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Joining forces: feedback and integration in plant development

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Feedback and integration of information are of paramount importance for the robust functioning and dynamics of biological systems. In plant developmental biology, experimentation is increasingly combined with computational modeling to obtain a better understanding of how such regulatory interactions shape the systems' behavior. Here we highlight experimental and modeling studies on feedback loops and integration mechanisms involved in plant development. These studies have substantially expanded our understanding of previously characterized gene regulatory networks (GRNs). In addition, they illustrate the pervasiveness of regulatory interactions between seemingly unrelated processes and levels of organization. Modelers in plant development will increasingly face the challenges of what level of detail, which processes and how many levels of organization to incorporate when trying to understand a particular process.

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Introduction

Within the current heyday of Systems Biology the importance of a multiscale approach to understand complex biological systems has become widely accepted. In its essence, the systems approach focuses on the feedback and integration among processes at the molecular, cellular, and multicellular levels and tries to explain how these interconnections together shape the behavior of a biological system. While a single feedback allows for coordination of separate modules, further integration leads to a strong dynamic coupling into a single larger system. Integration and feedback are extremely prevalent in biological systems and appear to be vital for their proper and robust functioning. To gain an understanding of these complex biological processes computer modeling is often necessary. Indeed, computational models are increasingly integrated with experimental research in plant developmental biology.

Plants develop continuously from the growing tips of roots and shoots. Each of these growth regions maintains a set of stem cells that fuel tissue differentiation through a continuous patterning process. As a consequence, plant morphogenesis proceeds as a life-long, sequential process. In this review we discuss recent experimental and modeling work in which evidence for important new feedback mechanisms involved in plant development is presented. First, we discuss a series of experimental papers on the regulatory interactions involved in the transition from shoot meristem to terminal differentiation of the flower meristem and in initiating new lateral root meristems. This work demonstrates how known regulatory networks become increasingly complex and intertwined, and illustrates the pervasiveness of feedbacks in plant development. In addition we discuss a series of recent modeling and experimental papers on a diverse set of plant developmental subjects that illustrate the increasing integration between gene regulatory networks (GRNs) and information from different processes and levels of biological organization.

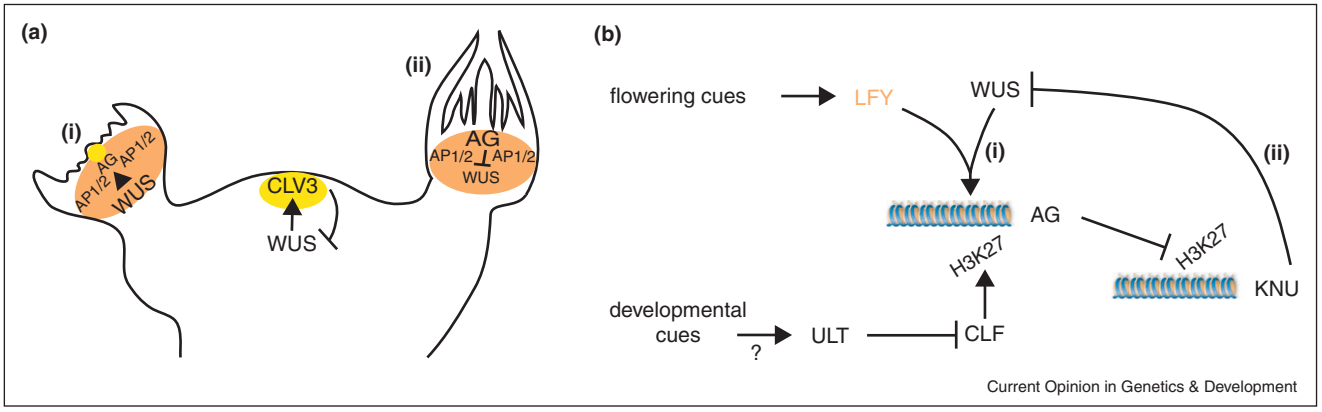
Feedback and integration at the GRN level

Recent experimental data have led to an intercalation of important new nodes into known GRNs involved in shoot stem cell maintenance and floral differentiation. These developments significantly deepen our understanding of state transitions in the growth regions of plants.

At the small gene-by-gene scale, explanations are beginning to emerge of how timing of stem cell termination is coordinated with onset of differentiation in developing flowers. Several studies are starting to reveal how WUS expression in the floral stem cell organizer activates the AG transcription factor that subsequently terminates WUS expression, allowing progression to terminal differentiation [1•,2•]. These studies highlight the importance of histone modifications in the temporal regulation of events, indicating that progressive change of epigenetic marks through repeated rounds of cell division can serve as timers for slow transitions (Figure 1). It will be interesting to derive dynamic parameters for the GRNs emerging from these studies and to use computer simulations to test whether this is indeed a sufficient explanation for the timing of floral differentiation.

At the other extreme, recent whole-genome level studies mapping the target genes of transcription factors involved in shoot stem cell maintenance and transition to flowering

Figure 1



Timing of stem cell activity during flower development. **(a)** Inflorescence apex with stem cells (WUS expressing domain, yellow) in the center maintained by WUS–CLV3 loop, surrounded by flower primordia (LFY expressing domain, orange) and subsequent stages of flower development (1) and (2). At early stages, WUS activates, together with the LFY transcription factor, the gene AG (1). At later stages, active AG subsequently represses WUS (2). The spatial distribution of floral transition regulators AP1 and AP2 occurs in a domain surrounding the AG domain, resulting from their activation by floral initiation cues and repression by AG. **(b)** Two recently discovered histone modification events control the speed of AG activation and AG-mediated WUS repression; for details see [1•,2•].

have led to a substantial extension of the GRNs surrounding the key factors WUS, AP1, and AP2 [3•,4•,5•] (Figure 1). Because of several methodological issues arising when GRNs are inferred from induced expression or chromatin occupancy studies, the size of putative target lists may in some cases be overestimated. Nevertheless, the data consistently indicate that these transcription factors comprise large hubs regulating hundreds of genes. The fact that numerous connections to signaling pathways and feedbacks to core network components are found indicate that a significant portion of these target genes are important for network functioning, in line with the known interlocked nature of shoot development [3•]. Not unexpectedly, the AP1 and AP2 flowering networks are extensively overlapping [4•,5•]. Here again the TF targets found indicate that extensive feedback regulation, in this case, repression of factors that promote the earlier non-flowering developmental state, is essential for developmental transitions.

Detailed analysis of transcription patterns can also hint at novel, hitherto undetected GRNs. An exciting recent example is the discovery of an amazingly large set of genes that are coordinately expressed in periodic waves, coinciding with waves of auxin sensor activity [6••]. These waves emanate from the root tip and determine the competence for future lateral root formation. Currently, both the mechanism producing the periodic waves and how these waves trigger lateral root initiation are largely unknown. While the authors interpret the periodic waves as to indicate the presence of an oscillator, others have pointed out that different mechanisms may produce periodic waves [7]. Furthermore, while the authors of an earlier study interpreted the auxin response waves as evidence for temporal variation in auxin levels [8•], Moreno-Risueno *et al.* argue that this may not be the case given that other auxin reporters do not show fluctuating dynamics. This would make the connection to regulatory modules of auxin responsive genes involved in the somewhat later stages of lateral root initiation less straightforward [9•,10]. Thus, it is important to explore further whether fluctuating auxin levels are involved in the periodic waves, whether the waves are formed by an oscillator, which type of regulatory interactions produce the waves and whether the oscillating genes are to a large extent involved in these interactions or lie downstream of a small regulatory core. Furthermore, it remains challenging to integrate these observations with proposed roles for mechanics and cell shape in lateral root formation [11,12].

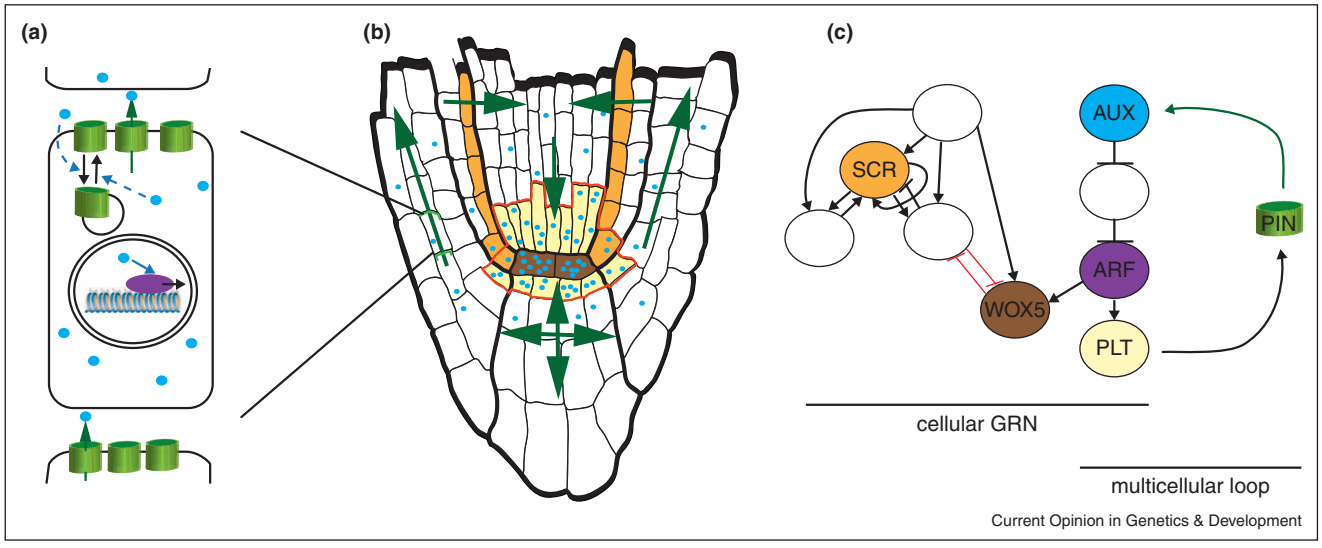
Feedback and integration across processes and levels of organization

Cell differentiation and tissue patterning

GRN models are used for understanding the differentiation and patterning of different cell types within tissues. These models seek to define multiple alternative attractors or steady states of gene activity associated with cell types or stages of differentiation together with their transitions and spatial relationships.

Using a Boolean network approach applied earlier to describe floral organ patterning, a model for the patterning of the root stem cell niche was recently developed [13•]. The model incorporates the PLETHORA pathway involved in longitudinal differentiation and the SHR/SCR factors involved in radial differentiation, with the overlay of these patterns defining the root stem cell niche (Figure 2). In addition, the model incorporates a WOX5 circuit relevant for root stem cell maintenance. The

Figure 2



The root stem cell niche area at different levels of organization. **(a)** Intracellular representation of polar transport (green arrows) of auxin (blue dots) by polarly localized PIN transmembrane proteins (green pipes). PIN proteins cycle between transport vesicles and plasma membrane and models postulating feedback from auxin levels to PIN recycling (dotted blue arrows) can generate polar PIN distributions at the cellular level and developmental patterns at the tissue level, see text. **(b)** Stereotyped polarization of PIN proteins leads to auxin transport (green arrows), accumulation of auxin (blue dots) and restriction of PLT expression (yellow) to stem cell niche. SCR (orange) is expressed in the layer surrounding the vasculature due to movement of its activator SHR from the stele and nuclear localization. WOX5 expression (brown) is dependent on SCR and auxin accumulation and restricted to the stem cell organizer. **(c)** Cellular gene regulatory network used in [13•] and a proposed extension with a PLT-PIN feedback loop at the tissue level, see text. Black arrows, proven interactions, red bars, example of inferred interactions in [13•] to explain observed expression patterns, green arrow, polar auxin transport.

authors demonstrate that the experimentally defined interactions are insufficient, and explore additional interactions capable of producing the gene expression signatures of the different root meristem cell types.

This study reveals how models can be used to ask whether experimental data are sufficient and nonambiguous, and to infer interactions that might be lacking. Indeed, new interactions between tissue layers are emerging as illustrated by a recent study that identifies miRNA-based intercellular signaling in the specification of root cell types [14••], providing opportunities to enlarge the model network. In addition, epigenetic regulation is also an obvious candidate for inclusion in future models [15].

Auxin transport and tissue patterning

The distribution of the plant growth regulator auxin plays a major role in development. An entire category of models aims at explaining the formation, maintenance and spacing of auxin maxima during phyllotaxis, maintenance of the root stem cell niche, formation of lateral roots, and leaf shape and vein formation [18–21]. The key defining aspect of auxin transport models mentioned above is the feedback of auxin on its own transporters, the PIN proteins, which are polarly localized at the cell membrane (Figure 2). This positive feedback mechanism leads to self-organized pattern formation, which allows for the robust formation of localized auxin maxima from small and transient initial heterogeneities.

Bilsborough *et al.* recently proposed a computational model for leaf shape serration patterns that links auxin maxima to a simple GRN [16•]. The model GRN incorporates the experimentally observed feedbacks between auxin level, PIN protein polarization and the transcription factor CUC2. Together these feedbacks produce an alternating pattern of auxin maxima and minima and corresponding CUC2 minima and maxima that serve as an instructional pattern for leaf serration. The model is capable of generating multiple leaf shapes when model parameters are modified.

Although very successful at generating developmental patterns, a major problem with auxin transport models is that mechanistic explanations for the feedback mechanism are still sparse. Previous models assumed either concentration-based or flux-based sensing mechanisms without incorporating much underlying molecular detail [17–20]. Recently, two models proposed more mechanistic explanations of how the sensing of auxin levels and consequent feedback on PIN polarity might occur [21•,22••]. One model proposes an extracellular auxin gradient between adjacent cells, relying on the assumptions that bound auxin

diffuses faster than free auxin and that ABP1 serves as an extracellular receptor for auxin [21•]. The second model stems from the interesting observation that PIN polarity and microtubule organization are aligned [22••]. It has previously been shown that mechanical stress instructs cortical microtubule orientation. The consistent alignment between microtubules and PIN proteins suggests that tissue stress also directs PIN polarity. This results in a model where stress orients PIN polarity and the resulting auxin concentrations influence cell wall composition and stress, thus producing a pattern-generating feedback loop capable of reproducing phyllotactic pattern.

However, the components that underlie the proposed mechanisms in both of these models currently remain mostly hypothetical. In addition, often such models incorporate a sort of global integration, allowing cells to compare auxin concentration, auxin flux or wall stress between different sides of the cell to determine where the highest level is and hence in which direction the positive feedback should occur. How such information integration at the cellular level could occur from typically local concentrations, stresses or fluxes remains unclear.

These problems might be resolved by more experimental data on both the regulation of intracellular PIN transport and on how the cell measures and compares auxin levels. Furthermore, different cell types express different amounts and types of PIN transporters (e.g. [23]). As a consequence the sensitivity of PIN protein orientation to auxin level may depend on cell type. At the same time, PIN orientation and auxin levels can influence which cell types arise where [24]. Thus, auxin-based patterning systems are under significant genetic control rather than being fully self-organized. Taking this genetic control into account may be essential to resolve the apparent paradox between up the gradient concentration-based models (used for phyllotaxis) and down the flux-based models (used for vein formation), and may significantly empower self-organizing auxin–PIN feedbacks, thus increasing robustness.

Cell division and morphogenetic models

Throughout plant development, the amount and orientation of cell division is critical for the maintenance of stem cell niches, the establishment of differentiated tissue layers and for organizing tissue shape.

Several models explore how cell division and differentiation are controlled to maintain shoot stem cell niches, an example of which is the model by Fleck and coworkers [25]. Earlier models incorporated the feedback loop between the WUS transcription factor expressed in the niche organizer and the CLV3 signaling peptide secreted by stem cells (e.g. [26]) (Figure 1). Geier *et al.* show that this simple negative feedback loop is not sufficient for explaining the maintenance of stem cell populations under changing growth conditions, and that more complex regulation is needed. A limitation of the model is that it is rather phenomenological, incorporating only the effects of CLV3 and WUS, without further gene expression or signaling regulating the incorporated cell division, differentiation or communication events. Indeed, a complex system of feedback loops involving cytokinin signaling has been proposed to produce a response gradient that serves as a spatial reference for the stem cell niche [27•].

Other studies aim at understanding how the orientation and timing of plant cell division both arise from and shape the surrounding tissue architecture [28•,29,30•,31]. In one such study the authors performed a careful set of measurements on division angles in differently shaped cells [28•]. This allowed them to formulate a model for how the division plane of symmetrically dividing cells is determined by the interactions between microtubules that emanate from the cell nucleus with the cells cortex, thus providing a mechanistic basis for how cell shape influences cell division. In another study, it is demonstrated how the anisotropy of cell properties and the resulting mechanical stresses determine the direction of cell division and how this profoundly influences tissue morphology [29]. Finally, Meyerowitz and coworkers recently demonstrated the role of cell division timing in creating the characteristic cellular shape pattern of sepals [30•]. These results begin to reveal the outlines of the intricate feedbacks between cell and tissue shape, timing and direction of cell division, and mechanics.

Simplified experimental systems, for example certain green algae [31], may be very useful for getting a basic understanding of the relationships between cell shape, division, expansion, tissue organization and mechanical forces. However, in higher plants different cell types may differ in their overall cell wall strength and anisotropy as well as in various other properties, influencing their sensitivity to mechanical strains as well as their tendency to divide in an apolar fashion. Therefore, more research is also needed on the genetic and signaling programs involved in controlling these processes

Finally, there is a subcategory of models that attempt to explain shape changes occurring during development. Ideally, these models should explain how the acquisition of final organ shape is encoded in developmental networks. In a recent model, Coen and coworkers demonstrate how the feedback interactions between dorsoventral flower genes controlling growth rate and growth anisotropy, hypothetical genes controlling tissue polarity orientation, and constraints arising from mechanical tissue properties together produce intricate spatiotemporally varying growth patterns that give rise to the complicated shape of snapdragon flowers [32••]. The model convincingly shows the shape-generating power of allowing gene expression to not only alter local growth

rate and anisotropy but also local polarity orientation. A mechanistic basis of how these genes influence growth rate and tissue polarity remains to be discovered. It is interesting for example to consider how feedback between organ shape and gene expression may be involved in explaining the transition between the currently separately modeled floral growth phases.

Taken together

The above discussed models encompass still relatively separate research areas aimed at understanding cell differentiation, auxin driven pattern formation, cell mechanics, and cell division governing organ shape.

As an example for future directions, we suggest how models of polar auxin transport that produce tissue level auxin flux patterns [21•,22••] and GRN models for root stem cell niche patterning [13•] may be combined into more comprehensive models (Figure 2). The root patterning GRN model described in [13•] currently incorporates the influence of *PLT* genes only via a linear pathway not yet integrated with the rest of the model. Resolving this will likely require an explicit modeling of the interactions between PLETHORA gene expression and auxin signaling. Likewise, as discussed, to increase the robustness of polar auxin flux models [21•,22••] and resolve the current discrepancies between PIN patterning mechanisms in venation and phyllotactic models, it may be essential to consider how differences in gene expression between distinct cell types affect the PIN–auxin feedback. Put concisely, auxin distribution affects gene expression patterns, while gene expression affects auxin. Note that to explain how the WOX5 (a WUS homolog) and CLE40 (a CLV3 homolog) expression domains come about [13•] even further extensions including the recently discovered RNA signals would be required [14].

On a similar note, it is well known that auxin and mechanics play an important role in gravitropic responses, lateral root outgrowth and phyllotaxis patterning. It seems likely that these shape changes, by causing changed mechanical strains and altered auxin fluxes, affect gene expression. This gene expression subsequently affects cellular growth, microtubule orientation, cell wall composition, orientation of cell division, localization of PIN proteins and auxin synthesis. At yet another level, these processes produce changes in tissue shape which subsequently again produce changes in auxin distributions and mechanical strains. Only if we also take the feedback between these different processes and levels of organization into account will we be able to truly speak of a multiscale, integrated systems approach.

Conclusions

The article discussed here nicely illustrates the pervasiveness and importance of feedback and integration in plant development, both within a process (transition to floral development, lateral root initiation) and between processes and levels of organization (cell differentiation, orientation, division, auxin transport, mechanics). Promising developments are taking place in unraveling the molecular basis behind timing related feedback mechanisms, in suggesting more concrete mechanisms for the important auxin–PIN feedback, and in increasingly explicit consideration of feedbacks between gene regulation, auxin transport, cell growth and division, and cell mechanics and morphogenesis. Nevertheless, for many of these feedbacks, the precise mechanism or their effect on systems behavior is incompletely understood. In addition, it is likely that more feedbacks remain to be discovered. The research also clearly indicates the breakdown of the concept of strict modularity of different subsystems involved in plant growth and patterning, although of course the modularity concept retains its utility in elucidating the initial key interactions of a process under study.

Although most of the experiments and models discussed here are still focused on one or two particular subjects, they reveal an important trend where increasing integration is achieved between GRNs governing cell differentiation, the multicellular auxin transport mechanism governing stem cell and vein patterning, mechanical forces, and the amount and orientations of cell division crucial for maintaining stem cell niches and shaping complex organs. The emerging overwhelming interconnectedness of processes involved in plant development begs the question of how we are going to make sense of it all. How are we to discover which connections are vital, when and for what, and how exactly they work mechanistically? With regard to experimental research, it will be important to design dynamical perturbation experiments and more spatially and temporally resolved measurements (e.g. [33]), to unravel interaction networks.

With regard to computer modeling research the important open question remains of how to incorporate all known interactions. Given the range of different space and timescales involved, the large number of players within each process, and the complexity of interactions within and between processes it may neither be realistic nor advisable to incorporate all factors into a single model. Instead, a parallel approach of using large detailed models when studying a particular process in isolation and collapsed core models per process when studying the feedbacks between different processes may be more promising. Determining the core networks behind different processes and the main interactions between them will be key to making this approach successful.

Acknowledgements

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