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GENE REGULATION NETWORKS WITH SIGNALING AND CELL DIVISION IN DEVELOPMENTAL SIMULATIONS*

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The shoot apical meristem (SAM) of *Arabidopsis thaliana* is an example of a developmental system which can be modeled at genetic and mechanical levels provided that suitable mathematical and computational tools are available to represent intercellular signaling, cell cycling, mechanical stresses, and a changing topology of neighborhood relationships between compartments.

A systematic approach to providing the relevant tools is through computer-algebraic representations of biological models, from which one can automatically generate mathematical models and simulate their behavior. In previous work we have introduced a mathematical framework for gene regulation networks combined with cell signaling [1] and the "Cellerator" package for automatic model generation from reactions relationships [2] and regulatory relationships along with cell division [3]. Here we combine these ideas to produce simulation tools capable simultaneously of transcriptional regulation, intercellular signaling, cell division, and mechanical deformation as appropriate to a developmental model. We illustrate this approach and the resulting developmental models in the case of the Arabidopsis meristem.

Two contrasting approaches to such tools are those represented by Cellerator, in which models are generated from biological descriptions, and handwritten simulations for particular problems. We pursue both approaches here in order to gain the experience and make the comparisons required to engineer an optimal combination. Generalizing from [1] we use the combined gene regulation and cell-cell signaling dynamics:

$$\frac{d}{dt} v_a(t) = \frac{1}{\tau_a}[g(u_a + h_a) - \lambda_a v_a] \tag{1}$$

where

$$u_a(t) = \sum_b T_{ab} v_b(t) + \sum_{i \in Nbrs} \Lambda^i \sum_b \hat{T}_{ab} v_b^i(t) + \sum_{i \in Nbrs} \Lambda^i \sum_b \sum_c \tilde{T}_{ac}^{(1)} \tilde{T}_{ac}^{(2)} v_c(t) v_b^i(t) \tag{2}$$

Here T is an intracellular gene regulation network, $\hat{T}$ is an intercellular network, and $\tilde{T}^{(1)}$ and $\tilde{T}^{(2)}$ represent a more detailed intercellular signaling network which separates the connection of receptors and ligands ($\tilde{T}^{(2)}$) from the connection of receptors and nuclear pathway target genes ($\tilde{T}^{(1)}$). To this is added a simple model for cell growth and cell division, which can be chosen from a variety of published models. The resulting system can now be simulated within Cellerator as otherwise described in [3]. Fig. 1 shows a regular initial condition for a two-dimensional (2D) meristem simulation, including five cell types for expression domains and outer cell layers. Similarly, the behavior of the handwritten special-purpose code implementing the same mathematical model demonstrates cell-cell signaling and cell division is shown in Fig. 2.

Figure 2 shows an example from a simulation of a simple 2D multi-cellular organism. The spatial and growth dynamics is modeled by a "spring" potential between neighboring cells as described in [3]. Each cell also have two proteins (PA ,PB) and the protein concentrations follow

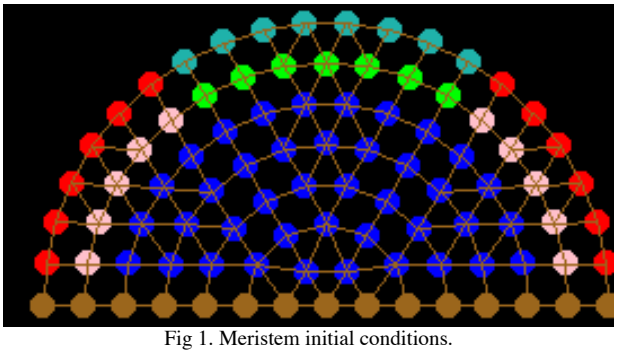

Fig 1. Meristem initial conditions.

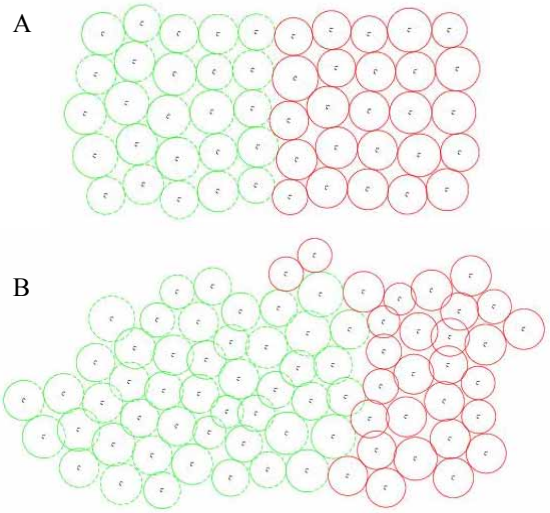

Fig. 2. Result of cell division.

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the dynamics described in equation (1). Two cell types are defined by whether the concentration of PA is above/below a given threshold indicated by colors (red/green) in the figure.

The cells are initiated on a two dimensional grid with a small random deviation in size and growth rate (which determines the period of the cell cycle). There are two different initial protein concentrations of the cells, dividing them into two regions of cell types (PA concentration above/below threshold).

In Fig. 2A, no cell division has yet occurred and the cells are all in the state in which they were initiated. The only difference from the initial system at t=0 is that cells have grown, and moved from their original positions. As time elapses further, the cells start to divide and in Fig. 2B the number of cells has increased. Also the intercellular interaction leads to change in protein concentrations, converting cells of one type into the other when the two cell types are adjacent, as may be the case for the central zone and rib meristem of the SAM. This is seen in Fig. 2B by the asymmetry of the different cell type regions although they have the same division behavior.

Some of the comparisons that will be drawn between these two approaches to implementing the same family of mathematical developmental models include the quantification of a tradeoff between simulation speed and model flexibility, and defining a new software framework capable of improving this tradeoff.

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