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Current Opinion in Plant Biology

Modeling plant growth and pattern formation

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Abstract

Plants continue to grow and generate new organs in symmetric patterns throughout their lives. This development requires an interconnected regulation of genes, hormones, and anisotropic growth, which in part is guided by environmental cues. Recently, several studies have used a combination of experiments and mathematical modeling to elucidate the mechanisms behind different growth and molecular patterns in plants. The computational models were used to investigate the often non-intuitive consequences of different hypotheses, and the *in silico* simulations of the models inspired further experimentation.

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Current Opinion in Plant Biology 2010, **13**:5–11

This review comes from a themed issue on
Growth and Development
Edited by Dominique C. Bergmann and Andrew J. Fleming

Available online 11th November 2009

1369-5266/$ – see front matter

DOI 10.1016/j.pbi.2009.10.002

Introduction

Plant development can be described as a dynamic system of molecular patterning, resulting from biochemical reactions and molecular transport [1,2], combined with a regulated growth, resulting from an isotropic turgor pressure and anisotropic mechanical properties of the cell walls [3]. The coordination between molecular patterning and morphogenesis suggests the existence of feedback between the two systems. Recent increase in the amount of available molecular data together with *in vivo* measurements of the cytoskeleton has enhanced the possibility to investigate the interactions between genes, hormones, and growth as a single system.

Computational modeling provides an important tool for examining the hormonal patterning, the genetic network modules that control differentiation, and the possibility of mechanical properties driving patterning. In this review we will discuss recent progress in modeling these processes including efforts combining molecular patterning with mechanical changes that alter growth dynamics. The examples given show that different modeling techniques can be successful and that the models in iterative combination with experiments present a powerful approach toward a more comprehensive understanding of plant development.

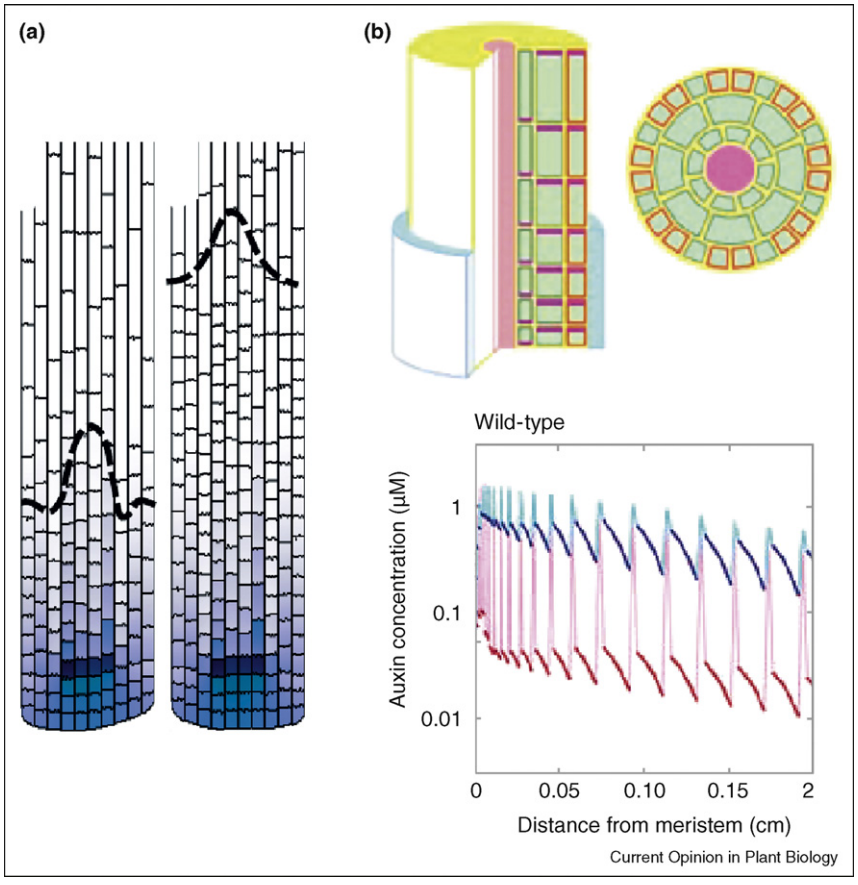
Modeling hormonal control of development

Phytohormones regulate many aspects of plant growth and development [2]. A prominent example investigated in many modeling studies is auxin. Auxin is fundamental to multiple physiological processes at different scales in the plant including embryonic patterning, phyllotaxis, tropism, and the development of leaf veins and root hairs [4]. Critical for auxin patterning is its polar movement between cells facilitated by membrane-bound influx and efflux mediators — AUX and PIN family of proteins, respectively.

In roots the transport mediators are expressed in a static pattern, which has been adopted in models using a predefined localization of transport mediators to predict auxin distribution. PIN efflux mediators are localized basally (toward the root tip) in internal tissues and apically in epidermal cells, with some lateral inward localization in outer cell layers suggesting a 'reflux' of auxin that creates a maximum at the root tip. Grieneisen *et al.* [5••] implemented these PIN patterns in a two-dimensional model showing that this was sufficient to create the experimentally verified stable auxin maximum at the root apex, and also predicted several perturbations and auxin-regulated growth (Figure 1a). A similar model was used to argue that changes in auxin concentration due to a geometric transformation could be responsible for the initiation of the lateral root [6]. Swarup *et al.* [7] used a three-dimensional model of the outer cell layers of the root to demonstrate the importance of the epidermally expressed AUX1 for apical transport of auxin and maintenance of the asymmetry in auxin localization caused by gravitropic response. Using a similar model, Jones *et al.* [8•] found that differentially expressed AUX1 in root-hair versus non-hair cells promotes a more uniform and long-ranged distribution of auxin (Figure 1b). These root models are examples of successful approaches where the models have been developed and challenged with direct comparisons with experiments. It would be interesting to compare predictions of a model including both internal tissue and influx mediators with increasingly resolved quantitative measurements of auxin in the root (e.g. [9]).

Other aspects of auxin patterning show dynamic expression and localization of transport mediators. Molecular models of leaf venation rely on the prevailing idea of canalization introduced by Sachs [10] and first

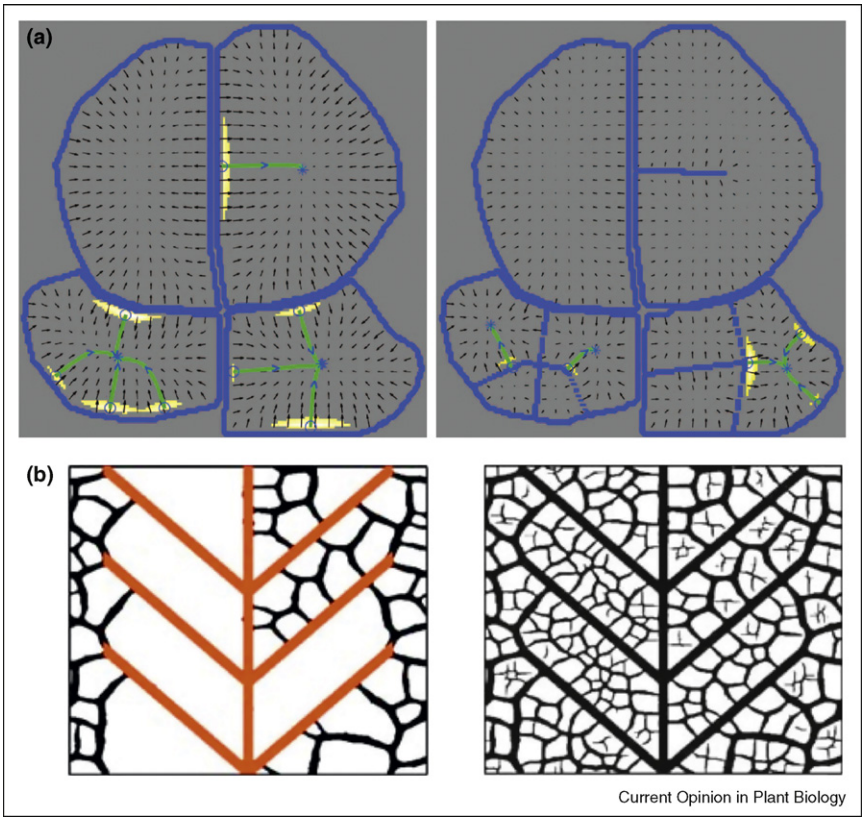
Figure 1



Models of auxin transport in the root demonstrating different topologies used in simulations. **(a)** Two-dimensional model from Grieneisen *et al.* [5••] including tissue growth. The figures show two time points from a root growth simulation using a Cellular Potts Model (left 12 h, right 8 d). Auxin concentration indicated in shades of blue (dark blue represents high concentrations). The simulation shows the maintenance of a stable auxin maximum during growth due to the transport paths defined by the localization of efflux (PIN) transport mediators (see main text). Adapted by permission from Macmillan Publishers Ltd: [Nature] [5••], copyright 2007. **(b)** Three-dimensional model of outer cell layers from Jones *et al.* [8•]. Top picture shows the cell layout and positioning of efflux and influx transport mediators. AUX1, shown in red, is positioned toward all sides in epidermal non-root-hair cells. On the right, a horizontal cut shows the root-hair cells without AUX1. PIN2, shown in purple, is localized apically in the outer two layers and basally in the third layer of cells. Bottom picture presents auxin concentrations in files of epidermal cells, red: hair cells, blue: non-hair cells. Adapted by permission from Macmillan Publishers Ltd: [Nature Cell Biology] [8•], copyright 2008.

implemented by Mitchison [11,12] 30 years ago. According to this idea, auxin regulates its own transport via a positive feedback from the auxin flux, which can lead to the formation of streaks between auxin sources and sinks. A problem with the flux-based approach has been the appearance of low auxin concentrations in the forming veins in contrast to experimental observations. Interestingly, it has been shown that a proper inclusion of PIN1 cycling in the model, such that there is a competition of PIN1 among a cell's membranes, is sufficient for generating high auxin concentration in the veins [13,14]. Also, including influx mediators allows for cells with high auxin concentrations to act as sinks [15]. Leaf veins often form loops, which the original flux-based hypothesis could not explain. Mitchison demonstrated that properly positioned auxin source cells could lead to loops, something revisited in several current models [16,17]. Dimitrov and Zucker [18] showed that constant production of auxin together with a flux-based transport rule can lead to loops in higher order vein formation (Figure 2a). There is also an ongoing debate whether a flux-sensing mechanism is probable. Mitchison argued that a directional auxin flux will lead to an internal gradient within the cells, which might be easier for the cell to measure. Recently this idea has been implemented in a model showing that it can result in the formation of a vein [19]. For some reason, robustness of patterning is rarely discussed for flux-based models. An exception is the work of Fujita and Mochizuki [14] who demonstrate high sensitivity of pattern-forming capabilities of a flux-based model to the choice of parameter values and initial conditions.

Figure 2



Models for secondary leaf vein formation. The figures show the development where the left pane is an early, and the right pane is a later time point. **(a)** Model with homogeneous auxin production by Dimitrov and Zucker [18]. Existing areoles (blue lines) act as sinks and provide zero auxin concentration boundary condition in the model. New veins (green lines) are created from sites of maximal auxin gradient (yellow) and progress toward auxin maximum at the center of areole. Adapted by permission Copyright 2006 National Academy of Sciences, USA. **(b)** The mechanical model from Laguna *et al.* [51•] explores a possible role of stresses in the formation of vein patterns. Compressive stress develops in the tissue due to different growth rates of mesophyll (internal, fast growing) and epidermal cells. The vein cells are assumed to have distinct elastic properties. In a leaf growth simulation seeded with an preexisting vein pattern (orange lines) new veins (black lines) develop as energetically favorable state of the system. Adapted form Laguna *et al.* [51•].

The regular and repeatable phyllotactic patterns of plant organs have inspired modelers for a long time. Auxin transport plays an essential role in this process where auxin peaks, directed by specific polarization of PIN1, form at the sites of incipient primordia [20]. Models have reproduced auxin peaks at the correct positions given experimentally extracted PIN1 polarization [21,22]. The more elusive problem, also addressed by modeling, is what kind of local mechanism can lead to the formation of such patterns in a growing meristem. Jönsson *et al.* [22] and Smith *et al.* [23] proposed that PIN1 polarizes toward cells with high auxin concentration. This produces a positive feedback loop for auxin, which flows toward maxima and depletes regions around them, and the models were able to generate phyllotactic patterns. Recently, the requirements for this novel pattern-forming mechanism were investigated in detail and it was shown that it is also capable of forming other patterns, such as stripes [24].

The idea of a concentration-based auxin-PIN1 coupling (up the gradient) seems to be incompatible with the original (down the gradient) flux-based concept proposed for leaf venation and several models have tried to overcome this. One proposed solution is the existence of different mechanisms in different tissues. The idea that auxin is localized to the primordia site in the epidermal cell layer via the concentration-based mechanism and switching to flux-based transport in internal layers to simulate outflow of the auxin toward vascular tissue has been introduced [25•,26•]. Also, a unified description where either a concentration-based approach [27] or a flux-based approach [28•] has been suggested. Stoma *et al.* [28•] successfully adapted the flux-based mechanism for phyllotaxis assuming low auxin concentrations in the primordia during part of its development.

Models of genetic regulation

The shoot apical meristem (SAM) is a stem cell niche regulating above-ground plant development [1]. Many

proteins important for SAM continuation have been discovered, among which the feedback loop between CLAVATA (CLV) and WUSCHEL (WUS) has attracted special attention. Jönsson *et al.* [29,30] used a multicellular model setup to investigate several aspects of the CLAVATA/WUSCHEL feedback. They provided a hypothesis for how the asymmetric localization of a CLV3 region from the activating WUS region could appear [29], and demonstrated how a spatially restricted activation of WUS via a reaction-diffusion dynamics was sufficient to explain the spontaneous organization and perturbed reorganization of the WUS domain [30]. Recently, Geier *et al.* [31] used a population-based model to investigate how experimentally measured variations in CLV and WUS expression regions could be explained by regulating differentiation rates and using experimental growth rates as input. They showed that the regulation of differentiation rates from a signal originating either from the CLV3 or WUS domain was sufficient to explain the variation, although the *clv* and *wus* mutants were hard to reconcile in their model. Although our understanding of the SAM regulation has been improved by recent experiments and models, the picture is still not complete. Additional known regulations will need to be included in the models and especially interactions between the CLV/WUS network and proteins in the peripheral zone could provide improvements for current models.

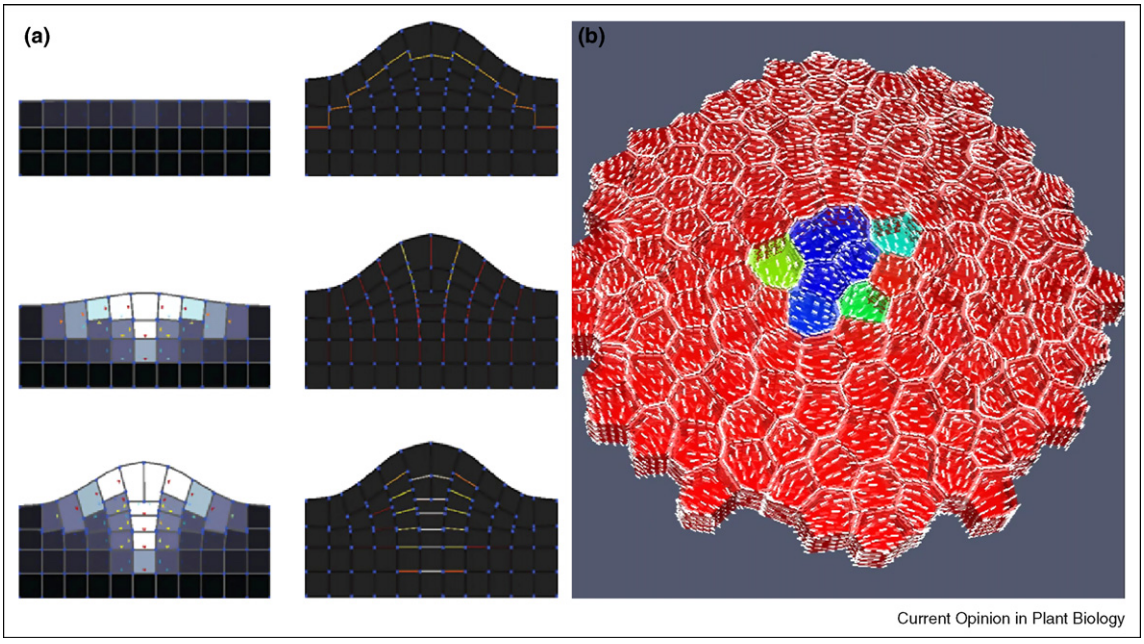
The genetic patterns defining flower development have been well characterized in experiments [32] and investigated in Boolean network models [33]. Boolean networks provide a simplistic model where genes can be only on or off, while the interactions are encoded in logic rules such as AND and OR. Although simplistic, the genetic network models result in basins of attractions correlating with the different cell-types found in flowers, and hence suggest that the defined network structure itself holds much of the regulatory information. Recently, stochastic noise has been introduced in the Boolean models, indicating that the differentiation path could be captured within these models [34]. It would be interesting to see a model including spatial aspects of flower development, which is disregarded in current models.

Cellular differentiation leading to trichome (hair cell) formation appears at the epidermis in young leaves and in roots, and the underlying genetic networks are similar [35]. The molecular mechanisms represent a classical reaction-diffusion model where protein activate and repress each other via formed complexes and where transport between cells are present, and this has inspired several recent models [36–38,39•,40•,41]. Digiuni *et al.* [39•] used a deterministic differential equation model to support their new data on protein transport and could discriminate between different hypotheses for the formation of a competing inactivated complex in the leaf. Savage *et al.* [40•], on the other hand, used a stochastic Boolean model to show that the often used self-activation of one of the activators could not explain all mutant data in the root. Since the proposed models typically describe a simplified picture addressing parts of the network, and the amount of data is continuously increasing, a more comprehensive model challenged by numerous mutants is expected in the near future.

Including growth and mechanics

A great current challenge is to understand plant morphogenesis from the cellular perspective. From a mechanical point of view the shape of a tissue is determined by equilibrium of forces, which at the cell level result from turgor, symplastic inhomogeneous growth of the whole tissue and stresses in the cell walls. Elastic properties of the cell walls are changing during the course of plant development, thereby guiding growth, and can achieve large degrees of anisotropy due to the presence of oriented cellulose fibrillar networks [3]. Two interesting questions are how molecular patterns can lead to morphogenetic patterns [42], and also whether mechanics itself can create patterning [43]. It has recently been shown in models how differential growth can lead to complex shapes [42,44,45], and this has also been included in cell-based tissue models [25•,46••] (Figure 3). The idea that mechanical buckling can initiate phyllotactic patterning [47] has recently been revisited [48,49•], where a continuous model generated phyllotactic patterns. Newell *et al.* [49•] showed that the mechanical solutions were very similar to a continuous implementation of the auxin transport model of Jönsson *et al.* [22]. Further, they connected the mechanical and molecular models and showed that the combination may alter the patterns from the individual models. An assumption in the buckling idea is that the epidermis is experiencing compressive stresses. Hamant *et al.* [46••] assume an epidermis under tension and show that microtubules organizing to orient microfibrils to resist stress can explain the microtubular patterns in the SAM also for several perturbation experiments. Auxin is used to loosen the cell walls leading to a circumferential microtubular alignment surrounding a new primordia, already before any visible morphological change (Figure 3b). This augments the directional growth of the primordia, and the resulting geometry of the tissue reinforces the stress pattern, thus generating a positive feedback known to amplify initial perturbations. The importance of growth anisotropy at the SAM was further investigated by Corson *et al.* [50], who showed that cells behaved similarly to soap bubbles in oryzalin-treated shoots where isotropic growth follows. Finally, mechanical rules for the initiation and development of leaf venation have also been proposed [51•,52] (Figure 2b). In contrast to the canalization hypothesis, looped venation patterns occur naturally in this case. The examples given in this section show the increased interest in investigating how molecular patterning, mechanics, and growth are connected. An improved analysis of these

Figure 3



Mechanical Finite Element Models for primordia initiation in the shoot. In the models, auxin is inducing cell growth. **(a)** Two-dimensional model from Dupuy *et al.* [25•]. A concentration-based auxin transport model is used in the top (epidermal) layer, and a flux-based auxin transport model is used in the lower (internal) layers. **Left pane**: time evolution of shape and auxin concentration. **Right pane**: transport mediator localizations. **Top**: AUX1 conveys auxin to L1 layer, **middle**: configuration of PIN1 directing auxin toward maxium in L1 layer, **bottom**: polarization of PIN1 facilitating canalization process. Adapted from Dupuy *et al.* [25•], by permission from Oxford University Press. **(b)** Finite Element Model similar to the one used in [46••]. Circumferential stresses (white bars) dynamically develop around cells with high auxin concentration (blue-green) in the epidermal tissue layer. This effect is due to an overall tension in the epidermal layer and increased growth due to wall weakening in cells with high auxin concentration. Image by PK.

interactions will follow with the development of detailed dynamical three-dimensional mechanical models.

Conclusions

Computational modeling might not yet be a standard tool in the investigation of plant development, but the selection of papers in this review shows that it is increasingly used in combination with experimental methods to deepen our understanding of specific hormonal signaling, genetic regulation, and morphogenetic events. The presented publications show that often several models can be used to explain single phenomena, and hence the models must always be challenged in new experiments driven by the predictions from the current models. Live imaging, where molecular and cytoskeleton dynamics is visualized, also directly following perturbations [53], increases our ability to compare and challenge our models with experimental data. The combination of molecular and cytoskeleton data opens up for direct testing of hypotheses on how genetic and morphological changes feed back to each other and provides an addressable modeling challenge for the near future. Another interesting experimental advance is the development of high throughput and auxin quantification techniques at a cell-type specific resolution [9,54–56]. Such data may be used to infer large-scale networks in unbiased computational approaches [57].

Modeling will be key to understanding the complex interactions driving plant development. The models have to be able to explain the inhomogeneities and anisotropies driving patterning. A molecular anisotropic description relies on the measurement of gradients, and hence on non-trivial integration of spatial information. The tensorial nature of stresses may play an important role here. In the coming years, computational modeling might be the optimal way to resolve the importance of different mechanisms.

Acknowledgements

Related research in the authors' group is supported by the Swedish Research Council and Human Frontier Science Program.

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