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

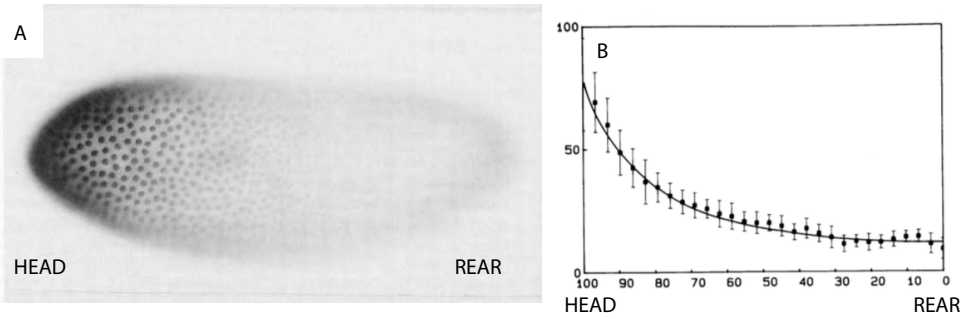

Figure 1: Distribution of the Bicoid gradient in an early embryo of the fruit fly, *Drosophilia* (syncytial stage). (A) Staining ("kleuring") of the Figure taken from Ref.[1]; (B) intensity of the staining along the head to rear axis of the embryo, given in arbitrary units

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 *Drosophila* this gradient of Bicoid gives rise to a pattern of finely delineated bands of "gap genes". Based on a reverse-engineering approach, in 1995 Sharp and Reinitz [4]have identified a set of interactions between the gap genes that can generate sharp bands of gap gene expression. Draw an interaction scheme of two hypothetical gap genes to illustrate this mechanism.

Question 1E

How, according to Sharp and Reinitz [4], can the Bicoid gradient regulate the correct ordering of gap gene expression stripes?

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" [6]. Gierer and Meinhardt [2] have rephrased the Turing model as,

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

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?

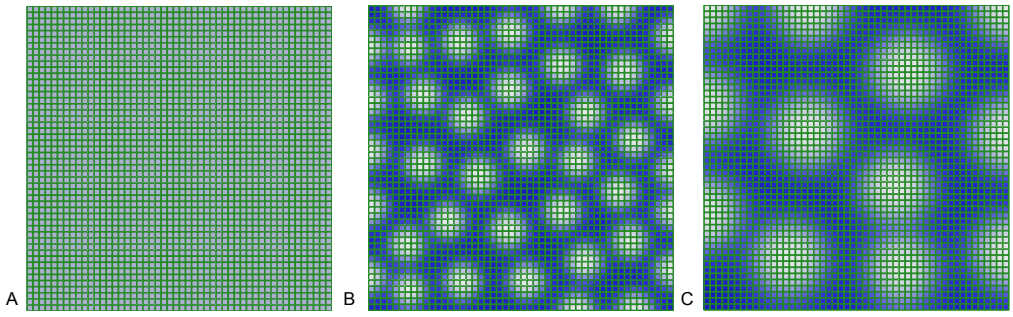

Figure 2: Numerical solutions of the system described in Eq. 1

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 $c_A = 0.2$, $\mu = 0.1$, $D_A = 0.1$, $\rho_A = 0.01$, $c_H = 0.1$, $\nu = 0.1$, $\rho_H = 0$, and $D_H = 0.1$. The initial values are $A = 1$ and $H = 1$ at each point in the field.

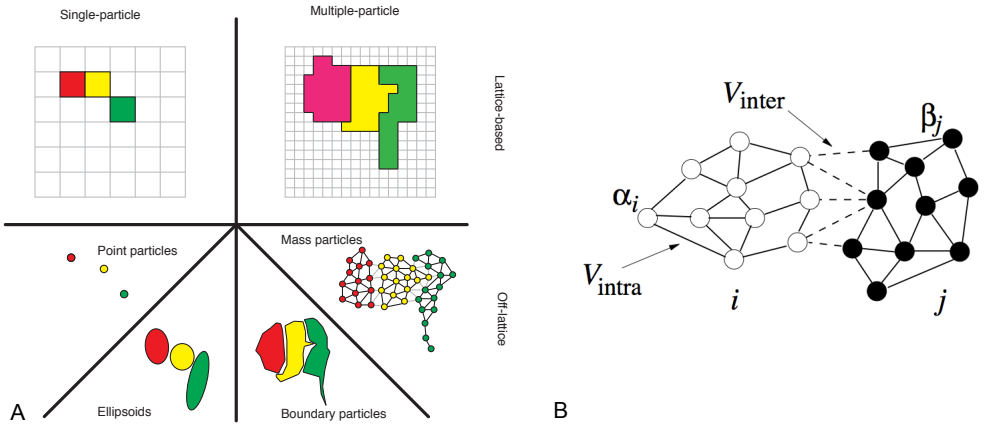

Figure 3: Overview of cellular representations in cell-based modeling technologies

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? Propose a suitable value for this parameter.

Question 2C

Under the given conditions, the parameter change proposed in Question 2C still does not yield periodic numerical solutions. After perturbing the system numerically, the system does evolve towards a periodic solution. What must you (or the software) do to 'perturb the system numerically'? Why is it required for obtaining periodic solutions?

Question 2D

Propose a change of one or two parameters that would lead to patterns with a longer wavelength, such as those shown in Figure 2C.

Question 3: Cell-based modeling

Question 3A

In Figure 3A, which quadrant shows the representation of cells in the cellular Potts model? Explain.

Question 3B

Give an example of a "boundary-particle" method (see Figure 3).

Question 3C

Figure 3B shows an example of a cell-based modeling methodology proposed by Newman [3]. Classify this methodology according to Figure 3A.

Question 3D

What is the name of the methodology in Figure 3B?

Question 3E

In 1970 John Conway proposed his *Game of Life*. Classify this model according to Figure 3A.

Question 3F

What are the rules of Conway's Game of Life?

Question 4: Cellular Potts model

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 the above equation, what biophysical mechanism(s) does the term $\sum_{(\vec{x},\vec{x}\prime)} J(\tau(\sigma(\vec{x})), \tau(\sigma(\vec{x}\prime)))$ usually represent?

Question 4B

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

Question 4C

Propose a parameter setting for which all the cells will disappear, *i.e.,* we are looking for parameter values for which the system will evolve towards a state $\forall \vec{x} : \sigma(\vec{x}) = 0$. What will be the value of H for this state?

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).

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 [5] model of the slime mold *Dictyostelium discoideum*.

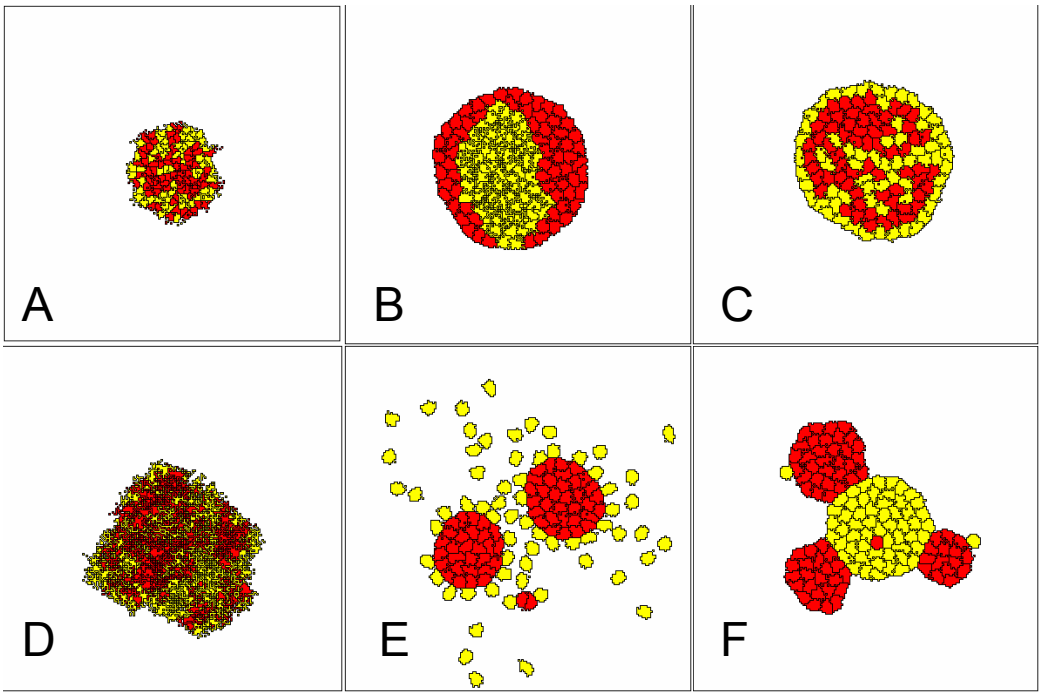

Figure 4: Simulations of the cellular Potts model on a lattice of 200×200 lattice sites. (A) Initial condition (0 MCS); (B-F) simulation results at 30000 MCS. Legend: White: cell type 0 ("medium"); red: cell type 1; yellow: cell type 2; cell-cell boundaries shown in black

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	30	10	20	10	10	50	50	50
4	0	30	10	20	50	50	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

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] TJ Newman. Modeling multicellular systems using subcellular elements. *Math Biosci Eng*, 2(3):613–624, 2005.

[4] J Reinitz and D H Sharp. Mechanism of eve stripe formation. *Mech Dev*, 49(1-2):133–158, 1995.

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

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