Exam: Multiscale Mathematical Biology

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17 January 2018, 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: Morphogen gradients (2.5 points)

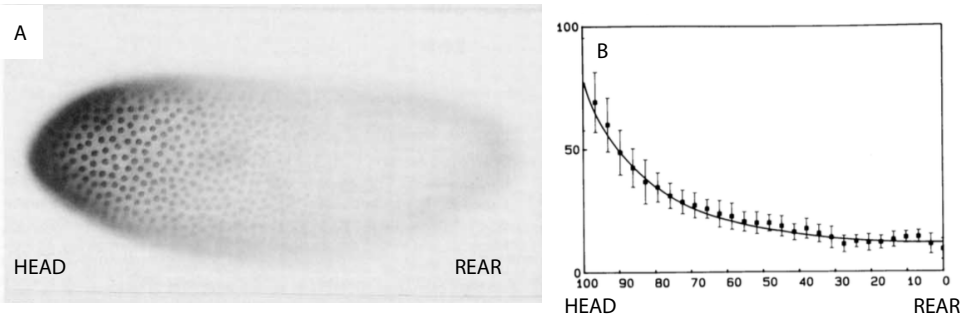

Figure 1: Distribution of the Bicoid gradient in an early embryo of the fruit fly, *Drosophilia* (syncytial stage). (A) Staining ("kleuring") of the Figure taken from Ref.[1]; (B) intensity of the staining along the head to rear axis of the embryo, given in arbitrary units

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 and "interpretation" 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. They concluded that mRNA forms a localized source of Bicoid protein, and hypothesized that the Bicoid protein diffuses along the embryo. (Ignore in this question the more recent observations by Ref. [4] that questioned Driever et al.'s conclusions.)

Question 1A - 0.3 points

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

Question 1B - 0.2 points

What is the *name* of the model that you wrote down in Question 1A?

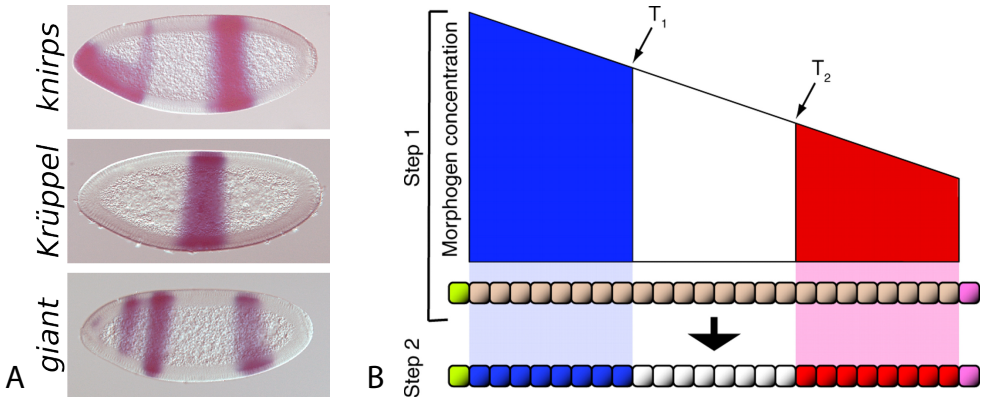

Figure 2: (A) Patterns of gap gene expression in the fruit fly; (B) Lewis Wolpert's model for translating a morphogen gradient into a gene expression pattern

Question 1C - 0.25 points

Figure 2A illustrates the expression of the so called "Hox-genes" in fruit flies, which determine the identify of segments in most animals. Figure 2B shows a simple model for the formation of such an ordered expression pattern from, e.g., a Bicoid gradient.

- Briefly describe this model (in words). Describe the purpose of T_1 and T_2 in this model.

Question 1D - 0.25 points

- What is a key problem with this model if morphogens occur at low concentrations (on the order of tens of molecules per cell)?

Question 1E - 1.0 points

Reinitz and Sharp [3] have proposed a model for how the Bicoid gradient instructs the expression pattern of gap genes. The model equations were,

$$\frac{dv_i^a}{dt} = R_a g_a \left(\sum_{b=1}^{N} T^{ab} v_i^b + m^a v_i^{[\text{Bicoid}]} + h^a \right) + D^a \left(v_{i-1} + v_{i+1} - 2v_i^a \right) - \lambda_a v_i^a, \tag{1}$$

where v_i^a is the concentration of protein a in nucleus i, R_a is a maximum production rate for gene a, g_a is a sigmoid function, m^a is a the effect of the concentration of bicoid on the transcription rate of gene a, $v_i^{[\text{Bicoid}]}$ is the concentration of Bicoid in nucleus i, and h^a is an independent gene transcription rate. The second term represents the diffusion of proteins between nuclei, and the third term represents the degradation rate of protein a.

- What does matrix T represent?
- What algorithm did Reinitz and Sharp use to estimate the values of T from experimental data? Give the name and a brief description of the algorithm.

Question 1F - 0.5 points

Imagine a system of two gap genes, and neglect the effect of Bicoid (*i.e.*, $\forall a : m^a = 0$).

- Give values of T_{ab} that would represent the main principle of the gap gene interactions as proposed in Ref. [3].

Question 2: Leaf hairs - 2.5 points

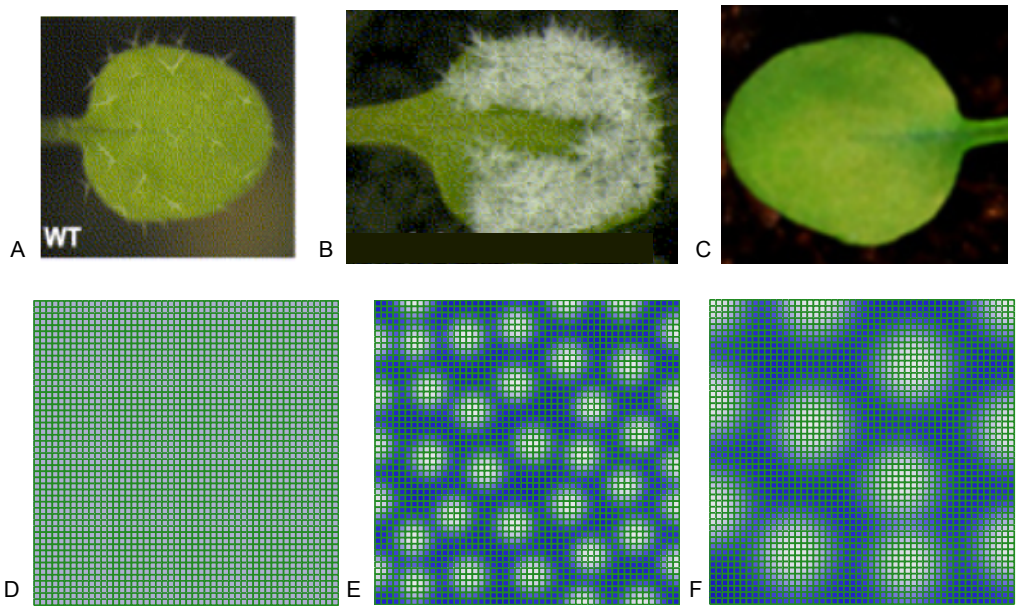

Figure 3: Phenotypes of two *Arabidopsis* gene knockouts and solutions of proposed model (A) Wild-type for comparison; (B) phenotype 1; (C) phenotype 2; (D-F) numerical solutions of proposed model as described in Eq. 2

Figure 3 shows three leaves of the thale cress *Arabidopsis thaliana*. Panel A is the wildtype (*i.e.*, "normal" leaf). Panels B and C are knockout phenotypes of the trichome (leaf hair) patterning system *i.e.*, leaves of plants in which a gene is made inactive.

A proposed model for the gene network that regulates the spacing of trichomes is,

$$\begin{aligned} \frac{\partial X}{\partial t} &= \frac{cX^2}{(k+eY)} - fX + D_x\nabla^2 X; \\ \frac{\partial Y}{\partial t} &= aX^2 - bY + D_y\nabla^2 Y. \end{aligned} \tag{2}$$

Question 2A - 0.5 points

- According to this model, which of the genes/proteins X or Y is inactive in Figure 3B, and which one in Figure 3C? Explain why.

Question 2B - 0.5 points

- Give suitable (relative) parameter values for D_X and D_Y in Eq. 2 so it can give rise to steady-state patterns like those observed in Figure 3E-F. Explain.
- In this case, which gene is likely to activate the formation of a trichome? Explain.

Question 2C - 0.5 points

- Propose a particle-based model of n point particles living on a regular, one-dimensional lattice $\Lambda = \mathbb{Z}$, that in the limit of $n \to \infty$ matches the behavior of $\frac{\partial X}{\partial t} = D\nabla^2 X$.
- What is the name of the physical process described by these models?

Question 2D - 0.5 points

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).

After you start the simulation, after some initial oscillations, the simulation settles upon the steady state in Figure 3D. Your neighbor gets the more interesting steady state shown in Figure 3E. You have meticulously compared your parameter settings, and they seem exactly the same.

- What is a likely cause of the differences between your simulations and your neighbor's? Explain.

Question 2E - 0.5 points

- Propose ONE parameter change after which patterns would develop such as those shown in Figure 3F (relative to the parameters used for panel E) .

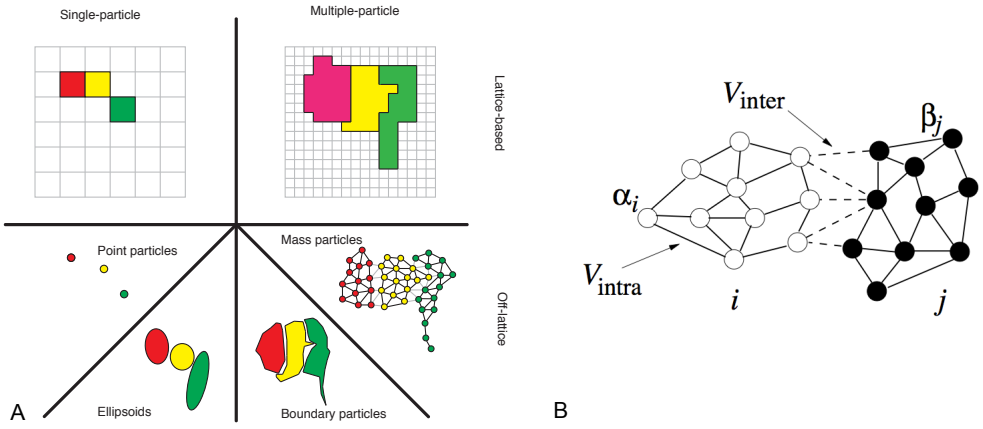

Figure 4: Overview of cellular representations in cell-based modeling technologies

Question 3: Cell-based modeling - 2.5 points

Question 3A - 0.5 points

- In Figure 4A, which quadrant shows the representation of cells in the cellular Potts model?
- Explain.

Question 3B - 0.5 points

- Give an example of a "boundary-particle" method (see Figure 4).

Question 3C - 0.5 points

Figure 4B shows an example of a cell-based modeling methodology proposed by Newman [2].

- Classify this methodology according to Figure 4A.

Question 3D - 0.5 points

In 1970 John Conway proposed his *Game of Life*.

- Classify this model according to the Wolfram classes.
- Explain.

Question 3E - 0.5 points

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

Question 4: Cellular Potts model - 2.5 points

Consider the following Hamiltonian, which defines the Cellular Potts model

$$H = \sum_{(\vec{x},\vec{x\prime})} J(\tau(\sigma(\vec{x})),\tau(\sigma(\vec{x\prime})))(1-\delta(\sigma(\vec{x}),\sigma(\vec{x\prime})))+\sum_{\sigma}\lambda(\sigma)(A(\sigma)-A_0)^2, \quad (3)$$

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

Question 4A - 0.5 points

- 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 - 0.5 points

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

Question 4C - 0.5 points

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

Question 4D - 0.5 points

Figure 5A shows the initial condition of a set of simulations of the Cellular Potts model. Figures 5B-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.

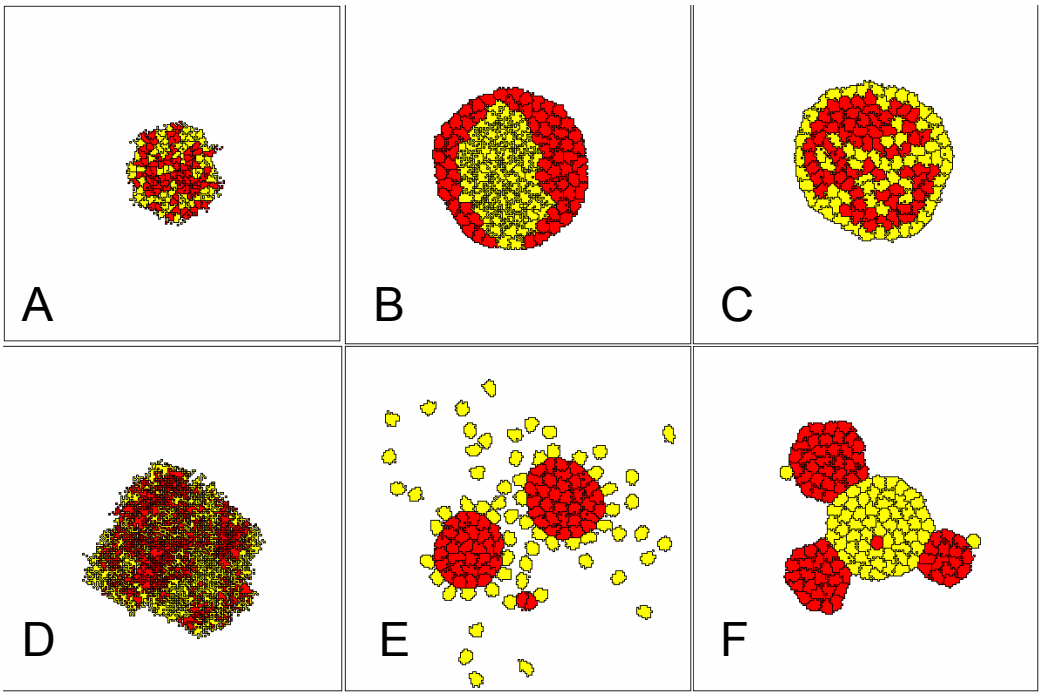

Figure 5: Simulations of the cellular Potts model on a lattice of 200×200 lattice sites. (A) Initial condition (0 MCS); (B-F) simulation results at 30000 MCS. Legend: White: cell type 0 ("medium"); red: cell type 1; yellow: cell type 2; cell-cell boundaries shown in black

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	30	10	20	10	10	50	50	50
2	0	20	10	20	10	3	50	50	50
3	0	30	10	20	10	10	50	500	50
4	0	20	10	20	40	10	50	50	50
5	0	30	10	20	50	50	50	50	50

Table 1: Parameter sets for the simulations shown in Figure 5 listed in random order

- Match the simulation outcomes in Figure 5 with the correct set of parameters, by writing for example: "Simulation A: Set 2" (not necessarily correct).

Question 4E - 0.5 points

You are modeling angiogenesis, and observe that the endothelial cells assume an elongated shape. You are not interested in the mechanism of cell elongation. Instead, you are interested in how cell shape affects the aggregation patterns of endothelial cells.

- Describe a suitable algorithm for cell elongation that you can use in these simulations.

Bonus Question: A new ant species - 1 points

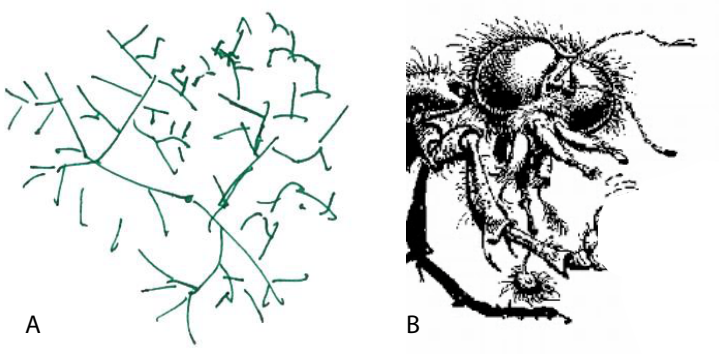

Figure 6: A. Sketch of Palombian ant roadway system; B. Palombian ant, close-up.

During an expedition to the Palombian rainforest, your entomologist colleague has identified an ant species still unknown to science. The ants have the habit of constructing elaborate, branched road systems on bare soil, made out of circular leaf cuts. They seem to find their way only if they are on the road system, on bare soil they walk around aimlessly, regularly changing direction.

Figure 6A shows a sketch of an ant road system that your colleague has drawn for you. She explains to you the ants' curious behavior: they cut

out bits of plant leaf and move to bare soil. Then they carry the bit of leaf around aimlessly, until they hit the road system, and they glue it to the road system. They then search a new plant, and continue the routine.

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

Question B.A - 0.25 points

What is the name of the mechanism that you would propose?

Question B.B - 0.25 points

You implement the mechanism using two-state cellular automata with two layers. Make the following simplifying assumptions. The road system is initiated with one piece of leaf. Ignore the 'leaf cutting', so you can initiate the simulation with n ants that each already carry a piece of leaf.

- Define suitable rules for these cellular automata.

Question B.C - 0.25 points

Describe the algorithm for Margolus diffusion.

Question B.D - 0.25 points

After showing the results of your simulation to your colleague, she shows you some interesting new observations. If the road systems of two colonies meet, they keep a regular distance from one another. In the 'no man's land' in between two colonies, there are hardly any ants present.

She concludes from this that the ants keep the ants from other colonies at a distance using a pheromone (a chemical message), and she sets out to identify that pheromone in the lab.

- Do you agree with her that this is the only plausible explanation for the observations? Why, or why not?

References

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

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

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

[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.