

Modeling the Shoot Apical Meristem in *A. thaliana*: Parameter Estimation for Spatial Pattern Formation

Tim Hohm and Eckart Zitzler

Computer Engineering (TIK), ETH Zurich
{hohm,zitzler}@tik.ee.ethz.ch
<http://www.tik.ee.ethz.ch/sop/>

Abstract. Understanding the self-regulatory mechanisms controlling the spatial and temporal structure of multicellular organisms represents one of the major challenges in molecular biology. In the context of plants, shoot apical meristems (SAMs), which are populations of dividing, undifferentiated cells that generate organs at the tips of stems and branches throughout the life of a plant, are of particular interest and currently studied intensively. Here, one key goal is to identify the genetic regulatory network organizing the structure of a SAM and generating the corresponding spatial gene expression patterns.

This paper addresses one step in the design of SAM models based on ordinary differential equations (ODEs): parameter estimation for spatial pattern formation. We assume that the topology of the genetic regulatory network is given, while the parameters of an ODE system need to be determined such that a particular stable pattern over the SAM cell population emerges. To this end, we propose an evolutionary algorithm-based approach and investigate different ways to improve the efficiency of the search process. Preliminary results are presented for the Brusselator, a well-known reaction-diffusion system.

1 Motivation

Ordinary differential equations (ODEs) represent a common approach to model genetic regulatory networks [1]. Such models are on the one hand used to quantitatively understand the interactions of multiple genes controlling specific cellular processes and on the other hand applied to make predictions about the cell behavior. One important and challenging problem in this context is the determination of the model parameters that lead to the desired temporal dynamics. For single cell networks, there has been a lot of work on parameter estimation using analytical as well as heuristic methods [13]; in particular, several studies make use of evolutionary algorithms to find suitable parameter settings [8,9,11].

This paper considers a slightly different problem where the focus is on multicellular systems, in particular the shoot apical meristems (SAMs) in the plant *Arabidopsis thaliana*. The main goal is to identify an ODE system that is capable of producing an (experimentally observed) spatial gene expression pattern

across the cell population, assuming that gene products can cross cell borders via diffusion. Starting with a given set of gene interactions in terms of an ODE system, we address the problem of model parameter determination for such a spatial scenario. In comparison to previous studies on parameter estimation, there are several differences with respect to the scenario under investigation:

- Instead of a single cell, multiple interacting cells are considered which requires a prespecified spatial cell structure and a cell interaction model;
- Instead of achieving a particular temporal behavior, we are interested in obtaining a stable, i.e., non-oscillating system state in which a particular gene expression pattern emerges over the spatial cell structure;
- Instead of considering absolute gene product concentrations as target values, the gene expression patterns are rather defined qualitatively since quantitative measurements in space are scarcely available.

It is an open question of how to efficiently search for model parameters in such a scenario and how to formalize spatial patterns in terms of an objective function.

In the following, we present a preliminary study for this problem where a more general goal is taken as a basis: we do not assume a given target pattern, but aim at finding parameter settings that produce arbitrary, non-chaotic patterns. We first propose a general modeling framework which allows to simulate genetic regulatory networks within multicellular systems. Secondly, for a simple reaction-diffusion system with two genes that has been part of a previously published model for the shoot apical meristem by Jönsson et al. [6], we investigate the issue of parameter estimation. To this end, we introduce and apply an evolutionary approach based on the Covariance Matrix Adaption Evolution Strategy (CMA-ES) [3,4] and investigate different ways to improve the efficiency of the search.

2 Background

2.1 The Shoot Apical Meristem (SAM)

A shoot apical meristem (SAM) consists of multiple dividing, undifferentiated cells and is located at the tips of stems or branches of a plant. It is responsible for generating organs throughout the life of a plant and determines the number, type and position of the resulting lateral organs. A SAM has a particular internal organization that is preserved through its existence and its position at the tip of the stem or a branch remains fixed, although the plant is growing. Therefore, a fundamental question in meristem research is what this structure looks like and how it is maintained.

In various experimental studies, a number of genes and gene interactions have been identified that are involved in the organization of a SAM. At the heart of preserving the organization and functioning of a SAM is a negative feedback loop with two critical elements, the transcription factor gene WUS and the CLAVATA (CLV) genes, which encode components of a ligand/receptor complex.