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Review

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Computational models of plant development and form

Author for correspondence:
Przemyslaw Prusinkiewicz
Tel: +1 403 220 5494
Email: pwp@cpsc.ucalgary.ca

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Przemyslaw Prusinkiewicz and Adam Runions

Department of Computer Science, University of Calgary, Calgary, AB T2N 1N4, Canada

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Summary

The use of computational techniques increasingly permeates developmental biology, from the acquisition, processing and analysis of experimental data to the construction of models of organisms. Specifically, models help to untangle the non-intuitive relations between local morphogenetic processes and global patterns and forms. We survey the modeling techniques and selected models that are designed to elucidate plant development in mechanistic terms, with an emphasis on: the history of mathematical and computational approaches to developmental plant biology; the key objectives and methodological aspects of model construction; the diverse mathematical and computational methods related to plant modeling; and the essence of two classes of models, which approach plant morphogenesis from the geometric and molecular perspectives. In the geometric domain, we review models of cell division patterns, phyllotaxis, the form and vascular patterns of leaves, and branching patterns. In the molecular-level domain, we focus on the currently most extensively developed theme: the role of auxin in plant morphogenesis. The review is addressed to both biologists and computational modelers.

I. A brief history of plant models

> How far mathematics will suffice to describe, and physics to explain, the fabric of the body, no man can foresee.
>
> D'Arcy Wentworth Thompson (1942, p. 13)

In Book VI of the *Enquiry into Plants*, Theophrastus (1948; *c.* 370–285 BCE) wrote: 'most [roses] have five petals, but some have twelve or twenty, and some a great many more than these'. Although this observation appears to be off by one (Fibonacci numbers of petals, 13 and 21, are more likely to occur than 12 and 20), it represents the longest historical link between observations and a mathematically flavored research problem in developmental plant biology. Numerical canalization, or the surprising tendency of some plant organs to occur preferentially in some specific numbers (Battjes *et al.*, 1993), was described quantitatively

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in the first half of the 20th century (Hirmer, 1931), analyzed geometrically at the end of that century (Battjes & Prusinkiewicz, 1998), and remains an active area of research. Its genetic underpinnings (e.g. the regulation of ray floret differentiation within a capitulum (Coen *et al.*, 1995; Broholm *et al.*, 2008)) continue to be studied. Less extensive in their historical span, many other links between early observations and current research problems also exist. For instance, several hypotheses attempting to characterize patterns of cell division were formulated in the 19th century (e.g. Errera, 1886) and discussed in the early 20th century (D'Arcy Thompson, 1942, first edition 1917), before becoming the subject of computational studies (Korn & Spalding, 1973), which continue to this day (Nakielski, 2008; Sahlin & Jönsson, 2010; Besson & Dumais, 2011; Robinson *et al.*, 2011).

A broad program of using mathematical reasoning in the study of the development and form of living organisms was initiated almost 100 yr ago by D'Arcy Thompson (1942) in his landmark book *On Growth and Form* (see Keller, 2002, for a historical analysis). One of his most influential contributions was the 'theory of transformations', which showed how forms of different species could be geometrically related to each other. The theory of transformations was extended to relate younger and older forms of a developing organism (Richards & Kavanagh, 1945), but did not incorporate the formation and differentiation of new organs. This limitation was addressed a quarter of a century later by Lindenmayer (1968, 1971), who introduced an original mathematical formalism, subsequently called L-systems, to describe the development of linear and branching structures at the cellular level. By the mid 1970s, computational models based on L-systems and other formalisms had been applied to study several aspects of plant development, including the development of leaves and inflorescences, and the formation of phyllotactic patterns (Lindenmayer, 1978). The questions being asked included the impact of distinct modes of information transfer (lineage vs interaction) on plant development, and the relationship between local development and global form. Similar interests underlied the independent pioneering work of Honda and co-workers on the modeling of trees (Honda, 1971; Borchert & Honda, 1984).

Another class of models was pioneered by Turing (1952), who showed mathematically that, in a system of two or more diffusing reagents, a pattern of high and low concentrations may spontaneously emerge from an initially uniform distribution. This was a surprising result, as it appeared to contradict the second law of thermodynamics: the general tendency of systems to proceed from more organized states toward disorder (the apparent paradox is resolved by jointly considering the reaction–diffusion system and its surroundings). Related models were introduced, under the name of activator–inhibitor and activator-substrate (depletion) systems, by Gierer & Meinhardt (1972), and extensively investigated by Meinhardt (1982). Reaction–diffusion systems showed how, in principle, molecular-level interactions may lead to morphogenesis and differentiation. In plants, reaction–diffusion-type models have been used to explain the patterning of trichomes in leaves and hair cells in roots (Digiuni *et al.*, 2008; Savage *et al.*, 2008; Jönsson & Krupinski, 2010; Benítez *et al.*, 2011). Nevertheless, the extent to which reaction–diffusion models apply to the plant kingdom appears to be limited (Kepinski & Leyser, 2005; Berleth *et al.*, 2007). A significant role is played instead by mechanisms involving active transport of the plant hormone auxin (Section V). In some cases, such as the generation of phyllotactic patterns, this reliance on active transport is difficult to explain in evolutionary terms, as reaction–diffusion systems can generate the same patterns. Spatio-temporal coordination of other developmental processes, however, such as bud activation, requires long-distance signaling. Active transport may thus have evolved to overcome the limitations of diffusion, which is very slow over long distances (Crick, 1971).

In the last decade, computational modeling has become a mainstream technique in developmental plant biology, as reflected in numerous reviews (e.g. Prusinkiewicz, 2004b; Prusinkiewicz & Rolland-Lagan, 2006; Grieneisen & Scheres, 2009; Chickarmane *et al.*, 2010; Jönsson & Krupinski, 2010; Jönsson *et al.*, 2012). On the one hand, the sequencing of the human genome put in focus the chasm between knowing the genome of an organism and understanding how this organism develops and functions. Computational models bridge this chasm. On the other hand, successes of early conceptual models that relate patterns of gene expression to the form of animals (Lawrence, 1992) and plants (Coen & Meyerowitz, 1991) have prompted a quest for a comprehensive, mechanistic understanding of development (Coen, 1999). Current experimental techniques for tracking growth and observing marked proteins in living tissues (Reddy *et al.*, 2004; Fernandez *et al.*, 2010) are yielding a wealth of data that correlate molecular-level processes with plant development and form. Computational models play an increasingly important role in interpreting these data.

The use of models has been accelerated by the advancements in computer hardware, software, and modeling methodologies. General-purpose mathematical software (e.g. Mathematica and MATLAB), modeling programs built on the basis of this software (e.g. GFtbox, Kennaway *et al.*, 2011) and specialized packages for modeling plants (e.g. the Virtual Laboratory and L-studio (Prusinkiewicz, 2004a), OpenAlea (Pradal *et al.*, 2008) and VirtualLeaf (Merks *et al.*, 2011)) facilitate model construction, compared with general-purpose programming languages. Furthermore, current computers are sufficiently fast to simulate and visualize many models at interactive or close-to-interactive rates, which is convenient for model exploration.

II. Modeling as a methodology

1. What can be expected from models?

The epistemological value of models in biology has been the subject of numerous inquiries and surveys, both of a general character (Haefner, 1996) and focused on the understanding of plant development (Room *et al.*, 1996; Prusinkiewicz, 1998b; Coen *et al.*, 2004; Chickarmane *et al.*, 2010; Jönsson *et al.*, 2012). Some arguments advanced in support of computational modeling are listed below.

Description of form. Developmental biology deals with dynamic forms, and description of form is the domain of geometry.

Computational models extend geometry to structures that are too complex to characterize in traditional geometric terms.

Analysis of causality. The understanding of causal relations underlying observed phenomena lies at the heart of science. Causal relations, however, are not observed directly, but inferred from observations and experiments. Modeling offers a powerful method for studying causality, because in models cause-effect relations can be defined explicitly, opening the door to rigorous study of their implications.

Analysis of self-organization. The form of plants is not coded directly in their DNA, but is produced by a hierarchy of developmental processes that link molecular-level phenomena to macroscopic forms. Many of these processes have a self-organizing character, which means that forms and patterns emerge from interactions between components of the whole system (Camazine *et al.*, 2001), in this case a growing plant. For a variety of reasons, such as the presence of multiple feedback loops and the spatial character of interactions, self-organizing processes are often 'complex': non-intuitive, and difficult to analyze and comprehend. Computational models are an essential tool for dissecting such processes. Simulations offer an insight into the role of low-level regulatory mechanisms and their parameters, and show how they can be integrated into the global behavior of the system.

Decomposition of problems. Thinking in computational terms creates a frame of mind that facilitates the description and analysis of complex systems by decomposing them into modules (also called components or agents) or levels of abstraction. It also leads to a precise characterization of their operation in terms of algorithms, interfaces, and information flow (Wing, 2006).

Hypothesis-driven experimentation. The process of model construction reveals gaps in our understanding, guides experiments where data are lacking, and facilitates comparisons of alternative hypotheses.

Integrative view of development. Models reveal whether different partial hypotheses and explanations are compatible with each other and can be combined, leading to a synthesis of knowledge.

2. What constitutes a good model?

In order to be credible and useful, models must be verified, validated and evaluated. The purpose of verification is to show that the model (computer program) is internally correct, that is, operates according to its specifications, in the way we believe it does. Good programming practices and verification methods devised within computer science can minimize programming errors, while an independent reproduction of the results can further confirm the internal correctness of the models.

In contrast to verification, validation proceeds by comparing model predictions with experimental data. An agreement of the model with new data, not used in the model construction, supports the model. One can never be certain that the model is valid, as its predictions may be contradicted by future experiments, and because different assumptions and models may lead to the same predictions. For example, Prusinkiewicz & Lindenmayer (1990, Section 3.3.3) present two distinct models of flowering sequences in a herbaceous plant that produce exactly the same result. The objective of validation is thus to support the model to the extent possible, or falsify the hypotheses of the model (Kemeny, 1959).

Once verified and validated, models can be evaluated by comparing the richness, precision and depth of the insights they provide (the output of the model) with the number and extent of the underlying assumptions (the input) (Gaines, 1977; Prusinkiewicz, 1998a). High output to input ratios may be found both in the abstract models designed to elucidate a fundamental principle with minimal assumptions and in the models that rely on extensive input to provide quantitatively accurate predictions. Applications of such models can be found in agriculture, horticulture and forestry. It thus depends on the purpose of the model whether increasing its precision by augmenting input data or introducing additional hypotheses will lead to a more useful model or detract from the essence of the phenomenon under study (Bak, 1996, pp. 41–45).

3. How does modeling fit into the process of scientific inquiry?

According to one scenario, rooted in the canon of the scientific method, a study in developmental biology may begin with the acquisition of experimental data, which are used to formulate one or more hypotheses. On this basis, computational models are constructed to verify whether postulated mechanisms do indeed produce the expected forms. The alternative scenario is to first explore theoretical relations between local processes and the emergent forms using abstract models, and then apply the results to guide experiments that search for the underlying mechanisms. In practice, these scenarios are complementary. Experiments are indispensable, but without models the essential information may be difficult to sift from the large amounts of unfocused data. Similarly, models constructed outside the scope of experimental data may diverge into mathematical investigations without clear biological significance. An interplay between experimentation and modeling is thus needed to focus both on the path of discovery. This interplay usually takes the form of coupled iterations of experimental and modeling efforts. Theoretical considerations combined with experimental data guide the construction of models, while models integrate these data into an increasingly comprehensive understanding of the studied phenomenon and highlight loopholes in the data set. The history of research on cellular patterns, phyllotaxis and branching structures, presented in the following sections, provides good examples of such interplay.

III. Mathematics of developmental models

1. Equations and algorithms

Systems of equations are at the heart of mathematical modeling. In some simple cases these equations can be solved analytically,

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that is, yield solutions that consist of mathematical expressions built from well-known functions (e.g. exponential or trigonometric). Such analytical or closed-form solutions may provide deep insight into the operation of a model for diverse combinations of model parameters. Unfortunately, most models of development do not admit analytical solutions and can only be solved numerically, yielding a solution in the form of a set of numbers. Numerical solutions provide a narrower view of a model's operation, as they are valid for a particular combination of parameter values and do not offer mathematical insights stemming from the analysis of expressions. They can, however, be obtained for a wider range of models, where analytical solutions do not exist or are impractically complex. This tradeoff was observed at the dawn of computational studies of morphogenesis by Turing (1952), who wrote:

> The difficulties [in following morphogenetic processes mathematically] are such that one cannot hope to have any very embracing theory of such processes, beyond the statement of the equations. It might be possible, however, to treat a few particular cases in detail with the aid of a digital computer. [...] The essential disadvantage of the method is that one only gets results for particular cases.

An intermediate level of insight is offered by qualitative analysis of equations. In this case, the general character of a solution, for example the presence of stable states or oscillations, may sometimes be predicted and analyzed even when the detailed solution is not known. An analysis of the qualitative behavior of equations is known as the theory of bifurcations or catastrophes (Arnold, 1992), and has been applied to many problems in mathematical biology. In the domain of plant development, recent examples include an auxin-driven model of bud activation (Prusinkiewicz *et al.*, 2009), and a model of polar auxin transport (Wabnik *et al.*, 2010).

The use of computational methods also brings to the foreground the notion of an algorithm, that is, the decomposition of a computation into a sequence of simple, well-defined steps. In the developmental context, these steps are often associated with the progress of time, which relates algorithms to the notion of a dynamical system. Most models of development have an inherently spatio-temporal character, as development is a dynamic process taking place in space. Time, space, and states of the model at specific locations can be described in a continuous or discrete manner – offering different levels of resolution, precision and computational efficiency – and this distinction has a deep impact on the mathematical structure of the models (Haefner, 1996; Giavitto *et al.*, 2002) (Table 1). Both the formalisms that have been previously devised in mathematics and mathematical physics (e.g. differential equations) and those devised specifically for biological modeling purposes (e.g. L-systems) have been used. New mathematical methods specific to the modeling of development are particularly indispensable when describing discrete spatial structures, such as tissues made of cells. The well-established formalism for describing processes taking place in continuous space – partial differential equations (PDEs) – applies only as an approximation of the discrete reality. A more faithful description is in terms of coupled ordinary differential equations (ODEs), that is, systems of ODEs that share selected variables. Coupling may involve both the equations associated with individual components of the system and the equations associated with neighboring components. The respective examples include genetic regulatory networks operating within each cell and the transport of signaling molecules between cells. The shift from PDEs to systems of coupled ODEs is complicated by the changing number and configuration of components in a developing structure. For example, an increase in the number of cells as a result of cell division leads to an increase in the number of variables and equations that describe the tissue as a whole. Systems that admit a changing number of equations are termed dynamic systems with a dynamic structure (Giavitto *et al.*, 2002) or variable structure systems (Mjolsness, 2005), and are the subject of ongoing theoretical investigation (Prusinkiewicz, 2009). The key problem of specifying changes to a system of equations is typically resolved by relating these equations to the topology of the system, which is discussed in the next section.

Table 1 Some formalisms used to specify structured dynamical systems according to the continuous (C) or discrete (D) nature of space, time, and state variables of the components. From Giavitto *et al*. (2002)

C : continuous D : discrete	PDE	Coupled ODE	Numerical solutions*	Cellular automata
Space	C	D	D	D
Time	C	C	D	D
States	C	C	C	D

*The heading 'Numerical solutions' refers to numerical solutions of partial differential equations (PDEs) and systems of coupled ordinary differential equations (ODEs).

2. Topology and structure

The physical principle of locality states that an object is only influenced by its immediate surroundings. Consequently, connections between the equations that describe a dynamical system with a dynamic structure typically reflect the changing topology of the system, that is, changing neighborhood relations between the system components. A tree moving in the wind provides an intuitive example of the distinction between geometry and topology. As the branches bend and leaves reorient, the geometry (shape) of the tree changes, but its topology, or the manner in which the elements are connected, remains fixed (unless some branches break off). At a smaller spatial scale, the neighborhood relations between cells in a plant tissue are also an example of a topological property. The cells of a plant are cemented together (Steeves & Sussex, 1989, p. 2), and thus growth affects the size and shape of the cells, but does not affect their neighborhoods, which can only change as a result of cell division (exceptions may occur, such as cell separation caused by the invasive growth of a pollen tube penetrating stygmatic and stylar tissues (Gossot & Geitmann, 2007)). As many features of a plant structure have a topological character, the type and representation of topology play an important role in model construction (Fig. 1). In

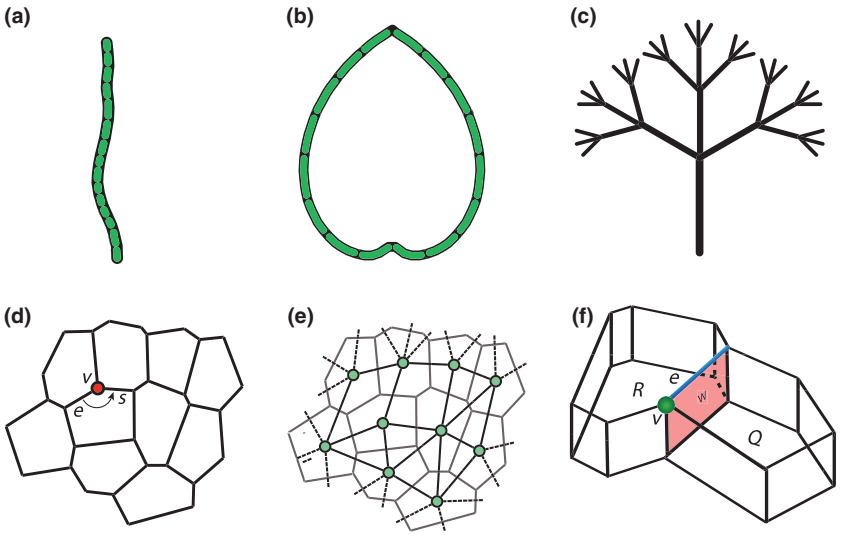

Fig. 1 Examples of biological structures with different topologies. A filament (a) and a leaf margin (b) are one-dimensional (1D) structures, which can be represented by strings of symbols. A tree or the skeleton of a compound leaf (c) is a branching 1D structure, which can be represented by a string of symbols with brackets (matching pairs of brackets enclose branches). Two-dimensional (2D) cellular layers can be modeled using planar graphs (d, e), with the vertices representing cell-wall junctions (d) or cells (e). A graph can be specified by listing all edges incident to each vertex in a circular order; this representation is also convenient when modifying or traversing the graph. For example, edge *s* is next to *e* in the counterclockwise list of edges incident in vertex *v*. Three-dimensional (3D) cellular tissues can be represented using cell complexes, which consist of 3D cells (*R*, *Q*) with the associated 2D walls (e.g. *w*), 1D edges (*e*), and 0D vertices (*v*). This representation suffices to specify the neighbors of any dimension and traverse the structure. For example, cell *Q* is the unique neighbor of *R* across wall *w*.

particular, they determine how the neighbors of each element are identified for simulating information flow (e.g. molecular signaling or mechanical interactions between cells) and to effect changes resulting from cell divisions.

A widely used representation of linear and branching structures was introduced in the theory of L-systems (Lindenmayer, 1968; Prusinkiewicz & Lindenmayer, 1990). In this representation, a sequence of elements (e.g. cells in a filament, or consecutive internodes forming a plant axis) is written as a string of symbols, each of which denotes an individual element. Branches are enclosed in brackets. Information about the neighbors is gathered, and changes in topology effected, using the mathematical construct called a rewriting rule or production. For example, the production $C < A \rightarrow SA$ may specify that an apical cell A in the neighborhood of a cell in state C will divide into a subapical cell S and a new apical cell A. To characterize developing structures in more detail, L-system symbols may be associated with numerical attributes. For instance, $C(l,d,a)$ may denote cell C with length l, diameter d and auxin concentration a. This simple textual notation for productions and elements on which they operate is the basis of several L-system-based modeling languages and programs, such as cpfg (Prusinkiewicz & Lindenmayer, 1990), L+C (Karwowski & Prusinkiewicz, 2003) and GroIMP (Hemmerling *et al.*, 2008).

Two-dimensional structures, such as projections or sections of cell layers, can be described by graphs: mathematical data structures consisting of vertices and edges. According to one interpretation (Fig. 1d), the edges represent cell walls, and the vertices denote junctions at which three or more walls meet (Prusinkiewicz & Lindenmayer, 1990). In the dual interpretation (Fig. 1e), the vertices represent cells rather than wall junctions (Honda, 1983). Graphs with both interpretations can be coupled and used simultaneously, thus providing an explicit representation for cells, cell walls and cell junctions. In either case, the edges emanating from a vertex can be circularly ordered, forming a graph rotation system (Edmonds, 1960). Graph rotation systems provide a complete description of the topology of two-dimensional cellular arrangements, can be easily searched for information about the neighbors of a given cell, and modified to model topological changes such as cell divisions. They are the foundation of the modeling system VV (Smith & Prusinkiewicz, 2004; Smith, 2006), which has been used, for example, to model dividing cells in the epidermis of a growing shoot apical meristem (Smith *et al.*, 2006a) and the longitudinal cross-section of the apex (Bayer *et al.*, 2009).

An emerging general approach, applicable to structures of any dimensions, is based on the topological notion of a cell complex (Brisson, 1993). In this case, all elements of a structure are related to their boundaries. Three-dimensional cells are thus related to their bounding faces, the faces are related to their one-dimensional edges, and the edges are related to the junction points at which they meet (Fig. 1f). It can be shown that such a representation can be systematically traversed to provide information regarding immediate (direct) and non-immediate (indirect) neighbors of each cell, and locally modified to model cell divisions (Lane *et al.*, 2010).

3. Growth and form

While topology characterizes neighborhood relations between components of a structure, geometry deals with metric attributes: distances, angles, areas and volumes. As the geometry of

biological forms results from growth, modeling of growth plays an essential role in the precise description of form (cf. Section II).

Growth can be described and modeled in a global or local manner. The global description has its origins in D'Arcy Thompson's observation that forms of related but different organisms can be obtained one from another by transforming the coordinate system in which they have been expressed (D'Arcy Thompson, 1942; Richards & Kavanagh, 1945). From the computational modeling perspective, transformations of the coordinate systems are related to computer graphics techniques for morphing (deforming) geometric objects (Gomes *et al.*, 1999). While providing a descriptive, rather than mechanistic, characterization of growth, transformations of the coordinate system and other morphing techniques are useful in coarsely representing growing surfaces and volumes in which more detailed morphogenetic processes take place. For example, transformations were applied to model the growth of leaves underlying the patterning of veins (Runions *et al.*, 2005) and the growth of shoot apical meristems in which phyllotactic patterning occurs (Smith *et al.*, 2006a,b).

Alternatively, growth can be described in a local manner, in terms of changes in size and dimensions of small regions of the developing structure (Fig. 2). At any time, and at each location, growth in size is characterized by a single number: the relative elementary rate of growth in length, area, or volume (Richards & Kavanagh, 1943, 1945). A complete characterization of growth at any point requires several numbers, because growth rates in different directions may be different (reviewed by Coen *et al.*, 2004). Silk & Erickson (1979), and Hejnowicz & Romberger (1984) observed that these sets of numbers are tensors: mathematical objects which can be represented as matrices obeying specific rules when transformed from one coordinate system to another (Dodson & Poston, 1997).

Global growth results from the integration of growth tensors in space and over time. This integration is subject to two key constraints. First, specific components of the growth tensor must be spatially continuous, so that the tissue grows symplastically (without tearing). Second, the tissue must fit in the available space. In some cases, this space is limited by other tissues or organs, such as the scales that constrain leaves growing within buds (Couturier *et al.*, 2009, 2011). Even empty ambient space, however, constrains the range of forms that can be embedded in it. For instance, fast growth at the margin compared with the interior necessarily produces surfaces with a wavy margin. Conversely, fast growth at the center compared with the margin yields surfaces formed like a cup. The distinction between these two cases is formalized in the notion of Gaussian curvature, reviewed in a biological context by Prusinkiewicz & Barbier de Reuille (2010).

Over the last decade, the relation between growth, metric, curvature, and the global form of surfaces became a subject of intensive research. This research combines a molecular genetic perspective (Nath *et al.*, 2003; Efroni *et al.*, 2008; Green *et al.*, 2010) with a physical perspective rooted in elasticity theory and differential geometry (Sharon *et al.*, 2002; Klein *et al.*, 2007; Marder *et al.*, 2007; Audoly & Pomeau, 2010; Liang & Mahadevan, 2011). The interdisciplinary links between these perspectives stem from the observation that the growth tensor is mathematically equivalent to the strain rate tensor used to characterize local deformations in continuum mechanics (Silk & Erickson, 1979; Silk, 1984). Both parts of continuum mechanics, the mechanics of fluids and the mechanics of solids, have been applied to characterize biological growth (Skalak *et al.*, 1982). The elasticity theory approach based on solid mechanics turned out to be particularly useful, as it offers an intuitive (although often computationally involved) solution to the problem of embedding a growing surface in the available space (Rodriguez *et al.*, 1994; Goriely & Ben Amar, 2007). Although geometric in nature, the embedding problem is most conveniently solved as a physical problem of minimizing the elastic energy of a surface or volume. Links between geometry and elasticity theory motivated by biological problems have been reviewed by Audoly & Pomeau (2010), and related material focused on the mathematics and mechanics of growth by Yavari (2010). Boudaoud (2010) presents an introductory overview of the vigorously developing field

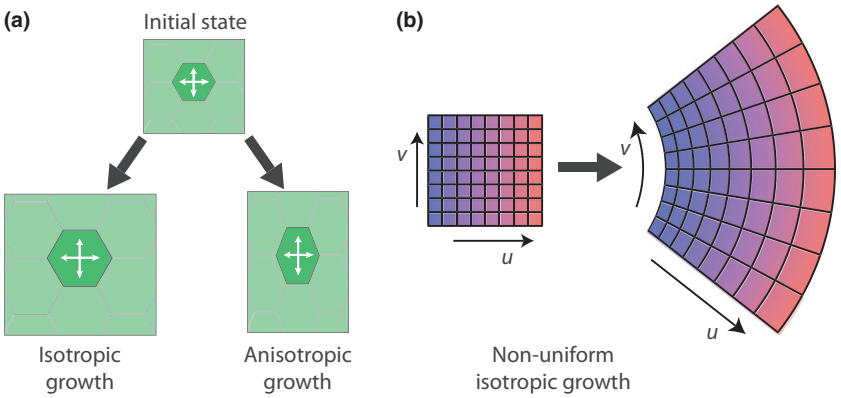

Fig. 2 Local growth and global changes of a growing tissue. In uniform growth (a), local growth rates (white arrows) are the same throughout the tissue. Isotropic growth occurs if the rates are also the same in all directions (left). The tissue changes in size, but not in shape. Anisotropic growth occurs if local growth rates depend on directions (right). The shape of the tissue changes. In non-uniform growth (b), local growth rates depend on the position in the tissue. In the example shown, growth is isotropic, but growth rates increase along the *u*-axis (blue to red). The rates are specified in the tissue's initial state and are carried with the tissue as it grows. The shape of the tissue changes, and many regions are rotated as a result of global integration of growth.

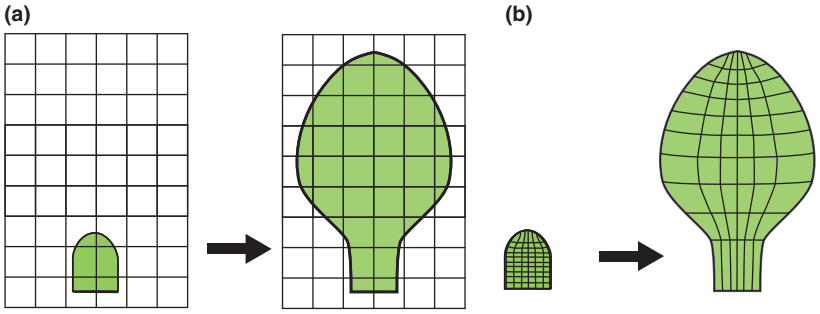

Fig. 3 A comparison of Eulerian (a) and Lagrangian (b) specifications of leaf growth. In the Eulerian setting (a), growth is specified by discretizing the simulation space and recording the contents of the grid points over time. In the Lagrangian setting (b), growth is specified by discretizing the growing tissue and tracking positions of the grid points over time.

of plant biomechanics from a more biological standpoint, and Hamant & Traas (2010) and Uyttewaal *et al.* (2010) present recent surveys of this field.

An important practical consideration in the description and modeling of growth is the distinction between Eulerian and Lagrangian viewpoints (Silk & Erickson, 1979; Coen *et al.*, 2004; Merret *et al.*, 2010). From the Eulerian viewpoint, growth is described as a flow of matter through space (Fig. 3a). By contrast, from the Lagrangian viewpoint, growth is described as a change of position of material points (e.g. cells) over time (Fig. 3b). Bridson (2008, Chapter 1.3) provides an intuitive explanation of this difference, using two ways of characterizing river flow as an example. From the Eulerian viewpoint, this flow is characterized by recording the velocity of the river at fixed points along the riverbed. From the Lagrangian viewpoint, it can be characterized by placing floating markers in the river and recording the position of each marker over time. Although the two descriptions are formally equivalent, in specific applications one of them may offer distinct advantages. For example, growth of plant axes has often been measured and modeled in Laplacian terms, by recording the length of internodes over time (Prusinkiewicz *et al.*, 1994; Mündermann *et al.*, 2005). By contrast, the Eulerian viewpoint has been adopted to model the growth of root (Hejnowicz & Karczewski, 1993) and shoot (Smith *et al.*, 2006a) apical meristems. In these models, the growth rates change for each individual cell as it is displaced within its meristem, but (in the steady state) these rates do not change over time when measured with respect to these meristems. This invariance makes the Eulerian viewpoint a more convenient choice.

IV. Geometric models of morphogenesis

In the process of development, new elements and patterns are formed and incorporated into a growing plant. Both the topology and geometry of the organism change. While these changes ultimately have a molecular origin, comprehensive understanding of the link between genetic information and form is facilitated by decomposition of problems into a hierarchy of intermediate levels of description and analysis (Section II). In this context, geometric models of morphogenesis elucidate the emergence of global patterns and forms by focusing on the temporal and spatial coordination of development (Prusinkiewicz, 2000). For example, such a coordination is manifest in the gradual progression of stages of flower development in racemose inflorescences, radial or bilateral symmetry of flowers, spiral phyllotactic arrangement of florets in flower heads, and the self-similar forms of compound leaves and inflorescences. Highly regular structures, such as flower heads with spiral phyllotactic patterns or self-similar fern leaves, are particularly conducive to analysis in geometric terms. Such structures are easy to quantify, which simplifies validation of the models and lends credibility to the explanations they provide. Interestingly, however, geometric models are also useful in the analysis of less regular patterns, such as the arrangements of cells into tissues, venation patterns in leaves, and branching architecture of shrubs and trees. In these cases, mathematical criteria validating the models are often difficult to formulate, and visual comparison of models with reality plays an important role (Prusinkiewicz, 1998a). In the remainder of this section, we review problems in which geometric models proved particularly useful. Some of these models incorporate a mechanical component, exemplifying a close interplay of geometric and mechanical considerations (Audoly & Pomeau, 2010).

1. Cellular patterns

Models of the division and arrangement of cells into tissues are important as a vehicle for understanding cellular patterns and as a means for creating cellular spaces for simulating higher-level processes, such as phyllotaxis and vascular patterning (Smith *et al.*, 2006a; Merks *et al.*, 2007; Bayer *et al.*, 2009; Wabnik *et al.*, 2010). Two-dimensional patterns have received the most attention, although one-dimensional (Mitchison & Wilcox, 1972; Lindenmayer, 1978) and three-dimensional (Lindenmayer, 1984) patterns have also been modeled.

Modeling the division of individual cells is a prerequisite for creating cellular-level models of tissue development. Several rules aiming to characterize the geometry of cell division were proposed as early as the 19th century. Focusing on isotropically growing tissues, Hofmeister (1863) postulated that the dividing wall is inserted at the right angle to the longitudinal axis of the cell, Sachs (1878) suggested that the new wall meets side walls at right angles, and Errera (1886) proposed that it is the shortest wall partitioning the cell into equally sized daughters (reviewed by Sahlin & Jönsson, 2010). Korn & Spalding (1973, p. 1364)

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observed that 'an understanding of the rules of Hofmeister, Sachs and Errera resides at the centre of the problem of plant cell organization', and proposed an early simulation model of cellular patterns generated with the rules of Hofmeister and Errera. More recently, Sahlin & Jönsson (2010) created computer models of tissues with the cells dividing according to the rule of Sachs, that of Errera, or randomly, and evaluated statistical properties as well as the visual appearance of the resulting patterns. The results demonstrated that division patterns are not purely random, and supported both the Sachs and Errera rules. However, experimental results show that neither rule is satisfied in all cases. Addressing this discrepancy, Besson & Dumais (2011) modified the Errera rule by proposing that the inserted wall has a locally rather than globally minimal length. The choice between multiple minima is inherently random, with probabilities depending on the energy associated with each minimum. The model of Besson & Dumais has an important conceptual consequence. In the deterministic framework of Errera, discrepancies between observations and the model are viewed as prediction errors, which suggests that a higher accuracy could potentially be achieved by refining the Errera rule. With the new model, discrepancies between observations and simulations are no longer considered errors, but instead represent unavoidable differences between two runs of a stochastic process. The quest for deterministic predictions of cell division patterns has thus been made meaningless.

Another extension of the Errera rule was introduced by Robinson *et al.* (2011) in a model of the asymmetric divisions of meristemoid cells that lead to the differentiation of stomata. In this model, a new division wall is defined as the shortest wall passing through the nucleus, which is displaced from the centroid of the cell by a molecular mechanism involving the BREAKING OF ASYMMETRY IN THE STOMATAL LINEAGE (BASL) protein (Dong *et al.*, 2009). A geometric argument shows that this displacement may affect both the position and the orientation of the division wall, explaining the characteristic triangular shape of the meristemoid cell.

The dynamic pattern of cell arrangement in a tissue not only is related to the position and orientation of division walls, but also incorporates timing of cell division and growth of the tissue. A historically significant early computational model of a developing tissue was devised by Korn (1969), using the colonial alga *Coleocheate scutata* as an example (Fig. 4a). In this model, cells were represented as sets of points on a planar hexagonal lattice. Growth was simulated by the addition of new points to a cell, and was constrained to the colony margin by the rules of simulation. The readiness for division was associated with cell size, and the dividing wall was the shortest wall dividing the cell into two cells of approximately equal area. When two or more equally likely lines of division arose, one was chosen at random. The lasting value of this model stems from its anticipation of more recent developments. For example, the representation of cells as arrays of points was reintroduced in the cellular Potts model (Merks & Glazier, 2005), which was subsequently applied to simulate root development (Grieneisen *et al.*, 2007). The same alga was chosen in a model study of cellular patterns by Dupuy *et al.* (2010) (Fig. 4b). A combination of the shortest-wall division rule with a random choice between walls of similar length is the cornerstone of the extension of Errera's rule by Besson & Dumais (2011).

A different approach to modeling cellular arrangements, focused on their topology rather than their geometry, was proposed by Lindenmayer and coworkers. Map L-systems (Lindenmayer & Rozenberg, 1979; Nakamura *et al.*, 1986; de Boer & de Does, 1990) and cellwork L-systems (Lindenmayer, 1984) extended the formalism of L-systems beyond branching structures, to tissues and organs modeled in two and three dimensions, respectively. In these models, cell divisions were triggered by the progress of time rather than the increase in size of growing cells. To specify how the cells divide, the insertion points of division walls, identified by labels, were introduced. These points represented the attachment points of preprophase bands of microtubules, predicting the position of the division plate. Cell walls were labeled as well, to distinguish between walls in different states. Map L-systems were applied, among others, to explain the contrasting forms of gametophytes of the ferns *Microsorium linguaeforme* (disc-shaped) and *Dryopteris thelypteris* (heart-shaped) in terms of different patterns of cell division (de Boer, 1990; Prusinkiewicz & Lindenmayer 1990). The notion of wall state preceded the recent use of wall age in the model explaining asymmetric division of meristemoid cells (Robinson *et al.*, 2011).

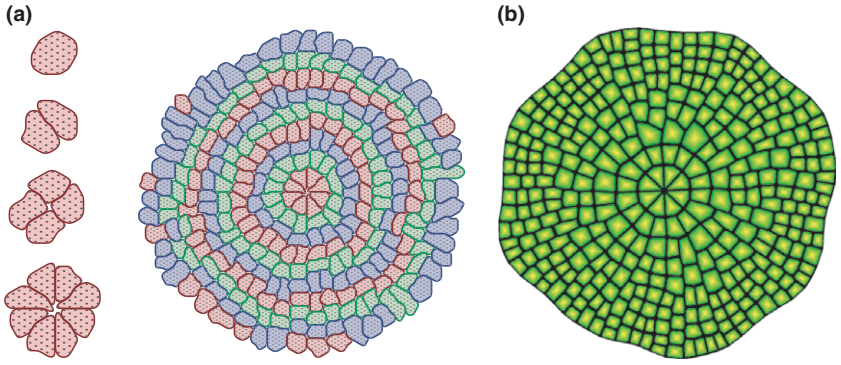

Fig. 4 Comparison of two models of the development of a multicellular pattern, using the colonial alga *Coleochaete scutata* as an example. (a) Steps 1, 15, 40, 62 and 383 of a simulation based on a gradual incorporation of lattice points into the growing colony, as proposed by Korn (1969). Early simulation steps lead to the generation of a ring of eight cells (left). Further progress of development is visualized using colored rings (center). (b) A physically based model inspired by Dupuy *et al.* (2010). Cell shape represents an equlibrium between wall tension and turgor pressure (Fracchia *et al.*, 1990). In both cases, growth is localized to the boundary of the colony, and cells divide according to the Errera rule.

The modeling of differentiating tissues was subsequently facilitated by introducing labelled cells (de Boer *et al.*, 1992).

To visualize map L-system models, Fracchia *et al.* (1990) introduced a physically based mass-spring interpretation. With its use, the shape of cells and the entire tissue is calculated as the equilibrium between the internal (turgor) pressure within the cells and the tension of walls (Lockhart, 1965; Hamant & Traas, 2010), modeled as elastic springs. The physically-based approach was first used to improve the geometric structure of the models of fern gametophytes (Fracchia *et al.*, 1990; Prusinkiewicz & Lindenmayer 1990). Recent improvements include the introduction of viscoelastic springs (Dupuy *et al.*, 2008), which approximate the mechanical properties of cell walls better than elastic springs. An appeal of mass-spring models stems from the simplicity of their implementation, compared with potentially more accurate finite element models, which are also used in studies of plant development (Coen *et al.*, 2004; Hamant *et al.*, 2008; Green *et al.*, 2010; Kennaway *et al.*, 2011; Liang & Mahadevan, 2011). As understanding of the mechanical properties of cells and cell walls advances (Baskin, 2005; Dyson & Jensen, 2010), one can expect models explaining the development of tissues with an even greater accuracy.

2. Phyllotaxis

Phyllotaxis, or the regular arrangements of organs such as leaves, petals or flowers on their supporting stems, is an inherently geometric phenomenon. Analysis of phyllotactic patterns, motivated by their visual beauty and intriguing mathematical properties, goes back to antiquity (Adler, 1974, Appendix G). The patterns emerge from sequential production of primordia on a growing surface of the shoot apical meristem (Kuhlemeier, 2007; Braybrook & Kuhlemeier, 2010). The divergence angle between consecutively issued primordia often assumes values close to the golden angle ($\phi \approx 137.5^\circ$) or – less frequently – Lucas angle ($\phi \approx 99.5^\circ$) (Jean, 1994). Furthermore, the primordia are arranged into a lattice, in which two sets of spirals called parastichies emerge, one turning in the clockwise and another in the counter-clockwise direction. Van Iterson (1907) showed that for the golden angle the numbers of parastichies in the clockwise and counter-clockwise directions are pairs of consecutive Fibonacci numbers (reviewed by Erickson, 1983, and Prusinkiewicz & Lindenmayer, 1990). The Fibonacci sequence starts with numbers 1 and 2, and continues with each subsequent number being the sum of the two previous ones: 3, 5, 8, 13, etc. Explanation of the causal structure of these relations and patterns has been the objective of extensive mathematical analysis and modeling.

The key question is how the position and time of primordia initiation are determined. Hofmeister (1868) and later Snow & Snow (1932) postulated that existing primordia exercise an inhibitory effect on the incipient primordia, which emerge at the locations where the inhibition is the weakest. In a purely geometric version of this model, each primordium is surrounded by a circular inhibition zone, and a new primordium is inserted when and where the space for it becomes available as the shoot apical meristem grows (Mitchison, 1977). In generalizations of this model (Mitchison, 1977; Douady & Couder, 1996; Smith *et al.*, 2006b), the inhibitory influence of each primordium decreases with the distance from the primordium center in a continuous rather than on-off fashion. The influences from different primordia sum up, determining the inhibition value at each point of the meristem. New primordia are created when and where the inhibition drops below a given threshold. This geometric model and its generalizations show that the golden angle underlying most spiral phyllotactic patterns can emerge robustly from the inhibitory interactions between consecutively produced primordia. Less common patterns, corresponding to different values of the divergence angle, result from other parameter values or initial conditions (placement of the initial primordia). Multijugate or whorled patterns, in which several primordia appear at once, are produced more readily if the inhibition falls off quickly outside the inhibition region (Douady & Couder, 1996, Part II) or the inhibitory function changes its profile over time (Smith *et al.*, 2006b). By stripping the logic of phyllotaxis down to its essentials, the geometric-level models thus demonstrate that primordia can self-organize into diverse phyllotactic patterns. An understanding of this self-organization provides the basis for more elaborate conceptual and computational models, which explain phyllotaxis in molecular terms (Section V).

Nonetheless, even at the geometric level, not all aspects of phyllotaxis are understood. In Asteraceae, new primordia often appear at the capitulum periphery rather than near the center. The distances between primordia across the receptacle are much larger than the distances between primordia along the parastichies, which suggests that the arrangement of primordia into a lattice may be the cause, rather than an effect, of specific divergence angles (Zagórska-Marek, 1987). Further complicating the matter, generation of phyllotactic patterns may be influenced by the vasculature in the stem (Larson, 1975; Banasiak, 2011). A challenging open problem is also the generation of phyllotactic patterns in mosses. It results from the activities of a single apical cell rather than interactions within a multicellular apical meristem, which suggests a distinct morphogenetic mechanism.

3. Leaf forms

The development of leaves is a particularly intriguing problem because of the diversity of leaf forms, ranging from geometrically simple to fractal. It is not clear what mathematical and modeling techniques are best suited to characterize and explain this diversity. The history of leaf modeling gives testimony to a variety of approaches.

Geometric modeling of simple leaves was pioneered by Scholten & Lindenmayer (1981). Their model characterized leaf forms in terms of propagation of the leaf margin (Fig. 5a–d). A related model was employed to simulate entire leaf blades as a basis for modeling leaf venation patterns (Runions *et al.*, 2005). In this case, not only the leaf margin, but also all points in the leaf blade propagated with explicitly specified velocities, dependent on the points' positions. A framework for more mechanistic modeling of developing leaves and petals was described by Coen *et al.* (2004). A critical aspect of this framework was the propagation

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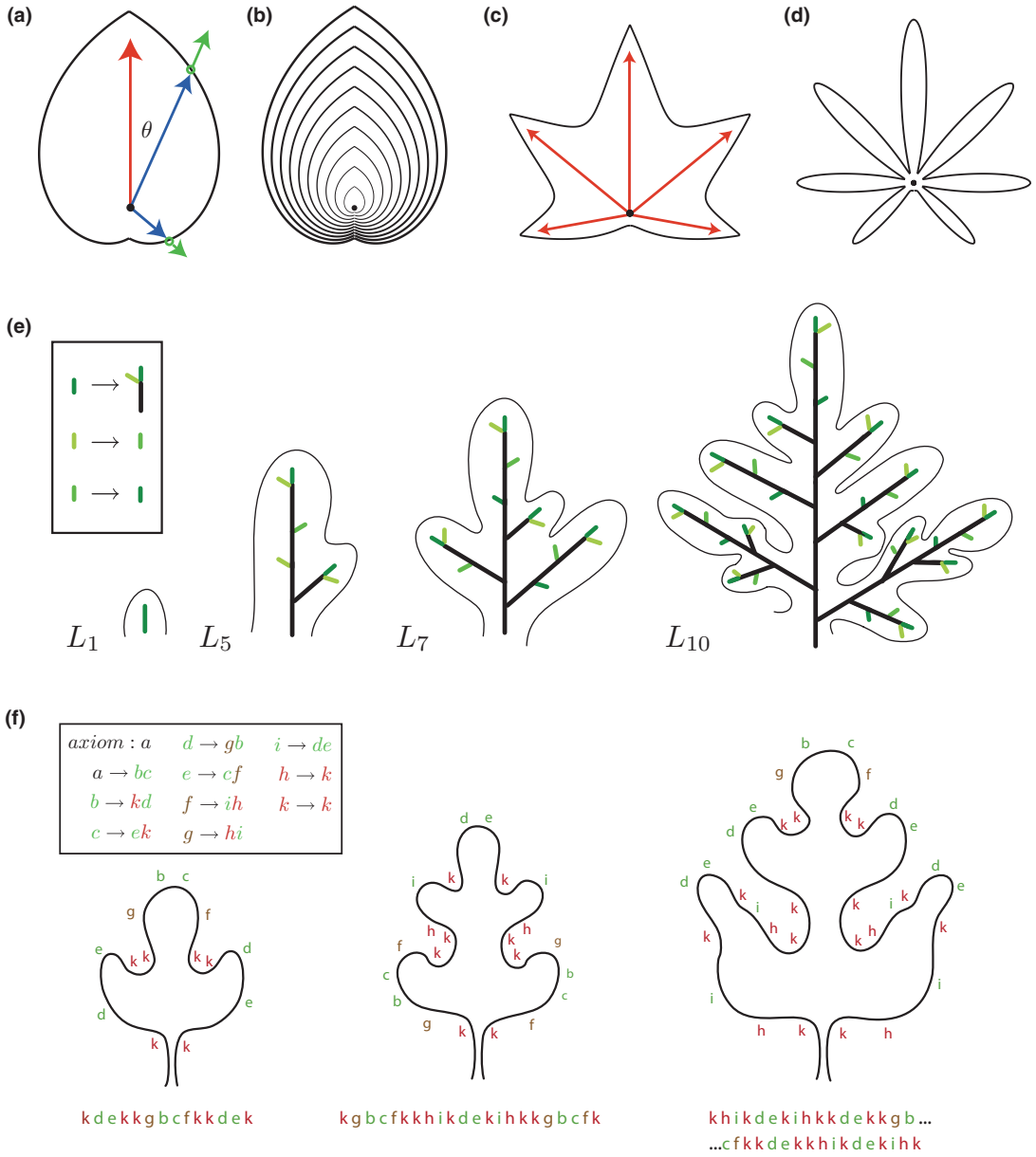

Fig. 5 Three classes of early computational leaf models. (a, b) Developmental model of a simple leaf (Scholten & Lindenmayer, 1981). Sample points on the leaf margin (green circles) are moved away from the growth center (black circle) according to the angle θ with respect to the midvein (red arrow, a). Iterative application of this process simulates the development of leaf form (b). A more complex dependence of the displacement rate on the angle θ produces palmate (c) and compound palmate (d) leaves. (e) A model of the branching structure of a compound leaf (Lindenmayer, 1978). L-system productions are shown in the inset. L_n represents the result of *n* simulation steps. An older tip (dark green) extends the current axis of the skeleton and initiates a lateral branch (light green). Young leaflets develop further after a two-step delay. The leaf contours suggested by the growing skeleton were drawn by hand. (f) A model of a lobed leaf margin (Rozenberg & Lindenmayer, 1973). The initial structure (axiom) and the L-system productions are shown in the inset. Green symbols represent protrusions and red symbols represent indentations. The interpretation of yellow symbols is context-dependent. The strings of symbols generated in three successive steps were interpreted geometrically by the draftsperson.

of hypothetical morphogens that controlled the rates and directions of petal growth. A growing surface was approximated with a set of triangles, and a finite-element method was applied to integrate their expansion into that of the entire surface. A refinement of this technique was more recently applied to model the development of *Antirrhinum majus* (snapdragon) flowers (Green *et al.*, 2010). The resulting model highlights the role of polarity and anisotropic growth in determining the final form of the flower, and captures the development in three dimensions caused by changes in metric and the resulting changes in curvature (Section III.3).

The branching structure of compound leaves was another target of early computational models (Lindenmayer, 1977, 1978) (Fig. 5e). The models were formulated in terms of L-systems. The focal problem was a characterization of the relation between local production of leaflets and the repetitive, recursive global structure of the resulting leaves. This relation was analyzed

further by Prusinkiewicz (2004c), who linked topological and geometric characterizations of self-similarity in compound inflorescences and leaves. Links between the self-similar geometry of compound leaves and the biology of the underlying developmental processes are open to further study.

Intermediate between simple and compound leaves, the third class of models was focused on the recursive distribution of protrusions and indentations along the margin of lobed leaves (Rozenberg & Lindenmayer, 1973; Lindenmayer, 1975) (Fig. 5f). The models were focused on the sequences in which protrusions and indentations appear in the course of development, rather than their exact geometry. Consequently, the generated structures could not be visualized automatically and were drawn by hand. The focus on the leaf margin pioneered by these models is consistent with the important role attributed to the margin by the current theoretical perspective (Hagemann, 1999) and molecular-level studies (Hay *et al.*, 2006; Nikovics *et al.*, 2006; Ori *et al.*, 2007; Barkoulas *et al.*, 2008; Blein *et al.*, 2008; Canales *et al.*, 2010). However, the potentially important morphogenetic role of changing metric relations in a growing leaf, for example the increase in distances between lobes and indentations, was ignored. These relations were introduced in the recent model explaining the development of serrations in Arabidopsis in terms of molecular processes operating on the leaf margin (Bilsborough *et al.*, 2011) (Section V). It is an interesting question whether a similar model can capture and explain the development of lobed and compound leaves as well.

An intriguing three-dimensional model of leaf development was proposed recently by Couturier *et al.* (2009, 2011). They found that the contour of many deeply lobed leaves is smooth when the leaf is folded within a bud, presumably fitting the confines of this bud (Fig. 6). Positions of folds are closely related to the pattern of main veins, linking the form of the leaf to its venation. The close correspondence of the geometry of real and modeled leaves is appealing, but whether the postulated role of folding is indeed consistent with the biology of leaf development remains an open question.

4. Venation patterns

Venation patterns in many leaves are relatively irregular, making their morphogenesis even more puzzling than that of phyllotactic patterns. Nevertheless, Runions *et al.* (2005) proposed a geometric model of leaf venation that suggests similarities between the two phenomena. The model operates by iteratively extending partially formed veins toward points thought of as sources of a vein-inducing signal (e.g. auxin), embedded in a growing leaf blade. The sources are dynamically added as the leaf grows, and removed as the veins approach them. Consequently, the veins 'colonize' the growing leaf blade without ever becoming too dense, in a process analogous to the emergence of well-spaced primordia during phyllotactic patterning. The model suggests that the apparent complexity of vascular patterns is likely a manifestation of a self-organizing process operating on a simple geometric principle, and highlights the importance of growth in driving this process. Although the model of Runions *et al.* (2005) was conceived as a geometric abstraction of molecular processes underlying vein pattern formation (canalization; c.f. Section V), it has not yet been re-expressed directly in molecular terms.

Leaf growth also plays an essential role in the biomechanical model of vein pattern formation proposed by Couder *et al.* (2002). This model exploits a hypothetical analogy between vein pattern formation and fracture propagation in a stretched material. In its physical implementation, cracks are introduced in a thin layer of drying gel (see Skjeltorp & Meakin, 1988, for a related model). Laguna *et al.* (2008) proposed a computational model of vascular patterning where vascular differentiation was induced by the compression of fast-growing mesophyll cells by a slow-growing epidermis, leading to the collapse of mesophyll cells along the lines of principal stresses in the tissue. The model produces hierarchical network patterns that are visually and statistically similar to actual vein networks, but leaves open the question of the relation between hormonal (auxin) and biomechanical control of vein patterning.

5. Branching architecture

Geometric modeling of the branching architecture of herbaceous and woody plants has a rich history, bridging developmental plant biology and computer graphics (Prusinkiewicz & Lindenmayer, 1990; Prusinkiewicz, 1998b, 2004b; Godin *et al.*, 2005).The key question is the relation between endogenous (internal to the plant) and exogenous (acting through the space embedding the plant) control of branching. Correspondingly, the models can be divided into two broad groups, excluding or including the morphogenetic role of environment.

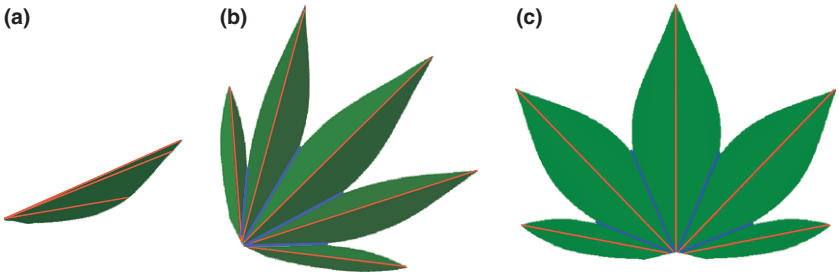

Fig. 6 Computer model of a folded (a), partially unfolded (b), and fully unfolded (c) palmate leaf. Anticlinal folds (red lines), corresponding to the primary veins, terminate at the lobe tips. Synclinal folds (blue lines), located between the primary veins, terminate at the indentations. The unfolded form (c) is determined by the pattern of folds and shape of the bud constraining the unfolded leaf (a).

Models in the first group can be traced to L-system models of inflorescences and herbaceous plants (Frijters, 1978; Prusinkiewicz *et al.*, 1988, 2007; Prusinkiewicz & Lindenmayer, 1990) and models of trees postulating their recursive structure (Honda, 1971; de Reffye *et al.*, 1988). The formalism of context-sensitive L-systems provides a particularly convenient means for incorporating long-distance signals that coordinate the development of branching systems. For example, an abstract representation of florigen and auxin propagating in the plant was used to simulate the putative mechanism regulating branch development and flowering in *Mycelis muralis*, a herbaceous plant, as early as the 1980s (Janssen & Lindenmayer, 1987; Prusinkiewicz & Lindenmayer, 1990). A recent L-system model addressed the related issue of bud ctivation in Arabidopsis at the molecular level (Prusinkiewicz *et al.*, 2009). The focus was on the feedback between the concentrations and flow of auxin, and the distribution of auxin transporters, in particular PIN-FORMED 1 (PIN1) proteins (Section V). The model demonstrated that this feedback suffices to explain the essence of bud activation in wild-type Arabidopsis as well as several mutant and manipulated plants.

The second broad group of models emphasizes the role of environment in the development of plants. It has its origins in the abstract models of branching structures proposed by Ulam (1962) and Cohen (1967). The models in this category assign a key morphogenetic role to the self-organization resulting from competition between branches for space or light. Sachs & Novoplansky (1995), and Sachs (2004) suggested that such competition indeed plays a key role in the development of trees in nature. Consistent with this claim, the space colonization algorithm by Runions *et al.* (2007) shows that plausible tree structures can be generated by ignoring all factors except for competition for space in a growing three-dimensional branching structure. Interestingly, this model is closely related to the geometric model of leaf venation by Runions *et al.* (2005), suggesting a geometric link between the two morphogenetic processes. The more complex model of Palubicki *et al.* (2009) extends competition for light with an endogenous mechanism biasing this competition, and shows that diverse tree forms may simply result from changes in this bias.

Relating the abstract mechanisms of geometric models to molecular-level mechanisms of growth regulation and environment perception continues to be open problem. It includes the incorporation of additional substances regulating branching and/or flowering, such as florigen, cytokinin and strigolactones, simulation of carbon acquisition and flow that may also affect development (Allen *et al.*, 2005), and incorporation of mechanical forces shaping branching structures (Jirasek *et al.*, 2000). Methodological aspects of the creation of comprehensive L-system models, integrating diverse aspects of the function and structure of plants, have recently been addressed by Cieslak *et al.* (2011).

V. Molecular-level models

A tight synergy between laboratory experiments and computational models underlies recent studies of growth regulation and patterning focused on the role of auxin. These studies complement each other in forming an emerging integrative view of plant development. According to this view, known as the reverse/inverse fountain model (Benková *et al.*, 2003), auxin performs diverse patterning, signaling and regulatory functions, fundamental to plant development, as it flows from the shoot to the root (Fig. 7). The morphogenetic role of auxin begins in the embryo, where a dynamic, differential distribution of auxin establishes the shoot–root polarity. In post-embryonic development, auxin is produced in the vicinity of the shoot apical meristem and is transported in the epidermis toward the peripheral zone of the apex. There it accumulates in emergent convergence points, which determine the phyllotactic pattern of the incipient plant organs: leaf or flower primordia (Reinhardt *et al.*, 2003; Jönsson *et al.*, 2006; Smith *et al.*, 2006a). As a leaf grows and becomes flat, new auxin convergence points appear at the leaf margin (Hay *et al.*, 2006; Scarpella *et al.*, 2006). These

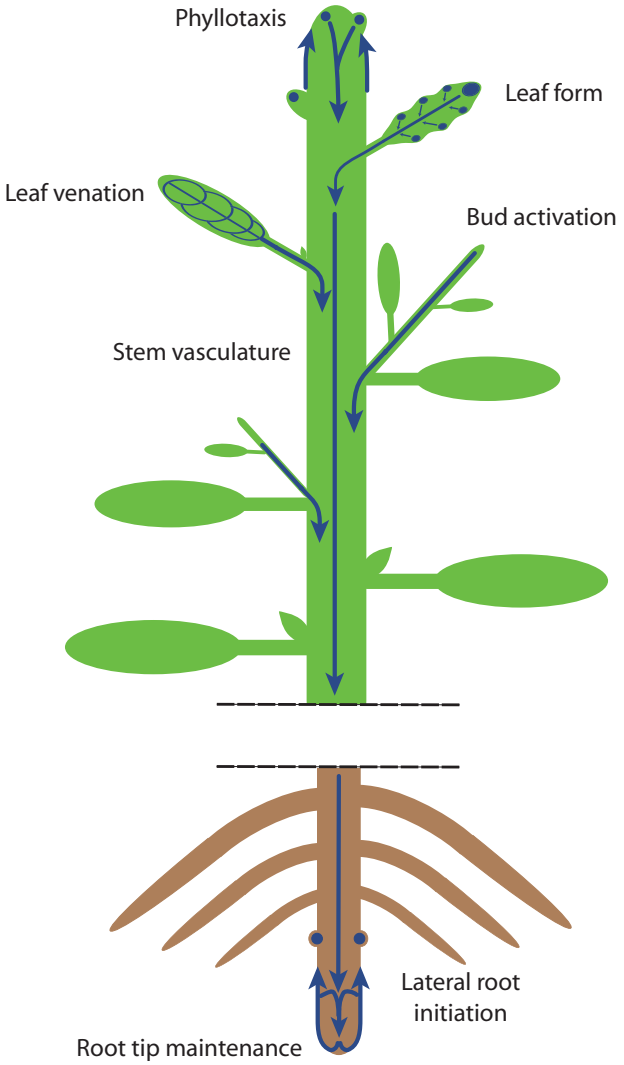

Fig. 7 Processes and patterns regulated by auxin in postembryonic development according to the reverse (shoot) and inverse (root) fountain model (Benková *et al.*, 2003). Blue arrows indicate the paths and directions of auxin flow. Blue circles mark points of auxin accumulation.

convergence points may be correlated with growth foci localized near the leaf margin, leading to the formation of serrated (Hay *et al.*, 2006; Bilsborough *et al.*, 2011), lobed, or compound (Barkoulas *et al.*, 2008; Koenig *et al.*, 2009) leaves. From the primordia auxin flows into the subepidermal layers of the apex and, subsequently, into the plant stem. In this process, it is 'canalized' into narrow paths (Sachs, 1969, 1991; Mitchison, 1980, 1981; Rolland-Lagan & Prusinkiewicz, 2005; Bayer *et al.*, 2009), which, in the case of leaves, mark the location of the primary vein and its extension into stem vasculature. Within the stem, auxin regulates the activation of lateral buds (Bennett *et al.*, 2006; Prusinkiewicz *et al.*, 2009; Crawford *et al.*, 2010), and thus coordinates the development of the branching plant structure (Leyser, 2011), which may reiterate the development of the main axis. From the stem, auxin continues on to the root system, controlling its development.

The fountain model suggests the exciting perspective of reducing fundamental features of plant development to a small number of general mechanisms. At a more immediate level, it presents a structured set of hypotheses regarding some of the key elements of plant development. We discuss these elements in more detail in the remainder of this section.

1. Auxin transport

The existence of a long-distance signaling substance mediating the reaction of plants to light and gravity was deduced by Darwin (1880); it was subsequently identified as indoleacetic acid and termed 'auxin'. Due to the pH difference between the interior and exterior of the cell, the export of auxin from a cell requires an active mechanism. Its fundamental properties were characterized by Rubery & Sheldrake (1974) and Goldsmith (1977), and are known as the chemiosmotic theory of auxin transport. This theory postulates that auxin enters cells passively, via diffusion, but once inside the cell auxin becomes protonated and can only leave the cell with the aid of an efflux carrier. Subsequent experimental work has identified PIN1 proteins as the key efflux carriers suggested by the chemiosmotic theory (Gälweiler *et al.*, 1998). Adding a level of precision, Kramer (2004) constructed a computational model operating at a subcellular scale to analyze the role of auxin diffusion in the intercellular space as a component of auxin transport. He concluded that diffusion, while not negligible, is significant only at relatively short distances (commensurate with the size of the cell). At longer distances, active transport prevails.

In principle, auxin could be exported from a cell in a non polar manner (equally in all directions) or in a polar manner (preferentially in some directions). There is ample experimental evidence that auxin transport is often, if not always, polar (Sachs, 1981, 1991). A fundamental question is how this polarity is established. In some cases the direction of auxin transport appears to be determined by external factors, such as gravity. In other cases, however, auxin appears to regulate its own transport. Such a feedback may lead to pattern formation; consequently, the modeling of auxin transport is intimately connected with the modeling of auxin-induced patterning in plants.

2. Phyllotaxis

The first morphogenetic process involving auxin, in the order implied by the reverse fountain model (Fig. 7), is the generation of a phyllotactic pattern of leaf and flower primordia on the shoot apical meristem (SAM). Microscopic observations of the meristems in Arabidopsis and tomato (*Solanum lycopersicum*) showed that PIN1 proteins are oriented toward spatially separated convergence points, creating auxin maxima that predict the location of new primordia (Reinhardt *et al.*, 2003). Following these observations, Reinhardt *et al.* proposed that phyllotactic patterns emerge from a competition for auxin, during which primordia drain auxin from their neighborhoods. This creates regions of low auxin concentration surrounding each primordium, in which new primordia cannot be formed. The conceptual model of Reinhardt *et al.* can thus be viewed as a molecular implementation of the inhibitory mechanism of phyllotaxis proposed by Hofmeister, in which the absence of auxin plays the role of an inhibitor. The model leaves open, however, the question of what information is used to polarize PINs toward a convergence point, and what biochemical or biomechanical mechanisms effect this polarization. Addressing the first question, Jönsson *et al.* (2006) and Smith *et al.* (2006a) postulated a feedback between auxin distribution and PIN localization. According to these models, active auxin transport by PINs creates localized auxin maxima. PINs orient themselves preferentially toward these maxima (i.e. the neighboring cell or cells with the highest auxin concentration), promoting further auxin flux which reinforces them. Simulations and mathematical analysis showed that this feedback mechanism can generate one- and two-dimensional periodic patterns of isolated auxin maxima (Jönsson *et al.*, 2006; Smith *et al.*, 2006a), as well as two-dimensional patterns of stripes (Sahlin *et al.*, 2009), similar to those emerging in reaction–diffusion models (Meinhardt, 1982, Chapter 12). Operating on a growing surface approximating the SAM, this mechanism creates semi-regular arrangements of primordia in a growing SAM. However, additional assumptions are needed to generate typical, highly regular spiral phyllotactic patterns. The assumptions considered included the immobilization of auxin maxima and the strengthening of PIN1 polarization toward the incipient primordia after their initiation (Smith *et al.*, 2006a).

3. Leaf development

Once positioned, a leaf primordium begins to grow, bulging out of the SAM and gradually flattening along the abaxial–adaxial axis. During this growth, new convergence points emerge along the leaf margin in addition to the convergence point that initiated the leaf, which remains at the leaf tip (Hay *et al.*, 2006; Scarpella *et al.*, 2006). The formation of convergence points along the leaf margin appears to be governed by a mechanism similar to phyllotactic patterning at the SAM (Smith & Bayer, 2009; Bilsborough *et al.*, 2011). As in the case of phyllotaxis, the existing convergence points inhibit the formation of new points nearby by draining auxin, and new points only emerge when sufficient space is created for them by leaf growth. Similar to their counterparts at

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the SAM, the convergence points at the leaf margin can mark locations of increased outgrowth, yielding serrations in the case of Arabidopsis leaves (Bilsborough *et al.*, 2011) and, possibly, lobes in leaves of other species (Barkoulas *et al.*, 2008; Koenig *et al.*, 2009). This similarity is consistent with the 'partial shoot theory' (Arber, 1950), which emphasizes parallels between the growth of shoots and leaves. The strikingly different appearance of spiral phyllotactic patterns and leaves would thus result not from fundamentally different morphogenetic processes, but from different geometries on which they operate: an approximately paraboloid SAM dynamically maintaining its form vs. a flattening leaf that changes its shape and size.

A recent computational model of leaf serration in Arabidopsis exploits and supports the above analogies (Bilsborough *et al.*, 2011). As in the case of phyllotaxis, an additional factor was needed to stabilize auxin maxima and thus robustly position the outgrowth. In the model, this role is fulfilled by the CUP-SHAPED COTYLEDON 2 (CUC2) protein, known to play a major role in leaf serration development (Nikovics *et al.*, 2006; Kawamura *et al.*, 2010). On the basis of experimental data (PIN1 convergence points do not form in *cuc2* mutants), it was hypothesized that PIN1 repolarization may only occur in the presence of CUC2. Auxin, in turn, down-regulates *CUC2* expression, thus fixing PIN1 localization at the convergence points. It is an interesting question whether a related mechanism might stabilize auxin maxima during phyllotactic pattern generation at the SAM as well, as suggested by Nikovics *et al.* (2006) and Berger *et al.* (2009).

4. Vascular patterning

The above models operate at the boundary of organs in the epidermis of the SAM and in the marginal part of the leaf epidermis. The localization of PIN1 proteins and the activation of the synthetic auxin-inducible promoter DR5 in emerging leaves indicate that auxin reaching convergence points is redirected there toward the leaf interior. Its flow is then organized into canals: narrow paths that define the position of future veins. A conceptual model of canal formation was proposed by Sachs (1969, 1981, 1991, 2003) and is known as the canalization hypothesis. Historically, it is the first model of morphogenesis involving auxin. According to this model, the export of auxin across a cell wall promotes further auxin transport in the same direction. Sachs (2003) postulated that this feedback creates canals of auxin flow in a manner analogous to the carving of riverbeds by rivers. Using a computational model operating on a square array of cells, Mitchison (1980, 1981) showed that the 'with-the-flow' polarization model proposed by Sachs can indeed generate canals of high auxin flux. A reimplementation of Mitchison's model by Rolland-Lagan & Prusinkiewicz (2005) and its reinterpretation in terms of a feedback between auxin flow and polarization of PIN1 proteins confirmed that the canalization hypothesis is in many respects consistent with experimental data concerning vein formation in developing leaves. However, Mitchison's model produces canals with a high flux and a low concentration of auxin, whereas experiments suggest that auxin concentration in canals is high (Scarpella *et al.*, 2006). Exploring this discrepancy, Feugier *et al.* (2005) proposed and analyzed several variants of Mitchison's models. These variants operate according to two scenarios: with PINs allocated to different membrane sectors independently, and with PINs allocated to membranes from a fixed pool within each cell. Simulations confirmed that, in the first case, the concentration of auxin in canals is lower than in the surrounding tissue, as predicted by the original Mitchison's model. In contrast, when cell membranes competed for the PINs encased within each cell, the models produced canals with auxin concentration higher than in the surrounding tissue. This result removed a key inconsistency between the canalization hypothesis and experimental data.

The proposed two modes of PIN polarization by auxin, up-the-gradient (Jönsson *et al.*, 2006, Smith *et al.*, 2006a) and with-the-flux (Sachs, 1969, Mitchison, 1980, 1981), give rise to the question of how a plant decides where and when to deploy each mode. Initially, efforts were made to explain up-the-gradient phenomena using with-the-flux models (Stoma *et al.*, 2008) and, conversely, with-the-flux phenomena using up-the-gradient polarization (Merks *et al.*, 2007). However, neither attempt fully reproduced the observed patterns of DR5 and PIN1 expression during midvein initiation in leaves. Searching for an explanation, Bayer *et al.* (2009) proposed a dual-polarization model, according to which both polarization modes may operate concurrently, with the weights dependent on the tissue type and auxin concentration. The dual-polarization model captured the spatio-temporal sequence of PIN1 orientation and auxin distribution in a leaf primordium as observed in microscopic data. Specifically, it showed that the up-the-gradient polarization of PINs supplying auxin to the convergence points may plausibly coexist with the with-the-flux polarization of PINs pumping auxin into the incipient veins. The model also captured the gradual narrowing of vein-defining canals during their formation, the basal orientation of PINs in the vein precursor cells, and the towards-the-vein orientation of PINs in neighboring cells. Finally, the model predicted a transient polarization of PIN1 proteins in the subepidermis toward the epidermis at the onset of the primordium formation. This phenomenon was subsequently observed microscopically, and thus supported the model.

A model that integrates the up-the-gradient polarization, leading to the formation of convergence points, and with-the-flow polarization, leading to the production of canals, captures the formation of the midvein and first-order lateral veins in open venation patterns, that is, patterns without loops (Smith & Bayer, 2009). Observations by Scarpella *et al.* (2006) suggest that loops in closed venation patterns are formed by anastomosis, that is, connection of canals. PIN1 proteins in these canals have opposite orientations, pointing away from a bipolar cell at which the two canals meet. Mitchison's 1980 model and its recreation (Rolland-Lagan & Prusinkiewicz, 2005) show that such a scenario of loop creation is possible if the bipolar cell is a source of auxin, turned on at a precisely defined time. A separate model of vein patterning in areoles developed by Dimitrov & Zucker (2006) also relies on elevated auxin concentration to localize the meeting point. However, the experimental data of Scarpella *et al.* (2006) did not show elevated auxin concentration at the meeting points.

Addressing this discrepancy, Feugier & Iwasa (2006) proposed a loop formation model in which anastomosing canals are guided toward each other by a hypothetical diffusing substance. The existence of such a sustance has not yet been experimentally confirmed. Another possibility is that bipolar cells are located at weak maxima of auxin concentration, not detected using the experimental techniques of Scarpella *et al.* (2006). Overall, the molecular mechanism of vein pattern formation beyond the formation of the midvein and first-order lateral branches remains unclear.

5. Molecular mechanism of PIN1 polarization

Although formulated in molecular terms, neither the up-the-gradient nor the with-the-flux model explains the molecular mechanism of PIN polarization. Addressing this question, Kramer (2009) proposed that the flux sensing inherent in the latter model could result from a readout of intracellular auxin gradients, and highlighted the potential role of the auxin-binding protein ABP1 as a guide for localizing PIN1. However, vascular strands in Kramer's model are initiated at auxin sinks, in contrast to the observations that suggest that they are initiated at sources (Bayer *et al.*, 2009). It is thus not clear whether this model can faithfully reproduce the dynamics of PIN polarization during vascular initiation.

Another step toward an explanation was made by Wabnik *et al.* (2010) (Fig. 8). They proposed that auxin gradients in the apoplast generate asymmetric binding of ABP1 to the outside of cell walls. The asymmetric localization of ABP1 proteins then guides the localization of PIN1. The proposed model reproduces numerous details of vascular patterning and regeneration. Interestingly, bifurcation analysis indicates that the model is capable of transitioning between up-the-gradient and with-the-flux polarization regimes. It is thus possible that this model could be extended to account for phyllotaxis and other up-the-gradient type phenomena. However, the question of whether the auxin gradient in a narrow intercellular space is sufficient to polarize PINs remains open.

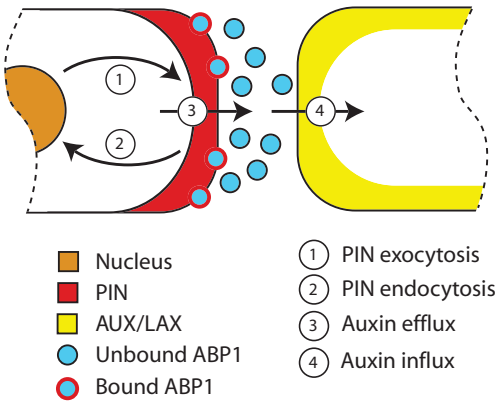

Fig. 8 Hypothetical relations underlying models of PIN1 polarization and auxin transport by Wabnik *et al.* (2010). The concentration of PIN proteins in the cell membrane is determined by an interplay between PIN exocytosis (1) and endocytosis (2). At the cell membrane, PINs transport auxin from the cell to the apoplast (3). The PIN proteins are localized to a portion of the cell membrane, which results in polar auxin transport. The AUXIN-BINDING PROTEIN 1 (ABP1), present in the apoplast, binds to the cell membrane and slows the rate of endocytosis. This binding is regulated by the auxin concentration in the region of the apoplast adjacent to the affected membrane. From the apolast, auxin is transported into cells with the help of AUX/LAX proteins (4), which are uniformly distributed along the cell membranes.

Yet another input for PIN polarization was proposed by Heisler *et al.* (2010). They showed experimentally that mechanical stresses affect the localization of PINs. Based on this result, they created a computational model demonstrating that the feedback between the localization of PINs by stresses in walls and the control of these stresses by auxin may lead to the formation of discrete auxin maxima. An intricate feedback between growth and mechanosensing may thus lead to PIN polarization and morphogenesis.

6. The role of auxin influx carriers

In addition to the polarized efflux controlled by PIN proteins, the flow of auxin is affected by the AUXIN RESISTANT 1 / LIKE AUX1 (AUX/LAX) proteins (Bennett *et al.*, 1996; Parry *et al.*, 2001). These proteins are auxin influx carriers, and are typically, although not always (Swarup *et al.*, 2001), located uniformly on the cell membranes. The computational model by Kramer (2004) showed the potential importance of AUX/LAX-based auxin accumulation to the maintenance of a high concentration of auxin in vascular strands. A subsequent model (Swarup *et al.*, 2005) pointed to the importance of AUX/LAX proteins in maintaining gradients of auxin concentration responsible for gravitropic responses in the root. Heisler & Jönsson (2006) used computational models to support the hypothesis that AUX/LAX proteins play a role in concentrating auxin in the epidermis of SAMs (Reinhardt *et al.*, 2003). Heisler & Jönsson (2006) also showed that AUX/LAX proteins may fix auxin maxima at the locations at which they emerged, and thus stabilize phyllotactic patterns. This prediction was experimentally confirmed by the observations of irregularities in the phyllotaxis of quadruple *aux1;lax1;lax2;lax3* mutants (Bainbridge *et al.*, 2008).

7. Root development

In the root, PINs are localized toward the root apex in the vasculature and away from it in the epidermis. Consistent with this localization, auxin flows toward the root apex in the subepidermal layers and away from it in the epidermis. From the epidermis, auxin leaks to subepidermal layers, where it is recycled toward the root tip. This recycling underlies the maintenance of an auxin maximum at the root apex, as modeled by Grieneisen *et al.* (2007) in a growing cellular template with static PIN localizations, and Stoma *et al.* (2008) in a static template with digitized cell shapes and PIN polarities. Grieneisen *et al.* (2007) used their model to propose that the recycling ('reflux') of auxin at the root tip produces an 'auxin capacitor', where auxin is gradually accumulated. An extension of this idea underlies the models of lateral root initiation proposed by Lucas *et al.* (2008a,b). In these models, the auxin capacitor at the root tip is charged by the basipetal flux of auxin and periodically discharges when the auxin

level exceeds a threshold. The models explain the timing of the initiation of lateral roots and, although they do not have a spatial character, they yield a spatial distribution of lateral roots when a rate of main root growth is assumed.

As with leaf primordia and serrations, lateral root primordia are initiated at discrete auxin maxima (Laskowski *et al.*, 2008). Similar to the SAM, the accumulation of auxin in incipient lateral roots provides a form of lateral inhibition. This inhibition suppresses the initiation of new roots in the proximity of existing ones and yields a pattern of lateral root distribution with well-defined statistical properties (Lucas *et al.*, 2008b). Furthermore, the location of lateral roots is primed by root geometry, as lateral roots tend to initiate on the convex side of a curved root. In the model proposed by Laskowski *et al.* (2008), the extended cells on the outside of the curve accumulate more auxin than the compressed cells on the inside, as a result of the relatively slow flux of auxin through cells (as opposed to the faster transport through cell walls). This accumulation is enhanced by auxin-dependent up-regulation of AUX/LAX protein production, which leads to additional auxin accumulation and the establishment of discrete auxin maxima correlated with the curvature of the root. The model of Laskowski *et al.*, (2008) thus suggests a mode of auxin-based patterning founded on selective retention of auxin by auxin-dependent up-regulation of AUX/LAX protein production rather than dynamic allocation of PINs (Smith & Bayer, 2009).

VI. Conclusions

Plant features of a mathematical character have been observed since antiquity. They are most conspicuous in geometrically regular or numerically repetitious patterns, such as phyllotaxis and the numerical canalization of plant organs. However, current mathematical notions and modeling techniques also elucidate less regular patterns and forms, such as leaf venation and the branching architecture of trees. As the mathematical and computational techniques used in developmental plant biology mature and their scope broadens, main directions of thought become increasingly clear. They can be grouped as follows.

- Mathematical description of growth, combining differential geometry with biomechanics. Pioneers include D'Arcy Thompson, Ralph Erickson, Wendy Silk, Zygmunt Hejnowicz and Paul Green. A recent development is the increasing recognition of the role of space in morphogenesis. Furthermore, biomechanics is increasingly applied to the modeling and analysis of phenomena at the subcellular level.
- The quest for rules of patterning. This direction of study can be traced to Hofmeister's conceptual model of phyllotaxis, Errera's rule for cell division, Turing and Meinhardt's reaction–diffusion framework for pattern formation, and the canalization model of vascular pattern formation by Tsvi Sachs. Patterning and morphogenesis are a very active area of research, as exemplified by recent extensions of the Errera rule.
- Development of new mathematical concepts and computational techniques for the description of growing spatial structures. Pioneering examples include Ulam and von Neumann's notion of cellular automata, and Lindenmayer systems. Recent advances include the introduction of the cellular Potts model and cell complexes to plant modeling. A current goal is to provide a unifying framework for modeling development in one, two and three dimensions.
- Development of specific models. Pioneering work includes Lindenmayer and Honda's models of branching structures, and Korn's models of cellular patterns. In the relatively mature domain of branching structure models, a recent advance is the recognition of the prominent role of self-organization in the development of trees. In addition, models combining the function and structure of different plants are being constructed to provide a predictive basis for horticultural, agricultural and forestry practices.

A fundamental advancement over the last decade is the link between computational modeling and molecular biology. It has opened the door to an integrative understanding of plant morphogenesis from molecules to entire plants and plant ecosystems. Interestingly, molecular considerations do not make geometric models obsolete, but put them in a new light as an important level of analysis and understanding of plant development.

Many open questions pertinent to plant morphogenesis remain. Some appear to be on the verge of being answered, which makes them particularly exciting. For example, given the ubiquitous role of auxin in plant morphogenesis, an important question is the mechanism of auxin transport regulation: How close to reality is the model of Wabnik *et al.* (2010)? A more general question is why mechanisms based on polar auxin transport have evolved to play a prevalent role in plant morphogenesis even when long-distance signaling is not needed.

Our most general observation concerns the crucial role of self-organization at all levels of plant development. The genome provides a very low-level description of an organism: its proteins (and RNA) and a mechanism for the regulation of their production. From these elements, plant forms and patterns emerge through a hierarchy of self-organizing processes. Almost by definition, emergent phenomena are characterized by a discrepancy between the simplicity of local rules and the complexity of the resulting form. This discrepancy is difficult to characterize without the use of computer models and simulations. For this key reason, computational models are becoming an indispensable part of developmental biology.

Some of the concepts reviewed in this paper, such as the morphogenetic role of spatial constraints and the reverse/inverse fountain model of plant morphogenesis, unite diverse emergent phenomena. The identification and study of general properties of such processes may provide a unifying insight into the mechanisms of development, gradually transforming developmental biology into an experimentally based deductive science.

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