Exam: Multiscale Mathematical Biology

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16 ~~February~~ January 2019, 14:00-17:00

Note: *Questions are phrased in English. Answers in Dutch or in English are both acceptable. Citations to the literature are given for completeness only – you will not need these papers for the exam.*

Question 1 - Fruit flies

This question concerns the first steps in the embryonic development of the fruit fly, *Drosophila melanogaster*.

Question 1A - 0.5 points

Figure 1A shows the concentration of Bicoid mRNA along the anteroposterior axis an early embryo of *Drosophila*, taken from the paper by Spirov et al. [3]. The length is measured in terms of a percentage of the total length of the embryo (% EL).

- Explain how Spirov et al. [3] propose that this gradient is formed, in terms of a simple particle-based or continuum based model.
- What biological components do the variables represent?
- Explain your answer.

Question 1B - 0.5 points

- For what biological case would you recommend using a particle-based model of diffusion?
- For what situations would you rather use a continuum model?

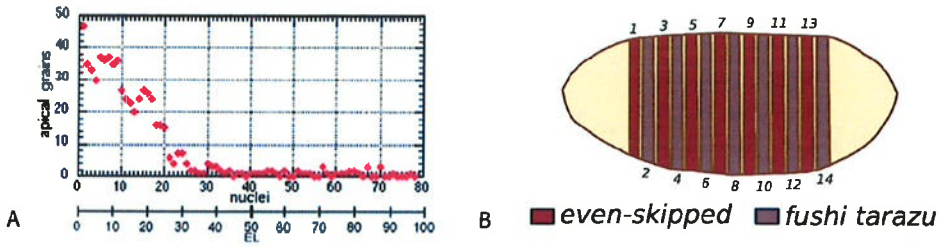

Figure 1: Patterning of the fruit fly, *Drosophila melanogaster*. A. Concentration of Bicoid mRNA along the anteroposterior axis an early embryo of *Drosophila* [3]. B. Schematic drawing of the expression pattern of the genes *even-skipped* and *fushi tarazu*.

Question 1C - 0.5 points

An earlier model proposed by Driever and Nüsslein-Volhard [1] proposed that the Bicoid protein was synthesized at the anterior end of the embryo, that it diffuses through the embryo, and that it is gradually broken down.

- What is the *name* of this model?
- Sketch the concentration of Bicoid protein predicted by this model after an arbitrary long amount of time (i.e., at $t \to \infty$).
- Show, using a second sketch, what concentration profile of mRNA the model by Spirov et al. [3] predicts after an arbitrary long amount of time. Explain the biological interpretation, if any.

Assume a close boundary condition at the anterior (head) end of the embryo, and an open boundary condition at the posterior (tail) end of the embryo.

Question 1D - 0.5 points

Figure 1B shows the pattern of the gene even-skipped, as it occurs during the development of *Drosophila melanogaster*. It has been hypothesized that this striped pattern is formed by the interaction between two morphogens X and Y, according to a Turing [4] mechanism.

- Discuss the key assumptions and conditions of the Turing [4] mechanism (possibly using terminology introduced by Gierer and Meinhardt [2]), which produce spots or stripes. Note that the mechanism

that we are looking for is not necessarily biologically correct for this situation.

Question 1E - 0.5 points

Later insights have made clear that in the fruit fly, each even-skipped stripe is switched on by a different set of regulatory genes. The regulatory genes, called gap genes, are each active in a separate domain of the embryo.

- Using two genes X and Y as an example, schematically draw the set of interactions between X and Y that explains why only one gap gene at a time is active in each domain of the embryo.
- Through what biological mechanism are the gap genes expressed in the correct order? Indicate it in the scheme above.

Question 2: Cell-based modeling (2.5 points)

Question 2A - 1.0 points

2 3 4 5 6
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Figure 3A shows an overview of cell-based modelling methodology.

- Give an example for each of the six fields in the scheme.

An example consists of (1) a name; (2) a brief description in words.

You may use equations if it is helpful for your explanation, but they are not necessary. It is not necessary to describe the algorithm in detail.

Question 2B - 0.5 points

Consider the following Hamiltonian, which defines a Cellular Potts model

$$H = \sum_{(\vec{x},\vec{x}\prime)} J(\tau(\sigma(\vec{x})),\tau(\sigma(\vec{x}\prime)))(1-\delta(\sigma(\vec{x}),\sigma(\vec{x}\prime)))+\sum_{\sigma}\lambda(\sigma)(A(\sigma)-A_0)^2, \quad (1)$$

with $\lambda(0) = 0$ and $\forall\sigma > 0 : \lambda(\sigma) > 0$

Figure 2A shows the initial condition of a set of simulations of the Cellular Potts model. Figures 2B-F show a series of simulation results after 200,000 Monte Carlo steps. The parameter settings were as in Table 1. These are listed in no particular order.

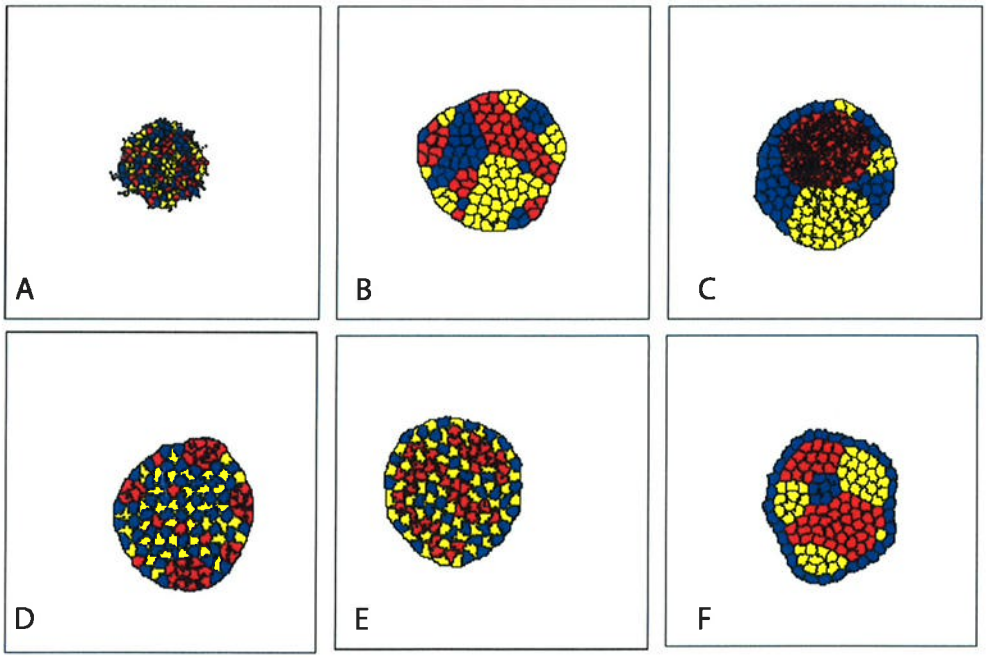


Figure 2: Simulations of the cellular Potts model on a lattice of 200 × 200 lattice sites. (A) Initial condition with 128 cells (0 MCS); cell types have been assigned at random; (B-F) simulation results at 200,000 Monte Carlo Steps.

Set	J	λ	T	A_0
2	$\begin{array}{c} \\ \text{medium} \\ \text{red} \\ \text{yellow} \\ \text{blue} \end{array} \begin{array}{c} \begin{array}{cccc} \text{medium} & \text{red} & \text{yellow} & \text{blue} \end{array} \\ \begin{pmatrix} 0 & & & \\ 40 & 5 & & \\ 40 & 20 & 30 & \\ 40 & 20 & 10 & 30 \end{pmatrix} \end{array}$	50	50	50
3	$\begin{array}{c} \\ \text{medium} \\ \text{red} \\ \text{yellow} \\ \text{blue} \end{array} \begin{array}{c} \begin{array}{cccc} \text{medium} & \text{red} & \text{yellow} & \text{blue} \end{array} \\ \begin{pmatrix} 0 & & & \\ 80 & 20 & & \\ 80 & 40 & 20 & \\ 80 & 40 & 40 & 20 \end{pmatrix} \end{array}$	50	50	50
4	$\begin{array}{c} \\ \text{medium} \\ \text{red} \\ \text{yellow} \\ \text{blue} \end{array} \begin{array}{c} \begin{array}{cccc} \text{medium} & \text{red} & \text{yellow} & \text{blue} \end{array} \\ \begin{pmatrix} 0 & & & \\ 80 & 5 & & \\ 40 & 7 & 30 & \\ 40 & 20 & 10 & 30 \end{pmatrix} \end{array}$	50	50	50
5	$\begin{array}{c} \\ \text{medium} \\ \text{red} \\ \text{yellow} \\ \text{blue} \end{array} \begin{array}{c} \begin{array}{cccc} \text{medium} & \text{red} & \text{yellow} & \text{blue} \end{array} \\ \begin{pmatrix} 0 & & & \\ 80 & 20 & & \\ 60 & 40 & 20 & \\ 20 & 40 & 40 & 20 \end{pmatrix} \end{array}$	50	50	50
6	$\begin{array}{c} \\ \text{medium} \\ \text{red} \\ \text{yellow} \\ \text{blue} \end{array} \begin{array}{c} \begin{array}{cccc} \text{medium} & \text{red} & \text{yellow} & \text{blue} \end{array} \\ \begin{pmatrix} 0 & & & \\ 80 & 2 & & \\ 40 & 20 & 7 & \\ 40 & 20 & 20 & 20 \end{pmatrix} \end{array}$	50	50	50

Table 1: Parameter sets for the simulations shown in Figures 2B-F, listed in random order

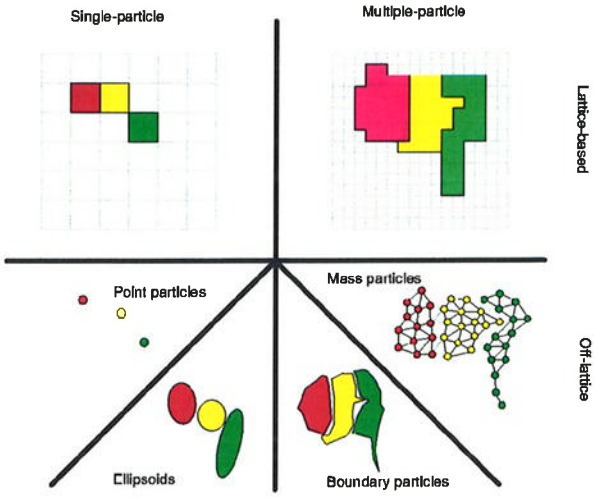


Figure 3: Overview of cellular representations in cell-based modeling technologies

- Match the simulation outcomes in Figure 2 with the correct set of parameters, by writing for example, "Simulation A: Set 2" (not necessarily correct), and add a short (one line) explanation.

Question 2C - 0.5 points

- Describe the steps of the cellular Potts algorithm in detail.

Question 2D - 0.5 points

- Why do cells in epithelial tissues have, on average, six neighbors?
- Explain.

Question 3: Further investigations of a new ant species - 2.5 points

During an expedition to the Palombian rainforest, your entomologist colleague has identified an ant species still unknown to science. These curious

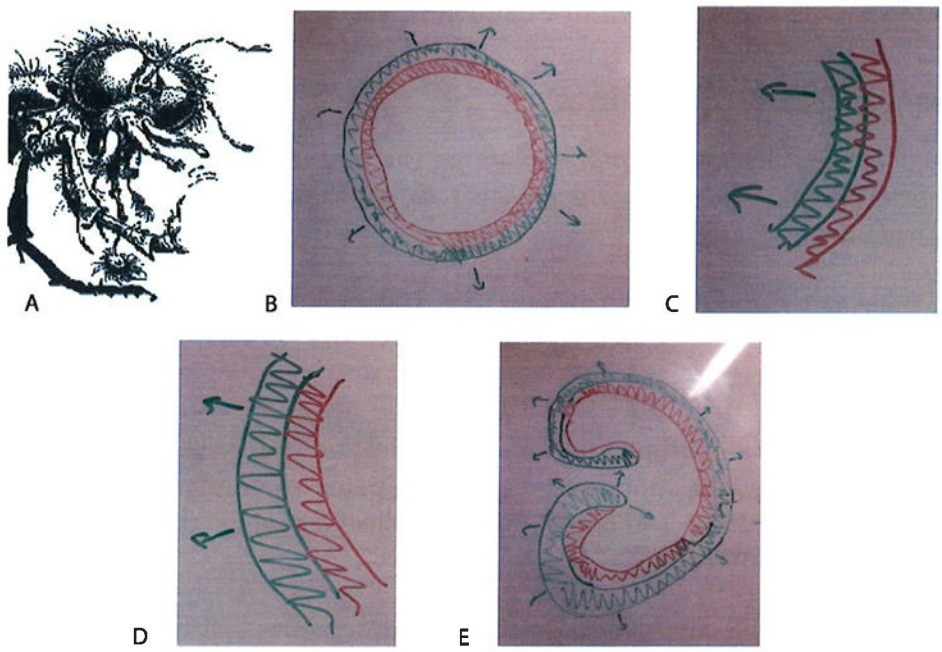


Figure 4: A. Palombian ant, close-up. Sketch by André Franquin; B. Sketch of circular leaf-fungi culture found in the highlands; C. Curved location of a fungi culture; D. Another curved location of a fungi culture; E. Sketch of spiral-shaped leaf-fungi culture found in the rocky mountain valleys. Green: fresh leaves; red: older leaves overgrown by fungi; arrows indicate movement direction of patterns

ants (Figure 4A) seem to be a kind of leaf-cutter ants: they culture fungi on small pieces of leaves which they organize on carefully cleared pieces of soil, forming the patterns shown in your colleague's sketch shown in Figure 4B. The white area indicates the soil, the green area shows fresh leaves, and the red area is already covered with fungi.

Your colleague explains to you the ants' curious behavior: they cut out bits of plant leaf and carry them to the area covered with bits of leaf. They seem to carefully seek out an empty part of the soil next to a fresh leaf, and place it there. During this behavior, the ants avoid the old leaves already covered in fungi. The ants quickly eat the fungi, leaving the soil empty again. The fungi cultures seems to move gradually over the soil in the direction

indicated by the arrows shown in Figure 4.

Question 3A - 0.5 points

Your colleague asks your help in explaining the pattern shown in Figure 4B. As a first model, you propose a physical model than can help explain the emergence of this pattern.

- What is the name of the system that you would propose?

Question 3B - 0.5 points

Propose a three-state cellular automata model for the system. Make the following simplifying assumptions. Initiate a patch of empty soil with one piece of leaf. Ignore the 'leaf cutting' and the 'leaf carrying'. Leaves covered in fungus are quickly eaten.

- Define suitable rules for these cellular automata
- What is the name of this model

Question 3C - 0.5 points

Figure 4C,D shows two locations of an ant fungus culture.

- Which location will move faster and why?
- Does the Cellular Automata model that you have proposed explain this?
- Why or why not?

Question 3D - 1.0 point

A couple of years later, a new paper on these curious leaf-cutter ants appears in *Palombian Naturalist.* It describes an ant species that cultures its fungi in spiral-like configurations, as shown in Figure 4E. It lives in a different environment: the original species lives in the highlands on flat soil, this new species lives in the mountain valleys, where rocks are scattered over flat soils; the ants cannot put leaves on the rocks.

Because of the large differences in the fungus culture system and the different environment, the authors conclude that the ant must be a new species. They have not observed any clear morphological differences between the two ant species; neither did they identify genetic differences.

You disagree with these authors.

- Write a short e-mail to the Palombian colleague with whom you collaborated in Questions 3A and 3B. Propose a simple experiment that may prove the authors of the article in *Palombian Naturalist* wrong: in fact both species can make spiral-like configurations. The experiment is performed in the highlands. Discuss the prediction of the model for the outcome of the experiment.
- Why are spiral configurations found in the rocky mountain valleys?
- What is the mechanism for spiral formation?

Question 4: Ecology and evolution

Question 4A - 1.0 points

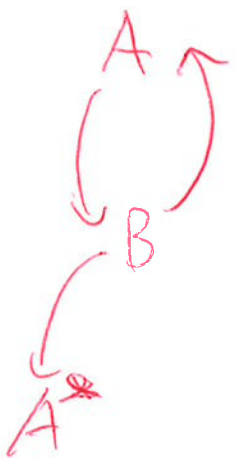
Consider the following 2-species bacterial eco-system growing in a well-mixed tube:

Species A produces and secretes an amino-acid a that is essential for the growth of a second species B. Species B secretes an amino-acid b, that is in turn essential for the growth of species A. So the species depend on each other for their growth.

- Due to a mutation, a bacterium of species A stops producing the molecular pump that secretes the amino acid. What happens to the ecosystem?
- Speculate on what could happen if the same experiment were run on a Petri dish.

Question 4B - 1.0 points

Consider the following experiment:



In a chemostat (a well mixed system kept at constant volume) you have three ribozymes (RNA enzymes) named X, Y, and Z. Ribozyme X converts a resource into ribozyme Y; ribozyme Y converts a resource into Z, and ribozyme Z converts a resource into X. All resources are abundant.

The chemical equations read:

$$R_1 + X \longrightarrow X + Y$$
$$R_2 + Y \longrightarrow Y + Z$$
$$R_3 + Z \longrightarrow Z + X$$

Assume that by chance a slightly more efficient ribozyme X' is generated. This mutant catalyses the formation of Y at a higher rate.

- Will this mutated X' be selected in favor of the original X?
- Explain why or why not.

Question 4C - 0.5 points + 0.5 bonus points

A philosopher tells you: "The theory of evolution is not a real scientific theory, because 'survival of the fittest' is a tautology: It is equivalent to 'survival of whomever survives'."

- What do you answer, making use of models you learnt in the course?

References

[1] W Driever and C Nüsslein-Volhard. A gradient of bicoid protein in drosophila embryos. *Cell*, 54(1):83–93, 1988.

[2] A Gierer and H Meinhardt. A Theory of Biological Pattern Formation. *Kybernetik*, 12:30–39, 1972.

[3] Alexander Spirov, Khalid Fahmy, Martina Schneider, Erich Frei, Markus Noll, and Stefan Baumgartner. Formation of the bicoid morphogen gradient: an mRNA gradient dictates the protein gradient. *Development*, 136(4):605–614, 2009.

[4] A M Turing. The Chemical Basis of Morphogenesis. *Phil. Trans. Roy. Soc. B*, 237:37–72, 1952.