Computational Approaches to Developmental Patterning

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the mRNA X and mRNA Y corresponding to protein X and protein Y, respectively. Although protein X and protein Y are coordinated for all four motifs in Fig. 3, this is not the case for their mRNA levels. This can be explained by the disparate time scales of mRNA and protein. Fast-degrading mRNA may exhibit fluctuations with a broad frequency bandwidth. Conversely, slow degradation of proteins filters out fast fluctuations but keeps slow fluctuations. Constitutively expressed mRNA X has both fast and slow fluctuations, but protein X only transmits the slow fluctuations downstream. The result is that the dynamics of mRNA X and mRNA Y are dominated by uncorrelated fast fluctuations, which overshadow their correlated slow fluctuations. On the other hand, protein X and protein Y only contain the better-correlated slow fluctuations. That is, two mRNA species can be mostly uncorrelated with one another, yet produce protein in a coordinated fashion. Gandhi *et al.* (*18*) observed such a circumstance in budding yeast, when they found very little correlation between pairs of transcripts that encode coordinated proteins of the same protein complex, including proteasome and RNA polymerase II subunits. They even found correlation lacking in two alleles of the same gene. In a related study, Taniguchi *et al.* (*27*) analyzed more than 1000 genes in *E. coli* and measured both mRNA and protein copy numbers in single cells. They found that for most genes, even the numbers of mRNA and protein molecules were uncorrelated. These studies suggest that understanding of regulatory phenomena requires one to consider regulation at both the mRNA and the protein level.

From these studies, it is now clear that variability in single-cell measurements contains a wealth of information that can reveal new insights into the regulatory phenomena of specific genes and the dynamic interplay of entire gene networks. As modern imaging techniques begin to beat the diffraction limitations of light (*28*) and flow cytometers become affordable for nearly any laboratory bench (*29*), we find ourselves in the midst of an explosion in single-cell research. With the advent of single-cell sequencing (*30*, *31*), it might be possible to determine the full transcriptome of many single cells in the near future and to determine the full expression distributions and correlations for all genes in the genome. We expect that the approaches described in this review, which have been pioneered with the model microbial systems, will be readily applied to mammalian cells and tissues (*32*, *33*).

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REVIEW

Computational Approaches to Developmental Patterning

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Computational approaches are breaking new ground in understanding how embryos form. Here, we discuss recent studies that couple precise measurements in the embryo with appropriately matched modeling and computational methods to investigate classic embryonic patterning strategies. We include signaling gradients, activator-inhibitor systems, and coupled oscillators, as well as emerging paradigms such as tissue deformation. Parallel progress in theory and experiment will play an increasingly central role in deciphering developmental patterning.

Animal and plant patterns amaze and perplex scientists and lay people alike. But how are the dynamic and beautiful patterns of developing embryos generated? Used appropriately, theoretical techniques can assist in the understanding of developmental processes (*1*–*5*). There is considerable art in this, and the key to success is an open dialogue between experimentalist and theorist. The first step in this dialogue is to formulate a theoretical description of the process of interest that captures the properties and interactions of the most relevant variables of the system at a level of detail that is both useful and tractable. Once formulated, the second step is to analyze the theoretical model. If the model is sufficiently tractable, it may be possible to understand its behavior with "pencil-and-paper" analysis and compare this analytical solution directly with experimental data. Very often, however, the number of variables and the complexity of their interactions preclude this approach, and the behavior of models must be solved or simulated by using computers in order to be understood and compared with data. This combined approach, which we refer to as computational biology, has become popular recently with the availability of powerful computers and increasingly sophisticated numerical algorithms.

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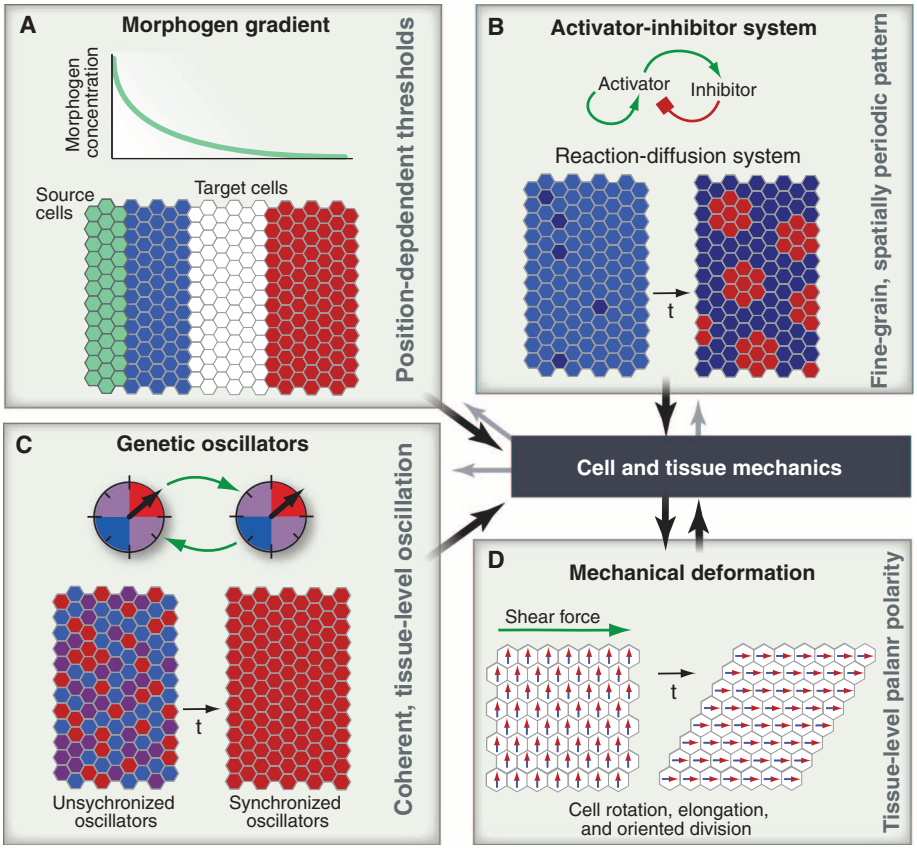

Fig. 1. Patterning strategies. (**A**) Signaling gradients supply global positional information. Horizontal axis is position within target tissue. Morphogen-producing cells are green; cells in tissue take identities (blue, white, and red) according to morphogen concentration. (**B**) Activator-inhibitor systems incorporate local positive and negative feedbacks to generate pattern. Distinct cell types are in red and blue. (**C**) Synchronization of genetic oscillators allows a tissue to generate a coherent temporal rhythm for patterning. In these snapshots, the phase of each oscillating cell is given by its color, which changes over time. (**D**) Tissue deformation can drive patterning reactions. Downstream of patterning information, the dynamic physical properties of tissues drive the morphogenesis of the embryo. *t*, time.

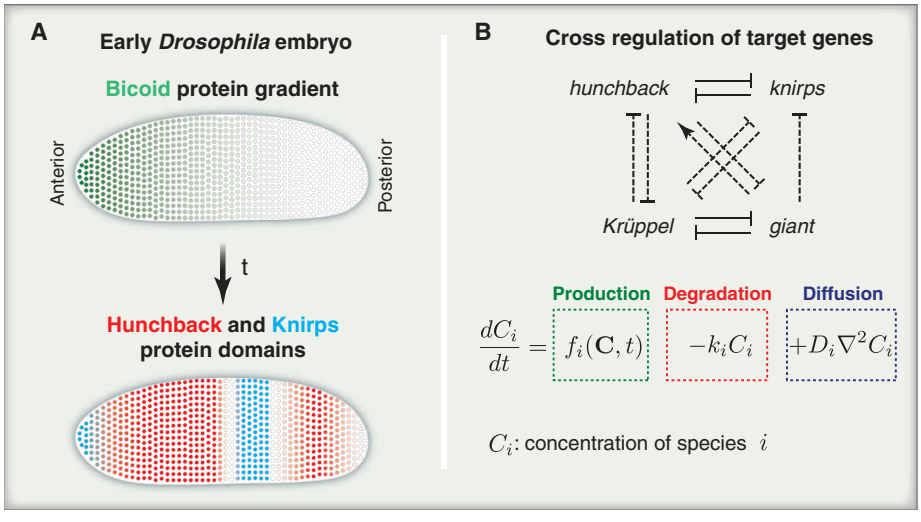

Fig. 2. Patterning with signaling gradients. (**A**) Schematic of early fruit fly embryo showing the maternal gradient of Bicoid protein at cycle 13 that directs the formation of precise target gene domains such as *hunchback* and *knirps*. (**B**) Proposed gene regulatory network showing cross-regulation of target genes (*9*). The four genes are also under control of Bicoid and other players. *t*, time.

In this Review, we hope to introduce scientists familiar with computational methods (geeks) to a selected set of interesting developmental problems (Fig. 1) and to illustrate to developmental biologists (nerds) a selected set of powerful tools. We focus on recent studies investigating four developmental patterning strategies: (i) gradients of signaling molecules released from localized source cells that guide global patterns across target cell populations (Fig. 1A). This external control contrasts with self-organizing strategies within the cell population that use local interactions, such as (ii) activator-inhibitor mechanisms (Fig. 1B) and (iii) the synchronization of cellular oscillations (Fig. 1C). (iv) Mechanical deformations can also change the pattern of a cellular population (Fig. 1D). Although models are often useful in explaining and predicting developmental phenomena, the eventual fate of a given model is to be proven wrong and then modified or replaced, as illustrated in the companion article on cell polarity by Mogilner and colleagues on page 175 of this special issue. Perhaps the greatest impact of computational approaches in developmental biology right now is to force hypotheses to be precisely stated and to stimulate corresponding new quantitative experiments to test them.

Patterning with Signaling Gradients

Morphogens are diffusible signaling molecules that can activate target genes in a concentration-dependent manner. During development, morphogen gradients are established across tissues, diffusing away from localized sources (Fig. 1A). It has been proposed that cells read morphogen levels to determine their position within the tissue and differentiate accordingly (*6*), and there is good evidence that morphogen gradients can direct cell differentiation in target cells. How these gradients are formed, and whether they are sufficient to control differentiation in very precise domains, are open questions that have benefited from computational approaches.

An important model system for studying these questions is the early embryo of the fruit fly *Drosophila*, in part because its geometry and symmetry simplify description and quantitation (Fig. 2A). One of the maternally deposited cues that breaks the symmetry along the embryo's long axis is *bicoid* mRNA, which is present only in the anterior pole. Bicoid protein is translated and transported (*7*), creating within an hour an exponentially decreasing concentration gradient over several hundred micrometers along the embryo's axis. This gradient directs the formation of precise domains of four target genes—among them *hunchback*—that establish the first segments of the future fly body (Fig. 2A). Given the stochastic nature of gene expression, discussed in the companion article by Munsky and colleagues on page 183 of this special issue, morphogen concentration is expected to fluctuate, both over developmental time and from one individual to another. The stunning precision in the position of the boundaries of the segmented out-

put pattern that is found despite these fluctuations puzzles both nerds and geeks. The field has wrestled with the issue of whether this precision can be achieved through the Bicoid gradient alone, or whether other mechanisms are required.

Contributing to this debate, recent papers by Manu *et al*. (*8*, *9*) formulated the interactions between four target genes downstream of the maternal gradients in the early embryo using a gene regulatory network (GRN) model, in which each variable represents the quantity of a molecular species (Fig. 2B). One of the limitations of GRN models is that great experimental effort is often required to estimate relevant values of the model's many parameters in the embryo. Parameters for this *Drosophila* segmentation model were obtained computationally by finding those combinations that best reproduced a time series of quantitative spatial gene expression data from the embryo. The model hinted that cross-regulatory interactions between target genes in the GRN reduce the variability in the position of their expression domains.

One problem in understanding a model is that as the parameters vary, the general dynamic behavior of the system can change dramatically. These changes are called bifurcations, and using powerful tools from dynamical systems theory (*10*), Manu *et al*. (*9*) performed a bifurcation analysis of the model to identify the fundamental behaviors that the system can display over a given set of realistic parameter values. The model predicts that cells in the anterior of the embryo select a stable state of the dynamics, and the concentrations of targets change as Bicoid levels drop. In the posterior of the embryo, the system never reaches a stable state because gastrulation happens first. Describing the simple behaviors of a complex regulatory network in this compact way is appealing because it makes similarities to other regulatory systems clearer and also makes falsifiable predictions about distinctive behaviors that can be experimentally tested.

Fluctuations in gene product levels generate molecular noise that limits the precision of signaling gradients and also degrades the targets' outputs. This problem can be formulated precisely by using the tools and concepts from information theory—originally used in engineering—which quantifies the flow of information through communication channels. A key concept is the mutual information between two variables, such as, for example, Bicoid and Hunchback levels. An elegant computation by Tkačik and Walczak used existing precise measurements of morphogen levels (*11*) to estimate the mutual information between Bicoid and Hunchback (*12*). On the basis of their result, they argued that if similar results hold for the other target genes under Bicoid control, the combined information conveyed by the four genes would be enough so that each of the roughly 100 rows of nuclei could unambiguously determine its position along the *Drosophila* embryo. To test this hypothesis, combined high-quality spatial expression data for the other target genes in the system will be necessary. Thus, information theory is emerging as a potentially powerful tool to quantify information transmission in developmental GRNs. As yet, it is unclear whether the *bicoid* gradient is sufficiently precise to instruct the precise boundaries of its target gene domains, or whether other mechanisms are necessary, but computational biology has a central role in this discussion.

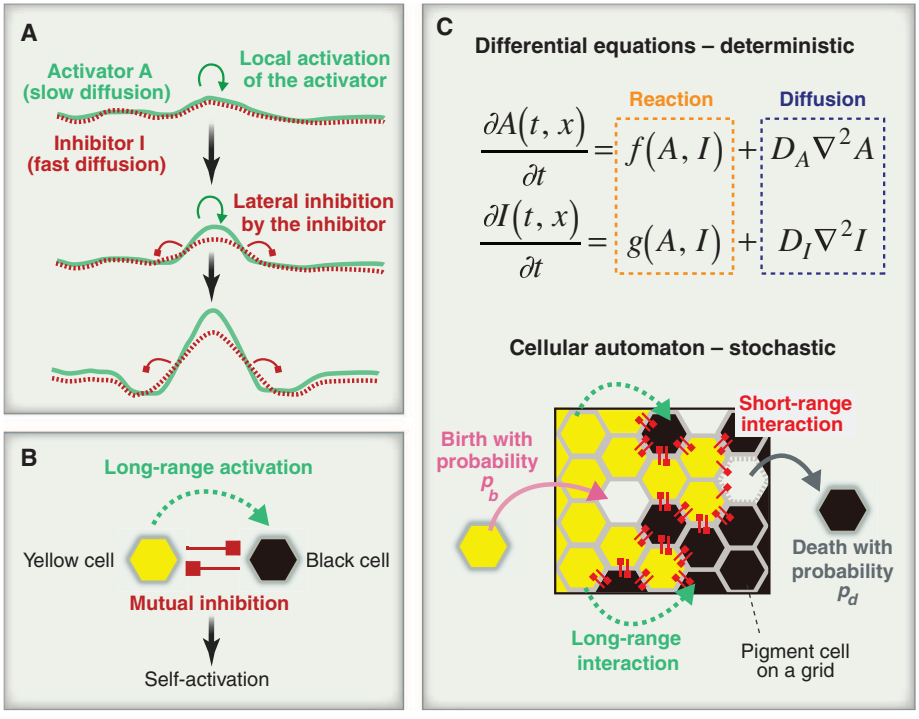

Fig. 3. Patterning with activator-inhibitor systems. (**A**) Local activation and lateral inhibition generates spatially heterogeneous patterns. (**B**) Interactions between black and yellow pigment cells produce Turing patterns in zebrafish skin. Mutual inhibition between them functions as self-activation for the yellow cells. Each yellow cell activates distant black cells. Therefore, inhibition of the yellow cell by the black cell works as a lateral inhibition. (**C**) Different modeling approaches to spontaneous pattern formation.

Patterning with Activator-Inhibitor Systems

Cells in a morphogen gradient use the local level of an externally provided signal to produce patterns (Fig. 1A). However, patterns such as spots and stripes can arise spontaneously from entirely local interactions. In 1952, Alan Turing proposed a reaction-diffusion (RD) mechanism to explain spontaneous pattern formation without signaling gradients (*13*). Specifically, he considered two diffusing chemical components, an activator and an inhibitor (Figs. 1B and 3A). By self-activation, the activator can locally increase its concentration (Fig. 3A). The activator in that region produces the inhibitor, which suppresses the activator in surrounding space because of faster diffusion. As a result, local peaks of activator self-organize from the almost homogeneous starting state, leading to the spontaneous formation of spatial patterns, such as stripes and spots in a two-dimensional (2D) space (so-called Turing patterns) (Fig. 1B).

Subsequently, RD systems have been considered to play important roles in spontaneous pattern formation (*14*, *15*). Although spatial structures very similar to simulated Turing patterns have been observed in development, until recently there was scant evidence showing that the Turing mechanism causes these structures. Indeed, conceptually elegant RD models of the *Drosophila* segmentation process introduced above proved to be entirely wrong (*16*), and this failure may even have left some developmental biologists wary of further theoretical efforts. However, identification of interaction rules and key molecular components in several putative RD systems (*17*, *18*) now suggests the potential of a long-awaited experimental verification of these ideas.

Skin pattern formation in fish has long been a candidate for patterning by use of the Turing mechanism (*19*). To identify key interaction rules in the system, Nakamasu *et al*. studied stripe formation in zebrafish skin (*20*). These black and yellow stripes are self-organized over 3 weeks by local interactions between black and yellow pigment cells, which fulfill the condition for Turing patterns (Fig. 3B). To confirm that the experimentally observed interactions between pigment cells can generate stripes, the authors first used deterministic partial differential equations to model cellular dynamics. However, because the width of each stripe in zebrafish is only ~10 cells, Nakamasu *et al*. pointed out that stochastic effects caused by smaller cell numbers might prevent stable stripe formation. In that situation, it would

be a better formulation to explicitly describe stochastic behaviors of each single pigment cell, such as birth, movement, and cell death. The authors developed a cellular automaton-based model (Fig. 3C) that includes the observed pigment cell interactions to study the robustness of stripe patterns against stochastic effects. Although such detailed models usually include several parameters not measured experimentally, simulations of the cell-based model produced patterns similar to those obtained by the deterministic model and observed on the zebrafish skin. Combining investigations of the molecular and cellular basis of the cellular-level interaction rules (*21*) with further theoretical studies should reveal whether this is indeed a Turing system.

Gradient patterning strategies can also be formulated as RD systems because gradients can arise from diffusion of morphogens, and the pattern emerges due to reactions that involve these morphogens. However, the different length-scales involved in activator-inhibitor systems give rise to qualitatively different patterns, which are local in nature. This is an example of how very different developmental patterning strategies can be described by using similar model formulations.

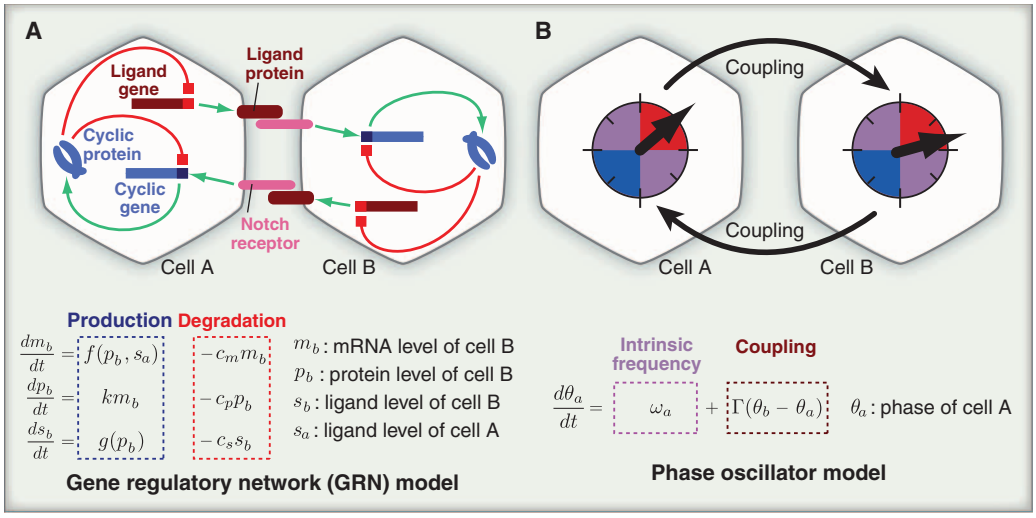

Fig. 4. Patterning with genetic oscillations. (**A**) Cyclic gene expression oscillates in individual cells because of a negative feedback loop, and oscillations are coupled to neighbor cells through the Notch pathway. (**B**) The mutual effects of cellular oscillators can be described by models of coupled phase oscillators.

Patterning with Genetic Oscillations

The growing body axis of all vertebrate embryos is rhythmically and sequentially subdivided into segments. For example, in the zebrafish embryo the multicellular segments are ~50 μm long and form with a periodicity of 30 min. Inspired by such clock-like regularity, Cooke and Zeeman proposed the Clock and Wavefront model in 1976 (*22*). In this model, a biological clock ticks at the posterior of the elongating embryo, and the distance advanced by a wavefront along the embryonic axis during a cycle of the clock sets the length of a forming segment. More than 20 years later, the model was revived with the discovery of genetic oscillations in the chick embryo (*23*). This segmentation clock appears to be a tissue-level rhythmic pattern generator (*24*), in which a population of progenitor cells behave as coupled oscillators, self-organizing a collective rhythm through mutual synchronization (Fig. 1C).

A clue to the existence of such a synchronized cell population came from zebrafish mutants that disrupt Delta-Notch intercellular signaling, in which coherent oscillations and segmental patterning are gradually lost (*25*). The current hypothesis is that in the wild-type embryo, Delta ligands under the control of a single-cell oscillator activate Notch receptors in the membrane of neighboring cells, and these receptors coordinate oscillating gene expression in the receiving cell (Fig. 4A). Without Delta-Notch signaling, the single cells' oscillations gradually lose synchrony. The plausibility of this synchronization hypothesis has been studied by using GRN models showing that the Delta-Notch mechanism described above could keep neighboring cells oscillating in synchrony (*26*, *27*).

Given the previously mentioned difficulty of determining GRN parameters from embryos (*28*), an alternative and complementary model formulation is to use an effective theory with variables that represent processes for which there is a particular interest or a possibility of experimental comparison. For the segmentation clock, this approach has been applied to investigate the synchronization hypothesis by using theories based on coupled phase oscillators (Fig. 4B). In a phase oscillator model, the variables corresponding to oscillating molecular species are substituted by a single variable: the phase of the oscillation cycle, which advances in time with a given intrinsic frequency. The effect of Delta-Notch signaling is captured by a coupling function that speeds up or slows down a cellular oscillator depending on the phase of neighboring cells. Phase oscillator models do not offer direct insight about dynamics of individual molecular species, but their simplicity allows powerful insights about system-level dynamics from paper-and-pencil analysis. Furthermore, they allow a direct fit to experimental data relying on a few coarse-grained parameters such as the period of the oscillations (*29*).

Using a phase oscillator model, the synchronization problem of the segmentation clock was formulated as a competition between noise and the intercellular coupling that keeps cells in synchrony (*30*). Together with quantitative experimental disruptions of Notch signaling in zebrafish, the model allowed estimation of the noise level and coupling strength relevant for the tissue-level synchrony of the clock. Coupling involves the new synthesis of Delta ligand every cycle (Fig. 4A), and to represent the anticipated duration of the ligand-receptor mechanism, Morelli *et al.* (*29*) included explicit time delays in the coupling function of a phase oscillator model. This delayed coupling theory made the prediction that changing the coupling strength could change the clock period and motivated the study of the dynamics of Notch mutants. Quantitative time-lapse measurements of segmentation period and analysis of clock gene-expression patterns in mutants matched the theoretical predictions and so identified the first candidates for segmentation clock period mutants (*31*).

Although these studies have revealed some surprising insights into the segmentation clock's dynamics, most quantitative data used to test models have come from static images (*28*, *31*), and the desynchronization of the clock has not been directly observed. The advent of new techniques to observe cyclic gene expression in vivo (*32*) will allow key assumptions of the existing models to be directly tested.

Patterning with Mechanical Deformations

We complete our roster of patterning mechanisms with a recently discovered case driven by tissue deformations. An apparently simple behavior for an epithelial sheet is to elongate along one axis while shrinking along the orthogonal axis. During *Drosophila* development, the wing blade epithelium stretches into the familiar elongate wing shape, and each of the hairs protruding from the wing cells points distally—an example of planar cell polarity (PCP) patterning (Fig. 5A). Although proximo-distal gradients of PCP pathway components have been observed, they are not sufficient to produce the final wing hair polarity (*33*). Examination of cell shapes and trajectories from time-lapse movies shows that sharp contraction of the neighboring hinge region exerts anisotropic tension on the wing blade (*34*). Over a period of 15 hours, the blade deforms with a shear gradient arising from the cellular flow in the tissue.

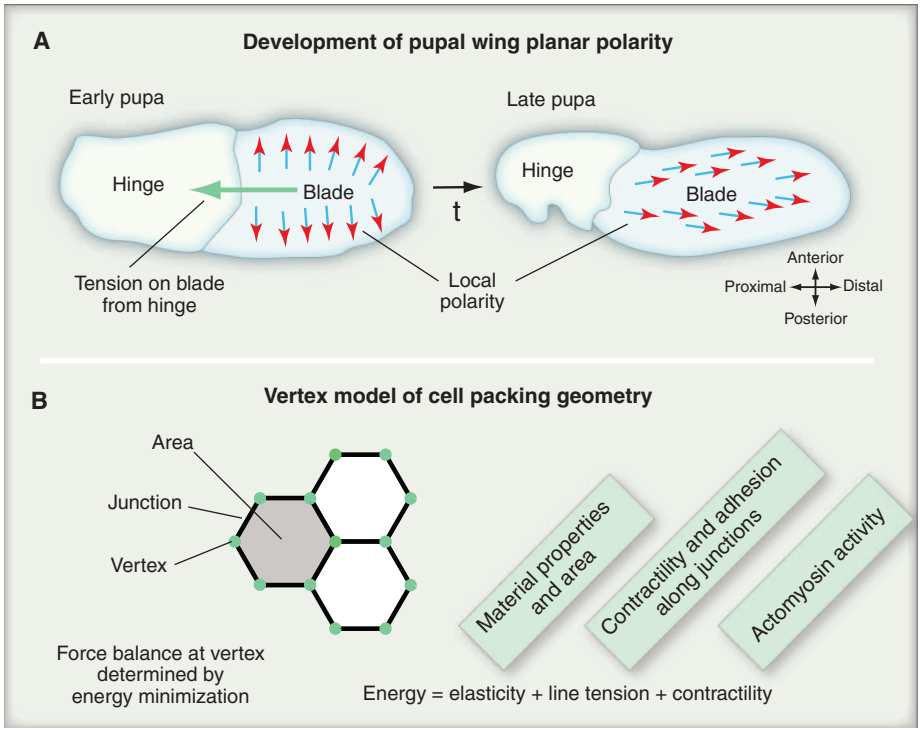

Fig. 5. Patterning by mechanical deformation. (**A**) Overview of *Drosophila* wing development during pupariation, when the wing blade elongates and proximo-distal planar polarity is established. (**B**) Schematic of the vertex model used to calculate stable cell-packing geometries.

Aigouy *et al*. explored the role of tissue shear in aligning the axis of cellular polarity with the proximo-distal axis of the wing blade by formulating a 2D vertex model of epithelial cell shape (Fig. 5B) (*35*), incorporating an effective description of the local recruitment of complementary PCP molecules to apposing cell boundaries (*34*). This new model predicts that polarity is reoriented by local rotation and cell flow–induced shear. Simulations show that shear associated with oriented cell division, proximo-distal cell elongation, and cell rearrangement also contribute to the alignment of cell polarity with the long axis of the wing. Future work can investigate how the 3D baso-lateral surfaces of the epithelial cells in the wing affect this description, and how the PCP protein complexes involved dynamically reorganize during cellular rearrangement. Thus, remarkably the final planar cell polarity of the completed wing may be a direct consequence of the externally applied stresses responsible for its extension, via simple physical rules such as those that determine molecular polarity in liquid crystals (*36*).

In this Review, we have mainly discussed chemical aspects of pattern formation as separate from downstream mechanics of morphogenesis (*37*, *38*). Turing already wondered whether a closer linkage might be at work (*13*), and it seems timely to reconsider development as having integrated mechanochemical aspects (*39*). For example, motivated by recent findings on cell cortex dynamics in the nematode *Caenorhabditis* (*40*), Bois *et al*. studied pattern formation in an active fluid in which mechanical contraction causes the flow of reactive chemical species (*41*). This theoretical analysis showed that an active fluid extends the parameter space in which classical Turing systems generate spatial patterns. To what extent continuous feedback between chemical and mechanical processes also underlies tissue-level phenomena in development is not yet clear, but it may be widespread.

Outlook

With the wide range of approaches in use, how should the developmental biologist select the appropriate modeling and computational methods? And where should the computational scientist dig for interesting problems in the vast field of developmental biology? Previous reviews have given multiple examples and advice (*1*–*5*). Here, we argue that the first step is key: The level of description and model type should be matched to the best available data. The data should be quantitative, accurate, and precise, and the model should make falsifiable predictions. Although some researchers are fluent in both domains, most often a successful computational approach to developmental biology will involve a long-term dialogue between experts across disciplinary boundaries. As advances in imaging and molecular methods increase experimental resolution and complexity, corresponding theoretical and computational developments will be required to assemble the puzzle. This co-dependence should generate a wealth of new opportunities for geeks and nerds alike.

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