Exam: Multiscale Mathematical Biology

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11 January 2017, 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)

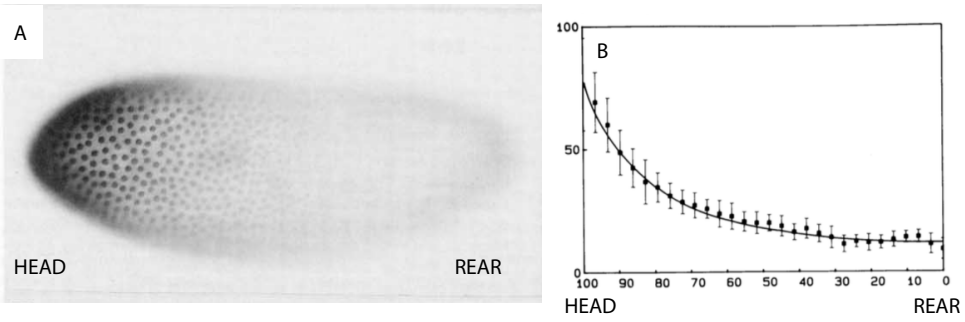

Figure 1: Distribution of the Bicoid gradient in an early embryo of the fruit fly, *Drosophilia* (syncytial stage). (A) Staining ("kleuring") of the Figure taken from Ref.[1]; (B) intensity of the staining along the head to rear axis of the embryo, given in arbitrary units

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. [5] 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. Also give the boundary conditions.

Question 1B - 0.2 points

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

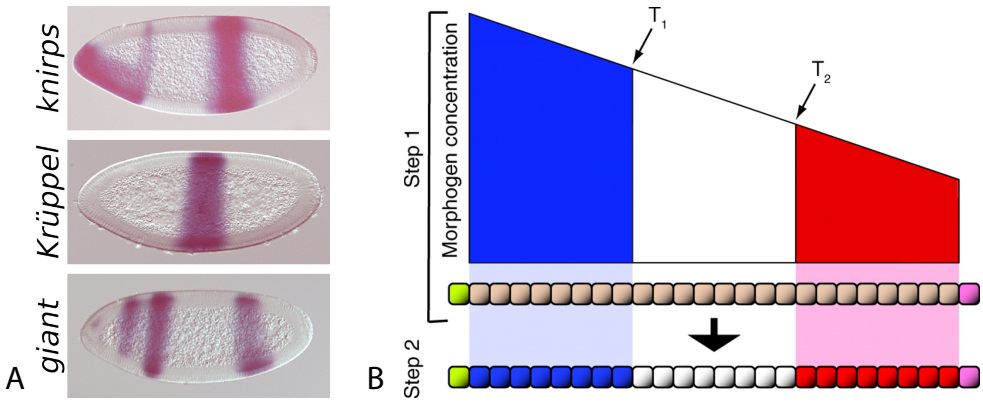

Figure 2: (A) Patterns of gap gene expression in the fruit fly; (B) Lewis Wolpert's model for translating a morphogen gradient into a gene expression pattern

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 [4] 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. [4].

Question 2: Turing patterns - 2.5 points

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]. He proposed a system of the following form,

$$\begin{aligned} \frac{\partial X}{\partial t} &= f(X,Y) + D_x \nabla^2 X \\ \frac{\partial Y}{\partial t} &= g(X,Y) + D_y \nabla^2 Y. \end{aligned} \tag{2}$$

Question 2A - 0.5 points

Propose forms for $f(X,Y)$ and $g(X,Y)$ for which this system has temporally stable, spatially periodic solutions (e.g., spots or stripes); for example those proposed by Gierer and Meinhardt [2], or those proposed by Turing [6].

Question 2B - 0.5 points

Although Turing [6] kept the system more general, Gierer and Meinhardt [2] had specific functions in mind for X and Y. What are the names given to the two morphogens to describe these functions?

Question 2C - 0.5 points

For a system in one spatial coordinate r, given an alternative notation for $\nabla^2 X$; what physical process does the term $\nabla^2 X$ represent? What is the key condition for D_A and D_H for spatial patterns? Bonus points (0.2) for an intuitive explanation.

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

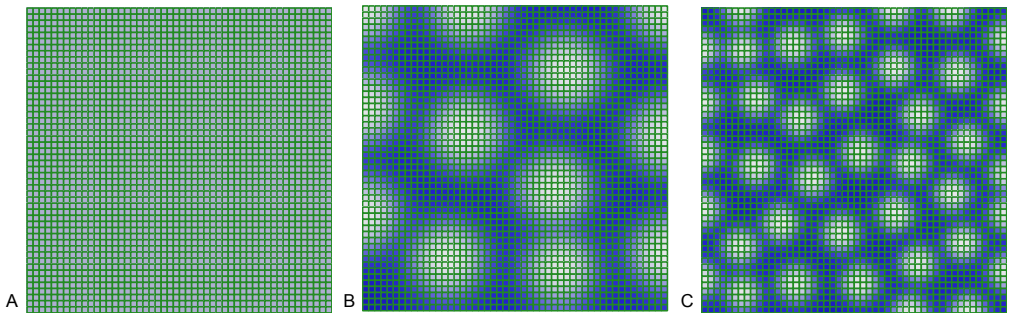

Figure 3: Numerical solutions of the system described in Eq. 2

computer labs.). You have set the parameters to $c_A = 0.2$, $\mu = 0.1$, $D_A = 0.01$, $\rho_A = 0.01$, $c_H = 0.1$, $\nu = 0.1$, $\rho_H = 0$, 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, after an initial oscillation you observe the steady state in Figure 3A. Whatever (s)he tries, your neighbor keeps on getting the steady state in Figure 3B. You have meticulously compared your parameter settings, and they seem exactly the same. What do you recommend to your neighbor? Explain.

Question 2E - 0.5 points

Propose ONE parameter change after which patterns with a shorter wavelength would develop, such as those shown in Figure 3C.

Question 3: Tumor growth and cellular automata (2.5 points)

Question 3A - 0.25 points

Figure 4A shows the setup of an in vitro model of tumor growth. Figure 4B gives the growth of the average radius, $< r >$, over time.

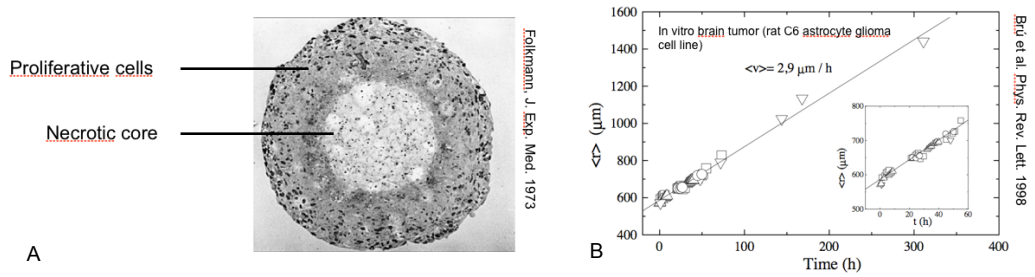

Figure 4: (A) In vitro model of tumor growth; (B) Growth of tumor radius over time

Imagine you read a paper in which the authors propose,

$$\frac{dN(t)}{dt} = kN, \tag{3}$$

with k, the growth rate, as a model for the in vitro tumor growth data of Figure 4. Do you agree with them? Why or why not?

Question 3B - 0.5 points

Write down the rules for a cellular automata model for tumor growth, which better explains the data in Figure 4B. What is the key reason that this model performs better?

Question 3C - 0.75 points

Your experimental collaborator shows you the results of an alternative in vitro model, in which the cells migrate out of the tumor, into the surrounding extracellular matrix. She shows you some movies, and the cells seem to have random motility.

Add an additional rule or step to the model proposed in Question 3B such that it better represents the new data. Describe the algorithm behind that rule, and its name.

Question 3D - 0.75 points

In the model that you proposed in Question 3C, do you expect that the cells will grow faster or slower than in your original model?

Question 3E - 0.25 points

What are the four Wolfram classes? What is so special about class IV?

Question 4: Cell-based models (2.5 points)

Consider the following Hamiltonian, which defines a Cellular Potts model

$$H = \sum_{(\vec{x},\vec{x\prime})} J(\tau(\sigma(\vec{x})),\tau(\sigma(\vec{x\prime})))(1-\delta(\sigma(\vec{x}),\sigma(\vec{x\prime})))+\sum_{\sigma}\lambda(\sigma)(A(\sigma)-A_0)^2, \quad (4)$$

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

Question 4A - 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.

Match the simulation outcomes in Figure 5 with the correct set of parameters, by writing for example, "Simulation A: Set 2" (not necessarily correct), and add a brief (one line) explanation.

Question 4B - 0.5 points

Give the values of $\gamma_{\text{red,yellow}}$ for Figure 5D, E, and F.

Question 4C - 0.5 points

Have a look at Figure 6, showing figure panels taken from Ref. [3]. Figures 6A shows the cell-cell adhesion strengths of the cells, and Figure 6B shows the cortical tension of the cells, with and without treatment with a chemical called 'Blebbistatin' (bleb).

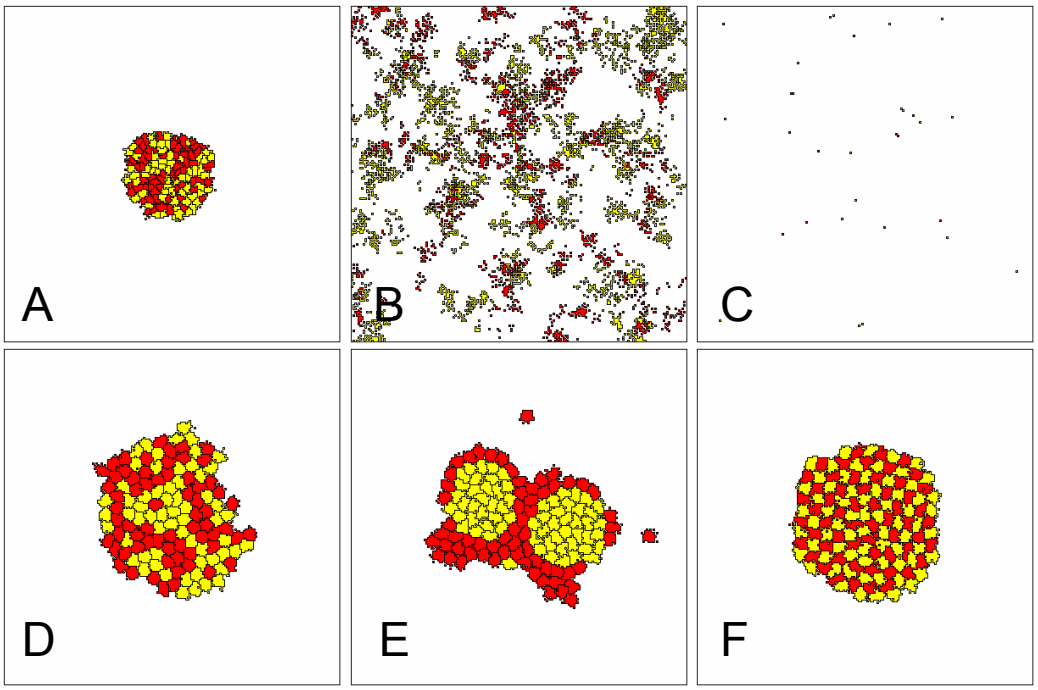

Figure 5: Simulations of the cellular Potts model on a lattice of 200×200 lattice sites. (A) Initial condition (0 MCS); (B-F) simulation results at 30000 MCS. Legend: White: cell type 0 ("medium"); red: cell type 1; yellow: cell type 2; cell-cell boundaries shown in black

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	10	20	10	20	20	50	50	50
2	0	10	20	10	20	10	50	50	50
3	0	10	20	10	20	20	50	5000	50
4	0	10	20	10	10	20	50	50	50
5	0	10	20	10	20	20	1	50	50

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

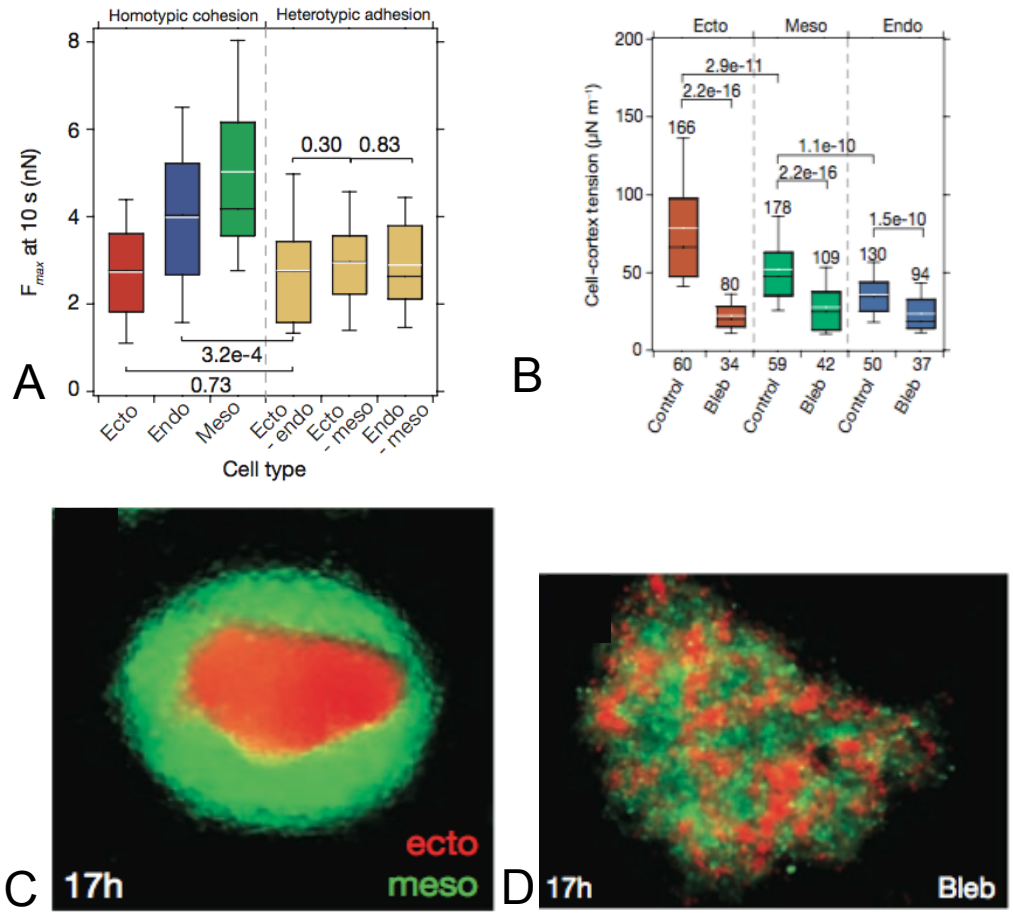

Figure 6: Cell sorting of zebrafish germ-layer cells. Figure panels taken from Ref. [3]. (A) Cell-cell adhesion; (B) Cortical tensions; (C) Wild-type configuration after 17h of culture; (D) configuration of ectodermal (red) and mesodermal (green) cells treated with Blebbistatin ('bleb') after 17h of culture

Which of the two configurations shown in panels C (normal) and D (treated with blebbistatin), most accurately describes the prediction of the differential-adhesion hypothesis, according to the measurements in panels A and B? Why?

Question 4D - 0.5 points

Add an additional term to the Hamiltonian given above to correct the model, according to the measurements given in Figure 6.

Question 4E - 0.5 points

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: Excitable media - 0.8 points[1]

This question can give you some additional points. Describe what is an excitable medium and propose a simple cellular automata model of an excitable medium. Discuss a phenomenon exhibited by this model that is thought to drive ventricular fibrillation, and show when it occurs in the model.

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] M M Krieg, Y Y Arboleda-Estudillo, P-H PH Puech, J J Käfer, F F Graner, D J DJ Müller, and C-P CP Heisenberg. (...) govern germ-layer organization in zebrafish. *Nature Cell Biology*, 10(4):429–436, March 2008.

[1] Or an 'honorable mention' if total score sums up to more than ten... :-)

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

[5] 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.

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