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Current Opinion in Plant Biology

# Back to the future: evolution of computational models in plant morphogenesis

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There has been a recent surge of studies in plant biology that combine experimental data with computational modeling. Here, we categorize a diversity of theoretical models and emphasize the need to tailor modeling approaches to the questions at hand. Models can start from biophysical or purely heuristic basic principles, and can focus at several levels of biological organization. Recent examples illustrate that this entire spectrum can be useful to understand plant development, and point to a future direction where more approaches are combined in fruitful ways — either by proving the same result with different basic principles or by exploring interactions across levels, in the so-called multilevel models.

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**Current Opinion in Plant Biology** 2009, **12**:1–9

This review comes from a themed issue on
Cell signalling and gene regulation
Edited by Jan U. Lohmann and Jennifer L. Nemhauser

1369-5266/$ – see front matter


**DOI** 10.1016/j.pbi.2009.07.008

## Introduction

The intertwining of experimental data and computer models has become increasingly popular in the plant sciences. The fundamental issues this alliance seeks to unravel, however, predate the genetic revolution, as far back as 1759, in the *Theoria Generationis* by the observer Wolff [1,2]. He concluded that shoot development was 'epigenetic', creating new growing points not previously present as rudiments. This observation led to a search for the underlying physical and physiological mechanisms by which patterns emerge [3]. We are now witnessing a renaissance in the quest for integrated mechanistic explanations, this time, however, encompassing modern knowledge on underlying gene regulatory networks. From 2006 onwards the area of plant developmental biology has yielded a string of papers dealing with inflorescence architecture, phyllotaxis, and root patterning that unravel developmental processes through an alliance of experiments and modeling [4–7,8••,9•,10].

What has happened to make the time ripe for integrated modeling studies in plant development, and what are the new challenges that we are currently facing? The wealth of biological knowledge on model species like Arabidopsis has opened many possibilities, but led to an increased awareness that information needs to be linked and disentangled to be understood. The initial successes of combined theoretical–experimental efforts have sparked great enthusiasm for the power of theoretical modeling, culminating in the notion of the 'digital plant' [http://iplantcollaborative.org/]. To explore what role modeling can play in plant developmental biology, we list existing models according to the type and level of description provided by the underlying formalisms. We discuss the diverse ways in which cells are implicitly or explicitly represented. We will show that modeling approaches to address different issues come in as many flavors as experimental work, and, like experimental designs, are prone to evolution. We discuss representative examples on how models were designed, what inspired them, and their contributions to plant biology. Lastly, we present our view on the future of this field.

## Plant development and morphogenesis

Plants elaborate a diverse and flexible architecture, based upon relatively simple repetitive units. The combination of plasticity and regularity of this iterative development has inspired mathematicians and computer scientists to create algorithms that capture plant morphogenesis [11–14]. In addition, plant tissues are accessible to simple mechanical experiments and material properties can usually be approximated in simple terms. Consequently, models based on physical laws that operate during development have been successful in plants [15]. However, we believe that the current surge of interest in modeling among plant developmental biologists has a distinct origin: the boundaries of understanding what can be achieved through traditional molecular genetic and physiological approaches are being reached, in two distinct ways. First, numerous genes/proteins that contribute to plant development have been identified. The intrinsic logic of genetics has traditionally been interpreted as one of hierarchical command chains. While experimentalists were searching for 'missing links' in such hierarchical chains, modeling work indicated that it is in fact the feedbacks, cross-talks, and physical embedding that is essential for bringing forth core properties of biological systems, such as bistability, stem cells and differentiation, homeostasis, and control mechanisms [16–18]. Indeed, wiring diagrams that combine genetic and physical



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interaction data which ought to represent the logic of development are no longer linear and easy-to-comprehend, but circular and nonintuitive. Perhaps owing to the plastic and iterative nature of plant development, such nonlinear diagrams seem to be rule rather than exception [19,20]. The human brain cannot deal with the qualitative modes of behavior and dynamics such a system allows for, nor with the sensitivity of these wiring diagrams to quantitative changes by calculations on the back of the hand. Consequently, computational models become a natural and necessary tool to explore the logic and dynamics of development. Second, development is a phenomenon that relies on multiple levels of organization: local decisions at one level (e.g. the cell) influence global patterns (e.g. molecular or force distributions within a tissue), which again feed back on the lower level [21,22]. The understanding of how different levels intertwine again defeats the intuitive powers of the human brain. So, computational models that can represent and analyze these interactions need to be called upon to deepen our insights into morphogenetic processes.

## Heuristic and biophysical models: mind and data

The strategies used in biological modeling can be positioned along a gliding scale, in between two extremes. On the one hand, there are models (often called 'heuristic' after the Greek 'heuretikos', inventive) that serve to explore ideas, without necessarily being concerned about how these ideas map back to the elements of the system under study. 'Biophysical models', on the other hand, are tightly based on the observables of the system under study, and have as main goal to describe a phenomenon quantitatively. Note, however, that while heuristic models explicitly deal with 'information processes', also in biophysical models one may expect — as a side-product — that parsimonious explanations of the system emerge.

Although serving as practical guidelines, we feel that neither the elegance of a potential explanation perceived by our mind nor the ease at which a mapping can be established between experimental data and theoretical models should be regarded as an ultimate goal. It seems that the only solid consensus among those in the field is that a model serves its purpose if it provokes either new thoughts or new experiments on the subject [23•,24•]. As insights from models and experiments progress, a rich palette of modeling strategies will keep on evolving, just like experimental procedures. Using examples drawn from the work on polar auxin transport, a key process in plant development [25–27], we can nicely illustrate how different models evolve along the graded scale.

Classical physiological experiments detected rapid polar auxin movement through vegetative tissue [28–31]. Using an essentially biophysical mathematical description — incorporating known pH differences between cell wall and cytoplasm, anionic transitions of auxin, and differential membrane permeability — velocities of auxin pulse movement could be explained [32,33]. While built on parameters with biophysical meaning, such as diffusion, permeability, and transport speed of auxin pulses, it should be noted that the original models also possess a heuristic nature, by employing simplifying components such as nondimensionality of cells and an infinite tissue. With the advent of increasing computational power, those initial simplifications could be easily overcome, and replaced by biophysically correct descriptions [34]. Most importantly, however, the early modeling work forcefully postulated polar transmembrane auxin efflux carriers, back in those days a purely heuristic guess. It took many years before the theoretically predicted efflux carriers were functionally characterized [35–37].

## Experimental-model cycle: imitation and insight

Once efflux carriers were postulated, the next important question became how their polar expression was regulated. To address this Sachs developed, on a more heuristic level, the canalization theory [38,39]. Inspired by vascular strand formation he assumed that once auxin fluxes take place there is a positive-feedback back to increase the flux, similarly to 'the formation of gullies when rain flows down a sandy slope' [40]. Under this assumption, efflux carriers would be expressed 'with-the-flux', offering a parsimonious explanation for the emergence of venation and a number of ramified patterns [41,42]. The model is heuristic in the sense that molecular players and sensing mechanisms necessary for this feedback are simply assumed (as Goldsmith assumed polar 'exporters'), and its power rests in the ability to make predictions.

Later research revealed that one of the predictions of the canalization theory — low auxin levels in the veins — did not fit experiments [43]. This discrepancy serves to illustrate the evolution of modeling strategies, and the importance of a modeling-experiment cycle. To solve this conflict, numerous extensions to the canalization model were evoked [44], resulting in the desired outcome. Roll-and-Lagan and Prusinkiewicz [45] give an excellent review on the evolution of vein models.

In parallel, a different set of heuristic laws, again seeking a mechanism for efflux carrier positioning, were developed, motivated by the problem of phyllotaxis. Often, efflux carriers locate toward neighboring cells with higher auxin concentration (up-the-gradient), which allows *in silico* meristems to present phyllotactic patterns of auxin concentrations [4–6]. However, the two developmental phenomena — meristem and vascular formation — are occurring concomitantly within the plant. Thus, a combination between the canalization mechanism (with-the-



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flux) and the efflux carrier-orienting mechanism (up-the-gradient) was proposed in a phyllotaxis model aimed to connect primordium and vein formation [46•]. Combining both mechanisms was possible, by evoking a switch that allows either one or the other mechanism to be used by a cell, but required an elaborate usage of heuristic terms and parameters. The increasing complexity of heuristic models has thus helped to fit results, but continues to pose a challenge to map the proposed feedback to molecular components involved [47•].

When a model successfully matches biological data, this can be accompanied by increased understanding of the underlying mechanism, but this is not necessarily the case. As a counterintuitive example of this relation, we cite the physical work of Douady and Couder [48], which were able to 'mimic' phyllotaxis in a nonbiological system. Using magnetic dipoles (droplets) that move upon an oil substrate because of an external magnetic field while simultaneously interacting with one another through electromagnetic repulsion, they obtained a dynamical system in which the periodic addition of droplets results in an ordered 'phyllotactic' pattern following the Fibonacci series. This work suggests that only two general interactions are required to generate the fascinating patterns found in plants: growth (the movement of the droplets because of the magnetic field) and repulsion (electromagnetic repulsion between droplets). The understanding derived from this parsimonious experiment can serve as a search-image for experimental biologists not for genes and proteins, but for networks regulating growth and repulsion.

## Plants through the looking-glass of a model: levels and questions

The level at which mathematical or computational formalisms simulate plant development has profound influence on the questions that can be addressed by the system. In the nonexhaustive list below, we describe five main levels at which models operate, going from macro-level to micro-level representations. Obviously, model formalisms can also be combined, blurring these level definitions.

### Plants as continuous mechanical entities

Thompson already pointed out that a developing organism should conform to the physical world in which it is immersed [49]. This constitutes the basis of numerous continuous mechanical models that describe plants or plant parts as entities that develop in response to mechanical strains and stresses, where biological control acts on their mechanical properties [15,50]. Data on expansins and pectins justify the idea that plants can regulate these physical parameters [51,52] and the existence of mechanotransduction mechanisms suggests that plants can sense stresses and strains [53]. A mechanical-continuous description of vegetative material has allowed for the understanding of why tendrils twist [54,55], how leaves bulge or straighten [56], roots bend [57], and how apical structures grow and deform [58,59]. Phyllotactic explanations on the basis of mechanical buckling have been proposed [60–63], and equilibrium shapes of cell walled structures [64], and tip-growth of pollen tubes and root hairs [65,55,66] have been formulated in this way. The advantage of the continuous mechanical approach is that a tight mapping is possible between models and biophysical measurements. However, just as a continuum mechanical approach to describe the bending of a bridge ignores that cement is made of atoms (it is not continuous) and granules (it does possess mesoscopic structure), biological continuum models ignore the cellular structure of organs. These models therefore allow for the approximation of physical quantities but prohibit a direct mapping of these quantities to cellular behavior.

### Plants as iterative branching systems

Plant development can be seen as an iterative addition of repeating structures, and if the logic of extension and branching is correctly described, models can be developed in which the topology of plant structures can be generated. To allow for a logical analysis of plant development, Lindemayer developed a formal system in which developmental structures of an organism are represented as connected functional units (those building blocks are coined 'metamers', which need not be interpreted as individual biological cells). Through specific local rules (generating grammars), the units can change their state, extend, and branch, leading to complex branching structures. This model formalism, named L-systems [67–69,11], has since generated an amazing repertoire of astonishingly beautiful plant forms [70,14]. Prusinkiewicz [13] gives an overview of how L-systems have been applied during the more recent years. While the generating grammars are typically heuristic and give little insight into how plants regulate branching architecture, they can be productively coupled to the action of regulatory genes known to change iterative patterns of development (e.g. the induction of flowering) [8••].

### Plants as continuous chemical vessels

On the basis of the notion that patterning processes involve chemistry, reaction-diffusion models describe development from the perspective of instructive molecules, whose distributions throughout tissues steer morphogenesis. Inspired by Wolpert's heuristic French-flag model [71], a large part of this kind of modeling in both animal and plant development is now focusing on morphogen gradients formed in embryos and tissues by means of localized production, decay, and diffusion [72–76]. Such models typically stay close to the biophysical end of the spectrum, using and determining quantitative characteristics of the chemicals involved, and developing insights on morphogen gradient formation, requirements



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for positional information, and robustness and scaling properties of the embryo or organism [77–79].

In contrast, in search for finding an explanation for the phenomenon of phyllotaxis, Turing [80] developed a heuristic mechanism for spatial patterns of chemicals which can arise without the need of a prepattern, such as localized sources or sinks. Models that present 'Turing instabilities' are able to spontaneously generate a vast range of patterns, but solely through the specific interactions among different species of chemicals and differential distribution kinetics. Even when such models become more complicated, and the number of chemicals involved larger, one can still reduce them to their core, which always contains the general and essential feature of a local activator and long range inhibitor [81,82]. However, the biomolecular implementations can be manifold, making the generality of the Turing instability both its strength and its weakness.

Turing-type models and other reaction-diffusion models can be used to study intracellular patterns as well [83,84]. When patterns are being studied over multiple cells, however, individual cells are not treated explicitly. The reaction term should be interpreted as the intracellular interactions that take place, while the diffusion term represents the propagation of intercellular communication.

### Plants as collections of cells

When zooming further into the plant tissue, cells emerge as building blocks, as the basic regulatory units of morphogenetic events. One can argue that cells are the fundamental computational unit of life. As such, since the eighties cellular-based models have helped us understanding how, through a combination of specific cellular properties and dynamics within a tissue context, patterns can be formed and maintained [85]. Such cell-based models facilitate analysis of the roles of factors like cell shapes and tissue topology. More than in any of the previous formalisms, they are intimately tied to computational methods, since a cell-based approach almost inevitably implies simulations, often of a more complex and object-orientated kind [86]. A broad scope of models falls under this category, ranging from representing a cell as a mere grid point on a lattice [87–89], to lattice-free models (e.g. Spherical cellular-based models [4] and Vertex-based models [90]). Also, the internal cell structure is often not taken into account, but recently this has been starting to change [91,7].

### Plants as collections of interaction networks

Arguably, the essence of a cell can be captured by the state of its gene regulatory network. This is often represented in a very straightforward manner using Boolean networks [92]. The concept of Boolean networks is based on the often (but not always) valid simplifying assumption that nonhierarchical and hence nonintuitive genetic regulation schemes can be modeled in terms of 'on-or-off' kinetics. This allows us to predict and study different state attractors of the regulatory network [93,94]. These states can be interpreted to represent different developmental outcomes. Problems ranging from flower organ identification to epidermal-root hair patterning can be treated through such models from the perspective of genes [95,96]. Finally, several networks can cross-talk and as such represent neighboring and interacting cells within tissue structures [97,98,99••].

## Addressing modeling artifacts by combined approaches

Every modeling formalism introduces its particular 'artifacts', attributes specific to the model that do not reflect a trait of the biological system. Analogous to the golden practice in experimental biology — supporting the same conclusion by independent methodologies — this can be overcome by a combination of different models, which will pin-point the underlying mechanisms that they can both support. An excellent recent example of this approach is the work of Savage *et al.* [99••] who elegantly formulated a Boolean network model based on genetic data, which inspired simple experiments that discriminated between alternative models of cross-regulatory fate determination between hair and nonhair cells in the root epidermis (Figure 1A,B). The least supported assumption in the Boolean representation, that protein levels of two of the regulators were determined by transcription in neighboring cells (Figure 1C,D), was then re-investigated using a reaction-diffusion representation of the genetic logic and cellular communication. The reaction-diffusion model showed that protein sequestration in complexes parsimoniously supports this assumption (Figure 1E,F). This work, in our opinion, bears another important message. By constructing a reaction-diffusion model inspired by the biological data, the authors were able to not only shed light on the underlying requirements for transport in the system and thereby adding more credit to their Boolean model, but also find a Turing-type instability, in which the 'activator' and 'inhibitor' have a direct biological mapping. Interestingly, almost all biological models on Turing patterns have been hitherto focusing on a particular subset of Turing instabilities (in which the activator activates the inhibitor, and the inhibitor inhibits the activator), whereas the epidermal patterns found by Savage *et al.* [99••] are a consequence of an activator (GL3/EGL3) which inhibits the inhibitor (CPC), while the inhibitor activates the activator. We believe that the rough mapping between Turing models and Boolean networks achieved here carries a profound message: perhaps the reason that Turing models, which have great explanatory power for pattern formation, have never obtained strong experimental support is because they are at a higher level (or maybe even too high level) of abstraction. We speculate that the real genetic networks



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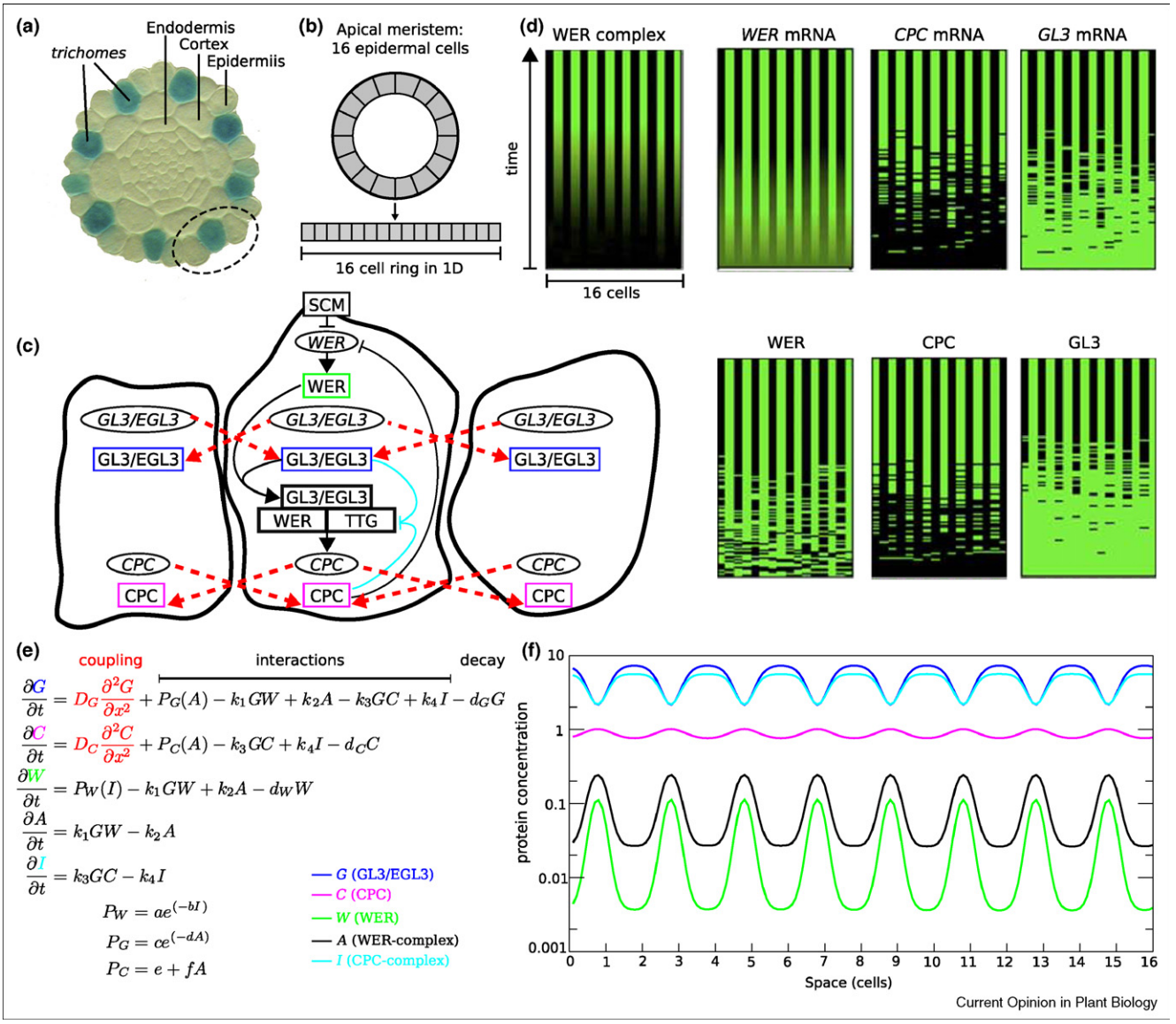
**Figure 1**




Multi-model approach: the root hair example. To study trichome patterning, Savage *et al.* [99••] use both a Boolean and a reaction-diffusion model. **(A)** Trichome identity patterns shown through blue GUS staining in a cross-section of an Arabidopsis root. **(B)** This cell fate is already established in the apical meristem, where the newly formed epidermal ring consists of 16 cells. **(C)** A core cross-talk circuitry on the level of protein–protein and transcription interactions is represented through a Boolean network. An individual cell is represented by the network, while intercellular communication takes place through the action of proteins that depends on the transcription rates within the neighboring cells (shown through the red dotted-arrows). **(D)** Simulation outcome of the Boolean network, showing the establishment of patterns within the protein and mRNA levels. Pattern formation is shown over time and in space that is a 1D representation of the epidermal cell ring. **(E)** On the basis of the logic used for the Boolean network, a reaction-diffusion model consisting of five coupled PDEs has been made. Cell coupling is given through diffusion terms, indicated in red. The functions $P_W$, $P_G$, $P_C$ represent the production rate of WER (monotonically decreasing with CPC-complex levels), GL3/EGL3 (monotonically decreasing with WER-complex) and CPC (monotonically increasing with WER-complex), respectively. **(F)** From a homogeneous state, an alternating pattern of high and low protein expression very similar to the patterns in (B) spontaneously emerges due to a Turing instability (figure and parameters adapted from Savage *et al.* [99••]).

captured by Boolean or other representations can in certain cases be 'emulated' by a higher level description such as a Turing formalism. This higher level description will contain parameters which are a complicated combination of the 'biophysical' parameters and therefore may not directly map to biological observables. The take-home message is: even if different models have a comparable representation power of certain biological phenomena, the parameters of the models may to a very different degree and in a very diverse way map to



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biological processes and thus more or less, or simply in a different way, guide experiments in a meaningful fashion.

## Transcending level boundaries by multilevel modeling

The essence of development is that it is self-organizing and robust. Gene networks, cell–cell interactions, growth, and morphogen patterning all occur simultaneously, and within this entanglement of biological levels the organism emerges. Turing — in biology mostly associated with reaction-diffusion models — had already the vision that explanations for biological pattern formation involve multilevel interactions. He realized that unraveling phyllotaxis would require a combination of reaction-diffusion models with descriptions of tissue growth [100]. This modern approach abruptly terminated with his sudden death, only rediscovered in the eighties with an increasing awareness that many relevant properties of systems with multiple layers arise through interactions between levels (e.g. [101,102]). The essential problem of leaving out different levels of organization can be described as follows: 'Local micro-interactions can generate a set of qualitatively different macrophenomena. These phenomena would seem to be unrelated if studied at the macro level only. Thus, [..] we would probably construct models for each of the phenomena separately, and fail to recognize their interrelationships' [102]. A multilevel modeling approach basically consists in describing from biological motivated data, different levels: molecular and genetic level, subcellular properties, cells, and organs — and allowing them to interact. The objective is to investigate whether level cross-talk yields results that have not been preset on the higher level and whether essential patterns for developmental regulation emerge on a mesoscopic level which are not coded for explicitly. For example, multilevel modeling of the life cycle of the cellular slime mold *Dictyostelium discoideum*, where because of low-level (single cell) feedbacks in production and response to one signal, mesoscopic patterns emerge (such as signal waves and directed cell sorting). These, in turn, direct self-organizing phenomena such as the formation of a multicellular body, coordinated motion, phototaxis, and culmination of a fruiting body [103–105]. Such an approach is now beginning to be explored in plant development. Laskowski *et al.* [106•] provide an explanation for the positioning of lateral root primordia on curves of the primary root through feedbacks that connect polar auxin transport to shape changes. Again, by incorporating 'lower level' properties such as cell shape, tissue structure, and PIN localization, the modeling reveals concepts on the level of mesoscopic 'reflux loops', which emerge as a natural control switch [107] for lateral root initiation at the macro-scale. Genetic data and simulations further indicate how an initial shape-based auxin bias is amplified to stabilize primordium position. Hamant *et al.* [9•], using a similar approach to understand phyllotaxis, provide a novel framework to explore links between subcellular microtubule organization, forces at the organ level, cell polarity, auxin accumulation, phyllotactic patterning, and organ shape. Using continuous mechanical models, finite element approaches and experimental validations, they show coupling between global stress patterns and local microtubule arrangement, which may constitute another across-level feedback loop whose emergent properties can influence organ shape.

## Concluding remarks

We believe that there is a bright future for the combination of modeling and experiment, particularly in the area of plant development. Current work indicates that this future has already begun. However, the objective of a model is not to imitate reality. For to do so would require introducing the whole complexity of the biological system into a computer (assuming that such computers would exist). The result would be obtaining again a system which is as complex and limited to understanding as the biological system itself. Rather, modeling approaches will have to be tailored to each question in terms of the levels that are being described and the desirable mapping of model parameters to measurable phenomena. Sometimes, heuristic models will probe whether an idea is feasible. Other times, a biophysical model will nail down what must be measured to validate a mechanism. In still another case, a multilevel model will produce a result at a higher level that could not be intuitively foreseen based on simple assumptions at a low level. Each of these cases can greatly contribute to our understanding of plant biology. We have entered an era in which we have the necessary computational power and accumulated experimental data that allow us to revive the classical questions on morphogenesis, but now through the integration of all levels and knowledge. And, while approaching the same problem from different angles, modeling tools will change, be revisited and re-adapted as the questions change: back to the future.

## Acknowledgements

We are grateful to helpful suggestions by Stan Marée and Paulien Hogeweg, for their comments on the text and stimulating discussions.

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