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Modeling plant morphogenesis

Przemyslaw Prusinkiewicz and Anne-Gaëlle Rolland-Lagan

Applications of computational techniques to developmental plant biology include the processing of experimental data and the construction of simulation models. Substantial progress has been made in these areas over the past few years. Complex image-processing techniques are used to integrate sequences of two-dimensional images into three-dimensional descriptions of development over time and to extract useful quantitative traits. Large amounts of data are integrated into empirical models of developing plant organs and entire plants. Mechanistic models link molecular-level phenomena with the resulting phenotypes. Several models shed light on the possible properties of active auxin transport and its role in plant morphogenesis.

Addresses
Department of Computer Science, University of Calgary, 2500 University Drive NW, Calgary, Alberta T2N 1N4, Canada

Corresponding author: Prusinkiewicz, Przemyslaw (pwp@cpsc.ucalgary.ca)

Current Opinion in Plant Biology 2006, **9**:83–88

This review comes from a themed issue on
Growth and development
Edited by David Smyth and Thomas Berleth

1369-5266/$ – see front matter
Published by Elsevier Ltd.

DOI 10.1016/j.pbi.2005.11.015

Introduction

The key objective of developmental biology is to understand development in mechanistic terms, with molecular processes being related to the resulting macroscopic forms across scales of organization. Owing to the complex spatio-temporal nature of development, mathematical modeling and computer simulations are useful tools for integrating experimental data and analyzing postulated mechanisms [1,2•]. In addition, quantitative traits, such as curvature and strain (growth) tensors, can be computed to characterize observed and modeled forms [3•,4]. In this review, we survey three aspects of the application of computational techniques to the study of plant morphogenesis: computer-assisted experimentation techniques, descriptive simulation modeling (also referred to as empirical or reconstruction modeling), and mechanistic simulation modeling.

Computer-assisted experimentation techniques

Experimental data are a prerequisite to the study of developing cellular structures, tissues, organs, and entire plants. Computational methods assist in the processing of raw data (usually images) and the extraction of useful information. For example, Dumais and Kwiatkowska [5] devised a technique for inferring the three-dimensional (3D) shape of meristem surfaces from stereo images of replicas observed under a scanning electron microscope. The replicas were obtained at a series of developmental stages, so that both the static descriptors of form (curvatures) and dynamic traits (growth rates) could be computed. This technique was applied to compare cellular growth patterns at the surface of the shoot apical meristem (SAM) in the wildtype and the *pin1* mutant of *Arabidopsis* [6•]. Another technique restricted to plant surfaces was developed by Kaminuma *et al.* [7], who calculated the orientation and curvature of *Arabidopsis* leaves by processing images obtained with a laser range finder. Volumetric data, which characterize not only the surface of the observed organ or structure but also its interior, can be obtained by combining stacks of images from confocal microscopy [8,9•,10•]. The more recently developed techniques of optical projection tomography [11] and selective plane illumination [12] should prove useful in acquiring volumetric data for samples of geometrically larger plant material.

A variety of computational techniques have been proposed to improve the visualization of data, discern biologically meaningful components such as individual cells and cell walls, and establish their geometry and connectivity [8,10•]. These techniques include image processing, digital morphology, computational geometry, and human-computer interaction (the latter might be required, for example, to localize seed points for image segmentation) [10•,13••]. One exciting recent advance is the use of *in vivo* confocal microscopy to visualize the development of the SAM of *Arabidopsis* at the cellular level [9•]. The resulting time-lapse animations rely on an algorithmic technique for aligning images that have been obtained at different time points. A specific problem that is related to the alignment and tracking of cells is the one-to-two correspondence caused by cell division; algorithms for solving this problem have been described by Gor *et al.* [14•]. A complementary technique is the use of transposon tagging to visualize cell lineages in living tissues as they develop [15]. Both techniques show great promise for the detailed study of patterns of cell division during morphogenesis.

Integration of developmental data is particularly difficult if samples are not easily accessible for tracking. Addressing this problem, Rolland-Lagan *et al.* [16,17•] proposed an alternative to tracking, which uses transposon tagging

and geometric growth simulation to infer tissue growth patterns from a large dataset of mature samples. This technique was applied to relate growth patterns and shape in developing *Antirrhinum* petals [16].

At the whole-plant level, the acquisition, organization and representation of architectural data present problems that range from labor-intensive measurements using manually operated 3D digitizers to the representation of the connectivity, geometry, and development of highly branching structures. A review of techniques is included in the survey paper by Godin *et al.* [18]. A new advance is the development of specialized devices for time-lapse digital image capture and automatic tracking of the features of many plants at once [19].

Reconstruction models

Reconstruction models integrate a large amount of experimental data into comprehensive representations of developing plant organs and entire plants. For instance, Fournier *et al.* [20] proposed an empirical model of the elongation of grass leaves, in which sheath and blade were divided into the cell division, cell elongation, and mature zones. The mathematical description of growth was reduced to one dimension by considering only the length of the leaves. The model was tested on data from wheat and tall fescue leaves. A related problem of fitting parameters to growth models was addressed by Hillier *et al.* [21].

In a recent model of *Arabidopsis* [22•], the development of a plant shoot from seedling to maturity was captured by correlating size data (such as the overall length and width of plant organs), obtained in a nondestructive manner, with shape data obtained by dissecting plants at specific developmental stages. This model simulates and represents in an integrated manner several quantitative aspects of *Arabidopsis* morphology and development, including correlated fluctuation in divergence angle and plastochron during early growth, and variation of leaf shapes in space and over time. A model of a similar character reproduces the development of rice [23•]. Both models simulate and realistically visualize development over large periods of time, and can be used as a reference for the kinetics of development.

Mechanistic simulation models

The objective of this category of models is to show how different components of the studied mechanism might work together and lead to the emergence of observed forms.

Models of timing

As development is a process that takes place over time, timing of developmental decisions has a significant impact on the resulting forms. For example, a delay in the switch to flowering (bolting) in *Arabidopsis* has a direct consequence of increasing the number of rosette leaves. Mechanisms that schedule developmental events should therefore be considered along with spatially explicit models in the description of morphogenesis. Recent examples of models that deal with time include genetic regulatory networks controlling the flowering time [24] and the circadian clock [25,26••] in *Arabidopsis*. The latter work is particularly interesting from the methodological point of view because it illustrates the interplay between the gradual refinement of a proposed network and the acquisition of experimental data.

Reaction–diffusion models

Two widely known paradigms for morphogenesis are positional information [27,28] and reaction–diffusion [29,30]. In both cases, pattern-forming substances (i.e. morphogens) are assumed to diffuse, for example, in a cell or a tissue. In the positional information model, the resulting concentration gradients provide spatial cues for differentiation. In the reaction–diffusion case, patterning is a result of chemical reactions between the morphogens.

Recent studies have aimed to bridge the gap between theoretical studies of reaction–diffusion and actual biological patterning. Pursuing this goal, Rauch and Millonas [31] proposed a conceptual framework for combining metabolic or genetic regulatory networks that act at the level of individual cells with diffusion-based signaling through the extracellular matrix or apoplast. The resulting extension of reaction–diffusion makes it possible to generate patterns using realistic diffusion rates for morphogens. Other extensions to reaction–diffusion include models that operate in non-homogenous [32] or growing [33,34] media. In both cases, a larger variety of biologically relevant patterns can be generated compared to the 'standard' reaction–diffusion model. Of particular relevance to morphogenesis is the potential feedback between molecular-level processes and growth [2•]. This is a mathematically difficult problem that is still far from having a comprehensive solution. Preliminary results are given by Harrison *et al.* [35].

One aspect of plant development that is being addressed using reaction–diffusion models is the maintenance of the shape and size of the SAM, as well as the expression domains of genes within this region. Experimental data suggest that *WUSCHEL* (*WUS*), a gene that is involved in the development of the *Arabidopsis* SAM, induces the *CLAVATA3* (*CLV3*) and *CLAVATA1* (*CLV1*) genes. The *CLV3* gene acts as a ligand for the *CLV1* receptor kinase which, upon binding, activates a signal that represses *WUS*. Jönsson *et al.* [13••] constructed two models for the regulation of the *WUS* pattern on the basis of experimental data. The models simulate *WUS* expression in a horizontal section at the top of the SAM, and take into consideration molecular reactions, gene regulation, and signaling between cells.

Auxin as a morphogen

Although positional information and reaction–diffusion are the most extensively studied theoretical paradigms of morphogenesis, their overall significance to plant development remains an open question [36]. As pointed out by Kepinski and Leyser [37], ''There are many beautiful examples of morphogenetic gradient patterning in animals, but strictly speaking, none at all in plants.'' On the other hand, many aspects of plant development appear to be related to the active transport of auxin. Examples include the establishment of embryo polarity, phyllotaxis, organ formation, root development, and vein patterning (see [38] for a review). In contrast to reaction–diffusion, which depends on the local production or destruction of morphogens coupled with passive (diffusive) transport, auxin-driven patterning appears to depend on the redistribution of a readily available morphogen (auxin) by a locally controlled active transport mechanism. A component of auxin-driven morphogenesis is the feedback between auxin transport and the abundance and localization of auxin transport facilitators [39].

These experimental results and concepts have triggered a renewed interest in the modeling of auxin transport and its role in plant morphogenesis. The point of departure is the notion of auxin canalization [40], according to which the flux of auxin in a particular direction promotes further flux in the same direction. The resulting feedback loop leads to the formation of patterns in a manner analogous ''to the formation of gullies when rain water flows down a sandy slope'' [41]. The first computational models based on the canalization hypothesis were developed by Mitchison [42,43]. The models showed that canals of high auxin flux and low auxin concentration can emerge in an initially almost homogeneous medium. In a recent reexamination of Mitchison's results, Rolland-Lagan and Prusinkiewicz [44•] explored canalization models in the light of data linking auxin to venation in wildtype and mutant *Arabidopsis* plants. The simulations showed, first, how vein formation can proceed in the acropetal direction (opposite to the direction of auxin flow); second, how the degradation of auxin transport in mutants or under the influence of an auxin transport inhibitor such as naphthylphthalamic acid (NPA) can affect the form of canals; and third, how veins can develop with gaps breaking their continuity, as observed in some mutants. In all of the above simulations, only very small tissues were considered: the models demonstrated the emergence of individual canals, but did not recreate the complex patterns found in mature leaves.

An apparent disagreement between experimental data and the canalization hypothesis concerns the concentration of auxin in the canals. For instance, experiments using the auxin-responsive DR5::β-glucuronidase (GUS) reporter construct [45] seem to indicate that concentrations of auxin are higher in the vascular strands than in the surrounding tissue [46]. By contrast, the canalization hypothesis predicts that auxin concentrations will be relatively lower in canals than in surrounding tissues. To examine this discrepancy, Kramer [47•] proposed a model of auxin transport based on experimental data on the localization of auxin influx and efflux carriers. His results suggest that the accumulation of auxin in canals might result from two strategies: i) the ubiquitous expression of efflux carriers (i.e. PIN proteins), or ii) the localization of efflux carriers in the canal and its border cells, combined with influx carrier (i.e. AUX/LAX protein) localization that is either ubiquitous or confined to the canal and border cells. Unlike the canalization hypothesis, however, Kramer's model does not address the question of what determines the polarization of auxin carriers in the first place.

This latter question was pursued by Feugier *et al.* [48•] who explored extensions to the canalization model in the context of patterns on the scale of entire (mature) leaves. The results showed that, depending on the equations chosen for controlling efflux carrier distribution and abundance, canalization can lead to the formation of channels that have high auxin flux and either high or low auxin concentrations. Although the generated patterns are not very similar to those observed in real leaves, it is possible that the reason is not the postulated interplay between auxin transport and position of auxin transporters but the absence of growth in the model. This is suggested by the model of Runions *et al.* [49•], who showed that venation patterns can be generated in a visually realistic manner if leaf blade growth is considered. However, their model was formulated in geometric terms, and its link to molecular mechanisms remains an open problem.

Canalization (and its variants) is not the only way in which actively transported auxin appears to be involved in morphogenesis. Pursuing alternatives, Chavarria-Krauser *et al.* [50] coupled growth with the distribution of auxin in a model of root growth, and Kramer [51] constructed a model of pattern formation in cambium. In the latter paper, a dominant role in pattern formation is attributed to the direction of auxin flow rather than to levels and gradients of auxin concentration. Thus, once again, the proposed mechanisms for patterning in plants departs from the positional–information and reaction–diffusion paradigms of morphogenesis.

Competition-driven morphogenesis

A long-standing question in plant development concerns the relative role of hormonal control and competition for resources as morphogenetic factors [52]. At the molecular level, phytohormones, and auxin in particular, have been at the center of interest, but mechanistic models built at the whole-plant level have also explored the resource-driven hypothesis. In this context, Minchin and Lacointe [53] reviewed current theories and mathematical models

pertinent to the transport and partitioning of carbon. Allen *et al*. [54] proposed a generic model of tree growth (motivated by a previous compartmental model of peach trees), which couples tree development with the production, competition for, and use of carbohydrates. The model qualitatively reproduces the effect of manipulations, such as fruit thinning and water stress, on the development of a tree. A model simulating competition for carbohydrates without explicitly simulating their transport was proposed by Yan *et al*. [55].

Modeling methodology and software

The number of components of a multicellular organism, such as cells or architectural modules, changes (usually increases) as the organism develops. The neighborhood relations that affect the flow of control signals between these components also change over time. Lindenmayer [56] recognized that modeling such dynamically changing systems requires fundamentally new mathematical techniques, and proposed the formalism of L-systems to address the specific case of modeling branching filaments. Over the years, L-systems have undergone a series of extensions, motivated by the growing needs of model construction (see [57] for a survey and [58,59] for additional results). An important recent advance was the development of the modeling language L+C [60], which combines the general features of L-system programing with the computational power of the general-purpose language C++. To date, L-systems and their extensions have primarily been applied to define descriptive [22•,23•] and mechanistic [54] models at the architectural level of plant organization. Nevertheless, L-system models may also include genetic regulatory networks that operate at the cellular level, as illustrated by a model of the differentiation of Anabaena heterocysts outlined by Coen *et al*. [2•]. Numerical methods for solving growing systems of ordinary differential equations involved in this class of models have been discussed by Federl and Prusinkiewicz [61].

In the case of L-systems, the formalism initially devised to describe developing organisms in discrete terms was retro-fitted with continuous terms and differential equations. A complementary approach is taken in the Computable Plant project [62], where a language previously devised for describing macromolecular networks is being extended to describe developing multicellular organisms.

As discussed earlier, simulation modeling is only a part of the manifold applications of computational methods in studies of morphogenesis. Taken together, these applications highlight difficult technical questions concerning: (i) the integration of various system components into a user-friendly system, (ii) the maintenance of models in the face of constantly changing programming environments, (iii) the construction of large and extensible models, (iv) the reuse of model components, (v) the possibility of integrating independently developed model components into larger systems, and (vi) the organization of databases that combine experimental data and the resulting models. This is a combination of well known yet still unsolved computer science problems and new problems that are specific to the systems biology of multicellular organisms. Solving all these problems may be as important as the acquisition of new experimental data to long-term progress in developmental plant biology.

A concluding remark

A comparison of papers surveyed in this and the preceding review [1] clearly indicates a surge of research that is deeply rooted in experiments and assisted by a wide range of computational methods. The role of such interdisciplinary work will undoubtedly increase in the future. This raises the question of the appropriate form for reporting research results. Current editorial guidelines for mainstream biological journals often impose a rigid structure on articles, which does not include modeling, and strictly limit page/word/character numbers. As a result, crucial aspects of model description or operation are routinely left to supplementary materials or separate theoretical publications. This breaks the flow of ideas, obscures the creative interplay between experiments and model construction, undermines the importance of presenting models in a reproducible manner, and distorts the validity of qualitative conclusions by downplaying the quantitative context in which these conclusions have been formulated. Several of the papers considered in this review showed one or more of these limitations. We believe that science would be better served if the guidelines for the structure and size of papers with a significant modeling component were observed less rigidly, allowing the authors to adequately present the results in a manner compatible with the inherent logic of investigation.

Acknowledgements

Support for our research from the Natural Sciences and Engineering Research Council of Canada, Alberta Ingenuity, and the Pacific Institute of Mathematical Sciences is gratefully acknowledged.

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