DEVELOPMENTAL BIOLOGY

Gradient Scaling and Growth

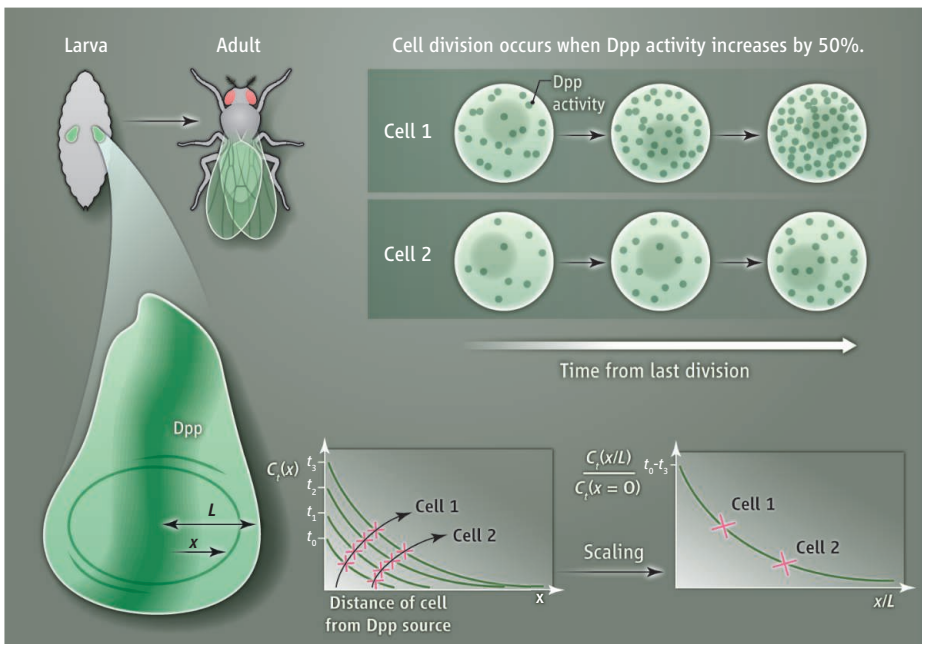
Tissue growth is controlled by the temporal variation in signaling by a morphogen along its concentration gradient.

Loïc Le Goff and Thomas Lecuit

What determines the final size of an animal? Secreted molecules called morphogens control tissue and organ growth during development (*1*). As morphogens diffuse away from their source, a concentration gradient forms. Target cells "read" the local concentration and activate genes involved in differentiation. One such morphogen is Decapentaplegic (Dpp), a member of the transforming growth factor–β family that controls fly (*Drosophila melanogaster*) development (*2*–6). Paradoxically, although Dpp forms a concentration gradient, it promotes seemingly uniform growth across its target tissue. Earlier studies argued that the slope rather than the concentration of the Dpp gradient may control growth (*7*), or that cell proliferation is modulated by mechanical constraints (*8*, *9*). On page 1154 of this issue, Wartlick *et al*. (*10*) propose instead that cells control growth by computing the relative temporal variation in Dpp activity.

Wartlick *et al*. draw on both quantitative observations and theory to make three fundamental observations about the dynamic nature of the Dpp morphogen gradient. The first is that the gradient scales with tissue size, an issue that has long been unresolved. The authors examined the Dpp gradient in the *Drosophila* larval wing imaginal disc (which develops into the adult wing). By measuring the intensity of fluorescent proteins attached to Dpp and Dad (a molecule whose expression is induced by Dpp), the authors show that Dpp concentration and signaling activity are well described by an exponential function. The decay length (λ) of this exponential increases over time, proportionally with the size (*L*) of the tissue, such that λ/*L* is constant (see the figure). Thus, Dpp concentration profiles at all stages of development can be described by one unique exponential master curve.

Considering that growth is spatially uniform–that is, the relative position of a cell in the tissue remains unchanged—Wartlick *et al*. conclude that all cells in the tissue experience the same relative temporal changes in Dpp signaling. Thus, as a cell is moved away from the Dpp source because of tissue growth, its Dpp concentration does not decrease, but rather, it increases in proportion to gradient amplitude (maximum at the source) due to the accumulation of Dpp.



Uniform growth. The secreted molecule Dpp is produced from source cells in the developing fly larval wing tissue and diffuses across target cells to control growth. Dpp concentration profile, [$C_t(x)$], for different times (*t*) of wing disc development is shown. *X* is the distance over which the gradient decays; *L* is the size of the target tissue; t_0 to t_3 represent different times during development. "+" indicates the concentration sensed by two cells (cell 1 and cell 2) as the tissue grows. In the scaled graph, these remain as stationary points. The two cells divide at the same rate because they experience the same relative increase in Dpp signaling.

The third observation of Wartlick *et al*. is that the gradient amplitude is related to the area of the target tissue by a power law—they are proportional on logarithmic scales. Because all cells in the tissue sense the same relative temporal variation in Dpp, this finding implies that the rate of tissue growth, and hence the rate of cell divisions, is proportional to the relative increase of Dpp concentration and activity. Putting this into numbers, a cell divides when its Dpp concentration and activity increase by, respectively, 40 and 50%. Wartlick *et al*. hypothesize that this phenomenological correlation underlies a deeper causal link, and propose that sensing such an increase in Dpp signaling triggers cells to divide.

The quantitative model of Wartlick *et al*. lends itself to rigorous experimental testing. In particular, it predicts that any experimental manipulation of Dpp gradient dynamics should be accompanied by a change in growth rate, such that cells divide when Dpp activity has increased by about 50%. Indeed, even in perturbed conditions (such as altering the production, diffusion, or degradation of Dpp), cells at all positions in the imaginal disc tissue divide after experiencing a 50% increase in Dpp activity.

The correlation works so well that one might fear a "hidden" constraint embedded in the system that couples Dpp activity increase and tissue growth. To address this possibility, Wartlick *et al*. examined a situation in which the rise of Dpp activity is regulated externally by controlling the rate of accumulation of a constitutively active Dpp receptor, and thus the extent of relative Dpp signaling change in the target cells. The rate of cell growth correlated with the induction of cell division by a ~50% increase in Dpp signaling.

The model presented by Wartlick *et al*. changes how we should now think about growth control by morphogens in several ways. It establishes Dpp as a genuine growth factor, a point debated until recently. (Whether the effect of Dpp on early fly wing develop-

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ment is mediated by the Fat-Hippo signaling pathway is possible but is not addressed in this study.) And it establishes a mechanistic link between the cellular computation of Dpp signal activity over time and cell growth. However, although the authors show that the model holds up to different experimental challenges and numerical simulations, the existence of a causal relationship is not firmly demonstrated. Direct observations, at the single-cell level, of cell division in response to an increase (by about 50%) in its Dpp activity should bolster the model.

The findings by Wartlick *et al*. point to new avenues of investigation. One question is how Dpp signaling activity is integrated over time, and the form in which this information is stored and measured in the cell (*11*). Another concerns how polarized cell divisions in some regions of the wing imaginal disc could affect homogeneity of tissue growth and consequently the temporal variations in Dpp signaling that cells experience. The authors report the intriguing observation that the degradation rate of Dpp is inversely proportional to tissue size and decreases over time, thereby potentially explaining gradient scaling. This suggests that tissue growth affects Dpp dynamics. The existence and mechanism of this feedback will be an important problem to address in the future.

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PHYSICS

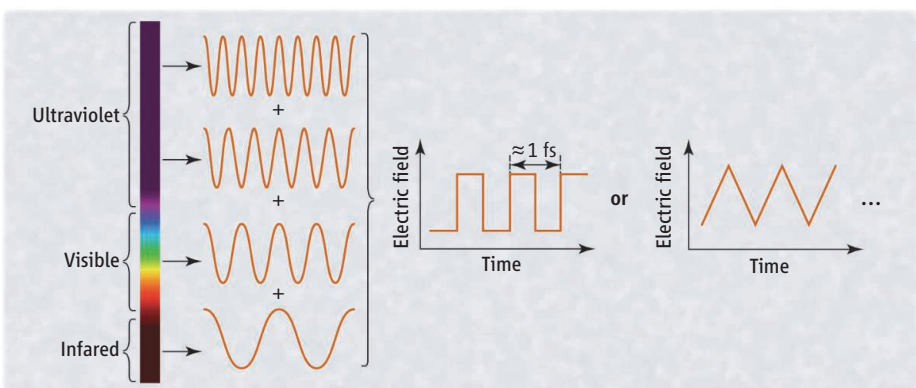
Toward Synthesis of Arbitrary Optical Waveforms

Light with different frequencies (colors) can be combined to synthesize optical waveforms such as square and sawtooth waves, as well as short pulses.

Deniz D. Yavuz

Waveform generation underlies the operation of many electronic devices, especially those used in broadcasting and signal processing. Electronic waveform generators produce a prescribed series of voltages or currents as a function of time, which may then be used as an input for a variety of circuits. The simplest versions of these devices, known as function generators, are used in undergraduate classes to produce the familiar sinusoidal, square, or sawtooth voltage waveforms seen on oscilloscopes. Arbitrary waveform generators (called synthesizers) that can create almost any pulse shape are now a common piece of equipment (and often used by graduate students to test misbehaving electronic equipment). By comparison, synthesizing optical waveforms, in which the electric and magnetic fields of light waves are not simply oscillatory but are specified functions of time, has proved to be difficult. This task has been a long-standing goal of physicists since the invention of the laser in 1960 provided a source of coherent light. On page 1165 of this issue, Chan *et al*. (*1*) demonstrate an important step toward synthesizing and characterizing arbitrary waveforms in the optical domain.

The key difference between electronic and optical synthesizers is the time scales of these devices. Electronic synthesizers are generally limited to nanosecond (10^{-9} s) time scales, or frequency scales of 1 gigahertz. Optical synthesizers need to produce waveforms with time scales of 1 femtosecond (1 fs = 10^{-15} s), and frequency scales of 1 petahertz (PHz), so processing must be faster by six orders of magnitude. Synthesizing arbitrary optical waveforms first requires broadband coherent light. Most lasers are narrowband: for example, a laser pointer may emit only in red or green wavelengths. Thus, a large number of laser beams emitting over infrared, visible, and ultraviolet spectral regions would be needed as a source. The required range of frequencies to cover the optical spectrum (the bandwidth) approaches 1 PHz.



Arbitrary can be good. An ideal arbitrary optical waveform generator will produce coherent light covering visible, infrared, and ultraviolet spectral regions. Appropriate superposition of light waves at different colors can create arbitrary waveforms, for example, square and sawtooth waveforms.

A second requirement is precise control over the phase and amplitudes of the frequencies (called spectral components) to allow for temporal shaping of the output (creating pulses of longer or shorter duration). As illustrated in the figure (see the figure), each beam of a particular color is a sinusoidal wave with a certain frequency, and appropriate superpositions of these waves result in arbitrary waveforms. Different waveforms are obtained by varying the phase and amplitude of the different frequencies.

At the heart of the approach of Chan *et al*. is molecular modulation (*2*–*7*). This technique, pioneered by Harris's group at Stanford University, uses the excitation of vibra-

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