**Einführung in die Systembiologie** **FDM Universität Freiburg**
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# Project Description June 23, 2022

## 1 Introduction

In this project you will be working on modelling patterning in the trichome system. Trichomes are small hairs found on top of the leaves of plants. The pattern formation can be understood using a reaction diffusion model, which you will apply in this project. One of the proteins involved in patterning plays a unique role: it is capable of trapping other proteins in the nucleus or transporting them to the cytoplasm. The question is how does this affect the formation of the trichome pattern?

## 2 Reading the Paper

### Exercise 1 Questions - Introduction

Carefully read the supplied paper [PSD+13]. Then answer the following questions:

1. Which genes are involved in the pattern forming process.
2. What is their specific role?
3. Which genes are activator/inhibitor?
4. Describe how they interact with each other?
5. Which simplifications could be possible in this system?

### Exercise 2 Questions - Results - Interactions with AtMYC1

Answer the following questions:

1. With which proteins does MYC1 interact?
2. In which parts of the cell are MYC1 and its reaction partners localized? (Figure 4,7) ??
3. How does this localization affect possible modeling of the system?

### Exercise 3 Questions - Discussion

The discussion of [PSD+13] mentions some open points for future work.

1. What predictions are made? How can we test them with a model?
2. Figure 8 describes a model hypothesized by the authors. What simplifications were applied?

## 3 Modeling

### Exercise 4 Setting up the Gene Regulatory Network

1. How many independent components does our system have (Figure 8)?
2. What type of interactions are occuring (Figure 8, Arrows)?
3. To simplify the system: Which components could you merge into a single classification?
4. Draw the simplified network. Which parameters do we need to supply?
5. Set up the reaction equations. Pay attention to cellular compartments. How can this be represented on a Partial Differential Equation (PDE) level?

### Exercise 5 PDE Solving

To determine how the diffusion of a protein is affected by the presence of another protein that acts as a trap, a reaction-diffusion model is used. This relatively simple system consists of terms representing a production source, degradation, diffusion and, in this particular case, a term for binding to a trap, causing removal from the system. The extent to which this removal affects the movement of the protein depends on the trap kinetics.
Use the provided solver to model this simple 1D system on $[0, L]$.

$$\dot{\rho} = D\Delta\rho - \lambda\rho - \alpha T\rho \tag{1}$$

$$\dot{T} = -\alpha T\rho \tag{2}$$

Use the following parameters: $D = 1.0, \lambda = 2.0, \alpha = 1.0, L = 1.0$ with Dirichlet boundary conditions $1.0$ at $x = 0$ and $0.0$ at $x = L$.

1. What do the individual terms in the equations represent?
2. How do the initial conditions for the trapping protein vary the results?

### Exercise 6 Modeling Trichome Patterning

Now you will implement the previously derived equations of the trichome patterning system in the supplied solver. Points on the mesh coincide with cell locations and are coupled by plasmodesmata. This way, we have a diffusion-like system described by coupled Ordinary Differential Equations (ODEs).

1. First neglect spatial transport phenomena and concentrate on the resulting ODEs
2. Numerically determine if they have a steady-state
3. Which role do the initial values of the system play? Which initial values need to be chosen for the simulation of the turing pattern?
4. Implement the correct equations and solve the system.
5. What patterns emerge when repeating the same simulation?
6. What technical challenges are you facing?

## 4 Parameter Space Exploration

The used parameters up to this time were only an educated first guess. In order to determine other working parameter sets, we want to explore the possible space of values. The next steps are

Ex. 7 Generate new parameter combinations

Ex. 8 Filter them based on stability analysis criteria

Ex. 9 Simulate the remaining ones

Ex. 10 Extract features that determine if a pattern was generated

If a pattern was generated successfully, save it, otherwise discard it

Test your results on a case-by-case basis

### Exercise 7 Sampling Algorithm

To generate parameter pairs, use Latin-Hypercube Sampling [MBC79, Wik22] to generate new values $q_i$ and then generate the parameters via

$$p_i = 10^{q_i} \tag{3}$$

For biological reasons, we restrict the parameters to the boundaries

$$p_i \in [0.05, 50.0] \tag{4}$$

Write your code such that the total number of combinations can specified as a parameter $M$. Initially, we restrict ourselves to $M < 10^6$. Do not yet solve the equations with these parameters; see next exercise.

### Exercise 8 Stability Analysis

A stability analysis can be performed to reduce the number of parameter sets that need to be simulated.

- Why is this method important?
- What are the two basic stability/instability preconditions?
- How does diffusion-like transport play a role?

Use the provided function to filter the parameters.

### Exercise 9 Solving

Write (parallelized?) code that solves for all possible parameter combinations. Store the results of the simulations along with their parameters. The code could look like the following:

```
import multiprocessing as mp

N_parallel = 4
p = mp.pool(N_parallel)
p.starmap(generate_result, parameter_combinations)
```

### Exercise 10 Feature Extraction

In order to only allow realistic patterns, we filter for results which show no clustering of trichomes. The wildtype behaviour never shows two or more trichomes next to each other.

1. Make sure that the solution has reached a final steady-state
2. Select cells which have more than $0.5$ of maximum activator concentration. These are designated as trichome cells.
3. If two neighboring cells show this property, we neglect the result.
4. Consider, storing the valid parameter sets to a file in case the program/computer crashes.

### Exercise 11 MYC1 Effect

Pick one verified parameter set and experiment with different initial and parameter values for the trapping protein MYC1.

1. Define a range for the MYC1 parameter value (include $0.0$ as initial value)
2. Solve the equation for every combination
3. Compare the results
4. Quantify the cluster density and density of trichomes. This time do not neglect clusters.
5. Present these results in a figure.

## 5 Discussion

We finalize the project by discussing our approach.

1. Why are patterns formed? (General discussion about the activator-inhibitor system)
    a) What role does the MYC1 play? (trapping proteins)
    b) What happens if we vary it?
    c) What happens if this is set to zero?
2. Using this model, can we predictexperimental results? How can we design an experiment to test it? (optional)
3. What are technical challenges (time-step, discretization, sampling)
4. What are implications of simplifications? (Internal discretization/diffusion, no cell-size, boundary conditions, spatial dimension, static domain, cell division/growth)
5. What else did you notice?

### Exercise 12 Presentation

Prepare a presentation of your results. The talk is ment to last 30min. Every participant should contribute equally. Follow this structure:

1. Introduction
2. Methods
3. Results
4. Discussion

## References


[MBC79] M. D. McKay, R. J. Beckman, and W. J. Conover. A comparison of three methods for selecting values of input variables in the analysis of output from a computer code. *Technometrics*, 21(2):239, May 1979.

[PSD+13] Martina Pesch, Ilka Schultheiß, Simona Digiuni, Joachim F. Uhrig, and Martin Hülskamp. Mutual control of intracellular localisation of the patterning proteins AtMYC1, GL1 and TRY/CPC in... *Development*, 140(16):3456–3467, August 2013.

[Wik22] Wikipedia. Latin hypercube sampling — Wikipedia, the free encyclopedia. `http://en.wikipedia.org/w/index.php?title=Latin%20hypercube%20sampling&oldid=1061603486`, 2022. [Online; accessed 23-June-2022].