Typo's zijn gecorrigeerd

Exam: Multiscale Mathematical Biology

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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: Morphogen gradients

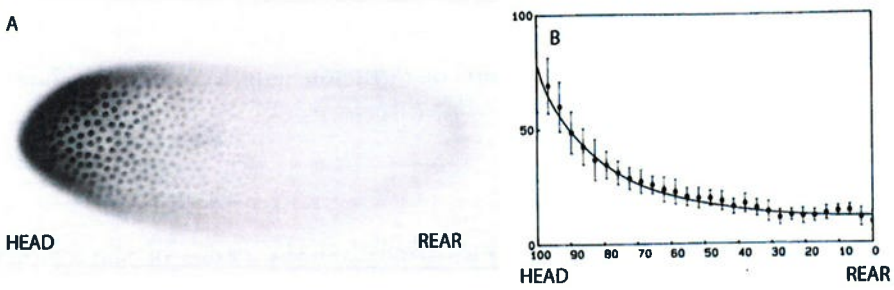

Figure 1: Distribution of the Bicoid gradient in an early embryo of the fruit fly, *Drosophilia* (syncytial stage). (A) Staining ("kleuring") of the Figure taken from Ref.[1]; (B) intensity of the staining along the head to rear axis of the embryo, given in arbitrary units

Figure 1A shows a staining ("kleuring") of the gradient of the Bicoid protein in an embryo of *Drosophila*, taken from the paper by Driever and Nüsslein-Volhard [1] of 1988. Figure 1B shows the intensity of the staining along the horizontal (head to rear) axis of the embryo. This is a good measure of the concentration of Bicoid. The head forms where the concentration of

Bicoid is high (on the left); the fly's rear end forms where the concentration of Bicoid is low (on the right).

Question 1 concerns the formation of this gradient of the Bicoid protein. Driever and Nüsslein-Volhard [1] observed a localized concentration of bicoid mRNA near the future head of the embryo. The mRNA forms a localized source of Bicoid protein, and it was hypothesized that the Bicoid protein diffuses along the embryo.

Question 1A

Write down the one-dimensional, partial-differential equation model that Driever and Nüsslein-Volhard have proposed to explain the observed gradient of Bicoid. Also give the boundary conditions.

Question 1B

What is the *name* of this model?

Question 1C

Use this model to explain the concept of *diffusion length*. What two factors control the diffusion length and in what direction?

Question 1D

In 2009 Spirov and coworkers [4] have revisited the cause of the gradient of Bicoid. Thanks to improvements in the experimental techniques, they observed that two key assumptions in the model of Driever and Nüsslein-Volhard were incorrect in the fruit fly.

Name at least two model assumptions that turned out to be incorrect.

Question 1E

Correct the model based on the new observations of Spirov et al., and describe how the new model explains the Bicoid gradient.

Question 2: Turing patterns

In 1952, Alan Turing showed that "that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis" [5]. Gierer and Meinhardt [2] have rephrased the Turing model as,

$$\begin{aligned} \frac{\partial A}{\partial t} &= c_A \frac{A^2}{H} - \mu A + D_A \nabla^2 A + \rho_A, \\ \frac{\partial H}{\partial t} &= c_H A^2 - \nu H + D_H \nabla^2 H + \rho_H. \end{aligned} \tag{1}$$

Question 2A

What is the biological or chemical function of substance A, and what is the function of substance H? Or: in other words, what are the *names* usually given to A and H?

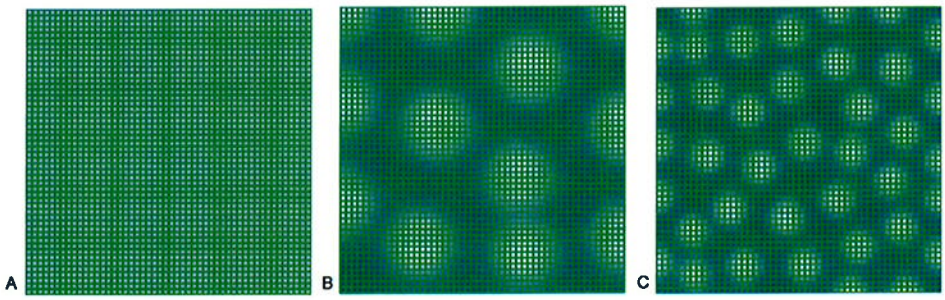

Figure 2: Numerical solutions of the system described in Eq. 1

Question 2B

Imagine you are running a numerical simulation of this model on a two-dimensional field (*e.g.*, using the software VirtualLeaf that was used in the computer labs.). You have set the parameters to $c_A = 0.2$, $\mu = 0.1$, $D_A = 0.2$, $\rho_A = 0.01$, $c_H = 0.1$, $\nu = 0.1$, $\rho_H = 0$, and $D_H = 0.2$. The initial values are $A = 1$ and $H = 1$ at each point in the field.

After you start the simulation, you observe an oscillation that settles down onto a steady state, as in Figure 2A. What single parameter value in the above list should at least be changed in order to obtain a solution like that in Figure 2B?

Question 2C

Propose a suitable value for the parameter mentioned in Question 2B, in order to obtain the solutions shown in Figure 2B.

Question 2D

Under the given conditions, the parameter change proposed in Question 2C still does not yield periodic numerical solutions. Explain why. What can you do to overcome the problem, i.e., what is also needed to obtain a solution similar the one shown in Figure 2B?

Question 2E

Propose a set of parameters by which patterns with a shorter wavelength would develop, such as those shown in Figure 2C.

Question 3: Cellular automata

Question 3A

Give a definition for "cellular automata".

Question 3B

Define "Moore neighborhood".

Question 3C

Write down the "voting rule".

Question 3D

Consider voting rule cellular automata, on a regular square lattice with a Moore neighborhood. Initialize the simulation with 50% of the cells in state '0' and 50% of the cells is state '1'. Sketch the outcome of the simulation after a few lattice updates. Sketch the solution after a couple of thousand additional lattice updates.

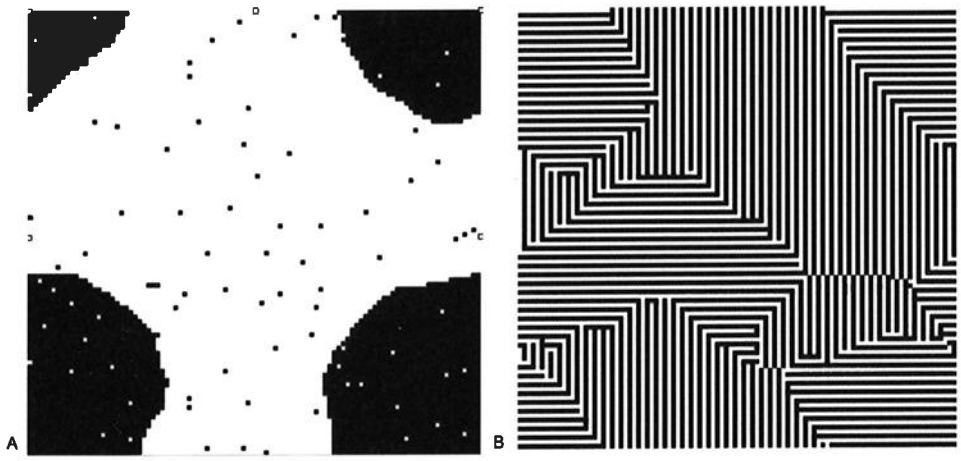

Figure 3: Snapshots of the simulations mentioned in Questions 3E-F

Question 3E

Propose a modification to the voting model so as to obtain the outcome shown in Figure 3A. How does this work?

Question 3F

Propose a modification to the parameters of the model meant in Question 3E so as to obtain the outcome show in Figure 3B. Explain.

Question 3G

Name a key property of class IV cellular automata that sets them apart from classes I to III. Give an example of class IV cellular automata.

Question 4: Cell-based models

Consider the following Hamiltonian, which defines the Cellular Potts model

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

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

Question 4A

In this equation, what are σ, τ, and $(\vec{x}, \vec{x}\prime)$?

Question 4B

What is the meaning of this term: $(1 - \delta(\sigma(\vec{x}), \sigma(\vec{x}\prime)))$?

Question 4C

Describe a configuration for which $H = 0$, independent of the parameter values.

Question 4D

Describe the *update rule* of the Cellular Potts model. Or, in other words, describe the algorithm underlying the cellular Potts model.

Question 4E

Figure 4A shows the initial condition of a set of simulations of the Cellular Potts model. Figures 4B-F show a series of simulation results after 30000 Monte Carlo steps. The parameter settings were as in Table 1. They are listed in no particular order. Match the simulation outcomes in Figure 4 with the correct set of parameters, by writing for example: "Simulation A: Set 2" (not necessarily correct).

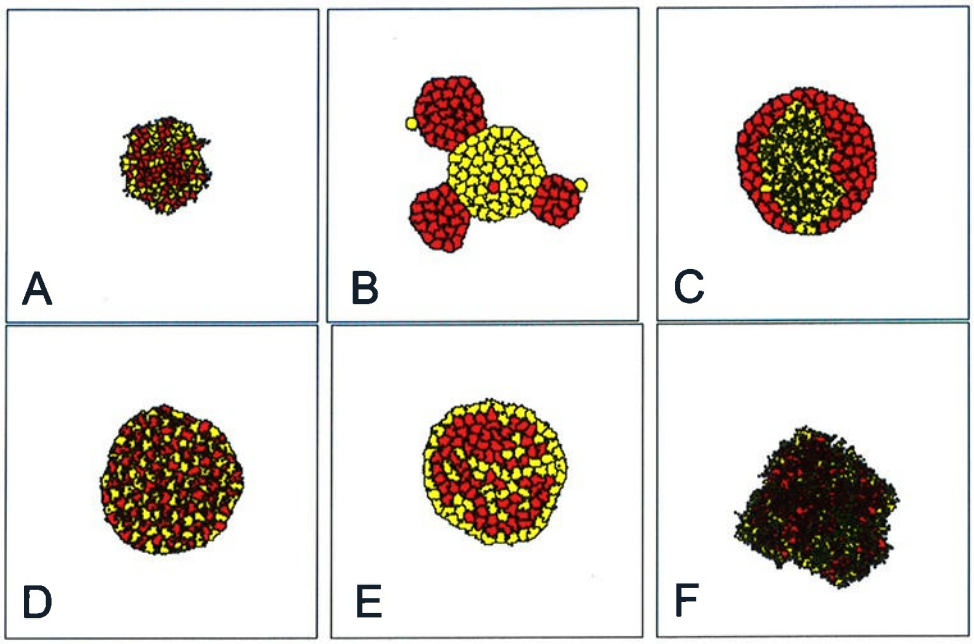

Figure 4: Simulations of the cellular Potts model on a lattice of 200 × 200 lattice sites. (A) Initial condition (0 MCS); (B-F) simulation results at 30000 MCS. Legend: White: cell type 0 ("medium"); red: cell type 1; yellow: cell type 2; cell-cell boundaries shown in black

Set	$J(0,0)$	$J(1,0)$	$J(1,1)$	$J(2,0)$	$J(2,1)$	$J(2,2)$	λ	T	A_0
1	0	20	10	20	10	3	50	50	50
2	0	30	10	20	10	10	50	500	50
3	0	20	10	20	3	10	50	50	50
4	0	30	10	20	10	10	50	50	50
5	0	20	10	20	40	10	50	50	50

Table 1: Parameter sets for the simulations shown in Figure 4 listed in random order

Question 4F

Consider a hybrid cellular Potts model on a square lattice of 200×200, with a chemical field defined as $c(\vec{x}) = c_0 * e^{-x_1/50}$, with $\vec{x} = \{x_1, x_2\}$. Describe a frequently used extension of the Cellular Potts model, by which a cell released close to $\vec{x} = \{0, 100\}$ will chemotact towards $x_1 = 200$.

Bonus Question: Multiscale modeling

This question can give you some additional points. Describe the key assumptions underlying the aggregation of amoebae in the Savill and Hogeweg [3] model of the slime mold *Dictyostelium discoideum*.

References

[1] W Driever and C Nüsslein-Voldhard. 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] N J Savill and P Hogeweg. Modelling morphogenesis: From single cells to crawling slugs. *Journal of Theoretical Biology*, 184(3):229–235, 1997.

[4] 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.

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