Computer models of auxin transport: a review and commentary

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Abstract
With the recent proliferation of computer models of auxin transport, it is important that plant biologists understand something about these techniques and how to evaluate them. The paper begins with a brief introduction to the parts of a computer model, followed by a discussion of the limitations of the most common auxin modelling technique. Lastly, several recent models of organ initiation in the shoot apical meristem (i.e. phyllotaxis) are reviewed. The cell and molecular biology of phyllotaxis is now understood well enough that computer models can go beyond a simple ‘proof of principle’ and start to provide insights into gene function.

Key words: AUX1, auxin, computer model, phyllotaxis, PIN1, plant development.

Introduction
The application of computer simulation techniques to topics in auxin-mediated plant development has become increasingly common in the last few years. These topics include phyllotaxis (de Reuille et al., 2006; Heisler and Jonsson, 2006; Jonsson et al., 2006; Smith et al., 2006), wood grain pattern formation (Kramer, 2002, 2006; Kramer and Groves, 2003; Kramer and Borkowski, 2004; Forest et al., 2005), and the development of vascular strands in stems and leaves (Mitchison, 1980b, 1981; Kramer, 2004; Feugier et al., 2005; Rolland-Lagan and Prusinkiewicz, 2005; Runions et al., 2005; Dimitrov and Zucker, 2006; Feugier and Iwasa, 2006). The primary motivation for most of these papers is (i) to predict the movement of auxin within a developing tissue and (ii) to show that some hypothesis for auxin’s role as a developmental signal, implemented in silico, gives a simulation output comparable with the observed patterns in vivo.

One continuing challenge for the field is that computer modellers and plant biologists often have very different perspectives on the proper role of modelling in the discovery process. Modellers often wish to reverse-engineer the general mathematical rules governing a class of biological patterns (e.g. leaf venation). Their training in computer science and mathematics tends to encourage the selection of the simplest reasonable model. Biologists, on the other hand, are interested in the cellular, biochemical, and genetic processes that give rise to patterns in plants. While they are often intrigued by the images produced by computer models of development, there is simultaneously a scepticism about the value of simulation as a tool for understanding gene function. This scepticism is understandable. Biologists have learned through first-hand experience that the complexity, diversity, and historical contingency present in living systems often frustrate attempts at simplification.

I would suggest that recent progress in auxin molecular biology has advanced sufficiently that computer models can make a contribution to the understanding of gene function. In Arabidopsis, gene families involved in auxin transport, biosynthesis, degradation, and signalling have all been characterized (Davies, 2004). With this progress has come a proliferation of conceptual models—models of auxin distribution and plant development described in words and pictures rather than mathematics. The principle application of current computer models is to refine these conceptual models, to make them quantitative, and to facilitate additional comparison with experiments. However, this research agenda can only succeed if biologists and modellers communicate effectively about their respective disciplines. Biologists need to know enough about modelling techniques to evaluate simulation results...
critically. Modellers need to understand and communicate the biologically relevant aspects of their work.

The focus of this paper is computer modelling as an applied technique. With the exception of phyllotaxis, I will avoid detailed discussions of plant development (additional reviews are provided by Prusinkiewicz, 2004; Heisler and Jonsson, 2006; Kramer, 2006; Mjolsness, 2006; Prusinkiewicz, 2006). The body of the paper is divided into three sections. The first is a relatively non-technical introduction to the parts of a computer model, with a focus on features relevant for the subsequent discussion of auxin transport. The second discusses some practical limitations of the most common modelling technique. The third reviews recent modelling approaches to phyllotactic patterns.

**A primer on computer models**

**Discretization**

Models of auxin transport describe a plant tissue as a collection of polygonal or polyhedral boxes (in two or three dimensions, respectively). There are many synonyms for ‘box’ in the literature, including lattice site, volume element, control volume, and cell. The technique of describing an object as a set of boxes to permit computer simulation is called discretization. The size and arrangement of boxes is not just a technical convenience. Rather, the discretization reflects many implicit and explicit assumptions about the relevant cell and molecular biology to be modelled.

Auxin transport is trans-cellular, which is to say it moves from the cytoplasm of one cell to the next by crossing both cell membranes and the cell wall that separates them. There are three gene families implicated in specific auxin transport across the cell membrane—PIN in efflux (Benkova et al., 2003; Petrasek et al., 2006), AUX/LAX in influx (Parry et al., 2001; Yang et al., 2006), and MDR/PGP in both (Geisler et al., 2005; Terasaka et al., 2005). Auxin is also weakly membrane permeable when protonated (Kramer and Bennett, 2006). Thus, a complete model of auxin transport may include (i) the diffusion of auxin within the cytoplasm and/or within the extracellular space (the apoplast); (ii) the partition of auxin between cytoplasm, vacuole, and other relevant subcellular compartments; and (iii) the spatial localization of carriers on the cell membrane and the resulting auxin fluxes. The most spatially detailed models published to date subdivide the cytoplasm and apoplast into enough boxes to resolve the subcellular auxin gradient and the U-shaped distribution of efflux carriers on the cell membrane (Kramer, 2004; Swarup et al., 2005). However, models with this level of resolution are rare.

The most common choice for the discretization of a plant tissue is an assignment of exactly one box per plant cell (Mitchison, 1980b, 1981; Feugier et al., 2005; Rolland-Lagan and Prusinkiewicz, 2005; de Reuil et al., 2006; Feugier and Iwasa, 2006; Jonsson et al., 2006; Smith et al., 2006). Obviously, a model of this kind cannot capture the gradient of auxin within the cell, nor can it resolve the distribution of auxin within different subcellular compartments (vacuole, cytoplasm, nucleus, etc.). The use of a cell model carries with it the assumption that such details are not relevant for the topic under investigation. The validity of this assumption will be considered in the next section.

A third choice for the discretization assigns many plant cells—tens to thousands—to each box (Mitchison, 1977; Douady and Couder, 1992; Kramer, 2002, 2006; Kramer and Groves, 2003; Kramer and Borkowski, 2004; Dimitrov and Zucker, 2006). These may be called ‘continuum’ or ‘coarse-grained’ models. The concentration of auxin and other hormones, as well as patterns of gene activation, are averaged over all the cells in the box. The main advantage of this approach is economy. Because individual cells are not represented, whole plant organs can be simulated in relatively short computer time. Additionally, in systems that have been poorly characterized experimentally, phenomenological models can be devised with just a few undetermined parameters. These advantages should be weighed against the fact that biologists usually have little training in continuum approaches, and understandably prefer models that resolve individual cells.

**The algorithm**

Computer models of auxin transport all work in much the same way. Each box contains an amount of auxin. The concentration of auxin in each box is repeatedly recalculated according to a set of mathematical rules. One calculation step, applied to the whole model tissue, is called one iteration. The core of any model is the algorithm that dictates how the amount of auxin in each box is updated during each iteration. Roughly speaking, the amount of auxin in a box can change due to de novo synthesis of auxin, metabolism of auxin, and transport of auxin in or out across the boundary of the box. The algorithm chosen depends in part on the choice of discretization, and in part on the cell biology one wishes to model.

The mathematical description of the fluxes in these models is based on well-established concepts in biophysics (Benedek and Villars, 2000; Jackson, 2006). Diffusion between a pair of adjacent boxes in the same compartment (e.g., two boxes in the same vacuole) is governed by Fick’s law. The flux of auxin across a membrane is described by Fick’s law for diffusive permeation of the neutral form and by the Goldman–Hodgkin–Katz current equation for the anion. The effects of carrier saturation, and pH-dependent or voltage-dependent carrier efficiency,
are also straightforward to include, although in this case one resorts to a phenomenological treatment.

In models where each plant cell is represented as a single box, the equations governing auxin flux are especially straightforward. There are no terms describing the diffusion of auxin within the cytoplasm or apoplasm, and the flux of auxin between each pair of adjacent cells is typically simplified so that the underlying biophysical and biochemical parameters are not immediately apparent (and may not even be provided). For example, Mitchison took the following general expression for the flux between two cells

\[ \phi = p a_1 + q (a_1 - a_2) \]  

(1)

where \( \phi \) is the flux across the membrane, \( a_1 \) and \( a_2 \) are the auxin concentrations in two adjacent cells, and \( p \) and \( q \) are parameters with units of permeability (cm h\(^{-1}\)) (Mitchison, 1980a, 1981). His work is unusual in that he subsequently derives expressions for \( p \) and \( q \) in terms of more fundamental membrane properties.

In models intended to capture the dynamic redistribution of auxin efflux carriers, the algorithm must also include rules for moving carriers to and from each membrane segment on the border of the cell (Jonsson et al., 2006; Smith et al., 2006). Since little is known about the signalling mechanism that controls the trafficking of carriers, this portion of the algorithm is phenomenological.

**The parameters**

Any algorithm modelling auxin transport requires real numbers as inputs. Parameters may include auxin membrane permeabilities, protein carrier efficiencies, auxin diffusion coefficients, and the rates of auxin synthesis and degradation. Additional parameters may be required to characterize the rates of auxin carrier synthesis, degradation, and redistribution. Ideally, every parameter should be quantified experimentally. However, in many cases one is left with educated guesses based in part on the underlying biophysics and biochemistry, and in part on inference from published values in other systems. A discussion of the parameters relevant for auxin transport may be found in the online supplementary information of Swarup et al. (2005) and Jonsson et al. (2006), and in the recent review by Kramer and Bennett (2006).

Rather than entering an empirical discussion about parameters, some modelling groups pursue a different approach. Model parameter values are invented with no reference to experiment. These parameter choices are then justified using two arguments: first, model parameters are typically validated *post hoc* by comparison between model output and plant morphology. Secondly, a range of parameter values are tested to see if the model output is robust under parameter variation. The use of robustness as a selection criterion for parameter values has precedent in studies of biochemical networks (Morohashi et al., 2002; El-Samad et al., 2006). To the extent that this technique succeeds, it is credited to the fact that evolution has tended to select for robustness in biological systems (Kitano, 2004; Li et al., 2004). Robustness analyses may be applied as a useful check on parameters whose values are poorly known. With caution, it may be used to fill in conspicuous gaps in the empirical knowledge of a system. Robustness analysis should not substitute for a careful comparison with experiment in cases where one is available.

**Verification**

The model algorithm is usually intended to approximate the exact solution to a set of differential equations. Verification is the process of showing that the simulation output is unique and accurate (Bassingthwaigte et al., 2006).

As an illustrative example, consider the following differential equation describing the auxin concentration \( c \) in an isolated box as a function of time:

\[ \frac{dc}{dt} = \frac{(c - a)}{\tau} \]  

(2)

where \( a \) is a constant with units of concentration and \( \tau \) is a constant with units of time. This equation might describe the concentration in an isolated cell that exhibits auxin homeostasis. If the concentration is greater than \( a \), auxin is metabolized. If the concentration is less than \( a \), auxin is synthesized. This equation has an exact solution

\[ c(t) = a + (c_0 - a)\exp(-t/\tau) \]  

(3)

where \( c_0 \) is the initial concentration of auxin in the box. At times long compared with \( \tau \), the concentration asymptotically approaches the steady-state value \( a \).

There are a variety of techniques for solving equation (2) on a computer (Press et al., 1989). One commonly used algorithm calculates the concentration only at a set of evenly spaced times, \( \{0, \Delta t, 2\Delta t, 3\Delta t, \ldots\} \), where \( \Delta t \) is called the time step. Starting with the initial concentration \( c_0 \), the concentration at subsequent times is calculated by repeated iteration of the equation

\[ c_{i+1} = c_i - \Delta t \frac{(c_i - a)}{\tau} \]  

(4)

where \( c_i \) is the concentration at time \( i\Delta t \).

Figure 1 shows the exact solution described by equation (3) and several approximate solutions generated using equation (4). If the time step is greater than \( \tau \), the approximate solution shows an oscillatory behaviour that is qualitatively different from the exact solution. If the time step is less than \( \tau \), solutions start at \( c_0 \) and decrease monotonically towards the steady-state concentration \( a \) on a time scale comparable with \( \tau \). As \( \Delta t \) is decreased further, the values approach the exact solution. The accuracy can
always be improved, with the computational cost of more iterations. It should also be noted that there are a range of other approximation schemes that could have been used instead of equation (4) (Press et al., 1989). With decreasing time steps, these alternatives generally approach the exact solution more quickly than the approximation given by equation (4). The proper choice of approximation scheme and time step depends on the goals of the model.

Instead of a single box, auxin models will typically track the concentration in hundreds or thousands of boxes. In this case, verification can be time-consuming, and it represents a significant fraction of the total effort involved in building a model. Three common verification techniques exist. (i) If any exact solutions to the differential equations are known—even simplistic ones—the simulation output should be verified by comparison. (ii) The simulation should be repeated multiple times using a range of time steps. If the model is well constructed, solutions should converge to a unique output as \( \Delta t \) is made smaller. (iii) If the underlying set of differential equations has any symmetries, then the approximate solution should respect these symmetries [e.g. during verification of a recent model of auxin transport in the Arabidopsis root, it was confirmed that auxin supplied uniformly around the circumference of the root retained that uniformity during subsequent transport (Swarup et al., 2005)]. One widespread weakness of auxin modelling work is the general absence of these checks in the published description of the model. One assumes that verification is a part of model construction, but at least some brief discussion should appear in the text. Without it, reviewers and interested readers are unable to evaluate the accuracy of the technique.

**Limitations of cell models**

The most common discretization in auxin transport simulations is the assignment of one box per plant cell (Mitchison, 1980b; Feugier et al., 2005; Rolland-Lagan and Prusinkiewicz, 2005; de Reuille et al., 2006; Feugier and Iwasa, 2006; Jonsson et al., 2006; Smith et al., 2006). For brevity, I will call these ‘cell models’. There are three assumptions implicit in the use of a cell model. First, by assigning a single auxin concentration to the cell interior, these models assume that the cytoplasmic auxin gradient is negligible. Secondly, by not explicitly including the apoplast, these models assume that lateral diffusion of auxin (i.e. diffusion within and parallel to the cell walls) is negligible. Thirdly, by simplifying the interface between each pair of cells, these models assume that the activity of a pair of membranes separated by a cell wall can be well approximated by a single equivalent membrane. The validity of each of these assumptions may be assessed quantitatively, and will be discussed in turn.

**Assumption 1. The auxin gradient inside a cell is small**

The path of auxin movement inside the cell has not been well characterized. Classical work by Goldsmith and co-workers found that the auxin flux through maize coleoptiles was not disrupted by a centrifugation procedure that displaced the vacuole to abut either the apical or basal end of transporting cells (Goldsmith and Ray, 1973). Transport was also not disrupted by a treatment with cytochalasin B that completely inhibited cytoplasmic streaming (Cande et al., 1973). They therefore concluded that the most likely means of auxin transport within the cell was diffusion through both cytoplasm and vacuole. These results were incorporated into computer models of auxin transport published by Mitchison (1980a) and by Goldsmith et al. (1981). Both models demonstrated that the typical auxin transport speed of \( \sim 1 \text{ cm h}^{-1} \) was consistent with a strictly diffusive transport through the cell interior.

Both Mitchison (1980a) and Goldsmith et al. (1981) were concerned with a topic that does not receive much comment in modern work. If auxin transport within the cell takes place by diffusion, then there must be an accompanying auxin gradient. The main practical consequence of the auxin gradient is the depletion of auxin from the cytoplasm adjacent to the efflux carriers. This depletion has been simulated in Mitchison (1980a), Goldsmith et al. (1981), Kramer (2004), and Swarup et al. (2005), and is illustrated in Fig. 1a of Mitchison (1980a) and Fig. 2c of Swarup et al. (2005). Cell models neglect this gradient, and thus may overestimate the efflux
of auxin from transporting cells. This is not necessarily a small correction.

The difference in auxin concentration between the apical and basal ends in a cylindrical compartment of length $L$ may be estimated as $(c_{\text{apex}}-c_{\text{base}})=cvL/D$ where $c$ is the mean auxin concentration, $v$ is the speed of auxin transport, and $D$ is the diffusion coefficient of auxin in the compartment [note that this is just a rewrite of Fick’s law (Benedek and Villars, 2000)]. Substituting a transport speed of 1 cm h$^{-1}$ and a diffusion coefficient equal to the aqueous value, $D=0.024$ cm$^2$ h$^{-1}$, this gives a concentration gradient of 4% in a cell 10 μm long and 40% in a cell 100 μm long. Based on this analysis, it seems reasonable that computer simulations can neglect the auxin gradient in short cells but not in long ones. However, this conclusion is based on an auxin transport speed of 1 cm h$^{-1}$, which has only been measured accurately in mature tissues composed of elongated cells (Goldsmith et al., 1981; Kramer, 2002). Apical meristems have small cells and relatively high levels of carrier expression, so one cannot rule out the possibility that transport is significantly faster there (Reinhardt et al., 2003; Blilou et al., 2005).

A discussion of auxin within the cell should mention recent speculation that cytoplasmic auxin is sequestered in vesicles and transported through the cell by vesicle trafficking (Baluska et al., 2003). Notably, application of the vesicle transport inhibitor brefeldin A (BFA) disrupts both PIN protein trafficking and auxin efflux (Delbarre et al., 1998; Geldner et al., 2001). The hypothesis of vesicle-mediated auxin transport has not gained wide acceptance, in part because of the evidence favouring diffusion cited above, and in part because the observed effects of BFA on transport appear to be explainable as secondary effects of the disruption of PIN protein trafficking (Delbarre et al., 1998; Geldner et al., 2001; Petrasek et al., 2003). However, the idea warrants additional experimental investigation.

Assumption 2. Lateral diffusion in the apoplast is negligible

The apoplast is the extracellular compartment that includes all cell walls, airspaces, and fluid-filled spaces. Cell models ignore the apoplast, so that auxin effluxed from one cell immediately enters an adjacent cell across their common interface. This neglects the possibility that auxin secreted into the apoplast may diffuse away from the interface and thus not enter either cell. To our knowledge, only four simulations have included the apoplast as a possible pathway for auxin diffusion (Kramer, 2004; Swarup et al., 2005; Heisler and Jonsson, 2006; Jonsson et al., 2006). In particular, the results of Kramer (2004) and Swarup et al. (2005) both suggest that apoplastic diffusion makes an important contribution to the flux of auxin through a plant tissue.

Kramer (2006) describes a mathematical analysis of apoplastic diffusion. The typical distance a secreted auxin molecule will diffuse through the apoplast before re-entering a cell is $(hD_{\text{wall}}/2P)^{1/2}$ where $h$ is the cell wall thickness, $D_{\text{wall}}$ is the auxin diffusion coefficient in the wall, and $P$ is the effective membrane permeability of auxin [note that the typical distance is somewhat smaller than the characteristic length scale defined in Kramer (2006)]. For a wall 100 nm thick bordered by cells that do not express an influx carrier, an auxin molecule will travel a distance of ~5 μm. This means, for example, that auxin secreted into an interface 5 μm wide would be unlikely to remain at that interface. The presence of influx carriers can increase the membrane permeability by an order of magnitude and so decrease the importance of this effect. Conversely, thicker walls will tend to increase the diffusive flux. The relative importance of the apoplastic space as a pathway for auxin movement should thus be evaluated on a case-by-case basis, and should not be presumed to be small.

Assumption 3. The interface between a pair of cells can be approximated using a single equivalent membrane

Cell models treat the interface between adjacent cells as a single membrane. This approximation is entirely valid if the previous two assumptions are valid. That is to say, if cytoplasmic auxin gradients and lateral apoplastic diffusion are both negligible, then one can define an ‘equivalent membrane’ whose transport properties are exactly equivalent to the composition of two opposed cell membranes and the cell wall that separates them. Mitchison (1980a) does exactly this calculation. Cell models thus have the potential to describe the combined activity of both influx and efflux carriers accurately.

Despite this, cell models have tended to ignore the activity of influx carriers. There are two facts about auxin transport that account for this bias. First, the most widely cited value for the diffusive membrane permeability of auxin (12 cm h$^{-1}$; Gutknecht and Walter, 1980) is nearly two orders of magnitude larger than its likely value in plants (0.2 cm h$^{-1}$; Delbarre et al., 1994, 1996). The larger value has contributed to the mistaken impression that the activity of influx carriers is supplemental to diffusion (Kramer and Bennett, 2006). Secondly, the most interesting feature of auxin transport—is its polarity—is usually determined by the polar localization of efflux carriers (Galweiler et al., 1998; Benkova et al., 2003) [influx carriers are usually not polar, although there are exceptions (Swarup et al., 2001; Reinhardt et al., 2003)]. These two facts have created a tendency for cell models to describe all carrier activity as efflux carrier activity.

There are a handful of exceptions to this trend. Kramer (2004), Swarup et al. (2005), and Heisler and Jonsson (2006) have published models that explicitly include the activity of influx carriers. Far from being a trivial addition,
the influx carriers function to accumulate auxin in some cells and to exclude it from others. Thus, models of plant development that depend on auxin concentrations or gradients should take influx carriers into account. This point has been missed by recent cell models.

Models of phyllotaxis

Perhaps no topic in plant development has received more attention from mathematical and computer modellers than phyllotaxis (Jean, 1994). The goal here is not to review the entirety of the field, but rather to use this rich field of published work to illustrate both the advantages and limitations of computer models.

Phyllotaxis is the name given to the regular spatial and temporal pattern of organ initiation in the apical meristem of stems and reproductive structures. One of the more visually arresting examples of pattern in phyllotaxis is the spiral arrangement of florets in the centre of composite flowers such as sunflower (*Helianthus annuus*). Patterns in spiral phyllotaxis have attracted an enormous amount of attention from mathematicians for more than a century (Jean, 1994). Of particular interest is the fact that the numbers of left- and right-handed spirals are often two consecutive terms in the Fibonacci series, \{1,1,2,3,5,8,13, 21…\} in which each term is the sum of the previous two.

The reproduction of the Fibonacci series would seem to provide a stringent test for any computer model of development. Surprisingly, this is not the case. Mitchison (1977), and later Douady and Couder (1992), used computer models of the apical meristem to demonstrate that models of spiral phyllotaxis will reproduce the Fibonacci series under a wide range of plausible conditions. These models treat the meristem as a two-dimensional surface (i.e. a flat or curved sheet) and organ primordia as points on this surface. Individual cells are not resolved. The conditions necessary and sufficient to reproduce phyllotactic patterns are the following: (i) new primordia can only arise in an annular region near the tip of the meristem; (ii) existing primordia inhibit the formation of new primordia via a signal whose strength decays with distance; and (iii) once formed, a primordium maintains its identity and is carried away from the tip of the meristem by ongoing tissue growth. The importance of this result for modellers is the fact that it is independent of the nature of the inhibition between primordia. Recently, two distinct theories of this inhibition have both been used to motivate computer models, and both produce realistic phyllotactic patterns. One class of models uses an inhibition based on auxin production and transport and will be discussed further below. The second class of models assumes the pattern arises due to the elastic buckling of the relatively stiff outer layer of the meristem as it is subjected to growth stresses (Green, 1999; Shipman and Newell, 2005). The work of Mitchison, Douady, and Couder shows that simulated phyllotactic patterns cannot be used to decide between these competing models of development. Instead, the nature of the inhibition must be determined by experiments.

The role of auxin in phyllotaxis has recently been clarified by numerous experiments involving auxin transport inhibitors, auxin carrier mutants, and auxin carrier visualization studies (Galweiler et al., 1998; Reinhardt et al., 2000, 2003; Stieger et al., 2002; Reinhardt, 2005). Both auxin influx and efflux carriers play important roles. In *Arabidopsis*, the AUX1 influx carrier expression is strongest in the outermost (L1) cell layer of the shoot apical meristem (SAM). The expectation is that this pattern of expression tends to restrict auxin to the outermost layer, thus explaining why primordium initiation is effectively two-dimensional. The inhibition between neighbouring primordia is explained by a feedback between the auxin concentration and the subcellular localization of the PIN1 efflux carrier. The idea is that PIN1 tends to point up the local auxin gradient, towards existing sites of auxin accumulation. Thus, a zone of auxin accumulation will tend to deplete auxin from adjacent cells and to inhibit the formation of nearby concentration maxima. The hypothesis is completed by assuming that localized sites of auxin accumulation differentiate to become organ primordia. Many aspects of this model remain poorly understood. In particular, the signal that conveys to a cell information about the auxin concentration in neighbouring cells is unknown, as is the means by which this signal is conveyed to the mechanism that controls PIN protein trafficking.

The conceptual model of auxin-mediated phyllotaxis was developed without the assistance of mathematical or computer models. Only subsequently, in the last 2 years, have several groups published computer models of auxin flux in the L1 layer of the *Arabidopsis* SAM. de Reuille et al. (2006) map the distribution of PIN1 obtained from microscopy directly onto a static cell model (one polygonal box per cell, no cell division or growth) and show that the sites of auxin accumulation in silico match the observed sites of primordium initiation. Smith et al. (2006) build a dynamic cell model of the SAM that includes cell division and expansion, auxin transport, and a feedback between the local auxin gradient and efflux carrier localization. They show that the model can reproduce a variety of realistic phyllotactic patterns, differing only in the choice of model transport parameters. Both these cell models are subject to the limitations described in the previous section. In addition, both groups use unitless model parameters. It is therefore difficult to assess whether their parameter values are consistent with available information on membrane permeability and carrier efficiency (Delbarre et al., 1996; Swarup et al., 2005).

Jonsson et al. (2006) apply two different modelling approaches to phyllotaxis. The first is a cell model of the
L1 layer including cell division and growth, and using unitless parameters. Like Smith et al. (2006), they find that the feedback between PIN polarity and local auxin concentration is sufficient to generate patterns of primordium initiation. Unlike Smith et al., they find that the spatial and temporal pattern of auxin accumulation into discrete zones is unstable, showing reversals of the spiral pattern and uneven time intervals between consecutive primordia initiations. The difference may be due to the fact that Smith’s model allows cells at the centre of an auxin accumulation zone to undergo an irreversible developmental transition to a primordium, after which the local transport parameters are changed to favour their continued stability. There is no irreversible developmental transition in the model of Jonsson et al. The second approach to phyllotaxis described by Jonsson et al. (2006) is similar in spirit to that of de Reuille et al. (2006). The authors map microscope observations of PIN1 polarity onto a static model of the L1 layer and locate the sites of auxin accumulation in silico. The model has two notable advantages over those previously described. First, the model explicitly includes the cell wall between each pair of cells. Thus, it can distinguish auxin influx from efflux and also quantify the possible importance of auxin diffusion through the apoplast. Secondly, all model parameters have units, allowing a comparison with experiment.

In a more recent paper, Heisler and Jonsson (2006) have continued their analysis of this model. They adopt parameter values for both diffusive and carrier-mediated transport that have a plausible foundation in experiment. In so doing, they avoid high membrane permeabilities that would lead to large cytoplasmic auxin gradients. From the perspective of molecular biology, the chief advance over their previous paper (Jonsson et al., 2006) is the incorporation of the AUX1 influx carrier into the model (recall that cell models historically tend to ignore influx carriers). Two new results emerge from this addition. First, they show that the experimentally observed high level of AUX1 expression in the L1 layer is adequate to accumulate auxin in this layer, supporting earlier speculation (Reinhardt et al., 2003). Secondly, they show that the observed up-regulation of AUX1 in cells at the sites of primordium initiation is sufficient to stabilize the position of auxin accumulation sites. This model in particular demonstrates that the integration of realistic biophysical and biochemical details into a computer simulation can illuminate the functional role of genes in plant development.

Even subject to the caveats of the previous two sections, cell models of phyllotaxis have proven their usefulness. They have shown that the conceptual model of phyllotaxis can be implemented plausibly and quantitatively as a set of interactions between cells in the L1 layer. Beyond this, the models highlight several important features that were obscure or missing in the conceptual model. First, the feedback between the local auxin gradient and PIN polarization requires a short-range signal between adjacent cells. Secondly, the stability and regularity of the phyllotactic pattern depend on the activity of genes other than efflux carriers (either a transition from SAM to primordium identity or an auxin-mediated regulation of influx carrier expression). Thirdly, despite differences in the final choice of differential equations, all three groups identified auxin homeostasis as an important feature of auxin dynamics in the L1 layer.

**Outlook**

In this review, I have tried to anticipate some of the questions biologists are likely to ask of modellers. How do computer models work? What are their limitations? Can they do more than demonstrate the plausibility of an idea? Can they illuminate gene function? These are questions that modellers should be prepared to answer.

In the course of this review, I have tried to indicate which unresolved topics in auxin biology hold the most promise for the future refinement of computer models. (i) The parameter values describing auxin movement through the tissue—diffusion coefficients, carrier efficiencies, etc.—are in many cases only known to within an order of magnitude and should be measured for each system of interest. (ii) The path of auxin movement within the cell, and its possible accumulation within some organelles, needs to be clarified. (iii) Many recent models propose a feedback between the auxin distribution in a tissue and cell polarity. The nature of this feedback—and whether it involves a single conserved mechanism or convergent evolution of distinct signalling pathways—is unknown. Experiments will need to clarify each of these points before truly quantitative models of plant development can be built.

I have also tried to indicate how modellers can present their research in a way that helps others evaluate the model. (i) Manuscripts should discuss the discretization and the time step used, including the rationales for each. (ii) Manuscripts should include some discussion of verification procedures. (iii) Model parameters should be cited with units or should be clearly derived from parameters with units. (iv) Manuscripts should include enough illustrative data to allow a quantitative comparison with related models. In particular, typical values of the membrane permeabilities should be provided.

During the construction of any new computer model, modellers must invariably make choices about parameter values and the governing equations despite an incomplete knowledge of the system. In these situations, I would suggest the following guidelines. In cases where parameter values are not accurately known, the conclusions drawn from model results should be demonstrably robust over a reasonable range of parameter values. In cases where the choice of a model equation is not constrained by available

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measurements, the equation used should be introduced with substantial explanation and, where possible, should rely on established standards from cell and molecular biology. For example, the saturation of an auxin efflux carrier should probably be described using the Michaelis–Menten equation, unless additional data are available to suggest more complicated kinetics (Jackson, 2006).

While still in its early stages, I expect that computer modelling of auxin transport will eventually become an established and productive part of plant developmental biology. The process will require modellers and biologists to communicate clearly about the strengths and limitations of simulation techniques. I look forward to this continued dialogue.

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