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On evaluating models in Computational Morphodynamics

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Recent advances in experimental plant biology have led to an increased potential to investigate plant development at a systems level. The emerging research field of *Computational Morphodynamics* has the aim to lead this development by combining dynamic spatial experimental data with computational models of molecular networks, growth, and mechanics in a multicellular context. The increased number of published models may lead to a diversification of our understanding of the systems, and methods for evaluating, comparing, and sharing models are main challenges for the future. We will discuss this problem using ideas originating from physics and use recent computational models of plant development as examples.

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Introduction

The approach of combining experimental work with computational models in an iterative fashion has become a powerful methodology within biology. The emerging field of *Computational Morphodynamics* is addressing spatial, mechanical, and molecular networks aspects of morphogenesis by integrating four-dimensional data acquisition, often in the form of time-lapse confocal microscopy, with multicellular computational models [1,2]. These developmental models are often built, in part, on indirect data and on assumptions of biophysical mechanisms not yet directly verified in experiments. This can lead to a diversification of models that describe the same biological system, and there is a need to evaluate models where hypotheses are introduced. We will discuss this problem following the ideas of a brilliant physicist, James Clerk Maxwell, who in 'On the Dynamical Evidence of the Molecular Constitution of Bodies' [3] provided theoretical arguments for the existence of molecules before the experimental evidence was available. We will use examples of recent computational models in plant biology, and relate them to Maxwell's methodology for justifying model assumptions [4] (Box 1). Our intention is to provide a useful example of how to evaluate computational models, also for non-modelers.

Hormonal control of development — are current models compatible with an apoplast-located auxin receptor?

Establishment of morphogenic gradients of auxin is largely connected with the polar transport of this phytohormone [5–7], in addition to its local biosynthesis. The responsibility for such directional movement of auxin between cells falls mainly on the subcellular polarization of its efflux mediators, the plasma membrane localized family of PIN proteins [8]. These proteins actively traffic auxin between cytosol and extracellular compartments [9], facilitating movement of auxin between cells and creation of concentration or flow patterns on the tissue scale. The details of the molecular regulation of PIN polarization are still largely unknown, and so far models have mainly explored two different concepts of how the auxin transport is coordinated between neighboring cells. The canalization idea [10,11] assumes positive feedback between auxin flux through the membrane and permeability of the membrane, leading to enhancement in the directional auxin flow [12–14]. The other idea is a concentration-based mechanism, in which cycling of PIN between membrane and endocytic compartments is dependent on the level of auxin in the neighboring cell in such a way that auxin is transported toward a cell with higher auxin content [15,16]. Both mechanisms have been motivated by comparing with experimentally observed auxin and PIN1 patterns on the tissue scale [11,15–18] (cf. Maxwell (ii) in Box 1), but while a flux-based mechanism typically has been connected to venation, the concentration-based mechanism has been proposed for phyllotactic patterning. Efforts to combine those ideas have been introduced, either by adapting a single mechanism to different systems [19,20], or by using both mechanisms [21]. Both proposed mechanisms, however, still suffer from the introduction of hypothetical flux-sensing or non-local concentration-sensing mechanisms not verified experimentally (cf. unobservables in Box 1), although some potentially verifiable consequences of these hypotheses have been derived [12,22] ((iii) in Box 1). It is therefore relevant to ask if these models are, or can be extended to be, compatible with some of the recent experimental findings. One example is the reports of ABP1 as an auxin receptor modulating non-transcriptional auxin responses; ABP1 has been proposed to be active in the membrane or apoplastic space [23,24]. Another example is the control of transitions between different phyllotactic patterns by

Box 1 Maxwell's strategy and its relation to Computational Morphodynamics models.

Maxwell's strategy James Clerk Maxwell (1831–1879) argued for the molecular constitution of bodies before molecules were experimentally verified [3]. We will discuss how his (successful) strategy for developing theories, including parts that are not fully experimentally known (unobservables), may be used to evaluate models in *Computational Morphodynamics* (*CM*). Maxwell's arguments for evaluating theoretical models can be divided into four categories [4]:

(i) *Independent warrant*. Independent indications of the 'postulated' unobservable are important to strengthen the plausibility of a hypothesis, and relate to observations arrived at independently from the model. This also includes arguments for fundamentality and simplicity of the model hypotheses. Maxwell uses a description of heat as a result of motion of non-detectable parts of bodies as an argument for his molecular theory.

(ii) *Explanation of known phenomena*. Although models include unobservables, 'large scale' (experimentally known) consequences need to be derived from 'microscopic' hypotheses. The models are needed to fully explore sometimes non-intuitive behavior of the system. Maxwell derived Boyle's gas law from interaction of bodies (molecules), including deviations from it.

(iii) *Theoretical predictions*. The idea here is to derive more 'information' about the system based on the unobservables, whether it yields currently testable predictions and explanations or not. The 'verification' of such predictions in experiments strengthens a model, especially if it is done independently of the model development. Maxwell calculated, for example, the distribution of velocities of the molecules (the Maxwell–Boltzmann distribution).

(iv) *Unsolved problems*. No models are perfect — hence it is of importance to describe limitations associated with the model. This pinpoints where further development is needed and 'defends' the model developer by showing the awareness of actual problems. Maxwell described problems with estimating the specific heat as a main difficulty for the molecular model.

Relation to Computational Morphodynamics models In Computational Morphodynamics, the aim is to compare and combine spatio-temporal results of experiments with computational models in an iterative fashion. The methodology includes new experimental techniques (e.g. live confocal imaging), new methods of data analysis (e.g. image processing), as described elsewhere [1,2], as well as development of models that can describe molecular interactions, growth, and dynamics in multicellular tissues, which are the focus here.

The most common approach to argue for CM models, including novel hypotheses of players or interactions (unobservables), is to derive (via simulations) large scale behavior observed in the experiments (e.g. spatial protein dynamics), which relates to (ii) above. A model that passes such a test can then be analyzed to find new consequences (iii), which, in turn, can inspire new experiments to confirm the suggested behavior. When there is a divergence between models and experiments (iv), the models can be further refined to better match with data.

The plausibility of the hypotheses always needs to be assessed (i) for simplicity (so that the model is not only performing a parameter fitting), and their relation to the fundamental processes (so that the models are connected to mechanisms which can be potentially perturbed in the experiments).

Still since models are an abstraction and a simplification of the reality, the complete models are never the case (iv), and it is important to acknowledge model limitations, so that their improvements are encouraged.

the *PLETHORA* (*PLT*) family, which modulates polar auxin transport [25•].

Two recent models describe how the realization of a flux sensing mechanism and polarization of the auxin transport during vein formation can be achieved without measuring flux directly, but rather by using gradients within cells [14], or cell walls [26••] (Figure 1a). Wabnik *et al.* [26••] constructed a model based on realistic PIN dynamics [27,28], using competitive utilization of extracellular auxin receptor signaling between neighboring cells to inhibit internalization of PIN proteins from the membrane, which is an experimentally suggested mechanism of ABP1 functioning ((i) in Box 1) [29•]. The model was shown to possess robust vein forming capabilities in several scenarios ((iii) in Box 1), but assumes substantial gradients of auxin across the thin plant wall, something that might be hard to realize in some conditions ((iv) in Box 1) [30].

The consequences of ABP1 significance in active auxin transport have not yet been explored in concentration-based phyllotaxis models. However, the idea of an auxin receptor active in the apoplast could be instrumental in explaining the communication of relative auxin concentrations between neighboring cells, for example by a mechanism where a cell with high auxin levels influences polarization of the PIN1 in neighboring cells toward itself by inhibiting PIN1 internalization in these cells via ABP1 receptors in the apoplast ((i) in Box 1). Such a scenario has been suggested as a potential realization of a concentration-based mechanism [31]. However, signaling from a single wall component has been shown to be insufficient to generate adequate phyllotactic patterns in this model ((iii) and (iv) in Box 1) [31].

Recently, a mechanism implicating mechanical forces in the transmission of the information about auxin levels between cells has been considered [32••](Figure 1), which addresses the non-locality of auxin sensing and can explain PIN1 patterns in local mechanical perturbations ((i) and (iii) in Box 1). Mechanics have been shown to be important for primordia formation and growth [33,34], and the behavior of growing and dividing plant cells has been connected to simple physical principles [35,36••]. There are indications that ABP1 can be involved in this process, since it has been implicated in regulation of ROP2 and ROP6 GTPases responsible for organization of the cytoskeleton [37•]. The importance of the cell wall has been shown, as manipulation of the cellulose synthesis can alter PIN1 polarization ((i) in Box 1) [38], but the mechanism of the mechanotransduction for PIN polarization is highly hypothetical at this point ((iv) in Box 1) [39].

Finally, even though the recent reports of the involvement of PLETHORA genes in the regulation of auxin transport have not been included in the phyllotaxis

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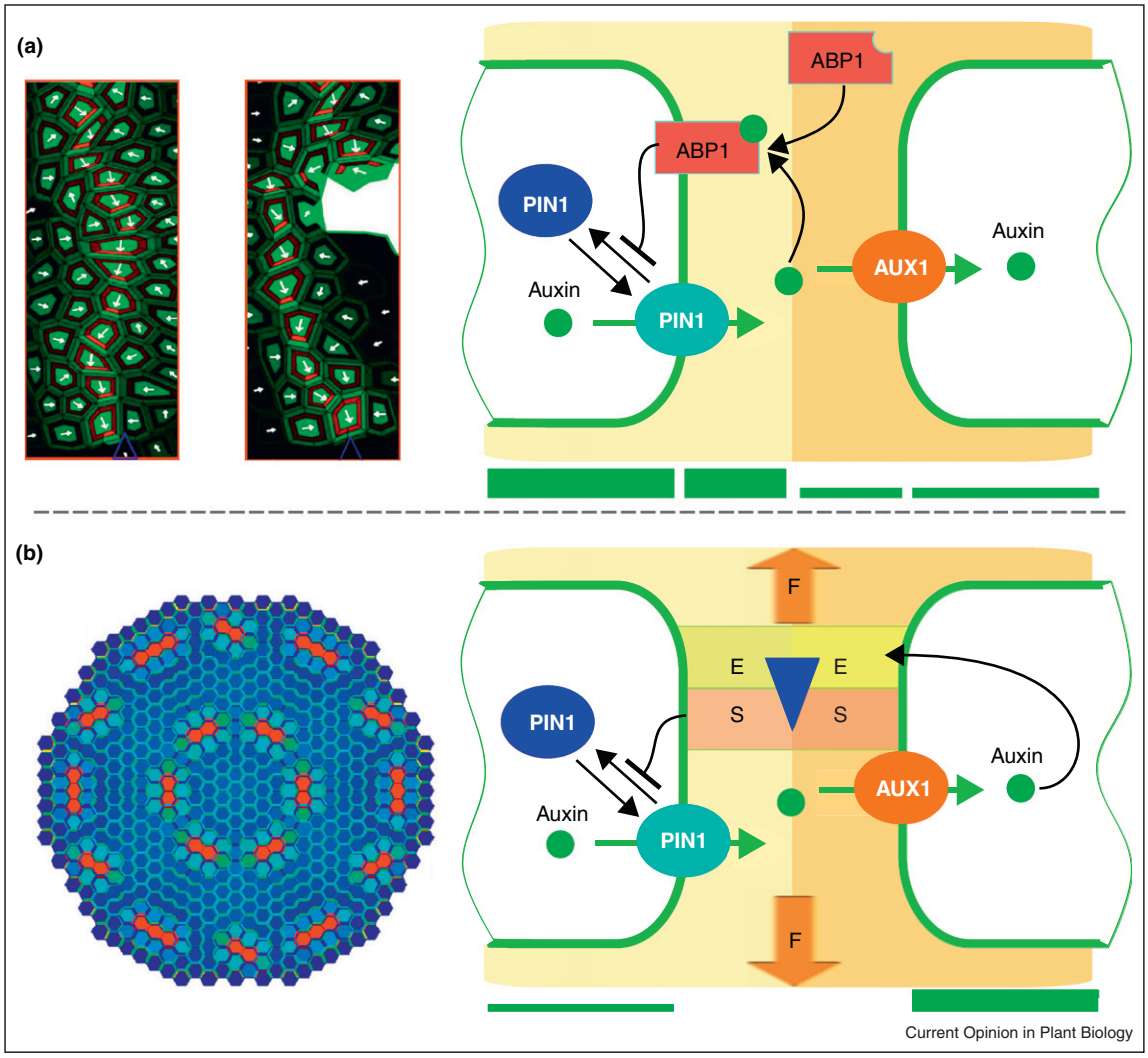
Figure 1



Schematic view of two mechanisms of auxin transport regulation. Two different models of venation and phyllotaxis patterning, respectively, utilize processes in the apoplastic space to coordinate polarization of efflux mediators (PIN1) in neighboring cells. The left part of the figure presents a graphical representation of the result of the simulations in a multicellular context. The right part shows a diagram explaining the main interactions constituting the models. The apoplastic space between cells is divided into two separate compartments (light and dark yellow) which can have different properties or concentration of the substances. **(a)** In the venation model [26••], the auxin receptor (identified with ABP1 in the picture) acts in the plant wall and is competitively (auxin bound receptor is not mobile, unbound receptor diffuses freely in the wall) used to signal auxin induced inhibition of endocytosis and PIN1 turnover from the membrane. Such a mechanism has been shown to canalize the auxin flow (left, red shows PIN localizations and green indicate auxin levels) and move auxin with the gradient (auxin levels are schematically marked by the green bars on the bottom of the diagram). The model is able to reproduce (second pane on the left) reappearance of the canalized flow of auxin after the vein ablation (white region). **(b)** A mechanism utilizing sensing of mechanical forces has been used [32••] to model the formation of phyllotactic patterns. Auxin in the cytoplasm uses a hypothetical pathway to weaken locally the elastic strength (E) of the plant wall under tension (F). Differences in the elastic properties of the two sides of the wall lead to differential forces perceived close to the membranes of the neighboring cells. Mechanical stress (S) inhibits internalization of PIN1. Such a mechanism results in auxin flow against the gradient (green bars on the bottom of the picture) and contributes to the spontaneous formation of auxin peaks (left).

models so far [15,16,19,32••], early theoretical work identified as an important parameter the relation between the size of the central zone (where no primordia are formed) and the size of (or distance between) primordia [40]. While the central zone (and its size) has not yet been mechanistically implemented in models [41•], several models have demonstrated capability of changing the distance between auxin peaks by tuning the relative strength of active and passive auxin transports [15,16,22,32••]. In light of the evidence that PIN1 expression is regulated by PLT genes [25•], this can be seen as a hint that a general mechanism of phyllotactic pattern formation has been captured in these models ((iii) in Box 1).

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The precise molecular details of the functioning of the polar auxin transport in different aspects of plant development still await the final answers. It seems, however, that systematic combined experimental and theoretical assays bring us closer to it with each iteration, and perhaps despite the apparent differences between the proposed polarization mechanisms, they are closer on a molecular level than it appears from the resulting global patterns. For sure, this process would be facilitated if we could easily compare the models between different groups, which calls for a standard language for describing models (as further discussed in 'Conclusions' section).

Stem cell regulation — similarities and differences between current models and justification steps used

The shoot apical meristem (SAM) is the source of all above-ground organs of a plant [42]. During growth, this stem cell niche constantly provides cells that later form differentiated tissues.

Several proteins and hormones have been implicated in the regulation of the SAM. The *CLV3/WUS* negative feedback loop has been shown to play a central role [43,42], and has been incorporated in most recent modeling efforts [44–48,49•,50•,51•].

The patterning of gene expression in the SAM is a challenging dynamical problem, given the spatially non-overlapping expression patterns that are not yet fully explainable from experimental data. The problem has been addressed by several modeling approaches [44–46,49•,50•], where some hypothetical extensions (cf. Maxwell's unobservables in Box 1) to the core *CLV/WUS* network have been included, and the main model evaluation strategy has been able to explain the observed expression patterns ((ii) in Box 1). A common aspect of the models is the use of reaction–diffusion differential equations for spontaneous generation of expression patterns [52,53], either with an activator upstream of *WUS* [45] or with *WUS* within a self-activating loop [49•,50•], generating a localized WUS domain (Figure 2a–c). While initially such strategies were indirectly motivated by the spontaneous reappearance of *WUS* expression from differentiated tissue [54,55] ((i) in Box 1), recent experimental data show that the phytohormone cytokinin induces *WUS* transcription and that the cytokinin receptor AHK4 is localized to the same spatial domain as WUS [48] ((iii) in Box 1). WUS has also been shown to modulate cytokinin signaling [56], which has been integrated in a dynamical model that explains cytokinin activated *WUS* expression using a network with multiple feedbacks [48] (Figure 2d).

For a complete *Computational Morphodynamics* description of the SAM stem cell regulation, the models have to be applicable to a three-dimensional growing meristem. In some cases the explicitly three-dimensional models have been shown to work [44]. In others they can be expected to work due to symmetries [45,49•] (see e.g. the simulation result of the model from [45] on a three-dimensional template extracted from experimentally measured nuclei positions in Figure 2a). Interestingly, in these models both groups have used a similar co-factor for *CLV3* activation, originating from the outer cell layer of the SAM (L1 in Figure 2a,b) [45,49•]. Such a signal was introduced to obtain a pattern of *CLV3* expression to match experimental data in wild type and perturbed situations ((ii) in Box 1). It was also weakly motivated by independent observations ((i) in Box 1) of perturbations where the L1 layer has been removed [54], as well as the fact that the outer cell layers of the meristem are distinct from the cells of the rib meristem (e.g. express specific transcription factors that could be the source of an unidentified signal important for stem cell maintenance).

Differential growth is an important feature in SAM dynamics [57], and a recent approach to introduce growth into a model of SAM regulation indicates the importance of growth dynamics, especially for explaining the dynamics of the *wus* loss-of-function mutants, which would be hard to explain using a static template (Figure 2c) [50•]. Despite these advances, a full *Computational Morphodynamics* model of SAM regulation remains a main challenge for the field.

While some perturbations have been used to further motivate the models (e.g. [54,58–60]), far more analysis of the consequences of such perturbations and more perturbations themselves are needed. Especially important would be the systematic comparison of different models, which could be made feasible by the introduction of a common modeling language standard (as further discussed in 'Conclusions' section). Furthermore, several aspects of the system are not represented by the current spatial models ((iv) in Box 1), which still present a crude approximation of the signaling pathways involved in the regulation of the studied genes. For instance, none of the models mentioned above describe the mechanics of receptor trafficking in the membranes, while the importance of receptor trafficking and turnover modulating signal transduction has been shown in other systems [61,62], and the internalization of CLV1 and its degradation upon binding of CLV3 has recently been described [63•]. Receptor internalization was recently included in a non-spatial model [51•], where also a more thorough analysis of the model parameters was used to extract biological implications from different hypotheses. Including those aspects of signaling pathways in future efforts could be important for understanding of experimental results such as the buffered reaction of WUS expression to variations of CLV3 production [64], which no model has yet been able to explain ((iv) in Box 1).

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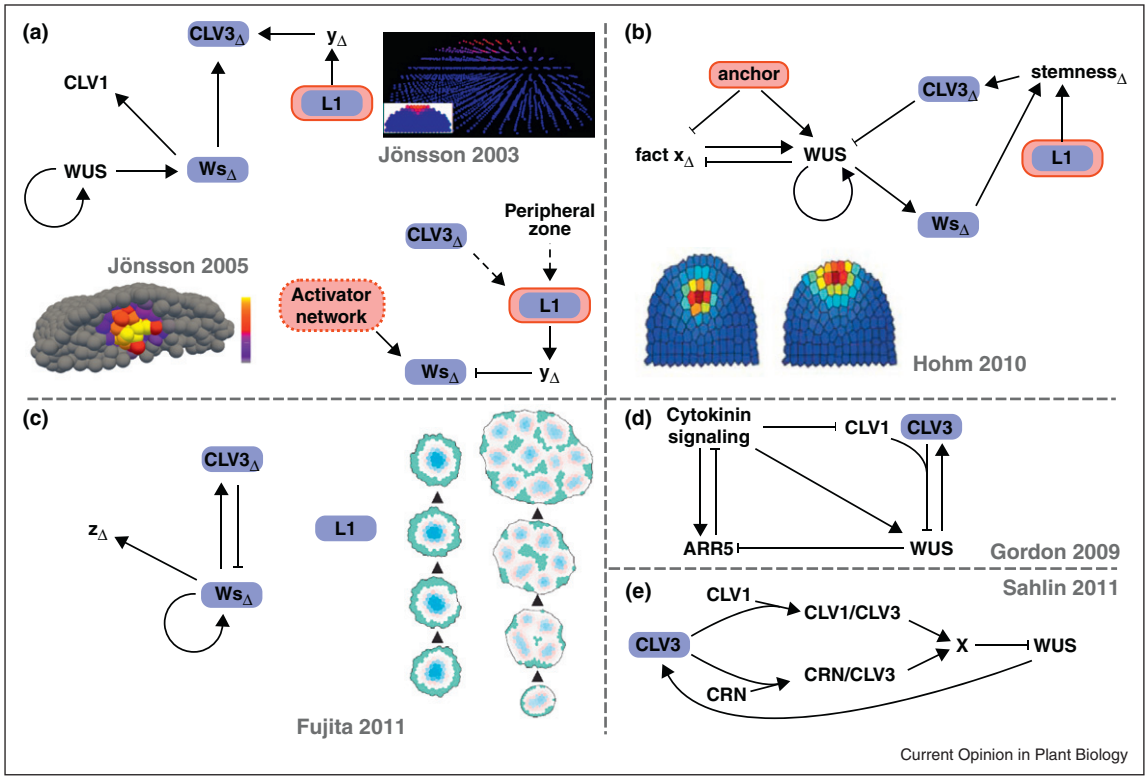
Figure 2



Models for stem cell regulation in the SAM. All models include the core network describing the interactions between *WUSCHEL* and *CLAVATA3*. *WUSCHEL* produces a hypothetical diffusing molecule that activates *CLAVATA3*. *CLAVATA3* produces the diffusing CLV3 peptide that represses the expression of *WUSCHEL*. Depending on the model, *WUSCHEL* can or cannot activate its own expression. Some models also make use of *anchors* to facilitate the positioning of the gene expression domains (marked with pink color). Δ indicates diffusing molecules. **(a)** Expression domain of *CLAVATA3* and *WUSCHEL* from [44] (top, color map from blue (low) to red (high)) and [45] (bottom). The simulation of the model from [45] is here extended to three dimensions where the cellular template is created from nuclei positions extracted from confocal microscopy data. **(b)** Expression domains of *WUSCHEL* (left) and *CLAVATA3* (right) from [49•]. The concentration color map goes from blue (null) to red (high). **(c)** Concentration of a hypothetical activator produced by the *WUSCHEL* domain in [50•]. The decreasing concentration color map goes from blue to light blue, defining the Central Zone, then from light red to white, defining the Peripheral Zone; finally in green is the differentiated zone. Dynamics of wild type (left) and a *WUS* loss-of-function mutant (right) are shown. **(d,e)** Examples of more elaborate treatment of the genetic network controlling stem cell regulation in SAM in single cell context, including additional signaling molecules and interactions. **(d)** A model extending *CLAVATA–WUSCHEL* core network by interactions with Cytokinin and ARFs providing CLV-dependent and CLV-independent pathways of *WUS* activation by Cytokinin [48]. **(e)** Schematic representation of a model including explicit receptors of CLV3, CLV1 and CRN/CLV2 [51•]. The combined action of alternative activation pathways for CLV3 can explain some non-intuitive phenotypes of the multiple mutants in this system.

Conclusions

We have provided examples of how modeling, motivated by the complexity of the studied systems and by recent experimental progress, is used within *Computational Morphodynamics*. Considering the increasing popularity of computational modeling, we want to highlight the need for a methodical way of evaluating the published models, and for building new models on existing ones (or explaining why they are not appropriate in a new setting).

Noticing the similarities of theoretical arguments in physics during late 19th and early 20th centuries and biology of today, we have set the modeling of developmental biology into the context of Maxwell's method for advocating that molecules — experimentally unobserved at the time — are the building blocks of matter, as one example on what basis one can evaluate different models (Box 1). We have pointed out different ways of arguing for a model in relation to experimental findings, but we also want to stress the importance of clearly stating the limitations of the models, for the development of the field as whole.

The main obstacle to easy evaluation of the current models is the variety of the implementations used. A huge step forward in this regard can be expected from current efforts to provide standards for formulating and describing multicellular models in general, and models of plant development in particular. Hopefully these efforts will facilitate extracting and sharing the tissue topologies

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and geometries used, as well as importing published models. These two features can make it easier to compare and to test the models for new challenges in the form of perturbation experiments or extended interaction networks. In the end, modeling can be expected to become an integral part in the merging of our understanding of different developmental processes, or at least to give a clear picture of divergences that appear as consequences of different hypotheses.

Acknowledgements

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- •• of outstanding interest

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