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The Chemical Kinetics of Shape Determination in Plants

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1. Introduction

Plants are integral to our lives, providing food, shelter and the air we breathe. The shapes that plants take are central to their functionality, tailoring each for its particular place in the ecosystem. Given the relatively large and static forms of plants, it may not be immediately apparent that chemical kinetics is involved in, for example, distinguishing the form of a spruce tree from that of a fern. But plants share the common feature that their shapes are continuously being generated, and this largely occurs in localized regions of cell division and expansion, such as the shoot and root apical meristems at either end of a plant's main axis; these regions remain essentially embryonic throughout the life cycle. The final regular structure of a plant, such as the arrangement of leaves along the main stalk, may seem to follow an overall spatial template; but in reality the spatial patterning is occurring at relatively short range, and it is the temporal unfolding of this small scale patterning which generates the plant's form. A key part of understanding plant morphogenesis, or shape generation, therefore, is to understand how the molecular determinants of cell type, cell division and cell expansion are localized to and patterned within the actively growing regions. At this scale, transport processes such as diffusion and convection are obvious components of localization, for moving molecules to the correct places; but the reaction kinetics for molecular creation, destruction and interaction are also critical to maintaining the molecular identity and the size regulation of the active regions.

It was Turing (1952) who first combined the ideas of reaction kinetics with diffusion into a theory of spatial pattern formation – how to establish, and maintain, molecules at specific concentrations in specific locations. The Turing mechanism involves two mutually interacting (activating and inhibiting) intermediates (which he termed 'morphogens'), which diffuse at different rates. While his paper chiefly introduced the kinetics required for pattern formation from homogeneous initial conditions (in particular, finding critical values of rate constants for this to occur), Turing was clearly thinking of the implications in embryonic tissues, as evidenced by his title, "The chemical theory of morphogenesis". In the 1960's, Prigogine and collaborators presented the first specific nonlinear chemical mechanism which could form stable spatial concentration waves (the 'Brusselator'; Prigogine & Lefever, 1968), as well as providing a thermodynamic basis for spontaneous pattern formation (see Nicolis & Prigogine, 1977). In the 1970's, reaction-diffusion (RD) mechanisms were introduced into biology by Meinhardt (see Meinhardt, 1982), Harrison (see Harrison, 1993),

Murray (see Murray, 1989) and many others, through computer simulations of RD mechanisms for particular embryonic phenomena. The Turing mechanism for pattern formation was experimentally confirmed in 1990 with the CIMA redox reaction in gel reactors (Castets et al., 1990; Ouyang & Swinney, 1991). RD is now a broad and mature field (with consistently over 150 citations per year of Turing's paper over the past decade).

This chapter focuses on the development of RD theory in plant morphogenesis, particularly in characterizing the interplay of pattern formation and domain growth (also see Holloway, 2010, for a short review). In contrast to animal embryogenesis, in which pattern formation generally occurs in fixed domains, the continuous growth of plants inextricably links chemical localization (patterning) and growth (shape change). Growth affects patterning: at the least patterns must be generated and maintained in the face of domain growth, since RD mechanisms (like other dynamic mechanisms) have harmonic solutions which depend on domain geometry, size and boundary conditions. But perhaps more importantly, patterning affects growth: plant cells expand through localized wall material addition or wall material relaxation, both chemically dependent processes. The patterning mechanisms which determine where expansion-associated chemicals are localized are therefore critical determinants in the shapes of plant tissues. The complex mechanical properties of plant cells are also important in the deformations leading to final overall shape, and will be discussed below in relation to chemical patterning. However, biochemical processes (interpreted broadly, e.g. genetic regulation, hormone response) generally precede shape change, and how these processes create spatial pattern is central to morphogenesis. (For further discussion on morphogenetic modelling in general, please see the recent reviews of Braybrook & Kuhlemeier, 2010; Grieneisen & Scheres, 2009; Jönsson & Krupinski, 2010; Roeder et al., 2011; and Zwieniecki & Dumais, 2011).

Many developmental phenomena depend on a sequence of patterns, for example from simple extending tip growth to branching. RD theory provides a means for understanding the kinetic constraints involved in such symmetry-breaking transitions. The development of RD theory for growing domains, in conjunction with experimental tests, illuminates how chemical kinetics shape the plants around us, from ferns to spruce trees.

2. The chemical kinetics of spatial pattern formation

The regulation of reaction rates is central to maintaining biological order. At its simplest, kinetics maintain a homeostasis of production and destruction of an organism's component molecules; at the somewhat more complex, nonlinear kinetic mechanisms underlie temporal regulation, such as the heartbeat. But reactions are local, and do not immediately provide a mechanism for establishing the spatial pattern or regulation necessary for forming and maintaining an organism's body plan. For this, Rashevsky (1940) was one of the first to publish the idea of combining simple Fickian diffusion, as a spatially-dependent process, with local reactions to regulate biological spacing. Turing (1952) formulated the first RD theory mathematically, demonstrating the conditions for these processes to spontaneously form pattern (stable concentration waves) from uniform initial conditions, i.e to self-organize pattern. These ideas have been greatly expanded, theoretically and experimentally, into a field of RD pattering. Since Turing, other spatially-dependent processes – such as convection, mechanical stresses and anisotropic diffusion – have been combined with reaction terms to explore the broader dynamics of chemical pattern formation. The

dynamics have been most fully explored for simple diffusion, however, and RD has become a very well-characterized means by which to study pattern formation in general.

2.1 Turing's ideas: How activation, inhibition and diffusion create concentration waves

Turing's focus was on how a uniformly distributed chemical could spontaneously form spatial pattern, or 'standing' concentration waves. This transition implies an instability in the uniform equilibrium condition; the final concentration waves exist (and must be held) away from thermodynamic equilibrium. (For further discussion of far-from-equilibrium thermodynamics, see Nicolis & Prigogine, 1977.) To reduce some of the mystique in this symmetry-breaking process, Turing used the analogy of an electrical oscillator – that what appears to be uniform concentration is in fact comprised of the elements of any spatial pattern necessary, as noise at the microscopic scale – and that there is a natural frequency of the oscillator, or the chemical system, such that this frequency can be amplified from the noise to achieve macroscopic proportions. Turing showed that such a chemical amplifier could be devised for two mutually reacting chemicals, X (activator) and Y (inhibitor), which diffuse at different rates. Fig. 1 illustrates the mechanism.
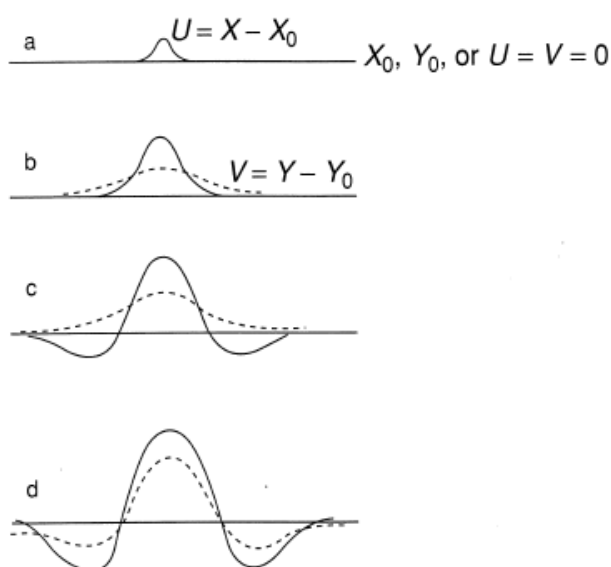

Fig. 1. Growth of perturbations into sinusoidal patterns (vertical – concentration, horizontal – distance). **a**) An initial small positive perturbation of X from its uniform steady-state value of X_0. **b**) If X is autocatalytic (enhances its own production) and cross-catalyzes Y, the initial X perturbation grows and begins to produce a Y peak. Y diffuses faster than X. **c**) If Y inhibits X, it begins to create troughs in X, which **d**) also become troughs in Y (since X activates Y). The pattern achieves a spacing dependent on reaction and diffusion constants. Reproduced from Harrison (1993), redrawn from Maynard Smith (1968), with permission.

Mathematically, for $U=X-X_0$, and $V=Y-Y_0$, the deviations of X and Y from the uniform state, the linear reaction-diffusion equations are:

$$\partial U / \partial t = k_1 U + k_2 V + D_X \Delta U \qquad (1a)$$

$$\partial V / \partial t = k_3 U + k_4 V + D_Y \Delta V \tag{1b}$$

with diffusivities D and Laplacian operator Δ (2nd partial derivative with respect to distance, 1 to 3 dimensions). The conditions illustrated in Fig. 1 correspond to k_1, $k_3 > 0$, $k_2 < 0$, and $D_X < D_Y$. Solutions for U and V take the form of (1D, for illustration)

$$U = \cos(\omega s) e^{\sigma t} \tag{2}$$

where s is the spatial dimension, t is time, ω^2 is the wavevector of the spatial pattern (for 1D, the spacing between peaks is given by wavelength $\lambda = 2\pi / \omega$), and σ is the eigenvalue or growth constant of the perturbations. In 1D, cos and sin solutions can be viewed as components of the Fourier representation of a pattern (in the uniform initial condition, Fourier components of the microscopic noise). In 2D and 3D, solutions to (1) similarly are harmonics of the Laplacian operator for the given geometry (e.g. Bessel functions on 2D discs; surface spherical harmonics for spherical shells, section **2.4**). Turing derived conditions for which $\sigma > 0$, indicating when pattern modes will amplify (below this 'Turing instability' $\sigma < 0$ and the uniform concentration is stable). The eigenvalue, σ, is a function of the wavevector ω^2; this functionality is a complex expression involving all the parameters in equations (1), but with the general form of $\omega^2 \propto k/D$. In 1D terms, wave*length* is shortened by increasing reaction rates (k's) or decreasing diffusivities (D's). There may be a number of wavevectors with positive σ fitting the particular boundary conditions (e.g. no-flux or fixed concentration); generally the wavevector with largest eigenvalue will grow to dominate the macroscopic pattern, analogous to the natural frequency of an electrical oscillator. For more on the mathematics of the linear Turing equations (1), please see Edelstein-Keshet (1988); Harrison (1993; 2011); or Holloway (1995).

2.2 The Brusselator, a nonlinear kinetic patterning mechanism

The linear rate equations (1) are an approximation from real chemical dynamics. In real chemical mechanisms, the reactions giving Turing dynamics are nonlinear; for example, autocatalysis gives a rate law for X which is greater than 1st order in X. Linear analysis is accurate for growth rates and wavevectors at the Turing instability, i.e. for conditions just supporting positive eigenvalues. For conditions with many growing wavevectors and for long times (beyond the exponential growth phase described by equation (2)), linear analysis is not as good a predictor of observed pattern. In these cases, numerical simulation or nonlinear analysis of the chemical mechanism is needed. Prigogine & Lefever (1968) devised the first chemical mechanism (the 'Brusselator') with Turing pattern-forming dynamics:

$$A \xrightarrow{\ a\ } X \tag{3a}$$

$$B + X \xrightarrow{\ b\ } Y + D \tag{3b}$$

$$Y + 2X \xrightarrow{\ c\ } 3X \tag{3c}$$

$$X \xrightarrow{\ d\ } E \tag{3d}$$

in which the *X* and *Y* morphogens are reactive intermediates in the creation of *D* and *E* from precursors *A* and *B*. Prigogine and Lefever commented that the termolecular step in equation (3c) could be unlikely in gas phase; but such conditions would be common in multi-step enzyme kinetics. Since *X* depletes *Y* in this 3rd step, *X* and *Y* waves form out-of-phase, in contrast to Fig. 1. The Brusselator has a strong tendency to form regular patterns which follow linear predictions (e.g. Lacalli, 1981; Holloway & Harrison, 1995), and we have found it very appropriate for modelling regular events in plant development, such as branching (Harrison et al., 1981; Harrison & Kolář, 1988; Holloway & Harrison, 1999; Harrison et al., 2001; Holloway & Harrison, 2008).

2.3 Early biological applications

Computer simulation of nonlinear RD mechanisms expanded greatly in the 1970's and 1980's, accompanied by an increase in applying RD to biological development. Gierer & Meinhardt (1972) derived an RD pattern-forming mechanism independent of knowledge of prior work in the 1960's and 1970's, but which has Turing dynamics. They used this mechanism and variants to successfully model numerous phenomena in animal and plant development (e.g. Meinhardt, 1982; 1984; 1986; 1988; 1995). A chief contrast with the Brusselator dynamics is the tendency for the Gierer-Meinhardt model to form 'spike', or isolated, peaks (Lacalli, 1981; Holloway & Harrison, 1995; Iron et al., 2001). This can be very appropriate for modelling localized structures, such as single organs (heads, hearts), and the dynamics can be derived from multi-step activation in enzyme kinetics (Holloway et al., 1994). In animal development, Murray (1981ab) developed RD models for animal coat markings; Kauffman and co-workers (Kauffman 1977; 1981; Kauffman et al., 1978; Hunding et al., 1990) began RD modelling of fruit fly segmentation, which was greatly expanded by many workers (e.g. Nagorcka, 1988; Lacalli et al., 1988; Lacalli, 1990; Lyons et al., 1990); and Nagorcka & Mooney (1982; 1985) developed an RD model for hair follicle patterning. Many of these early directions continue as active areas of research. Early work on RD modelling of plants, with the intrinsic challenge of coupling growth and patterning, will be presented in more detail in section **3**.

2.4 Geometry and pattern selection in 3D

As introduced in **2.1**, solutions to RD equations are harmonics of the Laplacian, dependent on boundary conditions (e.g. no-flux or fixed concentration) and geometry. In 1D, this dependence can be studied as the fit of the linear wavelength $\lambda = 2\pi/\omega$ to the system length. Many patterning forming events in plants tend to occur on growing tips, which are roughly dome shaped. In these cases, the geometry can be approximated by a hemisphere, and RD pattern formation understood in terms of the surface spherical harmonics, polynomials designated by Y_l^m. These functions are familiar as the hydrogen-like atomic orbitals, where *l* is the index denoting s, p, d, f, etc. orbitals, and *m* denotes different patterns within each of the *l* levels. For these harmonics, $\omega^2 = l(l+1)/r^2$: the wavevector depends on index *l* and the radius of the hemisphere. Linear analysis predicts that any patterns of the same *l* should grow at the same rate (i.e. equal eigenvalues). This has bearing on pattern selection in plants: at *l*=3, *m*=0 gives a circularly-symmetric annular pattern; $m = \pm 2$ gives 'quartered' patterns; and the equal mix of these modes gives a dichotomous branch pattern (Fig. 2). Linear analysis would predict the annular and quartered patterns to grow equally, and therefore to mix and always produce dichotomous branches. But both annular patterns

(underlying tip flattening) and dichotomous branches occur in plant development. Harrison et al. (2001) and Nagata et al. (2003) showed, through simulation and nonlinear analysis respectively, that RD dynamics can produce both types of patterns (i.e. linear analysis does not provide the full picture). Intriguingly, the Brusselator model shows about an 80:20 preference for dichotomous branching over annuli, and such proportional selection can be seen experimentally in conifer development (von Aderkas, 2002). Current work (Nagata, Zangeneh and Holloway, unpublished results) is addressing how pattern selection changes as a hemisphere is deformed into a disc (where Bessel functions are the natural harmonics), representing a tip-flattening sequence common to many plants.
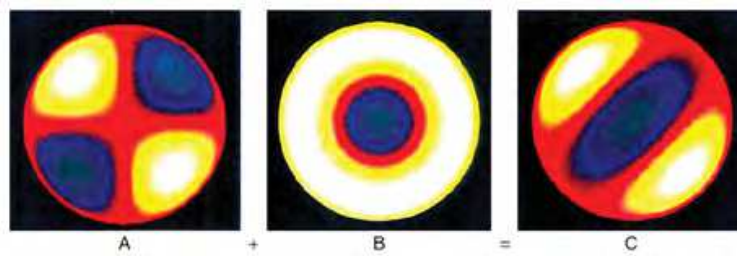
Fig. 2. Pattern selection on a hemisphere (approximating the growing tip of a plant). Surface spherical harmonics for index l=3: (A) $m = \pm2$; (B) m=0; (C) equal mix of (A) and (B) produces a dichotomous branch pattern. Linear analysis predicts (A) and (B) patterns would grow equally, therefore always producing (C). Plant development shows both (B) and (C) patterns. Simulation and nonlinear analysis show that the full RD dynamics (Brusselator model) do have the capacity to produce both (B) and (C) patterns. From Holloway & Harrison (2008), with permission.

3. Plant morphogenesis and reaction-diffusion: The challenge of growth-patterning feedback

RD theory is well-established for pattern formation on fixed-size domains. Understanding plant development, however, requires consideration of the interaction between pattern formation and growth, since plants grow throughout their life cycles. The interaction between patterning and growth can be considered at many levels. First, as discussed above, RD patterns (like other dynamic mechanisms) develop according to boundary conditions, system size and system geometry (as well as reaction and diffusion parameters). It must be understood, therefore, how patterns are formed, maintained, and respond to changes in size and geometry stemming from growth (Fig. 3, top arrow). I.e., how do the biochemicals (e.g. hormones, gene regulators) responsible for the differentiation of particular tissue types form and stay in the correct regions of the plant during growth? Or, moving beyond simple maintenance of pattern, do developmental changes in tissue size or location originate from the response of the dynamic mechanism (RD) to growth? As shown in Fig. 3, however, there is also a return arrow in the growth-patterning interaction to consider: the response of growth to patterning. Plant cell growth itself involves localized chemicals, for the localized relaxation of walls or the localized delivery of new wall materials. These patterns of growth catalysts can therefore shape the plant, and be, to use Turing's title, 'the chemical basis of morphogenesis'. This section addresses some of the dynamic issues involved in the full feedback cycle of Fig. 3.
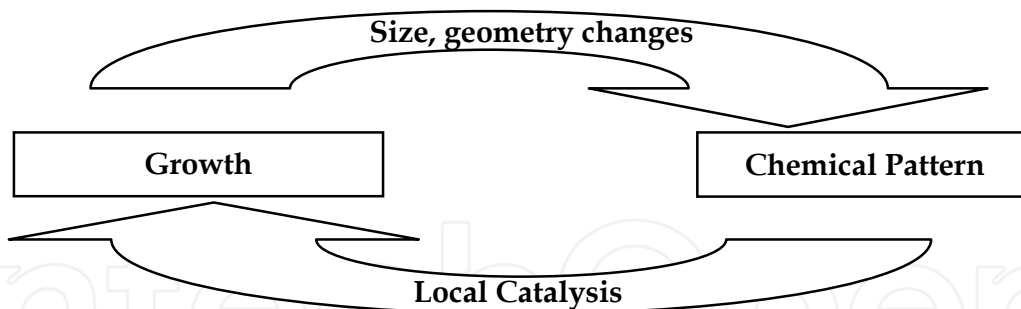
Fig. 3. The patterning-growth feedback involved in plant morphogenesis: Growth affects the types of chemical patterns which form; if the patterns are of growth catalysts, the pattern in turn affects growth.

3.1 RD response to uniform growth

The potential for RD spacing (e.g. the 1D wavelength) to produce pattern changes in response to growth has been recognized for some time. Lacalli & Harrison (1978) quantified how the fit of dominant wavelength to system size can produce increasingly complex pattern (additional morphogen peaks) as system size increases. This was developed for hemispherical surfaces in Harrison et al. (1981): Fig. 4A shows a succession of (circularly-symmetric) morphogen patterns caused by uniform growth of the hemisphere. If X were associated with growth, this sequence would correspond to successive cycles of tip extension followed by tip flattening; such cycles are seen in many events in plant
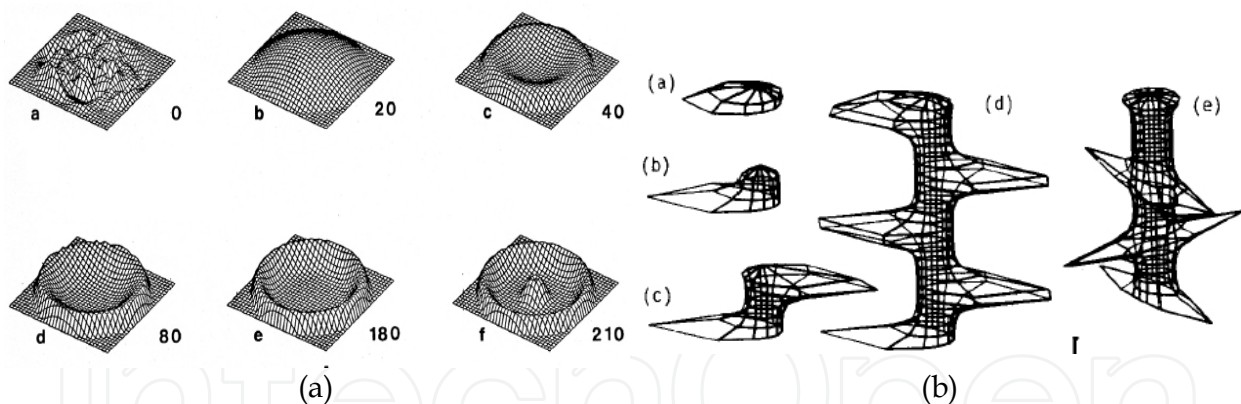

Fig. 4. RD pattern successions with uniform system growth. **A**) Brusselator computation from Harrison et al. (1981), with permission; planar projection of hemispherical shape (distance from centre is distance along a meridian). Vertical relief represents X morphogen concentration; numbers indicate computational time. As the hemisphere radius increases linearly in time, pattern forms first as a dome (b), then an annulus (c-e), then forms a new peak in the centre (f). **B**) Meinhardt's (1982) model for formation of lateral structures in a plant stalk. Computations are on a cylinder, with uniform growth produced by doubling the top cells at regular intervals. Morphogen (X) concentration is represented as lateral displacement. Inhibition (Y) flowing from established morphogen peaks (X, Y in-phase, as in Fig. 1) causes new peaks to form on opposite sides of the cylinder (a-d; 'distichous' branching). For larger cylinder radius or slower inhibitor diffusion, peaks can form at 90° angles (e; 'decussate' branching). From Meinhardt (1982), with permission.

development. Meinhardt (1982) computed RD patterning on a uniformly growing cylinder (Fig. 4B) to model different modes of lateral organ formation in plants. Both of these projects began to demonstrate the degree to which RD patterns could respond to growth and, to the degree morphogens are associated with cell growth or differentiation, for RD to determine events in plant development. But this and subsequent related work represents only the forward arrow of Fig. 3.

3.2 Full feedback: Driving growth with RD patterns

To investigate the degree to which RD pattern can determine plant shape, RD models needed to be developed in which morphogens explicitly cause localized growth (backward arrow, Fig. 3).

3.2.1 RD mechanism control of growth-rate boundaries required for morphogenesis

Harrison & Kolář (1988) first directly coupled RD and growth, with a Brusselator model for the morphogenesis of single-celled desmid algae of the genus *Micrasterias*. These cells develop elaborate stellate forms via repeated dichotomous branching (Fig. 5 H-N). Computations started with a circular initial shape in 2D, discretized into several hundred line segments. Growth per unit time was computed in proportion to the amount of *X* morphogen on the segment. The RD wave forming on the initial circle caused ripples of outgrowth in the shape; as system length increased, additional peaks (for the given wavelength) could fit in, leading to branching in pattern and shape. However, it was found that the branching morphology was transitory, due to the re-adjustment of peak positions following branching. In a sense, the RD wavelength is too good at spacing, and will erase old growth trajectories as it readjusts to the overall system length. In general terms, plant growth patterns need to be compartmentalized, such that separate structures (separate branches) develop relatively independently. Patterning may occur over the whole structure of the plant at early stages, but at later, larger stages patterning occurs in multiple active centres which are minimally coordinated. Plant shapes are composed of the integrated growth rates of the different regions of the whole organism, with shape critically depending on the placement and regulation of the boundaries between fast- and slow-growing regions. Chemical morphogenetic mechanisms, therefore, need both the symmetry-breaking power of RD, for example to account for branching phenomena, and the ability to segregate pattern-forming regions following a symmetry-breaking. To add this critical aspect to their model, Harrison and Kolář added an aging mechanism to the precursor *A* in the Brusselator. Where growth is rapid at high *X*, the cell surface is continually rejuvenated; at low *X*, growth is low and *A* decreases below a critical threshold, shutting off the pattern-forming mechanism. *X* peaks can in this way become segregated from one another, producing multiple active regions on the cell surface, each of which retains its own Turing dynamics. This mechanism succeeded in transforming RD branching patterns into branching shapes, the critical piece being a means by which the RD mechanism could control its own system boundaries; i.e. for each fast-growing *X* peak region to be able to control the size of said region.

3.2.2 Fast boundary control needed for acute branching

The Harrison-Kolář mechanism created branching morphologies, but all branches were obtuse-angled. The stellate shapes of *Micrasterias* are generated chiefly by acute branching,
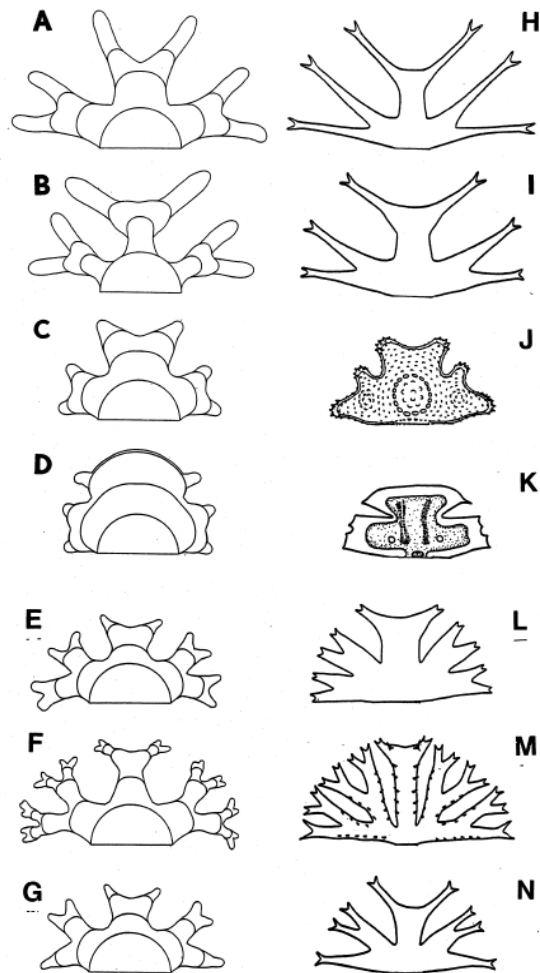
Fig. 5. RD driven growth in 2D: cellular morphogenesis of desmid algae. H-N) observed semicell outlines for six species of *Micrasterias* and one related *Euastrum* species (J). Whole *Micrasterias* are two semicells joined at their bases (bottom centre, as drawn). With mitosis, new semicells start as small 'bubbles' attached to the mature semicells; the new semicells then undergo repeated dichotomous branching to achieve the mature shape. A-G) corresponding outlines computed with a Brusselator-driven growth mechanism (Holloway & Harrison, 1999). Computations start from an initial semicircle shape (post-mitotic new semicell); outward growth occurs in proportion to local X morphogen concentration, with growth boundaries controlled by the X_{th} mechanism (see text). Outlines are shown at successive times during development of the shape, and correspond to experimentally observed developmental sequences. Differences between shapes are due to differences in X_{th} values. From Harrison (2011), with permission.

however (and acute branching is common in many other developmental phenomena as well). We approached this problem in Holloway & Harrison (1999), finding that new branches in a Brusselator would tend to spread apart, adjusting to their Turing wavelength, unless the boundary-specifying mechanism was fast enough to prevent this. The Harrison-Kolář aging mechanism was too slow. Instead of an aging threshold, we used a more direct X threshold (X_{th}), below which RD patterning shut off. This produced growth rate boundaries lateral to established X peaks, isolating fast-growing domains from one another;

but most importantly, it allowed for fast boundary creation at just-formed troughs following an X peak splitting, critical for acutely branched morphologies. With this mechanism, we were able to generate many of the diverse shapes seen across species of *Micrasterias* (Fig. 5 A-G). X_{th}, the coupling between the RD mechanism and the growth boundaries, was the key parameter for shaping the cells. Some shapes required shifting of the X_{th} over the course of development, a process which could be controlled by the cell's physiology.

More recently, there have been several mathematical studies further characterizing the dynamics of growth-patterning feedback in RD models (Neville et al., 2006; Crampin et al. 2002), including morphogen-driven growth (in 1D, without shape change). Also, see Baker & Maini (2007) for an application of 1D morphogen-driven expansion in insect wing development.

3.2.3 Pattern selection with 3D growth, a finite-element RD model

Micrasterias cells are relatively flat, with growth occurring along an edge, making them well suited to 2D modelling. Many cases of plant development, however, occur fully in 3D. What is a dichotomous branch in 2D could, in 3D, still be a dichotomous branch. But it could also be a planar section through a flattened tip or through a multiply-branched whorl structure (e.g. a flower). There are many more pattern modes available in 3D: how do RD dynamics select among them? Section **2.4** introduced some of the issues of pattern selection on fixed hemispheres. To address patterning questions for RD-growth mechanisms in 3D, we developed a finite-element model to solve RD systems on surfaces (i.e. no thickness) of arbitrary shape in 3D (Harrison et al., 2001), with growth (normal to the surface) catalyzed in proportion to local X concentration.

One of the first questions we addressed was how clefts are maintained between growing tips. In 2D, an arbitrary rule was needed to keep clefts in position and not be pulled up by fast growth in the tips. In 3D, computations demonstrated that geometry is sufficient: clefts are saddles, with a fast-growing plane through the tips orthogonally intersecting a slow-growing plane in the cleft (Harrison et al., 2001).

The finite-element model (with the X_{th} Brusselator mechanism) has allowed us to map pattern selection for large RD-driven deformations, and characterize the degree to which RD patterns can produce some of the fundamental morphogenetic sequences seen in plants. These results (Holloway & Harrison, 2008) are summarized in Fig. 6. Tip extension is one of the fundamental modes of growth seen in plants: Fig. 6A shows a computation in which an initial hemisphere has extended over ten times its original height. Tip growth depends on a balance between the X_{th} value and the X-catalyzed growth rate: X_{th} relatively too high kills off the tip; X_{th} relatively too low forms 'bubble' tips. Neither case extends. Large deformations in the computations require a continual relatticing of the finite element mesh specifying the surface. Local relatticing results in an irregular mesh (Fig. 6B), but does not affect shape or RD solution accuracy. Dichotomous branching occurs with decreased diffusivity (Fig. 6C) or increased reaction rates, selecting a higher order harmonic (c.f. higher *l* for hemispheres). The X_{th} mechanism is more effective at creating acute angles in 3D than in 2D; branching angles of nearly zero can be generated in 3D. Higher order branching, creating whorled structures, can be achieved with further decreased diffusivity (Fig. 6D) or increased reaction rates.
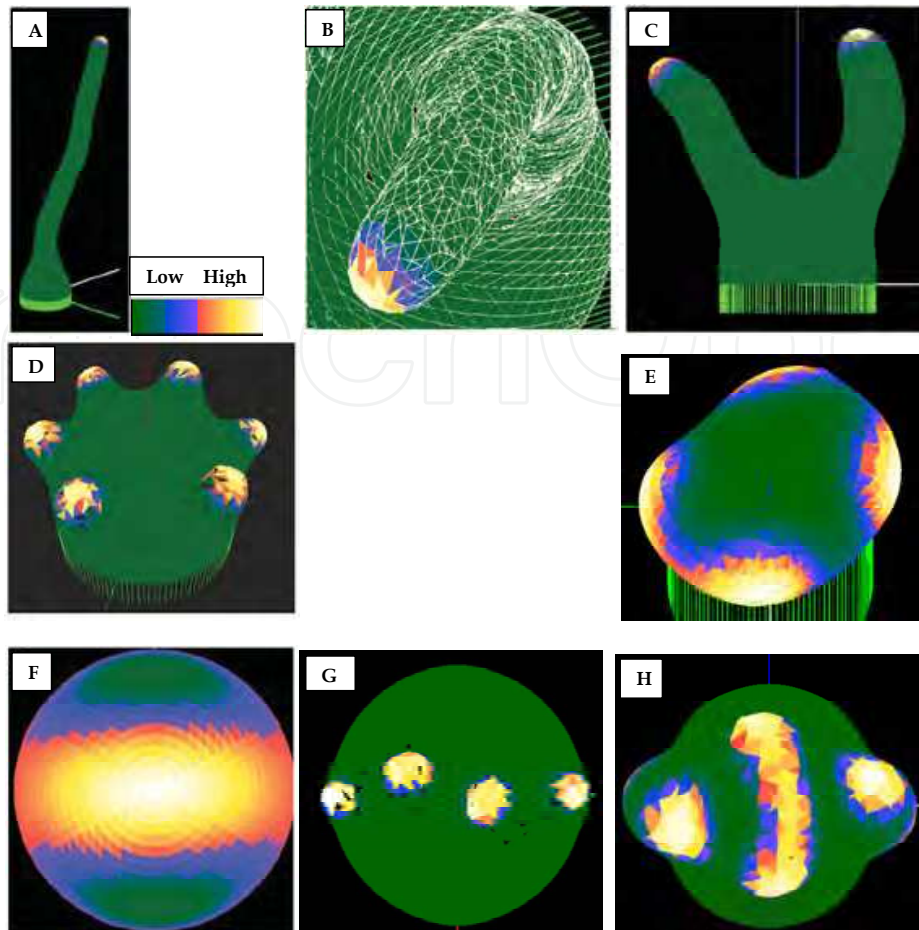
Fig. 6. Finite element computations of RD-driven growth in 3D. All shapes start from a hemisphere, growth is catalyzed according to local *X* morphogen concentration (colour-coded yellow, high – green, low). A) extending tip growth, over 10 times increase in height from original shape. B) shows the computational mesh used, and the mesh (but not shape or pattern) irregularity that develops from the local relatticing procedure. C, D) branching events of increasing complexity can be produced by decreasing diffusivity or increasing reaction rate constants (i.e. selecting higher order harmonics). E) RD patterns tend to produce successive branches in alternating planes. A chemical gradient in precursor *A* (F) can maintain a single branching plane (G), though this is more effective in wing lobes than in the polar lobe (H), as seen in real *Micrasterias* cells. Adapted from Holloway & Harrison (2008), with permission.

The flatness of *Micrasterias* allowed us to model them to good approximation in 2D. However, a deeper question might be why they are so flat. I.e. what keeps successive dichotomous branches in the same plane, when the natural tendency of RD patterns is to branch orthogonally (Fig. 6E; new peaks tend to avoid the inhibition of the old peaks; also note the orthogonal extension of the surface spherical harmonic in Fig. 2C). Lacalli (1976) discussed the idea of a 'morphogenetic template' affecting inheritance of the branching plane from the older semicell. This template could either be geometric, from the asymmetric (elliptical) shape of the isthmus between the semicells, or of a chemical nature. We tested the geometric hypothesis by running computations on ellipsoidal initial shapes (rather than hemispherical). Even with axial ratios up to 6:1 (far greater than experimentally observed), secondary branches are orthogonal: geometry is unlikely to define the branching plane for

chemical patterning. We then tested the ability for a chemical prepattern to specify and maintain a branching plane. A harmonic in the precursor A (the negative of Fig. 2C) is a natural way to define the plane (Fig. 6F). Subsequent branching events are successfully kept in this plane (Fig. 6G). The branching plane is more dominant in the wing (i.e. lower latitude) lobes than in the polar lobe (Fig. 6H). This reflects the lack of directionality of the harmonic (Fig. 6F) at the pole, and its strong gradient at lower latitudes. The polar lobe in real *Micrasterias* cells is generally the only branch which is out-of-plane; our computations indicate this may reflect the harmonics of a chemical pattern defining the branching plane.

3.3 A self-contained chemical mechanism for creating growth boundaries

Use of the X_{th} mechanism allowed us to study the interplay between patterning rates (the RD mechanism), growth rates (the rate of X catalysis of surface expansion), and the movement of patterning boundaries to either maintain pattern or break symmetry. However, though concentration thresholds are commonly invoked in developmental biology, the X_{th} mechanism does not explain where this threshold comes from: the change in pattern dynamics at the X_{th} is specified by instructions in computer code rather than by chemical dynamics.

More recently, we have devised a self-contained chemical mechanism which is capable of controlling boundary formation and movement (Harrison, Adams and Holloway, in preparation). The X_{th} mechanism defined the edges of the active Turing patterning region; our new mechanism uses a kinetic mechanism (2nd RD model) to perform this function. The full mechanism involves two coupled Brusselators, with the 1st Brusselator defining the region in which the 2nd Brusselator (which has the growth catalyst) can form pattern. I.e. Brusselator 1 controls the position of the Turing instability for Brusselator 2. Fig. 7 shows schematically how the double Brusselator mechanism operates.
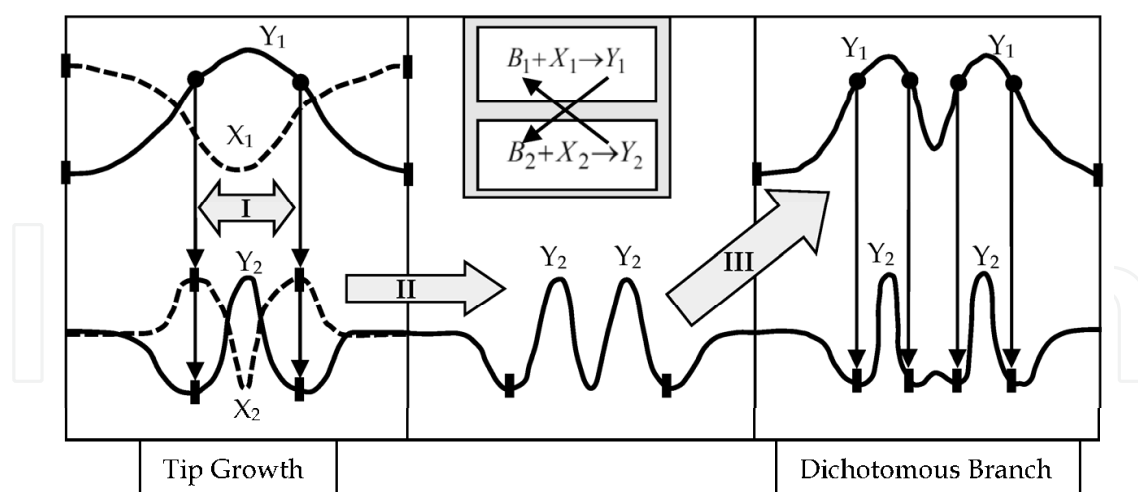

Fig. 7. Two coupled Brusselators provide a self-contained mechanism for the pattern formation, growth, and growth-boundary formation necessary for morphogenesis. Coupling occurs through the 2nd steps of the Brusselators, with Y_2 forming B_1, and Y_1 forming B_2 (grey box; top, centre). Left, Brusselator 1 (X_1, Y_1) is initiated with a single wave pattern. Vertical bars represent pattern formation boundaries. **I)** Y_1 controls threshold B_2 levels which define pattern formation boundaries for Brusselator 2 (X_2, Y_2), vertical arrows. Y_2 is the growth catalyst (Y used rather than X, since B directly controls its equilibrium value). Extending tip growth

occurs with a proper balance of Brusselator 1,2 wavelengths and rate of growth catalysis; or **II**) growth rate and wavelengths can allow peak splitting in Brusselator 2, centre (only Y_2 shown). **III**) Peak splitting in Brusselator 2 is transmitted to Brusselator 1, via $Y_2 \rightarrow B_1$ (only Y_1 shown). The two Y_1 peaks form 4 patterning boundaries for Brusselator 2 (via B_2), vertical arrows, isolating each new peak and forming a permanent dichotomous branch.

Having RD patterning ability in both stages is key to being able to complete transitions from one pattern to another (symmetry breaking): the model can stably propagate initial patterns over several-fold change in length (1D), but its key feature is that pattern changes in Brusselator 2 (due to its catalysis of growth) feed back and induce pattern changes in Brusselator 1. Since Brusselator 1 controls where Brusselator 2 operates, this defines the new growth boundaries necessary for transforming pattern into shape. Computations with this model have successfully simulated the growth patterns necessary for extending tips and for transforming tips into branches.

4. RD experiments in plants

So far, discussion has been on the development of RD theory for patterning and growth in plants, focusing on the particular kinetic issues that arise for regulating morphogenesis. Theories need experimental confirmation, however, and a number of efforts have been conducted over the years. Laboratory confirmation of Turing dynamics in the CIMA reaction (Castets et al., 1990; Ouyang & Swinney, 1991) was a major step for the RD field, but highlighted the subtleties in establishing that a particular dynamic mechanism is operating in a particular case. The CIMA reaction involves inorganic reagents in a small reactor vessel; establishing Turing dynamics in a biochemical system in vivo is a far greater challenge. But, circumstantial evidence from classical physical chemical experimental techniques can provide strong indications about the chemical dynamics underlying morphogenetic phenomena. And more recently the ability to visualize particular reactants via molecular biology techniques has allowed RD mechanisms to be identified for several cases in plant development.

4.1 Physical chemistry on algae

Beginning in the late 1970's, Harrison and co-workers began experiments on morphogenesis in the unicellular alga *Acetabularia*. Whorls of vegetative hairs (Fig. 8A) form every few weeks over a several month lifespan (in which the cells grow up to 5 cm long). Harrison et al. (1981) found that these hairs are evenly spaced. Spacing (λ) decreases with increasing temperature; this can be expected for an RD driven pattern, in which $\lambda \propto \sqrt{D/k}$ (section **2.1**), with exponential temperature dependence for rate constants (Arrhenius relation) and linear temperature dependence for diffusivities (Einstein relation). Plotting lnλ against 1/T does show a good fit to the Arrhenius relation (Fig. 8B), indicating that spacing is largely determined by reaction rates. Spacing was also found to increase for decreasing Ca^{2+} concentration (Fig. 8C; Harrison & Hillier, 1985). If spacing is proportional to the reciprocal of a rate constant and Ca^{2+} is considered as a substrate, the slope of a Lineweaver-Burk plot (1/k vs. 1/[substrate]; Fig. 8C; commonly used to characterize enzyme kinetics) can be used to calculate the Ca^{2+} binding constant. The temperature dependence of the binding constants (van't Hoff plot) can be used to calculate the entropy and enthalpy for Ca^{2+} binding. The
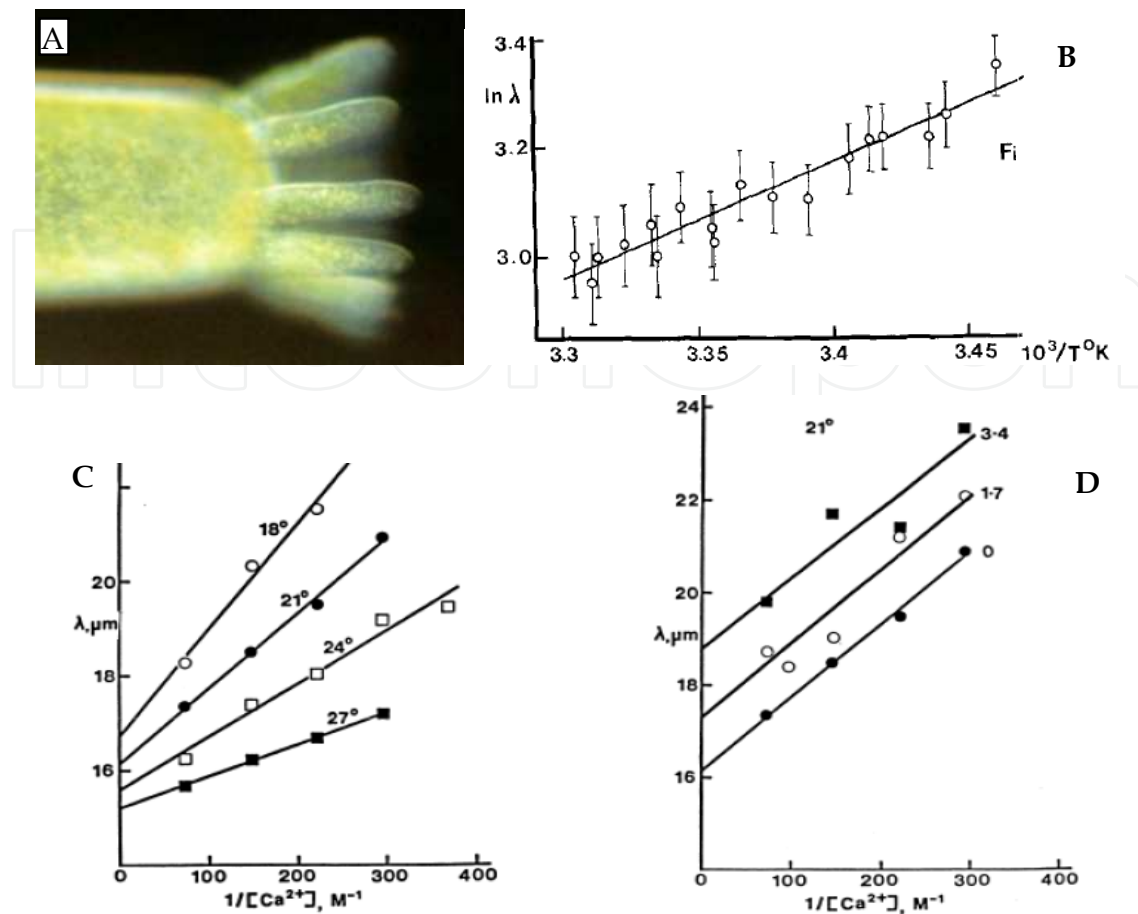
Fig. 8. Physical chemistry on algae: temperature and Ca^{2+} effects on hair spacing in *Acetabularia*. **A**) growing tip of an *Acetabularia* cell, showing a whorl of vegetative hairs. These hairs are evenly spaced, consistent with a wavelength from a pattern-forming process. **B**) The temperature dependence of the spacing (λ) follows an Arrhenius relation, suggesting the control of spacing is dominated by reaction rates (from Harrison et al., 1981, with permission). **C**) Linear plots of λ vs. $1/[Ca^{2+}]$ indicate that spacing is inversely proportional to a rate constant and Ca^{2+} activates the spacing process (reproduced from Harrison, 2011, with permission). Ca^{2+} binding constants and thermodynamics can be calculated from these slopes. **D**) EGTA (mM concentrations shown to right of lines) uncompetitively inhibits the Ca^{2+} activation (reproduced from Harrison, 2011, with permission). These relations indicate chemical kinetic control of hair morphogenesis in *Acetabularia*, consistent with the hypothesis that a membrane-bound Ca^{2+}-activated protein is a Turing morphogen.

Ca^{2+} hair-spacing effect can be inhibited with the chelate EGTA (Fig. 8D), with a concentration and temperature dependence indicating uncompetitive inhibition (Harrison et al., 1997). Harrison et al. (1988) were able to visualize membrane-bound Ca^{2+} patterns preceding tip flattening and hair morphogenesis with fluorescence microscopy. The thermodynamics and kinetics found in these studies are consistent with the hypothesis (e.g. see discussion in Harrison, 2011, Ch. 3) that a Turing morphogen controls hair spacing, and that this morphogen is a membrane bound protein activated by Ca^{2+} binding. Using classic physical chemical techniques, this series of experiments provided circumstantial evidence

that a macroscopic observable such as hair spacing was due to kinetics in the underlying chemistry, and was consistent with an RD mechanism.

4.2 Patterning of multicellular whorls: Conifer embryogenesis

Are these spacing effects seen in higher plants? von Aderkas (2002) found that embryos in a clonal population of conifer trees (larch; Fig. 9A) showed variable numbers of 'seed leaves', or cotyledons. This is a first indication of a constant spacing phenomenon (i.e., with a wavelength); Harrison & von Aderkas (2004) showed that indeed this number variability was due to embryo diameter variability, with cotyledons being evenly spaced on the tip of the embryo. Further, their data indicated that radial positioning of the cotyledons varied with the circumferential spacing, suggesting that a single pattern forming mechanism controlled both aspects of spacing. Their data is consistent with RD patterning on a flattened disc (Bessel function solutions); embryogenesis in conifers does proceed from dome-shaped to a flattened tip before cotyledons form. These patterning trends have now been corroborated in Douglas fir and spruce (Holloway et al., unpublished results), and experiments are under way, in the spirit of the *Acetabularia* experiments, to test the temperature dependence of cotyledon spacing and to find chemical reagents which can directly alter spacing, likely through hormonal growth control pathways.
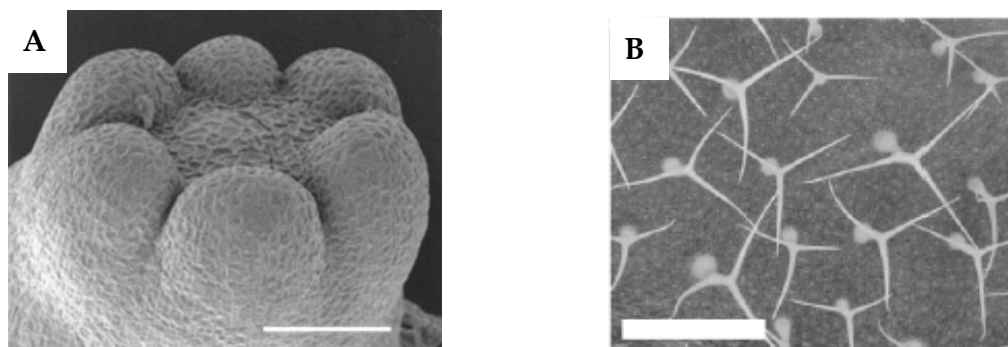

Fig. 9. RD in higher plants. **A)** Scanning electron micrograph (SEM) of the growing tip of a conifer tree embryo (larch). The cotyledons (bumps) are the first 'seed' leaves of the embryo. Harrison & von Aderkas (2004) found the cotyledons to be spaced, radially and circumferentially, by a single pattern-forming mechanism (from Harrison & von Aderkas, 2004, with permission). Work continues, to characterize whether RD acts at this developmental stage in some of the world's largest plants. **B)** SEM of trichomes (protective hairs) on the underside of a leaf of *Arabidopsis*; image from Deeks et al. (2007), with permission. Digiuni et al. (2008) found that trichomes are patterned by an RD mechanism, by quantitatively matching experimental manipulations of specific trichome genes with a dynamic (RD) model of trichome gene interactions.

4.3 RD in plant genetics

Knowledge of the genetic underpinnings of developmental phenomena have increased vastly in recent decades, with enormous strides in understanding not only the complete genomes of model organisms, but also the complex pathways regulating gene expression and tissue formation in development. With more complete sets of data on the molecules involved in development, and the tools to manipulate these molecules, it is becoming

increasingly possible to investigate the kinetics of pattern formation at the molecular level. *Arabidopsis thaliana* is the major model organism in higher plants, with the largest toolkit for genetic manipulation. Several groups have recently published work on RD mechanisms in specific genetic pathways in *Arabidopsis* development, identifying specific known molecules as Turing morphogens.

Digiuni et al. (2008) determined that trichomes, protective hairs on the undersides of *Arabidopsis* leaves (Fig. 9B), are patterned by an RD mechanism. They developed a dynamic model of the GLABRA/TRIPTYCHON reaction network known to underlie trichome formation. The network dynamics are RD, with activation occurring through catalyzed formation of an 'active complex', and inhibition occurring through several possible pairwise interactions of the constituent gene products. Matching model results to experiments allowed the authors to select a particular one of these inhibition pathways (interaction between GLABRA3 and TRIPTYCHON). This study not only investigated normal, wild-type trichome patterns, but used targeted manipulations (overexpression) of particular genes in the network to narrow down the kinetic possibilities.

As discussed in the Introduction, much of the shaping of higher plants occurs in localized zones, with the shoot apical meristem (SAM) at the top of a plant chief among these. For *Arabidopsis* and a selection of other plants, the genes expressed in the SAM and the interactions between them are very well characterized. The response of the SAM to perturbations can be very complex, however. A recent paper by Fujita et al. (2011) presents an RD model of the SAM gene network, identifying the activator as the *WUSCHEL* (*WUS*) product (i.e. protein) and the inhibitor as the *CLAVATA* (*CLV*) gene product. They invoked a 3rd morphogen for RD patterning to control the spatial extent of the SAM in the face of cell divisions, a means of approaching the growth-patterning issues discussed in prior sections. The authors were able to successfully model the complex patterning responses seen for a series of genetic knockdown and overexpression experiments, as well as for physical cell ablation and incision experiments. (Also see Jönsson et al., 2005, for an earlier RD model of SAM patterning.)

Finding RD mechanisms through detailed study of gene network dynamics is being paralleled in animal development, where for example Turing morphogens have been identified in skin patterning (e.g. Sick et al., 2006; Jung et al., 1998; Jiang et al., 1999). The molecular work in plants is reaching a point where we can begin to discuss the theoretical growth-patterning issues (section **3**) in terms of known molecules.

5. Other factors in plant morphogenesis

This chapter has focused on the development of RD theory, particularly with respect to the patterning-growth dynamics seen in plant development. RD mechanisms allow the chemical kinetic underpinnings of growth control to be explored, and experimental work is beginning to illuminate how RD operates in particular developmental phenomena. Something as complex as plant shape, however, has numerous aspects and can be approached from a number of complementary directions. Here, we will discuss newer developments in transport in plants, and the relation of chemical patterning to the mechanical properties of plant tissues in determining morphology.

5.1 Auxin transport

Auxin is a small organic molecule which has long been known to have powerful effects on plant growth. Mitchison (1981) developed a model for auxin's role in vein formation in leaves, in which the flow of auxin is autocatalytic: auxin flow in a particular direction will reinforce flow in that direction, leading to a 'canalization' and formation of veins. In more recent years, discovery of the auxin-transporter PIN genes has filled in much of the molecular biology of auxin transport (Friml, 2003). PIN genes are involved in cellular intake and efflux of auxin, and have been found to be active from embryogenesis to apical meristem activity. PIN localization is positively related to auxin. Models exist for this relation being proportional to either auxin concentration or to auxin flux (as in Mitchison's model), but the result of either is to create auxin flows *up* a gradient, as opposed to diffusion (down a gradient). A number of models have been developed for pattern formation via auxin transport in apical meristems, which have had a high degree of success in describing the morphogenesis of lateral structures (e.g. leaves) from the SAM (i.e. phyllotaxis; de Reuille et al., 2006; Jönsson et al., 2006; Smith et al., 2006) and growth patterns in the root apical meristem (Grieneisen et al., 2007; Laskowski et al., 2008). For further discussion, see Braybrook & Kuhlemeier, 2010, and references therein (e.g. Heisler & Jönsson, 2007; Kramer, 2008; Smith & Bayer, 2009). Auxin modelling and its close matching to newly discovered molecular biology has had a great impact on the use of mathematics to understand patterning and growth in plant development. In terms of pattern formation, while auxin flux and diffusion are different, they serve a similar purpose in introducing a spatial dependence to the dynamics. Mathematical analysis is far more developed for RD models at this point, though it is likely that pattern-forming dynamics in auxin transport models will be found to be similar. Due to the maturity of the RD mathematics, it is immediately more promising for elucidating the growth-patterning-boundary formation dynamic issues discussed in section **3**. But the auxin work shows that a diversity of transport mechanisms are likely significant in plant development, and the mathematics must keep abreast of differences and commonalities between the various types of transport.

5.2 Plant mechanical properties

While the focus of this chapter, and of genetic research into morphogenesis, is on the chemical pattern formation underlying growth, plants have unique mechanical characteristics which can also affect form.

5.2.1 Mechanical approaches to morphogenesis

Mechanically, plant cell shapes balance a high internal turgor pressure against the complex macromolecular structure of the cell walls. At relatively low turgor, the wall can act approximately elastically; at high pressure, deformation can be described as a viscoplastic flow (Dumais et al., 2006). Mechanical theories have been developed mathematically for rotationally symmetric shapes such as growing tips (Dumais et al., 2006; Ben Amar & Goriely, 2005), but the treatment of non-axisymmetric shapes, such as clefts and branches, remains unsolved and very challenging. The cell wall macromolecular structure also creates anisotropic mechanical properties, with, for example microtubule 'hooping' causing far greater extensibility in one direction than another (e.g. Green and Lang, 1981; Green et al.,

1998). The complex interplay between microtubule arrangements and cellulose wall structure has been explored in depth in recent years (e.g. see Paredez et al., 2008), for instance illuminating how microtubule arrangements dynamically control cell division planes (Besson & Dumais, 2011), which can affect growth directions. A recent growth model involving cellular-scale microtubule orientation successfully modelled the response of the apical surface to localized laser ablation experiments (Hamant et al., 2008). This is a very active area and the interested reader is directed to the present references for further exploration of the mechanical aspects of morphogenesis.

5.2.2 Combining mechanics and chemistry

Chemical models, involving genes or other biomolecules - whether RD, auxin-transport, or other - have largely been studied apart from mechanics, or the consideration of forces. This is generally justified since gene expression and pattern formation frequently precede shape change. At the same time, many purely mechanical models have had success describing a range of morphogenetic phenomena (e.g. Green & Poethig, 1982; Linthilac, 1984). It is likely that most phenomena in plant morphogenesis have contributions from both mechanical and chemical dynamics. Modelling needs to proceed in this direction, though not at the expense of fully understanding the dynamics of purely chemical or purely mechanical mechanisms. Chemistry can affect mechanics, through the local catalysis of wall changes (softening, addition of new material) which affect extensibility and allow internal turgor to push surface out (for instance see Zerzour et al., 2009, on wall softening preceding tip growth). But mechanics can also affect chemistry, for example stretch-activated Ca^{2+} channels have been found in tip growth (e.g. Kroeger et al., 2008), and there is evidence that stress can activate genes (e.g. Desprat et al., 2008, in animals). More complete models of morphogenesis will need to combine chemical dynamics with mechanics (see, for example, the recent synthesis for the SAM in Besnard et al., 2011); in the first instance to predict correct deformations for chemically catalyzed growth, but ultimately to account for mechanical effects on chemistry. Spontaneous pattern formation in mechanochemical dynamics should also be considered; Oster and co-workers developed and analyzed such a model in which Ca^{2+} effects on cytoskeleton were autocatalytic, but the spatial dependence of the patterning was through mechanical stress (Oster, 1983; Oster et al., 1983). See Howard et al. (2011) for a recent discussion of mechanical stress as the spatially dependent component of reaction-based patterning. Vast amounts are now known about the interplay between cytoskeleton chemistry and plant cell morphogenesis, with scope for extensive development of appropriate mathematical mechanochemical models (e.g. see review by Szymanski & Cosgrove, 2009; model of Jilkine et al., 2007). At a continuum level, focusing on tissue-wide interactions between patterning and deformation, recent morphogenetic models have combined chemical gradients with accurate mechanical representations of plant tissues (Kennaway et al., 2011; Matthews, 2002). With mathematical analysis of a combined mechanochemical model, Shipman & Newell (2005) have been able to provide an explanation for phyllotactic patterns, for example in sunflower heads. Such work opens the way for a more complete exploration of the pattern forming dynamics of integrated mechanochemical systems; i.e. can we proceed from a theoretical understanding of patterning via RD kinetics, combine this with continuum mechanics, and begin to understand how these interact in real plant morphogenesis?

6. Conclusion

This chapter has explored the development of RD theory and the role of RD dynamics in plant development. RD is a well-developed kinetic theory for spontaneous spatial pattern formation, and as such provides a framework for understanding how the biochemical patterns underlying embryonic development may be established. The theoretical challenge for applying RD to plant development is to understand how RD patterning operates in growing systems, and, if the localized growth catalysis responsible for morphogenesis is patterned by RD, what dynamics arise in the full feedback of RD-driven growth. A critical part of transforming chemical pattern into shape is the control of boundaries between fast- and slow-growing regions. Sections **3.2** and **3.3** presented potential mechanisms by which this can occur. Because their pattern-selection can be well-characterized in terms of reaction and transport rates, size and geometry, RD-growth models are particularly well-suited to describing and understanding developmental sequences which involve symmetry-breaking, for instance the tip growth to branching transition.

In addition to providing a theoretical framework for problems in patterning and growth, experimental evidence is accumulating for RD mechanisms in specific cases of plant development, with the molecular identification of Turing morphogens. Plant shapes are also affected by the unique mechanical properties of their cell walls. Ultimately, more complete understanding of how shapes are determined will require a synthesis of chemical and mechanical theories, but this synthesis will only be clear if both theories are fully characterized, so that the contributions of each, and the properties emergent from their interaction, are properly understood.

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8. References

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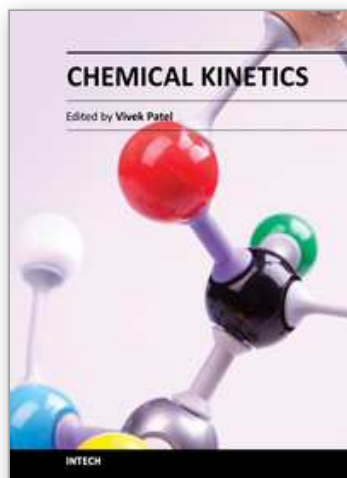
Chemical Kinetics

Edited by Dr Vivek Patel

Chemical Kinetics relates to the rates of chemical reactions and factors such as concentration and temperature, which affects the rates of chemical reactions. Such studies are important in providing essential evidence as to the mechanisms of chemical processes. The book is designed to help the reader, particularly students and researchers of physical science, understand the chemical kinetics mechanics and chemical reactions. The selection of topics addressed and the examples, tables and graphs used to illustrate them are governed, to a large extent, by the fact that this book is aimed primarily at physical science (mainly chemistry) technologists. Undoubtedly, this book contains "must read" materials for students, engineers, and researchers working in the chemistry and chemical kinetics area. This book provides valuable insight into the mechanisms and chemical reactions. It is written in concise, self-explanatory and informative manner by a world class scientists in the field.

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