Exam: Multiscale Mathematical Biology

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15 March 2019, 10:00-13:00

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 - Sharks

In this question we will be looking at the patterning of the skin of sharks, in particular the positioning of the scales. Figure 1A shows a stained image of an embryo of the small-spotted catshark, *Scyliorhinus canicula* [1]. Figures 1B-D show close-ups of these scales. A row of large scales is surrounded by smaller scales. The formation of a scale is initiated ("switched on") by the activity of the growth factors FGF-4 and BMP-4 (among a few other genes that we will not consider today). In birds, FGF-4 activates its own production, and it is assumed that FGF-4 has the same activity in the shark. A bead soaked in the compound SU5402 (dissolved in DMSO), which inhibits the activity of FGF-4, also inhibits BMP-4 (Figure 1E). As a control, beads soaked only in the solvent "DMSO" have no effect on BMP-4 expression (Figure 1F), showing that this effect is specific to SU5402. Finally, FGF-4 and BMP-4 are active at the same positions, as shown using a technique called in-situ hybridization (Figure 1G,H).

Question 1A - 0.5 points

- Propose a continuum model that could explain the periodic, spotted expression of FGF-4 and BMP-4 (Figure 1G,H). It is not necessary to explain why the FGF-4 and BMP-4 are expressed in a row, or why there are big and small scales.

Turing / Meinhardt

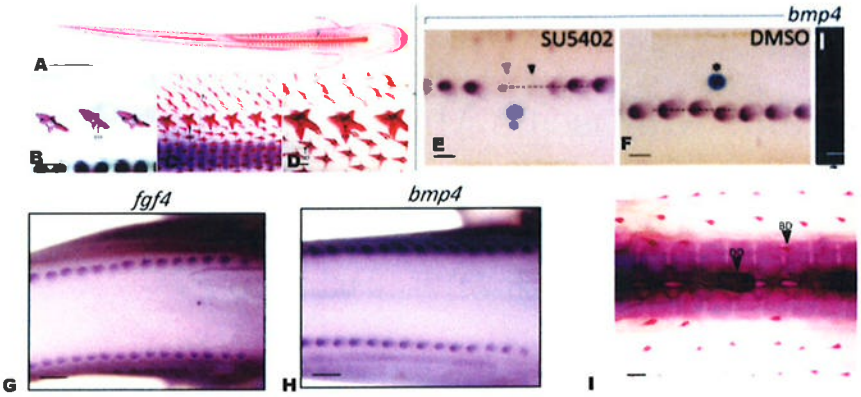

Figure 1: Patterning of the small-spotted catshark, *Scyliorhinus canicula*. A. Whole, stained embryo of the catshark showing the developing scales. B-D. Close-up of the developing scales. E. Local inhibition of FGF-4 expression using an implanted bead soaked with SU5402 inhibits BMP-4 expression; F. Control with a bead soaked with an inactive compound. G. Activity of FGF-4 in the early embryo; H. Activity of BMP-4 in the early embryo.

- What is the *name* of this model?

→ Turing / Meinhardt / Reaction / Diffusion

Question 1B - 0.5 points

- What can you conclude from the observation that inhibiting the activity of FGF-4 also inhibits BMP-4?

→ FGF activates BMP4

- What additional regulatory interaction between FGF-4 and BMP-4 do you need to assume to explain the observations?

BMP4 inhibits FGF4

- What does your model predict about the transport of FGF-4 and BMP-4 through the tissue?

BMP4 must diffuse faster than FGF4

Question 1C - 1.0 points

The answer to this question should discuss the next three bullets:

- Write the rules for a *cellular automata* model of shark scale patterning, making use of the *Margolus* algorithm. A standard model giving a field with equally sized spots is fine.

0,5

- Explain how the Margolus algorithm works.
- What physical mechanism does the Margolus algorithm represent?

0.5

Question 1D - 0.5 points

A related fish, called the thornback skate (*Raja clavata*) has the scale pattern shown in Figure 1-I. The fine scales are more widely spaced.

- Propose a change to the parameters of the model that could explain the wider spacing. → Faster diffusion of inhibitor

This question concerns only the small scales at the top and bottom side of the figure; do not worry about the big scales in the middle.

Question 2: Cell-based modeling (2.5 points)

Question 2A - 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.

- 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 2B - 0.5 points

- Describe a widely-used cellular Potts extension for chemotaxis.

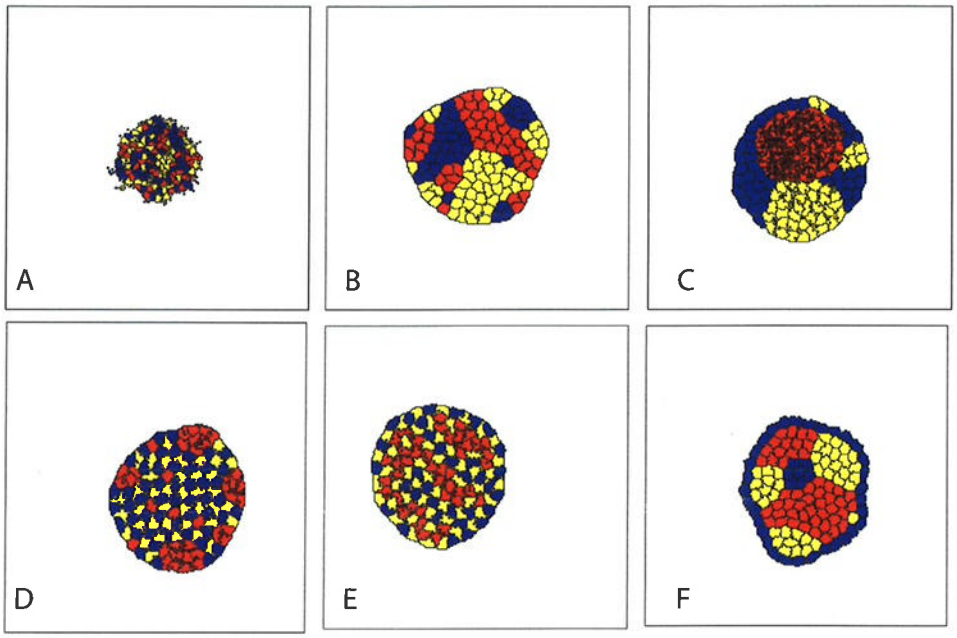

Figure 2: Simulations of the cellular Potts model on a lattice of 200 × 200 lattice sites. (A) Initial condition with 128 cells (0 MCS); cell types have been assigned at random; (B-F) simulation results at 200,000 Monte Carlo Steps.

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

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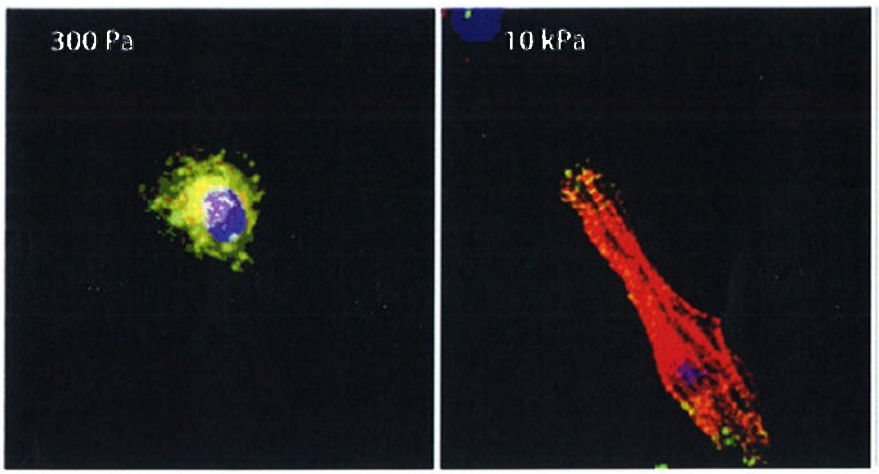

Figure 3: A mammalian cell on a soft (300 Pa) and on stiffer (10 kPA) matrix.

Question 2C - 0.5 points

As discussed in the lectures, Krieg et al. [2] have experimentally tested the assumptions of the differential-adhesion hypothesis. Their experiments contradicted with the differential-adhesion hypothesis.

- What observations contradicted the differential-adhesion hypothesis?
- Give an alternative interpretation of the term $\sum_{(\vec{x},\vec{x}\prime)} J(\tau(\sigma(\vec{x})),\tau(\sigma(\vec{x}\prime)))(1-\delta(\sigma(\vec{x}),\sigma(\vec{x}\prime)))$ in Eq. 1 that agrees with the findings of Krieg et al. [2].

Question 2D - 0.5 points

- Explain in words (no equations necessary) a possible mechanism by which the shape of cells depends on the stiffness of the extracellular matrix, as shown in Figure 3.

Question 2E - 0.5 points

Describe a configuration for which $H = 0$ (in Eq. 2), independent of the parameter values.

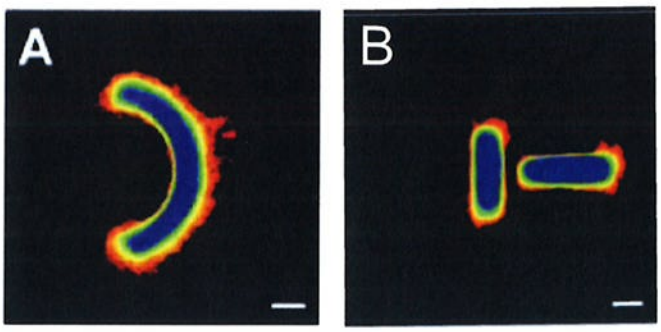

Figure 4: Frequency maps of cultured epithelial cells, showing sites of branching (red). (A) curved tubules; (B) perpendicular tubules. After Ref. [3]

Question 3: Multiscale Phenomena

Question 3A - 0.5 points

The cellular slime mould, *Dictyostelium discoideum* (or simply *Dicty*), live as individual amoebae in the soil. When hungry, the amoebae aggregate and eventually form a multicellular fruiting body.

- Describe the mechanism by which the aggregation signal (cAMP) spreads from cell to cell.
- Give the rules for a three-state cellular automata model that would capture the basics of this mechanism.

Question 3B - 0.5 points

After *Dicty* cells have aggregated, they first form a multicellular slug. This slug moves to a warm spot in the soil.

- Describe a possible mechanism for such *thermotactic* behavior.
- Can *Dicty* cells move to a warm spot on their own? Why, or why not?

Question 3C - 1.0 points

Figure 4 shows the behaviour of cultured, mammary epithelial cells in constrained shapes. These cells are responsible for forming breast gland tissue.

In the breast they form branched, tubular structures. The red 'ruffles' show enhanced sprouting activity of the epithelial cells.

- Why do the mammary cells predominantly sprout at the positively curved (convex) side of the structure shown in Figure 4A? And why is their hardly any sprouting at the concave side? Explain the mechanism.
- Why are there no sprouts in the cavity between the two perpendicular tubes show in Figure 4B? Explain using the model that you have proposed above.
- How does the above mechanism produce branching structures? Explain using words and propose a model with an equation.

Question 3D - 0.5

- Give an example of an L-system, and show a few steps of its development.

Question 4: Prebiotic Evolution (Enrico Colizzi)

Question 4A - 1.0 points

Explain what is the *Information Threshold* and why it shows a "paradox" for evolution.

Question 4B - 0.5 points

The formula for the Information Threshold is derived assuming that genomes are under selection. In reality, phenotypes are the target of selection and sometimes mutations are neutral (*i.e.*, they do not change the phenotype). It has been proposed to extend this formula by including a term n, which is the per-nucleotide probability of neutral mutations.

The information threshold for the genome of the fittest phenotype can be expressed as

$$L \leq \ln(s)/\left((1-n)*(1-q)\right). \tag{2}$$

- Compare this version of the information threshold with the one you learnt in class.
- Everything else being equal, do neutral mutations help maintain a longer sequence?
- Include in your answer the fact that typical (experimental) values for n are between 0.2 and 0.5.

Question 4C - 0.5 points

- Aside from genome length, what are the consequences of the modified information threshold of Question 4B for the information content in the genome?

Question 4D - 1.0 points

Consider the following experiment:

In a well-mixed tube you have three RNA molecules X, Y, Z (with an influx of resources R1, R2, R3 and an outflux of byproducts). X catalyses a reaction that converts itself (with some resources R) into Y, Y uses resources to turn into Z, and Z catalyses a reaction to convert into X, closing the circle.

The chemical equations read:

$$\mathrm{X} + \mathrm{R}_1 \longrightarrow \mathrm{Y} + \text{byproduct}$$
$$\mathrm{Y} + \mathrm{R}_2 \longrightarrow \mathrm{Z} + \text{byproduct}$$
$$\mathrm{Z} + \mathrm{R}_3 \longrightarrow \mathrm{X} + \text{byproduct}$$

By chance a slightly different ribozyme X' is generated, which is converted into Y at a larger rate.

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

References

[1] R L Cooper, A P Thiery, A G Fletcher, D J Delbarre, L J Rasch, and G J Fraser. An ancient (...) mechanism regulates skin denticle development in sharks. *Science Advances*, pages 1–11, November 2018.

[2] 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.

[3] C M Nelson, M M VanDuijn, J L Inman, D A Fletcher, and M J Bissell. Tissue (...) determines sites of mammary branching morphogenesis in organotypic cultures. *Science (New York, NY)*, 314:298–300, 2006.