J Plant Growth Regul (2006) 25:270–277
DOI: 10.1007/s00344-006-0069-7

J P G R
Journal of Plant Growth Regulation

The Growth and Development of Some Recent Plant Models: A Viewpoint

Eric Mjolsness*

Institute for Genomics and Bioinformatics, and Department of Computer Science, University of California, Irvine, California 92697, USA

Abstract

A nontechnical introduction to selected recent models of plant development and growth is presented. Problems of creating predictive, quantitative models for (1) regulatory networks and (2) the use of space by developing tissues are outlined. These problems can be addressed using suitable mathematical frameworks to represent the substantial variety of relevant biological mechanisms, including gene regulation, protein modification, and cell–cell signaling by ligand/receptor pairs and by polarized auxin transport; also relevant are cell growth and division, the changing topology of signaling relationships between cells, and mechanical interactions between cells. Modeling frameworks are briefly described for gene regulation networks, including signaling; for more general biochemical reaction networks; for mechanical interactions (using a weak spring model) and signaling mediated by a changing topology of neighbor relations among growing and dividing cells; and for approximating such models at the tissue level using spatially continuous descriptions with changing shape. Finally, a ''dynamical grammar'' framework allows naturally for integrative and multiscale models because it can, in principle, combine any or all of the foregoing mechanisms. With mathematical and computational tools such as these, and with the current rapid progress in instrumentation and imagery, the future looks bright for scientifically effective modeling of plant development.

Key words: Developmental model; Shoot apical meristem; Gene regulation network; Gene regulation signaling network; Dynamical grammar; Polarized transport; Weak spring model; Voronoi diagram; Active surface; Multiscale model.

Introduction

The goal of this article is to provide a nontechnical introduction to some of the ways that plant development and growth can be modeled with mathematics using a computer. The selection and presentation of topics is highly biased by the author's own experience, rather than being an attempt at an objective review. But it provides an internally cohesive view that favors some approaches over others for the near future. Thus it may help to introduce plant biologists to new and relevant ideas.

The structure and diversity of plant morphology inspires one to mathematical thoughts. The regular

Received: 29 June 2006; accepted: 30 June 2006; Online publication: 27 November 2006
*Corresponding author; e-mail: emj@uci.edu

and symmetric phyllotactic patterns of many flowers and pinecones, for example, inspired one of the earliest applications of the newly invented general-purpose stored-program computer to scientific simulation, in the 1951–54 unfinished work of Alan Turning (Swinton 2003), which was based on differential equations for reactions and diffusion. Since then, computer science related models have been applied to phenomenological modeling of plant visual appearance in computer graphics. One class of examples is given by L-system grammars (Prusinkiewicz and Lindenmeyer 1990). But only recently has detailed knowledge of the actual relevant molecules, such as the growth hormone auxin and its regulatory interactions, been brought from molecular biology into problems of predictive, computable modeling of plant development. Recent examples include the phyllotaxis models of Jönsson and others (2006), Barbier de Reuille and others (2006), and Smith and others (2006).

Regulatory Network Models

With great improvements in biological instrumentation, the known size and complexity of regulatory networks has increased to the point where it is often essential for understanding to build computational models.

Many ideas from mathematics could be applied to modeling regulatory networks, but we will start with those capable of reflecting molecular realities that underlie macroscopic biology. Molecules regulate one another's existence and state in biochemical networks. For example, spatial and temporal gene expression domains are key mechanisms for morphogenesis. They are frequently set up by networks of transcriptional regulation, augmented by communication between cells. In these networks, one gene can enhance or repress another in a feedforward or feedback manner within and between cells, resulting in a causal dynamical system that creates a spatiotemporal pattern of expression domains. Such networks may be only partially known, so it is advantageous to consider mathematical models of dynamical networks that can be ''trained'' in the sense of machine learning algorithms—that is, they can be fit to some data by parameter-optimization and used to predict other data.

A very early example of a trainable, dynamical network used to model transcriptional regulation was developed for fruit fly embryo (Mjolsness and others 1991; Reinitz and others 1995). It explained the observed expression patterns of the ''gap genes'' in specifying position along the anterior–posterior axis in the syncytial blastoderm, a stage of the embryo comprising one large cell with many nuclei that exchange transcription factors by diffusion rather than via cell–cell signaling. The model, derived from statistical mechanics, incorporated a continuous-time, real-valued artificial neural network (ANN) applied as a model of a gene regulatory network (GRN) (thus, an ANN-GRN). It consists of a coupled set of ordinary differential equations representing the dynamics of transcription factor levels, assuming there is a partially or completely unknown matrix of numerical interaction strengths (positive or negative for enhancement or repression, respectively) between genes within each nucleus. A substantially different framework based on Boolean networks has been applied to model the GRN governing cell fate during *Arabidopsis* flower development (Espinosa-Soto and others 2004).

In the *Drosophila* embryo example, additional features beyond the regulatory network itself were essential. Different nuclei are connected by diffusion, and they undergo DNA replication on a standard schedule. The replication of nuclei raises a qualitatively new situation in which biological objects such as nuclei change their number and interconnection patterns at necessary moments in time but, between such times, they evolve continuously according to differential equations. A general framework for formalizing such situations was introduced (Mjolsness and others 1991; Prusinkiewicz and others 1993; Mjolsness 2006): a ''dynamical grammar'' whose constitutive rules each model a biological process that takes place either continuously or discretely in time, and which together add up to determine the dynamics of a model system. Of course, this capability will be important in some form for almost any developmental model that treats cells as distinct objects.

Later, the ANN-GRN model was augmented to allow for cell–cell signaling in place of diffusion (the gene regulation and signaling network, GRSN [Marnellos and Mjolsness 1998]). The same kind of model was subsequently used to begin modeling dynamically stable gene expression domains in *Arabidopsis* shoot apical meristem (SAM) (Mjolsness and others 1999). In these early models, space was represented by a spatial grid that was either fixed (for example, hexagonal in two dimensions) or allowed cell division only according to a predetermined schedule. Thus geometry and topology (the connectivity of cells) were not true interacting players in the dynamical system model but were exogenous to it.

All such regulatory network models can be classified according to how they translate different biological mechanisms (such as transcriptional reg-

ulation, receptor-mediated intercellular signaling, post-translational protein modifications, and so on) into mathematical models. What is needed to begin this translation of biology into mathematical models is an abstract representation of the *types* of information-bearing molecules and other biological objects and the *types* of biological processes that are permitted to operate on particular object types, together with a translation for each object and process type. This can be represented as a small graph with nodes and links that encompasses and generalizes the central dogma (gene $\rightarrow$ mRNA $\rightarrow$ protein, where the first arrow represents the process of transcription and the second arrow represents the process of translation). We may refer to such an object type/process type network for cells as a central dogma-like network (CDLN), to allow for domain-specific dogmas whether central or not. The objects may be thought of as nouns and the processes as verbs, with suitable noun/verb relationships represented as links. In computer science, such a listing of the fundamental types of objects and processes and their relationships is often called an ''ontology.''

In addition to the CDLN, there is also a problem-specific regulatory network of specific molecules, objects, and regulatory interactions that agree with the types and type constraints set forth in the CDLN. This regulatory network represents a biological hypothesis whose consequences can sometimes be best drawn out by modeling. Many regulatory networks can be governed by the same CDLN. The primary inputs to formulating the regulatory network are biological knowledge, data, and expertise in a particular system.

The Cellerator (Shapiro and others 2003) and Sigmoid (Cheng and others 2005) software environments for modeling, among many others, are organized around such a process of translation from biological regulatory networks to mathematical dynamical models.

Major choices must be made in translating a regulatory network and its CDLN to a dynamical model. These choices include, for each molecular species, whether it is to be represented as a real-valued (continuous) concentration or as an integer number of molecules; whether each biological process is to be modeled as stochastic or (much more efficiently simulated if less accurate) deterministic in its dynamics; and whether time and space are each modeled as continuous, discrete, or both continuous and discrete. In the latter case there must be some kind of connection between the two representations (as for example in the dynamical grammar integration of continuous and discrete time representations). These choices are not arbitrary but rather can be fit into a hierarchy of approximations, with very detailed but impractical models near the ''bottom'' being systematically related to simpler, more computable, and more understandable models near the ''top'' of the hierarchy. These choices may also depend on the spatial and temporal scales at which a biological system is to be modeled, so that future multiscale models must be able to integrate all these different types of dynamical systems. The primary inputs into choosing a translation of a biological system ''picture'' to a dynamical system are mathematical and computational expertise.

From this point of view, what shall we make of the many perfectly good modeling reports that do not appear to follow the foregoing outline? We can conclude that such articles do follow the procedure, either partially or cryptically, despite an alternative form of presentation, or that they could have been further improved by doing so.

Developmental Space

In development, regulatory networks within a cell must be augmented with intercellular communication and the dynamics of growing, dividing cells that can change their neighborhood relationships. Thus, the dynamic use of space must be modeled simultaneously with the regulatory networks.

Space in a plant tissue is divided into many cellular compartments whose shape is roughly polyhedral in the shoot meristem but may have a great variety of other morphologies elsewhere—though not so great as in animals. The geometry, topology, and dynamics of this compartmentalization profoundly influence the regulatory networks within each cell and are in turn largely a function of mechanical forces that can be modeled (Murray 1989; Landau and Lifshitz 1986). Fortunately, plant development provides a major simplification from animal development in that the dynamics of the cellular compartmentalization of space doesn't include the evolutionary heritage of motility—cells push, shear, and pull on one another but do not actively locomote.

Initially the multicellularity of a developmental system was attractive for gene regulation network modeling as a sort of parallel assay of the same gene network under multiple regulatory input conditions (Kosman and others 1998), with replication and tissue growth being just potentially confounding factors. But it was also clear (Mjolsness and others 1991) that a general purpose developmental mod-

eling framework would require two-way interaction between regulatory and mechanical networks, in which a mechanical network influenced signaling topology in the regulatory network, which in turn regulated cell division and cell growth inputs to the mechanical network (Shapiro and Mjolsness 2001).

As a temporary measure, one may consider passive models of space in which multiple cells and the space between them serve as an arena for the diffusion of information-bearing molecules from one cell or nucleus to another. In the limit of infinitely many very small cells, we can obtain in this way the ''reaction-diffusion'' partial differential equation framework of Turing. Cells engage also in more active signaling processes that may be modeled in the GRSN framework. At least in *Arabidopsis*, polarized transport of signals such as auxin, using intracellular cytosol and membrane compartments, is a much better model than diffusion for some important signaling systems in plants including phyllotaxis in the shoot apical meristem, one of Turning's original intended systems for reaction-diffusion modeling. But none of these communication models directly address the active mechanics of cell movement through space.

What is needed is a network-like model of developmental space and, in particular, of the mechanics of cellular compartments. An example of a ''mechanical network'' would be a Tinker Toy style arrangement of linear mechanical elements, called ''struts'' or ''springs with nonzero resting length,'' which exert force only along their axes (Figure 1A). Truss bridges and structures can be modeled to first approximation with such elements. In our work and in computer graphics these are known as ''mass-spring models.'' However, connections between cells may dwindle in relative overlap or break entirely upon cell division, so that the springs should be ''weak springs'' that can smoothly break (Figure 1B–D). All of these relationships can be modeled very simply by potential energy functions that depend only on the actual length and the resting length of a spring or strut (Shapiro and Mjolsness 2001). This mechanical model has been used in modeling phyllotaxis (Jönsson and others 2006), where its flexible topology plays an essential role in allowing cell growth and division to make room for new primordia, allowing them to escape inhibition by the old ones.

Fortunately the weak spring model allows bidirectional coupling of mechanical and regulatory network models. The regulatory network governs gene expression, metabolism, the growth of cell volume, the synthesis structural molecules, and the cell cycle including mitosis and cell division, which again affects cell volume. Cell volume and the amounts of any structural molecules govern the individual properties (strength and resting length) of the idealized spring between neighbors. Cell positions automatically minimize the total mechanical energy, through fast Aristotelian dynamics with velocity proportional to force over viscosity. The cell positions determine their geometry, including the interface area between any two cells. This interface area modulates the strength of any intercellular communication impinging on the regulatory network of each cell from the others; if it is zero, there is no direct signaling. Thus, the GRN influences the mechanical network and the mechanical network influences the regulatory network.

However, it is a considerable oversimplification to represent all the mechanical forces between two plant cells by a single spring energy function connecting their centers. Relevant subcellular structure that is omitted this way includes the mechanics of the nucleus made of stiff DNA, its random motion through the cytosol, the branching fibrous cytoskeletal network, and the sheets consisting of strong parallel cellulose fibers within the walls (and all perpendicular to the single idealized spring). The biological picture is of a complex, heterogeneous medium made of a great many nonlinear springs at a molecular rather than cellular scale, with additional fluid and gel properties.

A more detailed approach to mechanical modeling, then, is to use continuum approximations to elastic, viscoelastic, or plastic media as outlined by Murray (1989), with homogeneous properties in each of a set of compartments such as nucleus, cytosol, and particular cell membranes and walls. These models can be derived as a limit of infinitely many very small springs as in a spring network model. The essential quantities to model are stress and strain tensors, representing forces per unit area and relative displacements per unit length, respectively. Teran and others (2003) work out one example for anisotropic tissue media that roughly conserves volume for skeletal muscle. With advances in imagery to constrain the geometries and material properties (such as stress–strain laws), such fine-scale modeling will become progressively more practical.

A standard route to mechanical modeling is to use the finite-element method (FEM) to discretize continuous (PDE) elastic material models in 1D, 2D, and/or 3D. Each finite element is a polygon or polyhedron representing a region of space occupied by biological material, and connected to its neighbors. Within each element the relevant functions are interpolated using low-degree polynomials of

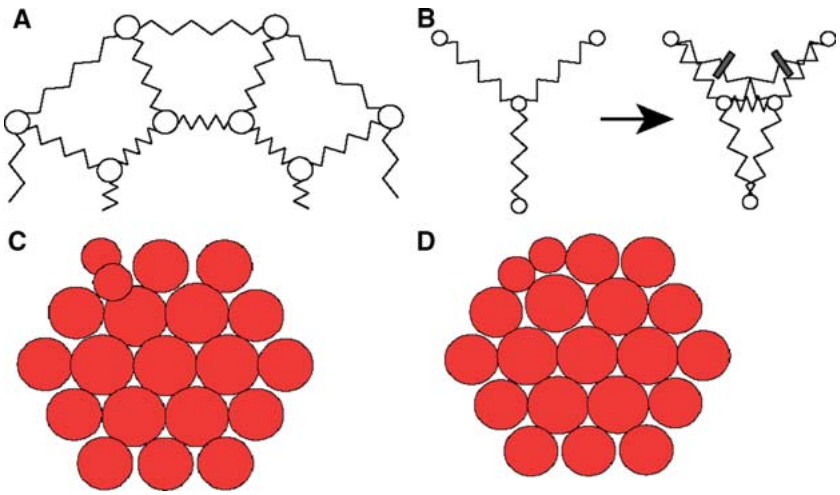

Figure 1. (**A**) Weak spring model with internal compression and external tension, along with (**B**) cell division in a (**C**) hexagonal array of cells with one recent cell division leads to (**D**) maintenance of a clonal outer layer (Mjolsness and others 2004). Panels (**C**) and (**D**) courtesy Henrik Jönsson, Lund University

the spatial variables satisfying continuity conditions at the boundaries. Where stresses and strains vary over a fine spatial scale, more finite elements are used to represent those changes. The goal is usually to approximate the behavior of a continuum elastic model using many finite elements with homogeneous mechanical properties, nevertheless using as few finite elements as is compatible with accurate simulation of the continuous model. In three dimensions, doing this adaptively as a simulation proceeds is a mathematical challenge. On the other hand, real cells and tissues are so heterogeneous spatially that one may question the goal of approximating a continuum model, and one may reinterpret finite elements or small collections thereof as something closer to heterogeneous biological structures, such as the nearly polyhedral cells and cell walls of the SAM.

Future Models

Weak spring mechanical network models are very coarse, having only a few mechanical degrees of freedom per cell. Conventional FEM models are very fine, approximating a continuum, but they can, as a result, incorporate more detailed and accurate physics. Between these two extremes lie other possibilities for modeling mechanical networks. One is based on the observation of similarity (Figure 2) between the irregular polyhedral tilings in SAM membrane slices and in Voronoi diagrams (Voronoi 1908; Dirichlet 1850). There is a Voronoi ''energy function'' in which a defined set of centers (such as cell nuclei) are used to calculate the distance to each point in the plane; each point associates with that center that minimizes its distance. The integral over the plane of the squared distance to its associated center is minimized by the Voronoi diagram. In this way one can make the vertices of a polyhedral tiling depend exclusively on its polyhedral centers. If one adds other mechanical energy functions that depend on the polyhedral tiling, they too become functions of the polyhedral centers. Very likely a minor generalization of Voronoi diagrams, which allows for a cell size parameter, is required to account for individual cell growth. (Such a generalization may arise from taking a slice through a Voronoi diagram of one higher dimension, or from a weighting on the distance measure, or both.) The result may be a mechanical model with the same degrees of freedom as the weak spring model, but able to represent a much greater variety of mechanical properties within each cell and cell wall.

Active, Smart Surfaces and Lively Manifold Embeddings

In image analysis, ''snakes'' are active contour models defined by an energy function that is minimized when an open or closed mathematical curve bends so as to follow a smoothed version of some important image feature such as a noisy boundary between cells. ''Active surfaces'' may be defined similarly, to find boundary or other surfaces in 3D data. In biology there are many essentially 2D tissues or layered structures built of 2D tissues. Their shape is actively controlled, but the information processing going on to control the shape is, as we have seen, much more elaborate, described by a large but structured regulatory network.

It may be useful to consider the following idealized abstraction of such tissues and layered tissue structures: each tissue is a 2D continuous surface in space (having no cell boundaries), with independent regulatory networks at each point in the con-

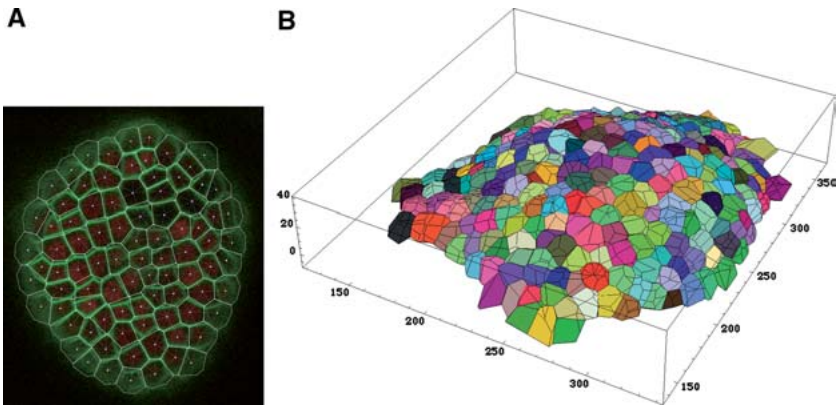

Figure 2. (**A**) Shoot meristem with plasma membrane and nucleus markers, with 2D Voronoi diagram superimposed; (**B**) 3D Voronoi diagram constructed from similar imagery. Courtesy Bruce Shapiro and Marcus Heisler, JPL/Caltech

tinuum. However there are multiple forms of communication between nearby points within the surface based on diffusion (as in reaction-diffusion models in an ordinary flat 2D space), receptor-ligand mediated intercellular signaling (as in the GRSN model), polarized transport (which apparently dominates over intercellular diffusion as the communication mechanism for phyllotaxis in *Arabidopsis* shoot meristem), and other coupling mechanisms that can all be modeled in an idealized way using spatial derivatives. The result is a network represented as a set of coupled partial differential equations (PDEs) within each surface.

Next, the foregoing PDEs are to be augmented by others that represent the continuum limit of a mechanical network, so that the entire surface can bend, fold, tear, or reconnect under the influence of its regulatory network. Neighboring surfaces in a layered structure can also communicate signals and stresses between layers, but signal communication may be less effective than within a surface, in which case, the model is 2D and layered rather than 3D. Such models would be mechanically ''active,'' computationally ''smart,'' and mathematically defined ''manifolds'' or ''manifold embeddings'' within ordinary 3D space. Their advantages would be to provide approximate descriptions of developmental processes that involve nontrivial manipulation of shape and form such as is well advanced in differential geometry; however, one would have to be careful to reinsert some form of cellular structure in the verification of computational application of such models to real systems.

One advantage of such continuum models is that they allow for analytic models of growth. For example, the regulation and patterns of growth are different in stem cell niches within adult organisms than within rapidly inflating tissues in juvenile organs (such as leaves) or the embryo. In one dimension one can create simple, completely solvable models of these alternative patterns of growth.

Multiscale Models through Dynamical Grammars

As suggested above, future multiscale models must be able to integrate all the major different types of dynamical systems models, including discrete and continuous time, discrete and continuous space, deterministic and stochastic dynamics, and so on, if only because the very same physical or biological system can be described with all of these alternative forms of modeling, at different scales. Future multiscale models must allow experimentation and integration of separate processes of these very different types. These goals are achieved by the modeling framework of dynamical grammars (Mjolsness 2006).

In dynamical grammars, each rule represents a process with input and output objects, much like a chemical reaction network in which the molecules bear information such as location and conformation that affect their reaction rates. Rules can represent processes that happen discretely in time, such as cell division and/or changes in attachment of a cell to neighboring cells, or continuously in time, as described by differential equations. Every rule and collection of rules is mapped to a particular mathematical object (an operator in a high dimensional space) that represents the time evolution of a system due to that process alone. The sum of all these time evolution operators, over all rules and all possible parameter values, gives the dynamics of the whole system. Fortunately, from this framework it is possible to deduce efficient discrete-time dynamics corresponding to simulation algorithms for use on a computer.

As an example, the phyllotaxis model of Jönsson and others (2006) can be thought of as a set of reaction rules at the molecular level, augmented with a set of cell division and attachment rules at the cellular level, resulting in an emergent dynamics of floral primordia at the tissue level. At

each scale, objects are born, move through space exchanging information, and are transformed into other objects or die.

Conclusions

There is a systematic approach to building useful models of complex biological systems that arise in developmental plant biology. It involves (1) building a representation of the biological regulatory and mechanical networks and processes known or hypothesized for a growing tissue, (2) translating these networks into mathematical models in the form of dynamical systems, (3) using relevant data (the more the better) to constrain the models and derive their most robust predictions, and (4) iterating the process. A key step is the translation of biological networks and processes to dynamical system models. Such dynamical frameworks as the ANN-GRN and GRSN models of regulatory networks, the weak spring and finite element models of mechanical networks, the dynamical grammars for integration of models of diverse processes including those that change the structure of the system, and perhaps future smart/active manifold models, can provide the necessary targets of the biology to mathematics translation in one or more ways.

With these various mathematical and computational tools for advanced modeling of developmental systems, and with new technologies for obtaining data with which to constrain such models, the future of scientifically effective modeling within botany and developmental biology looks very bright.

ACKNOWLEDGMENTS

Useful discussions with Christophe Godin, Marcus Heisler, Henrik Jönsson, Elliot Meyerowtiz, Sergei Nikolaev, Przemyslaw Prusinkiewicz, John Reinitz, Adrienne Roeder, Alex Sadovsky, and Bruce Shapiro are gratefully acknowledged. This work was supported in part by the National Science Foundation's Frontiers in Biological Research (FIBR) program, award number EF-0330786.

REFERENCES

Barbier de Reuille P, Bohn-Courseau I, Ljung K, Morin H, Carraro N, and others. 2006. Computer simulations reveal properties of the cell–cell signaling network at the shoot apex in *Arabidopsis*. Proc Natl Acad Sci USA 103:1627–1632.

Cheng J, Scharenbroich L, Baldi P, Mjolsness E. 2005. Sigmoid: towards an intelligent, scalable, software infrastructure for pathway bioinformatics and systems biology. IEEE Intelligent Systems May/June:68–75.

Dirichlet GL. 1850. Über die Reduktion der positiven quadratischen Formen mit drei unbestimmten ganzen Zahlen. J Reine Angewandte Math 40:209–227.

Espinosa-Soto C, Padilla-Longoria P, Alvarez-Buylla ER. 2004. A gene regulatory network model for cell-fate determination during *Arabidopsis thaliana* flower development that is robust and recovers experimental gene expression profiles. Plant Cell 16:2923–2939.

Jönsson H, Heisler M, Shapiro BE, Meyerowitz EM, Mjolsness E. 2006. An auxin-driven polarized transport model for phyllotaxis. Proc Natl Acad Sci USA 103:1633–1638.

Kosman D, Reinitz J, Sharp DH. 1998. Automated assay of gene expression at cellular resolution. In: Altman RB, Dunker AK, Hunter L, Klein T, editors. Pacific Symposium on Biocomputing 1998. Singapore, World Scientific, pp. 6–17.

Landau L, Lifshitz EM. 1986. Theory of Elasticity, 3rd Ed., Course of Theoretical Physics Volume 7. Oxford, England, UK, Butterworth-Heinemann, 187 p.

Marnellos G, Mjolsness E. 1998. A gene network approach to modeling early neurogenesis in Drosophila. In: Altman RB, Dunker AK, Hunter L, Klein T, editors. Pacific Symposium on Biocomputing 1998. Singapore, World Scientific, pp. 30–41.

Mjolsness E, Sharp DH, Reinitz J. 1991. A connectionist model of development. J Theor Biol 152:429–454.

Mjolsness E, Meyerowitz E, Gor V, Mann T. 1999. Morphogenesis in plants: modeling the shoot apical meristem, and possible applications. Proceedings 1999 NASA Workshop on Evolvable Hardware.

Mjolsness E, Jönsson H, Shapiro BE, Meyerowitz EM. 2004. Modeling plant development with gene regulation networks including signaling and cell division. In: Kolchanov N, Hofestaedt R, editors. Bioinformatics of Genome Regulation and Structure, Boston, MA, USA, Kluwer (Springer), pp. 311–318.

Mjolsness E. 2006. Stochastic Process Semantics for Dynamical Grammar Syntax: An Overview. Proceedings of the Ninth International Symposium on Artificial Intelligence and Mathematics (online at http://anytime.cs.umass.edu/aimath06/). Also archived as http://www.arxiv.org/pdf/cs.AI/0511073.

Murray JD. 1989. Mechanical models for generating pattern and form in development. Chapter 17 in Mathematical Biology, 2nd ed., Berlin, Germany, Springer-Verlag. 767 p.

Prusinkiewicz P, Lindenmayer A. 1990. The Algorithmic Beauty of Plants. New York, NU, USA: Springer-Verlag. p 224.

Prusinkiewicz P, Hammel MS, Mjolsness E. 1993. Animation of plant development,. Proceedings of SIGGRAPH 27:351–360.

Reinitz J, Mjolsness E, Sharp DH. 1995. Model for Cooperative Control of Positional Information in Drosophila by *bcd* and Maternal *hb*. J Exp Zool 271:47–56.

Shapiro BE, Mjolsness E. 2001. Developmental simulations with Cellerator. In: Yi TM, Hucka M, Morohashi M, Kitano H, editors. Proceedings of the Second International Conference on Systems Biology. Madison WI, USA: Omnipress, pp. 342–351.

Shapiro BE, Levchenko A, Meyerowitz EM, Wold BJ, Mjolsness ED. 2003. Cellerator: extending a computer algebra system to include biochemical arrows for signal transduction simulations. Bioinformatics 19:677–678.

Smith RS, Guyomarc'h S, Mandel T, Reinhardt D, Kuhlemeier C, et al., 2006. A plausible model of phyllotaxis. Proc Natl Acad Sci USA 103:1301–1306.

Swinton J. 2003. Watching the daisies grow: Turing and Fibonacci phyllotaxes. In: C.A. Teuscher (ed), Alan Turing: Life and Legacy of a Great Thinker. Springer 2003. See also: Allan Turing and Morphogenesis, Web site http://www.swin-

tons.net/jonathan/turing.htm and ''dynamic phyllotaxis'' link therein, dated 25 September 2003; last accessed 6/14/06. Analysis of unpublished works in the Turing Digital Archive http://www.turingarchive.org/browse.php/C/24-27, last accessed 6/14/06.

Teran J, Blemker S, Ng Thow Hing V, Fedkiw R. 2003. Finite volume methods for the simulation of skeletal muscle. In: Breen D, Lin M, editors. Eurographics/SIGGRAPH Symposium on Computer Animation, pp. 68–74.

Voronoi G. 1908. Nouvelles applications des paramètres continus à la théorie des formes quadratiques. J Reine Angewandte Math 133:97–178.