Aims

• HOW TO use modeling to gain insights in biotic systems

• Biological insights (theory) obtained through modeling

Lectures (Tuesday, Thursday 10.00-12.45)
Tutorials (Tuesday, Thursday 13.15-17.00)
Review tutorials (Monday afternoons (13.15-15.00))
Background Literature (Monday and ..)
Mini-project (model study, report (incl litt)
Literature Seminar
Preliminaries.....

- “De leerdoelen van de cursus”
  the "art" of biological modeling
  Basic modeling skills
  understanding modeling results: insights and limitations
  ability to read/understand present day modeling literature
  Knowledge of Biological Theory

- “Plaats in het curriculum (studiepaden bijvoorbeeld)”
  Core course Computational Biology / Biocomplexity (Bsc & Msc)

- “De manier van beoordeling”
  Written Exam (+ adequate miniproject and seminar)

- “Aanwezigheids- en inspanningseisen”
  written report on computational project
  literature seminar
  No mandatory presence requirements, except at seminars

  BUT

  ....
Biological systems are complex multilevel systems, which came about by evolution and are evolving: (how to) study them as such....

"models should be as simple as possible but not more so... (Einstein)"
Biotic system are multilevel systems: study them as such. *information transmission, transformation between levels and over multiple timescales*

Given known (or assumed) interaction at the micro level what are the (counterintuitive) consequences? *simple local interactions → complex behaviour*

*other names:*

*Complex systems, Biocomplexity, Bioinformatics, Systems biology, Theoretical biology*
Biological systems as complex systems

Hallmark of complex systems:
Emergence /Emergent phenomena

Structures/ Patterns/ Behavior which is:
not predefined
arise and persist for some time
Unexpected and often counter-intuitive
at space/time scales different from the 'rules'
“mesoscale patterns with a dynamics of their own”
Needs new concepts/words to describe

simple local rules to complex behavior

Self-organization
Sir Paul Nurse: Organisms are information networks
Speaking at the Royal Institution earlier this year, cell biologist and Nobel prizewinner Paul Nurse predicts that the complexity of life’s networks will take us into a strange and counterintuitive world

Biology faces a quantum leap into the incomprehensible
Physics had to come to terms with the transition from commonsense Newtonian theory to the counterintuitive world of relativity and quantum mechanics. Now it’s biology’s turn

counterintuitive - BUT through computational modeling potentially comprehensible
Structure of the course

- **Introduction:**
  - models and model formalisms: FSM, CA, Event-based, IOM, MAPS, ODE, PDE
  - basic modeling concepts: mesoscale patterns
  - examples: ecology, gene regulation networks, morphogenesis

- **Ecoevolutionary dynamics**
  - from population dynamics to multilevel evolutionary processes
  - spatial pattern formation and new levels of selection

- **Evolution of coding structures (genome/ regulome)**
  - genotype-phenotype mapping:
    - RNA folding, regulatory networks
  - neutrality and robustness, information integration
  - evolution of evolvability (EVOEVO)
  - evolution as modeling tool

- **Large scale models**
- **Multilevel modeling of Development**
- **Individual based models of behaviour**
Models are (often) caricatures...

Given complexity of (biotic) systems
drastic simplification is needed AND desirable

(needed to make them doable
desirable to be understandable)

Need of multiple different “points of view”

Multiple models

Multiple model formalisms

*Thinking in the most interesting simplifications*
model requirements: fully specified

Prototype: Finite State Machine

\[ <I, S, O, \Sigma, \Omega> \]

and subsets

Input-Output = Simulus Response: \( <I, O, \Omega> \)

Autonomous systems: \( <S, \Sigma> \) (or with output)

State: what is needed to get unique nextstate/output

Unique next state function \( \rightarrow \) attractor(s)

garden of eden states
Can be specified as table

<table>
<thead>
<tr>
<th>Input</th>
<th>State</th>
<th>Nextstate</th>
<th>Output</th>
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<tr>
<td>I_1</td>
<td>S_1</td>
<td>S_x</td>
<td>O_j</td>
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<td>I_1</td>
<td>S_2</td>
<td>S_y</td>
<td>O_k</td>
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</tr>
<tr>
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<td>S_1</td>
<td>S_z</td>
<td>O_l</td>
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an autonomous FSM
“short cuts” on full transition table specification modeling formalisms (heuristics)

1. Decomposition in many simple subsystems (each specified by transition table/transition function)

   - collective behavior of simple entities
   - IO relations between some entities

examples:

Cellular automata CA
(Boolean Networks)
Individual/agent based models
Cellular Automata

prototype for:
  simple local information processing leading to 
  complex "emergent" behaviour

Definition: (in)finite tessellation of 'simple' FSM

'simple' FSM:
- small number of states (2)
- output == state
- input from local neighbourhood
- synchronous updating next state function 
  collectively again FSM

"speed of light"

MESOSCALE PATTERNS
Example CA: Modulo Prime
Classical examples of Cellular automata  
(2) Game of life

Birth: if \# Neighbours is 3 then \( S = 1 \)
Survival: if in state 1
and \# Neighbours is 2 or 3 then \( S = 1 \)
Death: if \# Neighbours < 2 or > 3 then \( S = 0 \)

emergence of
mesoscale patterns
long range signaling

Conway: “life is universal”
(i.e. game of life can simulate universal Turing machine)

No machine can “predict” fate of every intitital configuration
no shortcutes : let it live its life

proof of fundamental principle
(not model of “something”)

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Classical examples of Cellular automata
(3) Majority rule

Moore 9 neighbourhood
if <= 4 Neighbours in state 1 nextstate=0; else nextstate=1;

Model for (too?) Many “somethings”
e.g. Physics: Ising model, social science: voting, biology...
Emergence
Mesoscale patterns with a dynamics of their own

Sometimes paraphrased as:

"the whole is more than the 'sum' of its parts(?)"

HOWEVER

This is because of a constraint of the possible states.

-- >

the whole is LESS than the sum of its parts

MOREOVER:

Emergent patterns not just WOW!
Mesoscale patterns (higher level entities) with a dynamics of their own

Example: Multilevel description of ECA54 (cf Crutchfield et al.)

REVIEW PAPER:
Cellular automata, emergent phenomena in
JE Hanson - Computational Complexity, 2012 - Springer
ECA 54, the rule under consideration here:

\[ \phi(\eta) = \begin{cases} 
0, & \eta \in \{111, 110, 011, 000\} \\
1, & \eta \in \{101, 100, 010, 001\}
\end{cases} \]

**Figure 1.** Space-time diagram of ECA 54, starting from an arbitrary initial condition. Boundary conditions are periodic. White squares are cells with value \( s_t^i = 0 \); black squares are cells with \( s_t^i = 1 \).

**Figure 2.** A portion of fig. 1 showing the domain \( \Lambda_{54} \). Note the spatial phase shift of 2 cells every two iterations.

**Figure 3.** Process graph of ECA 54's domain \( \Lambda_{54} \). The component on the left is \( \Lambda_A \); on the right is \( \Lambda_B \). As the dotted lines indicate, they are mapped onto one another by the CA ensemble evolution operator, \( \Phi_{54} \). In this and all following graphs of machines, inscribed circles and squares denote start and accept states, respectively.
Figure 4. The process graph of $M_{ST}(A_{54})$, the space-time machine for $A_{54}$. States are labelled to correspond to those in the (purely spatial) domain machine $M(A_{54})$ in fig. 3.

Figure 5. ECA 54's domain filter $T^0_{54}$, which maps sites in the domain to 0 and each defect to a unique output in \{1, \ldots, 8\}. Labelled machine states correspond to the domain states of fig. 3.

Figure 6. Space-time data of fig.1, filtered with the domain transducer $T_{54}$ of fig. 5. White cells correspond to sites participating in $A_{54}$; black cells, to sites with values
Figure 8. Basic wall structures ("fundamental particles") in space-time patterns of ECA 54. (a) Unfiltered space-time diagrams of the three types of particle $\alpha$, $\beta$, and $\gamma$ described in the text. (b) Filtered diagrams of the same data, produced by $T_{14}^\circ$. Domain symbols are white cells. All defects are shown in black, with the defect symbol inscribed in white. The temporal phases of the particles, chosen by convention, are printed alongside the filtered strings.

Figure 9. Filtered space-time diagrams of the fundamental interactions among ECA 54's fundamental particles, as listed in table 1. (a)–(e) are two-particle collisions; (f) and (g) are three-particle collisions. Filtering was done with the first version of particle filter $T_{14}^\circ$ described in the text. The domain is shown as white, the particles $\{\alpha, \beta, \gamma^+, \gamma^\circ\}$ are shown in black. Defects not corresponding to any of the particles are shown in black and have the corresponding $T_{14}^\circ$ output symbols inscribed in white.
<table>
<thead>
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<th>Reaction</th>
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<tbody>
<tr>
<td>(a)</td>
<td>$\alpha + \gamma^- \rightarrow \gamma^- + \alpha + 2\gamma^+$</td>
</tr>
<tr>
<td>(b)</td>
<td>$\gamma^+ + \alpha \rightarrow 2\gamma^- + \alpha + \gamma^+$</td>
</tr>
<tr>
<td>(c)</td>
<td>$\beta + \gamma^- \rightarrow \gamma^+$</td>
</tr>
<tr>
<td>(d)</td>
<td>$\gamma^+ + \beta \rightarrow \gamma^-$</td>
</tr>
<tr>
<td>(e)</td>
<td>$\gamma^+ + \gamma^- \rightarrow \beta$</td>
</tr>
<tr>
<td>(f)</td>
<td>$\gamma^+ + \alpha + \gamma^- \rightarrow \gamma^- + \alpha + \gamma^+$</td>
</tr>
<tr>
<td>(g)</td>
<td>$\gamma^+ + \beta + \gamma^- \rightarrow \emptyset$</td>
</tr>
</tbody>
</table>

Table 1. Fundamental interactions among ECA 54’s particles. Interactions (a) and (b) induce a spatio-temporal shift in the incident particles, as discussed in the text. Note that the spatial arrangement of input and output particles is respected by the interaction notation. $\emptyset$ denotes no particles.

Figure 11. Fraction of the CA lattice devoted to the fundamental particles ($\alpha, \beta, \gamma^+, \gamma^-$), to $\alpha$-$\gamma$ interactions (8), and to unrecognized defects $\{1, \ldots, 8\}$ versus time.
conclusions

Detection of mesoscale entities

*WITH A DYNAMICS OF THEIR OWN*

Description of system in variable set of interacting higher level entities (individual based models) ("beyond dynamical systems")

Description in terms of populations of these entities