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Modeling plant development: from signals to gene networks

Cyril Lavedrine[1], Etienne Farcot[2] and Teva Vernoux[1]

Mathematical modeling has become a common tool in plant developmental biology. Indeed, it allows for the prediction of complex and often unintuitive dynamics of the molecular networks driving plant development. This has enabled the test of their possible involvement in robust and specific developmental processes. Modeling has also been fruitful in predicting new interactions within gene networks, such as the *Arabidopsis* circadian clock. A new challenge is to integrate patterning issues with tissue growth and biomechanics. The development of new tools to gain resolution in data collection as well as new frameworks to confront models and data might provide even more robust predictions.

Addresses
[1] Laboratoire de Reproduction et Développement des Plantes, CNRS, INRA, ENS Lyon, UCBL, Université de Lyon, 46 Allée d'Italie, 69364 Lyon Cedex 07, France
[2] School of Mathematical Sciences & Centre for Plant Integrative Biology, University of Nottingham, NG7 2RD, United Kingdom

Corresponding authors: Farcot, Etienne (etienne.farcot@inria.fr) and Vernoux, Teva (teva.vernoux@ens-lyon.fr)

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Introduction

Patterning during development emerges from the interplay between morphogenetic signals acting at different scales, from single cells to entire tissues, and complex gene regulatory networks (GRNs) interpreting these signals in each cell. GRNs also transform environmental signals into developmental responses, thus controlling plant developmental plasticity. A strict regulation of the spatio-temporal distribution of morphogenetic signals in tissues provides another mechanism for controlling the activity of GRNs during plant development. In the recent years, with experimental data uncovering more and more complex GRN structures, mathematical and computational modeling have become indispensable to predict the behavior of these networks (Box 1). This review focuses on a selection of studies published over the past two years to highlight how modeling is currently being used to improve our understanding of plant development. It has notably suggested networks enabling robust pattern formation, often involving the plant hormone auxin. It has also helped in suggesting mechanisms underlying the integration of growth and patterning by GRNs, and to discover new interactions within these networks, especially for the circadian clock and floral transition networks.

Morphogenetic signal distribution and processing during development

The key plant hormone auxin is involved in regulating the activity of GRNs throughout plant development. Defined spatio-temporal distributions of auxin are established in tissues through active polar transport from cell to cell. The efflux carriers of the PIN-FORMED (PIN) family are polarly localized in most cells and are essential to control the directionality of the auxin flux [1–3]. Simple mechanisms where the asymmetric distribution of PIN proteins is established through a positive feedback involving auxin flux [4,5] or auxin concentration [6] have been suggested in the last decade. Computational modeling has shown that each mechanism alone can recreate experimentally observed auxin distribution, some studies relying on a combination of both mechanisms, in tomato [3] and more recently in Brachypodium [7]. Both mechanisms show a similar, complex range of patterning and dynamical properties as shown by mathematical analysis [8,9••,10,11]. This limits the capacity of existing models to identify the active mechanisms *in planta*. In addition, a comparative analysis of most available models suggests that none of them can autonomously self-organize the typical patterns of auxin distribution observed in shoot and root meristems [9••]. However several recent studies are now suggesting new mechanisms to be considered. A model of PIN polar localization analyzed the establishment of the apical-basal axis of the *Arabidopsis* embryo and indicates that local sources of auxin biosynthesis at both end of the embryo axis are required to organize PIN polarities [12•]. Local biosynthesis could be regulated by YUCCA genes that control a limiting step in auxin biosynthesis [13] and are expressed in domains coherent with model predictions [14]. Note that the relatively low rate of auxin biosynthesis further suggests that a tight regulation of auxin catabolism and conjugation could be involved [15]. Polar auxin transport also implicates auxin influx carriers of the AUX1/Like-AUX1 (LAX) family. LAX3 is necessary to drive the local auxin accumulation

Box 1 Differential equations

The dynamics of molecular and gene networks have been extensively modeled with differential equations (DE). DE contain functions of time and/or space, generically called 'variables', which typically represent the concentrations of proteins or other substances. The equations themselves are written relying on known interactions between the different substances, and relate these interactions to the rate of change of the variables in time or space. Two of the main classes of techniques are the *estimation*, or *fitting*, of unknown physico-chemical parameters of a DE model on experimental data, and the *simulation* of a model using a fixed set of parameter values. Different choices of parameters (fitted or not) lead to different simulations, making the two questions interdependent, and complex. For this reason notably, once a model has been established its mathematical or computational study is often a scientific challenge of its own.

that contributes to the formation of lateral root primordia and is induced by auxin [16]. A model of auxin-induced LAX3 transcription has shown that a robust distribution of auxin and LAX3 expression requires activation of an auxin efflux carrier, identified as PIN3 [17•]. Modeling of auxin transport based on experimentally determined distributions of PIN and AUX/LAX proteins similarly demonstrated that AUX/LAX influx carriers are required alongside the PIN proteins to reproduce measured auxin distribution in the root tip [18]. Thus a tight coordination of auxin influx and efflux is likely required to control auxin distribution, a vision supported by experimental data in the embryo [19]. Finally, in the hypocotyl, it has also been shown by combining modeling with genetic and pharmacological experiments that both tissue topology and apoplastic pH are crucial to establish a lateral auxin gradient during the phototropic response [20]. Apoplastic pH alters the protonation of the weak acid auxin and thus its capacity to enter freely into cells, pointing again at the importance of regulating auxin influx. More generally these studies identify, besides PIN proteins, a variety of mechanisms controlling auxin distribution that should help designing new models and new experiments to fully understand auxin-based patterning.

In addition to transport, the role of auxin signaling has been investigated using modeling. A reconstruction of this pathway in yeast [21••], coupled with a minimal mathematical model, revealed a central role for Aux/IAAs (which are repressors of auxin-induced transcription) and Aux/IAA auxin-induced degradation rates in setting the transcription dynamics of downstream genes. By manipulating the degradation rate of an Aux/IAA in lateral roots, a correlation was found between degradation rates and the timing of lateral root development [22], confirming *in planta* the model predictions. Aux/IAAs and Auxin Response Factors (ARFs) interact in many different ways [23], and structure the auxin signaling pathway in different modules. A mathematical model of this pathway further suggests a complementarity of the modules in controlling the amplitude, speed and sensitivity of the response [24•], providing testable hypotheses to better understand the control of patterning genes by auxin.

The role of gene regulatory networks in setting cell territories

Downstream the distribution and transduction of hormonal signals, models have also contributed to discovering multiple non-linear GRNs underlying the definition of cell territories. In the shoot apical meristem, modeling indicates the necessity for a mutual repression between WUSCHEL and a set of transcription factors involved in cell differentiation in the proliferation zone, to prevent premature differentiation of stem cell progenitors [25]. In the root, auxin acts on RETINOBLASTOMA-RELATED PROTEIN, itself involved in a positive feedback loop comprising mutual indirect repression with SCARECROW, to constrain asymmetric cell divisions to the stem cell region [26] (Figure 1a). In the embryo, finally, a double negative feedback loop is sufficient to maintain clear epidermal identity against fluctuations in the concentration of a ligand [27•] (Figure 1b).

Often, forming a pattern with sufficient stability requires a certain level of functional redundancy, and thus more complex networks. For instance connections between SHORTROOT, miRNA165/6 (both being mobile signals) and PHABULOSA alongside auxin transport as well as auxin and cytokinin signaling are required, together with an unknown negative regulator, to establish a stable bisymmetric patterning of the root vascular system [28•]. This network enables the formation of the system even when auxin and cytokinin are produced uniformly in all cells.

Morphogenetic signals and gene regulatory networks in the coordination of growth, mechanics and patterning

The studies cited above have considered only tissues with fixed geometries. Integrating tissue growth, realistic cell geometry and mechanics to signals and gene networks during pattern formation is a current frontier in plant morphogenesis modeling. A conceptual study [29•] has investigated the minimal mechanisms allowing for the emergence of the root stem cell niche in a context of cells exerting elastic forces on each other, and initially disposed at random position with random size. A correct pattern could emerge with only two rules: an auxin transport partially regulated by mechanical forces and an induction of cell division by auxin.

Tissue growth can also be accompanied by an inhomogeneity in growth rates among elongating cells. To counter the effect of these fluctuations and stabilize the total root growth rate, it has been shown that spatial cues, or some level of positional information were required in addition to cell-autonomous regulation [30••]. The antagonist hormones auxin and cytokinin have been proposed to