MMB Lab Session 2: Modeling the gap gene network in *Drosophila melanogaster*

Please answer the questions and hand them in by next week (02/11/2018) by e-mail to merksrmh@math.leidenuniv.nl. Subject line: HOMEWORK GAP GENE NETWORK.

Reinitz and Sharp [1] predicted gene regulatory networks that can be responsible for the regular domains of gap gene expression in the fruit fly, *Drosophila melanogaster*. They proposed networks of the form,

$$\frac{dv_i^a}{dt} = R_a g_a \left(\sum_{b=1}^{N} T^{ab} v_i^b + m^a v_i^{\mathrm{bcd}} + h^a \right) + D^a(n) \left[(v_{i-1}^a + v_{i+1}^a - 2v_i^a) \right] - \lambda_a v_i^a, \tag{0.1}$$

with $g(u)$ a sigmoid function,

$$g(u) = \frac{1}{2}((u/\sqrt{u^2+1}) + 1). \tag{0.2}$$

Before starting these exercises, read the article of Reinitz and Sharp [1].

Explanation of software

Application `gapgenes` simulates Eq. (0.1) with 5 regulatory genes, and *even-skipped*. To run it, follow the instructions below:

1. Download the application from the course website.
2. Open a terminal and type:

   ```
   tar xzf ~/Downloads/gapgenes.tgz
   ```

3. To start the `gapgenes` program, type:

   ```
   cd Drosophila
   ./gapgenes
   ```

4. To start the integration, press CTRL-S.

An exponential gradient of *Bicoid* rapidly appears, for which we have assumed the Synthesis-Diffusion-Degradation (SDD) model,

$$\frac{\partial c(x,t)}{\partial t} = D\nabla^2 c(x,t) - \epsilon c(x,t), \tag{0.3}$$

where, for simplicity, we use a boundary condition $c(0,t) = s$ to implement synthesis. In the standard parameter set, all elements of the genetic regulatory network T^{ab} have been set to zero, which is why all the gap genes have a homogeneous expression. To fill in the values identified in [1], open a parameter edit window by pressing CTRL-E. Enter the correct values under "Table 1, T-matrix" (or simply read in the parameter file `reinitz.xml` and click the button RESET to see the new values appear in the parameter window).

Exercise 1

1a. You can initiate the system with random values $v_i^a \in [0, 1]$ by pressing CTRL-R. Restart the simulation and show an image of the simulation in your report.

1b. Compare your results with what is reported in the Reinitz and Sharp [1] paper. What explains the differences between your simulations and the ones reported in the paper? Do we have all the required information to reproduce exactly what Reinitz and Sharp have reported? What information, if any, is missing from [1]?

Exercise 2

Let's try to reproduce qualitatively what Reinitz and Sharp report. First, consider a system of two interacting gap genes in a single nucleus, and ignore the effect of *Bicoid* for now.

2a. Rewrite Eq. (0.1) for this situation: two genes A and B in one nucleus, no diffusion, no *Bicoid*, and $h_a = 0$ for all a. Choose appropriate values for the elements T^{ab} so it correctly represents Reinitz and Sharps hypothesis.

2b. Perform a phase plane analysis of the resulting system of two ODEs: What are the equilibria of the system and what is their stability? Hint: the sigmoid function g makes the exact expressions for the isoclines extremely messy (Mathematica returned an expression of several pages), but you can still get insight into this system if you separately consider the situations $A > B, A < B$, and $A = B$.

2c. Based on these insights, can you propose values for the elements T^{ab} that will produce sharp domains of gap gene expression? Again assume that the *Bicoid* gradient has no effect on gene expression. Enter your values of T^{ab} into the parameter dialog window (CTRL-E), and start the simulation. Does it have the expected results? Try out a range of random initial conditions (CTRL-R).

2d. Now, include the regulation of *Bicoid* into your model. Remember that the sixth column in Table 1 gives the amount of *Bicoid* regulation. Can you get the three gap genes *kr*, *hb* and *kni* in the right order as in Figure 2e of [1]? (This is a bit tricky... Some hints: play with the amount of regulation from *Bicoid* and the relative amounts of cross-regulation, and be inspired by the "simulated annealing" strategy employed in [1]). Show your results.

2e. Next include *even skipped* in your model. The parameters for *eve* are in the last line of Table 1. What mechanism did Reinitz and Sharp [1] propose for the regulation of *even skipped*?

2f. How does this system depend on the diffusion coefficients of the transcription factors? Hint: parameter `df` in the computer simulation is a prefactor to the diffusion parameters.

2g. Discuss the similarities and differences of the gap gene system with a Turing pattern.

References

[1] Reinitz J. and Sharp D., *Mechanism of eve stripe formation*, Mechanisms of Development 49 (1995), 133-158