompressor are needed to see this picture.

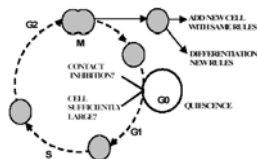


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Tissue modelling

Epithelial cell types

- Stem cells
- Transit amplifying cells
- Differentiating cells
- Fibroblasts
- Keratinocytes
- Corneocytes



The basic cell cycle

These cells form a society

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Epitheliome project

- We model each cell as an individual (agent)
- Experiment with different parameters to understand better:
 - Cell proliferation and development
 - Wound healing etc.
- Factors include: cell division (agent proliferation) and cell death;
- physical space model - the cells cannot divide if there is no room;
- intracell communication is important;
- cells role changes with age and circumstances.
- nutrient uptake, immune response, calcium, etc.
- physical forces

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Tissue culture

QuickTime™ and a
decompressor
are needed to see this picture.

QuickTime™ and a
decompressor
are needed to see this picture.

Simulations of urothelial monolayer - Tissue Responding to Wounds

QuickTime™ and a
DV-FPL decompressor
are needed to see this picture.

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are needed to see this picture.